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LETTER TO THE EDITOR

Disease Course and Risk of Relapse in Juvenile Localized Scleroderma: A Single-Center Retrospective Study

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Dear Editor,

Juvenile localized scleroderma (JLS), also known as morphea, is a rare autoimmune disorder characterized by inflammation and fibrosis of the skin and underlying tissues, often resulting in notable functional and cosmetic sequelae. Methotrexate (MTX), often administered alongside short-term systemic corticosteroids, remains the cornerstone of therapy. While systemic immunosuppression has been demonstrated to induce disease remission, relapse following treatment cessation remains a significant concern. Reported relapse rates in the literature vary widely, ranging from 12.5% to 53%, and pediatric patients appear more susceptible to relapse than adults [1–9]. Despite this, limited data exist on pediatric predictors of relapse, particularly in relation to clinical features such as age at onset, ANA status, JLS subtype, and duration of MTX therapy.

To address this knowledge gap, we conducted a retrospective cohort study at Alberta Children's Hospital (Calgary, Alberta, Canada), evaluating remission and relapse patterns in children with JLS patients treated with MTX over a 6-year period (2014–2019). Ethics approval was obtained from the University of Calgary Conjoint Research Ethics Board (REB 18-2039). Diagnosis was based on standard clinical criteria, and patients with more than one superficial plaque were treated according to Childhood Arthritis and Rheumatology Research Alliance (CARRA) protocols consensus treatment plans with systemic corticosteroids (either intravenous [IV] methylprednisolone or oral [PO] prednisone) for 3 months, along with maintenance MTX (PO or subcutaneous [SC]) if their JLS is felt to be active clinically and/or based on skin biopsy [10]. Duration of the MTX treatment was based on the clinical judgment of the treating physicians. The average weekly dose of methotrexate administered across the cohort was 15 mg/m^2, either PO or SC, depending on the patient's preference. Dosage for methylprednisolone was 30 mg/kg/day (up to a maximum of 1 g/day) IV for 3 consecutive days per month for 3 months. PO prednisone was also dosed according to the CARRA CTPs [10]. Patients who experienced a disease flare after discontinuing systemic therapy were restarted on the consensus protocol, which included 3 months of systemic corticosteroids along with maintenance methotrexate (MTX). For patients flaring while on MTX, treatment was adjusted by either increasing the MTX dose, switching to subcutaneous administration, or adding mycophenolate mofetil (MMF) [11, 12]. During active systemic therapy, adjunctive topical agents—such as calcipotriol/betamethasone and topical tacrolimus—were applied to specific active lesions. These topical treatments were typically discontinued prior to MTX cessation.

Following MTX discontinuation, no routine adjunctive or maintenance therapy was administered unless there was clinical evidence of a disease flare. In such cases, systemic and/or topical immunomodulatory therapy was reinstated.

A total of 24 patients were included in the cohort, of whom 22 (91.7%) completed a course of MTX therapy. Two patients opted not to continue systemic treatment for personal reasons and were managed with topical agents alone. All MTX-treated patients achieved disease remission. Eleven patients (50.0%) achieved remission within 6 months of treatment initiation, and 21 patients (95.5%) within 1 year. The mean duration of MTX therapy was

28.7 ± 14.5 months (range: 14.0–73.1 months), and the mean time to remission was 6.7 ± 3.8 months (range: 2.1–16.3 months).

The median age at baseline was 12.1 years (IQR = 10.6–14.3), with 70.8% ($n = 17$) of patients being female. Most had the linear subtype of JLS with trunk/limb distribution ($n = 14$; 58.3%), while six patients (25.0%) had craniofacial distribution, one of whom also had trunk/limb involvement. Another six patients (25.0%) had other JLS distributions, including one with a mixed subtype that also had linear trunk/limb involvement. ANA status was positive in 37.5% of the cohort. Extracutaneous manifestations were present in 45.8% of patients: neurologic ($n = 4$; 16.6%), ophthalmologic ($n = 1$; 4.2%), musculoskeletal ($n = 6$; 25.0%), and Raynaud's phenomenon ($n = 2$; 8.3%). Seven patients (29.2%) required physiotherapy or occupational therapy. The baseline cutaneous disease activity, as measured by the modified Localized Scleroderma Skin Severity Index (mLoSSI), ranged from 1.25 to 7.5, with a reported median score of 5.5.

Of the 22 patients treated with MTX, 20 completed an adequate course and subsequently discontinued therapy during the study, while 2 remained on MTX at their last follow-up after achieving remission. Among the 20 patients who discontinued MTX, 6 (30.0%) experienced disease relapse. An additional three patients relapsed while still receiving a lower dose of MTX, resulting in a total of nine relapses in the cohort. Relapses were managed with MTX plus corticosteroids in 6 patients (66.7%) and MTX monotherapy in three patients (33.3%), and no patients required mycophenolate. The mean MTX duration without subsequent relapse was 25.7 ± 8.6 months, compared with 32.1 ± 19.5 months in those who relapsed ($p = 0.45$). Mean time to relapse after discontinuation was 14.5 ± 10.3 months. Seven of the nine relapses (77.8%) occurred at the same anatomical site as the original lesion, and eight out of nine (88.9%) occurred in patients with linear trunk/limb disease. Figure 1 illustrates a patient experiencing a relapse at the same site.

Exploratory univariable and multivariable logistic regression analyses did not identify any statistically significant clinical predictors of relapse (Table 1). In the univariable analysis, no significant associations were found between relapse and sex ($p = 0.40$), age at disease onset ($p = 0.75$), ANA positivity ($p = 0.29$), or JLS subtype (trunk/limb, $p = 0.11$; other, $p = 0.32$). Similarly, multivariable logistic regression revealed no significant associations with sex ($p = 1.00$), age ($p = 0.85$), or ANA positivity ($p = 1.00$). Inclusion of JLS subtype in the multivariable model was not possible due to the limited sample size.

Our findings confirm the effectiveness of MTX in achieving disease remission in pediatric JLS, with nearly all patients achieving remission within 1 year of therapy initiation. Previous studies examining the association between MTX treatment duration and relapse have yielded mixed results. Some have suggested that shorter treatment duration may increase the risk of relapse, advocating for prolonged therapy to sustain remission [6, 9, 12]. Conversely, other studies have not found a significant relationship between treatment duration and relapse risk [5, 13], suggesting that additional factors—such as disease subtype or individual patient characteristics—may play a role. Our findings did not identify a significant difference in MTX duration between those who relapsed and those who did not. This may reflect underlying disease heterogeneity or a threshold effect beyond which continued therapy provides diminishing preventive benefit.

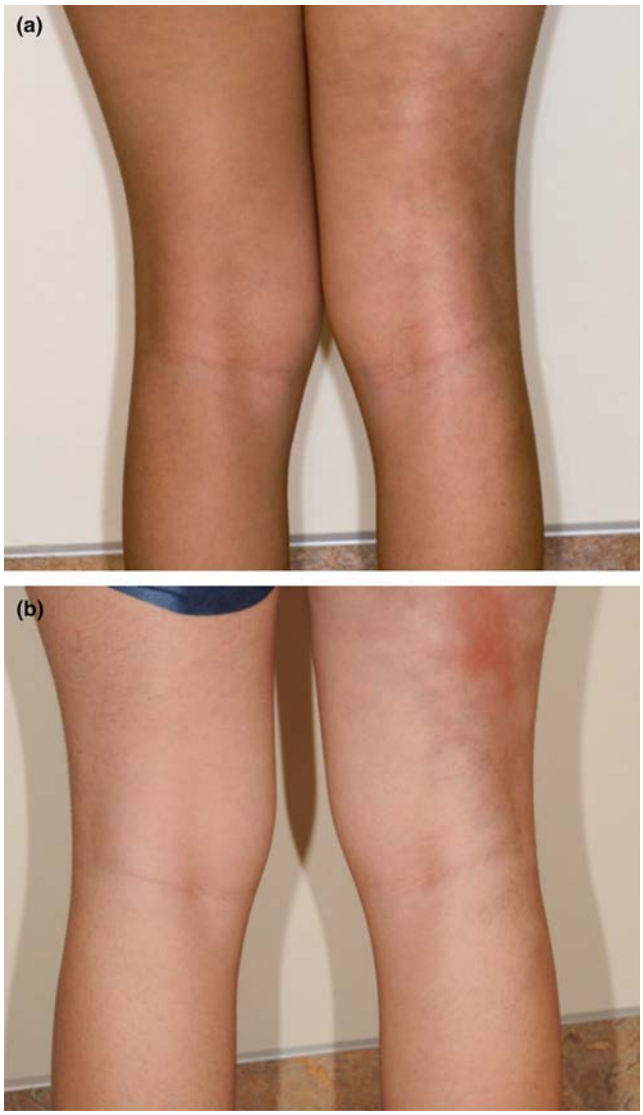

FIGURE 1 | (a) Inactive juvenile localized scleroderma. An ill-defined, thickened, mildly hyperpigmented lesion measuring 10–11 cm with underlying visible vessel, mild dermal atrophy in a linear distribution on the posterior aspect of the right thigh. (b) Active juvenile localized scleroderma. Disease relapse in same patient. An ill-defined, thickened lesion with moderate erythema in a linear distribution on the posterior aspect of the right thigh 18 months after methotrexate (MTX) discontinuation.

While most relapses in our study occurred in the linear subtype (89%), this was not statistically significant. Some studies have linked linear involvement to relapse due to a more systemic inflammatory process [4, 5, 14], but others found no association [2]. ANA positivity, which is thought to indicate higher immune autoreactivity [15], showed no consistent association with relapse risk in our study and prior studies [2, 4].

Importantly, MTX was well tolerated. No patients experienced serious adverse events requiring therapy discontinuation. Two patients required MTX dose reduction due to gastrointestinal intolerance; both remained in remission.

TABLE 1 | Univariable and multivariable analysis of clinical predictors of disease relapse after methotrexate discontinuation among our juvenile localized scleroderma (JLS) cohort.

Variable	Univariable OR (95% CI)	Univariable *p*	Multivariable OR (95% CI)	Multivariable *p*
Age	1.05 (0.67–1.33)	0.75	0.90 (0.59–1.39)	0.64
Sex (male)	2.00 (0.27–14.78)	0.50	0.74 (0.06–8.84)	0.81
ANA	0.32 (0.039–2.62)	0.29	0.34 (0.032–3.49)	0.36
JLS subtype—limb/trunk	7.20 (0.64–81.54)	0.11	—	—
JLS subtype—craniofacial	**	**	—	—
JLS subtype—other	0.29 (0.025–3.37)	0.32	—	—

Abbreviations: **, only one occurrence; —, limited sample size; ANA, anti-nuclear antibody; OR, odds ratio.

This study is limited by its retrospective, single-center design and small sample size, which restricts the ability to detect subtle associations. Nonetheless, the findings emphasize the necessity for long-term follow-up, as the mean time to relapse exceeded 1 year after MTX discontinuation. These results underscore the unpredictable nature of disease relapse and the need for vigilant monitoring even after prolonged disease quiescence.

In conclusion, MTX remains highly effective in inducing clinical remission in pediatric JLS. Nevertheless, disease relapse following treatment cessation is relatively common, underscoring the necessity for prolonged vigilance and individualized management. In our cohort, no statistically significant clinical predictors of relapse—including age at disease onset, sex, ANA positivity, JLS subtype or MTX treatment duration—were identified, reflecting the heterogeneous nature of disease pathophysiology. Future studies with larger, multicenter cohorts are warranted to systematically evaluate potential relapse risk factors. These may include clinical variables (disease subtype, lesion distribution, extent of cutaneous involvement, presence of extracutaneous manifestations), laboratory markers indicative of subclinical immune activity (ANA titers, erythrocyte sedimentation rate, C-reactive protein, cytokine profiles), imaging-based assessments of residual inflammation or fibrosis (on ultrasound or MRI), and genetic or environmental determinants. A comprehensive, multimodal approach may facilitate the identification of patients at heightened risk for relapse and inform evidence-based strategies for treatment duration, tapering, and post-remission monitoring.

Author Contributions

Merna Adly: data collection, synthesis and writing of manuscript. **Brendan C. Lethebe:** statistical analysis. **Vimal H. Prajapati, Rebeka Stevenson, and Nadia J. Luca:** revision and editing of manuscript.

Disclosure

The authors have nothing to report.

Ethics Statement

This study was conducted in accordance with ethical standards and received approval from University of Calgary Conjoint Research Ethics Board (REB 18-2039). Informed consent was obtained from all participants prior to their inclusion in the study.

Consent

All authors confirm that they have obtained informed consent from the patient(s) or their legal guardian(s) for the publication of this study, including any relevant images or data. Identifying details have been anonymized to protect patient confidentiality.

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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References

1. D. Cox, G. O'Regan, S. Collins, A. Byrne, A. Irvine, and R. Watson, "Juvenile Localised Scleroderma: A Retrospective Review of Response to Systemic Treatment," *Irish Journal of Medical Science* 177, no. 4 (2008): 343–346.

2. K. L. Kurzinski, C. K. Zigler, and K. S. Torok, "Prediction of Disease Relapse in a Cohort of Paediatric Patients With Localized Scleroderma," *British Journal of Dermatology* 180, no. 5 (2019): 1183–1189.

3. G. Martini, G. Fadanelli, A. Agazzi, F. Vittadello, A. Meneghel, and F. Zulian, "Disease Course and Long-Term Outcome of Juvenile Localized Scleroderma: Experience From a Single Pediatric Rheumatology Centre and Literature Review," *Autoimmunity Reviews* 17, no. 7 (2018): 727–734.

4. J. S. Mertens, M. M. Seyger, W. Kievit, et al., "Disease Recurrence in Localized Scleroderma: A Retrospective Analysis of 344 Patients With Paediatric- or Adult-Onset Disease," *British Journal of Dermatology* 172, no. 3 (2015): 722–728.

5. L. Mirsky, A. Chakkittakandiyil, R. M. Laxer, C. O'Brien, and E. Pope, "Relapse After Systemic Treatment in Paediatric Morphoea," *British Journal of Dermatology* 166, no. 2 (2012): 443–445.

6. F. Zulian, C. Vallongo, A. Patrizi, et al., "A Long-Term Follow-Up Study of Methotrexate in Juvenile Localized Scleroderma (Morphea)," *Journal of the American Academy of Dermatology* 67, no. 6 (2012): 1151–1156.

7. F. Zulian, G. Martini, C. Vallongo, et al., "Methotrexate Treatment in Juvenile Localized Scleroderma: A Randomized, Double-Blind,

Placebo-Controlled Trial," *Arthritis and Rheumatism* 63, no. 7 (2011): 1998–2006.

8. E. B. Kroft, M. C. Creemers, F. H. van den Hoogen, J. B. Boezeman, and E. M. de Jong, "Effectiveness, Side-Effects and Period of Remission After Treatment With Methotrexate in Localized Scleroderma and Related Sclerotic Skin Diseases: An Inception Cohort Study," *British Journal of Dermatology* 160, no. 5 (2009): 1075–1082.

9. L. Weibel, M. C. Sampaio, M. T. Visentin, K. J. Howell, P. Woo, and J. I. Harper, "Evaluation of Methotrexate and Corticosteroids for the Treatment of Localized Scleroderma (Morphoea) in Children," *British Journal of Dermatology* 155, no. 5 (2006): 1013–1020.

10. R. M. Laxer and F. Zulian, "Localized Scleroderma," *Current Opinion in Rheumatology* 18, no. 6 (2006): 606–613.

11. S. C. Li, K. S. Torok, E. Pope, et al., "Development of Consensus Treatment Plans for Juvenile Localized Scleroderma: A Roadmap Toward Comparative Effectiveness Studies in Juvenile Localized Scleroderma," *Arthritis Care & Research (Hoboken)* 64, no. 8 (2012): 1175–1185.

12. K. S. Torok and T. Arkachaisri, "Methotrexate and Corticosteroids in the Treatment of Localized Scleroderma: A Standardized Prospective Longitudinal Single-Center Study," *Journal of Rheumatology* 39, no. 2 (2012): 286–294.

13. M. S. Pequet, K. E. Holland, S. Zhao, et al., "Risk Factors for Morphoea Disease Severity: A Retrospective Review of 114 Paediatric Patients," *British Journal of Dermatology* 170, no. 4 (2014): 895–900.

14. S. Christen-Zaech, M. D. Hakim, F. S. Afsar, and A. S. Paller, "Pediatric Morphea (Localized Scleroderma): Review of 136 Patients," *Journal of the American Academy of Dermatology* 59, no. 3 (2008): 385–396.

15. K. Takehara and S. Sato, "Localized Scleroderma Is an Autoimmune Disorder," *Rheumatology (Oxford, England)* 44, no. 3 (2005): 274–279.

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REVIEW

The Multifaceted Role of p53 in Musculoskeletal Diseases: A Comprehensive Review

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ABSTRACT

Background: While extensively studied for its central role in tumor suppression (regulating cell cycle, DNA repair, and apoptosis), the p53 gene is now recognized for its significant involvement in musculoskeletal diseases. Aberrant p53 expression and function are key factors in the pathogenesis and progression, although the specific mechanisms and clinical change potential remain incompletely defined.

Objective: This review systematically summarizes the multifaceted roles of p53 in major musculoskeletal diseases, analyzes the molecular mechanisms driving disease progression, and evaluates its potential as a therapeutic target.

Methods: A comprehensive literature search was conducted in PubMed January 2008 to March 2025 using keywords including P53, osteoporosis, osteoarthritis, rheumatoid arthritis, gout, low back pain, and scoliosis. Original research, reviews, and clinical trials focusing on p53 mechanisms were included. 90 relevant articles were selected for analysis.

Results & Conclusion: p53 critically influences the development and progression of musculoskeletal diseases (osteoporosis, osteoarthritis, rheumatoid arthritis, low back pain, gout, and scoliosis) through diverse mechanisms: Disrupting bone formation/resorption balance (via the p53-Nedd4-Runx2 axis in osteoporosis). Promoting chondrocyte apoptosis (via the miR-34a-SIRT1-p53 pathway in osteoarthritis). Modulating inflammatory mediators (TNF-α, IL-6 in rheumatoid arthritis). Regulating oxidative stress responses (p53-SLC2A9 axis in gout). p53 exhibits dual roles (pro-apoptotic vs. anti-inflammatory), necessitating precise targeting strategies. Promising therapeutic interventions include p53-focused gene editing (CRISPR/Cas9), small-molecule inhibitors (PFT-α), and natural products (naringin). However, further clinical validation is essential. Future research requires multidisciplinary approaches to deepen understanding of p53 mechanisms and advance clinical applications in musculoskeletal disorders.

1 | Introduction

The p53 gene is a crucial tumor suppressor with biological functions that extend significantly beyond its traditional role in cancer biology. In addition to maintaining genomic integrity through mechanisms such as cell cycle arrest, DNA repair, and apoptosis induction [1], p53 also prevents the accumulation of oncogenic mutations via multiple regulatory pathways [2]. Recent research indicates that the p53 signaling network has expanded its functional landscape to encompass a variety of non-neoplastic conditions, including musculoskeletal diseases, thereby offering novel insights into their molecular underpinnings and potential therapeutic targets [3, 4].

Musculoskeletal disorders including osteoporosis, rheumatoid arthritis, osteoarthritis, low back pain, gout, and scoliosis

represent some of the most prevalent and disabling chronic diseases globally. These conditions impair the muscles, bones, joints, and connective tissues, leading to progressive loss of mobility and substantial long-term burdens on public health systems. With global populations aging, epidemiological evidence confirms that the incidence of musculoskeletal disorders is increasing steadily, especially among older adults whose symptoms often progress in severity over time [5, 6]. The etiology of these disorders is complex and multifactorial, shaped by the interplay of genetic susceptibilities and environmental exposures.

This review aims to provide a comprehensive synthesis of how the p53 signaling pathway contributes to the development, progression, and potential treatment of various musculoskeletal disorders. By analyzing disease-specific mechanisms and evaluating the feasibility of targeting p53 therapeutically, this work aims to establish a theoretical foundation for innovative strategies in musculoskeletal disease management.

2 | Data and Methods

2.1 | Data Source

A literature search was conducted by Marofe Hossain and Sun Hao in March 2025. The search time frame was from January 2008 to March 2025, utilizing the PubMed database. English search terms included (see Figure 1). The literature types included original research articles, review articles, clinical trials, systematic reviews, and methodological studies. A total of 504 relevant articles were retrieved.

2.2 | Literature Screening and Data Extraction

The literature screening was conducted independently by two reviewers (Marofe Hossain and Sun Hao). After retrieving 504 records, titles and abstracts were screened against the inclusion and exclusion criteria. The full texts of potentially relevant articles were then assessed for final eligibility. For the included studies, the same two reviewers independently extracted key data, including study design, biological models, p53-related mechanisms, and main conclusions. The methodological quality of each study was appraised based on its design-specific rigor (control use in experiments, blinding, statistical methods). Any disagreements during screening or data extraction were resolved through discussion or by consulting a third senior author (Yongxiang Wang).

#1 P53 [Title/Abstract]
#2 Osteoporosis [Title/Abstract]
#3 Post-Menopausal Osteoporosis [Title/Abstract]
#4 #1 AND #2 OR #3
#5 osteoarthritis [Title/Abstract]
#6 Degenerative Arthritis [Title/Abstract]
#7 Rheumatoid Arthritis [Title/Abstract]
#8 Gout [Title/Abstract]
#9 #1 AND #5 OR O#6 OR #7
#10 Low Back Pains [Title/Abstract]
#11 Low Back Ache [Title/Abstract]
#14 #1 AND #10 OR #11 OR #12 OR #13

FIGURE 1 | PubMed database search strategy.

2.3 | Inclusion Criteria

(1) Studies were included if they clearly involved the molecular mechanisms, signaling pathways, or therapeutic targets of p53 in musculoskeletal diseases. (2) Eligible study types included original research articles, reviews, clinical trials, and systematic reviews. (3) Only literature published between January 2008 and March 2025 was considered.

2.4 | Exclusion Criteria

(1) Studies were excluded if they only described clinical phenomena without an in-depth discussion of p53's molecular mechanisms. (2) Duplicate publications of the same study were excluded, with only the earliest or most complete version retained. (3) Studies with incomplete data or those for which the full text could not be obtained were also excluded.

2.5 | Data Integration

Following the systematic screening process, 426 articles were excluded, resulting in 90 articles being finally included for in-depth analysis. The literature screening and selection process is summarized (see Figure 2).

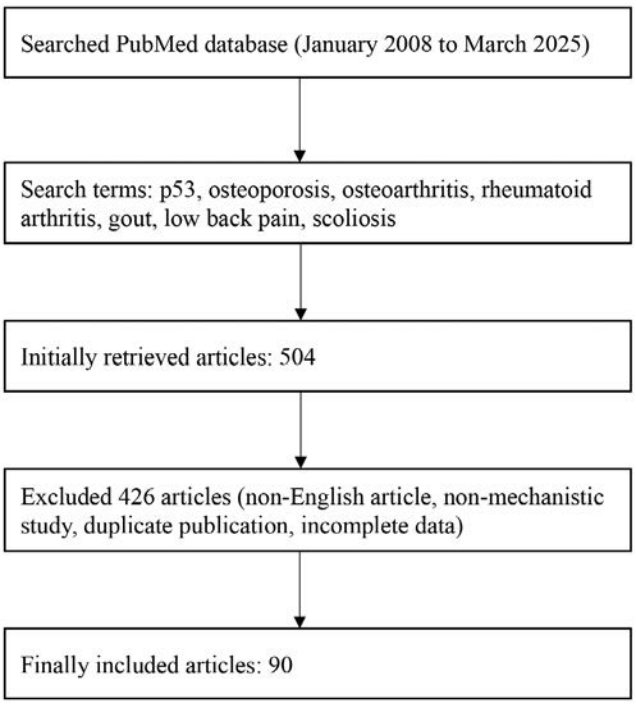

FIGURE 2 | Literature screening flow chart.

3 | Results

3.1 | Research Timeline

The research timeline is presented (See Figure 3).

3.2 | Biological Functions of p53

The p53 protein is a multifunctional transcriptional regulator with a structure comprising an N-terminal transcriptional activation domain, a core DNA-binding domain, a hinge region regulatory domain, and other key functional units [7]. Its amino acid sequence is highly conserved across vertebrates, ensuring structural and functional similarity. p53 specifically recognizes and binds to DNA sequences, precisely regulating its downstream gene networks. Its functions encompass various biological processes, including cell cycle control, DNA repair, apoptosis, cell senescence, and cellular metabolism [8].

Mouse Double Minute 2 (MDM2) acts as a core negative regulator of p53, directly binding to p53 and promoting its ubiquitination and subsequent degradation [9]. The functional activity of p53 is dynamically regulated by multiple levels of modification, such as phosphorylation, acetylation, methylation, and ubiquitination, which influence its subcellular localization, DNA-binding ability, and transcriptional activity, forming a complex signal integration network [10].

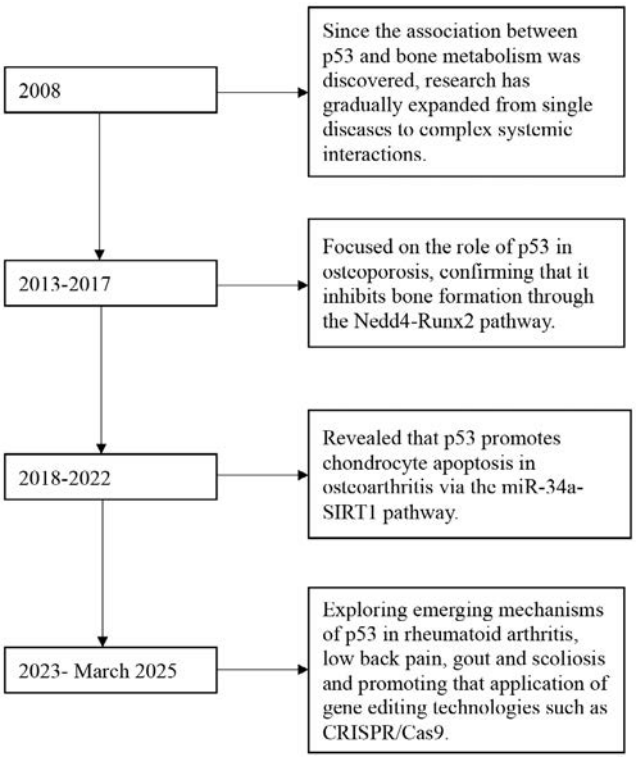

FIGURE 3 | Timeline of research on p53 in musculoskeletal diseases.

3.3 | p53 and the Cell Cycle

During the G1/S checkpoint regulation, p53 can block the cell cycle by activating the expression of p21 protein, a cell cycle inhibitor. This mechanism provides a crucial time window for DNA damage repair. If irreversible damage occurs, p53 activates cellular senescence or apoptosis to prevent uncontrolled proliferation of damaged cells, forming a core part of the body's tumor defense system [11]. Thus, p53 is crucial for maintaining genomic stability and preventing tumor development.

3.4 | p53 and Apoptosis

The p53 protein plays a central regulatory role in the mitochondrial apoptosis pathway by activating pro-apoptotic molecules like BAX, PUMA, and NOXA. Under specific pathophysiological conditions, p53 can also trigger apoptosis via the death receptor pathway. Its activity is finely regulated by both intracellular and extracellular environmental factors, ensuring timely activation of apoptosis and maintaining tissue cell population balance [12]. This balance between cell survival and programmed death serves as a core safeguard for tissue homeostasis.

3.5 | p53 and DNA Repair

As a key guardian of DNA repair, p53 is involved in various DNA repair pathways, including base excision repair, nucleotide excision repair, and mismatch repair. This function is vital for maintaining genomic stability, blocking mutation accumulation, and preventing gene damage and carcinogenesis [13]. By finely regulating DNA repair, p53 provides essential protection against genetic damage.

3.6 | p53 and Cellular Senescence

Cellular senescence is an irreversible growth arrest state where p53 exhibits unique biological functions. When cells experience persistent stress or oxidative damage, p53 promotes the expression of effector molecules like p21, driving the cell into senescence. This molecular surveillance mechanism prevents further proliferation of damaged cells, reducing potential harmful effects on the organism [14]. As a central regulator of molecular homeostasis, p53 acts as a guardian throughout the cell's life cycle, ensuring cell stability and overall health.

3.7 | p53 and Its Role in Osteoporosis

Primary osteoporosis, an age-related disease, shows a positive correlation with population aging [15]. Aging manifests at the cellular level, with cellular senescence being a key factor in the aging process. Osteoporosis, a common chronic age-related

disease, currently lacks targeted strategies for rebuilding bone microenvironment homeostasis, with clinical interventions mainly focusing on symptom management [16]. In osteoporosis pathogenesis, p53 influences osteocyte differentiation and bone metabolism, thereby impacting bone formation and maintenance [17].

3.8 | p53 Impact on Osteocyte Differentiation

1. Osteoblast differentiation: p53 significantly inhibits osteoblast differentiation, reducing bone formation by limiting osteoblast proliferation and accelerating osteoblast apoptosis. It affects aging and osteogenesis inhibition of aging bone marrow mesenchymal stem cells through the p53/miR-145a axis [18]. In bone marrow mesenchymal stem cells overexpressing p53, miR-145a expression significantly increases, while Cbfb mRNA expression substantially decreases [19]. Chromatin immunoprecipitation confirmed that p53 directly binds to the miR-145a promoter, activating its transcription. Cbfb deletion leads to decreased expression of osteogenesis markers (Runx2, Osterix) and increased expression of adipogenesis markers (PPARγ, C/EBPα). p53 knockout mice have significantly higher bone density than wild-type mice, suggesting the p53/miR-145a/Cbfb axis as a potential target for osteoporosis treatment [20].
2. Osteoclast differentiation: p53 significantly affects osteoclast differentiation by regulating related signaling pathways. Beraprost promotes osteoblast differentiation of mouse bone marrow mesenchymal stem cells via the PI3K-Akt pathway. Activated osteoblasts then suppress osteoclast genesis through a RANKL-dependent mechanism. Bone mass in p53 knockout mice remains stable regardless of beraprost administration, indicating p53's crucial role in bone mass regulation by beraprost [21]. These results highlight p53's key role in beraprost-influenced bone metabolism, especially in regulating osteoclast differentiation.
3. Bone formation and bone resorption: p53 promotes osteoclast activity and increases bone resorption. p53 activation is associated with enhanced proliferation and differentiation of osteoclast precursors, potentially leading to bone loss, particularly in high-fat diet-induced bone formation inhibition where insulin-like growth factor 1 signaling and p53 apoptosis pathway gene expression change [22]. In a high-fat diet-induced osteoporosis model, p53 activation significantly increased osteoclast precursor differentiation efficiency. Upregulation of TGFbR1 and IL-17a mRNA and decreased IL-4 expression were observed. Blocking p53 reduced RANKL-induced osteoclast activity by 45%, suggesting p53 may enhance RANKL signaling via the TGFbR1/IL-17a axis, stimulating bone resorption [23].

   p53 inhibits osteoblast proliferation and promotes osteoblast apoptosis, reducing new bone tissue formation. p53 interacts with the Nedd4 promoter, enhancing Nedd4 transcription. Nedd4, an ubiquitin ligase, binds to Runx2, promoting its ubiquitination and degradation, which significantly impacts bone formation. Thus, the p53-Nedd4-Runx2 axis is an important pathway regulating bone formation, suggesting that prostaglandin treatment for postmenopausal osteoporosis may have therapeutic value [21].

3.9 | The Role of p53 in Bone Remodeling

Bone remodeling is a lifelong metabolic process, a dynamic balance between osteoblast-mediated bone formation and osteoclast-dominated bone resorption, leading to mature bone structures. p53 exhibits bidirectional regulatory characteristics in maintaining bone microenvironment homeostasis through epigenetic networks.

1. Disruption of bone homeostasis: p53 promotes bone remodeling likely through bidirectional regulation involving osteoclast activation and osteoblast differentiation inhibition. Cyp27b1+/− mice show significant redox imbalance, sustained DNA damage response activation, reduced antioxidant enzyme expression [24], increased aged osteocytes and bone marrow mesenchymal stem cells, abnormal secretion of senescence-associated phenotypic molecules, and elevated p16, p19, and p53 protein levels [24], confirming p53's core regulatory role in maintaining bone metabolic homeostasis.
2. Inhibition of bone formation: p53 further exacerbates bone loss by suppressing osteoblast proliferation and promoting osteoblast apoptosis, which reduces bone formation. In aged bone marrow mesenchymal stem cells [25], acetylated p53 levels are significantly higher, accompanied by suppressed telomerase activity and increased reactive oxygen species (ROS). Applying the p53 inhibitor pifithrin-α enhances osteogenic differentiation and decreases apoptosis, all related to p53 regulation. Elevated acetylated p53, p21, and p16 proteins, decreased telomerase activity, and increased ROS may inhibit osteoblast function. Dexamethasone-induced osteoblast damage can be partially reversed by p53 inhibitors (pifithrin-α), revealing p53's role in osteoblast injury.

While osteoporosis (bone loss) and osteoarthritis (cartilage degeneration) have different pathophysiological characteristics, both are related to p53-mediated cellular regulation. In osteoporosis, p53 disrupts bone metabolic balance by inhibiting osteogenic differentiation and promoting osteoclast activity (Table 1). In osteoarthritis, p53 accelerates joint degeneration by inducing chondrocyte apoptosis and matrix degradation. The commonalities and differences in these mechanisms highlight p53's versatility in regulating bone homeostasis, providing a theoretical basis for designing cross-disease targeted therapies.

3.10 | The Role of p53 in Osteoarthritis

Osteoarthritis is a major global health challenge, affecting an estimated 240 million people worldwide in 2016 [26]. It can affect multiple joints [27, 28], with knee osteoarthritis being

TABLE 1 | The role of p53 in osteoporosis.

Function	Impact on cell phenotype	Mechanism	References
Effect of p53 on bone cell differentiation	Osteoblast differentiation	p53/miR-145a/Cbfb axis	[18]
	Osteoclast differentiation	PI3K-AKT pathway	[21]
	Bone resorption	RANK/RANKL pathway	[23]
	Bone formation	p53-Nedd4-Runx2 axis	[21]
Role of p53 in bone remodeling	Disruption of bone homeostasis	Activates osteoclasts and inhibits osteoblast function	[24]
	Inhibition of bone formation	Suppresses osteoblast proliferation and promotes apoptosis	[25]

Abbreviations: PI3K-AKT, phosphoinositide 3-kinase—protein kinase B; RANK/RANKL, receptor activator of nuclear factor-$_K$B/receptor activator of nuclear factor-$_K$B ligand.

particularly common [29]. p53 plays a multifaceted role in osteoarthritis, significantly influencing its progression through chondrocyte apoptosis and joint cartilage degeneration. p53 expression is higher in osteoarthritic chondrocytes than in normal ones, and its downregulation is directly associated with reduced chondrocyte apoptosis, potentially preventing and alleviating osteoarthritic changes. This may relate to the mitochondrial apoptosis pathway. The p53 signaling pathway is linked to osteoarthritis pathogenesis, with its activation leading to abnormal mRNA expression. By affecting the cell cycle and other factors, p53 activation induces cellular senescence and apoptosis. In chondrocyte fate regulation, p53 drives apoptosis and participates in autophagy fine-tuning, with chondrocyte senescence and apoptosis believed to be critical in osteoarthritis progression. Therefore, p53 pathway activation is essential for senescence regulation and may have therapeutic value for osteoarthritis.

3.11 | The Role of p53 in Chondrocyte Apoptosis

1. Promotion of cell apoptosis: In osteoarthritis, p53 promotes chondrocyte apoptosis by activating downstream apoptotic effector molecules like Bax and Puma, leading to mitochondrial dysfunction, further promoting cell apoptosis, and ultimately joint cartilage degeneration. Yan et al. [30] found p53 protein levels were twice as high and miR-34a expression threefold upregulated in osteoarthritic chondrocytes compared to normal tissue. In vitro, miR-34a overexpression reduced SIRT1 mRNA by 60%, activating the p53/p21 pathway and increasing chondrocyte apoptosis. miR-34a knockdown reduced apoptosis to baseline, suggesting miR-34a promotes apoptosis and inhibits proliferation by regulating the SIRT1/p53 pathway in primary human chondrocytes. miR-181a-5p directly targets Sirt1, inhibiting its expression and promoting cell apoptosis by enhancing p53-dependent signaling. Thus, miR-181a-5p antisense oligonucleotides may promote chondrocyte survival [31].
2. Antioxidant stress response: p53 participates in chondrocyte oxidative stress defense via epigenetic networks, protecting chondrocytes from oxidative damage by regulating antioxidant genes like superoxide dismutase 2 and catalase [32]. In osteoarthritis chondrocytes treated with hyaluronic acid, p53 (Ser15) phosphorylation decreases, while superoxide dismutase 2 and catalase expression increases. PKR inhibitor treatment blocks p38 MAPK-mediated p53 phosphorylation, increasing AKT and PGC-1α expression, significantly reducing ROS accumulation. This suggests hyaluronic acid lowers oxidative stress and phosphorylated AKT, and through phosphorylated p38 and p53 regulation, inhibits pro-inflammatory and pro-apoptotic events, protecting chondrocytes. PKR, via p38 MAPK-mediated p53 phosphorylation, affects oxidative stress response in human chondrocytes induced by TNF-α, inhibiting AKT and PGC-1α expression [33].
3. Regulation of inflammatory response: During inflammatory microenvironment remodeling in osteoarthritis, p53 achieves dual regulation through epigenetic networks, specifically inhibiting IL-38 expression and abnormal TNF-α secretion. These inflammatory mediators trigger chondrocyte apoptosis, becoming key factors in disease progression. Long non-coding RNA H19 can alleviate inflammation by upregulating TP53 and IL-38 expression and activating the IL-36 receptor, improving cartilage damage and chondrocyte apoptosis caused by osteoarthritis. H19 forms a p53-H19 molecular complex, enhancing IL-38 expression, which promotes IL-38-specific binding to the IL-36 receptor, constructing an anti-inflammatory pathway that significantly inhibits inflammatory factor production and reduces chondrocyte apoptosis [34].

3.12 | The Role of p53 in Articular Cartilage Degeneration

1. Inhibition of matrix synthesis: In osteoarthritis, p53 negatively regulates extracellular matrix key components (collagen and proteoglycans) biosynthesis in chondrocytes, accelerating cartilage tissue degeneration. Reduced matrix molecules directly lead to cartilage wear and damage. As osteoarthritis progresses, p53R2 expression may increase, and inhibiting p53R2 could positively impact human

chondrocyte synthetic metabolism, suggesting a positive correlation with disease progression for this ribonucleotide reductase regulatory subunit [35].

2. Promotion of matrix degradation: In osteoarthritis, p53 can activate the transcriptional activity of matrix metalloproteinase (MMP) family members, especially MMP-3 and MMP-13, which are crucial in cartilage matrix degradation and accelerate cartilage degeneration [36]. Pharmacological studies show that phytoestrogen metabolite S-Equol, by activating the PI3K/Akt pathway, regulates p53 and nitric oxide upstream, associating with cell apoptosis and matrix degradation. This pathway's activation can reduce sodium nitroprusside-induced MMP-13 secretion, suggesting S-Equol may influence osteoarthritis progression by regulating p53-related signaling pathways [36].
3. Impact on chondrocyte phenotype: In osteoarthritis, p53 affects chondrocytes through a dual mechanism: promoting cell apoptosis and regulating chondrocyte phenotype. This bidirectional regulation directly interferes with chondrocyte differentiation and maturation timing, ultimately determining cartilage tissue repair and regenerative capacity. Specifically, p53 can suppress SMRT expression via the Wnt/β-catenin pathway and increase acetylated p53 expression to promote chondrocyte senescence [37]. The p53 effector molecule p53AIP-1 significantly contributes to chondrocyte apoptosis by inducing mitochondrial membrane potential depolarization. Downregulating p53 expression can prevent shear strain-induced chondrocyte apoptosis [38].

3.13 | The Impact of p53 on the Progression of Osteoarthritis

1. Promotion of osteoarthritis pathological process: p53 plays a key role in osteoarthritis progression by accelerating its development through promoting chondrocyte apoptosis and matrix degradation. Studies show that Sirt1 loss in cartilage leads to abnormal activation of p53/p21-mediated senescence-associated secretory phenotype, hypertrophy, and cell apoptosis, accelerating osteoarthritis pathogenesis [39].
2. Impact on cartilage repair: p53 inhibits cartilage repair mechanisms, weakening chondrocyte regenerative capacity, leading to cartilage damage accumulation and osteoarthritis progression. Eicosapentaenoic acid, an antioxidant and $n-3$ polyunsaturated fatty acid, intervenes in osteoarthritis chondrocytes, reducing p38 MAPK phosphorylation, decreasing p53 phosphorylation at Ser15, lowering MMP-13 expression, and increasing cell survival [40]. This discovery offers a new osteoarthritis treatment strategy: protecting chondrocytes and reducing apoptosis by regulating p53-related pathways, thereby delaying osteoarthritis progression.

In conclusion, p53 participates in osteoarthritis progression through a bidirectional regulatory network, playing multiple roles in chondrocyte apoptosis and joint cartilage degeneration (Table 2). This suggests that developing targeted interventions against p53 effector molecules could be a key direction for future osteoarthritis treatment.

TABLE 2 | Role of p53 in cartilage-related processes.

Function	Impact on cell phenotype	Mechanism	References
Role of p53 in chondrocyte apoptosis	Promotes apoptosis	miR-34a-SIRT1-p53 signaling pathway	[30]
	Antioxidant stress response	PKR-p38MAPK-p53 signaling axis; inhibits AKT and PGC-1α expression	[33]
	Regulates inflammatory response	LncRNA H19 upregulates TP53, interleukin 38, and activates interleukin 36 receptor to attenuate inflammation	[34]
Role of p53 in articular cartilage degeneration	Inhibits matrix synthesis	Downregulation of p53R2	[35]
	Promotes matrix degradation	S-Equol activates PI3K/Akt pathway	[36]
	Promotes chondrocyte senescence	Activates Wnt/β-catenin signaling by downregulating SIRT-1 and increasing acetylated p53 expression	[37]
		Downregulates p53 and p53AIP-1 expression	[38]
Role of p53 in osteoarthritis progression	Promotes OA pathological processes	Sirt1 deficiency activates p53/p21-mediated senescence-associated secretory phenotype, hypertrophy, and apoptosis	[39]
	Affects cartilage repair	Eicosapentaenoic acid (EPA) inhibits phosphorylation of p38MAPK and p53	[40]

Abbreviations: AIP1, apoptosis-inducing protein 1; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PKR, protein kinase R; SIRT1, silent information regulator 1.

3.14 | The Role of p53 in Rheumatoid Arthritis

Rheumatoid arthritis is a major global public health issue with significant regional prevalence heterogeneity, greatly impacting patients' quality of life [41]. It causes joint pain and systemic symptoms like fever, fatigue, and appetite loss. Despite its severity, there is currently no cure, partly due to unclear etiology. In the WHO 2000 "Decade of Bone and Joint" program, rheumatoid arthritis was a priority disease for intervention to reduce social and economic burdens [42]. During rheumatoid arthritis pathogenesis, p53 plays a critical role in the inflammatory response, joint damage, and disease development.

3.15 | The Role of p53 in the Inflammatory Response

1. Regulation of inflammatory mediators: In rheumatoid arthritis pathogenesis, p53 regulates inflammatory mediators, influencing the inflammatory response by modulating TNF-α and IL-6 expression. Zhang et al. [43] found higher p53 expression in rheumatoid arthritis synovial fibroblasts than in healthy controls. p53 reduces TNF-α and IL-6 secretion by inhibiting the $NF\text{-}_{K}B$ signaling pathway. In a p53 knockout arthritis model, the synovial inflammation score increased, indicating p53 alleviates rheumatoid arthritis symptoms by suppressing inflammatory mediators.
2. Impact on immune cell function: p53 affects immune cell function in rheumatoid arthritis, including T and B cell activation, proliferation, and apoptosis. p53-deficient mice show enhanced T cell responses. In a collagen-induced arthritis model, p53-deficient mice had a stronger adaptive immune response, leading to more severe disease, not antibody-mediated but associated with increased T cell reactivity [44].

3.16 | The Role of p53 in Joint Destruction

1. Promotion of cell apoptosis: p53 can exacerbate joint destruction by accelerating synovial and chondrocyte apoptosis. Increased cell apoptosis may lead to joint tissue damage and bone erosion [45]. In rheumatoid arthritis synovial fibroblasts, p53 mutations lead to increased anti-apoptotic Bcl-2 expression, while p21WAF and Hdm-2 expression decrease. p53 regulates Bcl-2 family proteins, significantly inhibiting synovial cell apoptosis and promoting joint destruction [46].
2. Regulation of matrix metalloproteinases: Matrix metalloproteinases degrade the extracellular matrix, facilitating inflammatory cell invasion into joints in rheumatoid arthritis, exacerbating joint damage. Extracellular S100A4 protein enhances p53 tumor suppressor gene expression in rheumatoid arthritis synovial fibroblast-like cells and affects p53 target genes (Bcl-2, p21WAF, and Hdm-2) expression [47]. Regulating these target genes is crucial for controlling cell apoptosis and inflammatory responses. Therefore, p53 indirectly exacerbates joint damage by influencing MMP expression and activity.

3.17 | The Role of p53 in the Pathogenesis of Rheumatoid Arthritis

1. Cell cycle control: In rheumatoid arthritis, abnormal p53 expression may lead to cell cycle dysregulation, promoting excessive synovial cell proliferation. NK4 downregulates cell proliferation markers PCNA, cyclin D1, and cyclin B1, while upregulating p53 and p21 expression. This inhibits fibroblast-like synoviocytes and MH7A cells' proliferation in rheumatoid arthritis and blocks cell cycle progression [48].
2. DNA damage response: p53 participates in and regulates various DNA repair pathways. In rheumatoid arthritis, oxidative stress and inflammation can damage DNA. p53 activation is crucial for repairing DNA damage and preventing cellular transformation. p53 helps maintain genomic stability and inhibits abnormal cell proliferation in rheumatoid arthritis, playing a protective role [49].
3. Cellular senescence: In rheumatoid arthritis, p53 may promote cellular senescence to slow down inflammation and tissue damage. During senescent cell replication, cyclooxygenase 2 and prostaglandin E2 expression significantly increase, while fibroblast proliferative capacity decreases in vitro. This may be due to increased p53 protein expression and reduced PCNA protein expression [50].

   These studies suggest p53 plays a core role in rheumatoid arthritis pathological mechanisms by regulating cellular senescence and proliferative activity. It significantly alleviates pathological joint tissue damage by inhibiting pro-inflammatory factor release and maintaining extracellular matrix homeostasis (Table S1).

3.18 | The Role of p53 in the Occurrence of Lower Back Pain

The prevalence of lower back pain is a global public health challenge, significantly affecting patients' quality of life [51, 52]. Its pathological basis includes intervertebral disc degeneration, sacroiliitis, and facet joint syndrome [53]. Facet joint degeneration is a major factor in chronic low back pain, accounting for approximately 30% of cases [54]. Traditional physical therapy often fails to provide lasting relief, and surgery carries risks [55]. Studies suggest p53 can directly intervene in intervertebral disc cell aging and substance metabolic processes by regulating specific target genes [56].

3.19 | The Role of p53 in Intervertebral Disc Degeneration

1. Promotion of cell apoptosis: p53 activation promotes apoptotic pathways, affecting intervertebral disc cell survival. During intervertebral disc degeneration, p53

activation may lead to cell growth arrest and death, reducing cell number and disrupting normal function. Proanthocyanidins pretreatment can prevent IL-1β-induced nucleus pulposus cell apoptosis and inhibit p-p53, p21, and p16 expression in IL-1β-treated cells [57]. Sirt1 activation may delay nucleus pulposus cell apoptosis and aging by reducing p53-related protein expression. These findings suggest the Sirt1/p53 axis may be important in diabetes-related intervertebral disc degeneration pathogenesis and treatment [58]. Modulating this axis could be a new treatment approach.

2. Regulation of oxidative stress response: p53 can initiate antioxidant gene expression (e.g., superoxide dismutase, glutathione peroxidase), helping cells resist oxidative damage and reducing oxidative stress damage to intervertebral disc cells. Under non-physiological cyclic mechanical tension, DNA damage in nucleus pulposus cells increases, leading to enhanced oxidative stress responses [59]. Thus, p53 protects intervertebral disc cell function by regulating antioxidant gene expression and reducing oxidative stress damage.

3. Impact on cellular senescence: In intervertebral disc degeneration, p53 activation promotes cells to enter a senescent state more quickly, evidenced by increased senescence-associated β-galactosidase activity and p53-dependent senescence marker expression. Morroniside can prevent premature aging of nucleus pulposus cells by inhibiting the ROS-Hippo-p53 pathway, offering a new treatment approach for intervertebral disc degeneration [60]. Additionally, miR-325-3p, by activating the p53/p21 pathway, can slow chondrocyte senescence and improve lumbar facet joint degeneration caused by mechanical overload. This may be a potential therapeutic strategy for delaying lumbar facet joint degeneration progression. This highlights p53's role in intervertebral disc degeneration and lumbar facet joint degeneration [60], suggesting precise p53 signaling network modulation could be a new strategy for degenerative joint diseases.

4. Inflammatory response: p53 influences pain signal transmission and local inflammation development by regulating key inflammatory factors like IL-1β and TNF-α. Flavonoids can inhibit inflammation and senescence in nucleus pulposus cells, offering a new therapeutic strategy for intervertebral disc degeneration [61]. Flavonoids achieve this by suppressing the MAPK/NF-$_K$B pathway, reducing TNF-α-induced ECM degradation. They also downregulate ECM-degrading enzymes (MMP-3, MMP-9, and MMP-13) while upregulating SOX9 and COL2A1, alleviating the degenerative process [61].

3.20 | p53 in Muscle Injury and Repair

1. Promotion of muscle cell apoptosis: p53 activation can induce muscle cell death, impairing muscle repair and regeneration. In vivo experiments show exacerbated mitochondrial dysfunction in p53 knockout tissues, with reduced neuromuscular stress response capacity. This suggests p53 helps maintain organelle stability by regulating mitochondrial quality control pathways involved in muscle atrophy [62]. Therefore, p53 plays a dual role in muscle injury and repair—as both an apoptosis regulator and an organelle health guardian.

2. Regulation of muscle cell proliferation: Overexpression of dominant-negative p53 mutants in skeletal muscle disrupts muscle mass, fiber size, metabolic phenotype, and the dynamic balance between protein synthesis and degradation [63]. This indicates p53 not only regulates muscle cell apoptosis but may also influence repair efficiency by modulating muscle stem cell division capacity. Therefore, p53 may be a key determinant in successful muscle repair. Targeting p53 activity could offer a novel therapeutic approach to improve muscle regeneration after injury.

3. Antioxidant and anti-inflammatory effects: p53 helps alleviate oxidative stress and inflammation in muscle by enhancing antioxidant enzyme expression and suppressing inflammation-related signaling pathways. For example, exercise therapy reduces oxidative stress, pro-inflammatory cytokine levels, and abnormal p53 activation in low back pain patients [64]. Naringin can inhibit MMP degradation and inflammation in IL-1–stimulated human nucleus pulposus cells by downregulating the NF-$_K$B pathway and p53 activity, offering a potential strategy to delay intervertebral disc degeneration [65].

These findings highlight p53's potential role in low back pain treatment and provide new directions for future therapeutic strategies (Table S2).

3.21 | The Role of p53 in Gout

Gout is an autoimmune disease caused by purine metabolism abnormalities and impaired uric acid excretion [66, 67]. Global epidemiological studies show significant regional prevalence differences, ranging from 1% to 6.8% [68]. In China, gout incidence has steadily risen, with hyperuricemia and gout prevalence rates of 1.1% and 13.3% in 2000 and 2014, respectively [69]. The p53 protein plays a multifaceted regulatory role in gouty arthritis, particularly in inflammation induced by urate crystal deposition. By modulating antioxidant enzyme and anti-inflammatory mediator expression, p53 can alleviate oxidative stress damage and reduce local inflammation spread, promoting damaged muscle tissue repair.

3.22 | The Impact of p53 on Inflammation Induced by Uric Acid Crystals

1. Regulation of inflammatory factors: In gouty arthritis, inflammation triggered by urate crystals drives disease progression. p53 may influence this process by regulating inflammatory mediator expression. For instance, monosodium urate crystal stimulation of neutrophils leads to autophagy-related protein 7 production, which cooperates with p53 to enter the nucleus, activating PAD4 expression and promoting NETs release [70]. This reveals a mechanism where p53 amplifies inflammatory injury in gouty arthritis. By intervening in these inflammatory signaling

pathways, p53 helps control inflammatory activity and influences disease progression.

2. Promotion of apoptosis: Urate crystal-induced inflammation can aggravate cellular damage in gouty arthritis. As a key apoptosis regulator, p53 may trigger cell death to help clear urate crystals, affecting disease progression. A traditional Chinese medicine formula, Renal herb (RHF), developed under the "Kidney Network Regulation" theory, appears to modulate the p53-mediated apoptosis and NF-$_K$B signaling pathways, inhibiting renal cell apoptosis and inflammation [71]. These findings clarify multi-organ damage mechanisms in gout and offer therapeutic insights for secondary kidney injuries like diabetic nephropathy. Therefore, targeting critical molecules like p53 and NF-$_K$B may reduce inflammation and protect kidney function in gout patients.
3. Antioxidant effects: Oxidative stress is a major pathological feature of gouty arthritis. p53 helps counteract this by regulating antioxidant-related genes like superoxide dismutase (SOD). The recently identified p53–SLC2A9 pathway demonstrates a bidirectional regulatory role in uric acid metabolism. This pathway maintains ROS homeostasis and prevents ROS-related damage. Studies show p53 can induce SLC2A9 expression, and SLC2A9 inhibition significantly increases ROS levels, enhancing cancer cell sensitivity to chemotherapeutic drugs [72]. Conversely, SLC2A9 expression reduces ROS accumulation and protects cells from DNA damage and cell death, highlighting its antioxidant role [72, 73]. Thus, this pathway holds dual therapeutic potential in gouty arthritis—alleviating gout-associated oxidative stress and reducing the risk of other oxidative stress-related diseases.

3.23 | The Role of p53 in the Pathogenesis of Gouty Arthritis

1. Cell signaling: Beyond its traditional role in apoptosis regulation, p53 also modulates the inflammatory process via key signaling pathways like NF-$_K$B and MAPK. Abnormal NF-$_K$B activation is closely linked to inflammatory cytokine release and plays a central regulatory role in disease progression [74]. The MAPK pathway regulates inflammation-related gene expression and influences the inflammatory response in gouty arthritis [75]. Experimental research shows traditional Chinese medicine Simiao Powder can inhibit inflammatory signaling pathway overactivation by regulating TNF, IL-17, and p53, alleviating joint inflammation [76]. This finding highlights multi-target synergistic intervention and provides a pharmacodynamic foundation for treatment.
2. Cell cycle control: p53 may influence cell proliferation and apoptosis in gouty arthritis by modulating cell cycle-related protein expression. Research indicates kaempferol, a compound with therapeutic potential, may exert its effects on gouty arthritis through pathways involving IL-17, AGE-RAGE, p53, TNF, and FoxO [77], making it a promising candidate for novel therapies [78].

These findings underscore p53's critical role in gouty arthritis pathogenesis and lay the groundwork for future therapeutic strategies (Table S3).

3.24 | Role of p53 in Scoliosis

Scoliosis is a musculoskeletal disorder characterized by abnormal three-dimensional spinal curvature. Its pathogenesis involves a complex interplay of genetic susceptibility, biomechanical imbalance, and cellular metabolic abnormalities. Global epidemiological data indicate that adolescent idiopathic scoliosis (AIS) prevalence is approximately 2%–3%, with significantly higher incidence in females [79, 80]. Severe spinal deformities can result in cardiopulmonary impairment and nerve compression, posing major clinical treatment challenges [81]. Current treatment strategies focus on early orthopedic intervention and later-stage surgical correction. p53 may influence scoliosis pathological progression by regulating apoptosis and oxidative stress in paraspinal muscle cells. Therefore, p53 function dysregulation could be a key driving factor in scoliosis development and progression.

3.25 | Regulation of Paraspinal Muscle Cell Apoptosis by p53

Paraspinal muscle dysfunction is a key factor in the biomechanical imbalance associated with scoliosis. During denervation-induced muscle atrophy, Bax (pro-apoptotic protein) mRNA and protein levels significantly increase. Although Bcl-2 (anti-apoptotic protein) levels also rise, the Bax/Bcl-2 ratio markedly increases, indicating pro-apoptotic signaling predominates in muscle cells. Simultaneously, nuclear and cytoplasmic p53 protein content increases significantly, suggesting p53 may activate apoptotic signaling pathways by regulating Bax and Bcl-2 expression. This process contributes to muscle cell apoptosis and exacerbates muscle atrophy, which in turn may accelerate scoliosis progression [82].

3.26 | p53-Mediated Oxidative Stress and Intervertebral Disc Degeneration

Scoliosis is often accompanied by intervertebral disc degeneration, where oxidative stress plays a central pathological role. Oxidative stress-induced DNA damage activates p53, which in turn induces cell cycle arrest and cellular senescence through the p53-p21^{CIP1} pathway. Additionally, p53 influences cellular response to oxidative stress by regulating antioxidant enzyme expression. In intervertebral disc cells, p53 activation induced by oxidative stress leads to cellular senescence and secretion of senescence-associated secretory phenotype (SASP) factors like IL-6 and MMP-3. These pro-inflammatory mediators further exacerbate disc degeneration [83, 84]. This mechanistic insight provides a novel strategy for scoliosis prevention.

3.27 | p53 as a Potential Therapeutic Target in Musculoskeletal Diseases

3.27.1 | p53 as a Potential Therapeutic Target in Osteoporosis

Pharmacological intervention targeting p53 inhibitors or activators may offer promising approaches for regulating bone metabolism, promoting bone formation, and inhibiting bone resorption. In osteoblasts exposed to dexamethasone, senescence-associated markers p53 and p21 increase significantly. However, p53 inhibitors can reverse dexamethasone-induced osteoblast damage, while hydrogen sulfide alleviates this process by reducing osteoblast senescence [85, 86]. In gene therapy, CRISPR/Cas9 can specifically knock out or repair p53-related genes to ameliorate osteoporosis symptoms. In p53-knockout mice, bone mass remains stable regardless of beraprost treatment, suggesting p53's crucial role in beraprost-regulated bone mass modulation [87, 88]. Furthermore, collagen metabolism dysregulation and extracellular matrix–receptor interactions may contribute to impaired bone repair in osteoporotic mice. Upregulated genes like Ccnb2 and Rrm2 may participate in p53 pathway regulation, essential for bone healing [82]. These findings provide new therapeutic strategies and potential targets for osteoporosis treatment.

3.27.2 | p53 as a Potential Target for Osteoarthritis

Research suggests p53 can induce cell cycle arrest in chondrocytes and activate both extrinsic and intrinsic apoptotic pathways, promoting shear-induced chondrocyte apoptosis. Therefore, regulating chondrocyte apoptosis and extracellular matrix degradation signaling pathways could provide a new direction for intervening in osteoarthritis pathological progression, offering theoretical support for improved patient outcomes [83].

3.27.3 | p53 as a Potential Target for Rheumatoid Arthritis

In peripheral blood mononuclear cells from rheumatoid arthritis patients, several genes related to apoptosis regulation, cell survival, inflammatory mediator production, and proliferation are downregulated, and these genes are closely linked to rheumatoid arthritis pathogenesis. Among them, miR-16-5p, miR-34a-5p, and miR-335-5p are associated with TP53 and FOXO1 expression, suggesting them as potential therapeutic targets [88, 89]. Further exploration of p53's role in immune regulation and intervention strategies is warranted.

3.27.4 | p53 as a Potential Target for Low Back Pain

Studies show p53 drives apoptosis-related gene expression, accelerating degenerated intervertebral disc cell apoptosis. When intervertebral discs are subjected to abnormal mechanical stress or inflammatory stimuli, the p53 pathway is directly triggered, affecting intracellular signaling, regulating cell proliferation, differentiation, and extracellular matrix synthesis [85, 90]. Future research should delve deeper into p53 specific mechanisms in low back pain and explore its feasibility as a therapeutic target.

3.27.4.1 | p53 as a Potential Target for Gout. By regulating p53 activity and its downstream signaling pathways, inflammation and cell damage in gout can be inhibited. Further research needs to clarify p53's dynamic role in urate crystal-induced inflammatory cascades and develop precise intervention strategies.

3.27.4.2 | p53 as a Potential Target for Scoliosis. By modulating p53 activity, it may be possible to improve muscle dysfunction and alleviate oxidative stress damage, thereby delaying intervertebral disc degeneration progression. This finding not only offers potential for predicting scoliosis onset but may also provide an opportunity to halt or even reverse scoliosis progression.

Strategic Framework for p53-Targeted Therapy in Musculoskeletal Diseases (Table S4).

4 | Conclusions and Prospects

The p53 gene plays a significant regulatory role in musculoskeletal diseases, extending beyond its traditional tumor-suppressing function. However, existing studies have limitations: most focus on single diseases or isolated pathways, lacking integration. Secondly, p53 may exhibit conflicting effects (promoting apoptosis or inhibiting inflammation) at different disease stages, and its dynamic regulatory pattern is not fully understood. To reconcile these apparent contradictions, we propose a unifying 'p53 rheostat' model. The functional outcome of p53 activation is not random but is dictated by the integration of specific contextual cues:

- Signal Type and Intensity: Mild oxidative stress may bias p53 towards cell cycle arrest and antioxidant responses (in intervertebral discs), while severe DNA damage or inflammatory stress pushes it towards apoptosis (in osteoarthritic chondrocytes).
- Cellular Lineage and State: p53's effect is shaped by the cell's intrinsic programming. It inhibits osteoblast differentiation but can promote osteoclast activity, and it triggers apoptosis in chondrocytes but modulates inflammation in synovial fibroblasts.
- Interaction with Co-factors and Pathways: The final outcome is swayed by crosstalk with other key pathways, such as NF-κB, PI3K/Akt, and SIRT1. For instance, the balance between pro-arrest (p21) and pro-apoptotic (PUMA) target genes is critical.

This model positions p53 as a central processor of cellular well-being, interpreting diverse stresses to mount a context-appropriate response. The 'dual role' is therefore a reflection of its sophisticated regulatory capacity, not a biological inconsistency.

This article systematically reviews p53 multidimensional regulatory role in six major musculoskeletal diseases

(osteoporosis, osteoarthritis, rheumatoid arthritis, low back pain, gout, and scoliosis), breaking from the traditional single-disease research framework. It integrates mechanisms across multiple diseases and systematically summarizes p53 common mechanisms in various musculoskeletal diseases, revealing how p53 regulates apoptosis, oxidative stress, inflammation, and metabolism. For example, in osteoporosis, the p53-Nedd4-Runx2 axis regulates bone formation, while in osteoarthritis, the p53-miR-34a pathway mediates chondrocyte apoptosis.

Theoretically, this article identifies p53 as a "molecular hub" connecting degeneration, inflammation, and metabolic dysregulation. Practically, it provides evidence for developing p53-targeted gene therapies (CRISPR editing), small molecule drugs (p53 inhibitors), and natural products, advancing personalized medicine. Based on these findings, targeted regulation of p53 activity can effectively intervene in disease progression, achieving therapeutic purposes.

While p53 shows great potential in basic research, numerous challenges remain for clinical application. Future therapeutic strategies should move beyond broadly targeting p53 itself and instead focus on its most promising downstream effectors to achieve precision medicine. Based on the mechanisms elucidated in this review, several key molecules emerge as prime candidates:

- miR-34a: A critical mediator of the p53-induced chondrocyte apoptosis in osteoarthritis. Anti-sense oligonucleotides (ASOs) or small molecule inhibitors against miR-34a present a compelling strategy to protect cartilage.
- SIRT1: This deacetylase acts as a key negative regulator of p53 activity. SIRT1 activators (resveratrol analogs) could mitigate p53-driven cellular senescence and apoptosis in osteoarthritis and intervertebral disc degeneration.
- SLC2A9: In gout, the p53-SLC2A9 axis represents a unique bidirectional pathway that modulates antioxidant defense and uric acid transport. Enhancing this pathway could simultaneously alleviate oxidative stress and hyperuricemia.

However, translating these targets into therapies faces significant delivery challenges. The primary hurdle is achieving tissue-specific targeting to limit off-target effects and systemic toxicity. For instance, systemically inhibiting miR-34a could inadvertently promote oncogenesis, while broad SIRT1 activation might have unpredictable metabolic consequences. Promising solutions include:

1. Localized Delivery Systems: Utilizing intra-articular injections for osteoarthritis, intradiscal injections for disc degeneration, or topical applications for muscle injuries to confine the therapeutic agent.
2. Advanced Nanocarriers: Developing nanoparticles, liposomes, or exosomes functionalized with ligands that bind to receptors highly expressed on target cells (chondrocytes, osteoblasts, synovial fibroblasts).
3. Cell-Specific Promoters: For gene therapy approaches, employing promoters that are only active in specific musculoskeletal cell types could restrict the expression of therapeutic genes (CRISPR/Cas9 components or ASOs).

Given current research and development needs, future work should focus on:

1. Elucidating the tissue-specificity and context-dependence of p53 effector networks (miR-34a, SIRT1, SLC2A9) to identify the optimal therapeutic window for intervention.
2. Advancing multi-center clinical trials to validate the clinical efficacy and safety of therapies targeting these specific p53 downstream pathways.
3. Integrating targeted delivery technologies (nanocarriers, tissue-specific promoters) with bioinformatics, materials science, and clinical medicine to build a comprehensive and precise treatment system covering diagnosis, treatment, and rehabilitation.

In conclusion, p53 research in musculoskeletal diseases expands our understanding of disease pathology and provides direction for innovative therapeutic approaches. By integrating different research perspectives and findings, we can gain a more comprehensive understanding of p53's function and promote its clinical application. The current focus should be on breakthroughs in mechanism analysis, technological innovation, and clinical validation, ultimately transitioning from "molecular insights" to "clinical benefits".

Abbreviations used in this review are provided in (Table S5).

Author Contributions

M.H.: conception, design, and literature analysis of the review. M.H., S.H., and A.Y.: handled data compilation and figure/chart preparation. M.H., S.H.: methodological validation and statistical analysis. Y.W.: supervision and final manuscript review.

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Ethics Statement

This study is a systematic review. The data used were derived from previously published studies. Ethical approval for each individual study was obtained by the original authors. No new human or animal participants were involved in this research.

Consent

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 on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. S. K. Nayak, P. S. Panesar, and H. Kumar, "p53-Induced Apoptosis and Inhibitors of p53," *Current Medicinal Chemistry* 16, no. 21 (2009): 2627–2640.

2. A. V. Gudkov and E. A. Komarova, "Pathologies Associated With the p53 Response," *Cold Spring Harbor Perspectives in Biology* 2, no. 7 (2010): a001180.

3. J. G. Filep and D. El Kebir, "Neutrophil Apoptosis: A Target for Enhancing the Resolution of Inflammation," *Journal of Cellular Biochemistry* 108, no. 5 (2009): 1039–1046.

4. J. M. Hallett, A. E. Leitch, N. A. Riley, R. Duffin, C. Haslett, and A. G. Rossi, "Novel Pharmacological Strategies for Driving Inflammatory Cell Apoptosis and Enhancing the Resolution of Inflammation," *Trends in Pharmacological Sciences* 29, no. 5 (2008): 250–257.

5. V. Alt and P. V. Giannoudis, "Musculoskeletal Infections - A Global Burden and a New Subsection in Injury," *Injury* 50, no. 12 (2019): 2152–2153.

6. Z. S. Ma, H. J. Zhang, W. Lei, and L. Z. Xiong, "Musculoskeletal Trauma Services in China," *Clinical Orthopaedics and Related Research* 466, no. 10 (2008): 2329–2336.

7. L. J. Hernández Borrero and W. S. El-Deiry, "Tumor Suppressor p53: Biology, Signaling Pathways, and Therapeutic Targeting," *Biochimica et Biophysica Acta* 1876, no. 1 (2021): 188556.

8. A. B. Williams and B. Schumacher, "p53 in the DNA-Damage-Repair Process," *Cold Spring Harbor Perspectives in Medicine* 6, no. 5 (2016): a026070, https://doi.org/10.1101/cshperspect.a026070.

9. A. Hafner, M. L. Bulyk, A. Jambhekar, and G. Lahav, "The Multiple Mechanisms That Regulate p53 Activity and Cell Fate," *Nature Reviews. Molecular Cell Biology* 20, no. 4 (2019): 199–210.

10. D. W. Meek and C. W. Anderson, "Posttranslational Modification of p53: Cooperative Integrators of Function," *Cold Spring Harbor Perspectives in Biology* 1, no. 6 (2009): a000950.

11. H. Wei, L. Qu, S. Dai, et al., "Structural Insight Into the Molecular Mechanism of p53-Mediated Mitochondrial Apoptosis," *Nature Communications* 12, no. 1 (2021): 2280.

12. N. S. Mohamad Kamal, S. Safuan, S. Shamsuddin, and P. Foroozandeh, "Aging of the Cells: Insight Into Cellular Senescence and Detection Methods," *European Journal of Cell Biology* 99, no. 6 (2020): 151108.

13. S. Vadivel Gnanasundram, O. Bonczek, L. Wang, S. Chen, and R. Fahraeus, "p53 mRNA Metabolism Links With the DNA Damage Response," *Genes (Basel)* 12, no. 9 (2021): 1446.

14. V. Gorgoulis, P. D. Adams, A. Alimonti, et al., "Cellular Senescence: Defining a Path Forward," *Cell* 179, no. 4 (2019): 813–827.

15. J. E. Compston, M. R. McClung, and W. D. Leslie, "Osteoporosis," *Lancet* 393, no. 10169 (2019): 364–376.

16. T. Yu, Z. Wang, X. You, et al., "Resveratrol Promotes Osteogenesis and Alleviates Osteoporosis by Inhibiting p53," *Aging (Albany NY)* 12, no. 11 (2020): 10359–10369.

17. Y. Fang, Z. Xue, L. Zhao, et al., "Calycosin Stimulates the Osteogenic Differentiation of Rat Calvarial Osteoblasts by Activating the IGF1R/PI3K/Akt Signaling Pathway," *Cell Biology International* 43, no. 3 (2019): 323–332.

18. T. Komori, "Cell Death in Chondrocytes, Osteoblasts, and Osteocytes," *International Journal of Molecular Sciences* 17, no. 12 (2016): 2045.

19. C. Xia, T. Jiang, Y. Wang, X. Chen, Y. Hu, and Y. Gao, "The p53/miR-145a Axis Promotes Cellular Senescence and Inhibits Osteogenic Differentiation by Targeting Cbfb in Mesenchymal Stem Cells," *Frontiers in Endocrinology* 11 (2020): 609186.

20. M. Wu, Y. Wang, J. Z. Shao, J. Wang, W. Chen, and Y. P. Li, "Cbfβ Governs Osteoblast-Adipocyte Lineage Commitment Through Enhancing β-Catenin Signaling and Suppressing Adipogenesis Gene Expression," *Proceedings of the National Academy of Sciences of the United States of America* 114, no. 38 (2017): 10119–10124.

21. H. L. Zheng, W. N. Xu, W. S. Zhou, et al., "Beraprost Ameliorates Postmenopausal Osteoporosis by Regulating Nedd4-Induced Runx2 Ubiquitination," *Cell Death & Disease* 12, no. 5 (2021): 497.

22. Y. Xiao, J. Cui, Y. X. Li, Y. H. Shi, and G. W. le, "Expression of Genes Associated With Bone Resorption Is Increased and Bone Formation Is Decreased in Mice Fed a High-Fat Diet," *Lipids* 45, no. 4 (2010): 345–355.

23. J. Lange, T. Barz, A. Ekkernkamp, I. Klöting, and N. Follak, "Gene Expression Profile in Bone of Diabetes-Prone BB/OK Rats Fed a High-Fat Diet," *Genes & Nutrition* 8, no. 1 (2013): 99–104.

24. W. Qiao, S. Yu, H. Sun, et al., "1,25-Dihydroxyvitamin D Insufficiency Accelerates Age-Related Bone Loss by Increasing Oxidative Stress and Cell Senescence," *American Journal of Translational Research* 12, no. 2 (2020): 507–518.

25. Y. H. Kim, M. Park, K. A. Cho, et al., "Tonsil-Derived Mesenchymal Stem Cells Promote Bone Mineralization and Reduce Marrow and Visceral Adiposity in a Mouse Model of Senile Osteoporosis," *Stem Cells and Development* 25, no. 15 (2016): 1161–1171.

26. F. Gao, F. Xu, D. Wu, J. Cheng, and P. Xia, "Identification of Novel Genes Associated With Fracture Healing in Osteoporosis Induced by Krm2 Overexpression or Lrp5 Deficiency," *Molecular Medicine Reports* 15, no. 6 (2017): 3969–3976.

27. K. D. Allen, L. M. Thoma, and Y. M. Golightly, "Epidemiology of Osteoarthritis," *Osteoarthritis and Cartilage* 30, no. 2 (2022): 184–195.

28. B. R. Deshpande, J. N. Katz, D. H. Solomon, et al., "Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity," *Arthritis Care & Research (Hoboken)* 68, no. 12 (2016): 1743–1750.

29. J. Lo, L. Chan, and S. Flynn, "A Systematic Review of the Incidence, Prevalence, Costs, and Activity and Work Limitations of Amputation, Osteoarthritis, Rheumatoid Arthritis, Back Pain, Multiple Sclerosis, Spinal Cord Injury, Stroke, and Traumatic Brain Injury in the United States: A 2019 Update," *Archives of Physical Medicine and Rehabilitation* 102, no. 1 (2021): 115–131.

30. S. Yan, M. Wang, J. Zhao, et al., "MicroRNA-34a Affects Chondrocyte Apoptosis and Proliferation by Targeting the SIRT1/p53 Signaling Pathway During the Pathogenesis of Osteoarthritis," *International Journal of Molecular Medicine* 38, no. 1 (2016): 201–209.

31. H. Qi, Z. Zhao, L. Xu, et al., "Antisense Oligonucleotide-Based Therapy on miR-181a-5p Alleviates Cartilage Degradation of Temporomandibular Joint Osteoarthritis via Promoting SIRT1," *Frontiers in Pharmacology* 13 (2022): 898334.

32. C. C. Wang, C. T. Wang, W. C. Chou, C. L. Kao, and K. L. Tsai, "Hyaluronic Acid Injection Reduces Inflammatory and Apoptotic Markers Through Modulation of AKT by Repressing the Oxidative Status of Neutrophils From Osteoarthritic Synovial Fluid," *International Journal of Biological Macromolecules* 165, no. Pt B (2020): 2765–2772.

33. J. Jacob, A. Aggarwal, S. Bhattacharyya, D. Sahni, V. Sharma, and A. Aggarwal, "Fisetin and Resveratrol Exhibit Senotherapeutic Effects and Suppress Cellular Senescence in Osteoarthritic Cartilage-Derived Chondrogenic Progenitor Cells," *European Journal of Pharmacology* 997 (2025): 177573.

34. Y. Zhou, J. Li, F. Xu, E. Ji, C. Wang, and Z. Pan, "Long Noncoding RNA H19 Alleviates Inflammation in Osteoarthritis Through Interactions Between TP53, IL-38, and IL-36 Receptor," *Bone & Joint Research* 11, no. 8 (2022): 594–607.

35. K. Kawakita, T. Nishiyama, T. Fujishiro, et al., "Akt Phosphorylation in Human Chondrocytes Is Regulated by p53R2 in Response to Mechanical Stress," *Osteoarthritis and Cartilage* 20, no. 12 (2012): 1603–1609.

36. L. W. Huang, T.-C. Huang, Y.-C. Hu, et al., "S-Equol Protects Chondrocytes Against Sodium Nitroprusside-Caused Matrix Loss and Apoptosis Through Activating PI(3)K/Akt Pathway," *International Journal of Molecular Sciences* 22, no. 13 (2021): 7054, https://doi.org/10.3390/ijms22137054.

37. W. Li, Y. Xiong, W. Chen, and L. Wu, "Wnt/β-Catenin Signaling May Induce Senescence of Chondrocytes in Osteoarthritis," *Experimental and Therapeutic Medicine* 20, no. 3 (2020): 2631–2638.

38. S. Hashimoto, T. Nishiyama, S. Hayashi, et al., "Role of p53 in Human Chondrocyte Apoptosis in Response to Shear Strain," *Arthritis and Rheumatism* 60, no. 8 (2009): 2340–2349.

39. B. W. Wang, Y. Jiang, Z. L. Yao, P. S. Chen, B. Yu, and S. N. Wang, "Aucubin Protects Chondrocytes Against IL-1β-Induced Apoptosis In Vitro and Inhibits Osteoarthritis in Mice Model," *Drug Design, Development and Therapy* 13 (2019): 3529–3538.

40. S. Sakata, S. Hayashi, T. Fujishiro, et al., "Oxidative Stress-Induced Apoptosis and Matrix Loss of Chondrocytes Is Inhibited by Eicosapentaenoic Acid," *Journal of Orthopaedic Research* 33, no. 3 (2015): 359–365.

41. F. Coutant and P. Miossec, "Evolving Concepts of the Pathogenesis of Rheumatoid Arthritis With Focus on the Early and Late Stages," *Current Opinion in Rheumatology* 32, no. 1 (2020): 57–63.

42. N. Yagishita, S. Yamasaki, K. Nishioka, and T. Nakajima, "Synoviolin, Protein Folding and the Maintenance of Joint Homeostasis," *Nature Clinical Practice. Rheumatology* 4, no. 2 (2008): 91–97.

43. T. Zhang, H. Li, J. Shi, et al., "p53 Predominantly Regulates IL-6 Production and Suppresses Synovial Inflammation in Fibroblast-Like Synoviocytes and Adjuvant-Induced Arthritis," *Arthritis Research & Therapy* 18, no. 1 (2016): 271.

44. Y. Y. Jung, D. J. Son, H. L. Lee, et al., "Loss of Parkin Reduces Inflammatory Arthritis by Inhibiting p53 Degradation," *Redox Biology* 12 (2017): 666–673.

45. A. I. Dubikov and S. G. Kalinichenko, "Small Molecules Regulating Apoptosis in the Synovium in Rheumatoid Arthritis," *Scandinavian Journal of Rheumatology* 39, no. 5 (2010): 368–372.

46. V. V. Michael and K. E. Alisa, "Cell Cycle Implications in the Pathogenesis of Rheumatoid Arthritis," *Frontiers in Bioscience* 5 (2000): D594–D601.

47. L. Oslejsková, M. Grigorian, S. Gay, M. Neidhart, and L. Šenolt, "The Metastasis Associated Protein S100A4: A Potential Novel Link to Inflammation and Consequent Aggressive Behaviour of Rheumatoid Arthritis Synovial Fibroblasts," *Annals of the Rheumatic Diseases* 67, no. 11 (2008): 1499–1504.

48. W. Que, H. Liu, Q. Yang, and S. Xu, "NK4 Inhibits the Proliferation and Induces Apoptosis of Human Rheumatoid Arthritis Synovial Cells," *Cell Biochemistry and Function* 36, no. 5 (2018): 273–279.

49. G. S. Firestein, K. Nguyen, K. R. Aupperle, M. Yeo, D. L. Boyle, and N. J. Zvaifler, "Apoptosis in Rheumatoid Arthritis: p53 Overexpression in Rheumatoid Arthritis Synovium," *American Journal of Pathology* 149, no. 6 (1996): 2143–2151.

50. S. R. Kim, J. H. Park, M. E. Lee, J. S. Park, S. C. Park, and J. A. Han, "Selective COX-2 Inhibitors Modulate Cellular Senescence in Human Dermal Fibroblasts in a Catalytic Activity-Independent Manner," *Mechanisms of Ageing and Development* 129, no. 12 (2008): 706–713.

51. R. Chou, "Low Back Pain," *Annals of Internal Medicine* 174, no. 8 (2021): Itc113–itc128.

52. J. L. Dieleman, J. Cao, A. Chapin, et al., "US Health Care Spending by Payer and Health Condition, 1996-2016," *JAMA* 323, no. 9 (2020): 863–884.

53. J. Dowdell, M. Erwin, T. Choma, A. Vaccaro, J. Iatridis, and S. K. Cho, "Intervertebral Disk Degeneration and Repair," *Neurosurgery* 80, no. 3s (2017): S46–s54.

54. G. Carvajal Alegria, M. Voirin-Hertz, F. Garrigues, et al., "Association of Lumbosacral Transitional Vertebra and Sacroiliitis in Patients With Inflammatory Back Pain Suggesting Axial Spondyloarthritis," *Rheumatology (Oxford)* 59, no. 7 (2020): 1679–1683.

55. S. A. O'Leary, N. K. Paschos, J. M. Link, E. O. Klineberg, J. C. Hu, and K. A. Athanasiou, "Facet Joints of the Spine: Structure-Function Relationships, Problems and Treatments, and the Potential for Regeneration," *Annual Review of Biomedical Engineering* 20 (2018): 145–170.

56. K. R. Cohen, "Management of Chronic Low Back Pain," *JAMA Internal Medicine* 182, no. 2 (2022): 222–223.

57. H. W. Chen, M. Q. Liu, G. Z. Zhang, et al., "Proanthocyanidins Inhibit the Apoptosis and Aging of Nucleus Pulposus Cells Through the PI3K/Akt Pathway Delaying Intervertebral Disc Degeneration," *Connective Tissue Research* 63, no. 6 (2022): 650–662.

58. Z. Zhang, J. Lin, M. Nisar, et al., "The Sirt1/P53 Axis in Diabetic Intervertebral Disc Degeneration Pathogenesis and Therapeutics," *Oxidative Medicine and Cellular Longevity* 2019 (2019): 7959573.

59. C. Feng, M. Yang, Y. Zhang, et al., "Cyclic Mechanical Tension Reinforces DNA Damage and Activates the p53-p21-Rb Pathway to Induce Premature Senescence of Nucleus Pulposus Cells," *International Journal of Molecular Medicine* 41, no. 6 (2018): 3316–3326.

60. J. Zhao, C. Li, T. Qin, et al., "Mechanical Overloading-Induced miR-325-3p Reduction Promoted Chondrocyte Senescence and Exacerbated Facet Joint Degeneration," *Arthritis Research & Therapy* 25, no. 1 (2023): 54.

61. H. Yang, X. Yang, K. Rong, et al., "Eupatilin Attenuates the Senescence of Nucleus Pulposus Cells and Mitigates Intervertebral Disc Degeneration via Inhibition of the MAPK/NF-κB Signaling Pathway," *Frontiers in Pharmacology* 13 (2022): 940475.

62. J. M. Memme, A. N. Oliveira, and D. A. Hood, "p53 Regulates Skeletal Muscle Mitophagy and Mitochondrial Quality Control Following Denervation-Induced Muscle Disuse," *Journal of Biological Chemistry* 298, no. 2 (2022): 101540.

63. H. T. Langer, A. A. Mossakowski, R. Sule, A. Gomes, and K. Baar, "Dominant-Negative p53-Overexpression in Skeletal Muscle Induces Cell Death and Fiber Atrophy in Rats," *Cell Death & Disease* 13, no. 8 (2022): 716.

64. Y. Y. Cheng, C. L. Kao, H. I. Ma, et al., "SIRT1-Related Inhibition of Pro-Inflammatory Responses and Oxidative Stress Are Involved in the Mechanism of Nonspecific Low Back Pain Relief After Exercise Through Modulation of Toll-Like Receptor 4," *Journal of Biochemistry* 158, no. 4 (2015): 299–308.

65. N. Li, C. Whitaker, Z. Xu, M. Heggeness, and S. Y. Yang, "Therapeutic Effects of Naringin on Degenerative Human Nucleus Pulposus Cells for Discogenic Low Back Pain," *Spine Journal* 16, no. 10 (2016): 1231–1237.

66. N. Dalbeth, A. L. Gosling, A. Gaffo, and A. Abhishek, "Gout," *Lancet* 397, no. 10287 (2021): 1843–1855.

67. G. Cabău, T. O. Crișan, V. Klück, R. A. Popp, and L. A. B. Joosten, "Urate-Induced Immune Programming: Consequences for Gouty Arthritis and Hyperuricemia," *Immunological Reviews* 294, no. 1 (2020): 92–105.

68. M. Dehlin, L. Jacobsson, and E. Roddy, "Global Epidemiology of Gout: Prevalence, Incidence, Treatment Patterns and Risk Factors," *Nature Reviews Rheumatology* 16, no. 7 (2020): 380–390.

69. R. Liu, C. Han, D. Wu, et al., "Prevalence of Hyperuricemia and Gout in Mainland China From 2000 to 2014: A Systematic Review and Meta-Analysis," *BioMed Research International* 2015 (2015): 762820.

70. S. Huang, Y. Wang, S. Lin, W. Guan, H. Liang, and J. Shen, "Neutrophil Autophagy Induced by Monosodium Urate Crystals Facilitates Neutrophil Extracellular Traps Formation and Inflammation Remission in Gouty Arthritis," *Frontiers in Endocrinology (Lausanne)* 14 (2023): 1071630.

71. G. Y. Tang, S. Li, Y. Xu, et al., "Renal Herb Formula Protects Against Hyperuricemic Nephropathy by Inhibiting Apoptosis and Inflammation," *Phytomedicine* 116 (2023): 154812.

72. Y. Itahana, R. Han, S. Barbier, Z. Lei, S. Rozen, and K. Itahana, "The Uric Acid Transporter SLC2A9 Is a Direct Target Gene of the Tumor Suppressor p53 Contributing to Antioxidant Defense," *Oncogene* 34, no. 14 (2015): 1799–1810.

73. T. R. Merriman, "An Update on the Genetic Architecture of Hyperuricemia and Gout," *Arthritis Research & Therapy* 17, no. 1 (2015): 98.

74. T. Liu, L. Zhang, D. Joo, and S.-C. Sun, "NF-κB Signaling in Inflammation," *Signal Transduction and Targeted Therapy* 2 (2017): 17023.

75. Y. Jiang and X. W. Gong, "Regulation of Inflammatory Responses by MAPK Signal Transduction Pathways," *Sheng Li Xue Bao* 52, no. 4 (2000): 267–271.

76. Y. Fan, W. Liu, Y. Jin, et al., "Integrated Molecular Docking With Network Pharmacology to Reveal the Molecular Mechanism of Simiao Powder in the Treatment of Acute Gouty Arthritis," *Evidence-Based Complementary and Alternative Medicine* 2021 (2021): 5570968.

77. N. Li, S. Chen, W. Deng, et al., "Kaempferol Attenuates Gouty Arthritis by Regulating the Balance of Th17/Treg Cells and Secretion of IL-17," *Inflammation* 46, no. 5 (2023): 1901–1916.

78. C. Li, C. Wang, Y. J. Guo, et al., "Research on the Effect and Underlying Molecular Mechanism of Cangzhu in the Treatment of Gouty Arthritis," *European Journal of Pharmacology* 927 (2022): 175044.

79. O. H. Almahmoud, B. Baniodeh, R. Musleh, S. Asmar, M. Zyada, and H. Qattousah, "Overview of Adolescent Idiopathic Scoliosis and Associated Factors: A Scoping Review," *International Journal of Adolescent Medicine and Health* 35, no. 6 (2023): 437–441.

80. T. A. Hoelen, S. M. Evers, J. J. Arts, P. C. Willems, and G. A. van Mastrigt, "The Societal Burden Associated With Adolescent Idiopathic Scoliosis: A Cross-Sectional Burden-Of-Disease Study," *BMC Public Health* 24, no. 1 (2024): 3065.

81. J. Théroux, N. Stomski, C. J. Hodgetts, et al., "Prevalence of Low Back Pain in Adolescents With Idiopathic Scoliosis: A Systematic Review," *Chiropractic Manual Therapy* 25 (2017): 10.

82. P. M. Siu and S. E. Alway, "Mitochondria-Associated Apoptotic Signalling in Denervated Rat Skeletal Muscle," *Journal of Physiology* 565, no. Pt 1 (2005): 309–323.

83. P. Silwal, A. M. Nguyen-Thai, H. A. Mohammad, et al., "Cellular Senescence in Intervertebral Disc Aging and Degeneration: Molecular Mechanisms and Potential Therapeutic Opportunities," *Biomolecules* 13, no. 4 (2023): 686.

84. C. Feng, H. Liu, M. Yang, Y. Zhang, B. Huang, and Y. Zhou, "Disc Cell Senescence in Intervertebral Disc Degeneration: Causes and Molecular Pathways," *Cell Cycle* 15, no. 13 (2016): 1674–1684.

85. P. Li, W. W. Mao, S. Zhang, L. Zhang, Z. R. Chen, and Z. D. Lu, "Sodium Hydrosulfide Alleviates Dexamethasone-Induced Cell Senescence and Dysfunction Through Targeting the miR-22/sirt1 Pathway in Osteoblastic MC3T3-E1 Cells," *Experimental and Therapeutic Medicine* 21, no. 3 (2021): 238.

86. J. G. Quicke, P. G. Conaghan, N. Corp, and G. Peat, "Osteoarthritis Year in Review 2021: Epidemiology & Therapy," *Osteoarthritis and Cartilage* 30, no. 2 (2022): 196–206.

87. F. Zhu, P. Wang, A. Kontrogianni-Konstantopoulos, et al., "Prostaglandin (PG)D(2) and 15-Deoxy-Delta(12,14)-PGJ(2), but Not PGE(2), Mediate Shear-Induced Chondrocyte Apoptosis via Protein Kinase A-Dependent Regulation of Polo-Like Kinases," *Cell Death and Differentiation* 17, no. 8 (2010): 1325–1334.

88. H. Ebrahimian, M. Akhtari, M. Akhlaghi, et al., "Altered Expression of Apoptosis-Related Genes in Rheumatoid Arthritis Peripheral Blood Mononuclear Cell and Related miRNA Regulation," *Immunity, Inflammation and Disease* 11, no. 7 (2023): e914.

89. H. Ebrahimiyan, N. Rezaei, M. Vojdanian, S. Aslani, A. Jamshidi, and M. Mahmoudi, "microRNA Involvement in the Regulation of Survivin in Peripheral Blood Mononuclear Cells From Rheumatoid Arthritis Patients," *International Journal of Rheumatic Diseases* 22, no. 6 (2019): 1107–1114.

90. M. Yang, Y. Huang, J. Chen, Y. L. Chen, J. J. Ma, and P. H. Shi, "Activation of AMPK Participates Hydrogen Sulfide-Induced Cyto-Protective Effect Against Dexamethasone in Osteoblastic MC3T3-E1 Cells," *Biochemical and Biophysical Research Communications* 454, no. 1 (2014): 42–47.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Role of p53 in rheumatoid arthritis. **Table S2:** Role of p53 in lower back pain. **Table S3:** Role of p53 in gout. **Table S4:** Strategic framework for p53-targeted therapy in musculoskeletal diseases. **Table S5:** Abbreviations.

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LETTER TO THE EDITOR

Case Report: Fulminant Lupus Myocarditis With Concomitant Pulmonary Infarction

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Dear Editor,

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with multi-organ involvement. Cardiac manifestations are common and contribute significantly to SLE-related morbidity and mortality. Pericarditis is the most frequent cardiac involvement, while myocarditis is rare but potentially life-threatening, often presenting as fulminant heart failure [1]. While pericarditis represents the most common cardiac manifestation of SLE, myocarditis—though rarer—poses a significant risk of life-threatening complications, including fulminant heart failure. The incidence of lupus myocarditis ranges between 5% and 10% [2]. Diagnosis relies on clinical features, cardiac biomarkers, echocardiography, and cardiac magnetic resonance imaging (CMR) [3].

Pulmonary complications, such as pneumonitis and diffuse alveolar hemorrhage, are also recognized in SLE. However, the concomitant occurrence of lupus myocarditis and pulmonary infarction is extremely rare. Here, we report such a case and describe the diagnostic approach, treatment strategy, and outcome.

Case Report: A 47-year-old woman presented to our Rheumatology Department with a one-month history of progressively worsening dyspnea, now occurring even at rest. She reported orthopnea relieved by sitting forward. She also experienced increasing joint pain and facial skin lesions over the past 2 months. Skin biopsy performed at another hospital revealed features consistent with discoid lupus erythematosus (DLE). Although the patient had previously undergone a skin biopsy at an external center consistent with lupus, she had not received adequate disease-specific treatment; at presentation, she was only taking hydroxychloroquine 200 mg/day and prednisolone 7.5 mg/day.

Autoantibody testing showed positive ANA (1:3200, homogeneous), anti-centromere, and anti-Sm-RNP antibodies, confirming a diagnosis of SLE. On admission, inflammatory markers were elevated, with a CRP level of 54 mg/L (0–5 mg/L) and an ESR of 62 mm/h (< 20 mm/h); the BNP level was 423 pg/mL (< 100 pg/mL). Complement levels were reduced, with C3 at 35 mg/dL (90–180 mg/dL) and C4 at 3.6 mg/dL (10–40 mg/dL). Urinalysis revealed no evidence of proteinuria or active urinary sediment, and there were no findings suggestive of renal involvement.

Initial chest computed tomography (CT) demonstrated bilateral patchy ground-glass opacities, suggestive of lupus pneumonitis. A CT pulmonary angiogram showed bilateral pleural-based pulmonary infarctions. As the patient remained hemodynamically stable, subcutaneous enoxaparin was initiated.

During hospitalization, she developed sinus tachycardia, hypotension, and low-voltage QRS complexes on ECG. CT imaging revealed pericardial effusion. Bedside echocardiography revealed a globally dilated left ventricle with a reduced ejection fraction of 35%, along with a moderate-sized (1.5 cm) pericardial effusion located posterior to the lateral wall without echocardiographic signs of tamponade. High-sensitivity troponin I was elevated at 97.7 ng/L. Coronary angiography was proposed to exclude ischemic heart disease, but the patient declined the procedure.

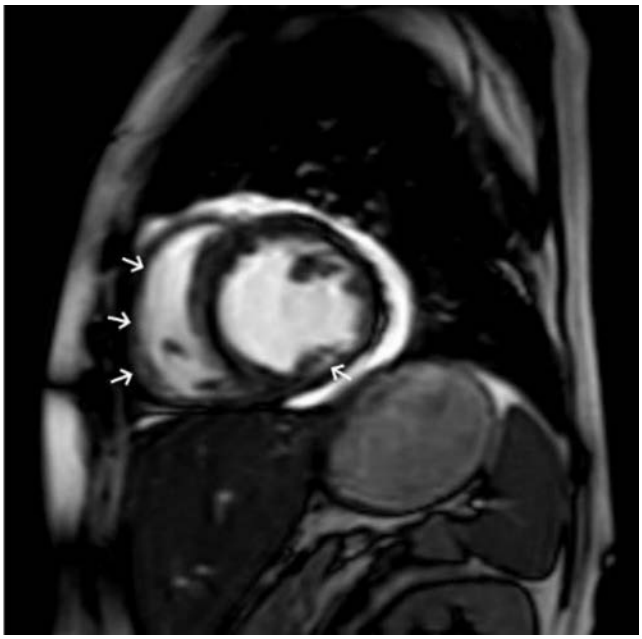

FIGURE 1 | CMRI showing late gadolinium enhancement (LGE) in a short-axis view. White arrows indicate patchy and predominantly transmural enhancement of the mid-to-basal inferolateral wall, consistent with myocardial injury.

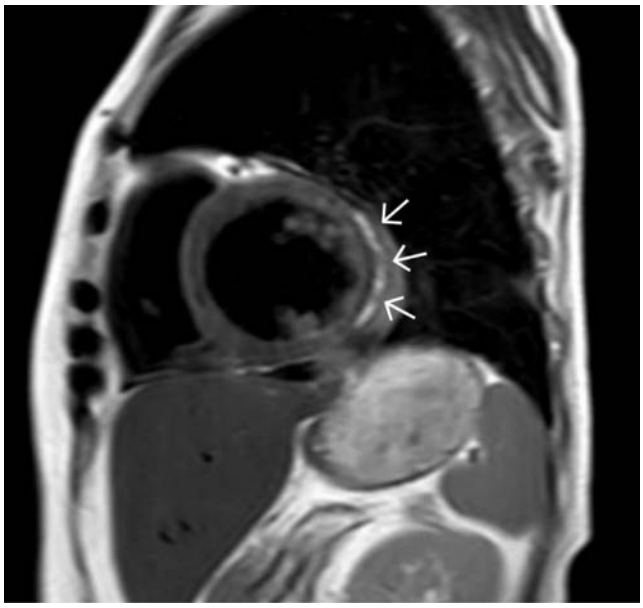

FIGURE 2 | CMRI short-axis view showing late gadolinium enhancement (LGE). White arrows indicate patchy, transmural, and heterogeneous enhancement involving the mid-to-basal inferoseptal and inferolateral walls. This appearance, described as a "tigroid enhancement pattern," supports the diagnosis of lupus myocarditis.

In the following days, she developed hemodynamic deterioration characterized by severe hypotension, oliguria, elevated creatinine, lactate, and liver enzymes. Repeat echocardiography excluded right ventricular dysfunction and pulmonary embolism. Left ventricular EF had decreased to 30%, and the clinical picture was attributed to low cardiac output.

Dobutamine and norepinephrine were initiated, resulting in gradual clinical and laboratory improvement. Suspecting fulminant lupus myocarditis, a cardiac MRI was performed. Cardiac Magnetic Resonance Imaging (CMRI) showed patchy late gadolinium enhancement in the mid and basal segments of the left ventricle with a tigroid pattern, predominantly transmural (Figure 1). T2 mapping met the criteria for myocarditis, though the enhancement pattern was considered atypical and suggestive of lupus-related cardiomyopathy (Figure 2).

Treatment included pulse methylprednisolone (1 g daily for 3 days), followed by intravenous cyclophosphamide 500 mg administered biweekly according to the Euro-Lupus protocol, colchicine, and ibuprofen 600 mg three times daily. Colchicine was initiated for the management of pericarditis, and the dose was reduced to 0.5 mg/day in consideration of renal function. Standard heart failure therapy (beta-blocker, spironolactone, furosemide, and SGLT-2 inhibitor) was also initiated.

The patient's clinical condition markedly improved. Ground-glass opacities and consolidation areas regressed on follow-up chest imaging, and pleural effusion resolved. She was discharged in stable condition.

Although rare, lupus myocarditis represents a potentially fatal SLE complication. Diagnosis can be challenging and typically requires a combination of clinical, biochemical, and imaging findings. Cardiac MRI provides valuable insights and may detect subclinical or atypical patterns of myocardial inflammation, as in our case [4]. The concomitant presence of myocarditis and pulmonary infarction suggests a shared inflammatory or thrombotic mechanism. Evaluation for antiphospholipid syndrome was negative, including lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I antibodies, indicating that the pulmonary infarction was more likely related to severe inflammation rather than secondary APS.

The simultaneous presentation of myocarditis and pulmonary infarction is exceptionally uncommon. Aggressive immunosuppressive therapy and supportive care, including inotropes and optimal heart failure treatment, were critical in achieving full recovery [5, 6]. Although hemodynamic support with vasoactive agents was necessitated by the patient's profound hypotension and unstable clinical status, we acknowledge that some recent guidelines, such as the Chinese Society of Cardiology guidelines on adult fulminant myocarditis (2024), advise caution regarding their use in fulminant heart failure. In this case, vasoactive support was carefully titrated and tapered as cardiac function recovered.

In conclusion, this case underlines the importance of early recognition and a multidisciplinary approach to fulminant lupus myocarditis, especially when accompanied by pulmonary complications. Prompt, aggressive treatment may lead to favorable outcomes even in critically ill patients.

Author Contributions

Beyza Parlatır: conceptualization, data collection, analysis, manuscript drafting, and literature review; contributed to the design and interpretation of the case report. **Adam Türk:** data collection, methodology, and analysis; provided clinical insights, edited the manuscript, and validated the data. **Safiye Bakkal:** conceptualization, data

collection, analysis, manuscript drafting, and literature review; contributed to the design and interpretation of the case report. **Semih Gülle:** supervision, project administration, and manuscript review; oversaw case study interpretation and validation; approved the final manuscript submission.

Consent

The participant provided written informed consent for the use of their medical records for the purpose of research.

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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Semih Gülle

References

1. T. Burkard, M. Trendelenburg, T. Daikeler, et al., "The Heart in Systemic Lupus Erythematosus – A Comprehensive Approach by Cardiovascular Magnetic Resonance Tomography," *PLoS One* 13 (2018): e0202105.

2. G. A. Ramirez, N. E. A. Holopainen, M. Gerosa, et al., "Distinctive Clinical Traits of Lupus-Related Myocarditis: A Multicentre Retrospective Study," *Rheumatology* 64 (2025): 1904–1911.

3. C.-L. H. Wei, S.-Y. Lyu, and C.-C. Lu, "Cardiac Magnetic Resonance Imaging Contributes to the Accurate Diagnosis of Lupus Myocarditis," *Journal of Rheumatology* 50 (2023): jrheum.210647.

4. R. du Toit, S. Karamchand, A. F. Doubell, H. Reuter, and P. G. Herbst, "Lupus Myocarditis: Review of Current Diagnostic Modalities and Their Application in Clinical Practice," *Rheumatology* 62 (2023): 523–534.

5. K. Meridor, Y. Shoenfeld, O. Tayer-Shifman, and Y. Levy, "Lupus Acute Cardiomyopathy Is Highly Responsive to Intravenous Immunoglobulin Treatment," *Medicine (Baltimore)* 100 (2021): e25591.

6. A. Fanouriakis, N. Tziolos, G. Bertsias, and D. T. Boumpas, "Update on the Diagnosis and Management of Systemic Lupus Erythematosus," *Annals of the Rheumatic Diseases* 80 (2021): 14–25.

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CLINICAL IMAGE

Paraneoplastic Amyopathic Dermatomyositis Suspect by Nailfold Capillaroscopy in a Patient With Breast Carcinoma

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A 42-year-old woman with newly diagnosed breast carcinoma was referred for evaluation of skin rash and angioedema. Examination revealed a heliotrope rash, a shawl sign, and nailfold telangiectasia without proximal muscle weakness or Raynaud's phenomenon. Laboratory findings included a positive ANA test, while ENA profiles were negative (including antibodies to Ro/SSA, La/SSB, Sm, RNP, Scl-70, and Jo-1). Anti-TIF1γ and anti-NXP2 were not assessed. Creatinine phosphokinase was normal, and MRI of proximal muscle was also normal. Drug-induced dermatoses, lupus-spectrum disease, and other paraneoplastic dermatoses were clinically excluded based on history, examination, and laboratory evaluation.

The nailfold capillaroscopy (NFC) findings are shown in Figure 1. NFC demonstrated hemorrhages, frequent dilated capillaries, avascular areas, and disorganized capillary architecture. These findings, consistent with active microangiopathy, supported a diagnosis of paraneoplastic amyopathic

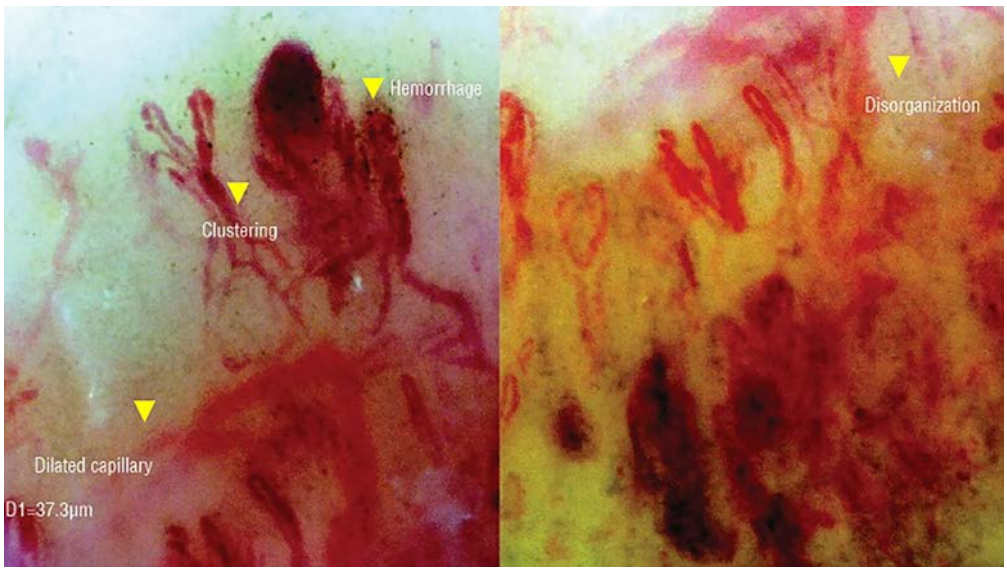

FIGURE 1 | Nailfold capillaroscopy findings in the patient showing hemorrhages (arrows), frequent dilated capillaries, clustering, avascular areas, and disorganized capillary architecture, consistent with dermatomyositis-related microangiopathy.

dermatomyositis. Oral prednisolone 40 mg daily, tapered gradually, resulted in complete resolution of the rash.

NFC is a non-invasive method for assessing microvascular abnormalities in connective tissue diseases [1]. In dermatomyositis, perivascular inflammation reduces capillary density and alters morphology [2, 3]. Although scleroderma-pattern capillaroscopic changes can be seen in dermatomyositis, systemic sclerosis typically shows more severe capillary loss and frequent giant capillaries, whereas dermatomyositis more often demonstrates ramified or giant-ramified capillaries [4].

In this case, NFC revealed hemorrhages, dilated capillaries, avascular area, which are features compatible with dermatomyositis-related microangiopathy. Furthermore, fast vascular remodeling has been described in cancer-associated dermatomyositis, with sequential changes such as loop shape modification, widening, disappearance, neoformation of new ramified capillaries, elongation and rearrangement observed within short-interval follow-up of the same nailfold areas [1]. This case highlights the pivotal role of NFC in clinical evaluation. NFC is a rapid and practical method and may serve as a useful bedside tool to differentiate amyopathic dermatomyositis from mimickers and could be considered as a non-invasive alternative when skin biopsy result is delayed.

Author Contributions

F.S. designed and wrote the manuscript, and collected the data. K.M. designed, wrote, and revised the manuscript. M.R.C. and Z.A. revised the manuscript. All authors approved the final version of the manuscript.

Funding

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient for publication of this image and clinical information.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

References

1. R. De Angelis, C. Bertolazzi, E. Filippucci, M. Gutierrez, and W. Grassi, "Fast Microvascular Remodelling in a Patient With Cancer-Associated Dermatomyositis: Capillaroscopic Follow-Up," *Rheumatology* 49, no. 2 (2010): 400, https://doi.org/10.1093/rheumatology/kep281.

2. D. Johnson, C. van Eeden, N. Moazab, et al., "Nailfold Capillaroscopy Abnormalities Correlate With Disease Activity in Adult Dermatomyositis," *Frontiers in Medicine* 8 (2021): 708432, https://doi.org/10.3389/fmed.2021.708432.

3. S. Shenavandeh and F. Rashidi, "Nailfold Capillaroscopy Changes With Disease Activity in Patients With Inflammatory Myositis Including Overlap Myositis, Pure Dermatomyositis, and Pure Polymyositis," *Reumatologia* 60, no. 1 (2022): 42–52.

4. A. Manfredi, M. Sebastiani, F. Campomori, et al., "Nailfold Videocapillaroscopy Alterations in Dermatomyositis and Systemic Sclerosis: Toward Identification of a Specific Pattern," *Journal of Rheumatology* 43, no. 8 (2016): 1575–1580.

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LETTER TO THE EDITOR

Deforming Arthritis as a New Rheumatologic Manifestation of Cocaine Use

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Dear Editor,
Cocaine use is a known mimic of a variety of rheumatologic diseases. We present a case of a patient for whom rheumatology was consulted on to investigate the etiology of arthritis and rash with concurrent cocaine use, and discuss features of cocaine use disorder and its possible rheumatologic manifestations that are further elaborated in our discussion.

A 39-year-old African American female with a past medical history of asthma and cervical cancer status post hysterectomy and bilateral oophorectomy was admitted to the hospital for joint pain and a rash. She reported ongoing joint pains for 2 months in her hands, knees, ankles, and feet that were worse with activity. One day prior, she noted a rash over her lower extremity that was painful and burning in nature. She was not taking any medications and reported intolerances to aspirin, citric acid, and sodium bicarbonate with unclear reaction types. A review of systems was benign, and family history was unrevealing. She denied alcohol use but did report cocaine use. Objectively, her vitals were all within normal limits and her physical exam was remarkable for tenderness over the MCP and PIP joints of her hands bilaterally, tenderness to palpation of her ankles, and multiple 1–3 cm erythematous palpable purpuric lesions with areas of skin necrosis over her lower extremities. Initial workup revealed a positive antinuclear antibody (ANA), an ESR of 63, a CRP of 7.4, and a negative rheumatoid factor. An RPR was nonreactive and a complete blood count was remarkable for a white blood cell count of 2.5×10^3/cmm. Given her joint pains and leukopenia with a positive ANA at her age, systemic lupus erythematosus was suspected. An ANA titer, ANCA, anti-double-stranded DNA, anti-Smith antibody, C3 and C4 levels were ordered for further evaluation, and she was started on a dose of prednisone 15 mg daily. Her skin rash was concerning for small vessel vasculitis. Further evaluation for the rash included labs for anticardiolipin antibody, anti-beta-2-glycoprotein 1, and lupus anticoagulant. Skin biopsy demonstrated leukocytoclastic vasculitis, and her ANA titer was less than 1:40. All other rheumatologic labs mentioned previously came back negative, and she left against medical advice at this time.

She underwent several inpatient hospital admissions during that year for similar joint pains with skin rash. During these admissions, she was treated as having either systemic lupus erythematosus or small vessel vasculitis and was continued on prednisone and mycophenolate mofetil. She was lost to follow-up until 2 years later, when she returned to the rheumatology clinic, where it was noted that each presentation in the emergency department with new skin lesions was associated with a positive urine drug screen test for cocaine. A lengthy discussion with the patient about the nature of her condition was had at this time, and she was advised that her joint pains and rash would likely improve or resolve with cocaine cessation.

Her skin lesions continued to worsen, and her joint pains were unresolved with opioid pain medication. Two years later, she noticed worsened hand deformities (Figure 1) and returned to the rheumatology clinic. She was noted to have swan-neck deformities, and hand X-rays confirmed this finding with no erosions (Figure 2). RF and anti-CCP were negative at this time, and she was started on a course of methotrexate and folate for her arthritic changes. The etiology of these changes was not clear, but it was suspected that it may be related to her cocaine use. She was lost to follow-up for 2 years, and her hand deformities were worse when she returned. We continued to suspect that her deforming arthritis was secondary to her cocaine use. She began a drug rehabilitation program and ceased her cocaine use at this time, and noted drastic

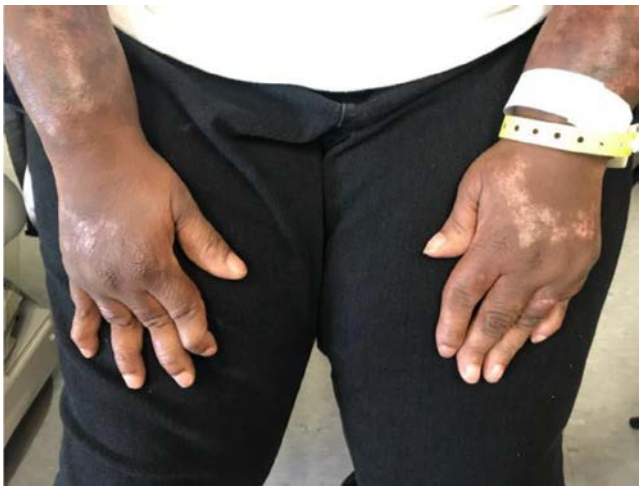

FIGURE 1 | Image of the patient's hands demonstrating swan-neck deformities bilaterally.

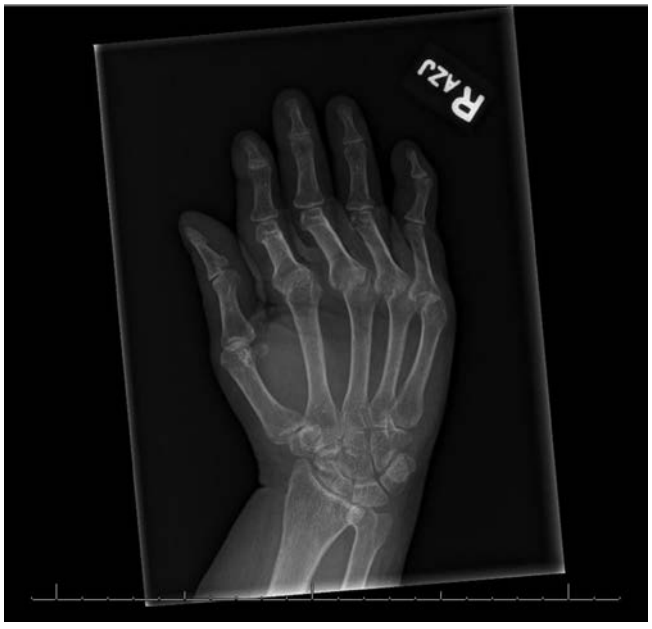

FIGURE 2 | Hand X-ray demonstrating swan-neck deformities without erosions.

improvement in her skin rash and pain afterward. However, the physical deformity remained and continues to cause her some pain. She was diagnosed with cocaine-induced arthritis as a diagnosis of exclusion based on symptom improvement with cocaine abstinence and extensive negative workup for other causes. We followed up this patient for a total of 8 years.

Cocaine use disorder is a subtype of substance use disorder (SUD), defined in the DSM-V as a pattern of symptoms by using a substance that an individual continues to take despite its negative effects [1]. Eleven criteria are assessed when diagnosing any SUD. Meeting one criterion may indicate risk of developing a SUD, 2–3 criteria indicate a mild SUD, 4–5 criteria indicate a moderate SUD, and 6 or more criteria indicate a severe SUD [1].

One difficult component of taking a history of substance use is the quantification of how much drug is being used. Variables include differences in measurements, purity variations of the substance, and differences in both routes of administration and efficiency of the route. Powder-only cocaine use is associated with less frequent cocaine dependence and decreased excess risk of side effects than those who started with powder and progressed to crack cocaine [2]. Another consideration is the increase in cocaine being mixed with levamisole, a veterinary medication that can induce a syndrome of retiform purpura, cutaneous necrosis, thrombotic microangiopathy with or without leukocytoclastic vasculitis, and autoantibodies (typically high titers of P-ANCA) [3]. A thorough substance use history is critical to fully understand the clinical scenario.

There are many possible rheumatologic manifestations of cocaine use, and it should be considered in the differential diagnosis if there is a history of cocaine use. Despite the variability, one case series consisting of 10 cases reported that half presented with purpura, pulmonary hemorrhage, nasal septum perforation, and a positive P-ANCA [4]. Cocaine-induced arthritis is a rarer phenomenon, and there is less literature around it. One case series reported that 40% of their cases presented with arthralgias, but none with obvious joint deformity [4].

Our case is remarkable because of the atypical presentation of a cocaine-induced pseudorheumatism in the form of arthritis. On initial presentation, the only symptom that was consistent with other reported cases of cocaine-induced pseudovasculitis was her rash, and her arthritis was initially nondeforming.

Although small vessel cutaneous vasculitis in association with positive ANCA test has been previously reported in the medical literature, this is the first case to our knowledge that focuses on cocaine-associated deforming arthritis. This patient's joint deformity without erosion suggests a form of Jaccoud's arthropathy, which has mainly been described in systemic lupus erythematosus and rheumatic fever in published case studies [5].

The deformities seen in Jaccoud's arthropathy are secondary to soft tissue abnormalities. These include laxity of ligaments and the joint capsule, with distension and secondary deviation of the tendon from its axis with the contribution of muscular imbalance. Additionally, the presence of synovitis is well documented and may somehow contribute to the process [6].

Levamisole is a synthetic compound derived from imidazothiazole, originally used as an anthelmintic agent in veterinary medicine and previously employed in humans for the treatment of cancer and various autoimmune diseases, due to its immunomodulatory characteristics [7]. Approximately 70%–80% of cocaine is contaminated with levamisole, which is added to enhance its volume and stimulating properties [8]. The exact mechanism by which levamisole induces vasculitis has not been fully determined. However, levamisole is associated with the generation of autoantibodies such as p-ANCA, ANA, and lupus anticoagulant. Levamisole acts as a hapten, triggering an immune response and upregulation of antibody formation. Consequently, it is thought that levamisole induces vasculitis due to immune complex deposition of IgM, IgG, IgA, and C3 complexes, and secondary hypercoagulability caused by the immune complexes, leading to tissue thrombosis and skin necrosis [9]. It is possible that the inflammatory changes in the ligaments

and tendons were induced by levamisole and caused Jaccoud's arthropathy in our patient.

Treatment of cocaine use disorder may help to resolve the pseudorheumatoid symptoms previously mentioned—without abstinence, it is difficult to treat these cases, particularly pseudovasculitis [10]. Currently, there are no FDA-approved medications to treat cocaine use disorder, but off-label pharmaceutical treatment options are available. Specifics in treatment are beyond the scope of this discussion, but some options including bupropion, psychostimulants, topiramate, and antipsychotics have all demonstrated efficacy [11]. Nonpharmacological options include cognitive behavioral therapy (CBT) and contingency management therapy. In a systematic review, contingency management alone reliably reduced cocaine use during active treatment in all trials whereas CBT only demonstrated a positive effect in three of five studies that met the inclusion criteria [12].

In conclusion, this case serves as an example of why a thorough history is the most important part of formulating a diagnosis. Pseudorheumatic disease, including Jaccoud's arthropathy, is often caused by cocaine use, and careful nonjudgmental interviewing skills can help refine the etiology of rheumatic complaints. Levamisole, a prevalent cocaine contaminant, is also implicated in Jaccoud's arthropathy and may have played a role in the development of this condition in our patient. Recent investigations suggest that contingency management programs may be the most effective treatment for cocaine use disorder, and CBT is currently the most widely used.

Author Contributions

Michael A. Vierra: original draft (lead), review and editing (equal). **Amr Edrees:** conceptualization (lead), review and editing (equal).

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The authors have nothing to report.

Ethics Statement

Our institution does not require ethics approval for reporting individual cases or case series. This research did not require IRB approval because there is no identifiable information presented in this report. Patient consent could not be obtained, as the patient no longer follows with our system.

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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References

1. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (American Psychiatric Association, 2013), https://doi.org/10.1176/appi.books.9780890425596.

2. M. Chandra and J. C. Anthony, "Cocaine Dependence: "Side Effects" and Syndrome Formation Within 1-12 Months After First Cocaine Use," *Drug and Alcohol Dependence* 206 (2020): 107717, https://doi.org/10.1016/j.drugalcdep.2019.107717.

3. J. Graf, "Rheumatic Manifestations of Cocaine Use," *Current Opinion in Rheumatology* 25, no. 1 (2013): 50–55, https://doi.org/10.1097/BOR.0b013e32835b4449.

4. S. Roverano, R. Calvo, A. Ortiz, and S. Paira, Rheumatic manifestations associated with cocaine addiction.

5. M. B. Santiago, "Jaccoud-Type Lupus Arthropathy," *Lupus* 31, no. 4 (2022): 398–406, https://doi.org/10.1177/09612033221082908.

6. F. L. Girgis, A. W. Popple, and F. E. Bruckner, "Jaccoud's Arthropathy. A Case Report and Necropsy Study," *Annals of the Rheumatic Diseases* 37, no. 6 (1978): 561–565.

7. M. J. Cascio and K. Y. Jen, "Cocaine/Levamisole-Associated Autoimmune Syndrome: A Disease of Neutrophil-Mediated Autoimmunity," *Current Opinion in Hematology* 25 (2018): 29–36.

8. J. Marquez, L. Aguirre, C. Muñoz, A. Echeverri, M. Restrepo, and L. F. Pinto, "Cocaine-Levamisole-Induced Vasculitis/Vasculopathy Syndrome," *Current Rheumatology Reports* 19 (2017): 36.

9. M. Berman, D. Paran, and O. Elkayam, "Cocaine-Induced Vasculitis Rambam Maimonides," *Medical Journal* 7, no. 4 (2016): e0036.

10. S. K. Bhinder and V. Majithia, "Cocaine Use and Its Rheumatic Manifestations: A Case Report and Discussion," *Clinical Rheumatology* 26, no. 7 (2007): 1192–1194, https://doi.org/10.1007/s10067-006-0327-x.

11. B. Chan, K. Kondo, M. Freeman, C. Ayers, J. Montgomery, and D. Kansagara, "Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-Analysis," *Journal of General Internal Medicine* 34, no. 12 (2019): 2858–2873, https://doi.org/10.1007/s11606-019-05074-8.

12. N. S. Farronato, K. M. Dürsteler-Macfarland, G. A. Wiesbeck, and S. A. Petitjean, "A Systematic Review Comparing Cognitive-Behavioral Therapy and Contingency Management for Cocaine Dependence," *Journal of Addictive Diseases* 32, no. 3 (2013): 274–287, https://doi.org/10.1080/10550887.2013.824328.

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REVIEW

The Taiwan College of Rheumatology Consensus for the Management of Systemic Lupus Erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) exhibits diverse clinical presentations and requires regionally specific management strategies. Building upon established international guidelines, the Taiwan College of Rheumatology developed the first set of recommendations for SLE management to focus on the unmet needs of clinical practice in Taiwan. This consensus aims to empower healthcare professionals and optimize patient outcomes in Taiwan. Rheumatologists from various practicing institutions formed a 15-member panel and, through a modified Delphi process, developed consensus statements that encompass various aspects of SLE care in Taiwan, including screening and diagnosis, disease monitoring, treatment strategies, and pregnancy. The expert panel reviewed and refined statements through two meetings with anonymous voting based on a 5-point Likert scale. Consensus is defined as ≥75% agreement to the proposed statements. In total, 32 statements achieved consensus. These statements incorporate the latest scientific evidence with insights from Taiwanese experts to address the unique disease characteristics and challenges faced by patients in the region, and could serve as a guide to specialists, family physicians, specialty nurses, and other healthcare professionals in Taiwan for the management of SLE.

1 | Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with diverse clinical manifestations and an unpredictable disease course. While international guidelines from bodies such as the European Alliance of Associations for Rheumatology (EULAR) and the Asia Pacific League of Associations for Rheumatology (APLAR) offer valuable evidence-based approaches, regional tailoring remains crucial due to genetic, ethnic, and geographical differences in disease presentation and comorbidities [1–3].

In Taiwan, where SLE affects 8.1 per 10000 people, patients may have higher incidences of certain manifestations, such as pulmonary arterial hypertension (PAH), which differ markedly from other populations [4–6]. Furthermore, local socioeconomic factors and treatment availability create unique management challenges.

Recognizing these challenges, these consensus recommendations present a local approach to SLE management for Taiwanese patients. Building upon the updated EULAR and APLAR recommendations [1, 3], this Taiwan College of Rheumatology consensus incorporates scientific evidence with local experts' insights, addressing screening, diagnosis, monitoring, treatment strategies, and pregnancy management to empower healthcare professionals across Taiwan to optimize outcomes for SLE patients.

2 | Methods

The consensus statements were developed through a modified Delphi process based on emerging evidence. A PubMed literature search (January 2018 to June 2023) addressed key clinical questions regarding SLE management, using search terms including "systemic lupus erythematosus," "lupus nephritis," and relevant treatment terms. Publications were limited to clinical trials, practice guidelines, and meta-analyses/systematic reviews. Evidence was graded using the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence (detailed methodology in Methods S1).

The 15-member expert panel, chaired by Wen-Nan Huang, included 14 rheumatology specialists from major Taiwan institutions. Preliminary statements covering screening, diagnosis, monitoring, treatment strategies, and pregnancy were drafted based on retrieved evidence and international guidelines.

Two consensus meetings were held (June 18 and July 16, 2023). Experts received preliminary statements and supporting evidence beforehand, then reviewed and modified statements considering local practice patterns. Anonymous voting used a 5-point Likert scale (A = accept completely; E = reject completely). Consensus required ≥ 75% agreement (A or B responses). Non-consensus statements were revised and revoted.

3 | Results

The task force achieved consensus on 32 statements, summarized in Table 1. (Detailed voting results for each statement are available in Table S1).

4 | Discussion

4.1 | Overarching Principles (Statements 1–3)

4.1.1 | Statement 1: Multidisciplinary Care and Shared Decision-Making

The management of SLE is challenging due to its multisystem nature, necessitating a multidisciplinary approach with collaboration among various specialists. A management plan based on shared decision-making between the physician and patient is essential.

4.1.2 | Statement 2: Optimal Outcomes Through Early Diagnosis and Appropriate Treatment

Delayed diagnosis and medication non-adherence hinder successful treatment [7, 8]. Despite increased disease understanding, patients face diagnosis delays of approximately 2 years between symptom onset and diagnosis [7]. Optimal outcomes in SLE require early diagnosis, timely referral to lupus specialists, appropriate treatment, and patient adherence. Prompt initiation of treatment prevents irreversible organ damage and improves long-term prognosis. Concerns about treatment toxicities often lead to non-adherence, highlighting the need for improved patient–physician communication and shared decision-making.

4.1.3 | Statement 3: Treatment Objectives

The primary treatment objectives are to minimize organ damage, promote long-term survival, and improve health-related quality of life. Achieving these goals requires balancing disease control with therapeutic toxicity, underscoring the importance of patient-centered care and shared decision-making to foster adherence.

4.2 | Disease Assessment (Statement 4)

SLE heterogeneity necessitates utilizing different disease-activity indices, depending on individual presentation [9]. Global indices include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure, and European Consensus Lupus Activity Measurement; organ-specific indices include the British Isles Lupus Assessment Group (BILAG), Cutaneous Lupus Disease Area and Severity Index (CLASI), and renal activity score [9]. Newer indices, such as the Systemic Lupus Collaborating Clinics and EULAR/American College of Rheumatology (ACR) criteria, have been validated in Asian patients [3]. Recent analysis demonstrated significant correlation between SLEDAI-2K scores and serum interferon activity [10], while Physician Global Assessment (PGA) showed strong correlations with established indices [11, 12]. Acknowledging SLE's multifaceted nature and utilizing appropriate assessment tools enables healthcare professionals to navigate disease complexities and improve patient outcomes.

4.3 | Treat-To-Target Approach (Statements 5–7)

4.3.1 | Statement 5: Treatment Goals of Remission or Low Disease Activity

The treatment of SLE should aim for remission or, if unattainable, a state of low disease activity (LLDAS) to prevent flares and organ damage accrual. The Definition of Remission in SLE (DORIS) is a desirable but often elusive goal. The LLDAS concept (e.g., SLEDAI ≤ 4, PGA ≤ 1, prednisone ≤ 7.5 mg/day) offers a pragmatic and crucial treatment target, as maintaining this

TABLE 1 | The consensus recommendations for the management of SLE.

No.	Statement
Overarching principle	
1	SLE requires multidisciplinary care. A shared decision between physician and patient should be obtained for a management plan
2	Optimal outcomes in SLE can be achieved through early diagnosis, timely referral to a specialist in lupus, appropriate treatment, and good patient adherence
3	The treatment objectives for SLE include minimizing organ damage by lupus or adverse event(s) of treatment, promoting long-term survival, and improving health-related quality of life
Disease assessment	
4	SLE should be classified by validated criteria. Disease activity should be assessed by validated disease-activity indices especially for research and administrative purposes [1/A]
Treat-to-target approach	
5	Treatment of SLE should aim at disease remission or low disease activity and prevention of flares, maintained with the lowest possible dose of glucocorticoids and considering a combination with immunosuppressive/biological therapy [1/A]
6	Periodic assessment of risk factors for cardiovascular disease, metabolic syndrome, and osteoporosis is recommended. This assessment should incorporate both conventional SLE risk factors and disease-related contributors, such as disease activity, antiphospholipid antibody positivity, chronic corticosteroid use, and renal disease [2/B]
7	Patients with SLE should be periodically monitored for factors associated with susceptibility to infection. This assessment should include clinical risk factors (e.g., advanced age, disease activity, comorbidities, renal involvement, and use of immunosuppressive therapy) and laboratory parameters that reflect humoral and cell-mediated immunity, such as immunoglobulin levels, complement levels, and lymphocyte counts. For patients receiving anti-CD20 therapy, monitoring of lymphocyte subsets should also be considered [3/B]
Glucocorticoid stewardship	
8	The doses and routes of administration of glucocorticoids should be based on the type and severity of organ involvement [1/A]
9	For chronic maintenance treatment, glucocorticoids usage should aim at less than 5 mg/day (prednisone equivalent) and, when possible, withdrawn. Prompt initiation of immunosuppressive/biological therapy can expedite the tapering/discontinuation of glucocorticoids [1/A]
Immunosuppressive/biological therapy	
10	Hydroxychloroquine is recommended for all patients with SLE unless contraindicated [1/A]. The maintenance dose should not exceed 5 mg/kg of real bodyweight per day but individualized based on the risk of flare and retinal toxicity [4/C]. Even in the absence of risk factors for retinal toxicity, ophthalmological screening (visual fields examination and/or spectral domain optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter
11	In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or in patients unable to reduce glucocorticoids to $\leq$ 5 mg/day, addition of immunosuppressive agents (e.g., methotrexate [1/B], azathioprine [2/C], mycophenolate [2/B]) and/or biologics agents (e.g., belimumab [1/A] or anifrolumab [1/A]) should be considered
12	Add-on treatment with belimumab or anifrolumab may be considered in patients with inadequate response to either one or any combination of glucocorticoids, hydroxychloroquine, and/or immunosuppressants (defined as residual disease activity, glucocorticoid dependence, and/or frequent relapses) [1/A]
13	For patients with major organ-threatening or life-threatening diseases, intravenous cyclophosphamide [2/C] should be considered. Rituximab [5/D] may be considered in refractory cases
Specific population	
14	First-line management of skin disease in SLE includes topical agents (glucocorticoids [5/D], calcineurin inhibitors) [2/B], antimalarials (hydroxychloroquine) [1/A], and/or systemic glucocorticoids [4/C]. Second-line management includes methotrexate [1/B], mycophenolate [4/C], belimumab [1/B], or anifrolumab [1/A]
15	Renal biopsy should be considered for suspected active lupus nephritis, unless contraindicated. Rebiopsy may be considered for patients with failure of induction therapy, relapse, or renal function deterioration

(Continues)

TABLE 1 | (Continued)

No.	Statement
16	For active lupus nephritis, first-line induction therapy, including mycophenolate (target dose mycophenolate mofetil 2 g/day or equivalent) [1/A] or intravenous pulse cyclophosphamide (Euro-Lupus or NIH regimen) [1/A], in combination with glucocorticoid is recommended
17	Calcineurin inhibitors with/without mycophenolate [1/A], or belimumab [1/A] in combination with cyclophosphamide or mycophenolate mofetil, are alternative induction regimens. Rituximab [2/B] or other biologics [5/D] may be considered for refractory cases
18	Mycophenolate or azathioprine may be considered as a maintenance immunosuppressive agent [1/A]. Mycophenolate is preferred if it has been used for induction therapy [1/A]. Low-dose calcineurin inhibitors are alternatives when mycophenolate and azathioprine are contraindicated [2/B] or not tolerated. Maintenance therapy for lupus nephritis should be continued for at least 3 years to prevent renal flares [2/B]
19	Neuropsychiatric SLE requires prompt diagnosis and management. Neuroimaging, cerebrospinal fluid study, autoantibodies, and considerations of clinical syndromes, timing in the course of SLE, patient age, and concomitant SLE disease activity, with rigorous exclusion of alternative causes, help in differentiation of SLE- and non–SLE-related neuropsychiatric manifestations. The therapeutic options include symptomatic, antithrombotic, and immunosuppressive agents (including pulses of intravenous methylprednisolone), tailored by the predominant putative pathogenic pathway and the type, severity, and activity of the neuropsychiatric manifestations
20	For severe neuropsychiatric manifestations of SLE with an inflammatory origin, the recommended first-line treatment involves a combination of moderate- to high-dose glucocorticoids along with immunosuppressive agents like cyclophosphamide [3/B]
21	For neuropsychiatric SLE that is thromboembolic with antiphospholipid antibodies, antiplatelet agents/anticoagulation [2/C] is required. Vitamin K antagonists are preferred to direct-acting oral anticoagulants [1/B]
22	Patients with a high-risk antiphospholipid antibody profile may receive primary prophylaxis with antiplatelet agents [2/C] such as low-dose aspirin (75–100 mg per day), especially if other atherosclerotic or thrombophilic factors are present, after balancing the bleeding hazard
23	Acute treatment of severe lupus thrombocytopenia includes high-dose glucocorticoids (including pulses of intravenous methylprednisolone) [4/C] and/or intravenous immunoglobulin G [4/C]. Immunosuppressive/glucocorticoid-sparing agents such as azathioprine [2/C], cyclosporine [4/C], or mycophenolate [2/C] can be used as maintenance therapy. Refractory cases can be treated with rituximab [2/B] or cyclophosphamide [4/C] or thrombopoietin receptor agonists [5/D]
24	Therapeutic plasmapheresis or plasma exchange [2/B] may be considered for thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, diffuse alveolar hemorrhage, refractory or severe neuropsychiatric SLE, or life-threatening hematological manifestations
Patient-centric approach	
25	For major organ–/life-threatening lupus, treat with an initial high-intensity immunosuppressive therapy until remission/low disease activity, followed by a longer period of less intensive maintenance therapy to prevent relapses [5/D]
26	Due to the potential adverse effects of therapies, immunosuppressive treatment should not be administered or altered based solely on serological activity [5/D]
27	Before immunosuppressive therapies (including high-dose corticosteroids), screening and treatment for active hepatitis B and C virus infections are recommended [1/A]. For patients undergoing B-cell depleting therapy or intensive immunosuppression, occult hepatitis B screening and pre-emptive treatment should be considered
28	Screening and treatment of latent tuberculosis are not routinely recommended. Active tuberculosis should be screened before using corticosteroids or immunosuppressive agents [5/D]
29	Inactivated vaccines (such as influenza, pneumococcus, human papillomavirus, herpes zoster, and COVID-19) are recommended for patients with SLE [1/A]
Pregnancy	
30	Women with SLE can safely become pregnant with pregnancy planning and preconception assessment. Patients will need to be maintained on medications that are compatible with pregnancy and should continue these medications in pregnancy to prevent lupus flares [1/A]

(Continues)

TABLE 1 | (Continued)

No.	Statement
Pulmonary hypertension	
31	In SLE patients who present with Raynaud's phenomenon, pleuritis, high disease activity, thrombocytopenia, acute/chronic cutaneous lupus, systemic hypertension, and ILD, as well as for those with anti–U1-RNP, anti-SSA, anti-SSB, and antiphospholipid antibodies, early screening for PAH should be considered [1/A]
32	Clinical management of SLE-PAH should follow a risk-directed approach using a simplified four-strata risk-assessment tool aiming to achieve and/or maintain a low-risk status. PAH can be managed with pulmonary vasodilator therapy in combination with immunosuppressant for the treatment of SLE [1/A]

Abbreviations: COVID-19, coronavirus disease 2019; ILD, interstitial lung disease; NIH, National Institute of Health; PAH, pulmonary arterial hypertension; RNP, ribonuclear protein; SLE, systemic lupus erythematosus.

state is associated with significantly better long-term outcomes and quality of life [13].

4.3.2 | Statement 6: Assessment of Cardiovascular, Metabolic, and Bone Disease Risk Factors

SLE increases the risk of cardiovascular disease (CVD) two- to three-fold, alongside elevated risks of stroke, myocardial infarction, and osteoporotic fractures, compared with the general population [2, 14, 15]. This stems from SLE-related inflammation directly damaging blood vessels, compounded by treatment-related factors such as glucocorticoid-induced weight gain and hypertension. Periodic assessment of risk factors for CVD, metabolic syndrome, and osteoporosis is recommended, incorporating both conventional risk factors and disease-related contributors, including disease activity, antiphospholipid antibody positivity, chronic corticosteroid use, and renal disease. Regular monitoring should include disease activity assessment (i.e., SLEDAI), antiphospholipid antibodies, renal function (urinalysis, creatinine, proteinuria), and documentation of cumulative glucocorticoid exposure.

4.3.3 | Statement 7: Assessment of Infection Risk Factors

SLE management requires balancing immunosuppressive therapy benefits against infection risks, particularly relevant in Asia, where certain infections are more prevalent. Patients with SLE should be periodically monitored for factors associated with infection susceptibility, including clinical risk factors (advanced age, disease activity, comorbidities, renal involvement, immunosuppressive therapy use) and laboratory parameters reflecting immunity (immunoglobulin levels, complement levels, lymphocyte counts). For patients receiving anti-CD20 therapy, lymphocyte subset monitoring should be considered.

In Taiwan, hepatitis B virus (HBV) infection rates range from 0.8% to 4.2% [16, 17], while hepatitis C virus (HCV) infection affects 16.5% of SLE patients [18]. *Pneumocystis jirovecii* pneumonia risk is elevated, particularly with long-term moderate- to high-dose glucocorticoids or mycophenolate mofetil [19]. Endemic tuberculosis necessitates vigilance for reactivation during immunosuppression. Comprehensive infection risk-assessment incorporating all factors in Table S2 enables appropriate monitoring intensity and prophylactic measures, recognizing that mortality significantly increases when SLE patients develop infections [20].

4.4 | Glucocorticoid Stewardship (Statements 8–9)

4.4.1 | Statement 8: Appropriate Dosing and Routes of Glucocorticoid Administration

Glucocorticoid doses and routes of administration should be tailored to the type and severity of organ involvement, ranging from topical preparations for mild skin disease to high-dose intravenous pulses for severe neuropsychiatric manifestations.

4.4.2 | Statement 9: Minimizing Long-Term Glucocorticoid Exposure

Long-term glucocorticoid therapy is associated with significant organ damage, especially when doses exceed 5 mg/day of prednisone equivalent [1–3]. To minimize adverse outcomes due to exposure to higher daily prednisolone doses, experts recommend using glucocorticoids as bridging therapy for SLE, at the lowest possible dose for the shortest possible time. For chronic maintenance, therefore, the dose should be tapered to the lowest effective level, ideally < 5 mg/day, with the ultimate goal of withdrawal. Promptly initiating immunosuppressive or biological therapy can facilitate this process.

4.5 | Immunosuppressive/Biological Therapy (Statements 10–13)

4.5.1 | Statement 10: Hydroxychloroquine as Backbone Therapy

Hydroxychloroquine is recommended for all patients with SLE unless contraindicated. The maintenance dose should not exceed 5 mg/kg of real bodyweight per day but is individualized based on the risk of flare and retinal toxicity. Even in the absence of risk factors for retinal toxicity, ophthalmological screening (visual fields examination and/or spectral domain optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter.

As a backbone therapy, hydroxychloroquine offers multiple benefits: It is associated with reduced flares, improved response in lupus nephritis, slower kidney-function decline, reduced organ damage, and fewer deaths [21–26]. It is also cost-effective [22–26]. While adherence remains a challenge, data are currently insufficient to recommend routine monitoring of drug blood levels [27]. Long-term use raises the concern of retinal toxicity, with risk increasing with dose, duration, and renal dysfunction [28, 29]. Careful management, adherence to the ≤5 mg/kg dose, and regular ophthalmological assessments are vital for early detection and prevention of complications (Figure 1) [28–30].

4.5.2 | Statement 11: Addition of Immunosuppressive Agents

In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or unable to reduce glucocorticoids to ≤5 mg/day, adding immunosuppressive agents (methotrexate, azathioprine, mycophenolate) and/or biologic agents (e.g., belimumab or anifrolumab) should be considered (Figure 1). This approach starts with conventional immunosuppressants with methotrexate and azathioprine serving moderate disease activity, while mycophenolate mofetil offers additional potency in renal and non-renal manifestations [31, 32].

4.5.3 | Statement 12: Belimumab and Anifrolumab as Add-On Therapy

Add-on treatment with belimumab or anifrolumab may be considered for patients with inadequate response to glucocorticoids, hydroxychloroquine, and/or immunosuppressants (defined as residual disease activity, glucocorticoid dependence, and/or frequent relapses). These biologics target specific pathways, B-cell activation, and type I interferon signaling, respectively, and are typically reserved for patients with complex refractory disease. The decision involves different considerations, including cost-effectiveness, biomarker profiles (interferon gene signature for anifrolumab), and regulatory approval criteria [1].

4.5.4 | Statement 13: Advanced Therapy for Severe and Refractory Disease

For major organ-threatening or life-threatening diseases, intravenous cyclophosphamide should be considered; rituximab may be considered in refractory cases. Cyclophosphamide's potent immunosuppressive effects make it valuable for severe lupus nephritis, diffuse alveolar hemorrhage, severe neuropsychiatric lupus, or rapidly progressive glomerulonephritis. However, significant toxicity (including gonadal toxicity), infection risk, hemorrhagic cystitis, and long-term malignancy risk necessitate careful cumulative dose monitoring and fertility preservation discussions, particularly in reproductive-age patients. Transition to less toxic medications for sustained management is recommended once initial disease control is achieved.

For refractory cases where cyclophosphamide has failed or is contraindicated, rituximab may be considered, though evidence is primarily from expert opinion and observational studies rather than large randomized controlled trials. Treatment decisions should be individualized, considering previous treatment failures, contraindications, specific clinical manifestations,

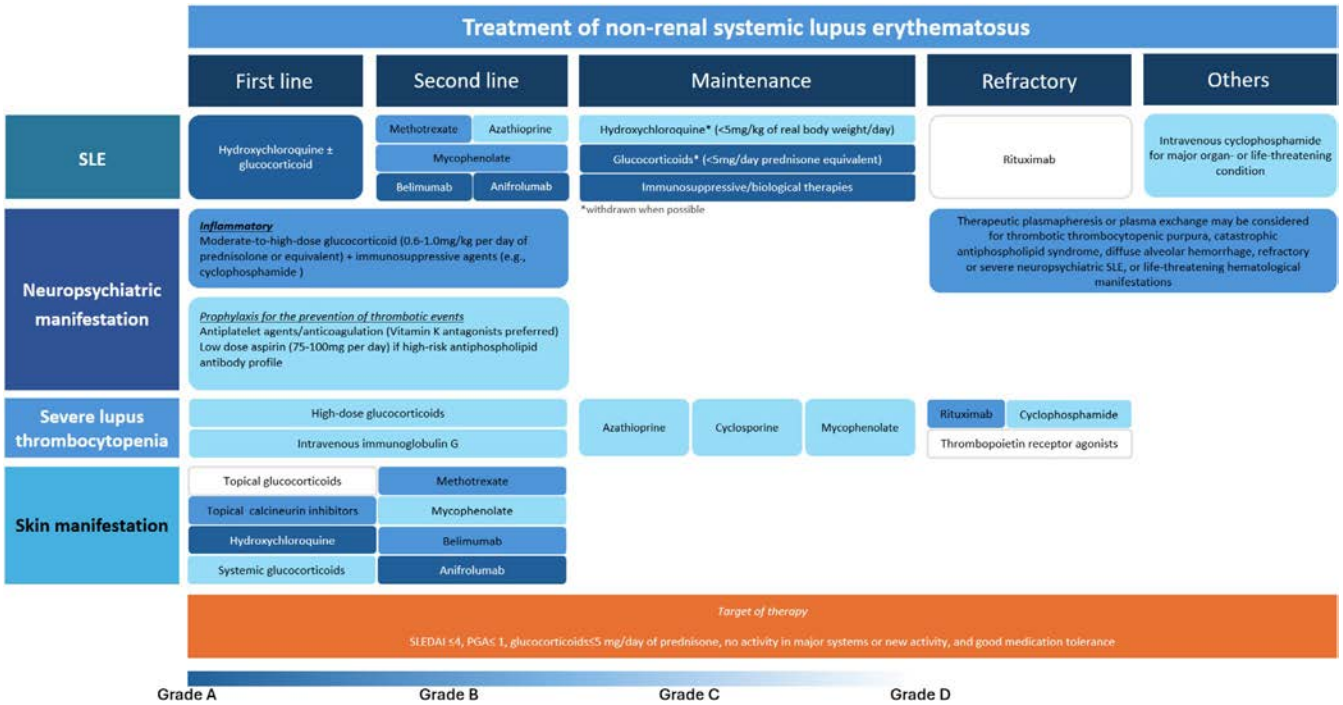

FIGURE 1 | Treatment of non-renal SLE. Medications in the same box are alternative options. Darker colors indicate stronger evidence. Choice of medication depends on patient factors, contraindications, and availability. PGA, physician global assessment; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.

patient age, comorbidities, and infection risk, with multidisciplinary discussion and careful patient counseling regarding uncertain benefit–risk profiles.

4.6 | Specific Populations (Statements 14–24)

4.6.1 | Statement 14: Management of Cutaneous Manifestations

First-line treatment includes topical agents (glucocorticoids and/or calcineurin inhibitors) and antimalarials (hydroxychloroquine), with or without systemic glucocorticoids [33–35]. Approximately 40% of patients require second-line treatment with methotrexate, mycophenolate, anifrolumab, or belimumab [32, 36–39]. While both anifrolumab and belimumab show promise, direct comparisons are challenging due to differing assessment tools; anifrolumab utilized CLASI specifically for skin involvement, while belimumab used broader measures (SLEDAI, BILAG).

4.6.2 | Statement 15: Renal Biopsy in Lupus Nephritis

Renal biopsy should be considered for suspected active lupus nephritis unless contraindicated. Rebiopsy may be considered for patients with failure of induction therapy, relapse, or renal function deterioration.

A renal biopsy is crucial, as clinical symptoms may not always reflect histological severity (Figure 2) [3]. It confirms the diagnosis, determines the histological class (I–VI), assesses active versus chronic lesions, and guides treatment selection. Biopsy should be performed promptly when lupus nephritis is suspected based on clinical evidence (e.g., proteinuria, hematuria, declining renal function). Contraindications include severe bleeding disorders, uncontrolled hypertension, or an unfavorable risk–benefit ratio. While routine repeat biopsy is not standard, this consensus suggests that rebiopsy may be considered in specific scenarios like induction failure or renal relapse, following multidisciplinary discussion.

4.6.3 | Statement 16: First-Line Induction Therapy for Lupus Nephritis

For active lupus nephritis, first-line induction therapy, including mycophenolate (target dose mycophenolate mofetil 2 g/day or equivalent) or intravenous pulse cyclophosphamide (Euro-Lupus or National Institute of Health regimen), in combination with glucocorticoid, is recommended [40].

For severe manifestations, pulse methylprednisolone (250–1000 mg intravenous daily for 1–3 days) is recommended. The mycophenolate mofetil dose of 2 g/day is standard for average Asian patients [3], who may have a lower tolerance to higher doses [3, 41]. The Euro-Lupus cyclophosphamide regimen is often preferred due to its reduced risk of gonadal toxicity.

4.6.4 | Statement 17: Alternative Induction Regimens for Lupus Nephritis

Calcineurin inhibitors with/without mycophenolate, or belimumab in combination with cyclophosphamide or mycophenolate mofetil, are alternative induction regimens. Rituximab or other biologics may be considered for refractory cases. Alternatives are considered when first-line therapies are inappropriate. Calcineurin inhibitors are preferred when cyclophosphamide is contraindicated (e.g., fertility preservation) or for pure membranous lupus nephritis. Belimumab combinations may be considered for aggressive glucocorticoid-sparing or significant

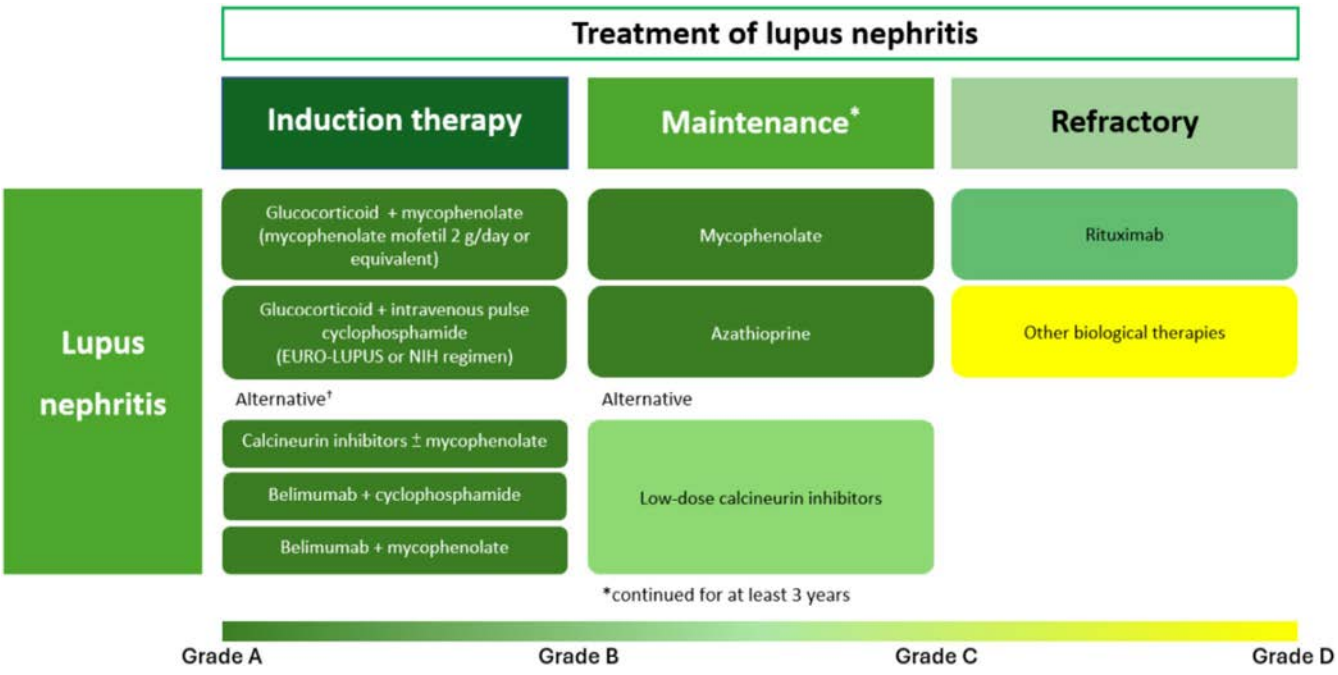

FIGURE 2 | Treatment of lupus nephritis. †Glucocorticoids are recommended as part of all induction therapy regimens shown in this algorithm, including alternative treatments, unless specifically contraindicated.

extrarenal SLE. Despite negative pivotal trial data [42], rituximab remains a promising option for refractory lupus nephritis, based on registry analyses [43]. Selection should be individualized based on patient factors, comorbidities, and reproductive goals.

4.6.5 | Statement 18: Maintenance Therapy for Lupus Nephritis

Mycophenolate or azathioprine may be considered as a maintenance immunosuppressive agent. Mycophenolate is preferred if it has been used for induction therapy. Low-dose calcineurin inhibitors are alternatives when mycophenolate and azathioprine are contraindicated or not tolerated. Maintenance therapy for lupus nephritis should be continued for at least 3 years to prevent renal flares.

Sustained maintenance is critical; both mycophenolate mofetil and azathioprine are effective in maintaining renal response [44, 45]. Data clearly link treatment durations shorter than 3 years to poorer long-term outcomes [46].

4.6.6 | Statement 19: Diagnosis and Management of Neuropsychiatric SLE

Neuropsychiatric SLE requires prompt diagnosis and management. Neuroimaging, cerebrospinal fluid study, autoantibodies, clinical syndrome considerations, timing in SLE course, patient age, and concomitant SLE disease activity, with rigorous exclusion of alternative causes, help differentiate SLE- and non–SLE-related neuropsychiatric manifestations. Therapeutic options include symptomatic, antithrombotic, and immunosuppressive agents (including pulses of intravenous methylprednisolone), tailored by the predominant pathogenic pathway and manifestation type, severity, and activity [47–50].

4.6.7 | Statement 20: Treatment of Severe Neuropsychiatric SLE

For severe neuropsychiatric manifestations with an inflammatory origin, the recommended first-line treatment involves moderate- to high-dose glucocorticoids (0.6–1.0 mg/kg per day of prednisolone or equivalent) combined with immunosuppressive agents like cyclophosphamide [51, 52].

4.6.8 | Statement 21: Management of Thromboembolic Neuropsychiatric SLE

For thromboembolic neuropsychiatric SLE with antiphospholipid antibodies, antiplatelet agents/anticoagulation are required. Vitamin K antagonists are preferred over direct-acting oral anticoagulants, targeting international normalized ratio (INR) 2.0–3.0 for arterial thrombosis, with some experts recommending higher intensity (INR 3.0–4.0) for recurrent events, balanced against bleeding risk [53, 54]. Recent studies suggest a potential increased thrombotic risk with direct oral anticoagulants, particularly rivaroxaban. Anticoagulation duration is typically indefinite for definite antiphospholipid syndrome with neuropsychiatric manifestations.

4.6.9 | Statement 22: Primary Prophylaxis for High-Risk Antiphospholipid Antibody Profile

Patients with high-risk antiphospholipid antibody profiles (persistently positive antibodies, high titres, triple positivity, lupus anticoagulant positivity) may receive primary prophylaxis with low-dose aspirin (75–100 mg daily), especially with other atherosclerotic or thrombophilic factors, after balancing bleeding hazard [55].

4.6.10 | Statement 23: Treatment of Severe Lupus Thrombocytopenia

Acute treatment of severe lupus thrombocytopenia includes high-dose glucocorticoids (including pulses of intravenous methylprednisolone) and/or intravenous immunoglobulin G [56]. Immunosuppressive/glucocorticoid-sparing agents (azathioprine, cyclosporine, mycophenolate) provide maintenance therapy. Refractory cases may be treated with rituximab, cyclophosphamide, or thrombopoietin receptor agonists.

4.6.11 | Statement 24: Therapeutic Plasmapheresis and Plasma Exchange

Therapeutic plasmapheresis or plasma exchange may be considered for thrombotic thrombocytopenic purpura (daily sessions until platelet normalization), catastrophic antiphospholipid syndrome (combined with glucocorticoids, anticoagulation, immunosuppression), diffuse alveolar hemorrhage, refractory or severe neuropsychiatric SLE, or life-threatening hematological manifestations [57–59]. Typical treatment involves 5–10 sessions with intensive monitoring of vital signs, electrolytes, coagulation parameters, and disease-specific markers.

4.7 | Patient-Centric Approach (Statements 25–29)

4.7.1 | Statement 25: Treatment Paradigm for Major Organ–/Life-Threatening Lupus

For major organ–/life-threatening lupus, treat with initial high-intensity immunosuppressive therapy until remission or low disease activity, followed by longer periods of less intensive maintenance therapy to prevent relapses. This addresses severe manifestations, including severe lupus nephritis, life-threatening neuropsychiatric manifestations, diffuse alveolar hemorrhage, severe cardiac involvement, severe hematologic complications, catastrophic antiphospholipid syndrome, and multiorgan involvement threatening vital functions. High-intensity induction combines high-dose glucocorticoids (including pulse methylprednisolone 250–1000 mg intravenous for 1–3 days) with potent immunosuppressants, aiming for remission (clinical SLEDAI = 0, PGA $\leq$ 0.5)

or low disease activity (SLEDAI ≤4, PGA ≤1) while minimizing irreversible organ damage.

4.7.2 | Statement 26: Avoiding Treatment Decisions Based Solely on Serological Activity

Immunosuppressive treatment should not be administered or altered based solely on serological activity, due to potential adverse effects. Serological markers (anti-dsDNA antibodies, complement levels, autoantibodies) may fluctuate without corresponding clinical disease activity. Treatment decisions should be guided primarily by clinical manifestations, organ function, and validated disease activity measures.

4.7.3 | Statement 27: HBV and HCV Screening and Treatment

Before immunosuppressive therapies, screening and treatment for active HBV and HCV infection are recommended. For patients undergoing B-cell depleting therapy or intensive immunosuppression, occult HBV screening and pre-emptive treatment should be considered. In Taiwan, HBV infection rates range from 0.8% to 4.2% [16, 17], while HCV infection affects 16.5% of SLE patients [18]. Comprehensive screening includes hepatitis B surface antigen, core antibody, surface antibody, and HCV antibodies.

4.7.4 | Statement 28: Tuberculosis Screening Recommendations

Active tuberculosis should be screened before corticosteroids or immunosuppressive agents, although routine latent tuberculosis screening and treatment are not routinely recommended, given limited cost-effective evidence for all patients.

4.7.5 | Statement 29: Vaccination Recommendations

Inactivated vaccines (influenza, pneumococcus, human papillomavirus, herpes zoster, COVID-19) are recommended for SLE patients [60–64]. Despite slightly lower immune responses, these vaccines are generally safe and effective, offering valuable infection protection. Live-attenuated vaccines are absolutely contraindicated in patients receiving immunosuppressive medications (glucocorticoids ≥20 mg prednisone daily for ≥2 weeks, mycophenolate, cyclophosphamide, calcineurin inhibitors, biological agents) due to vaccine-induced infection risk.

4.8 | Pregnancy (Statement 30)

With proper planning and preconception assessment, women with SLE can safely become pregnant. They will need to take medications compatible with pregnancy and continue taking them during pregnancy to prevent lupus flares. This statement emphasizes the critical importance of comprehensive preconception planning and ongoing management in achieving successful pregnancy outcomes in women with SLE.

Pregnancy planning for women with SLE requires a multidisciplinary approach involving rheumatologists, obstetricians who specialize in high-risk pregnancies, and other specialists as needed. Ideally, preconception assessment should begin 3–6 months before planned conception. It includes several key components: achieving optimal disease control with SLEDAI ≤4 or clinical remission for at least 6 months prior to conception; a comprehensive medication review, including a transition to pregnancy-compatible therapies; screening for antiphospholipid antibodies, anti-Ro/SSA, and anti-La/SSB antibodies due to their association with pregnancy complications; an assessment of organ function, particularly renal and cardiac status; optimization of general health, including folic acid supplementation, blood pressure control, and management of comorbidities; and counseling regarding pregnancy risks and outcomes.

Managing medications during pregnancy requires a careful balance between controlling the disease and ensuring fetal safety. Medications compatible with pregnancy that should be continued include hydroxychloroquine (which is safe and recommended for preventing flares), sulfasalazine, azathioprine (the preferred immunosuppressant), cyclosporine and tacrolimus (when necessary), low-dose corticosteroids (prednisolone ≤20 mg/day), and low-dose aspirin for individuals with antiphospholipid antibodies. Medications that must be discontinued before conception include methotrexate (stop 3 months before conception), mycophenolate mofetil (stop 6 weeks before conception and switch to azathioprine), cyclophosphamide (teratogenic), and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (switch to alternative antihypertensives).

Pregnancy monitoring should be intensified, including rheumatology visits every 4–6 weeks, monthly laboratory monitoring (complete blood count, comprehensive metabolic panel, urinalysis, and complement levels), regular obstetric monitoring (fetal growth, pre-eclampsia, and pregnancy complications), and serial echocardiography if cardiac involvement is present. Specific pregnancy complications in SLE include an increased risk of pre-eclampsia (particularly in patients with lupus nephritis), fetal growth restriction, preterm delivery, pregnancy loss, neonatal lupus (in mothers who are positive for anti-Ro/SSA), and congenital heart block.

Despite the increased potential for certain pregnancy complications, most women with SLE can safely conceive and carry a child with careful planning and management. Achieving good disease control before pregnancy and transitioning to pregnancy-safe medications are essential steps to ensure a healthy outcome for both mother and child [65–67].

4.9 | Pulmonary Hypertension (Statements 31–32)

4.9.1 | Statement 31: Early Screening for Pulmonary Arterial Hypertension

In SLE patients presenting with Raynaud's phenomenon, pleuritis, high disease activity, thrombocytopenia, acute/chronic cutaneous lupus, systemic hypertension, and interstitial lung disease, as well as in those with anti–U1-RNP, anti-SSA,

anti-SSB, and antiphospholipid antibodies, early screening for PAH should be considered. SLE patients face elevated PAH risk (prevalence 0.5%–17.5%), with early detection crucial for optimal outcomes [68, 69]. Anti–U1-RNP antibodies show the strongest association with SLE-PAH development.

Screening methodology includes detailed history (dyspnea, exercise tolerance, chest pain, syncope), physical examination for right heart strain, basic investigations (electrocardiography, chest radiography, brain natriuretic peptide [BNP]/N-terminal pro-BNP [NT-proBNP]), and transthoracic echocardiography assessing estimated pulmonary artery systolic pressure (ePASP), right ventricular function, and tricuspid regurgitation velocity. An ePASP > 35–40 mmHg or tricuspid regurgitation velocity > 2.8 m/s warrants right heart catheterization for definitive diagnosis.

4.9.2 | Statement 32: Risk-Directed Management Approach for SLE-PAH

Clinical management should follow risk-directed approaches using simplified four-strata risk-assessment tools, aiming to achieve/maintain a low-risk status (World Health Organization functional class I–II, 6-min walk distance > 440 m, BNP < 50 ng/L or NT-proBNP < 300 ng/L). PAH management requires dual approaches combining PAH-specific therapy (pulmonary vasodilators: phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostacyclin pathway agents) with SLE disease management including immunosuppressive therapy, continued hydroxychloroquine, and minimized corticosteroids [68, 70]. Regular monitoring every 3–6 months with multidisciplinary care involving pulmonary hypertension specialists and rheumatologists is essential.

5 | Comparison With International Guidelines

This Taiwan consensus aligns with core principles from recent APLAR and ACR guidelines, particularly on treat-to-target strategies, hydroxychloroquine as backbone therapy, and glucocorticoid stewardship. However, our recommendations are distinguished by several Taiwan-specific considerations: (1) enhanced HBV and HCV screening requirements, reflecting higher regional prevalence; (2) a modified tuberculosis screening approach, acknowledging endemic risk while recognizing limited evidence for routine latent infection treatment; (3) biological therapy recommendations adapted to local availability and reimbursement; (4) specific PAH screening protocols, reflecting higher prevalence in Asian SLE populations; and (5) integration with Taiwan's National Health Insurance system considerations for treatment accessibility. These adaptations complement international guidelines by addressing unique regional epidemiological patterns and healthcare characteristics specific to Taiwan.

6 | Conclusion

The Taiwan College of Rheumatology developed the first set of recommendations for SLE management focusing on unmet needs in Taiwan clinical practice. These recommendations could serve as a guide to specialists, family physicians, specialty nurses, and other healthcare professionals in Taiwan in the management of SLE.

Author Contributions

W.-N.H. planned the meeting and prepared the clinical questions. H.-S.S. and T.-J.L. assisted in the systematic literature review. All task force members contributed to the development of the manuscript by drafting, reviewing, and discussing the statements and supporting evidence, voting to refine and finalize statements, and reading and approving 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 from the corresponding author upon reasonable request.

References

1. A. Fanouriakis, M. Kostopoulou, J. Andersen, et al., "EULAR Recommendations for the Management of Systemic Lupus Erythematosus: 2023 Update," *Annals of the Rheumatic Diseases* 83 (2023): e19.

2. A. Fanouriakis, M. Kostopoulou, A. Alunno, et al., "2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus," *Annals of the Rheumatic Diseases* 78, no. 6 (2019): 736–745.

3. C. C. Mok, L. Hamijoyo, N. Kasitanon, et al., "The Asia-Pacific League of Associations for Rheumatology Consensus Statements on the Management of Systemic Lupus Erythematosus," *Lancet Rheumatology* 3, no. 7 (2021): e517–e531.

4. P. Y. Leong, J. Y. Huang, J. Y. Chiou, Y. C. Bai, and J. C. Wei, "The Prevalence and Incidence of Systemic Lupus Erythematosus in Taiwan: A Nationwide Population-Based Study," *Scientific Reports* 11, no. 1 (2021): 5631.

5. H. A. Chen, T. C. Hsu, S. C. Yang, et al., "Incidence and Survival Impact of Pulmonary Arterial Hypertension Among Patients With Systemic Lupus Erythematosus: A Nationwide Cohort Study," *Arthritis Research & Therapy* 21, no. 1 (2019): 82.

6. C. Y. Lin, C. H. Ko, C. Y. Hsu, and H. A. Chen, "Epidemiology and Mortality of Connective Tissue Disease-Associated Pulmonary Arterial

Hypertension: A National Cohort Study in Taiwan," *Seminars in Arthritis and Rheumatism* 50, no. 5 (2020): 957–962.

7. A. Kernder, J. G. Richter, R. Fischer-Betz, et al., "Delayed Diagnosis Adversely Affects Outcome in Systemic Lupus Erythematosus: Cross Sectional Analysis of the LuLa Cohort," *Lupus* 30, no. 3 (2021): 431–438.

8. N. Costedoat-Chalumeau, J. Pouchot, G. Guettrot-Imbert, et al., "Adherence to Treatment in Systemic Lupus Erythematosus Patients," *Best Practice & Research. Clinical Rheumatology* 27, no. 3 (2013): 329–340.

9. K. Ohmura, "Which Is the Best SLE Activity Index for Clinical Trials?," *Modern Rheumatology* 31, no. 1 (2021): 20–28.

10. K. Miyachi, T. Iwamoto, S. Kojima, et al., "Relationship of Systemic Type I Interferon Activity With Clinical Phenotypes, Disease Activity, and Damage Accrual in Systemic Lupus Erythematosus in Treatment-Naive Patients: A Retrospective Longitudinal Analysis," *Arthritis Research & Therapy* 25, no. 1 (2023): 26.

11. D. Apostolopoulos, R. Kandane-Rathnayake, W. Louthrenoo, et al., "Factors Associated With Damage Accrual in Patients With Systemic Lupus Erythematosus With no Clinical or Serological Disease Activity: A Multicentre Cohort Study," *Lancet Rheumatology* 2, no. 1 (2020): e24–e30.

12. E. Chessa, M. Piga, A. Floris, H. Devilliers, A. Cauli, and L. Arnaud, "Use of Physician Global Assessment in Systemic Lupus Erythematosus: A Systematic Review of Its Psychometric Properties," *Rheumatology (Oxford, England)* 59, no. 12 (2020): 3622–3632.

13. R. F. van Vollenhoven, G. Bertsias, A. Doria, et al., "DORIS Definition of Remission in SLE: Final Recommendations From an International Task Force," *Lupus Science & Medicine* 2021 (2021): 178–182.

14. X. Wang, S. Yan, C. Liu, et al., "Fracture Risk and Bone Mineral Density Levels in Patients With Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis," *Osteoporosis International* 27, no. 4 (2016): 1413–1423.

15. J. Yazdany, N. Pooley, J. Langham, et al., "Systemic Lupus Erythematosus; Stroke and Myocardial Infarction Risk: A Systematic Review and Meta-Analysis," *RMD Open* 6, no. 2 (2020): e001247.

16. R. Watanabe, T. Ishii, K. Nakamura, et al., "Prevalence and Time Course of Hepatitis B Virus Infection in Patients With Systemic Lupus Erythematosus Under Immunosuppressive Therapy," *Modern Rheumatology* 23, no. 6 (2013): 1094–1100.

17. W. Lin, Y. Chen, J. Lan, C. Chang, H. Yeh, and S. Yang, "Increased Risk of Hepatitis B Virus Reactivation in Systemic Lupus Erythematosus Patients Receiving Immunosuppressant: A Retrospective Cohort Study," *Lupus* 27 (2018): 66–75.

18. M. Chen, M. Chen, C. Tsai, et al., "Incidence and Antiviral Response of Hepatitis C Virus Reactivation in Lupus Patients Undergoing Immunosuppressive Therapy," *Lupus* 24 (2015): 1029–1036.

19. W. H. Wang, C. C. Lai, Y. F. Huang, et al., "Pneumocystis Jirovecii Pneumonia in Systemic Lupus Erythematosus: A Nationwide Cohort Study in Taiwan," *Arthritis Care & Research (Hoboken)* 74, no. 9 (2022): 1444–1450.

20. Y. Chen, L. Zhang, Q. Xue, and N. Wang, "Infection Profile and Risk Factors for Mortality in Patients With End-Stage Renal Disease Attributable to Systemic Lupus Erythematosus: A Two-Center Integrated Study," *Journal of International Medical Research* 50, no. 8 (2022): 18702.

21. E. Schrezenmeier and T. Dorner, "Mechanisms of Action of Hydroxychloroquine and Chloroquine: Implications for Rheumatology," *Nature Reviews Rheumatology* 16, no. 3 (2020): 155–166.

22. C. C. Mok, H. J. Penn, K. L. Chan, S. M. Tse, L. J. Langman, and P. J. Jannetto, "Hydroxychloroquine Serum Concentrations and Flares of Systemic Lupus Erythematosus: A Longitudinal Cohort Analysis," *Arthritis Care & Research (Hoboken)* 68, no. 9 (2016): 1295–1302.

23. N. Kasitanon, D. Fine, M. Haas, L. Magder, and M. Petri, "Hydroxychloroquine Use Predicts Complete Renal Remission Within 12 Months Among Patients Treated With Mycophenolate Mofetil Therapy for Membranous Lupus Nephritis," *Lupus* 15 (2006): 366–370.

24. G. J. Pons-Estel, G. S. Alarcon, G. McGwin, Jr., et al., "Protective Effect of Hydroxychloroquine on Renal Damage in Patients With Lupus Nephritis: LXV, Data From a Multiethnic US Cohort," *Arthritis and Rheumatism* 61, no. 6 (2009): 830–839.

25. H. Jung, R. Bobba, J. Su, et al., "The Protective Effect of Antimalarial Drugs on Thrombovascular Events in Systemic Lupus Erythematosus," *Arthritis and Rheumatism* 62, no. 3 (2010): 863–868.

26. G. S. Alarcon, G. McGwin, A. M. Bertoli, et al., "Effect of Hydroxychloroquine on the Survival of Patients With Systemic Lupus Erythematosus: Data From LUMINA, a Multiethnic US Cohort (LUMINA L)," *Annals of the Rheumatic Diseases* 66, no. 9 (2007): 1168–1172.

27. G. Ruiz-Irastorza, M. Ramos-Casals, P. Brito-Zeron, and M. A. Khamashta, "Clinical Efficacy and Side Effects of Antimalarials in Systemic Lupus Erythematosus: A Systematic Review," *Annals of the Rheumatic Diseases* 69, no. 1 (2010): 20–28.

28. T. Lenfant, S. Salah, G. Leroux, et al., "Risk Factors for Hydroxychloroquine Retinopathy in Systemic Lupus Erythematosus: A Case-Control Study With Hydroxychloroquine Blood-Level Analysis," *Rheumatology (Oxford, England)* 59, no. 12 (2020): 3807–3816.

29. J. W. Kim, Y. Y. Kim, H. Lee, S. H. Park, S. K. Kim, and J. Y. Choe, "Risk of Retinal Toxicity in Longterm Users of Hydroxychloroquine," *Journal of Rheumatology* 44, no. 11 (2017): 1674–1679.

30. M. F. Marmor, U. Kellner, T. Y. Lai, R. B. Melles, W. F. Mieler, and A. Academy, "Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)," *Ophthalmology* 123, no. 6 (2016): 1386–1394.

31. C. C. Mok, "Mycophenolate Mofetil for Non-Renal Manifestations of Systemic Lupus Erythematosus: A Systematic Review," *Scandinavian Journal of Rheumatology* 36, no. 5 (2007): 329–337.

32. R. Sakthiswary and E. Suresh, "Methotrexate in Systemic Lupus Erythematosus: A Systematic Review of Its Efficacy," *Lupus* 23, no. 3 (2014): 225–235.

33. A. Kreuter, T. Gambichler, F. Breuckmann, et al., "Pimecrolimus 1% Cream for Cutaneous Lupus Erythematosus," *Journal of the American Academy of Dermatology* 51, no. 3 (2004): 407–410.

34. A. Kuhn, K. Gensch, M. Haust, et al., "Efficacy of Tacrolimus 0.1% Ointment in Cutaneous Lupus Erythematosus: A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Trial," *Journal of the American Academy of Dermatology* 65, no. 1 (2011): 54–64.

35. F. Chasset, J. D. Bouaziz, N. Costedoat-Chalumeau, C. Frances, and L. Arnaud, "Efficacy and Comparison of Antimalarials in Cutaneous Lupus Erythematosus Subtypes: A Systematic Review and Meta-Analysis," *British Journal of Dermatology* 177, no. 1 (2017): 188–196.

36. E. Morand, R. Furie, I. N. Bruce, et al., "Efficacy of Anifrolumab Across Organ Domains in Patients With Moderate-To-Severe Systemic Lupus Erythematosus: A Post-Hoc Analysis of Pooled Data From the TULIP-1 and TULIP-2 Trials," *Lancet Rheumatology* 4, no. 4 (2022): E282–E292.

37. R. Kneeland, D. Montes, J. Endo, B. Shields, C. M. Bartels, and S. Garg, "Improvement in Cutaneous Lupus Erythematosus After Twenty Weeks of Belimumab Use: A Systematic Review and Meta-Analysis," *Arthritis Care & Research (Hoboken)* 75, no. 8 (2023): 1838–1848.

38. A. Kreuter, N. S. Tomi, S. M. Weiner, M. Huger, P. Altmeyer, and T. Gambichler, "Mycophenolate Sodium for Subacute Cutaneous Lupus Erythematosus Resistant to Standard Therapy," *British Journal of Dermatology* 156, no. 6 (2007): 1321–1327.

39. Y. H. Lee and G. G. Song, "Anifrolumab for the Treatment of Active Systemic Lupus Erythematosus: A Meta-Analysis of Randomized Controlled Trials," *Zeitschrift für Rheumatologie* 80, no. 10 (2021): 988–994.

40. M. Walsh, N. Solomons, L. Lisk, and D. Jayne, "Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis With Poor Kidney Function: A Subgroup Analysis of the Aspreva Lupus Management Study," *American Journal of Kidney Diseases* 61 (2013): 710–715.

41. F. A. Houssiau, C. Vasconcelos, D. D'Cruz, et al., "Immunosuppressive Therapy in Lupus Nephritis: The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide," *Arthritis and Rheumatism* 46, no. 8 (2002): 2121–2131.

42. B. H. Rovin, R. Furie, K. Latinis, et al., "Efficacy and Safety of Rituximab in Patients With Active Proliferative Lupus Nephritis: The Lupus Nephritis Assessment With Rituximab Study," *Arthritis and Rheumatism* 64, no. 4 (2012): 1215–1226.

43. C. Diaz-Lagares, S. Croca, S. Sangle, et al., "Efficacy of Rituximab in 164 Patients With Biopsy-Proven Lupus Nephritis: Pooled Data From European Cohorts," *Autoimmunity Reviews* 11, no. 5 (2012): 357–364.

44. M. Dooley, D. Jayne, E. Ginzler, et al., "Mycophenolate Versus Azathioprine as Maintenance Therapy for Lupus Nephritis," *New England Journal of Medicine* 365 (2011): 1886–1895.

45. F. A. Houssiau, D. D'Cruz, S. Sangle, et al., "Azathioprine Versus Mycophenolate Mofetil for Long-Term Immunosuppression in Lupus Nephritis: Results From the MAINTAIN Nephritis Trial," *Annals of the Rheumatic Diseases* 69, no. 12 (2010): 2083–2089.

46. C. C. Mok, K. Y. Ying, W. L. Ng, et al., "Long-Term Outcome of Diffuse Proliferative Lupus Glomerulonephritis Treated With Cyclophosphamide," *American Journal of Medicine* 119, no. 4 (2006): 325–333.

47. J. G. Hanly, M. B. Urowitz, L. Su, et al., "Short-Term Outcome of Neuropsychiatric Events in Systemic Lupus Erythematosus Upon Enrollment Into an International Inception Cohort Study," *Arthritis and Rheumatism* 59, no. 5 (2008): 721–729.

48. B. Pinto, S. Suresh, K. Ramyasri, et al., "Neuropsychiatric Manifestations Are Associated With Increased Mortality in Indian Patients With Lupus: A Single Centre Retrospective Observational Study," *Lupus* 2022, no. 31 (2022): 1563–1571.

49. A. Bortoluzzi, C. A. Scire, S. Bombardieri, et al., "Development and Validation of a New Algorithm for Attribution of Neuropsychiatric Events in Systemic Lupus Erythematosus," *Rheumatology (Oxford, England)* 54, no. 5 (2015): 891–898.

50. "The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes," *Arthritis and Rheumatism* 42, no. 4 (1999): 599–608.

51. A. Bortoluzzi, M. Padovan, I. Farina, E. Galuppi, F. De Leonardis, and M. Govoni, "Therapeutic Strategies in Severe Neuropsychiatric Systemic Lupus Erythematosus: Experience From a Tertiary Referral Centre," *Reumatismo* 64 (2012): 350–359.

52. A. Fanouriakis, C. Pamfil, P. Sidiropoulos, et al., "Cyclophosphamide in Combination With Glucocorticoids for Severe Neuropsychiatric Systemic Lupus Erythematosus: A Retrospective, Observational Two-Centre Study," *Lupus* 25, no. 6 (2016): 627–636.

53. M. Khamashta, M. Cuadrado, F. Mujic, N. Taub, B. Hunt, and G. Hughes, "The Management of Thrombosis in the Antiphospholipid-Antibody Syndrome," *New England Journal of Medicine* 332 (1995): 993–997.

54. V. Pengo, G. Denas, G. Zoppellaro, et al., "Rivaroxaban vs Warfarin in High-Risk Patients With Antiphospholipid Syndrome," *Blood* 132, no. 13 (2018): 1365–1371.

55. L. Arnaud, A. Mathian, A. Ruffatti, et al., "Efficacy of Aspirin for the Primary Prevention of Thrombosis in Patients With Antiphospholipid Antibodies: An International and Collaborative Meta-Analysis," *Autoimmunity Reviews* 13, no. 3 (2014): 281–291.

56. M. Olfat, E. Silverman, and D. Levy, "Rituximab Therapy Has a Rapid and Durable Response for Refractory Cytopenia in Childhood-Onset Systemic Lupus Erythematosus," *Lupus* 24 (2015): 966–972.

57. C. W. Yang, Y. C. Chen, P. Dunn, M. Y. Chang, J. T. Fang, and C. C. Huang, "Thrombotic Thrombocytopenic Purpura (TTP): Initial Treatment With Plasma Exchange Plus Steroids and Immunosuppressive Agents for Relapsing Cases," *Renal Failure* 25, no. 1 (2003): 21–30.

58. C. Ednalino, J. Yip, and S. E. Carsons, "Systematic Review of Diffuse Alveolar Hemorrhage in Systemic Lupus Erythematosus: Focus on Outcome and Therapy," *Journal of Clinical Rheumatology* 21, no. 6 (2015): 305–310.

59. G. Lorenz, L. Schul, F. Schraml, et al., "Adult Macrophage Activation Syndrome-Haemophagocytic Lymphohistiocytosis: 'of Plasma Exchange and Immunosuppressive Escalation Strategies' — A Single Centre Reflection," *Lupus* 29 (2020): 324–333.

60. M. Adawi, N. L. Bragazzi, D. McGonagle, et al., "Immunogenicity, Safety and Tolerability of Anti-Pneumococcal Vaccination in Systemic Lupus Erythematosus Patients: An Evidence-Informed and PRISMA Compliant Systematic Review and Meta-Analysis," *Autoimmunity Reviews* 18, no. 1 (2019): 73–92.

61. C. C. Mok, L. Y. Ho, L. S. Fong, and C. H. To, "Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in Patients With Systemic Lupus Erythematosus: A Case-Control Study," *Annals of the Rheumatic Diseases* 72, no. 5 (2013): 659–664.

62. Z. Liao, H. Tang, X. Xu, Y. Liang, Y. Xiong, and J. Ni, "Immunogenicity and Safety of Influenza Vaccination in Systemic Lupus Erythematosus Patients Compared With Healthy Controls: A Meta-Analysis," *PLoS One* 11, no. 2 (2016): e0147856.

63. C. C. Mok, K. H. Chan, L. Y. Ho, Y. F. Fung, W. F. Fung, and P. C. Y. Woo, "Safety and Immune Response of a Live-Attenuated Herpes Zoster Vaccine in Patients With Systemic Lupus Erythematosus: A Randomised Placebo-Controlled Trial," *Annals of the Rheumatic Diseases* 78, no. 12 (2019): 1663–1668.

64. J. K. Park, M. Kim, J. I. Jung, et al., "Immunogenicity, Reactogenicity, and Safety of Two-Dose Adjuvanted Herpes Zoster Subunit Vaccine in Patients With Systemic Lupus Erythematosus in South Korea: A Single-Centre, Randomised, Double-Blind, Placebo-Controlled Trial," *Lancet Rheumatology* 6, no. 6 (2024): e352–e360.

65. M. D. Russell, M. Dey, J. Flint, et al., "British Society for Rheumatology Guideline on Prescribing Drugs in Pregnancy and Breastfeeding: Immunomodulatory Anti-Rheumatic Drugs and Corticosteroids," *Rheumatology (Oxford, England)* 62, no. 4 (2023): e48–e88.

66. A. Braga, T. Barros, R. Faria, et al., "Systemic Lupus Erythematosus and Pregnancy: A Retrospective Single-Center Study of 215 Pregnancies From Portugal," *Lupus* 30 (2021): 2165–2175.

67. F. dos Santos, M. Ignacchiti, B. Rodrigues, et al., "Premature Rupture of Membranes – A Cause of Foetal Complications Among Lupus: A Cohort Study, Systematic Review and Meta-Analysis," *Lupus* 30 (2021): 2042–2053.

68. W. C. Huang, S. C. Hsieh, Y. W. Wu, et al., "2023 Taiwan Society of Cardiology (TSOC) and Taiwan College of Rheumatology (TCR) Joint Consensus on Connective Tissue Disease-Associated Pulmonary Arterial Hypertension," *Acta Cardiologica Sinica* 39, no. 2 (2023): 213–241.

69. Y. K. Xia, S. H. Tu, Y. H. Hu, et al., "Pulmonary Hypertension in Systemic Lupus Erythematosus: A Systematic Review and Analysis of 642 Cases in Chinese Population," *Rheumatology International* 33, no. 5 (2013): 1211–1217.

70. M. Humbert, G. Kovacs, M. M. Hoeper, et al., "2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension," *European Heart Journal* 43, no. 38 (2022): 3618–3731.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Detailed voting results for consensus statements. **Table S2:** Risk factors for infections in systemic lupus erythematosus. **Methods S1** Detailed literature search strategy and evidence grading.

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ORIGINAL ARTICLE OPEN ACCESS

Abnormal Resting-State Functional Connectivity Between the Dorsal Anterior Cingulate Cortex and the Limbic System Contributes to Pain and Emotion Regulation Impairment in Fibromyalgia Patients

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ABSTRACT

Objectives: The subdivisions of the anterior cingulate cortex (ACC) are involved in distinct functions in the processing of chronic pain and regulation of emotions. However, the specific impact of each ACC subdivision on fibromyalgia (FM) remains unclear. This study aimed to systematically investigate the abnormal resting-state functional connectivity (rsFC) patterns between the ACC (and its subregions) and other chronic-pain-related limbic cortices and subcortical nuclei in patients with FM.

Methods: Resting-state functional magnetic resonance imaging (fMRI) was conducted in 31 patients diagnosed with fibromyalgia (FM) and 32 demographically matched healthy controls (HCs). Using subdivisions of the anterior cingulate cortex (ACC) as regions of interest, we employed a seed-based resting-state functional connectivity (rsFC) approach to identify alterations in connectivity between limbic cortex and subcortical nuclei. A two-sample *t*-test was applied to compare functional connectivity differences between the two groups. Additionally, Pearson correlation analysis was performed to examine the relationships between rsFC alterations and measures of executive function and clinical symptom severity.

Results: Patients with FM demonstrated aberrant rsFC of the dorsal ACC (dACC) with the limbic system, notably the amygdala ($t = 2.840$, SE = 0.942, $p = 0.007$), parahippocampal gyrus ($t = 2.340$, SE = 0.905, $p = 0.024$), and insula (t = 2.159, SE = 0.835, $p = 0.036$). Subregion analyses further revealed heightened connectivity of the anterior midcingulate cortex (aMCC) with the parahippocampal gyrus ($t = 2.737$, SE = 1.064, $p = 0.009$), and increased connectivity of the superior anterior cingulate cortex (supACC) with the insula ($t = 2.596$, SE = 0.706, $p = 0.013$) and amygdala ($t = 2.398$, SE = 0.812, $p = 0.021$), which were significantly associated with pain severity and depressive symptoms in FM.

Yu Wang, Yixin Zhou and Aihui Liu contributed equally to this study.

Conclusion: This study revealed specific abnormalities in the rsFC between the dACC and the limbic cortices and subcortical nuclei in FM patients. The heightened connectivity of the aMCC with the parahippocampal gyrus and of the supACC with the insula and amygdala was closely associated with the regulation of emotion and processing of chronic pain.

1 | Introduction

Fibromyalgia (FM) is a prevalent chronic pain syndrome characterized primarily by widespread pain, fatigue, sleep disturbances, and accompanying emotional issues [1]. Chronic pain, fatigue, and associated emotional disorders significantly reduce patients' quality of life [2]. At the pathophysiological level, the etiology of FM is associated with central sensitization, which involves the hyperactivation of peripheral nociceptors and leads to hypersensitivity of the nervous system to both painful and non-painful stimuli [3]. Given these pathophysiological characteristics, researchers have focused on relevant brain regions that may be implicated in the disorder.

Abnormal plasticity within the sub-gray nuclei of the limbic system plays a crucial role in the mechanisms underlying the comorbidity of pain and emotion. As the center of emotion processing and memory integration, the limbic system transforms peripheral nociceptive signals into persistent pain perception and associated negative emotional responses [4]. This conversion occurs through the synergistic action of key nuclei, including the amygdala, hippocampus, hypothalamus, and anterior cingulate gyrus (ACC). Research has demonstrated that the basolateral nucleus of the amygdala drives anxiety-related behaviors associated with pain by enhancing glutamatergic projections to the dorsal anterior cingulate gyrus (dACC) [5]. Additionally, the ventral CA1 region of the hippocampus displays unique synaptic remodeling characteristics in the context of chronic pain [6]. The functional connectivity between the hippocampal CA1 and the infralimbic cortex in rats with a peripheral inflammation model is significantly decreased, which is restored through optogenetics and can effectively alleviate spontaneous pain behaviors [5]. Furthermore, the prelimbic cortex, a critical subregion of the medial prefrontal cortex (mPFC), contains deep pyramidal neurons that dynamically encode spontaneous pain intensity via gamma band (60–90 Hz) oscillations, forming a bidirectional regulatory network with the primary somatosensory cortex [4].

Understanding the ACC's role in processing pain signals and regulating emotional responses is essential for elucidating the pathological mechanisms underlying FM [7]. Although there is no definitive anatomical classification, the ACC is generally recognized as consisting of three subregions: the pregenual ACC (pgACC), dorsal ACC (dACC), and subgenual ACC (sgACC) [8, 9]. Studies have revealed a significant reduction in the gray matter volume of the dACC in FM patients [10, 11], as well as abnormalities in resting-state spontaneous activity [12] and task-related connectivity involving the dACC [13]. The dysregulation of the dACC contributes to hyperalgesia, indicating its role in the cognitive regulation of chronic pain and the bias in pain attention [14]. Furthermore, the altered connectivity between the sgACC and the medial orbitofrontal cortex (mOFC) is linked to emotional symptoms, suggesting its involvement in assessing the emotional valence of chronic pain [15]. Notably, gender differences in the connectivity between the pgACC and the caudate nucleus imply its function in the sensorimotor integration of chronic pain [16]. Thus, the three subregions of the ACC in FM patients display distinct functional abnormalities, which may be intricately connected to the pathophysiology and clinical manifestations of the condition.

The rsFC method can examine the temporal correlation between brain regions without external stimulation, thus gaining insight into the function of the brain and its pathological dysfunction. In other disease fields, rsFC studies based on ACC subregions have achieved remarkable accomplishments. Studies confirmed that the abnormal rsFC between the dACC and multiple brain regions, such as the superior frontal gyrus and the middle frontal gyrus, especially in the processes related to addiction, attention-deficit/hyperactivity disorder, and eating disorders [17]. The sgACC has abnormal rsFC with multiple brain regions in patients with depression and can be used as a reference indicator for predicting prognosis [18–20]. In a study of patients with treatment-resistant schizophrenia, it was found that the rsFC between the sgACC and the cuneus was increased, while the rsFC between the dACC and the thalamus was reduced [21]. In addition, the ACC subregions of patients with Internet addiction and subclinical depression also showed different abnormal rsFC patterns [22, 23]. However, regarding chronic pain populations, there is currently no consensus on the specific functions emphasized by each ACC subregion.

In this study, we undertook an exploratory investigation to examine the abnormal rs-FC patterns of the ACC and its three subregions concerning other brain regions associated with chronic pain in patients with FM. Additionally, we aimed to identify which subregion exhibited the most pronounced rs-FC alterations and had the most significant effect on the clinical symptoms of FM. The findings may enhance our understanding of the neurobiological mechanisms underlying FM and could aid in the identification of potential biomarkers.

2 | Methods

2.1 | Participants

From May 2023 to August 2023, a total of 63 participants were recruited for a study utilizing functional magnetic resonance imaging (fMRI). The cohort included 31 patients diagnosed with fibromyalgia (FM), with a mean age of 51.7 years, consisting of 21 women and 10 men. In addition, there were 32 healthy controls matched for age and sex, with a mean age of 49.1 years, including 22 women and 10 men. Given that the reported incidence ratio of women to men with FM ranges from 2:1 to 7:1 [24], each group gender ratio of women to men is close to 2:1. All patients fulfilled the 2016 American College of Rheumatology (ACR) diagnostic criteria for FM [1]. The study protocol was

reviewed and approved by the Ethics Committee of Zhejiang Provincial People's Hospital (IRB no. 2023KY053).

The inclusion criteria for patients with FM were as follows: (1) aged 24 years or older; and (2) meeting the 2016 American College of Rheumatology (ACR) diagnostic criteria, which require a Widespread Pain Index (WPI) score of >7 and a Symptom Severity Scale (SSS) score of ≥ 5, or a WPI score of 4–6 and an SSS score of ≥ 9; additionally, patients must have experienced widespread pain (affecting at least four of five regions) for at least 3 months, with the axial skeleton (e.g., neck, back, chest) being one of the affected regions. The exclusion criteria were: (1) current or historical use of opioid medications or narcotic analgesics; (2) a history of substance abuse; (3) comorbid autoimmune or inflammatory pain disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease); (4) concurrent participation in other clinical trials; (5) pregnancy or lactation; (6) psychiatric disorders, including active schizophrenia, major depressive disorder with suicidal ideation, or any substance abuse within the past 2 years; (7) use of medications such as antidepressants or gabapentinoids, or receipt of treatments including physical therapy, neural therapy, ozone therapy, dry needling, or acupuncture; (8) menopausal status or irregular menstrual cycles; (9) comorbid systemic diseases that may affect hormonal status or limbic system function (e.g., diabetes, hyperthyroidism, or hypothyroidism).

2.2 | Clinical Assessment

The clinical presentation of each participant was reassessed using standardized questionnaires administered in their native language prior to MRI imaging. Anxiety and depression were assessed using the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) [25]. The total scores classify individuals into four severity categories: normal (0–50), mild (50–59), moderate (60–69), and severe (≥ 70) for anxiety or depression. These questionnaires demonstrate strong internal consistency and construct validity and are suitable for evaluating anxiety and depression in patients with chronic pain.

The severity of fibromyalgia symptoms during the preceding week was evaluated using the Symptom Severity Scale (SSS), the Fibromyalgia Impact Questionnaire (FIQ), and the Widespread Pain Index (WPI). The SSS assesses the severity of fatigue, cognitive symptoms, and non-restorative sleep [1]. The FIQ consists of 10 items that measure the health status of FM patients, including physical function, pain, fatigue, work status, stiffness, anxiety, and depression. The WPI is a quantitative tool used to assess pain severity in diagnosed FM patients by counting the number of specific anatomical regions where the patient has experienced pain over the past week [26].

2.3 | MRI Acquisition

Neuroimaging data were acquired on a 3T General Electric scanner using an 8-channel head coil (GE Systems, Chicago, IL, USA). One T1 anatomical scan (3D fast spoiled gradient-echo [FSPGR] Irprep BRAVO) was performed to obtain anatomical information. The image covered the whole brain, including the brainstem and cerebellum, with the following parameters: repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle = 90°, matrix = 64×64, field of view (FOV) = 220×220 mm, slice thickness/interslice gap = 3.2/0.8 mm, and 44 slices. During the functional MRI scan, all subjects were instructed to close their eyes, relax, and remain awake. The fMRI images and subjects' compliance with the instructions were examined post-scan to ensure they met the requirements. If not, the fMRI data were discarded, and the subject was rescanned.

2.4 | Imaging Data Preprocessing

Preprocessing of rs-fMRI data was conducted using the Resting-State fMRI Data Analysis Toolkit (RESTplus) [27], available at http://restfmri.net/forum/RESTplus. The following steps were performed: (1) elimination of the first 10 time points to allow for stable magnetization and participant adaptation, (2) slice-timing correction, (3) head-motion correction, (4) spatial normalization to Montreal Neurological Institute (MNI) space using a new segmentation of structural images with a resampled voxel size of $3 \times 3 \times 3$ mm, (5) spatial smoothing via an isotropic Gaussian kernel with a full width at half maximum (FWHM) of 6 mm, (6) removal of linear drift within the time series, (7) regression to remove the effects of head movement using the Friston 24-parameter model, as well as cerebrospinal fluid (CSF) and white matter signal noise from the fMRI data, and (8) bandpass filtering within the frequency range of 0.01 to 0.08 Hz.

2.5 | Region of Interest Analyses of Functional Connectivity

In this study, regions of interest (ROI) corresponding to the pgACC, sgACC, and superior anterior cingulate cortex (supACC) were defined using the anatomical structures outlined in the automated anatomical labeling (AAL) template atlas [26, 28]. The delineation of the dorsal anterior cingulate cortex (dACC) was based on the boundaries described in a previous study [29], which were integrated with the AAL template. Furthermore, the limbic system ROIs, including the bilateral insula, amygdala, hippocampus, and parahippocampal gyrus, were defined in accordance with the AAL3 atlas [27].

2.6 | Statistical Analysis

2.6.1 | Statistical Analysis of Demographic Data and Clinical Scales

Statistical Analysis of Demographic Data and Clinical Scales Demographic and clinical data were analyzed using IBM SPSS 27.0 (IBM Corporation, Armonk, NY, USA). The continuous data, including age, years of education, years of disease, and the scores of WPI, SSS, SDS, SAS, and FIQ were analyzed using independent t tests. Categorical variables (e.g., gender) were compared between groups using Pearson's chi-square test for $R \times C$

contingency tables. The threshold of statistical significance was set at $p < 0.05$ [30].

2.6.2 | Functional Connectivity Analysis

Whole-brain functional connectivity analyses were conducted for each of the three subdivisions of the ACC, controlling for sex and age as covariates. Analyses were conducted using the Resting-State fMRI Data Analysis Toolkit (RESTplus) (http://restfmri.net/forum/RESTplus). One-sample *t*-tests were applied to identify brain regions exhibiting significant positive resting-state rsFC with each ACC subdivision within the gray matter mask. A family-wise error (FWE) corrected threshold of $p < 0.001$ was applied using Statistical Parametric Mapping.

Subsequently, rsFC between the ACC subdivisions and limbic system ROIs was extracted for each participant. Connectivity between two ROIs was calculated using Pearson correlation of their activity [31]. To assess connectivity differences between the two groups, a two-sample *t* test was performed. Pearson correlation analysis was used to analyze the correlation between rsFC value and clinical symptom severity. Correlation analyses were corrected for sex, age, and disease duration, and the significance level of the correlation was set at $p < 0.05$.

3 | Results

3.1 | Demographic, Clinical and Neuropsychological Test Results

The demographic and clinical symptom severity data of two groups were shown in Table S1. In this study, six FM patients and seven HCs were excluded from further analyses because of excessive head motion during the image acquisition. There were no significant differences in age ($p = 0.452$), gender distribution ($p = 0.841$), and years of education ($p = 0.326$) between the two groups with no statistically significant differences ($p > 0.05$).

3.2 | Whole-Brain Resting-State Functional Connectivity of the Three Divisions of the ACC

In our study, whole-brain functional connectivity analyses were conducted to examine the three subdivisions within the anterior cingulate cortex (ACC): the pgACC, sgACC, and dACC. Our results indicated significant differences in the functional connectivity of the left dACC to the entire brain when comparing the FM group to the HC group (FWE-corrected $p < 0.001$). Particularly, we identified distinctive patterns in the functional connectivity of the left dACC with several brain regions, including the medial superior frontal gyrus, insula, amygdala, precuneus, middle cingulate gyrus, superior temporal gyrus, parietal gyrus, and orbito-superior frontal gyrus, contrasting the FM group with the HC group. These significant findings are visually represented in Figure 1.

3.3 | Functional Connectivity of the Left dACC With the Limbic System

In order to explore the functional connectivity of the left dACC with key brain regions within the limbic system, namely the amygdala, insula, hippocampus, and parahippocampal gyrus, we carried out supplementary analyses. The results revealed noteworthy differences in the functional connectivity of the left dACC with the left amygdala ($t = 2.840$, SE = 0.942, $p = 0.007$), the left parahippocampal gyrus ($t = 2.340$, SE = 0.905, $p = 0.024$), and the left insula ($t = 2.159$, SE = 0.835, $p = 0.036$) between the FM group and HC group. These disparities in functional connectivity patterns are depicted in Figure 2.

3.4 | Subgroup Analysis of dACC Functional Connectivity

In the subsequent analysis, subgroup assessments were carried out to investigate the functional connectivity patterns of the primary components of the dACC, namely the anterior midcingulate cortex (aMCC) and the supACC, with the limbic system. The results indicated that the left supACC demonstrated

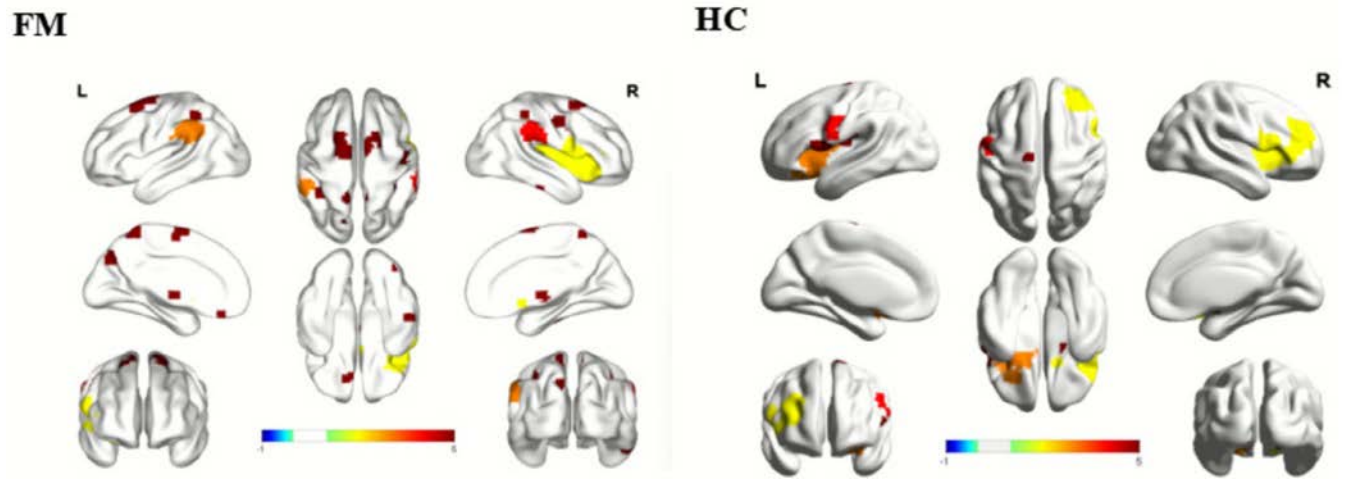

FIGURE 1 | Brain maps generated by one-sample *t* tests of the resting-state functional connectivity of the left dACC to the whole brain in the FM and HC groups. Threshold: FWE-corrected $p < 0.001$. FM, fibromyalgia; HC, healthy control.

variations in functional connectivity with the left insula ($t = 2.596$, SE = 0.706, $p = 0.013$) and the left amygdala ($t = 2.398$, SE = 0.812, $p = 0.021$) between the FM group and the HC group. Furthermore, the aMCC exhibited differences in functional connectivity with the left parahippocampal gyrus ($t = 1.064$, $p = 0.009$). These disparities are illustrated in Figure 3.

3.5 | Correlation Between Functional Connectivity and Clinical Characteristics in FM Patients

In our study, we conducted an in-depth analysis of the functional connectivity differences observed between the two groups. We specifically examined the correlations between

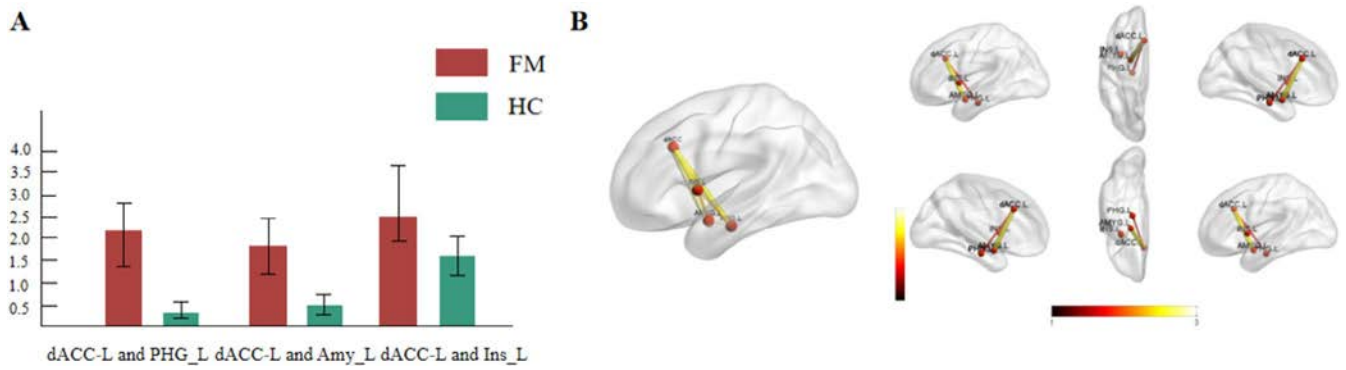

FIGURE 2 | (A) The illustration depicted the effect sizes of functional connectivity, demonstrating significant variances in neural coupling between the left dACC and other brain regions in individuals with FM as compared to HC. The brain regions involved are the left parahippocampal gyrus (PHG_L), left amygdala (Amy_L), and left insula (Ins_L). The connectivity effect sizes are visually represented with error bars denoting the 95% confidence interval, providing a measure of the accuracy of the estimated effect. (B) A visual representation was provided to demonstrate the functional connectivity between the aberrant brain regions. Each numerical value associated with a specific brain area indicates the strength of the functional connectivity effect size, with higher values signifying a stronger connection. INS.L, Insula_L; PHG.L, Parahippocampal_L; AMY.L, Amygdala_L; dACC_L, the left dorsal anterior cingulate cortex, PHG.L, Parahippocampal_L; Amy_L, Amygdala_L; Ins_L, Insula_L.

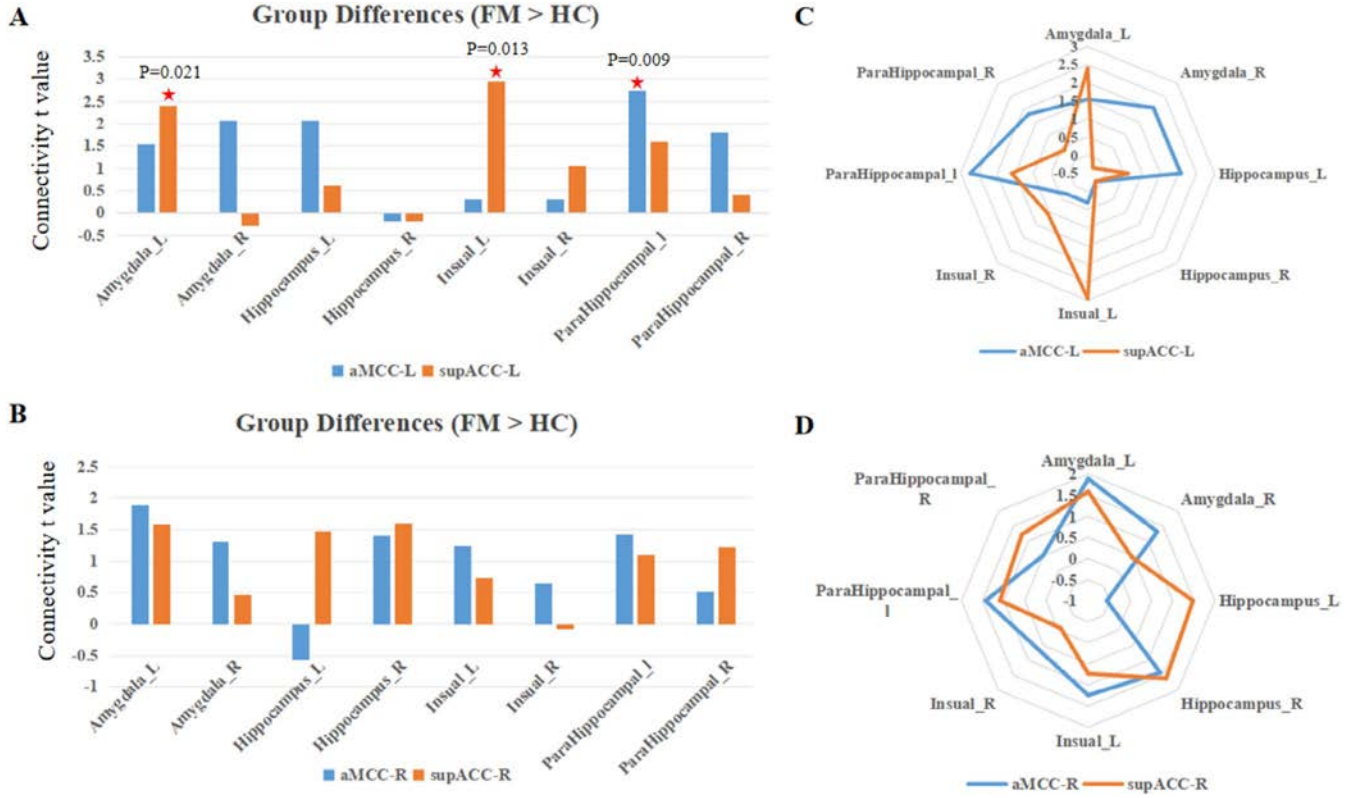

FIGURE 3 | (A, B) presents two bar charts depicting the *t*-values that reflect the differences in functional connectivity between and HC within the aMCC, the supACC, and several key limbic system brain regions. Asterisks indicate statistically significant differences in functional connectivity between the two groups ($p < 0.05$). (C, D) features two radar charts that offer a more intuitive visualization of the differences in functional connectivity among these brain regions. rsFC, resting-state functional connectivity; FM, fibromyalgia; HC, healthy controls; aMCC, anterior mid-cingulate cortex; supACC, subgenual anterior cingulate cortex.

these differences and the levels of pain, anxiety, and depression as indicated by scale scores. Our findings revealed significant associations within the FM group. Notably, the functional connectivity of the left supACC with the left amygdala ($r = 0.478$, $p = 0.021$) and the left insula ($r = 0.402$, $p = 0.046$) showed positive correlations with WPI. Furthermore, the functional connectivity between the left supACC and the left amygdala ($r = 0.445$, $p = 0.033$), as well as between the left supACC and the left insula ($r = 0.373$, $p = 0.048$), exhibited positive correlations with SDS scores. These results, along with accompanying data presented in Figure 4, suggest that heightened connectivity of these regions is linked to more widespread pain and higher levels of reported depressive symptoms.

4 | Discussion

The study systematically investigated the abnormal rs-FC patterns of the ACC and its three subregions with other chronic pain-related brain regions in patients with FM. The results identified enhanced rs-FC of the dACC with the limbic system, including the insula, amygdala, and parahippocampal gyrus. Subgroup analysis of the dACC revealed enhanced connectivity between the aMCC and the parahippocampal gyrus, and increased connectivity between the supACC and the insula and amygdala. In addition, we found a positive correlation between abnormal rs-FC patterns of the supACC and pain severity and depressive symptoms in FM patients. These findings suggest distinct functional roles for the components of the dACC: the supACC may be more involved in pain perception and emotional processing, and the aMCC may be critical for cognitive evaluation and regulation.

The group of patients with FM demonstrated significantly increased functional connectivity with various brain regions within the limbic system. An integrative analysis of neuroimaging and neurophysiological studies conducted by Russo identified the dACC as a crucial center for motivational and cognitive processes [32]. Previous research has indicated increased dACC activation during incentive-based cognitive tasks [33] and in the selection of motivated actions [34]. Moreover, deficiencies in cognitive control have been linked to depression [35]. Our study demonstrated a positive correlation between the enhanced functional connectivity of dACC subdivisions in FM patients and the severity of depressive symptoms. Grahek and other scholars found that cognitive control dysfunction in depression involves alterations in motivated behavior's core elements, including changes in reward anticipation, effort cost, and estimation of environmental controllability [36]. Additionally, the dACC is also a crucial component of the dorsal neural system in emotional cognition and regulation [37]. During emotional processing, the dorsal neural system modulates the activity of the

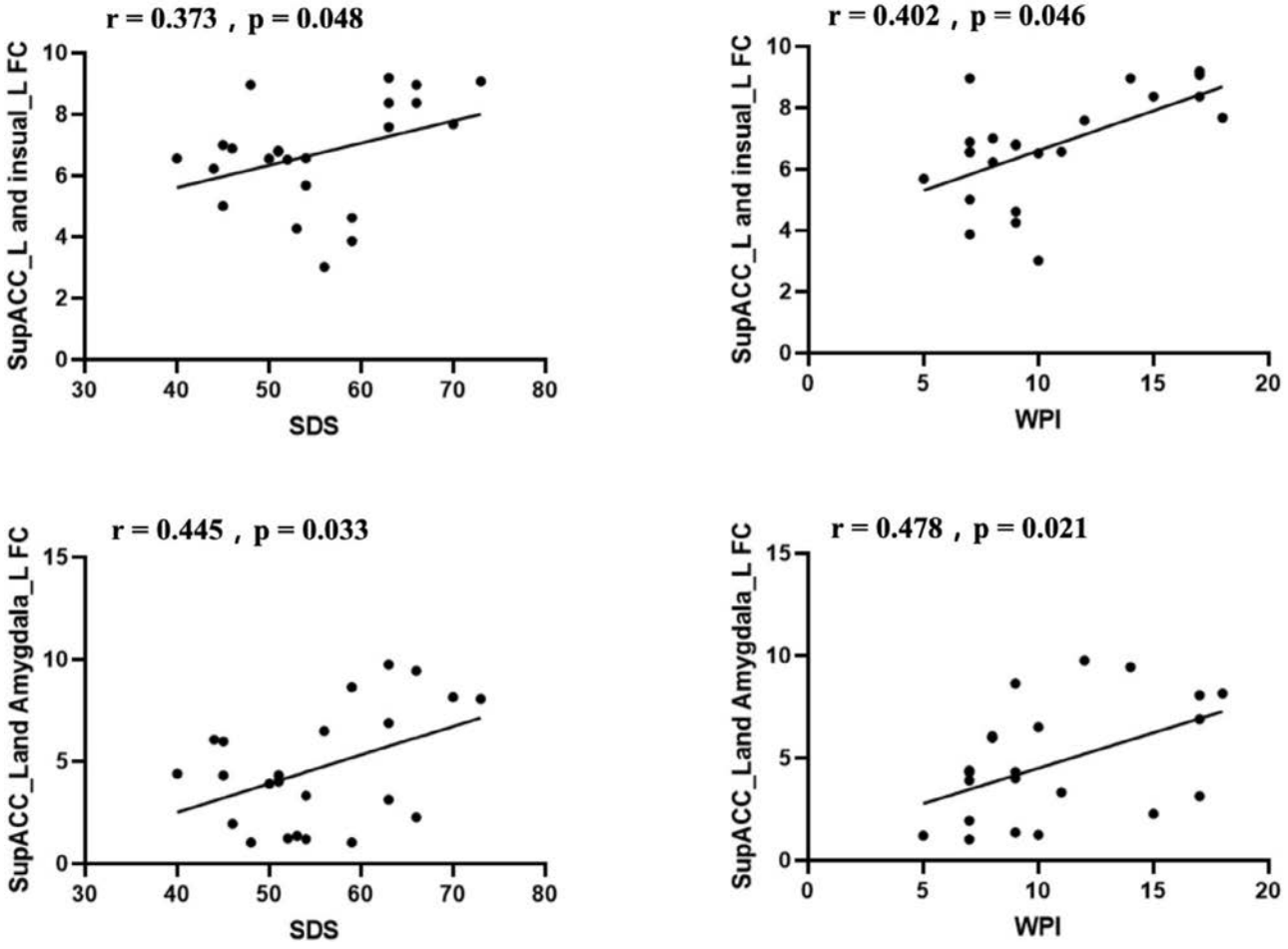

FIGURE 4 | Abnormal functional connectivity of supACC_L and the correlation of WPI and SDS scores. SDS, Self-Rating Depression Scale; WPI, Widespread Pain Index.

ventral neural system, particularly the activity of the amygdala and insula, and their functional coupling plays a significant role in emotional regulation [38, 39]. Our study findings further indicate enhanced functional connectivity of the dACC with the insula and amygdala within the limbic system, underscoring a close association between the chronic pain experienced by FM patients and emotional regulation disorders, as well as cognitive functional impairments.

The dACC is an intricate brain structure comprised of the supACC and the aMCC [40, 41]. In this study, we reveal significantly enhanced connectivity between the supACC and both the insula and amygdala in patients with FM. The supACC is recognized as a pivotal brain region in the regulation of chronic pain [42] and negative emotions, including emotional monitoring, conflict detection, and the implementation of adaptive emotional regulation strategies [43]. The insula plays a key role in the processing of nociception and the encoding of pain intensity [44, 45]. A recent study utilizing electrophysiology, optogenetics, and behavioral analysis demonstrated that overactivity of the ACC could alter the ACC-insula circuit, leading to changes in the spinal network responsible for nociceptive sensitization [46]. Our study's findings aligned with those of Garza-Villarreal EA and colleagues, who identified stronger functional connectivity between the ACC and the insula at rest in FM patients compared to healthy controls [47]. Additionally, the connectivity was negatively correlated with pain thresholds [48]. The amygdala is rich in various neuropeptides, which have been identified as important regulatory factors for pain-related neural plasticity and pain behavior [49]. Recent basic research showed that blocking the pathway from the basolateral amygdala to the ACC in mice could prevent depression-like behaviors induced by chronic pain without altering anxiety-like behaviors, aversion, or mechanical hyperalgesia [50]. Notably, clinical electrophysiological studies have revealed that over 85% of fibromyalgia (FM) patients exhibit hyperactive deep tendon reflexes (e.g., in the bilateral rectus femoris and triceps brachii muscles), with surface electromyography (sEMG) demonstrating increased amplitude, prolonged muscle activation duration, and shortened electromechanical delay [51]. Central sensitization not only affects reflex pathways but also leads to elevated resting muscle tone. FM patients show enhanced overall muscle activity (%EMG), reduced rest duration, and exhibit a dynamic pattern under cognitive stress: pain intensity increases during the stress phase, whereas muscle activity declines more markedly during the relaxation phase [52]. These findings indicate that central sensitization exerts an independent influence on pain pathways. Our study demonstrated that increased functional connectivity between the supACC, amygdala, and insula predominantly mediates nociceptive-affective integration, which encodes pain salience and modulates emotional valence.

In this study, we found that the aMCC, another subdivision of the dACC, showed increased functional connectivity with the parahippocampal gyrus in patients with FM. The aMCC is known to regulate the interaction between pain perception and action selection [53], while the parahippocampal gyrus is involved in memory processes, including memory encoding and retrieval [54]. Jones and colleagues used anterograde tracers to reveal direct projections from the cingulate cortex to the parahippocampal gyrus [55], thereby confirming the close functional connection between these two brain regions. The aMCC has been considered to play a central role in associative memory involving cognitive control, encompassing the modulation of associative memory processes [56]. Further research indicated that the aMCC significantly modulated the parahippocampal gyrus during memory encoding [57]. Based on our results, we suppose that memory encoding processes involving the dACC in FM are predominantly centered in the aMCC region.

The study on the ACC and its subdivisions in the context of FM presents intriguing findings. To the best of our knowledge, this is the first article to investigate the subdivisions of the ACC in relation to pain and mood disorders associated with fibromyalgia. Nevertheless, there are several limitations that require consideration. Firstly, the sample size of 47 participants, while adequate for initial exploratory studies, may not generalize the results to the broader FM population. Future research should increase the sample size. Secondly, the cross-sectional nature of this study limits the ability to infer causality or the progression of ACC connectivity changes over time in FM patients. Longitudinal studies would provide a more comprehensive understanding of the dynamics of ACC connectivity and their relationship with the progression of FM symptoms. To address these limitations, future studies could employ larger cohort designs to capture the temporal evolution of ACC connectivity in FM.

5 | Conclusion

In summary, the findings of our study enrich the evidence supporting the role of the dACC in modulating the perception of widespread pain and depressive symptoms. This study provides the first evidence of functional segregation within dACC subdivisions in FM pathophysiology. The dissociation between supACC-mediated affective processing and aMCC-driven cognitive modulation suggests that chronic pain and depression comorbidity may stem from parallel but distinct neural pathway dysregulations. This study enriches our understanding of the complex central mechanisms of FM. This study enriches evidence for supACC as targeted interventions (e.g., fMRI-guided rTMS) for pain-affective comorbidity. At the same time, it focused on cognitive remediation for maladaptive pain coping strategies of aMCC.

Author Contributions

Y.W. and Y.Z.: conceptualization, methodology, writing – original draft. A.L. and C.M.: formal analysis, visualization, writing – review and editing. S.L.: data curation. S.H.: methodology, formal analysis. X.Z. and H.J.: validation, writing – review and editing. Z.Y.: supervision, project administration. All authors have read and approved the final 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 from the corresponding author upon reasonable request.

References

1. F. Wolfe, D. J. Clauw, M. A. Fitzcharles, et al., "Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria," *Seminars in Arthritis and Rheumatism* 46, no. 3 (2016): 319–329.

2. A. L. Kratz, D. Whibley, S. Kim, M. Sliwinski, D. Clauw, and D. A. Williams, "Fibrofog in Daily Life: An Examination of Ambulatory Subjective and Objective Cognitive Function in Fibromyalgia," *Arthritis Care & Research (Hoboken)* 72, no. 12 (2020): 1669–1677.

3. W. Choi, M. Lim, J. S. Kim, and C. K. Chung, "Habituation Deficit of Auditory N100m in Patients With Fibromyalgia," *European Journal of Pain (London, England)* 20, no. 10 (2016): 1634–1643.

4. T. V. Bliss, G. L. Collingridge, B. K. Kaang, T. V. P. Bliss, and M. Zhuo, "Synaptic Plasticity in the Anterior Cingulate Cortex in Acute and Chronic Pain," *Nature Reviews. Neuroscience* 17, no. 8 (2016): 485–496.

5. D. L. Juarez-Salinas, J. M. Braz, A. Etlin, S. Gee, V. Sohal, and A. I. Basbaum, "GABAergic Cell Transplants in the Anterior Cingulate Cortex Reduce Neuropathic Pain Aversiveness," *Brain* 142, no. 9 (2019): 2655–2669.

6. T. J. Meeker, A. C. Schmid, M. L. Keaser, et al., "Tonic Pain Alters Functional Connectivity of the Descending Pain Modulatory Network Involving Amygdala, Periaqueductal Gray, Parabrachial Nucleus and Anterior Cingulate Cortex," *NeuroImage* 256 (2022): 119278.

7. N. Kolling, T. Behrens, M. K. Wittmann, and M. Rushworth, "Multiple Signals in Anterior Cingulate Cortex," *Current Opinion in Neurobiology* 37 (2016): 36–43.

8. F. Caruana, M. Gerbella, P. Avanzini, et al., "Motor and Emotional Behaviours Elicited by Electrical Stimulation of the Human Cingulate Cortex," *Brain* 141 (2018): 3035–3051.

9. A. Etkin, T. Egner, and R. Kalisch, "Emotional Processing in Anterior Cingulate and Medial Prefrontal Cortex," *Trends in Cognitive Sciences* 15 (2011): 85–93.

10. H. Shi, C. Yuan, Z. Dai, H. Ma, and L. Sheng, "Gray Matter Abnormalities Associated With Fibromyalgia: A Meta-Analysis of Voxel-Based Morphometric Studies," *Seminars in Arthritis and Rheumatism* 46, no. 3 (2016): 330–337.

11. B. Cagnie, I. Coppieters, S. Denecker, J. Six, L. Danneels, and M. Meeus, "Central Sensitization in Fibromyalgia? A Systematic Review on Structural and Functional Brain MRI," *Seminars in Arthritis and Rheumatism* 44, no. 1 (2014): 68–75.

12. A. C. Janes, S. Farmer, A. L. Peechatka, B. B. Frederick, and S. E. Lukas, "Insula-Dorsal Anterior Cingulate Cortex Coupling Is Associated With Enhanced Brain Reactivity to Smoking Cues," *Neuropsychopharmacology* 40, no. 7 (2015): 1561–1568.

13. J. R. Sato, M. Q. Hoexter, X. F. Castellanos, and L. A. Rohde, "Abnormal Brain Connectivity Patterns in Adults With ADHD: A Coherence Study," *PLoS One* 7, no. 9 (2012): e45671.

14. M. C. Bushnell, M. Ceko, and L. A. Low, "Cognitive and Emotional Control of Pain and Its Disruption in Chronic Pain," *Nature Reviews. Neuroscience* 14, no. 7 (2013): 502–511.

15. Z. Zhou, Y. Gao, W. Bao, et al., "Distinctive Intrinsic Functional Connectivity Alterations of Anterior Cingulate Cortex Subdivisions in Major Depressive Disorder: A Systematic Review and Meta-Analysis," *Neuroscience and Biobehavioral Reviews* 159 (2024): 105583.

16. J. Y. Lee, T. You, C. H. Lee, et al., "Role of Anterior Cingulate Cortex Inputs to Periaqueductal Gray for Pain Avoidance," *Current Biology* 32, no. 13 (2022): 2834–2847.

17. S. Lee, K. Ran Kim, J. Ku, J. H. Lee, K. Namkoong, and Y. C. Jung, "Resting-State Synchrony Between Anterior Cingulate Cortex and Precuneus Relates to Body Shape Concern in Anorexia Nervosa and Bulimia Nervosa," *Psychiatry Research* 221, no. 1 (2014): 43–48.

18. H. Wu, H. Sun, J. Xu, et al., "Changed Hub and Corresponding Functional Connectivity of Subgenual Anterior Cingulate Cortex in Major Depressive Disorder," *Frontiers in Neuroanatomy* 10 (2016): 120.

19. Y. Wang, C. Wang, J. Zhou, et al., "Contribution of Resting-State Functional Connectivity of the Subgenual Anterior Cingulate to Prediction of Antidepressant Efficacy in Patients With Major Depressive Disorder," *Translational Psychiatry* 14, no. 1 (2024): 399.

20. R. Ge, J. Downar, D. M. Blumberger, Z. J. Daskalakis, and F. Vila-Rodriguez, "Functional Connectivity of the Anterior Cingulate Cortex Predicts Treatment Outcome for rTMS in Treatment-Resistant Depression at 3-Month Follow-Up," *Brain Stimulation* 13, no. 1 (2020): 206–214.

21. Y. Liu, H. Huang, X. Qin, F. Zheng, and H. Wang, "Altered Functional Connectivity in Anterior Cingulate Cortex Subregions in Treatment-Resistant Schizophrenia Patients," *Neuroscience Letters* 814 (2023): 137445.

22. C. L. Philippi, J. C. Motzkin, M. S. Pujara, and M. Koenigs, "Subclinical Depression Severity Is Associated With Distinct Patterns of Functional Connectivity for Subregions of Anterior Cingulate Cortex," *Journal of Psychiatric Research* 71 (2015): 103–111.

23. D. Lee, J. Lee, K. Namkoong, and Y. C. Jung, "Subregions of the Anterior Cingulate Cortex Form Distinct Functional Connectivity Patterns in Young Males With Internet Gaming Disorder With Comorbid Depression," *Frontiers in Psychiatry* 9, no. 9 (2018): 380.

24. M. J. Bair and E. E. Krebs, "Fibromyalgia," *Annals of Internal Medicine* 172, no. 5 (2020): ITC33–ITC48.

25. M. K. Choe, M. Lim, J. S. Kim, D. S. Lee, and C. K. Chung, "Disrupted Resting State Network of Fibromyalgia in Theta Frequency," *Scientific Reports* 8, no. 1 (2018): 2064.

26. M. Lee, "Clinimetrics: The Revised Fibromyalgia Impact Questionnaire," *Journal of Physiotherapy* 67, no. 3 (2021): 220–221.

27. D. A. Dunstan and N. Scott, "Clarification of the Cut-Off Score for Zung's Self-Rating Depression Scale," *BMC Psychiatry* 19, no. 1 (2019): 177.

28. F. Wolfe, D. J. Clauw, M. A. Fitzcharles, et al., "The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity," *Arthritis Care & Research* 62, no. 5 (2010): 600–610.

29. D. A. Dunstan and N. Scott, "Norms for Zung's Self-Rating Anxiety Scale," *BMC Psychiatry* 20, no. 1 (2020): 90.

30. X. Z. Jia, J. Wang, H. Y. Sun, et al., "RESTplus: An Improved Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing," *Science Bulletin* 64, no. 14 (2019): 953–954.

31. H. Yan, X. N. Zuo, D. Wang, et al., "Hemispheric Asymmetry in Cognitive Division of Anterior Cingulate Cortex: A Resting-State Functional Connectivity Study," *NeuroImage* 47, no. 4 (2009): 1579–1589.

32. D. M. Yee, J. L. Crawford, B. Lamichhane, and T. S. Braver, "Dorsal Anterior Cingulate Cortex Encodes the Integrated Incentive

Motivational Value of Cognitive Task Performance," *Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 41, no. 16 (2021): 3707–3720.

33. C. Parro, M. L. Dixon, and K. Christoff, "The Neural Basis of Motivational Influences on Cognitive Control," *Human Brain Mapping* 39, no. 12 (2018): 5097–5111.

34. C. B. Holroyd and N. Yeung, "Motivation of Extended Behaviors by Anterior Cingulate Cortex," *Trends in Cognitive Sciences* 16, no. 2 (2012): 122–128.

35. P. L. Rock, J. P. Roiser, W. J. Riedel, and A. D. Blackwell, "Cognitive Impairment in Depression: A Systematic Review and Meta-Analysis," *Psychological Medicine* 44, no. 10 (2014): 2029–2040.

36. I. Grahek, A. Shenhav, S. Musslick, R. M. Krebs, and E. H. W. Koster, "Motivation and Cognitive Control in Depression," *Neuroscience and Biobehavioral Reviews* 102 (2019): 371–381.

37. I. Sezer, D. A. Pizzagalli, and M. D. Sacchet, "Resting-State fMRI Functional Connectivity and Mindfulness in Clinical and Non-Clinical Contexts: A Review and Synthesis," *Neuroscience and Biobehavioral Reviews* 135 (2022): 104583.

38. G. J. Quirk, R. Garcia, and F. González-Lima, "Prefrontal Mechanisms in Extinction of Conditioned Fear," *Biological Psychiatry* 60, no. 4 (2006): 337–343.

39. M. Domic-Siede, M. Guzman-Gonzalez, A. Sanchez-Corzo, et al., "Emotion Regulation Unveiled Through the Categorical Lens of Attachment," *BMC Psychology* 12, no. 1 (2024): 240.

40. A. R. Segerdahl, M. Mezue, T. W. Okell, J. T. Farrar, and I. Tracey, "The Dorsal Posterior Insula Subserves a Fundamental Role in Human Pain," *Nature Neuroscience* 18, no. 4 (2015): 499–500.

41. H. Kim, J. Park, M. Kuhn, M. J. Kim, and J. Hur, "Neuroticism Modulates Functional Connectivity of the Midcingulate Cortex During Emotional Conflict," *Scientific Reports* 15, no. 1 (2025): 13095.

42. L. L. Tan, P. Pelzer, C. Heinl, et al., "A Pathway From Midcingulate Cortex to Posterior Insula Gates Nociceptive Hypersensitivity," *Nature Neuroscience* 20, no. 11 (2017): 1591–1601.

43. O. Bouchatta, F. Aby, W. Sifeddine, et al., "Pain Hypersensitivity in a Pharmacological Mouse Model of Attention-Deficit/Hyperactivity Disorder," *Proceedings of the National Academy of Sciences of the United States of America* 119, no. 30 (2022): e2114094119.

44. E. A. Garza-Villarreal, Z. Jiang, P. Vuust, et al., "Music Reduces Pain and Increases Resting State fMRI BOLD Signal Amplitude in the Left Angular Gyrus in Fibromyalgia Patients," *Frontiers in Psychology* 6 (2015): 1051.

45. H. De la Corte-Rodriguez, J. M. Roman-Belmonte, C. Resino-Luis, J. Madrid-Gonzalez, and E. C. Rodriguez-Merchan, "The Role of Physical Exercise in Chronic Musculoskeletal Pain: Best Medicine-A Narrative Review," *Healthcare (Basel)* 12, no. 2 (2024): 242.

46. E. Ichesco, T. Schmidt-Wilcke, R. Bhavsar, et al., "Altered Resting State Connectivity of the Insular Cortex in Individuals With Fibromyalgia," *Journal of Pain* 15, no. 8 (2014): 815–826.

47. V. Neugebauer, M. Mazzitelli, B. Cragg, G. Ji, E. Navratilova, and F. Porreca, "Amygdala, Neuropeptides, and Chronic Pain-Related Affective Behaviors," *Neuropharmacology* 170 (2020): 108052.

48. L. J. Becker, C. Fillinger, R. Waegaert, et al., "The Basolateral Amygdala-Anterior Cingulate Pathway Contributes to Depression-Like Behaviors and Comorbidity With Chronic Pain Behaviors in Male Mice," *Nature Communications* 14, no. 1 (2023): 2198.

49. G. Misra and S. A. Coombes, "Neuroimaging Evidence of Motor Control and Pain Processing in the Human Midcingulate Cortex," *Cerebral Cortex* 25, no. 7 (2015): 1906–1919.

50. E. M. Aminoff, K. Kveraga, and M. Bar, "The Role of the Parahippocampal Cortex in Cognition," *Trends in Cognitive Sciences* 17, no. 8 (2013): 379–390.

51. I. Coskun Benlidayi, V. Deniz, C. Ornek, and A. Sariyildiz, "Diagnostic Utility of Deep Tendon Reflex Responses in Rectus Femoris and Triceps Brachii in Fibromyalgia: A Clinical and Electrophysiological Study," *Rheumatology International* 45, no. 3 (2025): 57.

52. T. Zetterman, R. Markkula, J. V. Partanen, T. Miettinen, A. M. Estlander, and E. Kalso, "Muscle Activity and Acute Stress in Fibromyalgia," *BMC Musculoskeletal Disorders* 22, no. 1 (2021): 183.

53. B. F. Jones and M. P. Witter, "Cingulate Cortex Projections to the Parahippocampal Region and Hippocampal Formation in the Rat," *Hippocampus* 17, no. 10 (2007): 957–976.

54. G. di Pellegrino, E. Ciaramelli, and E. Làdavas, "The Regulation of Cognitive Control Following Rostral Anterior Cingulate Cortex Lesion in Humans," *Journal of Cognitive Neuroscience* 19, no. 2 (2007): 275–286.

55. E. A. Woodcock, R. White, and V. A. Diwadkar, "The Dorsal Prefrontal and Dorsal Anterior Cingulate Cortices Exert Complementary Network Signatures During Encoding and Retrieval in Associative Memory," *Behavioural Brain Research* 290 (2015): 152–160.

56. H. Okon-Singer, T. Hendler, L. Pessoa, and A. J. Shackman, "The Neurobiology of Emotion-Cognition Interactions: Fundamental Questions and Strategies for Future Research," *Frontiers in Human Neuroscience* 9 (2015): 58.

57. E. Pazmany, H. G. Ly, L. Aerts, et al., "Brain Responses to Vestibular Pain and Its Anticipation in Women With Genito-Pelvic Pain/Penetration Disorder," *NeuroImage: Clinical* 16 (2017): 477–490.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Demographic and clinical characteristics of FM patients and healthy controls.

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CLINICAL IMAGE

SONK-Like Subchondral Osteonecrosis Associated With Immune Checkpoint Inhibition

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1 | Clinical Image Submission

1.1 | Mystery Summary

A 40-year-old woman with triple-negative breast cancer received combination immunotherapy with pembrolizumab, liposomal doxorubicin, and cyclophosphamide. During the third treatment cycle, she developed new-onset symmetrical polyarthritis involving both knees, shoulders, and elbows. An X-ray of the right knee showed only mild osteoarthritic changes (Figure 1A). However, magnetic resonance imaging (MRI) of the right knee revealed a focal lesion in the subchondral region of the medial femoral condyle and tibial plateau, with a characteristic double line sign on T2-weighted images (Figure 1B–D).

What is the most likely diagnosis in this patient without corticosteroid use, trauma, or autoimmune disease?

2 | Answer and Discussion

The MRI features were consistent with avascular necrosis, most likely representing spontaneous osteonecrosis of the knee (SONK)-like lesions. Although other potential causes such as steroid-induced osteonecrosis or metabolic risk factors were considered, these were ruled out based on the patient's history and laboratory data. While SONK is typically reported in elderly women and linked to mechanical overload or subchondral insufficiency fractures [1], this patient's presentation during immunotherapy raised the possibility of an immune-related vascular adverse event. Immune checkpoint inhibitors can promote endothelial inflammation by disrupting self-tolerance, leading to microvascular injury and local ischemia [2]. Notably, the MRI was obtained prior to corticosteroid therapy, which rapidly improved her polyarthritis. Similar vascular immune-related adverse events (irAEs) associated with immune checkpoint inhibitors have been previously reported in the literature [3, 4].

She had no known risk factors for osteonecrosis, including alcohol use, smoking, hyperlipidemia, or HIV infection [5]. This temporal relationship, together with the imaging findings, suggests a potential association between immune checkpoint inhibitor-induced endothelial dysfunction and localized ischemia in subchondral bone [3, 6, 7].

Conservative management was chosen, and no surgical intervention was required. Awareness of such bone-related immune adverse events is essential, particularly as immunotherapy becomes more common in oncology care. At six months follow-up, the patient's knee symptoms remained stable without progression on repeat imaging, and functional impact was minimal.

Author Contributions

Wan-Hao Tsai: data acquisition, image interpretation, and manuscript drafting. **Ko-Jen Li:** study conception, critical revision of the manuscript, and final approval. Both authors approved the final version and take responsibility for the integrity of the work.

Acknowledgments

The authors thank the patient for her consent to share this case, and the medical staff involved in her care.

Funding

The authors have nothing to report.

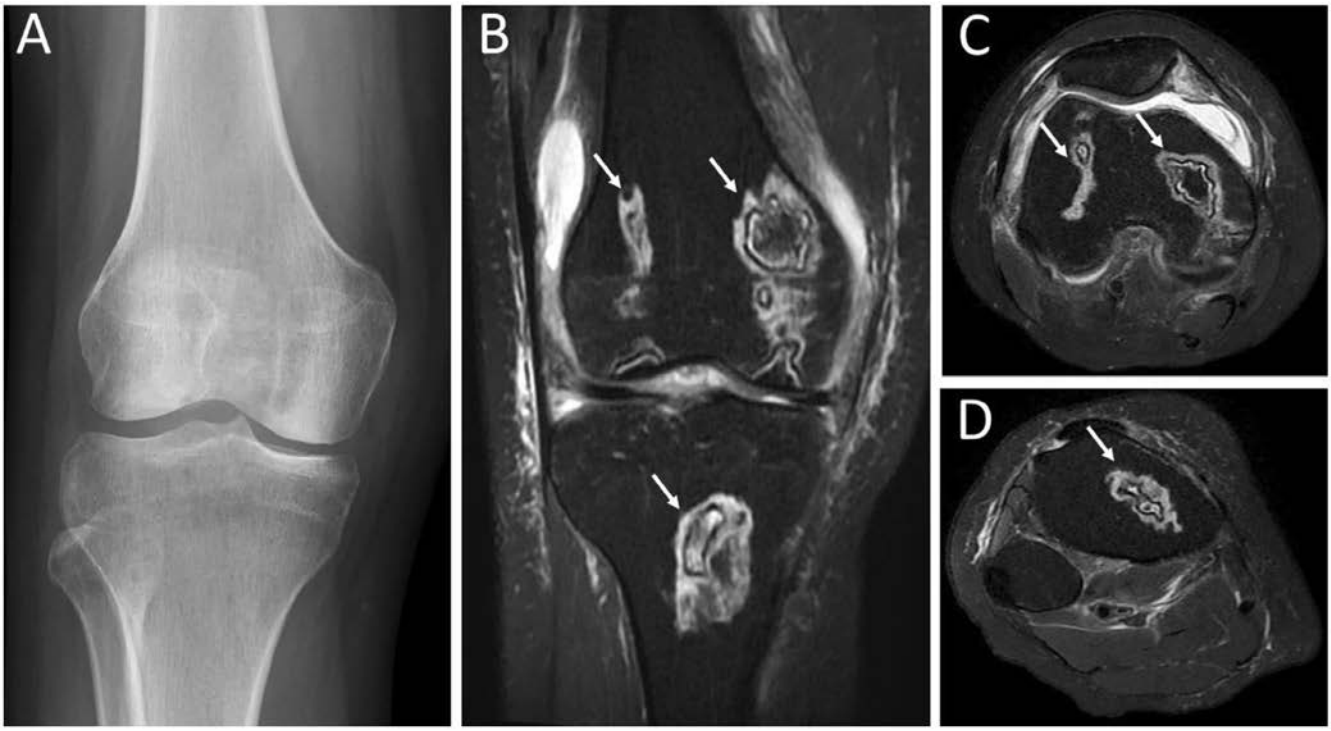

FIGURE 1 | Composite image showing (A) right knee X-ray with mild osteoarthritic changes, and (B–D) MRI T2-weighted images showing characteristic double line sign in the medial femoral condyle and tibial plateau (arrows).

Ethics Statement

Ethical approval was waived, as this is a single descriptive case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. D. B. Johnson, C. A. Nebhan, J. J. Moslehi, and J. M. Balko, "Immune-Checkpoint Inhibitors: Long-Term Implications of Toxicity," *Nature Reviews Clinical Oncology* 19, no. 4 (2022): 254–267, https://doi.org/10.1038/s41571-022-00600-w.

2. J. D. Terwoord, A. M. Beyer, and D. D. Gutterman, "Endothelial Dysfunction as a Complication of Anti-Cancer Therapy," *Pharmacology & Therapeutics* 237 (2022): 108116, https://doi.org/10.1016/j.pharmthera.2022.108116.

3. A. Daxini, K. Cronin, and A. G. Sreih, "Vasculitis Associated With Immune Checkpoint Inhibitors: A Systematic Review," *Clinical Rheumatology* 37, no. 9 (2018): 2579–2584, https://doi.org/10.1007/s10067-018-4192-7.

4. C. M. Lee, M. Wang, A. Rajkumar, C. Calabrese, and L. Calabrese, "A Scoping Review of Vasculitis as an Immune-Related Adverse Event From Checkpoint Inhibitor Therapy of Cancer: Unraveling the Complexities at the Intersection of Immunology and Vascular Pathology," *Seminars in Arthritis and Rheumatism* 66 (2024): 152440, https://doi.org/10.1016/j.semarthrit.2024.152440.

5. M. A. Mont, D. R. Marker, M. G. Zywiel, and J. A. Carrino, "Osteonecrosis of the Knee and Related Conditions," *Journal of the American Academy of Orthopaedic Surgeons* 19, no. 8 (2011): 482–494, https://doi.org/10.5435/00124635-201108000-00004.

6. F. Qureshi, M. M. Arani, S. Parvathareddy, et al., "Immune Checkpoint Inhibitor-Induced Multiorgan Vasculitis Successfully Treated With Rituximab," *Frontiers in Immunology* 14 (2023): 1171860, https://doi.org/10.3389/fimmu.2023.1171860.

7. C. Chang, A. Greenspan, and M. E. Gershwin, "The Pathogenesis, Diagnosis and Clinical Manifestations of Steroid-Induced Osteonecrosis," *Journal of Autoimmunity* 110 (2020): 102460, https://doi.org/10.1016/j.jaut.2020.102460.

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CLINICAL IMAGE

Beyond the Surface: The Dual Challenge of Dysphagia and Acrokeratosis

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A 49 year old female presented with 1 month history of dysphagia and proximal muscle weakness in both upper and lower limbs. She had a year-long history of Raynaud's phenomena, inflammatory polyarthritis, and fissuring with crusting of hands and feet. Dysphagia progressively worsened to such an extent that she was unable to swallow saliva. Examination

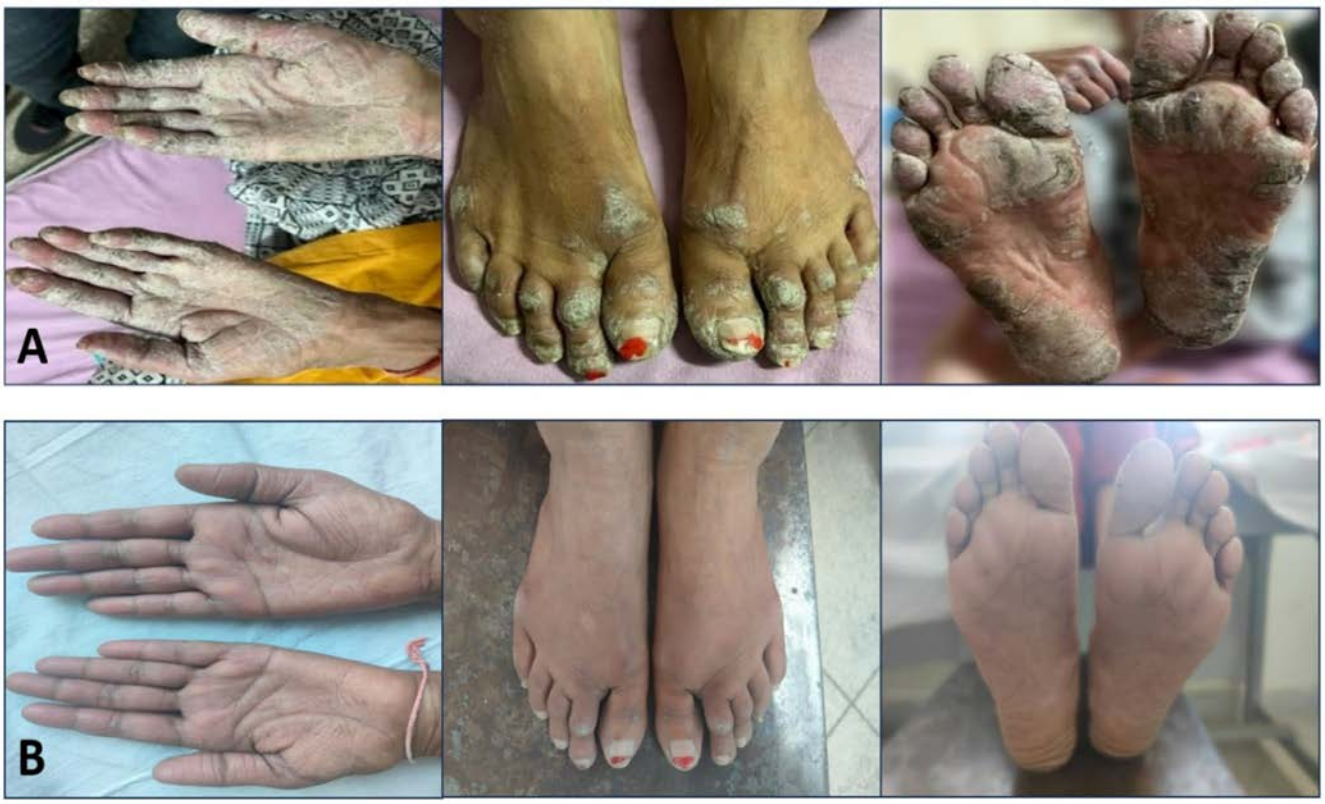

FIGURE 1 | Mechanic's hands and hiker's feet before (A) and after (B) treatment.

revealed knee synovitis, bibasilar velcro crepitations, depressed gag reflex, and mild proximal limb weakness (power 4/5). Hyperkeratotic white lesions with fissuring were noted on hands and feet (Figure 1A).

A clinical diagnosis of antisynthetase syndrome with mechanic's hands and hiker's feet was considered. Esophageal carcinoma with paraneoplastic tylosis palmaris at plantaris was a differential diagnosis. Labs revealed raised transaminases (AST>ALT: 91 > 49 U/L) with normal serum bilirubin and alkaline phosphatase, elevated muscle enzymes (CK NAC: 1410 U/L, LDH: 690 U/L), and positive ANA (1:100, nucleolar pattern). Myositis blot was positive for Mi-2α and PM-Scl antibodies. Skin biopsy showed morphological features of lichenoid dermatitis. Work-up for malignancy was negative, including whole-body PET scan and gastroduodenoscopy. HRCT thorax showed usual interstitial pneumonia pattern, with no functional impairment noted on pulmonary function test.

The patient was diagnosed with anti-Mi2 positive dermatomyositis overlapping with antisynthetase syndrome and treated with 500 mg intravenous methylprednisolone for 3 days followed by 1 mg/kg oral prednisolone. Cyclophosphamide was given as a steroid-sparing agent in a dose of 15 mg/kg monthly for 6 months. Ryle's tube feeding was used initially but removed as swallowing improved over 3 months. Limb weakness and skin lesions also resolved (Figure 1B).

Dysphagia may be the prominent symptom in antisynthetase syndrome [1]. Antisynthetase syndrome can present with atypical cutaneous features, including widespread mechanic's hands as in this case [2].

Author Contributions

J.D., D.M. managed the case and wrote the manuscript; G.N., V.D., S.S. are involved in the decision making; A.S., S.J. are involved in the final review of the manuscript. D.M. Trainee.

Consent

Written consent has been taken from the patient for publication.

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.

References

1. B. Labeit, M. Pawlitzki, T. Ruck, et al., "The Impact of Dysphagia in Myositis: A Systematic Review and Meta-Analysis," *Journal of Clinical Medicine* 9, no. 7 (2020): 2150.

2. K. Shinoda, Y. Hamaguchi, and K. Tobe, "Widespread Mechanic's Hands in Antisynthetase Syndrome With Anti-OJ Antibody," *Journal of Rheumatology* 48, no. 8 (2021): 1341.

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CLINICAL IMAGE

Flagellate Erythema: An Indicator of Underlying Malignancy in Dermatomyositis

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A 63-year-old Chinese man presented with a two-month history of pruritic truncal rash, facial erythema, and swelling. Examination revealed multiple linear erythematous plaques over the upper back and shoulders, consistent with flagellate erythema (Figure 1C). Additional clinical findings included macular facial erythema, shawl sign (Figure 1A) and Gottron's papules (Figure 1B).

Initial investigations revealed a creatine kinase of 1082 U/L (reference range 55-170 U/L for men), positive anti-nuclear

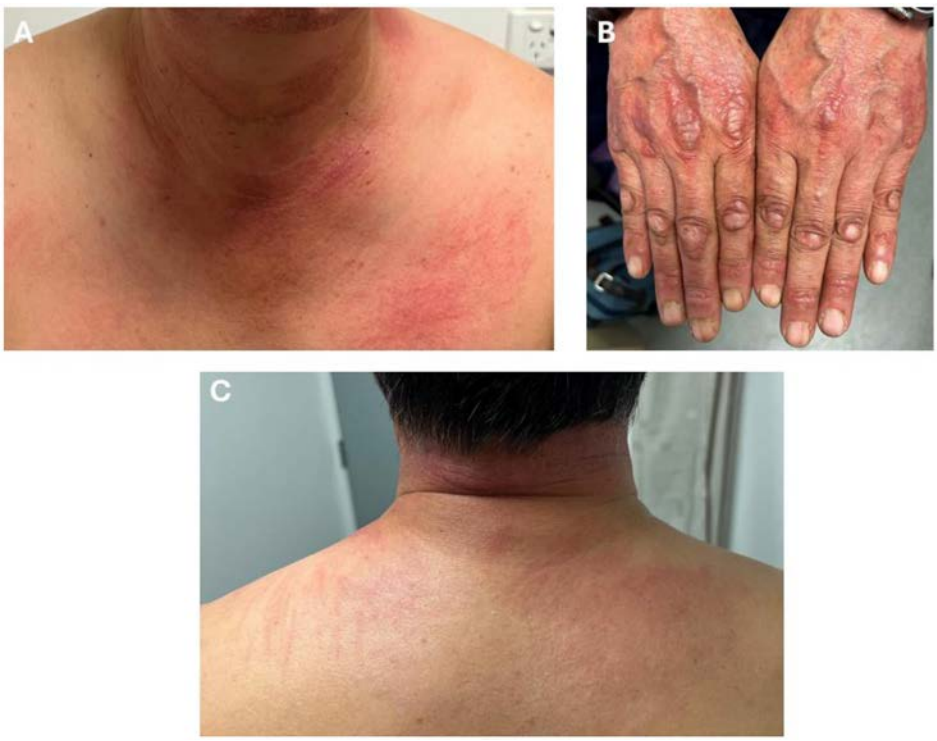

FIGURE 1 | Clinical photos. (A) Shawl sign. (B) Gottron's papules. (C) Flagellate erythema.

antibody at a titre of 1:640 with speckled pattern, and positive anti-transcriptions intermediary Factor 1 gamma (TIF1γ) autoantibodies, consistent with a myopathic dermatomyositis (DM). Subsequent imaging and surgical pathology confirmed a gallbladder adenocarcinoma. The patient was diagnosed with anti-TIF1γ positive DM associated with a malignancy. Despite cholecystectomy and adjuvant chemotherapy, the patient had persistent cutaneous disease recalcitrant to monthly intravenous immunoglobulin 85 mg for 10 months in combination with oral prednisolone (5-50 mg daily) and hydroxychloroquine 200 mg twice daily. Ongoing persistent facial erythema, heliotrope rash, Gottron's papules, and swelling were noted. A restaging CT scan revealed new pulmonary and hepatic metastases. He was diagnosed with unresectable metastatic gallbladder adenocarcinoma and commenced on palliative cisplatin/gemcitabine treatment.

Flagellate erythema is an easily recognizable but uncommon dermatologic sign observed in a subset of dermatomyositis (DM) patients. It is estimated to be present in 5% of DM patients [1], and may be an indicator of underlying malignancy [2, 3]. When present, flagellate erythema should raise clinical suspicion for DM and careful evaluation for associated malignancy, particularly in adult-onset cases. Likewise, anti-TIF1γ antibodies in adult DM are strongly associated with solid-organ malignancies, especially gastrointestinal and gynecological cancers [4], and frequently coincide with flagellate erythema [5]. A positive result should prompt immediate suspicion of paraneoplastic dermatomyositis. Careful physical examination and autoantibody testing are crucial for risk stratification and management of dermatomyositis patients.

Author Contributions

Hieu Chi Ha: investigation, writing – original draft, writing – review and editing, visualization. **On Bon Louis Chan:** conceptualisation, investigation, writing – review and editing, supervision. **Anousha Yazdabadi:** conceptualisation, writing – review and editing, supervision. **Christopher Meng Kit Fong:** conceptualisation, writing – review and editing, supervision.

Consent

Informed patient consent was obtained from the patient in line with Eastern Health Office of Research and Ethics guidelines.

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.

References

1. A. Parodi, M. Caproni, A. Marzano, et al., "Dermatomyositis in 132 Patients With Different Clinical Subtypes: Cutaneous Signs, Constitutional Symptoms and Circulating Antibodies," *Acta Dermato-Venereologica* 82, no. 1 (2002): 48–51.

2. D. z. Eichenfield and T. Paravar, "Zebra Stripes in Dermatomyositis: Case Report and Review of Flagellate Erythema-Associated Dermatomyositis," *Journal of the European Academy of Dermatology and Venereology* 31, no. 1 (2017): e7–e9.

3. V. Maione, C. Cozzi, and P. Calzavara-Pinton, "Flagellate Erythema as Sign of Paraneoplastic Dermatomyositis," *Rheumatology* 60, no. 4 (2021): 2009.

4. M. Marzęcka, A. Niemczyk, and L. Rudnicka, "Autoantibody Markers of Increased Risk of Malignancy in Patients With Dermatomyositis," *Clinical Reviews in Allergy & Immunology* 63, no. 2 (2022): 289–296.

5. T. Gono and M. Kuwana, "Current Understanding and Recent Advances in Myositis-Specific and -Associated Autoantibodies Detected in Patients With Dermatomyositis," *Expert Review of Clinical Immunology* 16, no. 1 (2020): 79–89.

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EDITORIAL

Reframing Osteoarthritis Therapy Through the Gut–GUDCA–FXR–GLP1 Pathway: Opportunities and Limitations

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1 | Introduction

Recent advances in immunometabolism and rheumatology have highlighted the role of gut-derived signals in modulating joint health. In particular, Yang et al. proposed that osteoarthritis (OA) may be influenced by intestinal bile acid metabolism through a mechanistic cascade involving the gut microbiota, Glycoursodeoxycholic acid (GUDCA), intestinal Farnesoid X receptor (FXR), and Glucagon-like peptide 1 (GLP-1) signaling. This emerging gut-to-joint communication axis invites new thinking about the pathogenesis and treatment of rheumatic diseases.

2 | Interplay Between Microbiota and Bile Acid Signaling

The gut microbiome plays a crucial role in regulating systemic immunity and metabolism, primarily through its modulation of the bile acid (BA) pool. It influences the composition and transformation of both primary and secondary bile acids. This process was previously thought to occur only in the liver, but recent studies have shown that gut bacteria also perform these transformations, increasing the diversity of bile acids [1–3]. Secondary bile acids play crucial roles in modulating immune cell function and differentiation, impacting systemic immunity [4]. Recent findings further suggest that bile acids act as immunoregulatory signals in the gut environment, shaping both innate and adaptive immune responses by promoting regulatory T cell differentiation and suppressing pro-inflammatory T helper cell development [5].

3 | GUDCA: An Intestinal FXR Antagonist

GUDCA is a conjugated bile acid formed by the glycine-conjugation of the secondary bile acid ursodeoxycholic acid (UDCA). FXR, a nuclear receptor expressed in the liver and intestine, plays a vital role in regulating bile acid homeostasis, lipid metabolism, and intestinal barrier function. When antagonized by GUDCA in the ileum, FXR activity is reduced, resulting in upregulation of pro-secretory hormones such as Glucagon-like peptide-1 (GLP-1) from enteroendocrine L-cells [1]. Yan et al. explored this feedback and found that GUDCA-induced inhibition of intestinal FXR significantly boosted GLP-1 levels and improved gut barrier function and glucose metabolism in diabetic mouse models [6].

4 | GLP-1: Beyond Glycemic Control

GLP-1, predominantly released by intestinal L-cells upon food consumption, while primarily known for its insulinotropic effects, also exerts anti-inflammatory and neuroprotective functions. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of therapeutic agents commonly prescribed for managing type 2 diabetes (T2D). Examples include exenatide, liraglutide, and semaglutide. These drugs exert their effects by imitating the activity of the naturally produced hormone GLP-1 [7]. Recent studies suggest that GLP-1RA may reduce joint inflammation through modulation of local immune responses [8, 9]. Yang et al. showed that targeting the gut-joint axis through FXR inhibition and GLP-1 modulation in osteoarthritis models led to pain

reduction and improved joint pathology, hinting at the therapeutic scope of GLP-1 in rheumatic diseases [10].

5 | The Gut–Joint Axis in Rheumatology

The gut–joint axis refers to the immunometabolic connection whereby gut dysbiosis increases intestinal permeability, allowing microbial metabolites like lipopolysaccharide to enter circulation. This triggers systemic inflammation via Th1 and Th17 cells, ultimately contributing to joint damage in OA [11, 12]. The vagus nerve may mediate communication between the gut and joints, influencing inflammation and pain perception in OA [13]. Understanding these mechanisms supports the gut as a therapeutic target in rheumatology.

6 | Clinical Relevance and Therapeutic Translation

The gut–GUDCA–FXR–GLP-1 axis offers novel therapeutic strategies for OA. Probiotics like *Lactobacillus acidophilus* improve gut microbiota composition, reducing joint inflammation and symptoms [11]. Bile acids such as GUDCA modulate NF-κB signaling, a key inflammatory pathway [14]. GLP-1 receptor agonists like liraglutide have demonstrated analgesic and cartilage-protective effects in OA models [8]. Recent evidence suggests that targeting intestinal FXR and enhancing GLP-1 signaling can prevent cartilage degradation [15]. While imeglimin, a mitochondrial modulator, does not directly link to OA, its metabolic effects may influence systemic inflammation [16]. The key components and therapeutic implications of the gut–GUDCA–FXR–GLP-1 pathway in osteoarthritis are summarized in Table 1.

7 | Key Challenges and Future Directions

Despite the promising connections, there remain knowledge gaps. The specific microbial strains responsible for GUDCA synthesis, the extent of FXR's role in joint immunity, and the potential systemic effects of long-term FXR inhibition must be carefully assessed.

Moreover, patient heterogeneity in microbiota composition presents challenges in universalizing microbiota-modulating interventions. Stratified approaches based on individual gut microbial signatures may be required.

8 | Conclusion

The gut–GUDCA–FXR–GLP1 signaling axis represents a compelling model that bridges gastrointestinal and rheumatologic systems. While the concept introduces new

TABLE 1 | Key Components and Functions of the Gut–GUDCA–FXR–GLP1 Axis in Osteoarthritis.

Component	Physiological Function	Relevance to OA	Supporting Reference
Gut Microbiota	Regulates bile acid metabolism and systemic immunity	Regulates bile acid metabolism and systemic immunity	Su, L., Zhang, M., Liu, Q., et al. (2023). Gut microbiota-derived bile acid metabolites maintain the homeostasis of gut and systemic immunity. Nature Communications, 14, 1234.
GUDCA	Antagonizes intestinal FXR; enhances GLP-1 secretion	Antagonizes intestinal FXR; enhances GLP-1 secretion	Y. Yan, Y., Chen, X., Xu, Y., et al. (2022). The water extract of Radix scutellariae and its active flavonoids inhibit CYP7A1 expression and improve bile acid and glycolipid metabolism in T2DM mice. Phytomedicine, 99, 154007. Yang, Y., Zhou, M., Li, T., et al. (2025). Osteoarthritis treatment via the GLP-1–mediated gut–joint axis targets intestinal FXR signaling. Cell Metabolism, 37(2), 155–172.
FXR	Regulates intestinal stem cell (ISC) proliferation and controls L cell and GLP-1 production	Regulates intestinal stem cell (ISC) proliferation and controls L cell and GLP-1 production	Yang, Y., Zhou, M., Li, T., et al. (2025). Osteoarthritis treatment via the GLP-1–mediated gut–joint axis targets intestinal FXR signaling. Cell Metabolism, 37(2), 155–172.
GLP-1	Regulates glucose homeostasis, suppresses inflammation via NF-κB, AMPK, and immune modulation	Regulates glucose homeostasis, suppresses inflammation via NF-κB, AMPK, and immune modulation	Alharbi, S. H. (2024). Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. Therapeutic Advances in Endocrinology and Metabolism, 15, 20420188231222367.
GLP-1 Receptor	Mediates GLP-1's action on immune modulation and metabolism	Mediates GLP-1's action on immune modulation and metabolism	Meurot, C., Martin, C., Sudre, L., et al. (2022). Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. Scientific Reports, 12, 1567.

therapeutic directions, several mechanistic questions and translational hurdles must be addressed before clinical application. Encouragingly, ongoing research and drug repurposing strategies—such as the use of UDCA or GLP1 receptor agonists—may accelerate this process. Ultimately, this axis exemplifies how metabolic and immune cross-talk can inform the future of precision rheumatology.

Author Contributions

Shangqi Guan: Conceptualization, Literature Review, Writing – Original Draft Preparation. Yifang Mei: Supervision, Writing – Review and Editing, Correspondence, and Manuscript Revision. All authors have 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

Research data are not shared.

References

1. Y. Li, L. Wang, Q. Yi, L. Luo, and Y. Xiong, "Regulation of Bile Acids and Their Receptor FXR in Metabolic Diseases," *Frontiers in Nutrition* 11 (2024): 1447878, https://doi.org/10.3389/fnut.2024.1447878.

2. Q. Zhao, J. Wu, Y. Ding, Y. Pang, and C. Jiang, "Gut Microbiota, Immunity, and Bile Acid Metabolism: Decoding Metabolic Disease Interactions," *Life Metabolism* 2, no. 6 (2023): load032, https://doi.org/10.1093/lifemeta/load032.

3. D. V. Guzior and R. A. Quinn, "Review: Microbial Transformations of Human Bile Acids," *Microbiome* 9, no. 1 (2021): 140, https://doi.org/10.1186/s40168-021-01101-1.

4. X. Su, Y. Gao, and R. Yang, "Gut Microbiota Derived Bile Acid Metabolites Maintain the Homeostasis of Gut and Systemic Immunity," *Frontiers in Immunology* 12, no. 5 (2023): 793, https://doi.org/10.3390/cells12050793.

5. A. D. Mohammed, R. A. W. Ball, and J. L. Kubinak, "The Interplay Between Bile Acids and Mucosal Adaptive Immunity," *PLoS Pathogens* 19, no. 6 (2023): e1011356, https://doi.org/10.1371/journal.ppat.1011356.

6. X. Yan, Y. Zhang, Y. Peng, and X. Li, "The Water Extract of Radix Scutellariae, Its Total Flavonoids and Baicalin Inhibited CYP7A1 Expression, Improved Bile Acid, and Glycolipid Metabolism in T2DM Mice," *Journal of Ethnopharmacology* 293 (2022): 115238, https://doi.org/10.1016/j.jep.2022.115238.

7. S. H. Alharbi, "Anti-Inflammatory Role of Glucagon-Like Peptide 1 Receptor Agonists and Its Clinical Implications," *Therapeutic Advances in Endocrinology and Metabolism* 15 (2024): 20420188231222367, https://doi.org/10.1177/20420188231222367.

8. C. Meurot, C. Martin, L. Sudre, et al., "Liraglutide, a Glucagon-Like Peptide 1 Receptor Agonist, Exerts Analgesic, Anti-Inflammatory and Anti-Degradative Actions in Osteoarthritis," *Scientific Reports* 12, no. 1 (2022): 1567, https://doi.org/10.1038/s41598-022-05323-7.

9. C. Meurot, C. Jacques, C. Martin, et al., "Targeting the GLP-1/GLP-1R Axis to Treat Osteoarthritis: A New Opportunity?," *Journal of Orthopaedic Translation* 32 (2022): 121–129, https://doi.org/10.1016/j.jot.2022.02.001.

10. Y. Yang, C. Hao, T. Jiao, et al., "Osteoarthritis Treatment via the GLP-1–Mediated Gut-Joint Axis Targets Intestinal FXR Signaling," *Science* 388, no. 6675 (2025): eadt0548, https://doi.org/10.1126/science.adt0548.

11. B. Gleason, E. Chisari, and J. Parvizi, "Osteoarthritis Can Also Start in the Gut: The Gut–Joint Axis," *Indian Journal of Orthopaedics* 56, no. 7 (2022): 1150–1155, https://doi.org/10.1007/s43465-021-00473-8.

12. L. Marchese, D. Contartese, G. Giavaresi, L. Di Sarno, and F. Salamanna, "The Complex Interplay Between the Gut Microbiome and Osteoarthritis: A Systematic Review on Potential Correlations and Therapeutic Approaches," *International Journal of Molecular Sciences* 25, no. 1 (2023): 143, https://doi.org/10.3390/ijms25010143.

13. D. Yang, Y. Chen, J. Guo, et al., "The Organ-Joint Axes in Osteoarthritis: Significant Pathogenesis and Therapeutic Targets," *Aging and Disease* 16, no. 5 (2024): 2999–3021, https://doi.org/10.14336/AD.2024.1223.

14. J. Sheng, Z. Yi, S. S. He, et al., "Cholic Acid Mitigates Osteoarthritis by Inhibiting the NF-κB/PERK/SIRT1 Signaling Pathway," *Biocell* 48, no. 7 (2024): 1095–1104, https://doi.org/10.32604/biocell.2024.028421.

15. C. J. Liu, "Beyond Wear and Tear at the Joint," *Science* 388, no. 6742 (2025): 30–31, https://doi.org/10.1126/science.adw4656.

16. S. Hallakou-Bozec, M. Kergoat, D. E. Moller, et al., "Imeglimin Amplifies Glucose-Stimulated Insulin Release From Diabetic Islets via a Mitochondrial Mechanism," *Cell Reports* 16, no. 2 (2021): e0241651, https://doi.org/10.1371/journal.pone.0241651.

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LETTER TO THE EDITOR

Painted Butterfly Rash: The Red Queen Effect in a Rembrandt Portrait

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Dear Editor,

This letter invites you to embark on a journey from the complex autoimmune disease of medicine to the representation of a woman in Rembrandt's painting. As in Alice's never-ending race with the Red Queen, the body affected by lupus is engaged in an internal race. The Red Queen Effect is a metaphor for the endless, exhausting battle that the immune system wages against its own tissues. The malar rash, which appears on the face in the form of a butterfly, features in Rembrandt's painting not only as a medical finding, but also as a reflection of the fragility and beauty of the woman's face, which has been hidden in art history.

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease with a relapsing and remitting course. It is multifactorial, and involving epigenetic, genetic, ecological, and environmental factors. Exposure to environmental factors such as UVB radiation, infections, and toxins can trigger a loss of immune tolerance in genetically susceptible individuals and leads to aberrant activation of autoimmunity. SLE is one of the most gender-specific autoimmune diseases. It is more prevalent in women aged 15–44 years. Studies have shown an increased risk of SLE associated with exposure to estrogen, whereas progesterone and testosterone play a protective role by counteracting its effects. Adults diagnosed before the age of 50 typically present with cutaneous symptoms such as a malar rash and lupus nephritis. The butterfly rash, also known as the malar rash, is a pathognomonic feature of acute cutaneous lupus erythematosus. It involves sun-exposed areas such as the cheeks and nasal bridge [1]. Alopecia is a less specific cutaneous feature of SLE. It typically affects the temporal regions, resulting in a patchy pattern of hair loss [2].

The term *lupus* comes from the Latin for *wolf*. There are two ideas about the origin of this name: one is that the rash resembles a wolf bite, and the other is that the rash seems to gnaw away at the flesh of the victim. The history of lupus dates to at least the 4th century BC, when Hippocrates recorded the first known documented case. Although the term *lupus* was first used to describe an ulcerative skin disease, it was not until the mid-nineteenth century that two specific skin diseases were classified as lupus erythematosus and lupus vulgaris. The term *lupus* may derive from the disease's rapacity and virulence; a work from 1590 described it as a malignant ulcer quickly consuming the nether parts; very hungry, like unto a wolf [3]. The butterfly rash or malar rash has been depicted in various paintings in art history [4–8]. da Mota et al. reported that Adele, the subject of Gustav Klimt's most famous painting, had facial erythema, which, if not artificially created with make-up, could represent a malar rash [4]. Ashrafian reported that Catherine of Aragon, the first wife of Henry VIII and Queen of England, had a malar rash, visible in a miniature portrait. While Catherine's portraits reveal red cheeks, which could easily have been the result of make-up, some images portray red cheeks and a red nose, suggesting the possibility of an underlying butterfly rash [5]. Ashrafian also reported that Botticelli's painting depicts a butterfly rash. Considered one of the world's greatest masterpieces, 'Primavera' (or 'Spring') was painted by Sandro Botticelli. The authors noted that the figure of Flora (or Spring) in the painting exhibits clear signs of a goiter, including bilateral ptosis and facial flushing consistent with a 'butterfly' malar rash, as well as the possibility of periorbital heliotrope rash, which is more prominent around the right eye. These features likely derive from the observations made on one of the models used by Botticelli when painting the piece [6]. Hayakawa et al. identified

a butterfly rash and digital deformities in Maria Bockenolle, the subject of a Rembrandt portrait [7]. They concluded that these were due to an overlap syndrome of rheumatoid arthritis and SLE. However, the authors also reported that, without additional information regarding Maria Bockenolle's clinical and physical signs and symptoms, as well as laboratory data, a definitive diagnosis could not be made. Nevertheless, a careful examination of representative paintings, such as those by 17th-century Dutch masters, combined with recent clinical and immunological findings, suggests the presence of an overlapping syndrome. This approach could be valuable for reconstructing the history of rheumatic disorders [7]. Marson et al. reported the presence of a typical malar rash on the face of a child in *Le Bénédicité* (Hermitage, St Petersburg), a painting by Jean-Baptiste Siméon Chardin (1699–1779), widely regarded as one of the greatest French painters of the 18th century [8].

Rembrandt Harmenszoon van Rijn (1606–1669), usually known as Rembrandt, is widely regarded as the greatest artist the Netherlands has ever produced [9]. Rembrandt produced more self-portraits and portraits than any other major artist in history. According to art historians, he aimed to master facial expressions and develop the tradition of the great painters who preceded him [10]. Figure 1 depicts a woman against a plain, dark background. The painting is rendered in a realistic and simple style. She is wearing a modest black dress with a high ruff collar, which was typical of 17th-century Dutch clothing. As with many of Rembrandt's portraits from the 1630s, the identity of the woman in this painting is unknown. As no additional information about the woman in the portrait is available, the assessment was based solely on visual observation. The butterfly rash is a characteristic dermatological finding in SLE. This rash appears as erythema in the shape of a butterfly, spreading across the cheeks and the nasal bridge. It is often triggered by sun exposure and may appear weeks or even months before a formal SLE diagnosis is made. Upon close inspection of the painting, it is evident that the woman is middle-aged and exhibits a malar rash. Another feature suggestive of SLE that can be identified in the portrait is frontal alopecia.

FIGURE 1 | Portrait of a Woman, Rembrandt van Rijn, 1633, oil on wood, 67.9×50.2cm, Object Number: 14.40.625, The Metropolitan Museum of Art, New York, https://www.metmuseum.org/art/collection/search/437390.

Artistic representations are often more related to the artist's personal inspiration, but sometimes notable diseases have become the subject of representation [11]. There is a strong link between art and medicine. Iconodiagnosis is the medical analysis of artworks in search of clinical signs indicative of medical disorders and diseases. The concept was first introduced in 1983 by the neuropsychiatrist Anneliese Pontius during her research into Crouzon's malformation in prehistoric art from the Cook Islands. The use of iconodiagnosis in medical education is an alternative and stimulating way to train students' observational skills, not only in the physical examination of the patient, but also in the information gathered from their posture, clothing, general demeanor and even their physical aids [12]. In addition to its educational value for medical studies, iconodiagnosis can provide a better understanding of the natural evolution of diseases, their social perception and their impact on history itself [13]. By carefully studying these paintings, healthcare professionals and medical students can combine artistic observation with clinical knowledge to identify and interpret visual indicators of diseases. This method improves interdisciplinary thinking and cultural sensitivity, as well as visual diagnostic skills.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in The Metropolitan Museum of Art's online collection database at: https://www.metmuseum.org/art/collection/search/437390. The specific image analyzed is in the public domain and accessible to all users.

Hulya Elbe

References

1. M. A. Ameer, H. Chaudhry, J. Mushtaq, et al., "An Overview of Systemic Lupus Erythematosus (SLE) Pathogenesis, Classification, and Management," *Cureus* 14, no. 10 (2022): e30330.

2. M. Cojocaru, I. M. Cojocaru, I. Silosi, and C. D. Vrabie, "Manifestations of Systemic Lupus Erythematosus," *Maedica* 6, no. 4 (2011): 330–336.

3. R. A. Norman, "The History of Lupus Erythematosus and Discoid Lupus: From Hippocrates to the Present," *Lupus Open Access* 1 (2016): 102.

4. L. M. da Mota, F. Neubarth, J. F. de Carvalho, et al., "Adele Bloch–Bauer (1881–1925): Possible Diagnoses for Gustav Klimt's Lady in Gold," *Journal of Medical Biography* 24 (2016): 389–396.

5. H. Ashrafian, "Catherine of Aragon (1485–1536): The Red Malar Rash of Familial SLE in a Tudor Red Rose Queen," *Rheumatology International* 35 (2015): 1949–1950.

6. H. Ashrafian, "Differential Diagnosis of a Thyroid Mass, Facial Malar Rash and Ptosis on the Flora in the Primavera by Sandro Botticelli (1445-1510)," *Journal of Endocrinological Investigation* 45, no. 3 (2022): 687–689.

7. S. Hayakawa, S. Komine-Aizawa, S. Osaka, et al., "Rembrandt's Maria Bockenolle Has a Butterfly Rash and Digital Deformities: Overlapping Syndrome of Rheumatoid Arthritis and Systemic Lupus Erythematosus," *Medical Hypotheses* 68 (2007): 906–909.

8. P. Marson, R. Rondinone, and M. Vicarioto, "Malar Rash in a Painting by Jean-Baptiste Siméon Chardin (1699–1779)," *Reumatismo* 53, no. 2 (2001): 175–179.

9. G. M. Weisz and W. R. Albury, "Diseases of Old Age in Two Paintings by Rembrandt," *Rambam Maimonides Medical Journal* 6, no. 4 (2015): e0042.

10. A. Rothenberg, "Depression, Physical Illness, and the Faces of Rembrandt," *Lancet* 354, no. 9187 (1999): 1392.

11. P. Charlier and P. D. Deps, "Possible New Evidence of Pre-Columbian Tuberculosis in America: Pott Disease in a Prehistoric Mexican Statue," *Tuberculosis (Edinburgh, Scotland)* 116 (2019): 35–36, https://doi.org/10.1016/j.tube.2019.03.011.

12. B. Lefrère, R. Libé, and L. Groussin, "Artistic Movements as Pitfalls in Iconodiagnosis," *Annales d'Endocrinologie* 85, no. 2 (2024): 163–165, https://doi.org/10.1016/j.ando.2023.12.002.

13. P. Charlier, A. Perciaccantec, N. Kluger, et al., "Iconodiagnosis: Guidelines and Recommendations," *Ethics, Medicine and Public Health* 31 (2023): 100951, https://doi.org/10.1016/j.jemep.2023.100951.

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LETTER TO THE EDITOR

Toll-Like Receptor 3 Activation in Lupus Nephritis: A Renal Signature Supporting "Pseudoviral" Immunity

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Dear Editor,

Damage-associated molecular patterns (DAMPs) and postulated viral pathogens contribute to the pathogenesis of systemic lupus erythematosus (SLE) and lupus nephritis (LN) [1]. Given that DAMPs, which include self-derived nucleic acids, are initially recognized by Toll-like receptors (TLRs), TLRs signaling is thought to play a role in the development of SLE and LN lesions [1, 2]. Among TLRs, TLR7 and 9 are primarily thought to be involved in the pathogenesis of LN [1, 2]. However, overexpression of glomerular TLR3, an endosomal sensor for viral dsRNA, has also been observed in biopsy specimens of patients with LN, correlating with clinicopathological indices [3]. Previously, a unique concept of self-nucleic acid-driven "pseudoviral" immunity that focuses on the implication of TLRs signaling was proposed as another concept in understanding the pathogenesis of LN [4]. While this hypothesis remains attractive, it requires further validation. We have studied the implication of TLR3 signaling in the pathogenesis of LN using cultured human glomerular intrinsic cells and renal biopsy specimens to date [5–8]. We identified a marked renal signature characterized by TLR3-dependent, but not TLR7- or TLR9-dependent, induction of interferon-stimulated genes (ISGs), which are type I IFN-dependent transcripts, in LN lesions [6–8]. These findings support the relevance of a concept of "pseudoviral" immunity in the pathogenesis of LN. Further, our findings may add possible implication of TLR3 signaling, except for TLR7 and 9 signaling in the pathogenesis of LN [3, 5].

Considering the implications of TLR3 signaling cascade in the pathogenesis of LN, we treated cultured human glomerular endothelial cells (GECs) with polyinosinic-polycytidylic acid (poly IC), a synthesized TLR3 agonist that elicits "pseudoviral" infection and assessed the expressions of representative ISGs, including IFN-induced transmembrane protein 1 (IFITM1), DExD/H-Box Helicase 60 (DDX60), and ISG20 [6–8]. Except for their antiviral roles, expression of these ISGs in immune cells has been recognized as a signature of type I IFN activation [9]. Based on our previous experiments using GECs, we observed that endothelial TLR3 activation induced de novo expression of IFITM1, DDX60, and ISG20 in GECs [6–8]. It is noteworthy, in contrast to poly IC (a TLR3 agonist), stimulation with R848 (a TLR7 agonist) or CpG (a TLR9 agonist) did not induce comparable ISG expression [7, 8], suggesting that these ISG responses are specific to TLR3 signaling in this cell type. Furthermore, we detected intense endothelial immunoreactivity for these ISGs in biopsy specimens from five patients with endothelial proliferative LN, whereas only weak and scattered expression was observed in specimens from six patients with non-endothelial proliferative LN, or four patients with diffuse mesangial proliferative IgA nephropathy [6–8]. Representative figures are shown in Figure 1.

Given previous reports that dysregulated type I IFN activation contributes to the pathogenesis of LN [1], the presence of a renal signature of TLR3-dependent ISGs in patients with LN suggests that TLR3 activation plays a significant role in the development of LN. Additionally, we demonstrated that pretreatment of glomerular cells with chloroquine attenuated poly IC-induced TLR3 signaling cascade in the early phase activation phase [10],

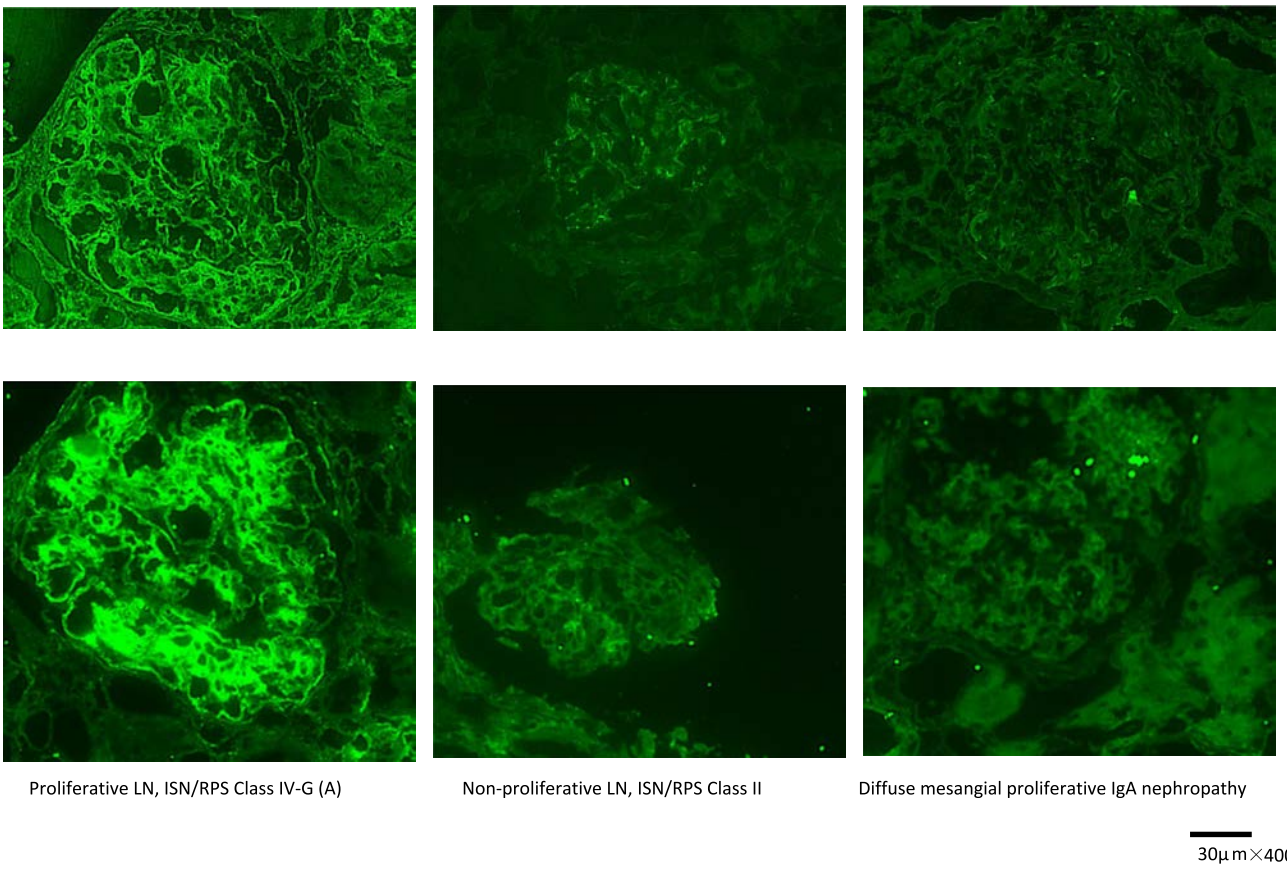

FIGURE 1 | Immunofluorescence staining of ISGs (upper panel, IFITM1; lower panel, DDX60) in renal biopsy specimens obtained from patients with endothelial proliferative LN (right), non-endothelial proliferative LN (middle), and diffuse mesangial proliferative IgA nephropathy (left). Snap-frozen sections stored at −80°C in good condition, from patients with diffuse endothelial proliferative LN [Class IV-G (A) in accordance with the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification for LN], non-endothelial proliferative LN (Class II in accordance with the ISN/RPS 2003 classification for LN), and diffuse mesangial proliferative IgA nephropathy were stained for ISGs (5 patients with Class IV-G (A), 6 with Class II, and 4 with mesangial proliferative IgA nephropathy, respectively). Anti-rabbit eligible ISG antibody (GeneTex, Irvine, CA, USA) was added at a dilution of 1:200. After incubation for 40 min, at room temperature and several washes with PBS, the slides were sequentially incubated with fluorescein isothiocyanate-conjugated secondary antibodies at a dilution of 1:20 for 40 min at room temperature. A significant increase in IFITM1 and DDX60 immunoreactivities was observed in proliferative LN specimens, whereas immunoreactivity was weak in the other specimens (×400 magnification).

further supporting the regional renoprotective effects of antimalarial agents in LN treatment. In conclusion, the presence of a renal signature of TLR3-dependent ISGs reinforces the relevance of a concept of "pseudoviral" immunity including possible implications of TLR3 activation in the pathogenesis of LN. Elucidating the specific mechanisms of glomerular TLR3 signaling may provide insights into the development of novel therapeutic strategies for LN.

Author Contributions

H.T. and T.I. designed the study; H.T., S.W., and T.I. performed the experiments; H.T. wrote the manuscript; and M.E. gave conceptual advice. K.J. performed immunostaining for ISGs in renal biopsy specimens.

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Ethics Statement

This article does not contain any studies with human participants or animals except for immunohistologic study using renal biopsy specimens, which was approved by the ethics committee of Hirosaki University Graduate School of Medicine (2018-098).

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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References

1. H. J. Anders, R. Saxena, M. H. Zhao, I. Parodis, J. E. Salmon, and C. Mohan, "Lupus Nephritis," *Nature Reviews. Disease Primers* 6 (2020): 7.

2. G. Lorenz, M. Lech, and H. J. Anders, "Toll-Like Receptor Activation in the Pathogenesis of Lupus Nephritis," *Clinical Immunology* 185 (2017): 86–94.

3. F. Conti, F. R. Spinelli, S. Truglia, et al., "Kidney Expression of Toll-Like Receptors in Lupus Nephritis: Quantification and Clinicopathological Correlations," *Mediators of Inflammation* 2016 (2016): 7697592.

4. H. J. Anders, "Pseudoviral Immunity – A Novel Concept for Lupus," *Trends in Molecular Medicine* 15 (2009): 553–561.

5. H. Tanaka and T. Imaizumi, "Inflammatory Chemokine Expression via Toll-Like Receptor 3 Signaling in Normal Human Mesangial Cells," *Clinical & Developmental Immunology* 2013 (2013): 984708.

6. S. Hashimoto, T. Imaizumi, T. Aizawa, et al., "Expression of IFN-Induced Transmembrane Protein 1 in Glomerular Endothelial Cells," *Pediatrics International* 63 (2021): 1075–1081.

7. T. Karasawa, R. Sato, T. Imaizumi, et al., "Glomerular Endothelial Expression of Type I IFN-Stimulated Gene, DExD/H-Box Helicase 60 via Toll-Like Receptor 3 Signaling: Possible Involvement in the Pathogenesis of Lupus Nephritis," *Renal Failure* 44 (2022): 137–145.

8. T. Karasawa, R. Sato, T. Imaizumi, et al., "Expression of Interferon-Stimulated Gene 20, an Antiviral Effector Protein, in Glomerular Endothelial Cells: Possible Involvement of ISG20 in Lupus Nephritis," *Renal Failure* 45 (2023): 2224890.

9. M. J. Wahadat, I. L. A. Bodewes, N. I. Maria, et al., "Type I IFN Signature in Childhood-Onset Systemic Lupus Erythematosus: A Conspiracy of DNA- and RNA-Sensing Receptors?," *Arthritis Research & Therapy* 20 (2018): 4.

10. T. Imaizumi, R. Hayakari, T. Matsumiya, et al., "Chloroquine Attenuates TLR3/IFN-β Signaling in Cultured Normal Human Mesangial Cells: A Possible Protective Effect Against Renal Damage in Lupus Nephritis," *Modern Rheumatology* 27 (2017): 1004–1009.

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EDITORIAL

Anti-Synthetase Syndrome—Advancing Disease Phenotyping, Classification and Treatment

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Anti-synthetase syndrome (ASyS) is characterized by the presence of antibodies against aminoacyl transfer RNA (tRNA) synthetase and distinct clinical constellations including interstitial lung disease (ILD), myositis, arthritis, mechanic's hands, fever and raynaud's phenomenon (RP). Since the discovery of anti-histidyl-tRNA synthetase (Anti-Jo1) antibody four decades ago, tremendous progress was made in discovering additional anti-synthetase antibodies [1]. There are 20 different aminoacyl-tRNA synthetase enzymes, and 10 distinct anti-synthetase antibodies (ASA) have been identified so far (Table 1). These antibodies are central to disease classification and may influence clinical phenotypes. There are evolving insights into pathophysiology, clinical heterogeneity, and treatment approaches in ASyS. This article aims to review and discuss the recent research advancements in disease sub-phenotyping, classification and therapeutics in ASyS.

ASyS exhibits significant clinical heterogeneity with varying disease courses and clinical manifestations among patients. Patients with non-Jo1 ASA were previously reported to have a worse survival than Jo1 patients (10-year cumulative survival of 47% vs. 70%, $p < 0.005$) by Aggarwal et al. [2], probably related to a delay in diagnosis by 8 months in the non-Jo1 positive patients. However, data from a multicenter registry in Hong Kong did not identify a similar survival difference between Jo1 and non-Jo1 positive patients [3]. Clinical phenotypes might exert a greater impact on survival than the presence of specific ASA. Wu et al. performed cluster analysis on more than 700 ASyS patients from China and identified three unique clinical phenotypes independent of ASA specificity: rapidly-progressive ILD (RP-ILD) cluster (23.7% of patients), dermatomyositis (DM)-like cluster (14.5%) and arthritis cluster (61.8%) [4]. The worst prognosis was observed in the RP-ILD cluster with a 10-year survival rate of 37.0%, compared to 69.5% in the DM-like cluster and 87.4% in the arthritis cluster, but the survival rates were comparable among different ASA. Transcriptomic analysis also revealed distinct gene signatures and biological processes in each cluster. Gene signatures implicated in coagulation and platelet activation were enhanced in the RP-ILD cluster, pathways related to viral infection and interferon-mediated signaling were enriched in the DM-like cluster, and lastly, B cell receptor signaling pathways were upregulated in the arthritis cluster. Whether or not the distinct biological pathways can predict treatment responses to targeted therapy, such as janus kinase inhibitors (JAKi) in the DM-like cluster or anti-CD20 in the arthritis cluster will require further research.

Apart from predicting prognosis, clinical manifestations are crucial in disease classification though there are controversies on universally accepted classification criteria of ASyS, which pose a great hurdle in research and clinical trials enrollment. Multiple criteria to classify ASyS were published over the years. In 2010, Connors et al. classified ASyS by positive ASA and any one of the following: myositis by Bohan and Peter criteria, presence of ILD, arthritis, unexplained and persistent fever, RP, or mechanic's hands [5]. In the subsequent year, Solomon et al. developed another set of classification criteria and defined myositis or ILD as major criteria while arthritis, RP, and mechanic's hands were considered minor criteria. The presence of ASA with two major criteria, or one major plus two minor criteria was classified as ASyS [6]. However, these criteria were not developed using a data-driven method. The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) published the first validated classification criteria of idiopathic inflammatory myopathy (IIM) in 2017 [7]. The presence of anti-Jo1 antibody, in addition to classic DM cutaneous manifestations, pattern of muscle weakness, and

TABLE 1 | Antibodies against aminoacyl-tRNA synthetase.

Anti-synthetase antibody	Antigen target	Prevalence in IIM
anti-Jo1	Histidyl-tRNA	15%–30%
anti-PL7	Threonyl-tRNA	5%–15%
anti-PL12	Alanyl-tRNA	5%–10%
anti-EJ	Glycyl-tRNA	< 5%
anti-OJ	Isoleucyl-tRNA	< 5%
anti-KS	Asparaginyl-tRNA	1%–8%
anti-Zo	Phenylalanyl-tRNA	1%
anti-YRS/Ha	Tyrosyl-tRNA	< 1%
anti-CARS/Ly	Cysteinyl-tRNA	—
anti-VRS	Valyl-tRNA	—

Abbreviations: IIM, Idiopathic inflammatory myopathy; tRNA, transfer ribonucleic acid.

muscle enzyme elevation contributed to the disease classification. However, the 2017 EULAR/ACR criteria did not include the presence of ILD or non-Jo1 ASA, nor did they define ASyS as a distinct IIM subtype.

Recently, a new Classification Criteria for Anti-synthetase Syndrome (CLASS) was presented to address the current gaps in ASyS classification [8]. A large international database of more than 2000 ASyS patients and controls, in which 16.7% were Asians, was utilized to identify key clinical and serological variables that define ASyS. The weighted scoring system with clinical (ILD, muscle involvement, joint involvement, Mechanic's hands, inflammatory rashes, RP, unexplained fever and pulmonary hypertension) and serological domains (presence of anti-Jo1 and non-anti-Jo1 antibody, anti-Ro52 or antinuclear antibodies (ANA) with cytoplasmic pattern) is used for disease classification. Though contributing to a lower weighted score than ASA positivity, the inclusion of anti-Ro52 positivity or ANA positivity with cytoplasmic pattern might facilitate ASyS classification in some APLAR regions in which myositis specific antibody testing is not widely available. However, external validation after final release of the new classification criteria, especially from populations not included in the CLASS database (such as Chinese or Southeast Asians), is essential before wide application in research and clinical trials.

Advancement in disease phenotyping and classification can potentially facilitate therapeutic development in ASyS, as there is a lack of evidence from RCTs to guide treatment of ASyS. Presence of major organ involvement, such as ILD reported in roughly 90% of ASyS patients [3, 4], often determines the intensity of treatment. Glucocorticoids (GCs) are commonly used as initial treatment. Conventional immunosuppressants, for example, mycophenolate mofetil (MMF) or calcineurin inhibitors (CNI), were frequently added; a recent systemic review revealed potential effectiveness in improving lung function parameters, but there was no conclusive difference in effectiveness between conventional immunosuppressants [9]. Cyclophosphamide (CYC) was usually reserved for severe ASyS-ILD, while the use of biologics and janus kinase inhibitors (JAKi) is emerging. CYC and rituximab improved forced vital capacity (FVC) and lung diffusion capacity (DLCO) to a similar extent [9]. Another retrospective cohort reported that anti-CD20 is more effective than conventional immunosuppressants to achieve low disease activity (LDA) and reduce GCs dosage in anti-Jo1 + ASyS patients [10]. Of note, this study proposed using LDA, a concept well studied in other rheumatological conditions, as a primary endpoint. The definition and long-term benefits of LDA in ASyS warrant further studies. Abatacept showed a trend to improve FVC and DLCO at week 48 but not week 24 in 20 ASyS-ILD patients compared to placebo [11]. Tocilizumab demonstrated potential efficacy in joint, muscle and lung involvement in refractory ASyS in case reports [12]. JAKi was reported to improve rashes, myositis and ILD in 14 out of 20 refractory ASyS patients in a retrospective cohort study [13].

Future ASyS research on validating the new classification criteria and exploring targeted therapies based on distinct clinical phenotypes would be important to improve patient outcomes.

Author Contributions

Iris Yan Ki Tang: conceptualization, writing – original draft, writing – review and editing. **Lijun Liu:** writing – original draft, 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 analyzed during the current study.

References

1. A. S. Galindo-Feria, A. Notarnicola, I. E. Lundberg, and B. Horuluoglu, "Aminoacyl-tRNA Synthetases: On Anti-Synthetase Syndrome and Beyond," *Frontiers in Immunology* 13 (2022): 283.

2. R. Aggarwal, E. Cassidy, N. Fertig, et al., "Patients With Non-Jo-1 Anti-tRNA-Synthetase Autoantibodies Have Worse Survival Than Jo-1 Positive Patients," *Annals of the Rheumatic Diseases* 73, no. 1 (2014): 227–232.

3. H. S. Tang, I. Y. K. Tang, R. T. C. Ho, et al., "Clinical Heterogeneity and Prognostic Factors of Anti-Synthetase Syndrome: A Multi-Centred Retrospective Cohort Study," *Rheumatology* 64 (2023): 10258.

4. S. Wu, X. Xiao, Y. Zhang, X. Zhang, G. Wang, and Q. Peng, "Novel Endotypes of Antisynthetase Syndrome Identified Independent of Anti-Aminoacyl Transfer RNA Synthetase Antibody Specificity That Improve Prognostic Stratification," *Annals of the Rheumatic Diseases* 83, no. 6 (2024): 775–786.

5. G. R. Connors, L. Christopher-Stine, C. V. Oddis, and S. K. Danoff, "Interstitial Lung Disease Associated With the Idiopathic Inflammatory Myopathies: What Progress Has Been Made in the Past 35 Years?," *Chest* 138, no. 6 (2010): 1464–1474.

6. J. Solomon, J. J. Swigris, and K. K. Brown, "Myositis-Related Interstitial Lung Disease and Antisynthetase Syndrome," *Jornal Brasileiro de Pneumologia* 37, no. 1 (2011): 100–109.

7. I. E. Lundberg and A. Tjarnlund, "Response to: '2017 EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory

Myopathies and Their Major Subgroups: Little Emphasis on Autoantibodies, Why?' By Malaviya," *Annals of the Rheumatic Diseases* 77, no. 11 (2018): e78.

8. G. Zanframundo, E. Dourado, I. Bauer-Ventura, et al., "The Role of Multicriteria Decision Analysis in the Development of Candidate Classification Criteria for Antisynthetase Syndrome: Analysis From the CLASS Project," *Annals of the Rheumatic Diseases* 84, no. 7 (2025): 1207–1220.

9. K. Kouranloo, M. Dey, H. Elwell, V. Yioe, L. G. Spencer, and C. V. Cotton, "Management and Outcomes of Interstitial Lung Disease Associated With Anti-Synthetase Syndrome: A Systematic Literature Review," *Rheumatology (Oxford, England)* 64, no. 1 (2025): 45–55.

10. S. Sun, J. Jin, J. Chen, et al., "Effectiveness and Safety of Anti-CD20 Monoclonal Antibodies Versus csDMARDs in Anti-Jo-1 Antisynthetase Syndrome: A Retrospective Cohort Study," *Seminars in Arthritis and Rheumatism* 72 (2025): 152712.

11. R. Aggarwal, N. Pongtarakulpanit, D. I. Sullivan, et al., "Abatacept for the Treatment of Myositis-Associated Interstitial Lung Disease (ATtackMy-ILD)," *Rheumatology (Oxford, England)* 25 (2025): 456.

12. F. Baumann Benvenuti and J. Dudler, "Long-Lasting Improvement of Refractory Antisynthetase Syndrome With Tocilizumab: A Report of Two Cases," *RMD Open* 9, no. 4 (2023): e003599.

13. X. Shan, S. Wu, X. Chen, and Y. Ge, "Janus Kinase Inhibition (JAKi) Therapy in Refractory Anti-Synthetase Syndrome: A Retrospective Cohort Study," *Seminars in Arthritis and Rheumatism* 68 (2024): 152474.

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REVIEW

Biomechanics and Obesity in Osteoarthritis: From Mechanism to Precision Medicine

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ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease driven by complex biomechanical and inflammatory mechanisms, particularly in weight-bearing joints such as the knee. This review explores the pivotal role of biomechanics in OA pathogenesis, focusing on abnormal joint loading, malalignment, and instability as key contributors to cartilage degeneration and subchondral bone remodeling. Special attention is given to the interplay between obesity and OA, highlighting how mechanical overload and adipokine-mediated inflammation synergistically accelerate disease progression. Emerging interventions—including physical therapy, gait retraining, orthotics, high tibial osteotomy (HTO), and total knee arthroplasty (TKA)—are analyzed for their biomechanical impact. Novel technologies such as wearable sensors, finite element analysis (FEA), and digital twin models are discussed as tools for real-time assessment, predictive modeling, and personalized treatment planning. The review emphasizes the need for integrated, multiscale research strategies that account for individual biomechanical profiles and systemic factors like obesity. Advancing biomechanical precision in OA management holds promise for improving early diagnosis, optimizing interventions, and informing regenerative therapies aimed at restoring joint function and delaying disease progression.

1 | Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder, particularly affecting weight-bearing joints like the knee, hip, and spine [1]. It is one of the leading causes of disability worldwide [2], with an increasing prevalence due to the aging population and the rising rates of obesity [3, 4]. OA is characterized by the degeneration of articular cartilage, subchondral bone changes, and chronic inflammation, leading to pain, stiffness, and diminished mobility. The knee joint is most commonly affected, with a study showing that OA impacts 22.9% of individuals aged over 40, with higher rates observed in women [5]. This chronic condition has a significant economic burden, with costs related to medical treatments, joint replacement surgeries, and lost productivity. For instance, in the United States, the total economic burden of knee OA is estimated to exceed $270 billion annually, a figure that continues to rise as the population ages [6].

Biomechanics plays a critical role in both the initiation and progression of OA. Abnormal mechanical loading, joint malalignment, and gait abnormalities are major contributors to the disease's onset and its exacerbation over time [7–12]. Altered joint mechanics can lead to uneven stress distribution across the joint surfaces, accelerating cartilage wear and triggering inflammation, which in turn worsens the disease [13]. For example, in knee OA, mechanical factors such as increased knee adduction moments (KAM) are associated with more rapid cartilage degeneration, as they contribute to asymmetric loading on the joint surfaces. Similarly, misalignments or altered joint

geometry, whether due to congenital factors or OA progression, can exacerbate the mechanical stress placed on the joint, further accelerating disease progression [14–16].

The role of obesity in OA is also a biomechanical issue, as excess body weight places additional stress on the knee joints, exacerbating mechanical loading and accelerating cartilage degeneration [17, 18]. Furthermore, the use of computational models, such as finite element analysis (FEA), has enhanced our understanding of how specific mechanical forces contribute to OA progression, providing insights into how joint tissues respond to various loading conditions [19]. Advances in wearable technology, which allows for real-time monitoring of joint motion and gait dynamics, have also provided valuable data to assess the biomechanics of OA in everyday life [20].

This review aims to explore the intricate relationship between biomechanics and OA by synthesizing recent findings from various studies. By examining how mechanical loading, joint alignment, and gait mechanics influence OA progression, this review seeks to provide a comprehensive understanding of the biomechanical factors that contribute to cartilage degeneration, subchondral bone changes, and joint inflammation. We will also investigate the role of systemic factors, such as obesity, in modifying the biomechanical environment of OA, as well as the implications of these changes for treatment and intervention strategies.

In addition to exploring the biomechanical mechanisms of OA, this review will focus on current and emerging interventions designed to modify mechanical loading in OA patients. These interventions include physical therapy, gait retraining, orthotics, and surgical options such as joint realignment or replacement, all of which aim to alleviate symptoms and slow disease progression. Finally, we will discuss the potential of new technologies, including personalized biomechanical treatments and regenerative medicine, to address the underlying mechanical factors driving OA progression.

2 | Biomechanical Pathomechanisms of Osteoarthritis

2.1 | Mechanical Load and Its Impact on Chondrocyte Function

Mechanical loading plays a central role in regulating chondrocyte metabolism and the maintenance of cartilage homeostasis. Cartilage, being an avascular tissue, relies on mechanical forces to stimulate cellular activity and facilitate nutrient exchange through compression and shear forces [21]. Chondrocytes, the sole cellular component of articular cartilage, are sensitive to mechanical stimuli. These stimuli influence gene expression, extracellular matrix (ECM) metabolism, and cartilage turnover, which are key factors in the development and progression of OA [22].

Chondrocytes respond to mechanical loading by modulating gene expression, which in turn influences ECM metabolism [23–25]. Both static and dynamic loads, such as compressive forces or shear stress, are involved in mechanotransduction pathways that activate signaling cascades. The most well-characterized mechanosensitive pathways in chondrocytes are those involving the mitogen-activated protein kinase (MAPK), integrins, and the Wnt/β-catenin signaling pathways [26, 27]. Mechanical loading can upregulate the expression of anabolic genes such as aggrecan and collagen type II, which are essential for the structural integrity of cartilage [28, 29]. Conversely, excessive or inappropriate mechanical loading can lead to the upregulation of catabolic enzymes like matrix metalloproteinases (MMPs) and disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which degrade the ECM, promoting cartilage degradation typical of OA [30–32].

Studies have shown that moderate loading enhances chondrocyte function, promoting ECM synthesis and homeostasis [33]. However, excessive or abnormal loading can disrupt these processes, resulting in a catabolic imbalance and accelerating the onset of OA [34]. The adaptive responses of chondrocytes to mechanical stimuli depend on the frequency, magnitude, and duration of the applied load [35]. For example, prolonged compression or high frequency loading leads to increased expression of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), further driving cartilage degradation and promoting OA progression [36, 37].

2.2 | Subchondral Bone Response to Mechanical Stimulation

Subchondral bone, the bone layer located just beneath the cartilage, plays a pivotal role in the biomechanical response of the joint. In OA, altered mechanical loading, either due to joint instability or abnormal force distribution, leads to changes in the subchondral bone [38]. Subchondral bone sclerosis, characterized by increased bone density, and subchondral bone cysts are common features of OA. This increased bone remodeling is thought to be a compensatory response to mechanical stress and may exacerbate cartilage degeneration by transmitting abnormal loads to the articular surface [39, 40].

The remodeling of subchondral bone is regulated by osteoblasts and osteoclasts, which respond to mechanical stimuli through the RANK/RANKL/OPG pathway. This pathway controls bone resorption and formation, and its dysregulation leads to bone changes observed in OA [41]. Alterations in subchondral bone properties, such as increased stiffness or uneven bone distribution, can further disturb the biomechanical environment of the joint and contribute to the progression of OA [42].

2.3 | Micro-Mechanical Changes in Bone and Cartilage

The biomechanical properties of both bone and cartilage undergo microstructural changes in OA. These changes at the cellular and tissue levels are crucial for understanding the pathophysiology of the disease.

2.3.1 | Cartilage Microstructure and Its Interaction With Mechanical Properties

The microstructure of cartilage, including its collagen network and proteoglycan content, is critical for its mechanical properties. In OA, cartilage loses its structural integrity, leading to the breakdown of the collagen network and a reduction in proteoglycan content. This results in decreased cartilage stiffness and an increased propensity for cartilage wear under mechanical stress [43]. The mechanical behavior of cartilage is influenced by its hierarchical structure, with the superficial zone providing resistance to shear forces and the deeper zones providing resistance to compressive forces [44, 45]. In OA, this structure becomes disorganized, resulting in a loss of the tissue's ability to withstand mechanical forces and leading to further degradation [46, 47].

2.3.2 | Subchondral Bone Response to Mechanical Stimulation

Subchondral bone acts as a shock absorber, distributing mechanical forces between the overlying cartilage and the deeper bone structures [48]. In OA, the mechanical loading on subchondral bone becomes altered, leading to changes in its microarchitecture. These changes include increased bone turnover, bone resorption, and sclerosis, which together alter the force transmission dynamics between cartilage and bone [49]. The altered subchondral bone properties contribute to cartilage breakdown by modifying the mechanical loading on the articular surface, thereby perpetuating the cycle of degeneration.

2.4 | Biomechanics and Cartilage Degeneration: From Healthy to OA Progression

The degeneration of articular cartilage in OA results from complex biomechanical and biochemical interactions. As elaborated in the previous sections, the transition from healthy to osteoarthritic cartilage involves viscoelastic property loss, ECM breakdown, and altered load distribution due to changes in tissue microstructure and joint mechanics. These insights highlight the pivotal role of mechanical stress in OA pathogenesis [50–53].

The relationship between biomechanics and the development of OA is central to understanding the pathophysiology of this debilitating joint disease. Mechanical loading directly influences chondrocyte behavior, ECM turnover, and cartilage integrity. Disruptions in this delicate balance lead to cartilage degradation, bone remodeling, and the onset of OA. Understanding these biomechanical processes opens the door to novel therapeutic strategies aimed at modulating mechanical forces to prevent or slow the progression of OA. An integrated overview of these biomechanical pathways is illustrated in Figure 1, which summarizes the key mechanisms linking mechanical stress to osteoarthritic degeneration at the cellular, tissue, and structural levels.

3 | Joint Biomechanics and Disease Progression in Knee Osteoarthritis

The knee joint is one of the most commonly affected joints in OA, and understanding its biomechanics is crucial in elucidating the progression of the disease. Mechanical forces acting on the knee during various activities, particularly during walking, can significantly influence cartilage degradation and the onset of OA [54]. Key mechanical parameters, such as the knee adduction moment (KAM) and knee flexion moment (KFM), provide valuable insights into joint loading and its correlation with OA development [55, 56].

3.1 | Clinical Significance of the KAM and KFM in Gait Analysis

KAM is a key biomechanical parameter that reflects the distribution of loading across the medial and lateral compartments of the knee. The KAM is strongly associated with the progression of knee OA, as it is a measure of the medial tibiofemoral joint loading. Increased KAM, often observed in patients with varus alignment (bow-legged), is linked to accelerated degeneration of the medial compartment of the knee [57]. It has been demonstrated that high KAM levels during walking can increase the risk of cartilage breakdown by promoting excessive compressive forces on the medial tibiofemoral joint. Reducing KAM through gait modifications or interventions such as valgus knee bracing has been shown to alleviate symptoms and slow the progression of knee OA [58, 59].

On the other hand, the KFM reflects the loading on the knee during the flexion phase of walking. A higher KFM, typically observed in patients with reduced quadriceps strength or altered joint mechanics, has been associated with an increased risk of OA progression [60]. Altered KFM patterns can lead to abnormal joint loading, contributing to cartilage wear [61, 62]. Thus, both KAM and KFM provide crucial insights into the mechanical environment of the knee joint and are clinically relevant in understanding disease progression and identifying potential therapeutic targets.

3.2 | Relationship Between Knee Joint Instability and Disease Progression

Knee instability, often resulting from ligamentous injury, joint malalignment, or muscle weakness, is a significant factor in the progression of knee OA [63]. Instability leads to altered load distribution within the joint, increasing mechanical stress on cartilage and subchondral bone [64]. In patients with ACL (anterior cruciate ligament) deficiency or varus malalignment, knee instability exacerbates OA progression by altering the normal kinematic and kinetic patterns of the joint [65].

Instability can also disrupt the balance of dynamic forces across the knee, leading to abnormal movement patterns, such as excessive joint rotation or abnormal knee flexion [66]. These changes can accelerate the breakdown of cartilage, particularly

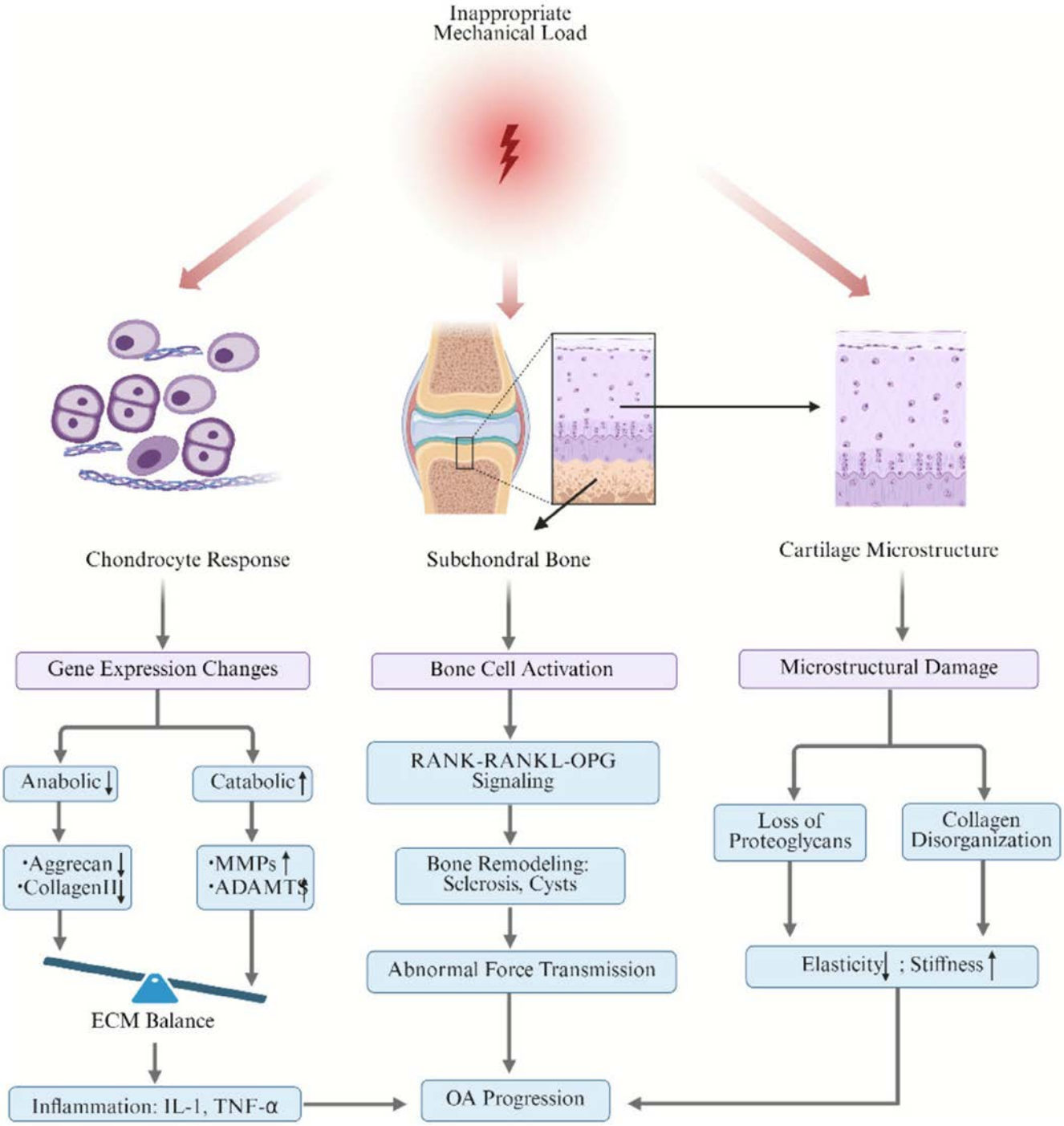

FIGURE 1 | Biomechanical pathomechanisms driving osteoarthritis progression. This diagram illustrates how inappropriate mechanical load contributes to the progression of osteoarthritis through biomechanical and cellular pathways. Mechanical stress influences chondrocyte behavior by altering gene expression, leading to an imbalance between anabolic and catabolic processes, disruption of extracellular matrix homeostasis, and increased inflammation. In the subchondral bone, altered forces activate bone remodeling via RANK-RANKL-OPG signaling, resulting in sclerosis and cyst formation, which further affect load transmission. Concurrently, cartilage undergoes microstructural changes including the loss of proteoglycans and collagen disorganization. These alterations reduce elasticity, increase stiffness, and impair the tissue's ability to distribute mechanical loads effectively. Together, these changes drive the degenerative cycle that leads to osteoarthritis.

in the areas that bear the highest loads, such as the medial tibiofemoral compartment [67]. Furthermore, joint instability often leads to compensatory strategies, such as altered gait or muscle imbalances, which further stress the joint and contribute to OA progression [68]. Effective management of knee instability through interventions like corrective surgery, physical therapy, or bracing is crucial in slowing disease progression and improving joint function [69].

Biomechanical changes play a central role in the development and progression of osteoarthritis. In the knee joint, the KAM and KFM provide valuable insights into abnormal joint loading,

which can accelerate OA progression. Knee instability and altered gait patterns further exacerbate the disease process. Understanding these biomechanical factors is critical in developing effective treatment strategies to slow disease progression and improve joint function.

4 | Obesity and Joint Load

Obesity is a major systemic risk factor for OA, particularly in weight-bearing joints such as the knee, hip, and spine. The relationship between obesity and OA is no longer viewed as a simple additive effect of weight gain on joints, but rather as a complex synergistic interplay between biomechanical overload and metabolic inflammation.

4.1 | Synergistic Effect of Mechanical Overload and Inflammation

Excessive body mass increases joint loading, especially during locomotion, resulting in abnormal contact pressure and shear forces across the articular cartilage. These mechanical stimuli can activate mechanoreceptors and initiate pro-inflammatory pathways, such as the NF-κB and MAPK signaling cascades, leading to upregulation of catabolic mediators including matrix metalloproteinases (MMPs) and aggrecanases [70]. Microtrauma-induced chondrocyte activation promotes extracellular matrix degradation, particularly in the medial compartment of the knee [71].

Concurrently, adipose tissue functions as an endocrine organ, secreting proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [72, 73]. These mediators lower the biomechanical threshold needed to trigger inflammatory responses in cartilage and synovium, making joints more vulnerable to loading-induced damage. This mechanoinflammatory loop accelerates OA progression, especially when inflammatory sensitization precedes mechanical insult [74].

4.2 | Adipokines and Mechanobiological Crosstalk

Adipokines such as leptin, adiponectin, and resistin are critical mediators linking obesity to altered joint homeostasis. Leptin, in particular, not only enhances cytokine production but also increases cartilage catabolism by stimulating MMP expression and nitric oxide release in chondrocytes [75]. These changes sensitize cartilage to mechanical stimuli, reinforcing the destructive feedback loop between inflammation and loading.

Furthermore, the distribution of adipose tissue—especially visceral fat—alters postural balance and shifts the body's center of mass, resulting in increased KAM and uneven load distribution during gait [76, 77]. These biomechanical distortions, compounded by systemic inflammation, enhance focal joint stress, promote cartilage breakdown, and impair repair capacity. Collectively, these findings highlight the need to address obesity not merely as excess weight but as a mechanobiological amplifier in OA pathogenesis.

5 | Biomechanical Interventions and Treatments in OA

Biomechanical interventions play a significant role in managing OA by addressing the underlying mechanical dysfunctions that contribute to joint degeneration. These interventions include conservative treatments, surgical procedures, emerging technologies, computational modeling, and regenerative medicine. Rather than relying on broad descriptors like "realign limb loading axis," modern approaches target quantifiable biomechanical parameters such as reducing peak KAM, modifying medial-lateral load distribution, or adjusting ground reaction force (GRF) trajectories to improve joint mechanics (Table 1).

5.1 | Conservative Interventions

5.1.1 | Physical Therapy, Gait Retraining, and Orthotic Use

Physical therapy (PT) is a foundational noninvasive treatment for OA. Targeted strengthening exercises improve periarticular muscle support, thereby enhancing joint stiffness and load-sharing. Gait retraining has demonstrated efficacy in reducing pathological external KAM, a key predictor of medial compartment OA progression, by modifying step width, toe-out angle, and cadence [78–80]. Likewise, orthotic devices, such as valgus unloader knee braces or lateral wedge insoles, aim to laterally shift the center of pressure and redistribute ground reaction forces, thereby reducing medial compartment loading and alleviating localized stress [81–83].

5.1.2 | Functional Exercise in Joint Stability and Load Distribution

Functional exercise protocols improve neuromuscular control and dynamic stability under physiological loading conditions. These interventions target the enhancement of proprioception and muscular co-contraction around the joint, thus stabilizing joint kinematics during locomotion [84–86]. Specifically, strengthening the quadriceps and hamstrings has been shown to modulate aberrant loading trajectories in knee OA, especially during stance phase and stair ascent/descent tasks [87, 88].

5.2 | Surgical Interventions

5.2.1 | High Tibial Osteotomy (HTO) and Total Knee Arthroplasty (TKA)

High Tibial Osteotomy (HTO) is a joint-preserving surgical procedure primarily used in younger, active patients with medial compartment knee OA. It functions by correcting varus deformity through the mechanical realignment of the lower limb axis—typically shifting the weight-bearing line laterally through a valgus-producing osteotomy. This reduces excessive medial knee compartment loading and decreases the internal

TABLE 1 | Summary of biomechanical interventions for OA management.

References	Biomechanical target/outcome	Therapeutic strategy	Intervention	Category
Bennell and Hinman (2011) Booij et al. (2020)	Improves load distribution, dynamic joint stability, reduces KAM, and delays cartilage degeneration Lower KAM by ≥ 10%, altered muscle activation patterns, changes in co-contraction index (CCI)	Muscle strengthening, proprioception enhancement, neuromuscular reeducation, and gait modification using real-time biofeedback to reduce KAM	Physical therapy Gait retraining	Conservative
Zafar et al. (2020) Sharma (2023)	Reduce KAM, shift ground reaction force vector, decrease medial compartment stress Improve joint proprioception, postural stability, and neuromuscular function	Adjust medial-lateral load distribution via custom foot orthoses Employ staged dynamic balance and joint control training to enhance functional biomechanics	Orthotic use Sensorimotor training	Conservative
Constantin et al. (2024)	Shift load from medial to lateral knee compartment to delay degeneration	Restore coronal plane alignment by valgus-producing osteotomy	High tibial osteotomy (HTO)	Surgical
Hamahashi et al. (2021) Reddy et al. (2024)	Restore joint line congruency and full limb alignment Improve hindfoot biomechanics via proximal realignment	Use prosthesis to normalize joint biomechanics and correct varus deformity	Total knee arthroplasty (TKA)	Surgical
Wang et al. (2020)	Reduce KAM during stance phase through gait feedback	Modify foot progression angle and cadence using wearable inertial sensors and auditory–visual feedback	Wearable technology	Emerging technologies
Mononen et al. (2024) Dean et al. (2024)	Simulate cartilage stress and predict OA progression Optimize implant fit and load transfer via virtual models	Integrate machine learning and FEA data to stratify risk and guide treatment planning	FEA + digital twin modeling	Emerging technologies

KAM, which is strongly correlated with OA progression [89–92]. Biomechanically, HTO reduces the medial tibiofemoral contact force by redistributing load more evenly across the tibial plateau. In contrast, Total Knee Arthroplasty (TKA) replaces the degenerated articular surfaces with prosthetic components, aiming to restore joint line orientation, minimize abnormal torque, and normalize joint kinematics. A comparative study reported lower postoperative pain levels (measured via J-KOOS) in TKA than in HTO, although joint-preserving benefits make HTO preferable for select populations [93].

5.2.2 | Postsurgical Biomechanical Function Recovery and Challenges

Despite the surgical corrections, restoring optimal postoperative biomechanics remains challenging. After TKA, patients may still exhibit abnormal joint moments, asymmetrical ground reaction force patterns, and impaired dynamic limb alignment during gait due to altered joint geometry and muscle imbalances [94]. Rehabilitation plays a vital role in reestablishing neuromuscular control, restoring physiological joint loading symmetry, and optimizing the interaction between prosthetic alignment and soft tissue function [95, 96]. Long-term biomechanical success is influenced by precise implant positioning, restoration of mechanical axis, and mitigation of abnormal joint kinetics that could otherwise lead to implant wear or joint instability.

5.3 | Emerging Technologies and Computational Tools

Recent advancements in wearable technology enable continuous and real-time assessment of joint biomechanics during functional activities. Sensor-equipped devices can monitor parameters such as knee adduction moment, ground reaction forces, and gait asymmetry, all of which are critical indicators of abnormal joint loading that contribute to OA progression [97].

These biomechanical datasets are essential for refining individualized interventions, including targeted gait retraining and optimization of orthotic configurations to minimize pathological loading patterns in the joint.

5.3.1 | Computational Modeling and Predictive Analysis

Finite Element Analysis (FEA) has emerged as a powerful tool for simulating the mechanical environment within joints, allowing the assessment of stress and strain distribution in cartilage, bone, and meniscus under varying conditions [98].

Recent integration of machine learning techniques with FEA enables the prediction of OA progression based on patient-specific biomechanical profiles and loading histories [99, 100]. These technologies facilitate the development of precision medicine strategies by correlating joint mechanics with biological and clinical markers.

5.3.2 | Digital Twin Technology in Surgical Planning and OA Progression Prediction

Digital twin technology constructs dynamic, patient-specific biomechanical simulations by integrating individual musculoskeletal geometry, joint kinematics, and tissue material properties into virtual models that replicate real joint behavior [101]. These models are particularly useful in preoperative planning, where surgeons can simulate and evaluate the mechanical consequences of procedures such as osteotomy or total joint arthroplasty. For instance, by modifying surgical parameters—such as the wedge angle in high tibial osteotomy or prosthesis alignment in knee replacement—the digital twin can predict alterations in joint contact forces and load distribution [102–103]. Such simulations allow for iterative optimization to achieve maximal biomechanical efficiency and minimize postoperative complications like malalignment or implant wear [104].

5.4 | Regenerative Medicine and Biomechanical Stimulation

Regenerative medicine strategies increasingly utilize biomechanical cues to enhance cartilage repair. Stem cell-laden scaffolds and hydrogel matrices are now applied under physiologically relevant mechanical conditions such as magneto-mechanical stimulation. These biomechanical stimuli promote chondrogenic differentiation, enhance extracellular matrix synthesis, and restore mechanical functionality of the damaged cartilage. For example, magnetically responsive scaffolds can direct in situ stem cell alignment and tissue formation in response to external fields, mimicking the mechanical environment of a healthy joint. Furthermore, biomechanically conditioned constructs exhibit improved integration with host tissue and resistance to degeneration. Thus, the combination of mechanical stimulation and regenerative biomaterials holds promise for restoring both structural integrity and load-bearing capacity in OA-affected joints [105, 106].

6 | Future Perspectives and Translational Challenges

Although extensive research affirms the central role of biomechanics in OA, several translational gaps persist across experimental and clinical domains. First, the mechanobiological regulation of cartilage via MAPK, Wnt/β-catenin, and integrin pathways has been well documented. However, precise thresholds for mechanical loading, time-dependent signaling kinetics, and interindividual variability remain insufficiently quantified. This limits the ability to define safe and effective "mechanical dosing" strategies for cartilage regeneration in clinical settings. Second, the bulk of current findings stems from in vitro and animal models, which cannot fully mimic the complex loading environment, biochemical heterogeneity, and cartilage-bone interactions present in human joints. Static or unphysiologically excessive loading protocols often fail to represent early OA conditions. Moreover, models focusing on joint biomechanics—such as gait parameters (KAM,

KFM), joint instability, or muscle coordination—frequently lack integration with systemic factors like inflammation or obesity-induced metabolic stress. The synergistic interplay between biomechanical overload and proinflammatory cytokines (e.g., IL-6, TNF-α) remains conceptually recognized but mechanistically underexplored. Few studies directly model the amplification of mechanical damage by chronic inflammatory states in vivo. Computational approaches (e.g., FEA, mechanobiological simulations) show promise in simulating load-tissue interactions, but they often rely on idealized cartilage properties, lack validation across populations, and fail to incorporate patient-specific inputs such as neuromuscular function, adipokine profiles, or structural alignment.

In the obesity-OA axis, research shows that adipokines like leptin not only mediate inflammation but also modulate chondrocyte mechanosensitivity. Yet, sex- and fat-distribution-specific differences are rarely incorporated into biomechanical models or intervention trials, leaving a significant precision gap.

On the therapeutic front, conservative interventions (e.g., gait retraining, proprioceptive training, orthotics) show short-term biomechanical benefits, but their long-term sustainability and mechanistic efficacy remain ambiguous due to heterogeneity in protocols and adherence challenges. Similarly, surgical procedures like HTO and TKA, though biomechanically effective, require better integration with preoperative motion profiles and postoperative neuromuscular rehabilitation to optimize outcomes. Emerging technologies, including wearable sensors, digital twins, and AI-enhanced modeling, are poised to revolutionize personalized OA management. However, these remain in early-stage development and face significant technical, computational, and regulatory hurdles before clinical adoption. Moving forward, future research must quantify load-response thresholds across biological scales, integrate systemic inflammation and obesity into joint mechanics models, develop real-time multimodal datasets, standardize biomechanical modeling protocols, and validate interventions through personalized, longitudinal clinical trials. Only through such integrated, multiscale strategies can biomechanical insights transition from bench to bedside.

7 | Future Research Directions

Building upon the translational challenges outlined above, future research in osteoarthritis biomechanics should embrace integrated, multiscale methodologies that can bridge mechanistic insights with individualized clinical applications. Longitudinal studies combining three-dimensional gait kinematics, dynamic loading data from wearable sensors, synovial fluid biomarkers, and patient-reported outcome measures will be vital to capturing OA's evolving pathophysiology.

The development of personalized "biomechanical fingerprints"—profiles that incorporate joint geometry, neuromuscular function, alignment, and gait asymmetries—holds promise for stratifying patients and predicting disease progression. These profiles can serve as the foundation for digital twin models, enabling in silico simulations of load redistribution, tissue adaptation, and therapeutic responsiveness.

To realize these advances, machine learning-enhanced finite element models must undergo real-time validation through high-fidelity, patient-specific data inputs. Standardized modeling protocols and open-access validation datasets are essential for reproducibility and clinical adoption.

Additionally, future research should investigate how biomechanical interventions interact with inflammatory and metabolic pathways, particularly in obese individuals where systemic inflammation amplifies load sensitivity. Understanding this mechanoinflammatory crosstalk may reveal novel therapeutic targets.

Finally, regenerative approaches—such as stem cell-laden scaffolds, injectable hydrogels, or bioprinted cartilage constructs—must be evaluated under physiologically relevant mechanical conditions in large-scale, randomized controlled trials. Only through such comprehensive, translationally informed strategies can biomechanical research meaningfully transform OA prevention and treatment.

Author Contributions

Shangqi Guan: conceptualization, literature review, writing – original draft preparation. **Yifang Mei:** supervision, writing – review and editing, correspondence, and manuscript revision. All authors have 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

Research data are not shared.

References

1. X. Jiang, Q. Wang, C. Wang, et al., "The Association Between Genetic Polymorphisms of Matrix Metalloproteinases and Knee Osteoarthritis: A Systematic Review and Meta-Analysis," *International Journal of Rheumatic Diseases* 27, no. 3 (2024): e15123.

2. S. Guan and Y. Mei, "Editorial: The Role of Piezo 1 in Osteoarthritis: Implications for Pathogenesis and Therapy," *International Journal of Rheumatic Diseases* 27, no. 10 (2024): e15348.

3. I. J. Wallace, S. Worthington, D. T. Felson, et al., "Knee Osteoarthritis Has Doubled in Prevalence Since the Mid-20th Century," *Proceedings of the National Academy of Sciences of the United States of America* 114, no. 35 (2017): 9332–9336.

4. D. J. Hunter and S. Bierma-Zeinstra, "Osteoarthritis," *Lancet* 393, no. 10182 (2019): 1745–1759.

5. Y. Wang, J. Lu, Z. Wang, et al., "The Association Between Patella Alignment and Morphology and Knee Osteoarthritis," *Journal of Orthopaedic Surgery and Research* 19, no. 1 (2024): 509.

6. K. L. Ong, F. Niazi, E. Lau, et al., "Knee OA Cost Comparison for Hyaluronic Acid and Knee Arthroplasty," *Journal of Orthopaedic Surgery and Research* 15, no. 1 (2020): 305.

7. M. C. Hochberg, M. Lethbridge-Cejku, W. W. Scott, Jr., et al., "The Association of Body Weight, Body Fatness and Body Fat Distribution With Osteoarthritis of the Knee: Data From the Baltimore Longitudinal Study of Aging," *Journal of Rheumatology* 22, no. 3 (1995): 488–493.

8. B. D. Jackson, A. E. Wluka, A. J. Teichtahl, M. E. Morris, and F. M. Cicuttini, "Reviewing Knee Osteoarthritis—A Biomechanical Perspective," *Journal of Science and Medicine in Sport* 7, no. 3 (2004): 347–357.

9. L. S. Lohmander, P. M. Englund, L. L. Dahl, and E. M. Roos, "The Long-Term Consequence of Anterior Cruciate Ligament and Meniscus Injuries: Osteoarthritis," *American Journal of Sports Medicine* 35, no. 10 (2007): 1756–1769.

10. M. Englund, "The Role of Biomechanics in the Initiation and Progression of OA of the Knee," *Best Practice & Research. Clinical Rheumatology* 24, no. 1 (2010): 39–46.

11. F. Guilak, "Biomechanical Factors in Osteoarthritis," *Best Practice & Research. Clinical Rheumatology* 25, no. 6 (2011): 815–823.

12. L. Willinger, P. Foehr, A. Achtnich, et al., "Effect of Lower Limb Alignment in Medial Meniscus-Deficient Knees on Tibiofemoral Contact Pressure," *Orthopaedic Journal of Sports Medicine* 7, no. 2 (2019): 2325967118824611.

13. P. Krakowski, A. Rejniak, J. Sobczyk, and R. Karpiński, "Cartilage Integrity: A Review of Mechanical and Frictional Properties and Repair Approaches in Osteoarthritis," *Healthcare* 12, no. 16 (2024): 1648.

14. T. Neogi, M. A. Bowes, J. Niu, et al., "Magnetic Resonance Imaging-Based Three-Dimensional Bone Shape of the Knee Predicts Onset of Knee Osteoarthritis: Data From the Osteoarthritis Initiative," *Arthritis and Rheumatism* 65, no. 8 (2013): 2048–2058.

15. S. Tanamas, F. S. Hanna, F. M. Cicuttini, A. E. Wluka, P. Berry, and D. M. Urquhart, "Does Knee Malalignment Increase the Risk Ofdevelopment and Progression of Knee Osteoarthritis? A Systematic Review," *Arthritis & Rheumatism* 61, no. 4 (2009): 459–467.

16. L. Sharma, J. Song, D. T. Felson, S. Cahue, E. Shamiyeh, and D. D. Dunlop, "The Role of Knee Alignment in Disease Progression and Functional Decline in Knee Osteoarthritis," *JAMA* 286, no. 2 (2001): 188–195.

17. J. Aaboe, H. Bliddal, S. P. Messier, T. Alkjær, and M. Henriksen, "Effects of an Intensive Weight Loss Program on Knee Joint Loading in Obese Adults With Knee Osteoarthritis," *Osteoarthritis and Cartilage* 19, no. 7 (2011): 822–828.

18. R. I. Issa and T. M. Griffin, "Pathobiology of Obesity and Osteoarthritis: Integrating Biomechanics and Inflammation," *Pathobiology of Aging & Age-Related Diseases* 2, no. 2012 (2012): 17470.

19. X. Ma, Q. Liu, D. Xu, et al., "Biomechanical Impact of Progressive Meniscal Extrusion on the Knee Joint: A Finite Element Analysis," *Journal of Orthopaedic Surgery and Research* 19, no. 1 (2012): 754.

20. D. K. Verma, P. Kumari, and S. Kanagaraj, "Engineering Aspects of Incidence, Prevalence, and Management of Osteoarthritis: A Review," *Annals of Biomedical Engineering* 50, no. 3 (2022): 237–252.

21. E. Belluzzi, S. Todros, A. Pozzuoli, P. Ruggieri, E. L. Carniel, and A. Berardo, "Human Cartilage Biomechanics: Experimental and Theoretical Approaches Towards the Identification of Mechanical Properties in Healthy and Osteoarthritic Conditions," *Processes* 11, no. 4 (2023): 1014.

22. M. Segarra-Queralt, K. Crump, A. Pascuet-Fontanet, B. Gantenbein, and J. Noailly, "The Interplay Between Biochemical Mediators and Mechanotransduction in Chondrocytes: Unravelling the Differential Responses in Primary Knee Osteoarthritis," *Physics of Life Reviews* 48 (2024): 205–221.

23. D. Shi, Y. Mei, W. Hao, J. Li, S. Liu, and X. Lin, "Biological Functions and Applications of LncRNAs in the Regulation of the Extracellular Matrix in Osteoarthritis," *Frontiers in Cell and Developmental Biology* 11 (2024): 1330624.

24. A. Destouni, K. C. Tsolis, A. Economou, et al., "Chondrocyte Protein Co-Synthesis Network Analysis Links ECM Mechanosensing to Metabolic Adaptation in Osteoarthritis," *Expert Review of Proteomics* 18, no. 7 (2021): 623–635.

25. W. Que, H. Liu, and Q. Yang, "CircPRKCH Modulates Extracellular Matrix Formation and Metabolism by Regulating the miR-145/HGF Axis in Osteoarthritis," *Arthritis Research & Therapy* 24, no. 1 (2022): 216.

26. N. Ma, X. Teng, Q. Zheng, and P. Chen, "The Regulatory Mechanism of p38/MAPK in the Chondrogenic Differentiation From Bone Marrow Mesenchymal Stem Cells," *Journal of Orthopaedic Surgery and Research* 14, no. 1 (2019): 434.

27. R. Castro-Viñuelas, N. Viudes-Sarrión, S. Monteagudo, R. Lories, and I. Jonkers, "Excessive Wnt Signalling Alters the Cartilage Response to Physiologic Loading," *Orthopaedic Proceedings* 105-B, no. SUPP_8 (2023): 21.

28. M. Nomura, H. Moriyama, Y. Wakimoto, and Y. Miura, "Disuse Atrophy of Articular Cartilage Can Be Restored by Mechanical Reloading in Mice," *Molecular Biology Reports* 51, no. 1 (2024): 1018.

29. A. Engstrøm, F. S. Gillesberg, S. S. Groen, et al., "Intermittent Dynamic Compression Confers Anabolic Effects in Articular Cartilage," *Applied Sciences* 11, no. 16 (2021): 7469.

30. H. Zhang, Y. Shao, Z. Yao, et al., "Mechanical Overloading Promotes Chondrocyte Senescence and Osteoarthritis Development Through Downregulating FBXW7," *Annals of the Rheumatic Diseases* 81, no. 5 (2022): 676–686.

31. K. Sauerland, A. Wolf, M. Schudok, and J. Steinmeyer, "A Novel Model of a Biomechanically Induced Osteoarthritis-Like Cartilage for Pharmacological In Vitro Studies," *Journal of Cellular and Molecular Medicine* 25, no. 24 (2021): 11221–11231.

32. Y. Y. Lai, D. Li, and S. W. Chang, "Computational Insights Into the Substrate Recognition Mechanism of Cartilage Extracellular Matrix Degradation," *Computational and Structural Biotechnology Journal* 19 (2021): 5535–5545.

33. R. Issa, M. Boeving, M. Kinter, and T. M. Griffin, "Effect of Biomechanical Stress on Endogenous Antioxidant Networks in Bovine Articular Cartilage," *Journal of Orthopaedic Research* 36, no. 2 (2017): 760–769.

34. M. Segarra-Queralt, G. Piella, and J. Noailly, "Network-Based Modelling of Mechano-Inflammatory Chondrocyte Regulation in Early Osteoarthritis," *Frontiers in Bioengineering and Biotechnology* 11 (2023): 1006066.

35. H. D. Welhaven, C. N. McCutchen, and R. K. June, "Effects of Mechanical Stimulation on Metabolomic Profiles of SW1353 Chondrocytes: Shear and Compression," *Biology Open* 11, no. 1 (2022): bio058895.

36. X. Cai, C. Warburton, O. F. Perez, et al., "Hippo Signaling Modulates the Inflammatory Response of Chondrocytes to Mechanical Compressive Loading," *bioRxiv*, (2023), https://doi.org/10.1101/2023.06.09.544419.

37. A. S. Eskelinen, P. Tanska, C. Florea, et al., "Mechanobiological Model for Simulation of Injured Cartilage Degradation via Pro-Inflammatory Cytokines and Mechanical Stimulus," *PLoS Computational Biology* 16, no. 6 (2020): e1007998, https://doi.org/10.1371/journal.pcbi.1007998.

38. K. Arakawa, K. Takahata, Y. Usami, and T. Kokubun, "Characteristic Differences in Tibial Subchondral Bone Changes in the Post-Traumatic Knee Osteoarthritis Model," *bioRxiv* 10, no. 6 (2023): 1369.

39. P. Luo, Q. L. Yuan, M. Yang, X. Wan, and P. Xu, "The Role of Cells and Signal Pathways in Subchondral Bone in Osteoarthritis," *Bone & Joint Research* 12, no. 9 (2023): 536–545.

40. W. Colyn, F. Azari, J. Bellemans, G. H. van Lenthe, and L. Scheys, "Microstructural Adaptations of the Subchondral Bone Are Related to the Mechanical Axis Deviation in End Stage Varus Oa Knees," *European Cells and Materials* 45 (2023): 60–71.

41. R. Feng, W. Hu, Y. Li, et al., "Mechanotransduction in Subchondral Bone Microenvironment and Targeted Interventions for Osteoarthritis," *Mechanobiology in Medicine* 2, no. 2 (2024): 100043.

42. J. Ying, P. Wang, Z. Shi, et al., "Inflammation-Mediated Aberrant Glucose Metabolism in Subchondral Bone Induces Osteoarthritis," *Stem Cells* 41, no. 5 (2023): 482–492.

43. B. Raikov, M. Lipina, K. Azarkin, et al., "Methods for Determining the Molecular Composition of Knee Joint Structures in Osteoarthritis: Collagen, Proteoglycans and Water Content: A Systematic Review," *Collagen & Leather* 6 (2024): 30, https://doi.org/10.1186/s42825-024-00173-7.

44. M. Ferretti, L. A. Veloso Costa, and N. O. Foni, "Articular Cartilage: Functional Biomechanics," in *Cartilage Injury of the Knee* (Springer, 2021), 1–9.

45. P. Szarek, M. B. Lilledahl, N. C. Emery, C. G. Lewis, and D. M. Pierce, "The Zonal Evolution of Collagen-Network Morphology Quantified in Early Osteoarthritic Grades of Human Cartilage," *Osteoarthritis and Cartilage Open* 2, no. 4 (2020): 100086.

46. S. A. Elahi, P. Tanska, R. K. Korhonen, R. Lories, N. Famaey, and I. Jonkers, "An In Silico Framework of Cartilage Degeneration That Integrates Fibril Reorientation and Degradation Along With Altered Hydration and Fixed Charge Density Loss," *Frontiers in Bioengineering and Biotechnology* 9 (2021): 680257, https://doi.org/10.3389/fbioe.2021.680257.

47. M. Ebrahimi, M. A. Finnilä, A. Turkiewicz, et al., "Elastic, Dynamic Viscoelastic and Model-Derived Fibril-Reinforced Poroelastic Mechanical Properties of Normal and Osteoarthritic Human Femoral Condyle Cartilage," *Annals of Biomedical Engineering* 49, no. 9 (2021): 2622–2634.

48. G. Li, J. Yin, J. Gao, et al., "Subchondral Bone in Osteoarthritis: Insight Into Risk Factors and Microstructural Changes," *Arthritis Research & Therapy* 15, no. 6 (2023): 223.

49. A. Sangiorgio, L. Andriolo, W. Gersoff, et al., "Subchondral Bone: An Emerging Target for the Treatment of Articular Surface Lesions of the Knee," *Journal of Experimental Orthopaedics* 11, no. 3 (2024): e12098, https://doi.org/10.1002/jeo2.12098.

50. K. Yudoh, Y. Sugishita, and Y. Takahashi-Suzuki, "NAD-Dependent Deacetylase Sirtuin-1 Mediates the Mechanical Stress-Induced Degeneration of Articular Cartilage in Osteoarthritis: Mechanical Stress Stimulates the Expression of Osteogenic Transcription Factor Runx2 via the Srituin-1 Activation in Chondrocytes," *Osteoarthritis and Cartilage* 32 (2024): S426.

51. E. Catalano, "Biophysical and Biomechanical Properties of Cartilage," *arXiv*:2305.01529, (2023), https://doi.org/10.48550/arXiv.2305.01529.

52. L. de Roy, G. Q. Teixeira, J. Schwer, et al., "Structure-Function of Cartilage in Osteoarthritis: An Ex-Vivo Correlation Analysis Between Its Structural, Viscoelastic and Frictional Properties," *Acta Biomaterialia* 190 (2024): 293–302.

53. M. M. Rahman, P. N. Watton, C. P. Neu, and D. M. Pierce, "A Chemo-Mechano-Biological Modeling Framework for Cartilage Evolving in Health, Disease, Injury, and Treatment," *Computer Methods and Programs in Biomedicine* 231 (2023): 107419.

54. F. Bensalma, N. Hagemeister, A. Cagnin, et al., "Biomechanical Markers Associations With Pain, Symptoms, and Disability Compared to Radiographic Severity in Knee Osteoarthritis Patients: A Secondary Analysis From a Cluster Randomized Controlled Trial," *BMC Musculoskeletal Disorders* 23, no. 1 (2022): 896.

55. L. Hutchison, J. Grayson, C. Hiller, N. D'Souza, S. Kobayashi, and M. Simic, "A Systematic Review and Meta-Analysis of the Relationship Between Knee Biomechanics and Pain in People With Knee Osteoarthritis," *Journal of Science and Medicine in Sport* 75, no. 6 (2022): 1351–1361.

56. S. Van Rossom, J. Emmerzaal, R. van der Straaten, et al., "The Biomechanical Fingerprint of Hip and Knee Osteoarthritis Patients During Activities of Daily Living," *Clinical Biomechanics* 101 (2022): 105858.

57. R. Dionísio, "Higher Knee Flexion Moment During Walking Is Associated With a Lower Risk of Knee Pain Developing Among the Elderly After 24 Months," *European Journal of Physical and Rehabilitation Medicine* 59, no. 3 (2023): 386–395.

58. S. J. Snyder, E. M. Bell, S. Oh, et al., "Walking With Different Emotions Significantly Influences Knee Adduction Moment," *Medicine and Science in Sports and Exercise* 41, no. 3 (2023): 233–240.

59. Y. Li, R. Luo, S. Luo, M. Liu, and H. Liu, "Influencing Factors Analysis of Asymmetry in Knee Adduction Moment Among Patients With Unilateral Knee Osteoarthritis," *BMC Musculoskeletal Disorders* 25, no. 1 (2024): 832.

60. H. L. Teng, T. D. MacLeod, T. M. Link, S. Majumdar, and R. B. Souza, "Higher Knee Flexion Moment During the Second Half of the Stance Phase of Gait Is Associated With the Progression of Osteoarthritis of the Patellofemoral Joint on Magnetic Resonance Imaging," *Journal of Orthopaedic & Sports Physical Therapy* 45, no. 9 (2015): 656–664.

61. J. Favre and B. M. Jolles, "Gait Analysis of Patients With Knee Osteoarthritis Highlights a Pathological Mechanical Pathway and Provides a Basis for Therapeutic Interventions," *EFORT Open Reviews* 1, no. 10 (2017): 368–374.

62. H. L. Teng, N. E. Calixto, T. D. MacLeod, et al., "Associations Between Patellofemoral Joint Cartilage T1ρ and T2 and Knee Flexion Moment and Impulse During Gait in Individuals With and Without Patellofemoral Joint Osteoarthritis," *Osteoarthritis and Cartilage* 24, no. 9 (2016): 1554–1564.

63. B. B. Rothrauff, M. A. Fox, R. S. Murray, P. W. Winkler, and V. Musahl, *Biomechanics of Instability and Its Relationship to OA* (Springer, 2022), https://doi.org/10.1007/978-3-030-79485-9_8.

64. B. Kacprzak, M. Stańczak, J. Surmacz, and M. Hagner-Derengowska, "Biophysics of ACL Injuries," *Orthopedic Reviews* 16 (2024): 126041.

65. K. Takahata, Y. Y. Lin, B. Osipov, et al., "Concurrent Joint Contact in Anterior Cruciate Ligament Injury Induces Cartilage Micro-Injury and Subchondral Bone Sclerosis, Resulting in Knee Osteoarthritis," *bioRxiv*, (2024), https://doi.org/10.1101/2024.05.08.593114.

66. F. Ikuta, K. Yoneta, T. Miyaji, et al., "Knee Kinematics of Severe Medial Knee Osteoarthritis Showed Tibial Posterior Translation and External Rotation: A Cross-Sectional Study," *Aging Clinical and Experimental Research* 32, no. 9 (2020): 1767–1775.

67. M. Ciba, E. M. Winkelmeyer, J. Schock, et al., "Comprehensive Assessment of Medial Knee Joint Instability by Valgus Stress MRI," *Diagnostics (Basel, Switzerland)* 11, no. 8 (2021): 1433.

68. T. Kageyama, "Effect of Suppression of Rotational Joint Instability on Cartilage and Meniscus Degeneration in Mouse Osteoarthritis Model," *Cartilage* 13, no. 1 (2022): 194760352110692.

69. L. Andriessanto and S. Kambey, "Efficacy of High Tibial Osteotomy in the Treatment of Medial Compartment Osteoarthritis: A Systematic Review," *Eduvest – Journal of Universal Studies* 4, no. 9 (2024): 8307–8316.

70. U. Nedunchezhiyan, I. Varughese, A. R. Sun, et al., "Obesity, Inflammation, and Immune System in Osteoarthritis," *Frontiers in*

Immunology 13 (2022): 907750, https://doi.org/10.3389/fimmu.2022.907750.

71. B. A. Sanford, J. L. Williams, A. Zucker-Levin, et al., *Hip, Knee and Ankle Joint Forces in Healthy Weight, Overweight and Obese Individuals During Walking* (Springer, 2014), 101–111, https://doi.org/10.1007/978-1-4939-0745-8_8.

72. V. Mocanu, D. Timofte, C.-M. Zară-Dănceanu, D. V. Timofte, and L. Labusca, "Obesity, Metabolic Syndrome, and Osteoarthritis Require Integrative Understanding and Management," *Biomedicine* 12, no. 6 (2024): 1262.

73. U. Nedunchezhiyan, I. Varughese, A. R. Sun, et al., "Obesity, Inflammation, and Immune System in Osteoarthritis," *Frontiers in Immunology* 13 (2022): 907750.

74. S. N. Wijesinghe, A. Badoume, D. E. Nanus, et al., "Obesity-Defined Molecular Endotypes in OA Synovium," *Clinical and Translational Medicine* 13, no. 4 (2023): e1232.

75. A. Economou, I. Mallia, A. Fioravanti, et al., "The Role of Adipokines Between Genders in the Pathogenesis of Osteoarthritis," *International Journal of Molecular Sciences* 25, no. 19 (2024): 10865.

76. S. P. Messier, M. E. Gill, S. L. Mihalko, et al., "Clinical, Health-Related Quality of Life, and Gait Differences Among Obesity Classes in Adults with Knee Osteoarthritis," *Arthritis Care & Research (Hoboken)* 76, no. 4 (2023): 503–510.

77. M. Adouni, M. Adouni, T. R. Faisal, et al., "The Effect of Body Weight on the Knee Joint Biomechanics Based on Subject-Specific Finite Element-Musculoskeletal Approach," *Dental Science Reports* 14, no. 1 (2024): 13777.

78. S. J. Preece, N. Brookes, N. Brookes, et al., "A New Integrated Behavioural Intervention for Knee Osteoarthritis: Development and Pilot Study," *BMC Musculoskeletal Disorders* 22, no. 1 (2021): 526.

79. R. Safari, J. Jackson, and D. Sheffield, "Digital Self-Management Interventions for People With Osteoarthritis: Systematic Review With Meta-Analysis," *Journal of Medical Internet Research* 22, no. 7 (2020): e15365.

80. M. J. Booij, R. Richards, J. Harlaar, et al., "Effect of Walking With a Modified Gait on Activation Patterns of the Knee Spanning Muscles in People With Medial Knee Osteoarthritis," *Knee* 27, no. 1 (2020): 198–206.

81. S. M. A. Bierma-Zeinstra, M. van Middelkoop, J. Runhaar, et al., "Nonpharmacological and Nonsurgical Approaches in OA," *Best Practice & Research. Clinical Rheumatology* 34, no. 2 (2020): 101564.

82. J.-P. Berteau, "Knee Pain from Osteoarthritis: Pathogenesis, Risk Factors, and Recent Evidence on Physical Therapy Interventions," *Journal of Clinical Medicine* 11, no. 12 (2022): 3252.

83. A. Q. Zafar, R. Zamani, and M. A. Akrami, "The Effectiveness of Foot Orthoses in the Treatment of Medial Knee Osteoarthritis: A Systematic Review," *Gait & Posture* 76 (2020): 238–251.

84. H. Patel and M. Balaganapathy, "Effect of a Sensorimotor Training on Pain, Proprioception, and Functional Activities in Participants with Chronic Knee Osteoarthritis: A Randomized Controlled Clinical Trial," *Annals of Physiotherapy & Occupational Therapy* (2024) [cited November 2025], https://doi.org/10.23880/aphot-16000268.

85. M. Sharma, "Effect of Sensorimotor Training on Pain, Balance and Functional Ability in Patients with Knee Osteoarthritis," *International Journal of Health Sciences and Research* (2023) [cited November 2025], https://doi.org/10.52403/ijhsr.20231109.

86. J. Knoop, J. Dekker, M. van der Leeden, et al., "OP0309-HPR Knee Joint Stabilization Therapy in Patients With Osteoarthritis of the Knee: A Randomized, Controlled Trial," *Annals of the Rheumatic Diseases* (2013) [cited November 2025], https://doi.org/10.1136/ANNRHEUMDIS-2013-EULAR.514.

87. Ö. Gezginaslan, E. A. Ozturk, M. Cengiz, et al., "Effects of Isokinetic Muscle Strengthening on Balance, Proprioception, and Physical Function in Bilateral Knee Osteoarthritis Patients With Moderate Fall Risk," *Turkish Journal of Physical Medicine and Rehabilitation* 64, no. 4 (2018): 353–361.

88. J. Qiu, T. Zhou, H. Jin, et al., "Effect of Adding Hip Exercises to General Rehabilitation Treatment of Knee Osteoarthritis on Patients' Physical Functions: A Randomized Clinical Trial," *BMC Sports Science, Medicine and Rehabilitation* 15, no. 1 (2023): 158.

89. S. J. Shim, Y.-G. Park, and Y. S. Lee, "Comparison of the Effect of Total Knee Arthroplasty and High Tibial Osteotomy on Coronal Pelvic and Ankle-Hindfoot Alignment," *Knee* 42 (2023): 170–180.

90. T. Ishimatsu, R. Takeuchi, H. Ishikawa, et al., "Clinical Outcomes of Hybrid Closed Wedge High Tibial Osteotomy for Advanced Osteoarthritis of the Knee Compared With Total Knee Arthroplasty," *Journal of Orthopaedic Surgery* 30, no. 3 (2022): 102255362211377.

91. H. Constantin, L. J. Salmon, V. Russell, et al., "20-Year Outcomes of High Tibial Osteotomy: Determinants of Survival and Functional Outcome," *American Journal of Sports Medicine* 52, no. 2 (2024): 344–351.

92. J. Erard, A. Schmidt, C. Batailler, et al., "Higher Knee Survivorship in Young Patients With Monocompartmental Osteoarthritis and Constitutional Deformity Treated by High Tibial Osteotomy Then Total Knee Arthroplasty Compared to an Early Total Knee Arthroplasty," *Bone & Joint Open* 4, no. 2 (2023): 62–71.

93. K. Hamahashi, G. Mitani, T. Takagaki, et al., "Total Knee Arthroplasty Is Superior to Open Wedge High Tibial Osteotomy in Terms of Pain Relief for Patients With Osteoarthritis," *Arthroplasty Today* (2021) [cited November 2025], https://doi.org/10.1016/j.artd.2020.11.010.

94. J. Wilson, S. Civiero, A. F. Laudanski, et al., "The Association of Biomechanical Outcomes of Knee Arthroplasty Surgery With Pre-Operative Joint Kinematics," *Osteoarthritis and Cartilage* (2024) [cited November 2025], https://doi.org/10.1016/j.joca.2024.02.230.

95. S. Kara and A. E. Nokay, "What are the Novel Rehabilitation Methods in Knee Arthroplasty? A Bibliographic Review," *Technology and Health Care* 32, no. 5 (2024): 3643–3648.

96. N. R. Shaikh, T. Chandra, and M. Kj, "Evaluating the Impact of Total Knee Arthroplasty on Hindfoot Alignment and Function," *South Eastern European Journal of Public Health* 2024 (2024): 2257–2263 [cited November 2025], https://doi.org/10.70135/seejph.vi.2408.

97. C. Wang, P. P. K. Chan, B. M. F. Lam, et al., "Real-Time Estimation of Knee Adduction Moment for Gait Retraining in Patients With Knee Osteoarthritis," *Neural Systems and Rehabilitation Engineering* 28, no. 4 (2020): 888–894.

98. M. Yan, T. Liang, H. Zhao, et al., "Model Properties and Clinical Application in the Finite Element Analysis of Knee Joint: A Review," *Orthopaedic Surgery* 16, no. 2 (2024): 289–302.

99. M. E. Mononen, M. K. Liukkonen, and M. J. Turunen, "Machine Learning Model Trained with Finite Element Modeling Can Predict the Risk of Osteoarthritis: Data from the Osteoarthritis Initiative," *Applied Sciences* (2024) [cited November 2025], https://doi.org/10.3390/app14209538.

100. A. Paz, J. Lavikainen, M. J. Turunen, et al., "Knee-Loading Predictions with Neural Networks Improve Finite Element Modeling Classifications of Knee Osteoarthritis: Data from the Osteoarthritis Initiative," *Annals of Biomedical Engineering* 52, no. 9 (2024): 2569–2583.

101. J. P. J. Peitola, A. Esrafilian, A. S. A. Eskelinen, et al., "Comparison of Knee Cartilage Biomechanics in Finite Element Analysis Using Inputs From AnyBody and OpenSim," *Research Square* (2023) [cited November 2025], https://doi.org/10.21203/rs.3.rs-3457777/v1.

102. M. C. Dean, J. F. Oeding, P. Diniz, et al., "Leveraging digital twins for improved orthopaedic evaluation and treatment," *Journal of Experimental Orthopaedics* 11, no. 4 (2024): e70084.

103. E. Mikolajewska, J. Masiak, and D. Mikolajewski, "Applications of Artificial Intelligence-Based Patient Digital Twins in Decision Support in Rehabilitation and Physical Therapy," *Electronics*, (2024). [cited 2025 November] Available from, https://doi.org/10.3390/electronics13244994.

104. A. Mukherjee, S. K. Sarkar, A. A. Poundarik, and B. Das, "The Role of Cartilage Tissue Engineering in Osteoarthritis Treatment: The Bench to Bedside Translation," *Journal of Polymer Science* (2024) [cited November 2025], https://doi.org/10.1002/pol.20240353.

105. G. Hoyer, K. T. Gao, F. G. Gassert, et al., "Foundations of a Knee Joint Digital Twin from qMRI Biomarkers for Osteoarthritis and Knee Replacement," *npj Digital Medicine* 8, no. 1 (2025): 118.

106. C. Deng, Z. Li, L. Lu, et al., "Sophisticated Magneto-Mechanical Actuation Promotes In Situ Stem Cell Assembly and Chondrogenesis for Treating Osteoarthritis," *ACS Nano* 17, no. 21 (2023): 21690–21707.

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LETTER TO THE EDITOR

An Enigmatic Link Between Arthritis and Dysphagia in an Elderly Male!

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Dear Editor,

Histoplasmosis is an opportunistic fungal infection caused by *Histoplasma capsulatum*, typically affecting immunocompromised individuals. However, in rare instances, it can present in immunocompetent elderly individuals with atypical manifestations. We present a case of disseminated histoplasmosis initially presented with musculoskeletal manifestations like arthritis, tenosynovitis, and entrapment neuropathy, later progressing to systemic symptoms with dysphagia and hoarseness of voice.

A 78-year-old male with no known comorbidities presented with pain and swelling in the left wrist joint of 3 weeks duration. It was also associated with tingling and numbness of the left thumb and index finger. He denied any history of any rash or recent travel. On clinical examination, the left wrist was tender and swollen. There was no lymphadenopathy. Tinel's and Phalen's tests were positive. His hematological and biochemical parameters revealed raised CRP (85 mg/L), hypercalcemia (11.6 mg/dL), and significantly raised serum angiotensin-converting enzyme (ACE) levels (95.5 U/L, normal: 8–52 U/L).

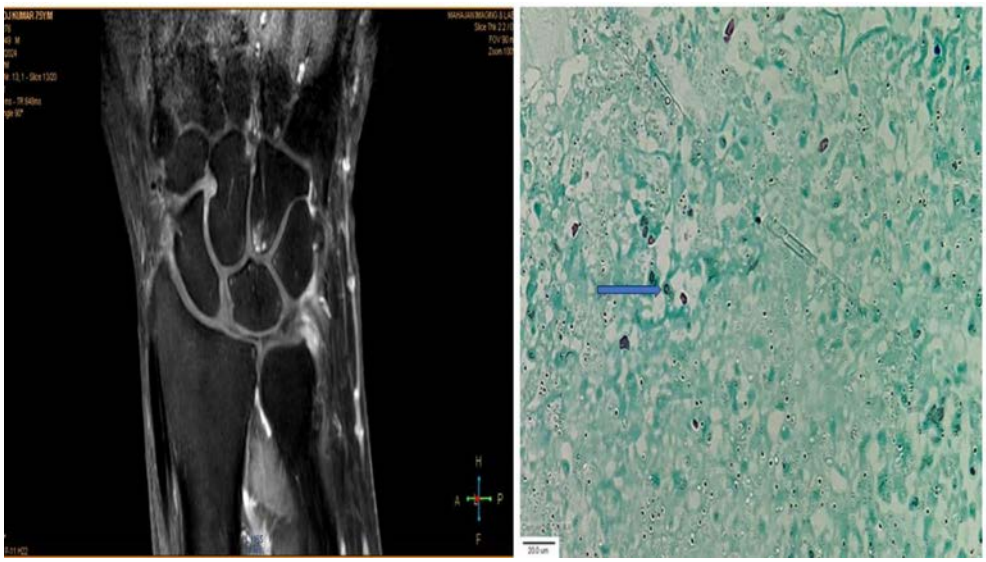

FIGURE 1 | Panel 1- MRI left wrist showing thickening of flexor retinaculum with multiple collections. Panel2- Biopsy from the lesion in the larynx showing histoplasma on grocott staining.

Key Message

- Disseminated histoplasmosis can present with arthritis, hypercalcemia, elevated ACE levels, and peripheral neuropathy mimicking other granulomatous diseases.

Contrast enhanced computed tomography (CECT) of the chest revealed well-defined ground-glass opacities in the left lower lung zone. Bronchoalveolar lavage was negative for *Mycobacterium tuberculosis* and fungal etiology. MRI of the left wrist demonstrated irregular fibrous thickening of the flexor retinaculum with tenosynovitis of the palmaris tendon. Nerve conduction studies of the left hand confirmed the diagnosis of carpal tunnel syndrome. Surgical decompression was performed, and histopathological examination of the flexor retinaculum biopsy showed multiple granulomas with histiocytic inflammation and giant cells, without evidence of acid-fast bacilli. His Mantoux test and IGRA were negative. Based on the clinical findings, hypercalcemia, raised ACE levels, and histopathological evidence of granulomas with negative AFB staining, a probable diagnosis of sarcoidosis was made and he was started on low dose steroids with oral methotrexate.

A month later, the patient developed progressive dysphagia and hoarseness of voice. He underwent an ENT evaluation which revealed a small proliferative lesion at the right anterior pillar and soft palate junction, along with a similar lesion at the interarytenoid area. He was managed as leucoplakia with fluconazole, only with partial improvement. In view of worsening dysphagia, he underwent an upper GI endoscopy and laryngoscopy, which revealed a suspicious ulcerated lesion at the posterior glottis.

Histopathological examination of the biopsy from the lesion demonstrated dense inflammatory infiltrates with multiple 2–5-micron yeast forms with a perinuclear halo. Grocott and periodic acid–Schiff (PAS) stains were positive, confirming the diagnosis of histoplasmosis (Figure 1, Panel 2). While his swelling in left wrist persisted and he underwent a repeat MRI of left wrist, multiple fluid collections in the volar aspect of wrist with thickening and scarring of underlying flexor retinaculum and palmaris longus tendon slips (Figure 1, Panel 1). Now we tried to connect the dots together. Per cutaneous needle aspiration and examination of fluid from the left wrist also confirmed the diagnosis of histoplasmosis. The patient was diagnosed as a case of disseminated histoplasmosis and initiated on itraconazole 200 mg twice daily, leading to significant symptomatic improvement of dysphagia and hoarseness over 2–3 weeks. He completed 3 months of itraconazole with significant improvement in symptoms of dysphagia, arthritis, and neuropathic symptoms with normal serum calcium levels. A repeated MRI of the left wrist showed complete resolution of collection and tenosynovitis. He

TABLE 1 | Summary of clinical course of the patient.

Time	Clinical events	Investigations	Treatments
July 2023	Left wrist pain and swelling, tingling in thumb/index finger	↑ CRP (85 mg/dL) ↑ Calcium (11.6 mg/dL) ↑ ACE (95.5 U/L) NCS → carpel tunnel syndrome (Left>Right)	Under evaluation
		CECT Chest: GGOs (Left lower lobe) MRI left wrist: Tenosynovitis (Palmaris tendon) and thickened flexor retinaculum Histopathology (flexor retinaculum): Non-caseous granulomatous inflammation, giant cells, and AFB/ Gene Xpert MTB Negative	Carpal tunnel decompression
Aug 2023	Referred to Rheumatology	Provisional Diagnosis: Sarcoidosis based on elevated ACE levels + granulomas on biopsy	Steroids + Methotrexate
Oct 2023	Developed dysphagia and hoarseness	ENT: Laryngeal lesions → treated as leukoplakia	Oral Fluconazole
Nov 2023	Worsening ENT symptoms along with progressive left wrist swelling	Laryngoscopy biopsy: PAS+ and GMS+ yeast → Histoplasmosis	Itraconazole 200 mg BID started
		MRI left wrist: Multiple loculated collections in volar aspect along with thickened palmaris longus tendon and flexor retinaculum PET–CT: No active lesions elsewhere	
Jan 2024	Resolution of symptoms	MRI: Significant resolution of loculated collections and thickened tendon/flexor retinaculum	Planned 1-year itraconazole therapy

also underwent a PET CT with no evidence of histoplasmosis elsewhere. He was scheduled for a 1-year course of itraconazole therapy.

Summary of events is given in Table 1.

Disseminated histoplasmosis is a rare systemic fungal infection in immunocompetent individuals, often mimicking other granulomatous disorders such as sarcoidosis and tuberculosis [1]. Histoplasma capsulatum, is endemic in certain regions, including parts of India. It primarily affects the lungs, but extrapulmonary manifestations—such as mucosal lesions, tenosynovitis, and entrapment neuropathies—are increasingly recognized, particularly in the elderly even without immunocompromised status [2, 3]. Few case reports have documented hypercalcemia, elevated ACE levels, and granulomatous pathology which may resemble sarcoidosis, leading to diagnostic delays and progression of infection. Diagnosis requires a high index of suspicion and confirmation with fungal stains (PAS, Grocott) or culture of the tissue [4]. Itraconazole remains the mainstay of treatment, with amphotericin B reserved for severe cases [5]. Timely recognition and treatment are essential to avoid progression and complications [6]. A summary of differential diagnosis of granulomatous diseases in Table 2.

In our patient, initial findings of hypercalcemia and elevated ACE levels with no evidence of tuberculosis and fungal etiology favored diagnosis of sarcoidosis. Though the presence of granulomatous inflammation in the wrist raised suspicion for an infectious etiology, however, definitive diagnosis of histoplasmosis was made only after the development of laryngeal involvement.

Disseminated histoplasmosis should be kept in mind even in immunocompetent elderly patients with tenosynovitis and arthritis, especially with a granulomatous inflammation on histopathological examination [9, 10]. This case highlights the clinical challenges we faced and the need for heightened clinical suspicion and repeated histopathological investigations to establish an early diagnosis and ensure timely treatment in case of histoplasma-related arthritis in endemic countries.

TABLE 2 | Differential diagnosis of granulomatous diseases [7, 8].

Features	Histoplasmosis	Sarcoidosis	Tuberculosis	Non-tuberculous mycobacteria (NTM)
Clinical features	Fever, arthritis, tenosynovitis, dysphagia, mucocutaneous lesions, and neuropathy	Pulmonary infiltrates, hilar adenopathy, uveitis, and erythema nodosum	Chronic cough, fever, weight loss, hemoptysis, and night sweats	Bronchiectasis and nodular lung disease
Laboratory	↑ ACE, ↑ Calcium possible; fungal antigen/antibody positive	↑ ACE, ↑ Calcium; Mantoux negative	Mantoux/IGRA +.	AFB culture positive
Imaging	Nodules, GGOs, and mediastinal nodes	Bilateral hilar lymphadenopathy and ILD	Cavitary/miliary opacities, and consolidations	Nodular/bronchiectatic changes and multifocal infiltrates
Histopathology	Granulomas with intracellular yeast (PAS+, Grocott+)	Non-caseating granulomas	Caseating granulomas (AFB +)	Caseating or suppurative granulomas (AFB/Auramine+)

Abbreviations: ACE, angiotensin-converting enzyme; AFB, acid-fast bacilli; GGO, ground-glass opacity; IGRA, interferon-gamma release assay; ILD, interstitial lung disease; PAS, Periodic acid–Schiff.

Author Contributions

A.C., J.S., S.P., N.G., and R.C. managed the case. A.C. and J.S. wrote the manuscript. H.J., N.G., A.K., K.S., and V.V. reviewed the manuscript.

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The authors have nothing to report.

Consent

Written consent was taken 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 on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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References

1. L. J. Wheat, M. L. V. French, and J. L. Wall, "Sarcoid Like Manifestations of Histoplasmosis," *Archives of Internal Medicine* 149, no. 11 (1989): 2421–2426.

2. S. Staffolani, D. Buonfrate, A. Angheben, et al., "Acute Histoplasmosis in Immunocompetent Travelers: A Systematic Review of Literature," *BMC Infectious Diseases* 18, no. 1 (2018): 673.

3. N. C. Bahr, S. Antinori, L. J. Wheat, and G. A. Sarosi, "Histoplasmosis Infections Worldwide: Thinking Outside of the Ohio River Valley," *Current Tropical Medicine Reports* 2, no. 2 (2015): 70–80.

4. J. Guarner and M. E. Brandt, "Histopathologic Diagnosis of Fungal Infections in the 21st Century," *Clinical Microbiology Reviews* 24, no. 2 (2011): 247–280.

5. D. S. McKinsey and J. K. Smith, "Treatment of Histoplasmosis in the Modern Era: New Insights and Evidence-Based Regimens," *Journal of Fungi (Basel)* 7, no. 6 (2021): 429.

6. K. V. Liang, J. H. Ryu, and E. L. Matteson, "Histoplasmosis With Tenosynovitis of the Hand and Hypercalcemia Mimicking Sarcoidosis," *Journal of Clinical Rheumatology* 10, no. 3 (2004): 138–142.

7. S. Ohshimo, J. Guzman, U. Costabel, and F. Bonella, "Differential Diagnosis of Granulomatous Lung Disease: Clues and Pitfalls," *European Respiratory Review* 26, no. 145 (2017): 170012.

8. D. Valeyre, M. Brauner, J. Bernaudin, et al., "Differential Diagnosis of Pulmonary Sarcoidosis: A Review," *Frontiers in Medicine* 10 (2023): 1150751.

9. V. Gupta, V. Singhal, and M. K. Singh, "Disseminated Histoplasmosis With Hypercalcemia," *Journal of the American Academy of Dermatology* 68, no. 5 (2013): 816–818.

10. J. W. Liu, T. C. Huang, and Y. C. Lu, "Acute Disseminated Histoplasmosis Complicated With Hypercalcaemia," *Journal of Infection* 39, no. 1 (1999): 88–90.

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LETTER TO THE EDITOR

Cat Scratch to Vascular Damage: A Rare Case of Bartonella-Induced Large Vessel Vasculitis

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Dear Editor,

Although *Bartonella henselae*, the causative agent of cat scratch disease, has been associated with various systemic inflammatory conditions and small-vessel vasculitis—particularly mimicking ANCA-associated vasculitis or presenting in the context of infective endocarditis—large vessel vasculitis (LVV) related to *B. henselae* has not been reported in the pediatric population to date. Here, we present a pediatric case with a history of cat exposure and confirmed *B. henselae* infection who subsequently developed large vessel vasculitis during follow-up. This case highlights the need to consider infectious triggers, including *Bartonella*, in the differential diagnosis of pediatric LVV.

A 12-year-old girl was admitted with a 1-month history of right axillary swelling and painful skin lesions on her lower extremities. Approximately 1.5 months prior to admission, she had been scratched by an unvaccinated stray cat. At the time of the incident, she was asymptomatic and received tetanus and rabies prophylaxis. Due to axillary lymphadenopathy, she was prescribed oral amoxicillin-clavulanic acid for 1 week.

On admission, her vital signs were as follows: body temperature 36.8°C, heart rate 92 bpm, respiratory rate 18 breaths/min, and blood pressure 110/70 mmHg. On physical examination, ultrasonography revealed a 15 × 40 mm right axillary lymphadenopathy. Purple, painless, non-edematous lesions consistent with erythema nodosum were observed on the anterior tibial surfaces of both legs. Bilateral radial pulses were palpable and symmetric. No bruits were detected on auscultation of the neck or chest.

Laboratory findings showed elevated acute phase reactants, with an erythrocyte sedimentation rate (ESR) of 73 mm/h and C-reactive protein (CRP) of 10 mg/L (normal: 0–5 mg/L). Complete blood count revealed a hemoglobin level of 12 g/dL, white blood cell count of 8310/μL, and platelet count of 492 000/μL—all within normal limits. Liver and kidney function tests were normal. *Bartonella* serology showed IgG positive and IgM negative; antinuclear antibody (ANA) was negative.

Initial cervical ultrasonography revealed significant vascular wall thickening in the right common carotid artery, suggestive of vasculitis (Figure 1a: longitudinal view; Figure 1b: transverse view). MRI and Doppler studies demonstrated diffuse wall thickening in the right common carotid artery and minimal pleural effusion. Echocardiography showed a patent foramen ovale (PFO). Thoracoabdominal CT angiography revealed diffuse concentric wall thickening extending from the proximal segment of the superior mesenteric artery to the level of the celiac trunk bifurcation, consistent with vascular involvement. At the 4-week follow-up, the IgG titer had increased threefold.

The patient was hospitalized for targeted antibiotic therapy and management of vasculitis secondary to *Bartonella* infection. Initial treatment with azithromycin was switched to doxycycline, rifampin, and teicoplanin due to insufficient response. Vasculitis treatment included a 3-day pulse of methylprednisolone, followed by maintenance therapy with prednisolone (40 mg/day) and azathioprine (75 mg/day).

Following 14 days of teicoplanin and 28 days of doxycycline and rifampin, along with corticosteroid and azathioprine therapy, the patient's clinical condition stabilized, and follow-up imaging demonstrated regression of the lymphadenopathy.

At the 3-month follow-up, ultrasonography showed complete resolution of the previously identified vascular involvement

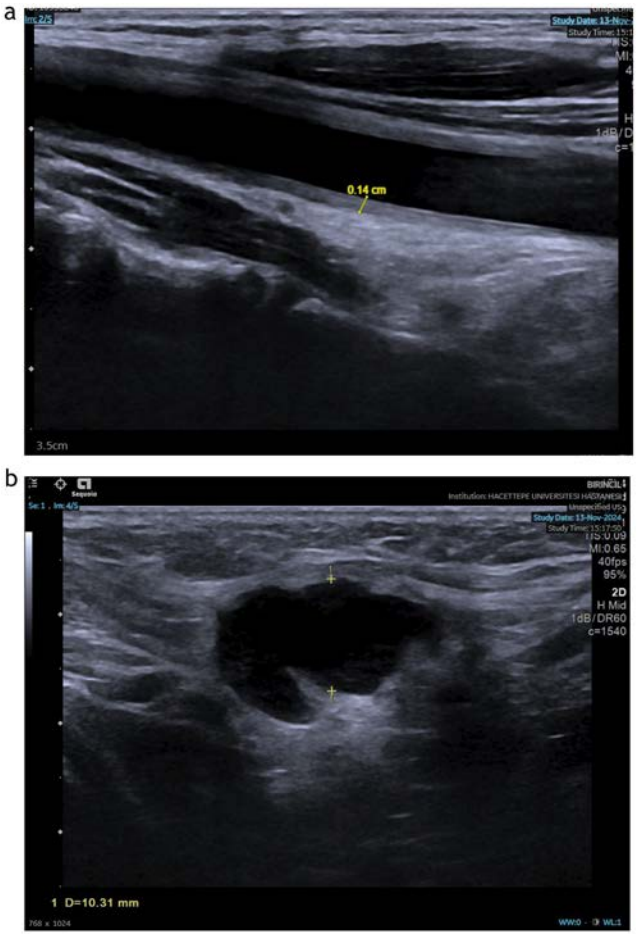

FIGURE 1 | (a) Right carotid ultrasound imaging in longitudinal plane (pre-treatment). This ultrasound image shows a longitudinal view of a blood vessel, most likely an artery, with a visible hypoechoic (dark) thickening along the vessel wall. The measured thickness is 0.14 cm (1.4 mm), which may indicate early signs of vessel wall thickening. (b) Right carotid ultrasound imaging in transverse plane (pre-treatment). The ultrasound images demonstrate a hypoechoic, well-defined, hypoechoic perivascular thickening within the carotid artery region, measuring approximately 10.31 mm in diameter. The transverse and longitudinal views reveal vessel wall thickening with potential evidence of inflammatory involvement.

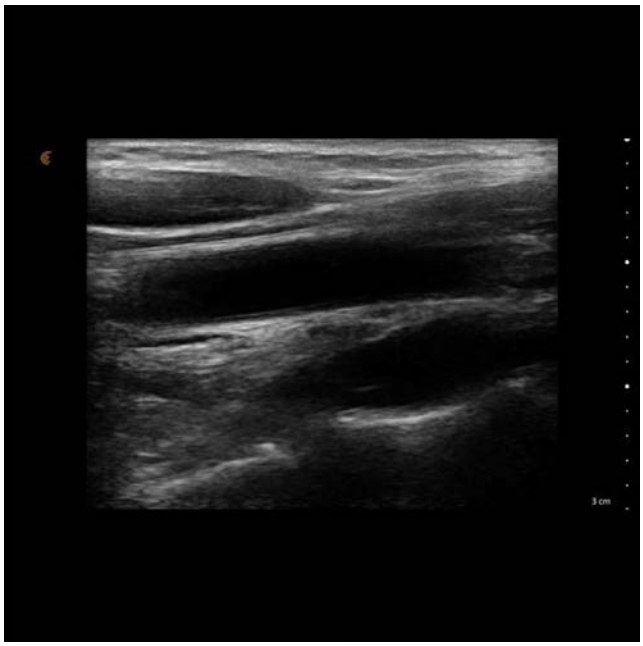

FIGURE 2 | Follow-up ultrasound imaging showing resolution of vascular involvement. Post-treatment ultrasound imaging reveals improved vascular architecture with reduced wall thickening and diminished hypoechoic inflammatory changes. The previously observed cystic lesion has regressed significantly, and the vessel lumen appears more patent. Measurement shows the current vessel wall thickness to be approximately 3.0 mm, indicating a positive response to treatment. These findings suggest a reduction in inflammatory burden and improved vascular flow dynamics. Continued monitoring is recommended to assess long-term disease control and prevent reoccurrence.

(Figure 2). The vascular wall thickening had resolved, with no signs of inflammation or luminal narrowing. Concurrently, the patient's acute phase reactants, including ESR and CRP, had returned to normal levels under the ongoing treatment regimen. At the 6-month follow-up, control CT imaging confirmed complete resolution of the vascular findings, and corticosteroid therapy was discontinued.

Although *Bartonella henselae* is most frequently associated with benign lymphadenopathy, it has been increasingly recognized as a potential trigger for systemic inflammatory responses, including vasculitis. Most reported cases of *Bartonella*-associated vasculitis involve small vessels and are frequently linked with infective endocarditis, glomerulonephritis, or ANCA-associated vasculitis-like syndromes. Beydon et al. [1] reviewed 16 patients with *Bartonella* or *Coxiella* infections who presented with systemic vasculitis; the majority had small-vessel involvement, and only a few exhibited larger vessel abnormalities [1]. Notably, large vessel vasculitis related to *Bartonella* remains exceedingly rare, especially in children.

A similar observation was reported by Houpikian et al. (2005), who described *Bartonella* as a rare but important cause of culture-negative endocarditis, with associated immune-mediated vasculitic features [2]. Similarly, Fishman et al. (2022) presented a case of *Bartonella henselae* prosthetic valve endocarditis mimicking p-ANCA-associated necrotizing glomerulonephritis. The patient developed renal and cardiac involvement severe enough to require temporary dialysis, illustrating how *Bartonella* infection can imitate systemic autoimmune vasculitis, complicating diagnosis and management [3].

To date, the literature contains very limited reports of pediatric LVV potentially triggered by *Bartonella* infection. In our case, *Bartonella* infection was confirmed through the development of a compatible clinical picture and a subsequent increase in IgG titers on serial testing. Laboratory findings supported systemic inflammation, and imaging revealed localized vascular involvement. Interestingly, the vascular inflammation was localized to the right common carotid artery, the same side as the axillary lymphadenopathy and the presumed site of the cat scratch. This laterality is consistent with *Bartonella*'s tendency to cause regionalized manifestations, such as lymphadenopathy near the site of inoculation.

The literature gives mixed messages about both the best treatment and how long it should be continued [1]. In practice, management really depends on how severe the disease is and on the treating clinician's judgment [4]. For patients with milder signs, a short course of corticosteroids can be helpful [5] When there is a pauci-immune glomerulonephritis–type picture, plasma exchange or cyclophosphamide may be needed [6]. Even in these more serious cases, steroids are usually tapered quickly [4]. In our patient, we also chose to keep corticosteroid use shorter than is typical for other LVV. As for azathioprine, there is no clear evidence on the ideal duration, but we plan to review the need for ongoing therapy and consider stopping it at around 1 year.

This case underscores the potential severity of *Bartonella* infections, particularly when complicated by large vessel vasculitis, and highlights the critical role of a multidisciplinary team, including rheumatologists, infectious disease specialists, and radiologists, in the management of such cases. In this patient, a combination of antibiotic therapy and immunosuppressive treatment proved to be effective in stabilizing the condition.

Author Contributions

Hulya Ercan Emreol and Veysel Cam were involved in the clinical evaluation of the patient, data collection, and interpretation of the findings. Veysel Cam contributed to the literature review and drafted the initial version of the manuscript. Ozge Basaran supervised the study, critically revised the manuscript for important intellectual content, and served as the corresponding author. All authors read and approved the final version of the 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 on request from the corresponding author.

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References

1. M. Beydon, C. Rodriguez, A. Karras, et al., "Bartonella and Coxiella Infections Presenting as Systemic Vasculitis: Case Series and Review of Literature," *Rheumatology (Oxford, England)* 61, no. 6 (2022): 2609–2618.

2. P. Houpikian and D. Raoult, "Blood Culture-Negative Endocarditis in a Reference Center: Etiologic Diagnosis of 348 Cases," *Medicine (Baltimore)* 84, no. 3 (2005): 162–173.

3. T. J. Fishman, E. Irizarry, A. Kaleem, R. Yancey, and U. G. Iyer, "Bartonella Henselea Prosthetic Valve Endocarditis Mimicking Vasculitis: A Case Report With Literature Review," *HCA Healthcare Journal of Medicine* 3, no. 2 (2022): 63–67.

4. M. Poursheykhi, F. Mithani, T. Garg, et al., "A Case of Cerebral Vasculitis due to Neurobartonellosis," *Neurology(R) Neuroimmunology & Neuroinflammation* 7, no. 5 (2020): e791.

5. E. Cozzani, E. Cinotti, P. Ameri, A. Sofia, G. Murialdo, and A. Parodi, "Onset of Cutaneous Vasculitis and Exacerbation of IgA Nephropathy After *Bartonella henselae* Infection," *Clinical and Experimental Dermatology* 37, no. 3 (2012): 238–240.

6. S. H. Shah, C. Grahame-Clarke, and C. N. Ross, "Touch Not the Cat Bot a Glove*: ANCA-Positive Pauci-Immune Necrotizing Glomerulonephritis Secondary to *Bartonella henselae*," *Clinical Kidney Journal* 7, no. 2 (2014): 179–181.

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EDITORIAL

Do Psoriasis Patients on Biologics Need Concomitant Methotrexate? Revisiting the Evidence in the Biologic Era

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1 | Introduction

Before the advent of biologic therapy of Phase II, methotrexate (MTX) has long served as the cornerstone of systemic treatment for psoriasis and psoriatic arthritis (PsA). Current international guidelines including GRAPPA 2022, EULAR 2023, and APLAR 2025 continue to recommend MTX as the first-line conventional synthetic DMARD in PsA management [1–3]. The TICOPA and SEAM-PsA trials further demonstrated modest but clinically relevant improvements in joint outcomes during the initial treatment phase, supporting MTX's role as an early therapeutic option prior to biologic escalation [4, 5].

The therapeutic landscape for moderate to severe psoriasis has evolved dramatically in the past two decades. The emergence of targeted biologic therapies, particularly interleukin (IL)-17 and IL-23 inhibitors, has redefined clinical goals, shifting the benchmark of treatment from partial disease control to sustained skin clearance and improved quality of life. These agents offer rapid onset of action, superior efficacy, and more favorable safety profiles compared to conventional systemic treatments.

Nonetheless, amidst this therapeutic progress, a persistent clinical dilemma remains: Is MTX, a decades-old conventional immunomodulator, still necessary when initiating biologic therapy?

The question is more than historical—it reflects current debates in clinical practice and guidelines. MTX has traditionally been co-prescribed with tumor necrosis factor (TNF)-α inhibitors to reduce the development of anti-drug antibodies (ADAs) and improve drug persistence. This practice, mainly rooted in rheumatologic data, was extended to psoriasis treatment with limited psoriasis-specific validation. However, newer biologics, including IL-17 and IL-23 inhibitors, have inherently low immunogenicity and high intrinsic drug survival, calling into question the continued relevance of routine MTX co-therapy.

2 | Background & Evidence Review

Historically, the rationale for combining MTX with biologics in psoriasis was threefold: suppressing immunogenicity, prolonging drug survival, and enhancing clinical efficacy. While this logic was initially supported by data from rheumatoid arthritis and early TNFi studies in psoriasis, its relevance to newer biologic agents is increasingly challenged by emerging real-world data and trial evidence.

A 2024 network meta-analysis of clinical trials in PsA evaluated the comparative efficacy of biologics with and without concomitant MTX. The analysis revealed no significant differences in ACR20/50/70 response rates across TNFi, IL-17, and IL-23 inhibitors between monotherapy and MTX combination groups

Abbreviations: ADA, anti-drug antibody; IL, interleukin; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RCT, randomized controlled trial; TNFi, tumor necrosis factor-alpha inhibitor.

[6]. These findings undermine the assumption that MTX enhances joint control when added to modern biologics.

For cutaneous psoriasis, the most compelling data come from a 2025 *emulated target trial* using data from the BADBIR registry, which compared adalimumab monotherapy versus adalimumab plus MTX in over 1700 patients. The study found no significant difference in drug survival or PASI75 response at 1 or 3 years between the two groups, although patients receiving MTX did have slightly lower ADA levels [7]. While immunogenicity was modestly reduced, this did not translate into improved clinical outcomes.

Further analyses from BADBIR also demonstrated that IL-23p19 inhibitors (e.g., risankizumab, guselkumab) had superior durability compared to TNFi and IL-17 inhibitors [8]. Notably, MTX use did not significantly improve persistence across any of the biologic classes, including agents with traditionally higher immunogenicity such as adalimumab.

These findings suggest that, in modern psoriasis treatment, the blanket application of MTX co-therapy may no longer be justified.

3 | Critique

While the data are compelling, several methodological considerations warrant discussion. The majority of available evidence comes from observational studies and registry analyses. Although emulated target trials improve causal inference, they remain vulnerable to confounding and selection bias. For example, patients with more severe disease or prior biologic failure are more likely to receive combination therapy, potentially skewing outcomes.

Moreover, immunogenicity varies by biologic class. TNFi agents, particularly adalimumab, are prone to ADA formation, which may reduce drug levels and clinical efficacy. In such cases, MTX might have a protective effect. However, IL-17 and IL-23 inhibitors demonstrate significantly lower immunogenicity, reducing the theoretical benefit of MTX co-administration [9].

Individual patient factors also complicate the equation. Comorbidities such as obesity, metabolic syndrome, or hepatic dysfunction may alter MTX metabolism and affect both efficacy and tolerability. Additionally, MTX's toxicity profile, particularly its risks of hepatotoxicity and bone marrow suppression, necessitates routine laboratory monitoring, which adds logistical and economic burdens.

Recent safety data from the BIOBADADERM registry offer reassurance: combination therapy with MTX did not significantly increase serious adverse events compared to biologic monotherapy over 15 years of observation [10]. Still, minor toxicities and adherence issues may limit MTX's long-term practicality, especially in elderly or multi-morbid patients.

Given these limitations, the utility of MTX co-therapy may be best reserved for selected scenarios, such as biologic-experienced patients with prior ADA development, or those with overlapping joint involvement inadequately controlled by monotherapy.

4 | Implications for Clinical Practice

From a clinical standpoint, the routine co-prescription of MTX with biologics is not recommended, particularly with IL-17 and IL-23 inhibitors. The modest and often statistically insignificant benefits must be weighed against the increased complexity, monitoring requirements, and potential for toxicity.

In selected patient populations, particularly those with prior biologic failure, known immunogenicity, or concurrent PsA, short-term or individualized MTX co-therapy may remain appropriate, ideally guided by shared decision-making and risk–benefit assessment.

Health systems must also consider cost implications. While MTX itself is inexpensive, its monitoring burden and potential for side effects increase resource utilization. Targeted use of MTX, informed by risk stratification or emerging biomarkers, may help optimize outcomes while maintaining cost-effectiveness.

Looking forward, randomized controlled trials examining MTX's impact on newer biologic classes (e.g., IL-23p19 inhibitors) are needed. The integration of AI-assisted predictive tools and pharmacogenomic profiling may also pave the way toward precision biologic therapy, allowing clinicians to identify those who truly benefit from combination regimens.

5 | Conclusion

In conclusion, MTX remains a recommended first-line agent in the initial management of psoriatic disease; however, current evidence does not support the routine use of MTX with biologics in the treatment of moderate to severe psoriasis. While TNFi may derive limited benefit from MTX co-administration in high-risk or treatment-resistant cases, the majority of patients—especially those receiving IL-17 or IL-23 inhibitors—are unlikely to benefit from combination therapy.

The future of psoriasis care lies in personalized, evidence-based treatment algorithms. As our understanding of immunogenicity, biologic durability, and patient variability deepens, so too must our therapeutic strategies evolve. MTX should no longer be viewed as a default add-on, but rather as a strategic adjunct to be deployed only when it demonstrably enhances the therapeutic outcome.

Author Contributions

Yi-Hsuan Tu: writing – review and editing, writing – original draft, conceptualization. **Hao-Yun Chen:** writing – original draft, conceptualization. **Yun-Cheng Tsai:** writing – original draft, conceptualization. **Ning Yi Fu:** writing – original draft, conceptualization. **An-Ping Huo:** supervision, writing – review and editing.

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Conflicts of Interest

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Data Availability Statement

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References

1. L. C. Coates, E. R. Soriano, N. Corp, et al., "Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): Updated Treatment Recommendations for Psoriatic Arthritis 2021," *Nature Reviews Rheumatology* 18, no. 8 (2022): 465–479, https://doi.org/10.1038/s41584-022-00798-0.

2. L. Gossec, A. Kerschbaumer, R. J. O. Ferreira, et al., "EULAR Recommendations for the Management of Psoriatic Arthritis With Pharmacological Therapies: 2023 Update," *Annals of the Rheumatic Diseases* 83, no. 6 (2024): 706–719. Published 2024 May 15, https://doi.org/10.1136/ard-2024-225531.

3. Y. Y. Leung, P. Bird, M. Haroon, et al., "The APLAR Recommendations for the Management of Psoriatic Arthritis," *International Journal of Rheumatic Diseases* 28, no. 8 (2025): e70372, https://doi.org/10.1111/1756-185x.70372.

4. L. C. Coates, A. R. Moverley, L. McParland, et al., "Effect of Tight Control of Inflammation in Early Psoriatic Arthritis (TICOPA): A UK Multicentre, Open-Label, Randomised Controlled Trial," *Lancet* 386, no. 10012 (2015): 2489–2498, https://doi.org/10.1016/S0140-6736(15)00347-5.

5. P. J. Mease, D. D. Gladman, D. H. Collier, et al., "Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial," *Arthritis and Rheumatology* 71, no. 7 (2019): 1112–1124, https://doi.org/10.1002/art.40851.

6. P. J. Mease, S. Reddy, S. Ross, et al., "Evaluating the Efficacy of Biologics With and Without Methotrexate in the Treatment of Psoriatic Arthritis: A Network Meta-Analysis," *RMD Open* 10, no. 1 (2024): e003423, https://doi.org/10.1136/rmdopen-2023-003423.

7. T. T. Cheng and Y. Lo, "Role of Methotrexate in Biologics Use With Psoriasis and Psoriatic Arthritis," *Dermatologica Sinica* 43, no. 2 (2025): 81–90, https://doi.org/10.4103/ds.DS-D-24-00194.

8. L. Motedayen Aval, Z. Z. N. Yiu, O. A. Alabas, et al., "Drug Survival of IL-23 and IL-17 Inhibitors Versus Other Biologics for Psoriasis: A British Association of Dermatologists Biologics and Immunomodulators Register Cohort Study," *Journal of the European Academy of Dermatology and Venereology* 39 (2025): 1785–1795, https://doi.org/10.1111/jdv.20739.

9. D. Thein, M. L. Nielsen, J. T. Maul, S. F. Thomsen, J. P. Thyssen, and A. Egeberg, "Impact of the Pre-Biologic Treatment Journey on Biologic Drug Survival in Psoriasis: A Nationwide Cohort Study," *Journal of the European Academy of Dermatology and Venereology* 39, no. 7 (2025): 1315–1323, https://doi.org/10.1111/jdv.20259.

10. J. J. Lluch-Galcerá, J. M. Carrascosa, A. González-Quesada, et al., "Safety of Biologic Therapy in Combination With Methotrexate in Moderate to Severe Psoriasis: A Cohort Study From the BIOBADADERM Registry," *British Journal of Dermatology* 190, no. 3 (2024): 355–363, https://doi.org/10.1093/bjd/ljad382.

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LETTER TO THE EDITOR

Anti-Mitochondrial Antibody-Positive Myositis: Analyses of 123 Adult-Onset Cases With Cardiac Evaluation

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Dear Editor,

Idiopathic inflammatory myopathies (IIM) represent a heterogeneous group of autoimmune disorders characterized by muscle inflammation and various extra-muscular manifestations. The determination of myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) in IIM has enabled precise diagnosis, categorization of heterogeneous populations into homogeneous subgroups, and prognostic stratification [1]. Anti-mitochondrial antibody (AMA) is a serological hallmark of primary biliary cholangitis (PBC), which is the autoimmune liver disease characterized by chronic injury to small bile ducts [2]. Recently, AMA has been recognized as MAAs associated with a specific IIM subtype [1, 3]. Our recent study clarified multiple cardiac lesions resistant to immunosuppressants that frequently require electronic cardiac devices in AMA-positive myositis [4]. However, there is no clear consensus on whether it represents an independent subtype among IIM [5]. In this study, we conducted a systematic literature review to provide a clearer picture of AMA-positive myositis.

PubMed/Medline and Scopus were searched for English language articles published up to April 2025 using keywords related to IIM, AMA, and PBC. Publications including adult IIM cases with cardiac evaluation were selected. Exclusion criteria were juvenile cases, animal studies, AMA-negative cases, reviews, or insufficient clinical data. Two reviewers independently screened and assessed eligibility, resolving disagreements by discussion. Data extracted included demographics, clinical data, pathological findings, treatments, and outcomes. Continuous variables were expressed as median (interquartile range), and categorical variables as numbers (percentages). Group differences were analyzed using the Mann–Whitney *U* or Fisher's exact test, with significance set at $p < 0.05$. Statistical analyses were conducted using GraphPad Prism 7.03 and GraphPad QuickCalcs (GraphPad Software). Detailed screening process is provided in Supplementary Methods: Data S1.

A total of 50 articles describing 123 cases of AMA-positive myositis were included in the review (Table S1). The results of the screening process are shown in Figure 1. The inter-rater agreement was $\kappa = 0.73$ (95% confidence intervals [CI]: 0.64–0.82) for title/abstract screening, $\kappa = 0.68$ (95% CI: 0.57–0.79) for full-text eligibility assessment, and $\kappa = 0.61$ (95% CI: 0.48–0.74) for data extraction. As shown in Table 1, the median age was 54.5 years, 66.7% were female, and the median disease duration was 18 months. Limb muscle weakness (90.7%), trunk weakness (64.9%), and muscle atrophy (58.4%) were common. Interstitial lung disease occurred in 32.9%. Cardiac involvement (CI) was present in 58.5%, including arrhythmia (55.7%), cardiomyopathy (44.6%), myocarditis (29.5%), and pulmonary hypertension (30.0%). Among cardiac evaluations, cardiac magnetic resonance imaging (CMR) was reported in 18 patients, 16 of whom had specific CMR findings. These included late gadolinium enhancement ($n = 15$), myocardial edema or T2 hyperintensity ($n = 6$), and reduced left ventricular ejection fraction ($n = 5$). PBC coexisted in 52.5%. Muscle pathology commonly showed necrotic and regenerating fibers (87.3%), fiber size variation (83.0%), major histocompatibility complex class I (MHC-I) expression (72.7%), and membrane attack complex (MAC) deposition (65.5%). Most patients (92.1%) received glucocorticoids, and 39.1% also received immunomodulators or immunosuppressants. Muscle strength improved in 77.5%, but 20.7% experienced relapse. Among cardiac cases, 44.1% required electronic devices. Indications included pacemaker implantation for sick

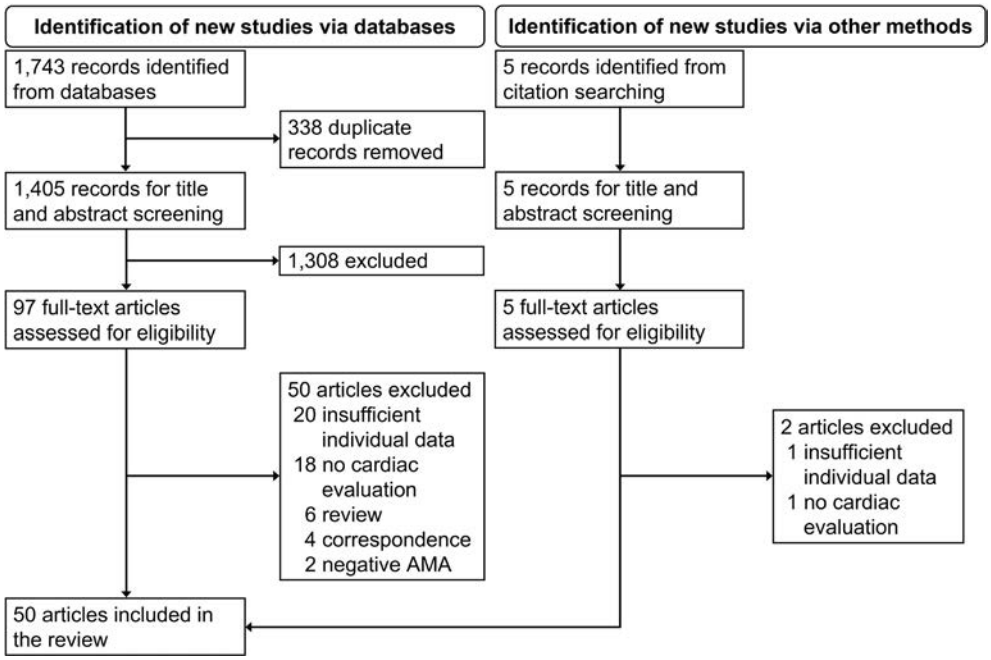

FIGURE 1 | Flow diagram of the search and screening process. Databases: PubMed/Medline and Scopus; Other methods: Manual search of references cited in initially identified papers.

sinus syndrome ($n=7$) and atrioventricular block ($n=2$), implantable cardioverter defibrillator for ventricular tachyarrhythmias ($n=7$), cardiac resynchronization therapy with defibrillator for heart failure ($n=5$), and catheter ablation for various arrhythmias ($n=14$), with some patients requiring multiple procedures. Respiratory support was required in eight patients, including invasive mechanical ventilation ($n=2$) and noninvasive positive pressure ventilation ($n=6$). Mortality was 7.1% during a median 15-month follow-up. The causes included unknown causes ($n=3$), cardiorespiratory failure ($n=2$), ventricular tachycardia ($n=1$), cardiogenic and septic shock ($n=1$), and cancer metastasis ($n=1$). Patients with PBC more often had cardiac and autoimmune comorbidities, while those without PBC had more malignancies (Table S2). Of the 14 patients with malignancy, only six had reported detailed MSAs/MAAs. Of these, only two cases tested positive: one for the anti-nuclear matrix protein 2 antibody, and the other for anti-Ro52 antibody. Furthermore, significant differences in disease duration, muscle involvement as an initial manifestation, cutaneous lesions, PBC, and follow-up duration were detected between patients with and without CI (Table S3). Quality assessment results are presented in Table S4 (case reports) and Table S5 (case series). Overall, 43 studies (86.0%) were at low risk of bias, seven studies (14.0%) were at moderate risk, and no studies were classified as high risk of bias.

This is the first systematic review to examine clinical manifestations, muscle pathology, and disease outcomes in adult-onset AMA-positive myositis patients who underwent cardiac evaluation, providing the findings to enhance the understanding of this rare disorder.

In our review, muscle involvement was present in 98.4% of AMA-positive patients diagnosed with IIM. In contrast, although the positivity of AMA in PBC is high, myositis is rare in PBC populations, with a co-occurrence rate ranging from 0.13% to 3.6% [6, 7]. This discrepancy reflects differences in the target populations. Because this study required a diagnosis of IIM for inclusion, our analyses describe the clinical phenotype of AMA-positive myositis rather than indicating a high prevalence of myositis in PBC.

A substantially higher complication rate of CI was observed in AMA-positive myositis than in other IIM subtypes [8]. The mechanism remains unclear, but prolonged diagnostic delay may allow chronic inflammation, potentially leading to myocardial damage. Thus, cardiac complications may be proactively considered, particularly in longer-course AMA-positive myositis. Additionally, CI was more frequent in patients with concurrent PBC, suggesting a synergistic autoimmune mechanism [9]. PBC-related immune activation or shared human leukocyte antigen polymorphisms may promote myocardial inflammation [10]. Enhanced cardiac monitoring is recommended in patients complicated by PBC. Interestingly, patients with PBC showed fewer malignancies, despite the general cancer risk in PBC, indicating a protective effect that requires further studies.

Muscle inflammation improved in most patients treated with glucocorticoids or immunosuppressants. However, cardiac dysfunction often persisted. Despite immunosuppressive therapies, 44.2% of patients with CI showed worsening, and 44.1% required invasive intervention with electronic devices. This indicates that CI in AMA-positive myositis can be difficult to manage and requires alternative approaches.

This study demonstrated a high prevalence of necrotic and regenerating fibers, variation in muscle fiber size, MHC-I expression, and MAC deposition, but no remarkable perifascicular atrophy on muscle biopsy samples. These features partly overlap

TABLE 1 | Clinical backgrounds in patients with AMA-positive myositis.

	Total ($n=123$)
Demographics	
Age, years	54.5 (47.0–61.3)
Female	66.7% (82/123)
Disease duration, months	18.0 (5.0–48.0)
Clinical characteristics	
Initial manifestations	
Muscle involvements	57.9% (62/107)
CK level elevation without myositis	12.1% (13/107)
CIs	19.6% (21/107)
Others	10.3% (11/107)
Muscle involvements	98.4% (121/123)
Limb weakness	90.7% (107/118)
Trunk weakness	64.9% (72/111)
Muscle atrophy	58.4% (52/89)
Dysphagia	24.4% (21/86)
Respiratory disturbance	36.7% (40/109)
Max CK level, U/mL	1157 (575.8–2213)
CIs	58.5% (72/123)
Arrhythmia	55.7% (64/115)
Sick sinus syndrome	6.1% (7/115)
Cardiac block	20.9% (24/115)
Supraventricular tachyarrhythmia	43.5% (50/115)
Ventricular tachyarrhythmia	29.6% (34/115)
Cardiomyopathy	44.6% (50/112)
Myocarditis	29.5% (18/61)
Pulmonary hypertension	30.0% (12/40)
Interstitial lung disease	32.9% (24/73)
Skin involvements	20.0% (12/60)
Arthralgia/Arthritis	17.3% (9/52)
Malignancy	13.9% (14/101)
PBC	52.5% (51/97)
Preexisting PBC	37.0% (10/27)
Preexisting PBC duration, months	84.0 (17.0–108.0)
Other autoimmune diseases	24.5% (25/102)
Treatments	
Glucocorticoids	92.1% (105/114)
Intravenous methylprednisolone	20.8% (22/106)
IS	39.1% (43/110)
Hydroxychloroquine	1.8% (2/110)
Azathioprine	12.7% (14/110)
Methotrexate	13.6% (15/110)
Mycophenolate mofetil	8.2% (9/110)
Tacrolimus	4.5% (5/110)
Cyclosporin	1.8% (2/110)
Cyclophosphamide	3.6% (4/110)
Rituximab	6.4% (7/110)
Intravenous immunoglobulin	15.5% (17/110)
Plasma exchange	0.9% (1/110)
Electronic devices for CIs[a]	44.1% (30/68)
Outcomes	
Follow-up period, months	15.0 (6.0–36.0)
Improvement of myositis	77.5% (79/102)
Relapse of myositis[b]	20.7% (12/58)
Worsening of CIs[a]	46.0% (23/50)
Mortality	7.1% (8/112)
Histopathological findings of muscle	
Necrotic and regenerating fibers	87.3% (55/63)
Inflammatory cell infiltration	68.2% (60/88)
Perifascicular atrophy	3.8% (2/53)
Variation in muscle fiber size	83.0% (39/47)
Vacuole	33.3% (9/27)
Granuloma	18.0% (9/50)
Mitochondrial abnormalities	61.3% (19/31)
Membrane attack complex deposition	65.5% (19/29)
MHC class I expression	72.7% (40/55)

Note: Data available in the literature are expressed as median (interquartile range) or percentage.
Abbreviations: AMA, anti-mitochondrial antibody; CIs, cardiac involvements; CK, creatinine kinase; IS, immunomodulatory/immunosuppressive therapies; MHC, major histocompatibility complex; PBC, primary biliary cholangitis.
[a]Among patients who had CIs.
[b]Among patients who experienced improvement of myositis.

with immune-mediated necrotizing myopathy but with more inflammation.

Notably, histopathological findings of skeletal muscle mitochondrial abnormalities were commonly reported, and marked mitochondrial degeneration in endomyocardial biopsy specimens was also detected using electron microscopy [11]. Immunostaining

for pyruvate dehydrogenase complex-E2 subunit (PDC-E2), a major autoantigen recognized by AMA [12], revealed granular staining in the cytoplasm of myocytes and cardiomyocytes in patients with AMA-positive myositis, but not in those with AMA-negative myositis. These findings suggest that PDC-E2 released by mitochondrial damage triggers inflammatory activation against damaged cells, resulting in myositis and myocarditis [11]. A critical mechanism underlying the development of AMA-positive myositis may be mitochondrial damage, which potentially creates a vicious cycle amplifying the activation of immune response.

This study had some limitations. First, the study included only 123 patients, which may reduce the statistical power of comparisons. Second, missing data and varying criteria for outcome assessment may prevent the accuracy of clinical characterization. Particularly, the pathological findings in muscle tissue were reported inconsistently across the studies, and insufficient data were available on the detailed immunohistochemical characterization of inflammatory cell infiltration. Third, this analysis could not fully account for pivotal confounding factors, such as comorbidities and medication for cardiac complications, which may influence disease manifestations and treatment outcomes. Fourth, because the included studies were reported predominantly from East Asian countries, limiting generalizability. Fifth, a high prevalence of pulmonary hypertension was observed in AMA-positive myositis. Although right heart catheterization is the gold standard for the diagnosis and classification of pulmonary hypertension, most cases relied on echocardiography rather than right heart catheterization. This limitation prevented accurate determination of the underlying mechanisms of pulmonary hypertension. Sixth, because of the heterogeneous reporting in the literature, it was difficult to analyze the impact of other MSAs or MAAs on clinical characteristics in AMA-positive myositis. Seventh, the severity grading of limb muscle weakness was inconsistently reported across studies. While various assessment methods were adopted, some studies did not provide specific grading of muscle weakness or the affected limb regions, limiting our ability to perform a detailed analysis of the severity and distribution patterns.

In conclusion, this systematic review revealed clinical profiles of AMA-positive myositis. Understanding this disease entity may aid in early diagnosis and improve clinical management.

Author Contributions

Tomoyuki Mutoh: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, writing – original draft. **Mikihiro Takahashi:** data curation, formal analysis, investigation, writing – review and editing. **Hiroshi Fujii:** data curation, supervision, writing – review and editing.

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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.

Tomoyuki Mutoh
Mikihiro Takahashi
Hiroshi Fujii

References

1. N. A. Allameen, A. I. Ramos-Lisbona, L. R. Wedderburn, I. E. Lundberg, and D. A. Isenberg, "An Update on Autoantibodies in the Idiopathic Inflammatory Myopathies," *Nature Reviews Rheumatology* 21, no. 1 (2024): 46–62, https://doi.org/10.1038/s41584-024-01188-4.

2. A. Lleo, G. Q. Wang, M. E. Gershwin, and G. M. Hirschfield, "Primary Biliary Cholangitis," *Lancet* 396, no. 10266 (2020): 1915–1926, https://doi.org/10.1016/s0140-6736(20)31607-x.

3. J. A. Gonzalez-Chapa, M. B. Macedo, and C. Lood, "The Emerging Role of Mitochondrial Dysfunction in the Pathogenesis of Idiopathic Inflammatory Myopathies," *Rambam Maimonides Medical Journal* 14, no. 2 (2023): e0006, https://doi.org/10.5041/rmmj.10493.

4. T. Mutoh, M. Takahashi, H. Satake, K. Daikoku, and H. Fujii, "Anti-Mitochondrial Antibody-Positive Inflammatory Myopathy With Multiple Arrhythmias Resistant to High-Dose Glucocorticoids and Intravenous Cyclophosphamide: A Case-Based Review," *Clinical Rheumatology* 44, no. 6 (2025): 2561–2571, https://doi.org/10.1007/s10067-025-07439-3.

5. Y. Nishimori, J. Tanboon, M. Oyama, et al., "Anti-Mitochondrial M2 Antibody-Positive Myositis May Be an Independent Subtype of Autoimmune Myositis," *Journal of Neurology* 272, no. 3 (2025): 206, https://doi.org/10.1007/s00415-025-12945-0.

6. S. Bian, H. Chen, L. Wang, et al., "Cardiac Involvement in Patients With Primary Biliary Cholangitis: A 14-Year Longitudinal Survey-Based Study," *PLoS One* 13, no. 3 (2018): e0194397, https://doi.org/10.1371/journal.pone.0194397.

7. C. Efe, M. Torgutalp, I. Henriksson, et al., "Extrahepatic Autoimmune Diseases in Primary Biliary Cholangitis: Prevalence and Significance for Clinical Presentation and Disease Outcome," *Journal of Gastroenterology and Hepatology* 36, no. 4 (2021): 936–942, https://doi.org/10.1111/jgh.15214.

8. S. Faghihi-Kashani, A. Yoshida, F. Bozan, et al., "Clinical Characteristics of Anti-Synthetase Syndrome: Analysis From the Classification Criteria for Anti-Synthetase Syndrome Project," *Arthritis & Rhematology* 77, no. 4 (2025): 477–489, https://doi.org/10.1002/art.43038.

9. P. Jiang, Z. Feng, L. Sheng, et al., "Morphological, Functional, and Tissue Characterization of Silent Myocardial Involvement in Patients With Primary Biliary Cholangitis," *Clinical Gastroenterology and Hepatology* 20, no. 5 (2022): 1112–1121, https://doi.org/10.1016/j.cgh.2021.08.035.

10. B. Terziroli Beretta-Piccoli, G. Mieli-Vergani, and D. Vergani, "HLA, Gut Microbiome and Hepatic Autoimmunity," *Frontiers in Immunology* 13 (2022): 980768, https://doi.org/10.3389/fimmu.2022.980768.

11. T. Saito, E. Kodani, H. Katayama, and Y. Kusama, "Eosinophilic Myocarditis Associated With Anti-Mitochondrial M2 Antibodies: A Mechanism Underlying the Onset of Myocarditis," *European Heart Journal* 39, no. 37 (2018): 3480–3481, https://doi.org/10.1093/eurheartj/ehy246.

12. F. Colapietro, A. Lleo, and E. Generali, "Antimitochondrial Antibodies: From Bench to Bedside," *Clinical Reviews in Allergy and*

Immunology 63, no. 2 (2022): 166–177, https://doi.org/10.1007/s12016-021-08904-y.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supplementary Methods. **Table S1:** The reference list of 50 articles included in this study. **Table S2:** Clinical differences in patients with AMA-positive myositis stratified by PBC. **Table S3:** Clinical differences in patients with AMA-positive myositis stratified by CI. **Table S4:** Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports ($n = 38$). **Table S5:** Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series ($n = 12$).

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CORRECTION

Correction to "Anti-Inflammatory Mechanisms of Antidiabetic Therapies: Metabolic Regulation and Inflammatory Pathways"

Yen, F.S., Y.H. Lee, P. Kuo, M.C. Wu and P.Y. Leong. 2025. "Anti-Inflammatory Mechanisms of Antidiabetic Therapies: Metabolic Regulation and Inflammatory Pathways." *International Journal of Rheumatic Diseases* 28, no. 4: e70201.

In the above article, both Poi Kuo and Pui-Ying Leong were listed as the corresponding authors. The corresponding author should be Pui-Ying Leong only.

The online article has been corrected.

We apologize for this error.

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LETTER TO THE EDITOR

Case Report: Telitacicept in Sequential Treatment After Ripertamab for Rheumatoid Peripheral Ulcerative Keratitis

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Dear Editor,

Peripheral ulcerative keratitis (PUK) is a devastating ocular inflammatory disease that can progress from corneal ulceration to perforation and even loss of vision, with an estimated incidence of 3 cases per 1 million inhabitants per year [1]. However, rheumatoid arthritis (RA) is observed in 34%–42% of definitively diagnosed PUK cases. RA is the most common cause of non-infectious PUK, and in a retrospective study including 589 patients with RA, 1% (6/589) developed PUK [2]. Typical PUK occurs 10–14 years after the diagnosis of RA, and it is worth noting that PUK may not correlate with joint symptoms and may also present as the first symptom of RA in a few cases [3]. It is considered a manifestation of SRV and is associated with decreased life expectancy. Therefore, these patients require early diagnosis and immunosuppressive therapy.

A 56-year-old female presented with a 4-year history of bilateral xerophthalmia, ocular pain, and progressive visual impairment, alongside a 20-year history of untreated symmetric polyarticular arthritis. Ophthalmological examination revealed PUK in both eyes, but topical treatments such as prednisolone acetate ophthalmic suspension and levofloxacin eye drops were not effective. Based on the positive results of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), she was definitively diagnosed with rheumatoid-PUK and treated with oral prednisolone acetate 40 mg/day, methotrexate 10 mg/week, and leflunomide 10 mg/day.

However, during glucocorticoid tapering, her left corneal ulcer recurred and progressed to corneal perforation: a 2 × 10 mm arcuate ulcer was observed in the inferior region of the left eye, with corneal perforation at the 5 o'clock position (Figure 1A). Pathogenic examination of corneal ulcer scrapings revealed no bacteria or fungi, so emergency amniotic membrane transplantation was performed. During the procedure, a corneal lenticule graft was used to repair the perforation site, and a single layer of amniotic membrane was applied to the conjunctival surface approximately 1 cm posterior to the limbus. A bandage contact lens was placed on the ocular surface for protection after the operation. Postoperatively, the patient's left eye symptoms of pain and blurred vision did not resolve, and the right eye gradually developed worsening redness and pain. Subsequent ophthalmic reexamination revealed a 5 × 6 mm ulcer in the central region of the right cornea (Figure 1B). The visual acuity test revealed that the left eye retained only 30 cm manual vision, while the right eye could count fingers at 10 cm.

The patient was referred to the rheumatology department and underwent further systemic examination. Physical examination revealed no obvious swelling, tenderness, or limited range of motion of the extremities' joints; the Disease Activity Score 28 based on Erythrocyte Sedimentation Rate (DAS28-ESR) was 3.7, indicating a moderately active state. Serum immunologic findings showed RF 94.56 IU/mL (0–20 IU/mL), ACPA 59.75 (0–3), anti-nuclear antibody 1:320, anti-SSA antibody positive, ESR 40 mm/h, immunoglobulin IgG 14.95 g/L, immunoglobulin IgA 4.67 g/L, and ANCA negative. Additionally, labial gland tissue biopsy revealed 4 lymphocytic aggregates, suggesting the presence of secondary Sjögren's syndrome. Echocardiography showed no cardiac valve lesions or pericardial effusion, and chest computed tomography did not indicate interstitial lung disease or other manifestations of pulmonary involvement. Meanwhile, screening for infectious diseases was performed, with negative results for hepatitis B, hepatitis C, human immunodeficiency virus infection, syphilis, and tuberculosis, which ruled out the presence of active infection.

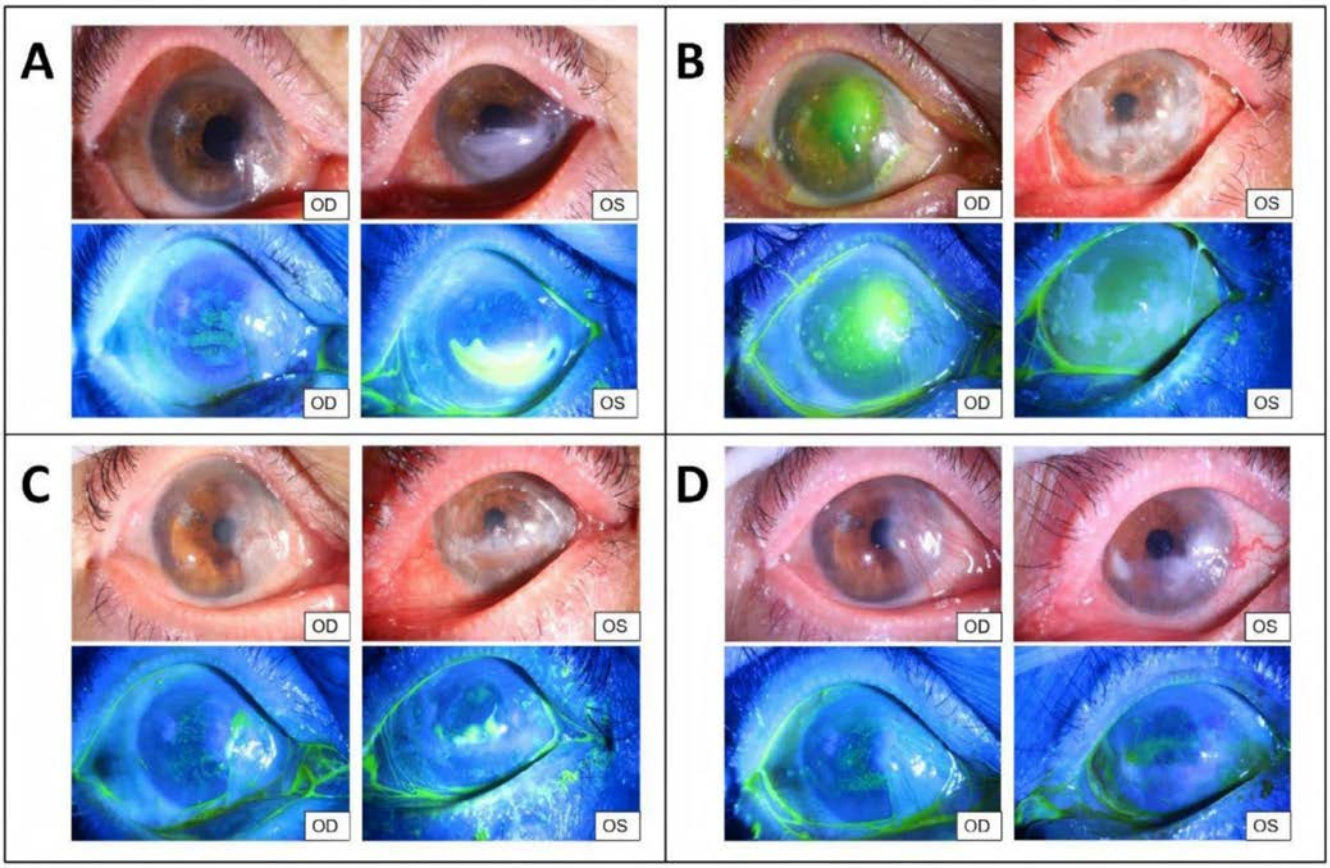

FIGURE 1 | Changes in anterior segment photography and corneal fluorescein staining during treatment. (A) Pretreatment: Bilateral conjunctival hyperemia, punctate staining of the right cornea, and a crescent-shaped corneal ulcer with perforation at the 3–6 o'clock position of the left eye. (B) Amniotic membrane grafting was performed on the left eye, with a bandage contact lens applied. A new corneal ulcer has developed on the temporal side of the right pupil. (C) After one month of treatment: Bilateral conjunctival hyperemia had subsided. The temporal ulceration of the right pupil had healed, with peripheral vascular ingrowth. The corneal graft in the left eye remained in place, and the ulceration had resolved. (D) After 6 months of treatment: The corneal ulcers in both eyes have nearly completely healed, and conjunctival hyperemia has subsided.

An intensive immunosuppressive treatment regimen has been established to prevent permanent vision loss. Initially, she received pulse therapy with methylprednisolone at a dose of 500 mg/day for 3 consecutive days, followed by a switch to oral prednisone at an initial dose of 40 mg/day with a gradual tapering schedule thereafter. Ripertamab was given at a weekly dose of 600 mg (administered at a dose of 375 mg/m^2) for 4 weeks, followed by a sequential regimen of telitacicept 160 mg/week. Bilateral corneal ulcers were nearly healed at 1 month (Figure 1C). The regimen was adjusted to maintenance with prednisone 2.5 mg/day and telitacicept 160 mg/10 days at 3 months. At 6-month follow-up, visual acuity recovered to 20/40 with complete corneal ulcer healing (Figure 1D), joint symptoms resolved. No recurrent joint swelling or pain was observed. The ESR returned to normal, RF turned negative, and DAS28-ESR decreased to 1.96 (Figure 2). No infections or other adverse events occurred during the entire treatment period.

The exact pathophysiological mechanisms of PUK are unknown, but unequivocally both humoral and cellular immunity are involved in the inflammatory process. The peculiar avascular structure of the cornea makes it accessible to nutrients only through the peripheral area close to the capillary bed [4], which makes this region susceptible to immune complex deposition and activation of the complement pathway. TH lymphocytes in the scleral-corneal limbus cause tissue damage by producing cytokines and recruiting leukocytes from the circulation, which promotes local invasion by immune cells. Macrophages and mast cells from immune cells are recruited to the peripheral cornea, where they release collagenases that disrupt the outer corneal stroma, promoting ulcer development [1]. Treatment of PUK is aimed at reducing inflammation, promoting epithelial healing, and minimizing stromal loss. Early pharmacological intervention can decrease rates of blindness and mortality.

There is no consensus on immunosuppressive therapy for PUK. Previous experience has shown that the combination of glucocorticoids and csDMARDs is usually the first-line treatment option, and high-dose glucocorticoids pulsatile therapy can rapidly control inflammation. However, this therapy increases the risk of infection during corneal healing, and the likelihood of recurrence increases as the dosage of glucocorticoids is reduced. Cyclophosphamide has shown some efficacy in the treatment of PUK, yet it has poor safety and does not reduce mortality [5]. In recent years, biological agents have become a new option, with TNF inhibitors being the most commonly used. However, case–control studies have shown that 48% of patients receiving anti-TNF therapy required a switch to a second biologic agent during

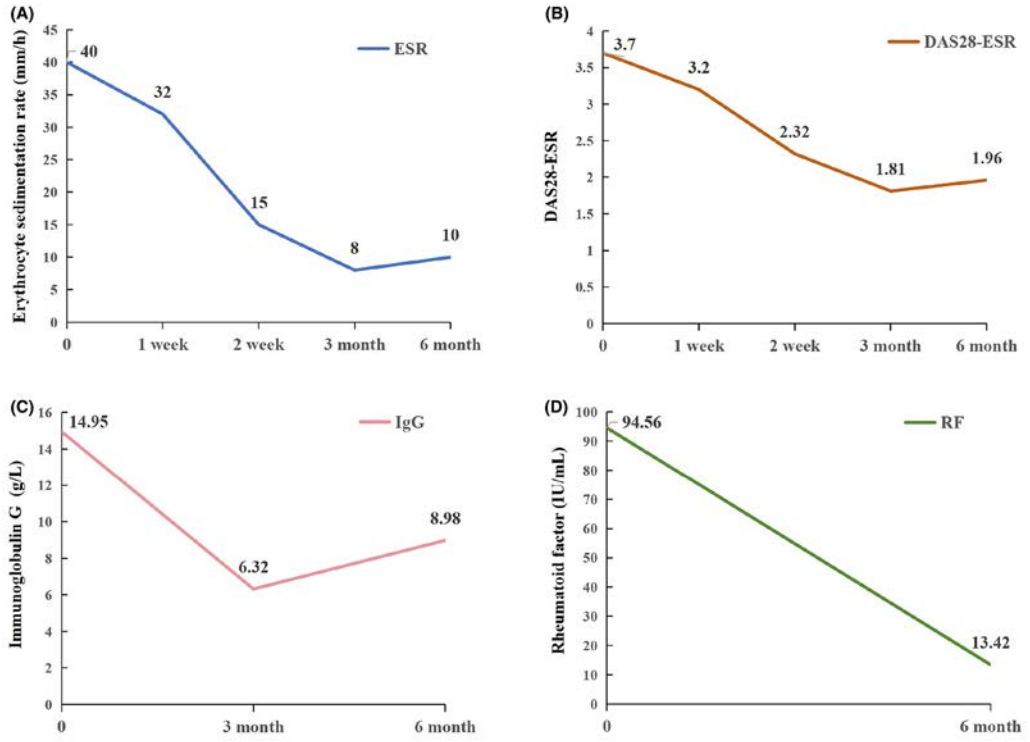

FIGURE 2 | Changes in ESR (A), DAS28 (B), IgG (C), and RF (D) before and after treatment.

follow-up due to recurrence [6]. In addition, PUK has been frequently reported in RA patients treated with tocilizumab. Investigators have considered that the depletion of IL-6 at the level of the cornea may play a deleterious role through dysregulation of corneal epithelial healing [7]. Higher titres of RF and ACPA are usually detected in patients with RA-associated PUK, suggesting a central role of B lymphocytes and immune complexes in the pathogenic process [8].

CD20 monoclonal antibody, the best-known treatment targeting B lymphocytes, has been proven to be an effective induction therapy for SRV, but 18% of patients subsequently experience relapse [5]. The shortcomings of CD20-targeted therapy pose multiple challenges to long-term disease control. First, it can only deplete CD20-positive B cells in the peripheral circulation, but has no effect on differentiated plasmablasts, long-lived plasma cells, or upstream activation signals, which has become an important inducement for protracted disease course [9]. Second, the B cell depletion mediated by CD20 monoclonal antibodies can trigger negative feedback regulation in the body, promoting the significant upregulation of cytokine levels such as B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), accelerating the abnormal reconstitution, proliferation, and differentiation of B cells, and thereby causing disease rebound [10]. Third, patients who repeatedly receive CD20 monoclonal antibody monotherapy are prone to produce anti-drug antibodies and promote the generation of memory B cells, thereby increasing the production of pathogenic plasma cells, activating immune responses, and significantly reducing the effectiveness of long-term treatment [9].

As a novel recombinant fusion protein drug, telitacicept can simultaneously target BLyS and APRIL. By blocking B cell differentiation and maturation, inhibiting abnormal B cell activation, and reducing the secretion of pathogenic autoantibodies and immunoglobulins, it has demonstrated definite efficacy in autoimmune diseases. Different from the single-target limitation of CD20 monoclonal antibodies, telitacicept exerts intervention effects throughout the differentiation stages from early immature B cells to late plasma cells, enabling a more comprehensive suppression of B cell-mediated autoimmune responses and laying a key foundation for achieving long-term disease remission.

In this case, the patient received ripertamab for induction of remission followed by sequential telitacicept for maintenance therapy, achieving significant clinical benefits: corneal ulcer achieved clinical healing within 1 month of treatment, visual acuity recovered from hand motion/30 to 20/40 at 6 months, joint inflammation remained stable, and glucocorticoid dosage was successfully tapered smoothly. This therapeutic effect confirmed the synergistic effect of the sequential regimen: ripertamab can rapidly deplete circulating CD20-positive B cells to achieve quick control of acute inflammation, while telitacicept can continuously regulate plasma cells and abnormal B cell subsets to consolidate remission and prevent disease recurrence. In terms of safety, compared to the long-term monotherapy with CD20 monoclonal antibodies, which may cause sustained B cell depletion and lead to severe impairment of the body's humoral immune function, telitacicept can selectively target abnormally activated B cells instead of completely eliminating the entire B cell population, demonstrating superior safety characteristics.

Although no infection-related adverse events were observed in this case, it should be clarified that this sequential regimen still belongs to an intensified immunosuppressive strategy. Despite

its higher targeting specificity than repeated CD20 monoclonal antibody therapy, it can't completely avoid the risk of infection. Particularly in cases of difficult-to-treat RA, which are characterized by long-term disease activity, failure of multiple treatment methods, severe immune dysfunction, and various complications such as diabetes or interstitial lung disease, placing them at high risk for infections. Therefore, rigorous infection control strategies must be implemented in clinical practice. Pretreatment screening for infection history and assessment of immune function are essential. High-risk patients may receive low-dose oral trimethoprim-sulfamethoxazole for prophylactic infection prevention. During treatment, close monitoring for infection-related symptoms is required. Once disease control is achieved, timely reduce glucocorticoid dosage and attempt to gradually extend the dosing interval of telitacicept to further mitigate infection risk.

In summary, the sequential regimen of CD20 monoclonal antibody and telitacicept provides a new paradigm for autoimmune diseases. However, this study is limited to a single case report, with constraints including a small sample size and lack of long-term follow-up data. Future large-scale prospective cohort studies are needed to further validate the long-term efficacy and safety of this regimen, clarify its applicable population and dosage adjustment strategies, thereby optimizing the treatment plan to maximize clinical benefits.

Author Contributions

Xi Zhao: writing original draft, data curation, investigation. Mingfang Sun and Fei Xiao: follow up of patient. Huanzi Dai: reviewing and editing, supervision. All authors have read and approved the final manuscript.

Consent

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

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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References

1. M. Artifoni, P. R. Rothschild, A. Brézin, L. Guillevin, and X. Puéchal, "Ocular Inflammatory Diseases Associated With Rheumatoid Arthritis," *Nature Reviews Rheumatology* 10, no. 2 (2014): 108–116.

2. R. Watanabe, T. Ishii, M. Yoshida, et al., "Ulcerative Keratitis in Patients With Rheumatoid Arthritis in the Modern Biologic Era: A Series of Eight Cases and Literature Review," *International Journal of Rheumatic Diseases* 20, no. 2 (2017): 225–230.

3. A. Makol, E. L. Matteson, and K. J. Warrington, "Rheumatoid Vasculitis: An Update," *Current Opinion in Rheumatology* 27, no. 1 (2015): 63–70.

4. V. Calvo-Río, L. Sánchez-Bilbao, C. Álvarez-Reguera, et al., "Baricitinib in Severe and Refractory Peripheral Ulcerative Keratitis: A Case Report and Literature Review," *Therapeutic Advances in Musculoskeletal Disease* 14 (2022): 1759720x221137126.

5. X. Puéchal, J. E. Gottenberg, J. M. Berthelot, et al., "Rituximab Therapy for Systemic Vasculitis Associated With Rheumatoid Arthritis: Results From the AutoImmunity and Rituximab Registry," *Arthritis Care & Research* 64, no. 3 (2012): 331–339.

6. L. C. Dominguez-Casas, L. Sánchez-Bilbao, V. Calvo-Río, et al., "Biologic Therapy in Severe and Refractory Peripheral Ulcerative Keratitis (PUK). Multicenter Study of 34 Patients," *Seminars in Arthritis and Rheumatism* 50, no. 4 (2020): 608–615.

7. F. Cohen, E. E. Gabison, S. Stéphan, et al., "Peripheral Ulcerative Keratitis in Rheumatoid Arthritis Patients Taking Tocilizumab: Paradoxical Manifestation or Insufficient Efficacy?," *Rheumatology* 60, no. 11 (2021): 5413–5418.

8. C. Turesson, L. T. Jacobsson, G. Sturfelt, E. L. Matteson, L. Mathsson, and J. Rönnelid, "Rheumatoid Factor and Antibodies to Cyclic Citrullinated Peptides Are Associated With Severe Extra-Articular Manifestations in Rheumatoid Arthritis," *Annals of the Rheumatic Diseases* 66, no. 1 (2007): 59–64.

9. E. Crickx, P. Chappert, A. Sokal, et al., "Rituximab-Resistant Splenic Memory B Cells and Newly Engaged Naive B Cells Fuel Relapses in Patients With Immune Thrombocytopenia," *Science Translational Medicine* 13, no. 589 (2021): eabc3961.

10. L. M. Carter, D. A. Isenberg, and M. R. Ehrenstein, "Elevated Serum BAFF Levels Are Associated With Rising Anti-Double-Stranded DNA Antibody Levels and Disease Flare Following B Cell Depletion Therapy in Systemic Lupus Erythematosus," *Arthritis and Rheumatism* 65, no. 10 (2013): 2672–2679.

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CLINICAL IMAGE

Gouty Arthritis With Normouricaemia and Diffuse Urate Deposition

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A 57-year-old man presented with recurrent polyarthralgia involving bilateral sternoclavicular joints, right shoulder, wrists, sacroiliac joints, knees, and ankles over 3 years, accompanied by low-grade fever (< 38°C). The patient had a 6-year history of type 2 diabetes. Physical examination revealed no synovial swelling, skin lesions, or tophi (Figure S1A–E). Laboratory investigations showed normal autoantibody profiles (Antinuclear antibody, Rheumatoid factor, Anti-cyclic citrullinated peptide, antineutrophil cytoplasmic antibodies), negative human leukocyte antigen B27, and serum uric acid levels persistently within normal range (240 μmol/L at presentation; historical peak 308 μmol/L). Acute-phase reactants were elevated during flares (Erythrocyte sedimentation rate (ESR) 64 mm/h; C-reactive protein (CRP) 9.3 mg/L). Dual-energy CT demonstrated urate deposits in sternoclavicular, sacroiliac, and knee joints (Figure 1A–C). Ultrasonographic examination revealed small effusions with synovitis in the right wrist and left knee joints, as well as hyperechoic deposits within the periarticular soft tissues of the left first metatarsophalangeal (MTP) joint, suggestive of urate deposition (Figure S1F–H). Ultrasound-guided knee aspiration revealed needle-shaped birefringent crystals under polarized microscopy, though notably smaller and more delicate than typical monosodium urate (MSU) crystals (Figure 1D,E). Synovial fluid analysis excluded infection and microcrystalline deposits other than urate.

The diagnosis of normouricaemic gouty arthritis was established based on imaging evidence of urate deposition and crystal confirmation. Treatment with NSAIDs achieved rapid symptom resolution. Long-term management with febuxostat 20 mg every other day, colchicine 0.5 mg daily, and sodium bicarbonate 0.5 g twice daily maintained disease remission. Follow-up over 12 months showed normalized inflammatory markers (ESR < 10 mm/h, CRP ≤ 3 mg/L) and stable uricaemia (210–225 μmol/L). Our patient demonstrates that clinically significant urate deposition can occur at sub-saturation levels. It is noteworthy that the urate crystals in the synovial fluid of this case exhibited delicate, hair-like alterations under polarized light microscopy. This morphological characteristic may be intrinsically linked to the patient's persistently normouricemic status, and potentially correlates with both axial joint deposition and febrile manifestations during gout attacks, warranting further clinical investigation.

Author Contributions

The author takes full responsibility for this article.

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Ethics Statement

This study describes a clinical case and does not fall within the scope of an ethics committee or an institutional board. The participant gave informed consent to participate in the study before taking part.

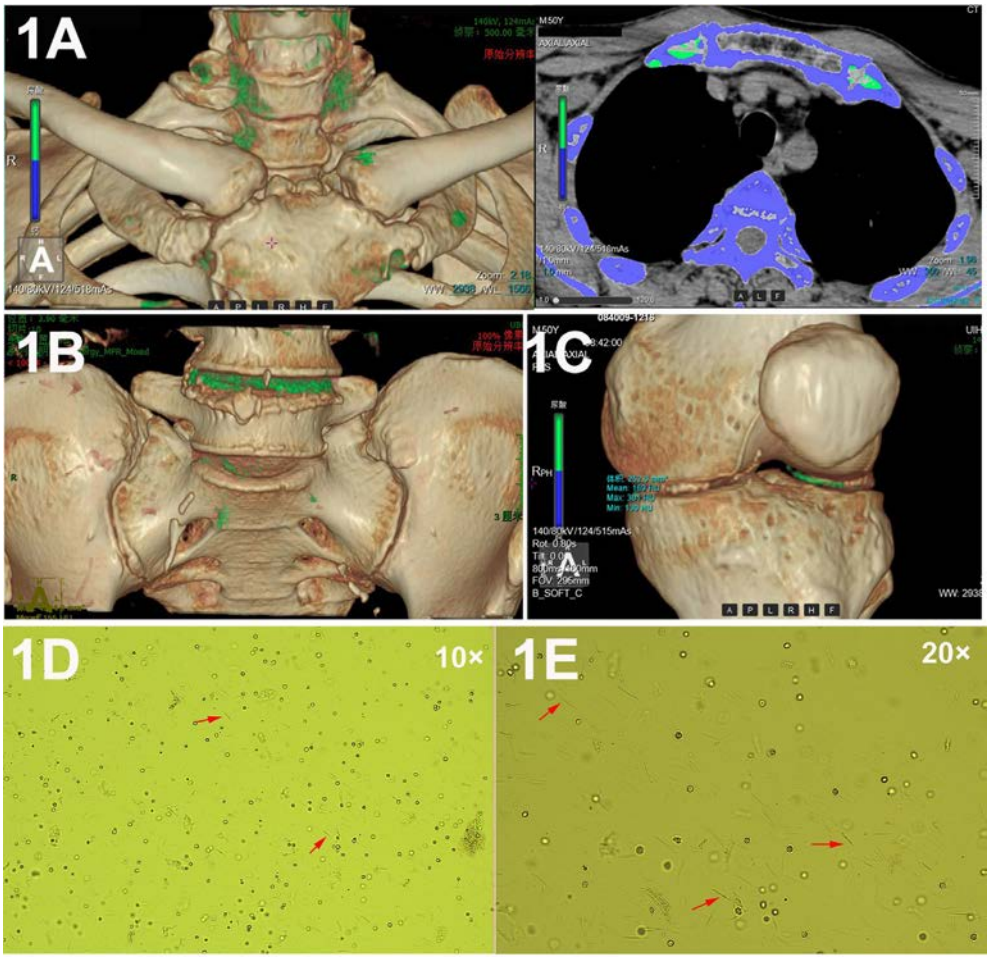

FIGURE 1 | Dual-energy CT urate mapping (green) in sternoclavicular (A), sacroiliac (B), and knee joints (C); polarized microscopy of synovial fluid demonstrating atypical urate crystals (D, E).

Conflicts of Interest

The author declares 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.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Physical examination showing absence of joint swelling/tophi, thoracic cage (A), buttocks (B), bilateral knees (C), bilateral hands (D), and bilateral feet (E); ultrasonography revealed minimal effusion with synovitis in right wrist (F), left knee(G), and first metatarsophalangeal joints (H).

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CLINICAL IMAGE

Temporomandibular Joint Uptake on Gallium Scintigraphy in Elderly-Onset Rheumatoid Arthritis

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Keywords: gallium radioisotopes | radionuclide imaging | rheumatoid arthritis | temporomandibular joint

An 85-year-old Japanese woman was admitted with a two-week history of fever and appetite loss. Physical examination revealed no significant abnormalities. Laboratory tests were unremarkable except for an elevated serum C-reactive protein level (11.78 mg/dL; reference: 0.00–0.14) and an increased erythrocyte sedimentation rate (110 mm/h; reference: 3–15).

Additional tests showed a rheumatoid factor (RF) level of 21 IU/mL (reference: 0–15), an anti-cyclic citrullinated peptide antibody (ACPA) level of < 0.6 U/mL (reference: 0.0–0.6), and an antinuclear antibody (ANA) speckled pattern at a titer of 1:640 (reference: < 1:40). The anti-SS-A/Ro antibody level was > 1200 U/mL (reference: 0.0–7.0). Blood cultures were negative. Contrast-enhanced computed tomography (from the neck to the pelvis), upper gastrointestinal endoscopy, colonoscopy, transthoracic echocardiography, bone marrow aspiration, and random skin biopsy revealed no significant findings.

Three weeks after admission, she developed inflammatory arthritis of the right temporomandibular joint (TMJ). Gallium scintigraphy showed increased uptake in the right TMJ as well as in multiple large joints (Figure 1). She subsequently developed generalized joint pain.

1 | What is the Diagnosis?

Diagnosis: Elderly-onset rheumatoid arthritis (EORA) with concomitant Sjögren syndrome.

She fulfilled the 2010 ACR/EULAR rheumatoid arthritis (RA) classification criteria (total score 6). Concomitant Sjögren syndrome was supported by a positive Schirmer test.

TMJ involvement in RA has been reported with a wide prevalence range (approximately 4.7% to 84%) and may be clinically silent [1]. Ilhanli et al. [2] reported no significant difference in TMJ involvement between EORA and young-onset RA. Gallium scintigraphy can demonstrate uptake in inflamed joints in RA [3]. However, to our knowledge, gallium-detected TMJ involvement in RA has not been reported.

In this diagnostically challenging early presentation characterized by fever and limited focal findings, whole-body gallium scintigraphy visualized the distribution of inflammatory joint involvement, thereby helping to generate a diagnostic hypothesis before overt polyarthritis developed. TMJ involvement in RA has also been evaluated using other imaging modalities; a systematic review summarized the utility of CT and MRI and discussed functional imaging such as PET/CT, while noting limitations and evidence gaps in early or asymptomatic TMJ involvement [4]. Concomitant Sjögren's disease in RA has been associated with higher disease activity and functional disability, underscoring the clinical relevance of recognizing this overlap [5].

Treatment with prednisone (20 mg/day) and methotrexate (6 mg/week) led to rapid symptom resolution. Methotrexate was escalated up to 16 mg/week while prednisone was tapered;

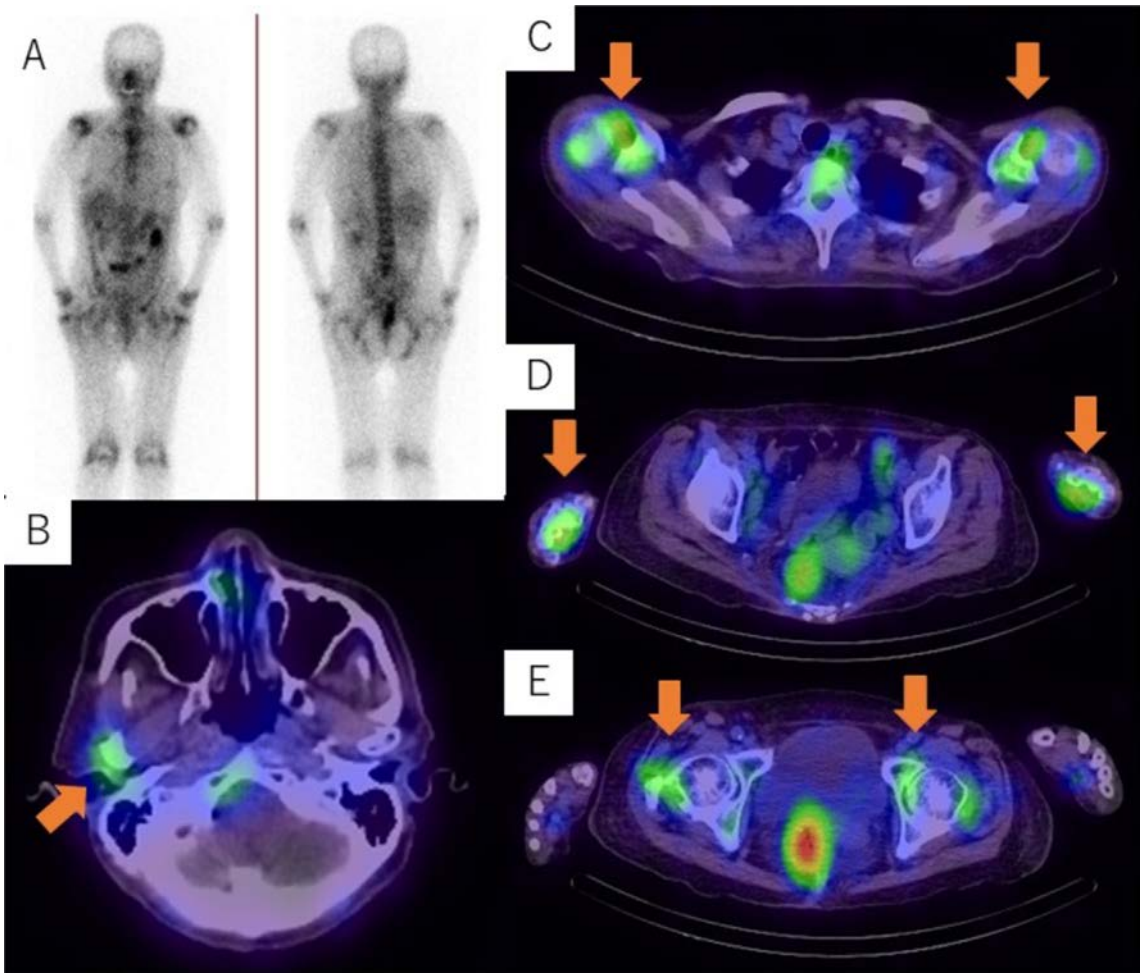

FIGURE 1 | (A) Gallium scintigraphy showing uptake in major joints throughout the body. (B) Focal uptake in the right temporomandibular joint (arrow). (C) Uptake in bilateral shoulder joints (arrows). (D) Uptake in bilateral wrist joints (arrows). (E) Uptake in bilateral hip joints (arrows).

methotrexate was discontinued at 6 months because of pancytopenia and switched to sulfasalazine. She remained clinically stable without relapse at one-year follow-up.

Author Contributions

T.N. drafted the manuscript. R.T. supervised the preparation of the manuscript. T.N. and R.T. were responsible for patient care.

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The authors have nothing to report.

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.

References

1. N. Bayar, S. A. Kara, I. Keles, et al., "Temporomandibular Joint Involvement in Rheumatoid Arthritis: A Radiological and Clinical Study," *Cranio* 20, no. 2 (2002): 105–110.

2. M. Ilhanli and I. Ilhanli, "Temporomandibular Joint Involvement in Elderly Onset and Young Onset Rheumatoid Arthritis Patients," *Revista da Associação Médica Brasileira* 69, no. 8 (1992): e20230411.

3. I. W. McCall, H. Sheppard, M. Haddaway, et al., "Gallium 67 Scanning in Rheumatoid Arthritis," *British Journal of Radiology* 56, no. 664 (1983): 241–243.

4. M. Mupparapu, S. Oak, Y. C. Chang, et al., "Conventional and Functional Imaging in the Evaluation of Temporomandibular Joint Rheumatoid Arthritis: A Systematic Review," *Quintessence International* 50, no. 9 (2019): 742–753.

5. T. Tomizawa, T. Cox, F. Kollert, et al., "The Impact of Concomitant Sjögren's Disease on Rheumatoid Arthritis Disease Activity: A Systematic Review and Meta-Analysis," *Clinical and Experimental Rheumatology* 41, no. 12 (2023): 2484–2492.

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ORIGINAL ARTICLE

The Comorbidity Burdens of Osteoarthritis and 174 Diseases, 1990–2021: A Modeling Study Based on the Global Burden of Disease Study 2021

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ABSTRACT

Aim: Using data from the Global Burden of Disease (GBD) Study 2021, this study aims to estimate the comorbidity burdens of osteoarthritis (OA) at global, regional, and national levels from 1990 to 2021.

Methods: The age-standardized prevalence and years lived with disability (YLD) rate for OA and 174 other Level-3 diseases from 204 countries and territories were extracted. A modified formula was employed to determine the comorbidity burdens for the co-occurrence of OA and one of the other 174 diseases. Cluster analysis was performed to identify different patterns in the comorbidity burden.

Results: Globally, the top three comorbidity burdens for OA in 2021 were from oral disorders, headache disorders, and age-related and other hearing loss (age-standardized comorbidity YLD rates 130.80/100 000, 124.09/100 000, and 79.54/100 000, respectively). From 1990 to 2021, the age-standardized comorbidity YLD rates for diabetes mellitus exhibited the greatest increases, with percentage changes of 108.41%. In high socio-demographic index (SDI) regions, the leading comorbidity burdens for OA were from headache disorders, oral disorders, and low back pain, whereas in low SDI regions, they were oral disorders, dietary iron deficiency, and headache disorders. Six clusters were identified, including oral disorders and headache disorders in the highest comorbidity burden with a mild changing cluster, and diabetes mellitus in the high comorbidity burden with a rapid growth cluster.

Conclusions: The comorbidity burdens of OA have increased and show different patterns. These findings underscore the importance of addressing the comorbidity burdens in conjunction with tackling the OA burden.

Haowei Chen, Qin Dang, and Yongbin Shi contributed equally to this work.

1 | Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and represents a major global health challenge since it significantly contributes to pain, disability, and reduced quality of life [1]. It affects over 500 million individuals globally, with heterogeneous pathogenesis and limited disease-modifying therapies [2, 3]. While OA has traditionally been regarded as a degenerative joint disease, emerging evidence suggests that it may be considered a systemic disease [1]. This evolving perspective highlights the need for a global reassessment of OA, moving away from a narrative of inevitable decline and toward recognition of its dynamic and multifactorial nature to inform more effective management strategies [4].

Comorbidities are increasingly recognized as integral to understanding the multifactorial burden of OA [5]. A recent systematic review has confirmed that compared to non-OA controls, OA patients had a 1.2-fold higher likelihood of having any comorbidity and a 2.5-fold higher likelihood of having more than three comorbidities [6]. Recent studies have also found that people with OA have almost three times the risk of developing severe comorbidities [7]. These comorbidities exacerbate disability, complicate clinical management, and amplify healthcare costs [8]. Investigating the comorbidity burden of OA can help elucidate interrelated causal mechanisms and the complexities involved in person-centered disease management, thereby improving understanding of the multifactorial burden of OA [9].

Despite growing recognition of the comorbidity burden of OA, relevant research is still in its early stages [6]. Swain et al. conducted a multicenter study across four European countries to examine the comorbidity burden of OA, encompassing more than 60 chronic conditions [10]. Another study examined 30 comorbid conditions among individuals with OA in the UK and found that highly prevalent comorbidity clusters were mainly characterized by hypertension, circulatory diseases, and metabolic disorders [11]. However, substantial variation in OA and comorbidity definitions, sample sizes, and the number of conditions examined across previous studies has limited the comparability of comorbidity burden estimates [6]. Therefore, it is essential to employ uniform methods when estimating the comorbidity burden of OA to reduce variation and improve comparability. What's more, the global and regional variations in comorbidity patterns, shaped by socioeconomic disparities, healthcare access, and environmental factors, remain underexplored.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is an authoritative research work that quantifies human health by estimating a range of epidemiological quantities for different years, age groups, sexes, geographical locations, providing uniform estimations of the burden of 371 diseases and injuries [12]. However, no prior analysis has systematically quantified the comparable comorbidity burden for OA. This study aims to comprehensively estimate the global, regional, and national comorbidity burden for OA, over a 32-year period, by using the latest GBD release, GBD 2021. We first examined age-standardized comorbidity years lived with disabilities (YLDs) rates for the co-occurrence of OA and one of the other 174 GBD Level-3 diseases. The analysis then stratified the findings by year, sex, and geographic location. Furthermore, we performed a clustering analysis to identify different patterns of the OA comorbidity burden and its temporal change.

2 | Materials and Methods

2.1 | Data Source

We derived data from the GBD 2021, which is publicly available through the GBD Results Tool on the Institute for Health Metrics and Evaluation (IHME) website (https://vizhub.healthdata.org/gbd-results/). The diseases and injuries included in GBD 2021 were organized within a cause hierarchy with four levels. A full list of causes by level can be found in GBD capstone publications [12]. In GBD 2021, the reference case definition of OA is symptomatic OA, defined as the presence of Kellgren–Lawrence (KL) grades 2 to 4 plus at least 1 month of pain for the past 12 months [13]. Specific definitions of other diseases can be found in previous reports [14]. The International Classification of Diseases (ICD)-9 codes and ICD-10 codes used in Level-3 causes were listed in Table S1. Ethical approval and informed consent were waived because the GBD database is publicly available, and no identifiable information was included in the analysis.

2.2 | Estimation of Comorbidity YLDs

To measure the independence variations in quantifying the prevalence of comorbidities, we assumed the independence of prevalence and multiplicativity when calculating each disability weight (DW) for individuals with multiple diseases [15]. We incorporated a correlation-adjustment multiplier (ρ) to account for potential dependence between two co-occurring conditions, following the approach described by Mansourian et al. [16] Similarly, we applied a multiplier (β) to each DW among individuals with two diseases. These parameters do not represent empirically estimated effect sizes but serve as scaling factors to adjust disability weights and joint prevalence under non-independence assumptions. When all multipliers are set to 1, the equations reduce to the standard multiplicative approach adopted in the GBD study, ensuring methodological consistency [16]. This framework allows flexible modeling of comorbidity while maintaining comparability with GBD estimates. Therefore, if DW_{OA} and DW_C represent the DWs of OA and another comorbidity condition respectively, the formula for calculating the total comorbidity DWs (DWC) of the two diseases can be:

$$DWC = DW_{OA} \times \beta_1 + DW_C \times \beta_2 - DW_{OA} \times \beta_1 \times DW_C \times \beta_2 \quad (1)$$

Accordingly, the calculation formula of the total age-standardized comorbidity YLD rates (YLDC) for OA and another comorbidity condition can be:

$$YLDC = \left(P_{OA} - P_{OA} \times P_C \times p\right) \times DW_{OA} + \left(P_C - P_{OA} \times P_C \times p\right) \times DW_C + P_{OA} \times P_C \times p \times DWC \quad (2)$$

The first two components of the formula [2] represent the contributions of OA and another comorbidity condition individually, and the last component represents the contribution of the co-occurrence of the two diseases (named age-standardized comorbidity YLD rates).

2.3 | Statistical Analysis

In this study, we included participants with OA in any joint (knee, hand, hip, and other joint sites) as well as 174 other diseases at Level-3 causes (study flow diagram in Figure S1). Diseases with negative YLD estimates were excluded because such values arise from statistical uncertainty and smoothing procedures in the GBD modeling process and do not represent interpretable disease burden. Neonatal disorders were excluded because they are restricted to the first 28 days of life and are biologically incompatible with osteoarthritis. COVID-19 was excluded because it was introduced into GBD estimates only after 2019, limiting temporal comparability across the full study period. Then we excluded those diseases that did not include both prevalence and YLD data. Finally, OA and 167 other Level-3 causes were included in the global analysis set. We extracted the age-standardized prevalence and age-standardized YLD rates for OA and other Level-3 diseases from 1990 to 2021 to investigate the age-standardized comorbidity YLD rates for the co-occurrence of OA and one of the Level-3 diseases. DWs for each Level-3 disease were calculated by taking age-standardized YLD rates divided by age-standardized prevalence.

Using the two equations above, we calculated global age-standardized comorbidity YLD rates for the co-occurrence of OA and each GBD Level-3 disease and ranked conditions accordingly. This analysis was further stratified by year (from 1990 to 2021), sex (males and females), and geographic location (5 socio-demographic index [SDI] quintiles, 21 GBD regions, and 204 countries/territories). Percentage change was calculated as the relative difference in age-standardized comorbidity YLD rates between 1990 and 2021.

Furthermore, we used a clustering analysis to identify clusters of the age-standardized comorbidity YLD rates in 1990 and 2019 as well as the percentage changes from 1990 to 2021 using the K-means clustering algorithm, an unsupervised machine learning method. Elbow method was performed to identify the appropriate cluster numbers. All statistical analyses were conducted using R software (version 4.3.2) in this study.

3 | Results

3.1 | Global Level

Globally, oral disorders had a leading comorbidity burden for OA in 1990, followed by headache disorders and low back pain, with the age-standardized comorbidity YLD rates of 122.51 (95% UI, 78.01–237.36), 112.86 (95% UI, 71.03–217.19), and 76.53 (95% UI, 55.54–116.46) per 100 000, respectively (Table 1; Figure 1). In 2021, the global top three comorbidity burdens for OA were from oral disorders, headache disorders, and age-related and other hearing loss, with the age-standardized comorbidity YLD rates of 130.80 (95% UI, 83.20, 252.99), 124.09 (95% UI, 77.89, 238.87), and 79.54 (95% UI, 57.04, 132.96) per 100 000, respectively, which accounted for 25.17%, 14.92%, and 10.34% of the total age-standardized comorbidity YLD rates (named YLDC in the Equation 2) for OA and other diseases in the presence of comorbidity (Table 1; Figure S2). Among the leading 25 comorbidity burdens for OA, 19 co-occurrence conditions showed an increasing trend in age-standardized comorbidity YLD rates from 1990 to 2021 (Table 1). Diabetes mellitus, other musculoskeletal disorders, and anxiety disorders exhibited the most significant increases in the comorbidity burdens, with percentage changes of 108.41%, 37.42%, and 28.93%, respectively. Intestinal nematode infections, vitamin A deficiency, and road injuries exhibited the most significant decreases, with percentage changes of −67.72%, −55.03%, and −35.86%, respectively (Table 1; Figure 1).

3.2 | Global Level by Sex

In 2021, the global top three comorbidity burdens for OA in males were from oral disorders, headache disorders, and age-related and other hearing loss, with the age-standardized comorbidity YLD rates of 106.20 (95% UI, 67.42–206.89), 88.11 (95% UI, 55.73–172.03), and 69.35 (95% UI, 49.76–116.79) per 100 000, respectively (Figure 2A; Table S2). The global top three comorbidity burdens for OA in females were from headache disorders, gynecological diseases, and oral disorders, with the age-standardized comorbidity YLD rates of 163.71 (95% UI, 101.48–313.88), 159.37 (95% UI, 109.78–284.07), and 153.5 (95% UI, 97.94–296.73) per 100 000, respectively (Figure 2B; Table S3). Among the leading 25 comorbidity burdens for co-occurrence conditions with OA, diabetes mellitus, other musculoskeletal disorders, and anxiety disorders exhibited the most significant rise in both males and females from 1990 to 2021 (Figure 2).

3.3 | Regional Level

The ranking of co-occurrence conditions for the comorbidity burdens with OA varied across SDI levels. In the high SDI region, the top three comorbidity burdens for OA were from headache disorders, oral disorders, and low back pain (age-standardized comorbidity YLD rates 161.85, 133.43, and 111.03 per 100 000, respectively). On the other hand, in the low SDI region, the top three comorbidity burdens for OA were from oral disorders, dietary iron deficiency, and headache disorders (age-standardized comorbidity YLD rates 106.65, 93.10, and 89.47 per 100 000, respectively) (Figure 3). Across 21 GBD regions, the highest age-standardized comorbidity YLD rate was from headache disorders in High-income North America (186.77 per 100 000), followed by oral disorders in Andean Latin America (185.90 per 100 000) and oral disorders in Southern Latin America (176.50 per 100 000) (Figure 3; Table S4). Among the leading 25 comorbidity burdens for co-occurrence conditions with OA, diabetes mellitus exhibited the most significant rise among 20 of the 21 GBD regions from 1990 to 2021, and North Africa and Middle East, Central Asia, and High-income North America had the top three percentage changes of 199.37%, 165.28%, and 158.03%, respectively (Figure S3).

TABLE 1 | Global leading 25 Level-3 causes of age-standardized comorbidity YLDs rates due to each condition alone and to comorbidity for OA.

	Age-standardized YLDs rates (per 100 000), 2021 (95% UI)			Percentage of comorbidity[b]		
Comorbidity cause	OA alone	Each comorbid condition	Comorbidity[a]	1990	2021	Percentage change from 1990 to 2021[c]
Oral disorders	132.25 (71.57, 275.94)	256.69 (160.67, 394.32)	130.80 (83.20, 252.99)	24.07	25.17	6.77
Headache disorders	159.97 (86.89, 332.69)	547.39 (159.56, 1136.22)	124.09 (77.89, 238.87)	14.01	14.92	9.95
Age-related and other hearing loss	200.32 (109.17, 416.09)	489.23 (352.06, 675.77)	79.54 (57.04, 132.96)	9.56	10.34	15.39
Hemoglobinopathies and hemolytic anemias	176.26 (96.09, 366.05)	88.25 (61.84, 121.53)	74.62 (45.84, 145.88)	19.10	22.00	18.14
Low back pain	226.25 (123.39, 470.17)	774.20 (535.67, 1121.95)	74.19 (53.86, 112.46)	6.61	6.90	−3.06
Dietary iron deficiency	204.32 (111.32, 424.40)	394.22 (279.82, 553.59)	68.67 (48.95, 116.39)	9.81	10.29	−5.33
Gynecological diseases	198.59 (108.32, 412.62)	310.72 (218.19, 449.95)	68.37 (47.07, 121.54)	11.16	11.83	5.54
Blindness and vision loss	205.91 (111.53, 427.07)	318.90 (190.53, 566.64)	61.64 (40.79, 120.31)	8.66	10.51	26.18
Tuberculosis	186.76 (101.55, 387.77)	50.43 (33.8, 71.69)	61.38 (36.71, 124.04)	23.43	20.56	−17.27
Depressive disorders	234.70 (127.68, 487.29)	633.69 (430.29, 927.01)	55.59 (39.86, 83.16)	5.48	6.02	23.33
Cirrhosis and other chronic liver diseases	194.86 (106.27, 404.43)	6.89 (4.85, 9.55)	50.14 (29.06, 102.50)	19.55	19.90	10.66
Other musculoskeletal disorders	229.97 (125.20, 477.43)	471.87 (315.33, 707.92)	48.63 (34.8, 77.01)	5.66	6.48	37.42
Diabetes mellitus	229.53 (124.90, 476.68)	443.76 (317.49, 618.96)	47.04 (34.96, 71.57)	4.78	6.53	108.41
Anxiety disorders	233.69 (127.22, 485.19)	487.80 (315.85, 757.46)	46.06 (32.13, 73.34)	5.37	6.00	28.93
Sexually transmitted infections excluding HIV	205.59 (111.97, 426.57)	13.56 (8.53, 23.10)	39.90 (23.3, 82.56)	14.94	15.40	12.67
Falls	228.72 (124.62, 475.07)	268.50 (179.77, 399.56)	35.19 (24.9, 58.68)	6.62	6.61	−4.52
Upper digestive system diseases	219.32 (119.54, 455.20)	92.96 (56.16, 160.26)	31.90 (21.07, 61.52)	8.85	9.27	10.55
Chronic kidney disease	224.93 (122.41, 467.28)	97.54 (70.99, 127.79)	26.62 (17.92, 47.93)	7.47	7.63	9.23
Neck pain	238.53 (129.81, 495.54)	225.42 (134.85, 393.46)	22.26 (14.72, 38.85)	4.39	4.58	9.35
Fungal skin diseases	225.46 (122.78, 468.20)	40.37 (19.67, 83.77)	21.96 (14.11, 43.81)	7.16	7.63	16.49

(Continues)

TABLE 1 | (Continued)

Comorbidity cause	Age-standardized YLDs rates (per 100 000), 2021 (95% UI)			Percentage of comorbidity[b]		Percentage change from 1990 to 2021[c]
	OA alone	Each comorbid condition	Comorbidity[a]	1990	2021	
Intestinal nematode infections	223.89 (121.92, 464.71)	13.58 (8.43, 22.05)	21.59 (12.93, 44.31)	21.89	8.33	−67.72
Other skin and subcutaneous diseases	226.61 (123.56, 470.83)	36.95 (20.32, 65.81)	20.56 (13.18, 39.79)	6.40	7.24	24.60
Endocrine, metabolic, blood, and immune disorders	230.59 (125.55, 478.26)	84.64 (49.04, 159.82)	20.03 (13.06, 40.62)	5.97	5.97	5.48
Chronic obstructive pulmonary disease	238.36 (129.92, 495.22)	162.22 (127.52, 201.20)	17.87 (13.68, 26.16)	4.11	4.27	10.98
Asthma	236.33 (128.60, 490.87)	121.94 (77.33, 198.02)	16.98 (11.85, 29.70)	5.87	4.52	−34.21

Abbreviations: OA, osteoarthritis; UI, uncertainty intervals; YLDs, years lived with disability.
[a]The age-standardized comorbidity YLDs rates for the co-occurrence of OA and one of the other diseases.
[b]Percentage of the age-standardized comorbidity YLDs rates to the total age-standardized comorbidity YLD rates (named YLDC in the Equation 2).
[c]Percentage change was calculated as the relative difference in age-standardized comorbidity YLD rates between 1990 and 2021.

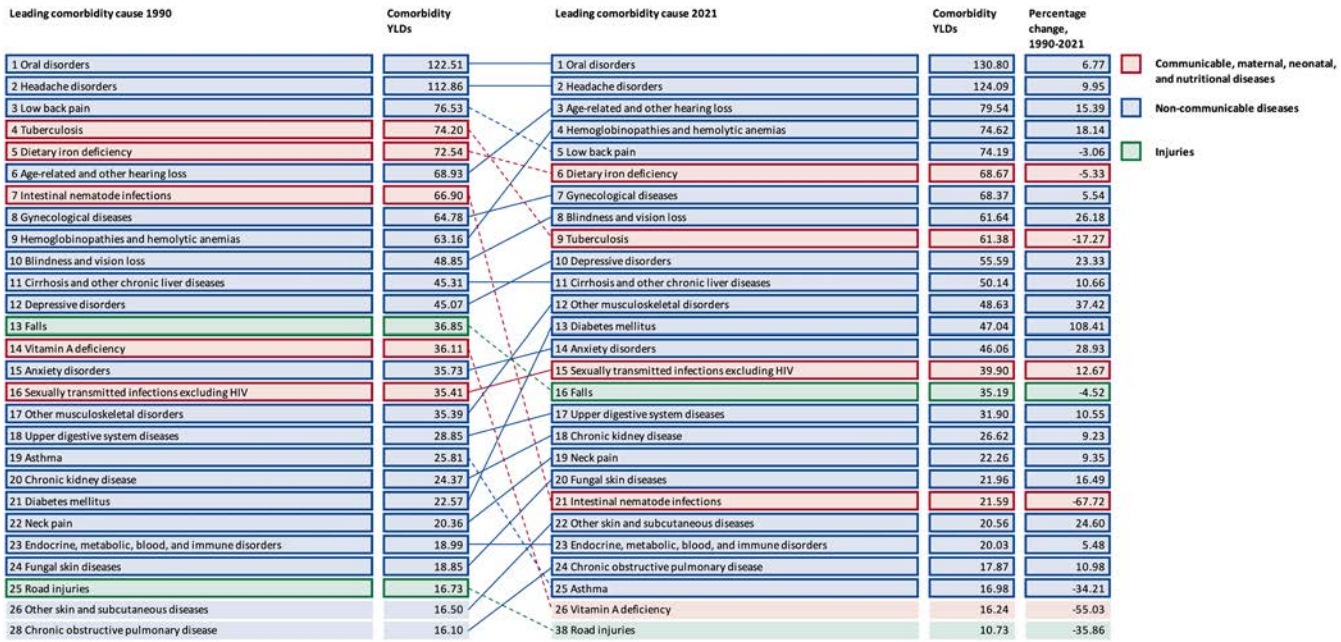

FIGURE 1 | Leading 25 Level-3 causes of global age-standardized comorbidity YLDs rates for OA in 1990 and 2021, with the percentage change in the age-standardized comorbidity YLD rates from 1990 to 2021. Causes are connected by lines between time periods; solid lines are increases and dashed lines are decreases. Percentage change was calculated as the relative difference in age-standardized comorbidity YLD rates between 1990 and 2021. OA, osteoarthritis; YLDs, years lived with disability.

3.4 | National Level

Nationally, oral disorders and headache disorders were the major comorbidity burdens for OA in 1990 and 2021 in most countries/territories. In 1990, oral disorders had the leading comorbidity burden for OA in 133 countries/territories, and headache disorders had the leading comorbidity burden for OA in 38 countries/territories. In 2021, oral disorders had the leading comorbidity

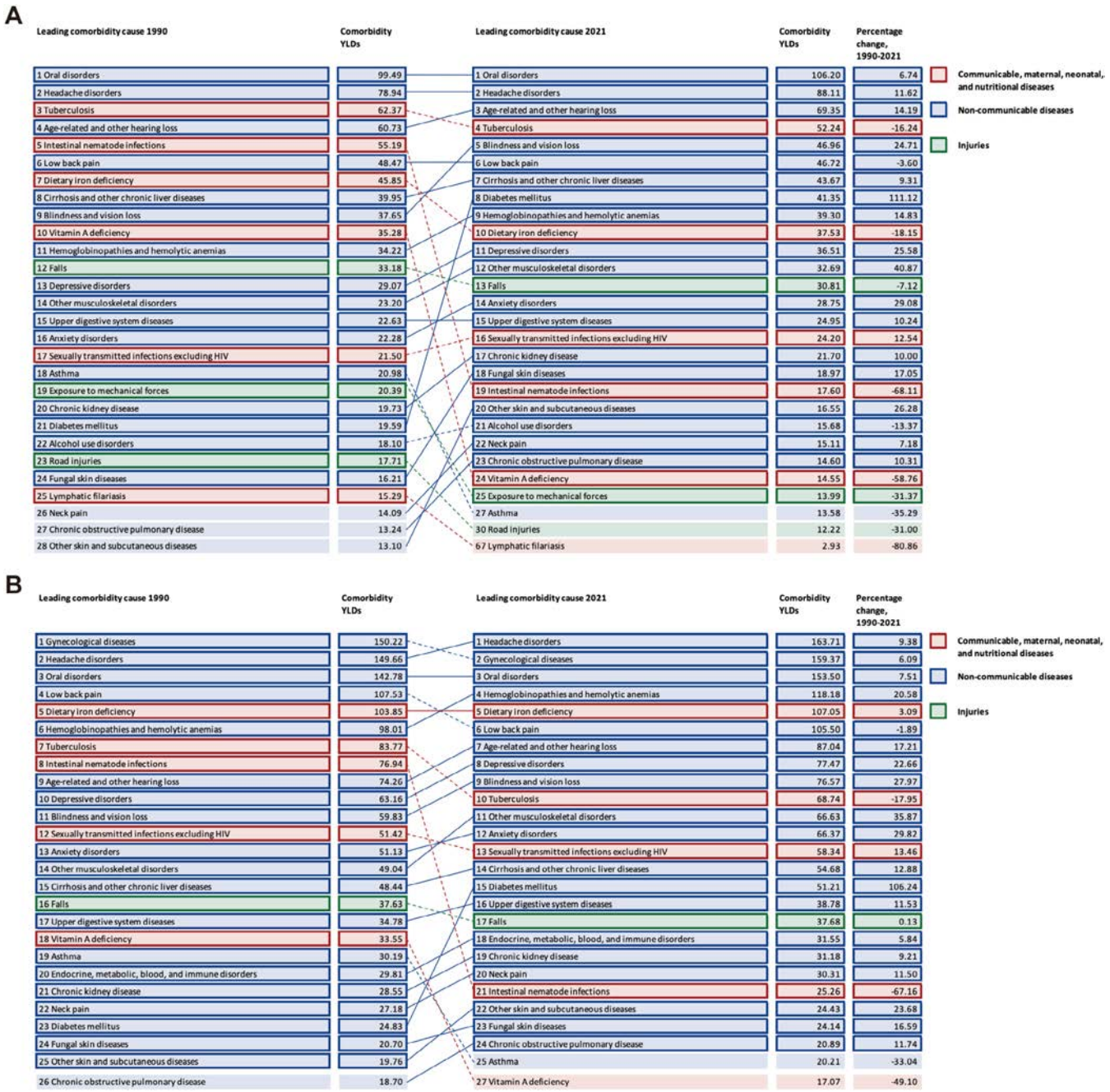

FIGURE 2 | Leading 25 Level-3 causes of global age-standardized comorbidity YLDs rates for OA in 1990 and 2021, with the percentage change in the age-standardized comorbidity YLD rates from 1990 to 2021 in males (A) and females (B). Causes are connected by lines between time periods; solid lines are increases and dashed lines are decreases. Percentage change was calculated as the relative difference in age-standardized comorbidity YLD rates between 1990 and 2021. OA, osteoarthritis; YLDs, years lived with disability.

burden for OA in 134 countries/territories, and headache disorders had the leading comorbidity burden for OA in 47 countries/territories (Figure S4).

3.5 | Clustering Analysis

According to the elbow method, six comorbidity burden clusters were found. The mean age-standardized comorbidity YLD rate in 2021 was highest in cluster 2 (127.44 per 100 000) and lowest in cluster 6 (1.96 per 100 000). The mean age-standardized comorbidity YLD rate in 2021 was 31.50 per 100 000 and the mean percentage change of the age-standardized comorbidity YLD rate from 1990 to 2021 was 22.47% in cluster 1. Oral disorders and headache disorders were in cluster 2, with the highest comorbidity burdens and mild changes, and diabetes mellitus was in cluster 1, with high comorbidity burden and rapid growth (Figure 4).

Cause	Global	High SDI	High-middle SDI	Middle SDI	Low-middle SDI	Low SDI	Andean Latin America	Australasia	Caribbean	Central Asia	Central Europe	Central Latin America	Central Sub-Saharan Africa	East Asia	Eastern Europe	Eastern Sub-Saharan Africa	High-income Asia Pacific	High-income North America	North Africa and Middle East	Oceania	South Asia	Southeast Asia	Southern Latin America	Southern Sub-Saharan Africa	Tropical Latin America	Western Europe	Western Sub-Saharan Africa
Oral disorders	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3	2	1	1	1	2	1	2	1	2	3
Headache disorders	2	1	2	2	2	3	2	2	2	2	2	2	3	2	2	4	1	1	2	2	3	1	2	3	2	1	1
Age-related and other hearing loss	3	6	3	3	6	5	8	8	7	5	4	7	9	3	5	2	5	9	9	5	6	3	7	11	5	8	10
Hemoglobinopathies and hemolytic anemias	4	11	8	4	4	4	12	12	5	12	13	15	2	5	15	3	19	12	5	7	5	5	16	9	13	9	2
Low back pain	5	3	4	8	7	8	9	3	9	3	3	3	8	8	3	10	2	3	4	8	9	6	3	12	4	3	6
Dietary iron deficiency	6	25	16	9	3	2	16	36	4	4	11	19	11	18	13	5	30	34	12	6	2	9	21	8	11	34	4
Gynecological diseases	7	4	5	7	8	6	3	6	6	6	5	5	7	7	4	6	7	10	3	12	8	7	5	7	8	4	5
Blindness and vision loss	8	14	7	6	5	7	6	14	12	10	16	9	12	6	7	11	12	19	11	11	4	8	15	5	7	12	8
Tuberculosis	9	17	6	5	10	9	17	20	13	8	15	10	4	4	10	9	11	18	13	3	11	4	13	4	12	24	13
Depressive disorders	10	5	9	11	9	10	13	5	10	9	10	11	5	13	8	7	9	5	7	15	10	15	8	10	9	6	11
Cirrhosis and other chronic liver diseases	11	13	10	10	12	11	15	15	15	7	12	14	10	9	11	12	13	17	6	9	13	10	18	13	15	13	7
Other musculoskeletal disorders	12	7	14	12	11	16	10	9	16	22	24	6	23	11	28	20	4	4	14	17	7	12	4	17	10	11	21
Diabetes mellitus	13	9	12	14	13	14	14	13	3	11	9	4	17	10	17	21	6	8	8	4	12	11	11	14	16	10	16
Anxiety disorders	14	8	11	13	14	17	5	7	11	19	8	12	18	12	9	15	10	7	10	14	15	14	6	15	3	5	20
Sexually transmitted infections excluding HIV	15	15	15	15	16	12	7	16	8	14	18	8	6	14	12	8	16	13	17	10	19	13	10	6	6	18	9
Falls	16	10	13	16	18	23	19	4	22	16	7	17	38	16	6	37	8	14	18	22	16	20	14	36	17	7	31
Upper digestive system diseases	17	19	17	17	15	18	11	17	14	15	14	13	20	25	14	17	21	15	15	25	14	24	12	16	14	17	18
Chronic kidney disease	18	21	20	18	17	21	23	24	24	13	23	18	22	19	19	25	17	20	19	20	17	16	22	18	19	23	23
Neck pain	19	20	18	20	23	22	20	35	23	21	19	21	25	17	20	24	20	23	16	24	27	19	26	21	20	16	22
Fungal skin diseases	20	31	27	22	21	19	18	19	21	26	26	26	21	33	27	14	24	49	43	30	23	17	28	20	23	20	14
Intesti-l nematode infections	21	64	40	23	19	15	4	-	19	43	-	16	15	32	-	16	52	-	25	13	20	25	30	19	18	-	19
Other skin and subcutaneous diseases	22	18	21	21	24	31	22	18	25	24	21	22	29	20	22	29	14	16	21	29	24	23	19	23	26	15	25
Endocrine, metabolic, blood, and immune disorders	23	26	19	19	25	29	26	39	18	28	28	24	28	15	23	28	44	27	26	18	28	18	36	24	29	27	27
Chronic obstructive pulmo-ry disease	24	28	25	24	20	24	44	45	42	33	31	36	26	24	36	34	38	22	27	27	18	26	47	25	36	32	28
Asthma	25	12	30	29	28	25	21	11	17	30	17	27	31	37	33	23	25	11	23	32	35	28	17	43	22	14	24
Vitamin A deficiency	26	77	53	41	22	13	33	111	28	35	25	34	16	47	90	13	80	90	36	23	22	33	32	28	24	77	17
Stroke	27	33	22	26	32	34	51	43	49	23	30	48	30	21	26	31	27	31	30	28	42	21	40	30	51	39	26
Dermatitis	28	22	23	27	29	38	28	30	29	17	27	29	42	30	21	40	15	21	32	31	32	27	25	35	27	19	36
Interperso-l violence	29	41	26	28	26	30	40	50	34	42	40	30	27	23	30	26	45	42	29	21	30	37	44	22	31	48	32
Acne vulgaris	31	30	32	32	39	35	30	34	41	46	49	43	37	27	44	30	26	36	34	37	44	30	34	32	41	21	35
Alcohol use disorders	32	24	29	37	34	40	37	22	31	20	20	25	43	34	18	35	37	24	63	45	36	47	24	27	25	22	60
Autism spectrum disorders	33	27	35	36	35	36	38	26	38	29	29	37	36	38	31	36	18	29	35	42	38	36	29	33	40	31	34
Exposure to mechanical forces	34	23	24	40	51	57	24	10	20	18	6	20	54	52	16	49	22	33	28	57	58	39	9	50	34	25	49
Gallbladder and biliary diseases	35	32	28	31	59	66	25	31	32	25	22	23	62	26	35	62	28	37	39	38	76	32	23	55	30	26	63
Scabies	37	65	36	25	33	51	27	90	30	65	48	32	65	22	80	51	95	96	58	16	33	22	101	60	21	130	65
Road injuries	38	36	34	35	41	55	41	41	43	41	38	35	35	31	29	61	40	26	24	36	50	40	31	31	32	41	56
Ischemic heart disease	40	48	37	34	30	42	42	47	35	27	33	44	52	35	25	50	56	53	20	41	29	43	51	42	45	51	43
Drug use disorders	42	16	42	49	63	67	56	21	53	40	46	50	67	43	24	68	43	6	45	53	57	53	45	47	42	28	70
Diarrheal diseases	43	62	66	48	27	26	66	84	64	76	101	62	32	78	68	27	47	115	55	43	21	41	71	29	66	55	30
Viral skin diseases	45	29	41	46	57	58	54	27	63	53	50	59	64	39	47	38	23	25	52	47	53	49	27	56	59	30	59
Malaria	46	150	145	75	53	20	91	-	98	-	-	97	14	147	-	22	138	-	76	26	85	87	-	85	99	-	12
Bipolar disorder	48	39	47	45	49	50	29	23	33	44	39	31	48	62	43	44	41	39	33	61	55	52	37	46	28	29	46
Iodine deficiency	50	80	59	54	36	28	107	87	76	77	90	71	19	50	88	33	83	94	65	100	26	68	96	63	100	59	61
Other unintentio-l injuries	52	42	46	53	55	65	46	25	46	32	32	58	66	59	34	64	39	41	40	59	56	44	41	62	39	45	62
Idiopathic developmental intellectual disability	54	73	69	56	37	46	75	71	72	60	70	79	68	70	72	72	97	68	46	66	25	64	68	79	75	69	79
Schistosomiasis	58	119	104	62	50	27	-	-	50	-	-	90	24	68	-	18	-	-	64	-	-	94	-	26	50	-	15
Fire, heat, and hot substances	61	45	49	58	65	62	34	37	26	31	37	28	57	65	41	46	36	47	70	39	64	59	20	44	49	46	54
HIV/AIDS	64	76	77	57	61	33	76	94	54	93	106	78	34	93	48	19	113	64	100	58	87	73	65	1	71	75	29
Conflict and terrorism	70	128	90	69	71	32	67	139	92	64	76	61	33	133	83	32	147	122	22	90	75	62	121	91	143	110	67
Lymphatic filariasis	73	-	108	74	60	61	-	-	66	-	-	-	51	-	-	66	142	-	92	19	48	57	-	92	131	-	51
Onchocerciasis	80	-	-	116	90	37	-	-	-	-	-	146	13	-	-	56	-	-	129	-	-	-	-	-	156	-	39

Ranking legend
1-10
11-20
21-30
31-50
51-90
91-169

FIGURE 3 | Variation in ranking the Level-3 causes of age-standardized comorbidity YLDs rates for OA at global and regional level in 2021. Causes in the figure are ordered according to global ranks for causes. The figure shows all causes that are in the 25 leading causes in at least one region. Ranks are also color shaded to indicate rank intervals. OA, osteoarthritis; YLDs, years lived with disability.

4 | Discussion

In this novel modeling analysis, we identified several key findings in the burden of comorbidities for OA. Globally, oral disorders and headache disorders had the major comorbidity burden when coexisting with OA, with the highest comorbidity burdens and slight changes for the past decades. We also found that diabetes mellitus exhibited the greatest increase in the comorbidity burden for the past decades, emphasizing an importance of focusing on OA and metabolic health. The results remained consistent and robust across sex and regions.

Comorbidity associated with OA is a serious public health concern [17]. It is reported that among the general practitioners in the UK, OA patients had a 2.35 times higher likelihood of having any comorbidities compared to non-OA individuals, and a 1.94 times higher likelihood of having over three comorbidities [18]. Besides the comorbidity number, the comorbidity patterns among OA patients also influence clinical decisions. OA was one of the most prevalent comorbid conditions reported in comorbidity research for other common chronic diseases and ranked as the top five non-cardiovascular comorbidities in various cardiovascular diseases (CVDs) [17, 19]. A recent meta-analysis found that stroke, peptic ulcer, and metabolic syndrome were major comorbidities associated with OA [6]. Another study identified six comorbidity patterns among OA patients and found that hypertension, circulatory, and metabolic diseases were located in the clusters with a high comorbidity prevalence [11]. However, the key challenges for the comorbidity research in OA are the small amount of diseases investigated, and the wide heterogeneity that exists in the diagnosis of OA and other comorbidity diseases [20]. As a result, it is critical to have an agreement on both the amount and definitions of comorbidity diseases to be researched in order to make comparable estimates. Swain et al. designed a multicenter study protocol on OA comorbidities in four European countries involving over 60 diseases, to examine the causal association [10]. However, this research is still in its early stages and does not address the urgent need to understand

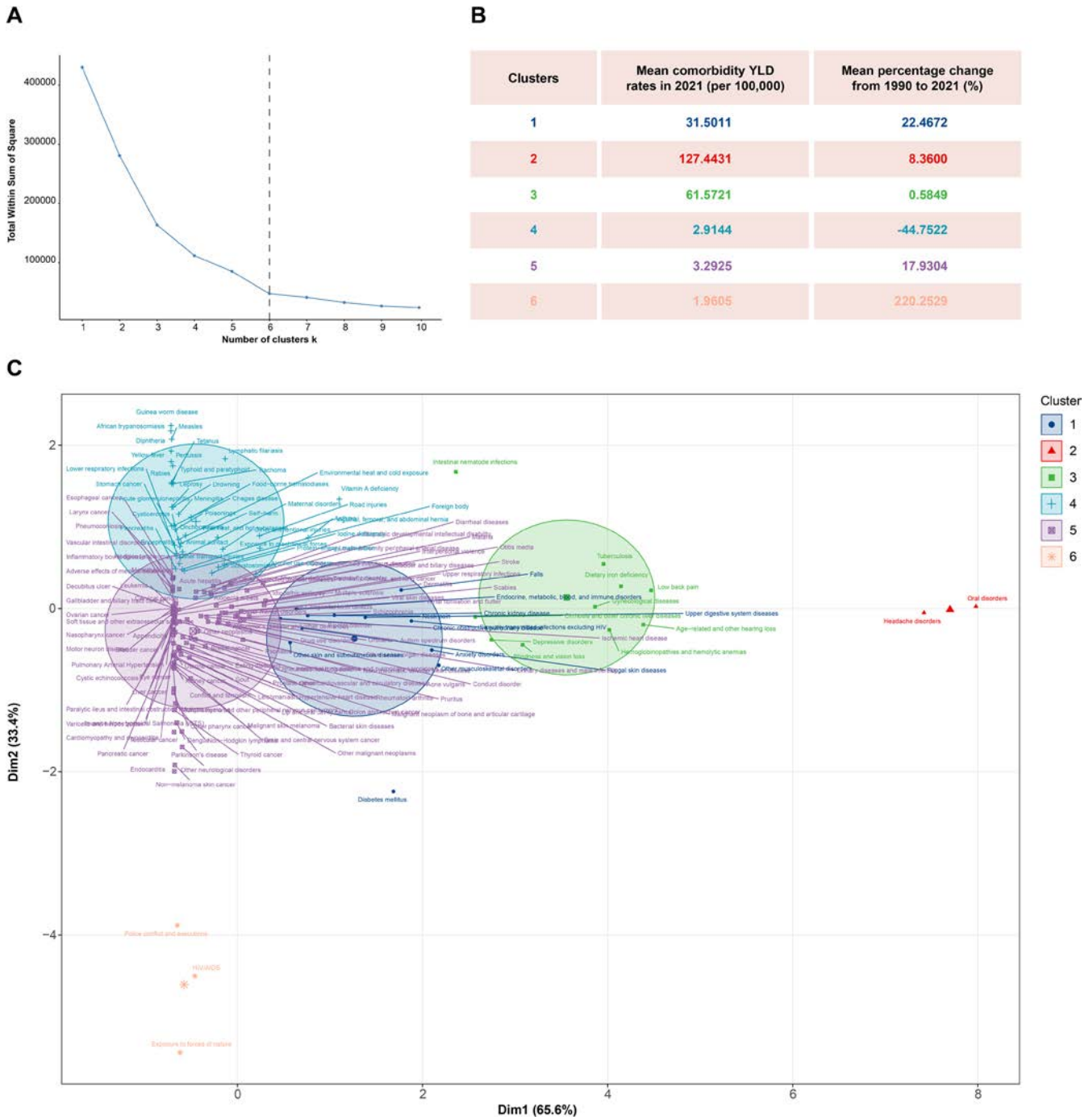

FIGURE 4 | Clusters of the global age-standardized comorbidity YLDs rates for OA with Level-3 causes in 1990 and 2021, and their percentage changes from 1990 to 2021. (A) Elbow method to identify the appropriate number of clusters. (B) Mean age-standardized comorbidity YLD rates in 2021 and mean percentage change from 1990 to 2021 for the clusters. (C) Six clusters were found using the *K*-means method with Euclidean distance. OA, osteoarthritis; YLDs, years lived with disability.

the comorbidity of OA. Our study used population-based data with a wider coverage of diseases and was comparable based on uniform model estimates of GBD, which addressed the above challenges to some extent.

This study found the highest comorbidity burden between OA and oral disorders. In GBD 2021, oral disorders were the most prevalent Level-3 causes in 2021, combined of caries of deciduous teeth, caries of permanent teeth, periodontal diseases, edentulism, and other oral disorders [21]. It has been reported that adults with poor oral health may lead to temporomandibular joint OA [22]. What's more, emerging evidence suggests that dysbiosis of the oral microbiome can influence distant musculoskeletal tissues through microbial metabolites, low-grade systemic inflammation, and immune modulation, potentially contributing to joint degeneration. Specifically for

OA, distant transmission, oral-gut microbial transfer, and inflammatory responses are the most widely recognized pathways [23]. Current research has revealed a higher prevalence of oral opportunistic pathogens, including *Porphyromonas*, *Streptococcus*, *Actinomyces*, and *Fusobacterium*, among OA patients compared to healthy individuals [24]. Studies have shown that *Porphyromonas gingivalis* can promote synovial fibroblast activation through dendritic cells, macrophages, and neutrophils that infiltrate the joints in mouse models of collagen-induced arthritis [25]. Additionally, the oral microbiome has been found to modify the osteogenic differentiation capacity of bone marrow-derived mesenchymal stem cells, induce chondrocyte death, and disrupt the osteoblast–osteoclast equilibrium [26–28]. While these mechanisms support the concept of an oral–joint axis and may partly explain the substantial comorbidity burden observed in this study, the underlying mechanisms require further investigation.

Another major comorbidity condition with OA we found was headache disorders. This strong comorbidity burden may be partially explained by shared pain-processing mechanisms, including central sensitization [29]. Both conditions have been associated with altered nociceptive signaling, glial activation, and dysregulation of neurotransmitters involved in pain modulation [30]. These overlapping neurobiological pathways may contribute to heightened pain perception and disability when the two conditions coexist.

Our study found that the comorbidity burden of diabetes mellitus and OA has the greatest increase from 1990 to 2021, consistent with current consensus [31]. Arruda et al. identified a genome-wide genetic link between diabetes mellitus and OA and significant colocalizing signals at 18 genomic regions [32]. They integrated multi-omics and functional data to resolve the association-signal colocalization and identified high-confidence effector genes, including fat mass and obesity associated (FTO) and Iroquois Homeobox 3 (IRX3), and the enrichment for lipid metabolism and skeletal formation pathways for signals underpinning the knee and hip OA comorbidities with type 2 diabetes mellitus, respectively [32]. Additionally, Mendelian randomization analysis has indicated the causal relationship between antidiabetic medication targets with 12 OA phenotypes [33]. Recent studies also demonstrated the beneficial effects for novel antidiabetic drugs in OA treatment [34, 35].

The relationships between OA and comorbidities are bidirectional and multifactorial, and should not be ignored [36]. Shared risk factors such as aging, obesity, and sedentary lifestyles contribute to both OA and conditions like CVDs and diabetes [37, 38]. Conversely, OA-related pain and functional limitations may indirectly precipitate comorbidities by reducing physical activity, worsening metabolic profiles, or necessitating long-term analgesic use [39].

The clinical implications may include consideration for education and care of oral health among OA patients, choosing personal analgesic therapy for those with central sensitization. Furthermore, the increased comorbidity burden for OA and diabetes further underscores the importance of metabolic health in OA patients and calls for in-depth studies of the metabolic mechanism of OA. For public health policy making, comorbidities in the prevention, monitoring, and management of OA should be included.

This study also had potential limitations. First, our study was a data-driven estimation. It was unclear if the comorbidity conditions simply coexisted with OA, or were causes or results of OA. More study is required to clarify the connection between OA and the comorbidity conditions to enhance prevention and management approaches. Second, although we used a validated method to calculate the comorbid DW, these estimates could not fully represent the real-life data of multiple situations occurring simultaneously [16]. Moreover, we only considered the co-occurrence assumption of two conditions. The burden of multiple comorbidities for OA has not been estimated. Last, the limitations related to inconsistencies in the source data availability of GBD should also be considered [21].

5 | Conclusions

This study showed that the burden of comorbidities for OA has risen and shows different patterns, with the major comorbidity burden due to the co-occurrence of OA with oral disorders and headache disorders. The increased comorbidity burden for OA and diabetes underscores the importance of metabolic health in OA patients. These findings may have important clinical and public health implications for addressing the comorbidity burden while tackling the burden of OA.

Author Contributions

H.C., Q.D., Y.S., D.J.H., C.D., Z.Z., and Y.L. contributed to the study design and conceptualization. H.C., Q.D., Y.S., H.Y., and X.W. were responsible for data collection. H.C., Q.D., Y.S., D.J.H., L.S., C.D., Z.Z., and Y.L. analyzed the data and contributed to its interpretation. H.C., Q.D., Y.S., and Y.L. drafted the manuscript and verified the data. All co-authors contributed to the critical revision of the manuscript. C.D., Z.Z., and Y.L. had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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Ethics Statement

This study utilized exclusively publicly available, anonymized data from the Global Burden of Disease Study 2021 and no identifiable information was included in the analyses.

Conflicts of Interest

Prof. David J. Hunter is the editor of the osteoarthritis section for *UpToDate*, and co-Editor-in-Chief of *Osteoarthritis and Cartilage*; and

provides consulting advice on scientific advisory boards for Pfizer, Lilly, TLCBio, Novartis, Tissuegene, and Biobone. All other authors declare that they have no competing interests.

Data Availability Statement

The data used from this study can be accessed openly through the GBD 2021 online database (https://vizhub.healthdata.org/gbd-results/).

References

1. S. Tang, C. Zhang, W. M. Oo, et al., "Osteoarthritis. Nature Reviews Disease Primers," *Nature Reviews Disease Primers* 11, no. 1 (2025): 10, https://doi.org/10.1038/s41572-025-00594-6.

2. GBD 2021 Osteoarthritis Collaborators, "Global, Regional, and National Burden of Osteoarthritis, 1990–2020 and Projections to 2050: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet Rheumatology* 5, no. 9 (2023): e508–e522, https://doi.org/10.1016/s2665-9913(23)00163-7.

3. V. Duong, W. M. Oo, C. Ding, A. G. Culvenor, and D. J. Hunter, "Evaluation and Treatment of Knee Pain: A Review," *Journal of the American Medical Association* 330, no. 16 (2023): 1568–1580, https://doi.org/10.1001/jama.2023.19675.

4. C. Jinks, A. van Botto- Bemden, S. Bunzli, et al., "Changing the Narrative on Osteoarthritis: A Call for Global Action," *Osteoarthritis and Cartilage* 32, no. 4 (2024): 414–420, https://doi.org/10.1016/j.joca.2024.02.004.

5. A. Kamps, J. Runhaar, M. A. J. de Ridder, et al., "Occurrence of Comorbidity Following Osteoarthritis Diagnosis: A Cohort Study in The Netherlands," *Osteoarthritis and Cartilage* 31, no. 4 (2023): 519–528, https://doi.org/10.1016/j.joca.2022.12.003.

6. S. Swain, A. Sarmanova, C. Coupland, M. Doherty, and W. Zhang, "Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies," *Arthritis Care & Research* 72, no. 7 (2020): 991–1000, https://doi.org/10.1002/acr.24008.

7. A. Dell'Isola, F. Recenti, M. Englund, and A. Kiadaliri, "Twenty-Year Trajectories of Morbidity in Individuals With and Without Osteoarthritis," *RMD Open* 10, no. 2 (2024): 4164, https://doi.org/10.1136/rmdopen-2024-004164.

8. L. K. King, "Osteoarthritis and Comorbidity: Time for Action," *Osteoarthritis and Cartilage* 31, no. 4 (2023): 423–424, https://doi.org/10.1016/j.joca.2023.01.007.

9. J. G. Quicke, P. G. Conaghan, N. Corp, and G. Peat, "Osteoarthritis Year in Review 2021: Epidemiology & Therapy," *Osteoarthritis and Cartilage* 30, no. 2 (2022): 196–206, https://doi.org/10.1016/j.joca.2021.10.003.

10. S. Swain, A. Kamps, J. Runhaar, et al., "Comorbidities in Osteoarthritis (ComOA): A Combined Cross-Sectional, Case-Control and Cohort Study Using Large Electronic Health Records in Four European Countries," *BMJ Open* 12, no. 4 (2022): e052816, https://doi.org/10.1136/bmjopen-2021-052816.

11. D. T. Zemedikun, H. Lee, K. Nirantharakumar, et al., "Comorbidity Phenotypes and Risk of Mortality in Patients With Osteoarthritis in the UK: A Latent Class Analysis," *Arthritis Research & Therapy* 24, no. 1 (2022): 231, https://doi.org/10.1186/s13075-022-02909-4.

12. GBD 2021 Diseases and Injuries Collaborators, "Global Incidence, Prevalence, Years Lived With Disability (YLDs), Disability-Adjusted Life-Years (DALYs), and Healthy Life Expectancy (HALE) for 371 Diseases and Injuries in 204 Countries and Territories and 811 Subnational Locations, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet* 403 (2024): 2133–2161, https://doi.org/10.1016/s0140-6736(24)00757-8.

13. S. Chen, M. Chen, C. Chen, et al., "Epidemiological Trends and Characteristics of Osteoarthritis in China During 1990-2021," *Journal of Orthopaedic Translation* 51 (2025): 218–226, https://doi.org/10.1016/j.jot.2025.02.006.

14. GBD 2021 Causes of Death Collaborators, "Global Burden of 288 Causes of Death and Life Expectancy Decomposition in 204 Countries and Territories and 811 Subnational Locations, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet* 403 (2024): 2100–2132, https://doi.org/10.1016/s0140-6736(24)00367-2.

15. L. J. Stovner, E. Nichols, T. J. Steiner, and T. Vos, "Headache in the Global Burden of Disease (GBD) Studies," in *Societal Impact of Headache: Burden, Costs and Response*, ed. T. J. Steiner and L. J. Stovner (Springer International Publishing, 2019), 105–125.

16. M. Mansourian, K. Ghasemi, A. Haghdoost, J. A. Kopec, N. Sarrafzadegan, and S. M. S. Islam, "Measuring the Burden of Comorbidity for Ischaemic Heart Disease and Four Common Non-Communicable Diseases in Iran, 1990-2017: A Modelling Study Based on Global Burden of Diseases Data," *BMJ Open* 12, no. 11 (2022): e054441, https://doi.org/10.1136/bmjopen-2021-054441.

17. J. Buddeke, M. L. Bots, I. van Dis, et al., "Comorbidity in Patients With Cardiovascular Disease in Primary Care: A Cohort Study With Routine Healthcare Data," *British Journal of General Practice* 69, no. 683 (2019): e398–e406, https://doi.org/10.3399/bjgp19X702725.

18. U. T. Kadam and P. R. Croft, "Clinical Comorbidity in Osteoarthritis: Associations With Physical Function in Older Patients in Family Practice," *Journal of Rheumatology* 34, no. 9 (2007): 1899–1904.

19. N. Garin, A. Koyanagi, S. Chatterji, et al., "Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study," *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 71, no. 2 (2016): 205–214, https://doi.org/10.1093/gerona/glv128.

20. R. John, D. S. Kerby, and C. H. Hennessy, "Patterns and Impact of Comorbidity and Multimorbidity Among Community-Resident American Indian Elders," *Gerontologist* 43, no. 5 (2003): 649–660, https://doi.org/10.1093/geront/43.5.649.

21. GBD 2021 Oral Disorders Collaborators, "Trends in the Global, Regional, and National Burden of Oral Conditions From 1990 to 2021: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet* 405, no. 10482 (2025): 897–910, https://doi.org/10.1016/s0140-6736(24)02811-3.

22. L. M. Ward, S. A. Cooper, L. Hughes-McCormack, L. Macpherson, and D. Kinnear, "Oral Health of Adults With Intellectual Disabilities: A Systematic Review," *Journal of Intellectual Disability Research* 63, no. 11 (2019): 1359–1378, https://doi.org/10.1111/jir.12632.

23. W. Hu, S. Chen, X. Zou, et al., "Oral Microbiome, Periodontal Disease and Systemic Bone-Related Diseases in the Era of Homeostatic Medicine," *Journal of Advanced Research* 73 (2024): 443–458, https://doi.org/10.1016/j.jare.2024.08.019.

24. B. Chen, Y. Zhao, S. Li, et al., "Variations in Oral Microbiome Profiles in Rheumatoid Arthritis and Osteoarthritis With Potential Biomarkers for Arthritis Screening," *Scientific Reports* 8, no. 1 (2018): 17126, https://doi.org/10.1038/s41598-018-35473-6.

25. S. H. Jeong, Y. Nam, H. Jung, et al., "Interrupting Oral Infection of *Porphyromonas gingivalis* With Anti-FimA Antibody Attenuates Bacterial Dissemination to the Arthritic Joint and Improves Experimental Arthritis," *Experimental and Molecular Medicine* 50, no. 3 (2018): e460, https://doi.org/10.1038/emm.2017.301.

26. J. Tang, T. Wu, J. Xiong, et al., "*Porphyromonas gingivalis* Lipopolysaccharides Regulate Functions of Bone Marrow Mesenchymal Stem Cells," *Cell Proliferation* 48, no. 2 (2015): 239–248, https://doi.org/10.1111/cpr.12173.

27. N. Pischon, E. Röhner, A. Hocke, et al., "Effects of *Porphyromonas gingivalis* on Cell Cycle Progression and Apoptosis of Primary Human Chondrocytes," *Annals of the Rheumatic Diseases* 68, no. 12 (2009): 1902–1907, https://doi.org/10.1136/ard.2008.102392.

28. W. Zhang, E. B. Swearingen, J. Ju, T. Rigney, and G. D. Tribble, "*Porphyromonas gingivalis* Invades Osteoblasts and Inhibits Bone Formation," *Microbes and Infection* 12, no. 11 (2010): 838–845, https://doi.org/10.1016/j.micinf.2010.05.011.

29. J. Nijs, S. Z. George, D. J. Clauw, et al., "Central Sensitisation in Chronic Pain Conditions: Latest Discoveries and Their Potential for Precision Medicine," *Lancet Rheumatology* 3, no. 5 (2021): e383–e392, https://doi.org/10.1016/s2665-9913(21)00032-1.

30. C. J. Woolf, "Central Sensitization: Implications for the Diagnosis and Treatment of Pain," *Pain* 152, no. 3 (2011): S2–s15, https://doi.org/10.1016/j.pain.2010.09.030.

31. N. Veronese, C. Cooper, J. Y. Reginster, et al., "Type 2 Diabetes Mellitus and Osteoarthritis," *Seminars in Arthritis and Rheumatism* 49, no. 1 (2019): 9–19, https://doi.org/10.1016/j.semarthrit.2019.01.005.

32. A. L. Arruda, A. Hartley, G. Katsoula, G. D. Smith, A. P. Morris, and E. Zeggini, "Genetic Underpinning of the Comorbidity Between Type 2 Diabetes and Osteoarthritis," *American Journal of Human Genetics* 110, no. 8 (2023): 1304–1318, https://doi.org/10.1016/j.ajhg.2023.06.010.

33. K. Fu, S. Si, X. Jin, et al., "Exploring Antidiabetic Drug Targets as Potential Disease-Modifying Agents in Osteoarthritis," *eBioMedicine* 107 (2024): 105285, https://doi.org/10.1016/j.ebiom.2024.105285.

34. H. Zhu, L. Zhou, Q. Wang, et al., "Glucagon-Like Peptide-1 Receptor Agonists as a Disease-Modifying Therapy for Knee Osteoarthritis Mediated by Weight Loss: Findings From the Shanghai Osteoarthritis Cohort," *Annals of the Rheumatic Diseases* 82, no. 9 (2023): 1218–1226, https://doi.org/10.1136/ard-2023-223845.

35. H. Bliddal, H. Bays, S. Czernichow, et al., "Once-Weekly Semaglutide in Persons With Obesity and Knee Osteoarthritis," *New England Journal of Medicine* 391, no. 17 (2024): 1573–1583, https://doi.org/10.1056/NEJMoa2403664.

36. S. J. Duffield, B. M. Ellis, N. Goodson, et al., "The Contribution of Musculoskeletal Disorders in Multimorbidity: Implications for Practice and Policy," *Best Practice & Research. Clinical Rheumatology* 31, no. 2 (2017): 129–144, https://doi.org/10.1016/j.berh.2017.09.004.

37. F. E. Watt and E. M. Wise, "Osteoarthritis and Associated Comorbidities: New Answers and More Questions," *Rheumatology* 60, no. 9 (2021): 3966–3968, https://doi.org/10.1093/rheumatology/keab405.

38. J. X. Huang, S. Z. Xu, T. Tian, et al., "Genetic Links Between Metabolic Syndrome and Osteoarthritis: Insights From Cross-Trait Analysis," *Journal of Clinical Endocrinology and Metabolism* 110, no. 2 (2025): e461–e469, https://doi.org/10.1210/clinem/dgae169.

39. S. Swain, C. Coupland, C. Mallen, et al., "Temporal Relationship Between Osteoarthritis and Comorbidities: A Combined Case Control and Cohort Study in the UK Primary Care Setting," *Rheumatology* 60, no. 9 (2021): 4327–4339, https://doi.org/10.1093/rheumatology/keab067.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apl70548-sup-0001-DataS1.docx.

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LETTER TO THE EDITOR

Prevalence, Treatment Patterns, and Outcomes Among Australian SLE Patients With Inadequately Controlled Disease Activity

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Dear Editor,

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical manifestations and a relapsing–remitting course [1]. Inadequately controlled disease activity is associated with greater organ damage, higher corticosteroid exposure, and poorer outcomes [2–4]. In recent years, the treat-to-target approaches aimed at controlling inflammatory disease activity in SLE through adequate immunosuppression have gained widespread expert endorsement; however, uncertainty remains regarding the optimal strategies needed to achieve this goal [5].

Current therapeutic options for SLE remain limited in Australia, relying on general approaches that include the use of antimalarials, conventional immunosuppressants, and corticosteroids [6]. Clinicians often combine these three classes of medications into the so-called triple therapy (TT) to manage disease activity. The selection of immunosuppressant is typically empirical and predominantly "off-label." Approved advanced therapies such as belimumab and anifrolumab, along with off-label biologics such as rituximab, have seen limited use in Australia due to funding restrictions.

Using data from the Australian Lupus Registry and Biobank (ALRB), we sought to describe the prevalence, characteristics, medication patterns, and outcomes of patients with inadequately controlled disease within a universal healthcare setting [7]. We applied the following definition for inadequately controlled disease [8]: either (i) ever attainment of High Disease Activity Status (HDAS), defined as an ever attainment of SLEDAI-2K of 10 or greater [9]; or (ii) time-adjusted mean SLEDAI-2K (AMS) > 4 [10]. We also separately examined those who never achieved Lupus Low Disease Activity State (LLDAS-never). These capture different clinical perspectives: disease severity that carries a prognostic significance, sustained disease activity, and failure to achieve minimal disease activity.

Among 520 patients followed for a median of 3.8 years (IQR 2–7), 32.1% experienced HDAS and 33.9% had an AMS > 4 (Table 1). Combined, these groups accounted for 41% (213/520) of the cohort, classified as having inadequate disease control. LLDAS was achieved at least once in the majority of patients (87.6%), with the median percentage of time spent in LLDAS of 47.3% (IQR 21.9–67.9) during the observation period. Notably, approximately one in eight patients never achieved LLDAS throughout the study.

Patients with AMS > 4 or HDAS were significantly younger at diagnosis and had a longer duration of follow-up. In contrast, those who never attained LLDAS had the shortest median period of observation (1.8 years vs. 4.3 years, $p < 0.001$). Across all definitions, patients with inadequate control had higher

TABLE 1 | Patient characteristics and longitudinal outcomes of the study cohort, stratified by better-controlled SLE versus inadequately controlled SLE patient groups.

	All patients	Better-controlled SLE	Inadequately controlled SLE	
	n = 520	*n* = 307	*n* = 213	
		Median [IQR] or *n* (%)		*p*
Demographics				
Age at enrolment (years)	40 [31, 51]	42 [33, 54]	37 [28, 47]	< 0.001
Age at diagnosis (years)	29 [22, 42]	31.5 [24, 45]	27 [20, 36]	< 0.001
SLE disease duration at enrolment (years)	7 [2, 15]	7 [2, 14]	7 [2, 15]	0.90
Study duration (years)	3.8 [2.0, 7.0]	3.4 [1.7, 6.2]	4.3 [2.4, 7.6]	< 0.001
Females	462 (88.8%)	274 (89.3%)	188 (88.3%)	0.72
Asian ethnicity[a]	187 (37.5%)	93 (31.8%)	94 (45.4%)	0.002
Family history of SLE[b]	41 (8.6%)	24 (8.6%)	17 (8.6%)	0.99
Current smoker at enrolment[c]	59 (12.1%)	34 (11.8%)	25 (12.4%)	0.84
Tertiary education level[d]	256 (52.1%)	149 (51.9%)	107 (52.5%)	0.91
Serological profile at enrolment[e]				
ANA+	500 (97.5%)	290 (96.7%)	210 (98.6%)	0.17
Anti-dsDNA	393 (76.6%)	199 (66.3%)	194 (91.1%)	< 0.001
Low complement	391 (76.2%)	203 (67.7%)	188 (88.3%)	< 0.001
Medications use				
Glucocorticoids at least once (—ever)	352 (67.7%)	166 (54.1%)	186 (87.3%)	< 0.001
TAM-PNL (mg/day)	2.5 [0.0, 6.3]	0.5 [0.0, 3.3]	5.7 [3.1, 8.8]	< 0.001
Cumulative PNL dose (g)	2.4 [0.0, 8.3]	0.3 [0.0, 3.7]	7.4 [2.4, 13.4]	< 0.001
Antimalarials (AM)—ever	473 (91.0%)	270 (87.9%)	203 (95.3%)	0.004
Immunosuppressants (IS)—ever	362 (69.6%)	174 (56.7%)	188 (88.3%)	< 0.001
Mycophenolate (MMF/MPA)	204 (39.2%)	67 (21.8%)	137 (64.3%)	< 0.001
Azathioprine (AZA)	157 (30.2%)	83 (27.0%)	74 (34.7%)	0.060
Methotrexate (MTX)	91 (17.5%)	53 (17.3%)	38 (17.8%)	0.86
Triple therapy (GC + AM + IS)—ever	275 (52.9%)	116 (37.8%)	159 (74.6%)	< 0.001
Biologics—ever	31 (6.0%)	3 (1.0%)	28 (13.1%)	< 0.001
Rituximab (RTX)	29 (5.6%)	3 (1.0%)	26 (12.2%)	< 0.001
Belimumab (BEL)	9 (1.7%)	0 (0.0%)	9 (4.2%)	< 0.001
Clinical profile				
TAM-SLEDAI (AMS)	3.2 [1.6, 4.8]	2.0 [0.8, 2.9]	5.0 [4.2, 6.3]	< 0.001
TAM PGA	0.4 [0.2, 0.6]	0.3 [0.2, 0.4]	0.6 [0.4, 0.9]	< 0.001
Flares (mild/moderate or severe)—ever	347 (66.7%)	159 (51.8%)	188 (88.3%)	< 0.001
Organ damage present at study enrolment	247 (48.2%)	129 (43.0%)	118 (55.7%)	0.005
New damage accrued	130 (25.4%)	61 (20.3%)	69 (32.5%)	0.002

(Continues)

TABLE 1 | (Continued)

	All patients	Better-controlled SLE	Inadequately controlled SLE	
	n = 520	*n* = 307	*n* = 213	
		Median [IQR] or *n* (%)		*p*
Attained LLDAS?				
Never	64 (12.4%)	11 (3.6%)	53 (24.9%)	< 0.001
Ever (yes, at least once)	452 (87.6%)	292 (96.4%)	160 (75.1%)	
3 m sustained LLDAS	351 (67.5%)	243 (79.2%)	108 (50.7%)	< 0.001
6 m sustained LLDAS	301 (57.9%)	215 (70.0%)	86 (40.4%)	< 0.001
12 m sustained LLDAS	186 (35.8%)	147 (47.9%)	39 (18.3%)	< 0.001
AMS > 4	176 (33.8%)	0 (0.0%)	176 (82.6%)	< 0.001
HDAS	167 (32.1%)	0 (0.0%)	167 (78.4%)	< 0.001
Deceased patients	10 (1.9%)	5 (1.6%)	5 (2.3%)	0.56
SF36 (v2) survey-assessed HRQoL				
TAM PCS score	45.3 [37.8, 51.0]	45.7 [38.4, 51.3]	45.1 [37.3, 50.6]	0.57
TAM MCS score	47.6 [39.8, 53.1]	49.0 [40.5, 54.3]	46.9 [39.6, 52.3]	0.11

Note: Data missing for [a]21, [b]44, [c]32, [d]29, and [e]7 patients.
Abbreviations: AMS, adjusted mean SLEDAI; HDAS, high disease activity status; HRQoL, health-related quality of life; LLDAS, lupus low disease activity state; MCS, mental component summary; PCS, physical component summary; PNL, prednisolone; TAM, time-adjusted mean.

annualized flare rates, ranging from 1.0 to 1.2 flares per year. Patients with inadequately controlled disease had a higher proportion who experience flares, baseline damage and were more likely to accrue new organ damage during follow-up (Table 1).

Corticosteroid exposure was notably higher in the inadequately controlled group. Median time-adjusted mean prednisolone (TAM-PNL) dose was 5.7 mg/day in these patients, compared to 0.5 mg/day in those with better control ($p < 0.001$) (Table 1). The highest median TAM-PNL was observed in the LLDAS-never group at 9.6 mg/day (IQR 5.7–15.6).

Mycophenolate (MMF/MPA) was the most frequent immunosuppressant prescribed (64.3% of inadequately controlled patients), followed by azathioprine (34.7%) and methotrexate (17.8%) (Table 1). Among HDAS patients, 44.9% (75/167) were on triple therapy, with at least 7.5 mg of prednisolone daily. Overall, 14.4% of the entire cohort had at least one visit with HDAS while receiving triple therapy with prednisolone ≥ 7.5 mg daily.

Use of advanced therapies was low overall but significantly more common among patients with inadequate control. Rituximab was prescribed to 12.2% of inadequately controlled patients, versus 1.0% of those with better control ($p < 0.001$). Belimumab, though more recently available, was used exclusively in the inadequately controlled disease group (4.2% vs. 0%, $p < 0.001$).

Sustained LLDAS was rarely achieved in these groups (Figure 1). For patients on mycophenolate, 62.8% failed to achieve 6 months of sustained LLDAS; similarly, among rituximab and belimumab users, 61.5% and 77.7% were unable to achieve this milestone. This highlights the limitations of currently available therapies in achieving disease control.

Our study did not detect associations between these definitions of disease control and patient-reported HRQoL measures, in contrast to a larger study that demonstrated a weak but statistically significant association for inadequate disease control and reduced HRQoL [8]. Although HRQoL and other patient-reported outcomes represent important dimensions of disease impact, the well-documented discordance between patient and physician assessments of disease activity in SLE [11], suggests that these constructs are only partially overlapping constructs. This highlights the influence of factors beyond disease activity on HRQoL in individuals with SLE.

Inadequate disease control remains a significant concern in Australian SLE management. While current definitions are not universally agreed, they offer complementary insights. HDAS is clinically intuitive and applicable in real time; AMS > 4 reflects persistent disease burden but may be influenced by follow-up duration; LLDAS-never is stringent but sensitive to observation time. Additional scenarios that merit consideration to include into the operational definition of inadequate disease control may include frequent flares, glucocorticoid dependence, and failure to achieve sustained remission.

These real-world data reinforce the importance of early identification and intervention in high-risk patients with inadequate disease control and emphasize the urgent need for accessible advanced therapies for patients living with SLE. The heavy reliance on corticosteroids and off-label immunosuppressants reflects a treatment landscape constrained by limited access to approved options. Expanded subsidized access to advanced therapies, alongside the development of treatment strategies, is essential to improving outcomes in SLE. While the use of biologics in our cohort was limited prior to the recent change in PBS-reimbursed

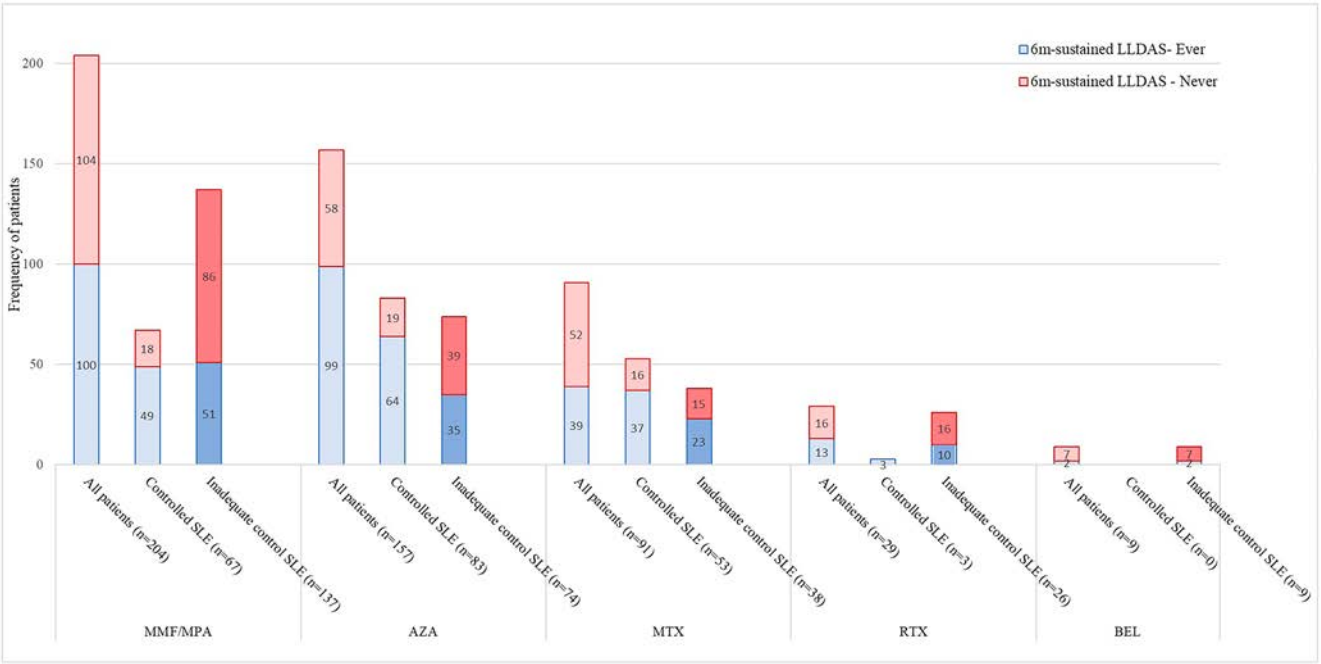

FIGURE 1 | Distribution of immunosuppressant use by disease control status and sustained LLDAS attainment. Among patients using different immunosuppressants, those with inadequately controlled SLE had a significantly higher proportion unable to achieve at least 6 months of sustained LLDAS (red) compared to better-controlled patients. The proportion of patients who have achieved at least 6 months of sustained LLDAS is shown in blue.

indication, we hope that patients with refractory disease or those unable to tolerate existing therapies will now have broader and more equitable access to advanced treatment options. Future research should prioritize refining operational definitions of inadequate disease control, identifying predictors of sustained LLDAS, and evaluating the efficacy of novel therapies or strategies to improve disease control and quality of life.

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A.Y.-B.H. and R.K.-R. conceived the study. R.K.-R. and R.K. analysed data, and wrote the manuscript and all authors reviewed and approved final version.

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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.

References

1. V. Golder and A. Hoi, "Systemic Lupus Erythematosus: An Update," *Medical Journal of Australia* 206, no. 5 (2017): 215–220.

2. T. Stoll, "Analysis of the Relationship Between Disease Activity and Damage in Patients With Systemic Lupus Erythematosus—A 5-Yr Prospective Study," *Rheumatology (Oxford, England)* 43, no. 8 (2004): 1039–1044.

3. D. D. Hill, A. M. Eudy, P. J. Egger, Q. Fu, and M. A. Petri, "Impact of Systemic Lupus Erythematosus Disease Activity, Hydroxychloroquine and NSAID on the Risk of Subsequent Organ System Damage and Death: Analysis in a Single US Medical Centre," *Lupus Science & Medicine* 8, no. 1 (2021): e000446.

4. K. Franklyn, C. S. Lau, S. V. Navarra, et al., "Definition and Initial Validation of a Lupus Low Disease Activity State (LLDAS)," *Annals of the Rheumatic Diseases* 75, no. 9 (2016): 1615–1621.

5. R. F. van Vollenhoven, M. Mosca, G. Bertsias, et al., "Treat-To-Target in Systemic Lupus Erythematosus: Recommendations From an International Task Force," *Annals of the Rheumatic Diseases* 73 (2014): 958–967.

6. A. Y. Hoi and E. F. Morand, "Treatment Update in Systemic Lupus Erythematous," *Rheumatic Diseases Clinics of North America* 47, no. 3 (2021): 513–530.

7. S. O'Neill, E. F. Morand, and A. Hoi, "The Australian Lupus Registry and Biobank: A Timely Initiative," *Medical Journal of Australia* 206, no. 5 (2017): 194–195.

8. R. Kandane-Rathnayake, W. Louthrenoo, A. Hoi, et al., "'Not at Target': Prevalence and Consequences of Inadequate Disease Control in Systemic Lupus Erythematosus—A Multinational Observational Cohort Study," *Arthritis Research & Therapy* 24, no. 1 (2022): 70.

9. R. Koelmeyer, H. T. Nim, M. Nikpour, et al., "High Disease Activity Status Suggests More Severe Disease and Damage Accrual in Systemic Lupus Erythematosus," *Lupus Science & Medicine* 7, no. 1 (2020): e000372.

10. D. Ibañez, D. D. Gladman, and M. B. Urowitz, "Adjusted Mean Systemic Lupus Erythematosus Disease Activity Index-2K Is a Predictor of Outcome in SLE," *Journal of Rheumatology* 32, no. 5 (2005): 824–827.

11. V. Golder, J. J. Y. Ooi, A. S. Antony, et al., "Discordance of Patient and Physician Health Status Concerns in Systemic Lupus Erythematosus," *Lupus* 27, no. 3 (2018): 501–506.

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LETTER TO THE EDITOR

BHLHE40 Expression in Synovial CD4$^+$ T Cells of Rheumatoid Arthritis Patients

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Dear Editor,

We identified BHLHE40 protein expression in synovial CD4$^+$ T cells from patients with rheumatoid arthritis (RA), complementing our previous transcriptomic findings [1]. Our previous RNA sequencing study revealed elevated *BHLHE40* gene expression in synovial fluid CD4$^+$ T cells compared to peripheral blood in RA patients [1, 2]. Interleukin (IL)-1 contributes to BHLHE40 upregulation in CD4$^+$ T cells. The concentration of IL-1β in RA synovial fluid is elevated compared to that in patients with osteoarthritis or non-inflammatory joint disease [3]. In this study, we examined paraffin-embedded synovial tissue sections from RA patients undergoing joint biopsy to validate this finding at the protein level. Initial hematoxylin and eosin staining (Figure 1A) confirmed characteristic RA histopathology, including synovial hyperplasia and infiltration of inflammatory cells. CD4 and BHLHE40 immunofluorescent staining demonstrated the presence of CD4$^+$ T cells within the inflamed synovium aligning with known pathological features of RA. Critically, BHLHE40 immunostaining revealed an expression with CD4$^+$ T cells, indicating that a substantial proportion of these infiltrating T cells express BHLHE40 (Figure 1B–E). As in the heatmap shown, in synovial fluid-derived central memory CD4$^+$ T cells and effector memory CD4$^+$ T cells, the gene expression of *BHLHE40* was found to correlate with clinical parameters Health Assessment Questionnaire (HAQ) (Figure 1F). This observation supports and extends our prior transcriptomic findings, offering robust protein-level confirmation [1]. The high expression of BHLHE40 in CD4$^+$ T cells within the synovium suggests a functional role in sustaining T cell activation and inflammatory activity in RA. BHLHE40 is a basic helix–loop–helix transcription factor known to regulate various immune functions. It has been implicated in regulating the expression of key cytokines such as tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, and IL-22 [4], all of which are critically involved in RA pathogenesis. Notably, BHLHE40 is expressed across diverse immune cell types—including activated CD4$^+$ T cells and macrophages/monocytes—in line with prior reports. It is also responsive to hypoxic conditions and has been linked to metabolic and transcriptional reprogramming under inflammatory stress in the synovial microenvironment [5, 6].

These findings support the notion that BHLHE40 may serve as a potential therapeutic target in RA, given its role in modulating pro-inflammatory cytokine production within synovial CD4$^+$ T cells. Future studies will examine the downstream pathways governed by BHLHE40 in these cells, including its effects on cytokine secretion, cell persistence, and migratory behavior. Investigating whether BHLHE40 inhibition can ameliorate synovial inflammation and joint destruction in preclinical RA models is warranted [7].

In summary, our immunofluorescence analysis demonstrates that BHLHE40 is expressed in synovial CD4$^+$ T cells in RA, and transcriptomic analyses further show that BHLHE40 expression positively correlates with HAQ scores in synovial-fluid CD4$^+$ T-cell subsets. These results reinforce the hypothesis that BHLHE40 contributes significantly to local immune dysregulation in RA and may represent a promising target for therapeutic intervention.

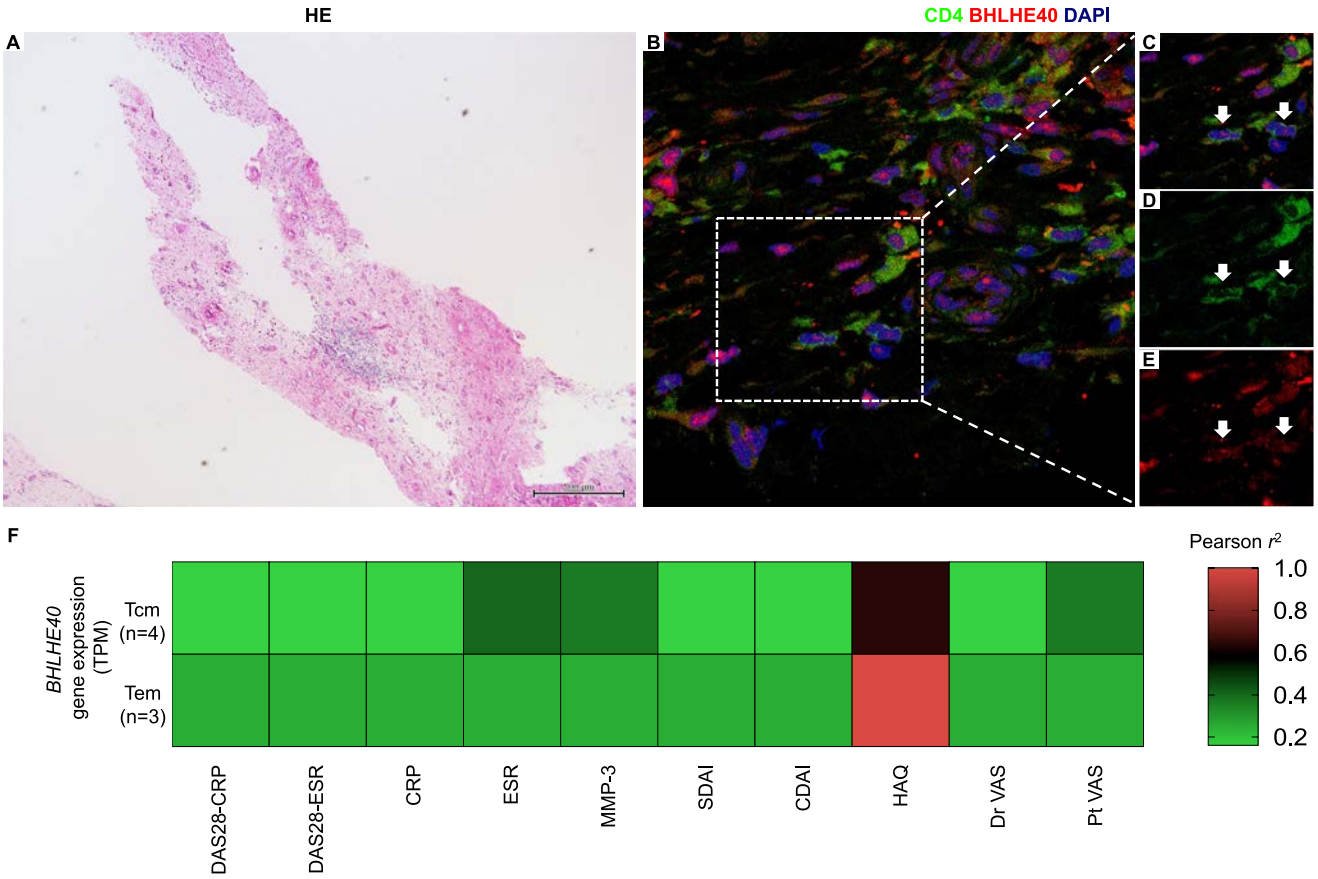

FIGURE 1 | (A) Hematoxylin–eosin (HE) staining of rheumatoid arthritis synovium showing lining hyperplasia and inflammatory cell infiltration. Scale bar, 500 μm. (B) Low-magnification immunofluorescence of synovium with CD4 (green), BHLHE40 (red), and nuclei (DAPI, blue). (C) High-magnification merged view of the boxed region in (B); arrowheads indicate $CD4^+$ $BHLHE40^+$ cells. (D–E) Single-channel high-magnification images corresponding to (C): (D) CD4; (E) BHLHE40. (F) Heatmap of Pearson correlation across clinical indices and BHLHE40 transcript levels in synovial fluid $CD4^+$ central-memory and effector-memory T cells. Clinical indices include disease activity and laboratory measures. CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28-CRP, disease activity score 28 using C-reactive protein; DAS28-ESR, disease activity score 28 using erythrocyte sedimentation rate; Dr VAS, physician's visual analogue scale; Tem, effector memory $CD4^+$ T cell; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MMP-3, matrix metalloproteinase-3; Pt VAS, patient's visual analogue scale; RA, rheumatoid arthritis; SDAI, simplified disease activity index; Tcm, central memory $CD4^+$ T cell; TPM Transcripts Per Million.

Author Contributions

S.I.: formal analysis, investigation, methodology, writing the original draft, writing of the review, and editing. M.T. and M.K.: methodology. K.S. and Y.K.: supervision, writing of the review, and editing.

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Ethics Statement

Ethics Committee of Keio University School of Medicine (protocol #20140335) and conducted in accordance with the principles outlined in the Declaration of Helsinki.

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.

Sho Ishigaki
Katsuya Suzuki
Masaru Takeshita
Masatoshi Kawai
Yuko Kaneko

References

1. S. Ishigaki, K. Suzuki, M. Takeshita, and Y. Kaneko, "Identification of BHLHE40-Expressing CD4+ T Cells Producing GM-CSF in Rheumatoid Arthritis," *International Journal of Rheumatic Diseases* 28, no. 4 (2025): e70219, https://doi.org/10.1111/1756-185X.70219.

2. M. Takeshita, K. Suzuki, Y. Kondo, et al., "Multi-Dimensional Analysis Identified Rheumatoid Arthritis-Driving Pathway in Human T Cell," *Annals of the Rheumatic Diseases* 78, no. 10 (2019): 1346–1356, https://doi.org/10.1136/annrheumdis-2018-214885.

3. J. Kay and L. Calabrese, "The Role of Interleukin-1 in the Pathogenesis of Rheumatoid Arthritis," *Rheumatology* 43, no. 3 (2004): iii2–iii9, https://doi.org/10.1093/rheumatology/keh201.

4. S. Emming, N. Bianchi, S. Polletti, et al., "A Molecular Network Regulating the Proinflammatory Phenotype of Human Memory T Lymphocytes," *Nature Immunology* 21, no. 4 (2020): 388–399, https://doi.org/10.1038/s41590-020-0622-8.

5. M. E. Cook, N. N. Jarjour, C. C. Lin, and B. T. Edelson, "Transcription Factor Bhlhe40 in Immunity and Autoimmunity," *Trends in Immunology* 41, no. 11 (2020): 1023–1036, https://doi.org/10.1016/j.it.2020.09.002.

6. K. Miyazaki, T. Kawamoto, K. Tanimoto, M. Nishiyama, H. Honda, and Y. Kato, "Identification of Functional Hypoxia Response Elements in the Promoter Region of the DEC1 and DEC2 Genes," *Journal of Biological Chemistry* 277, no. 49 (2002): 47014–47021, https://doi.org/10.1074/jbc.M204938200.

7. Y. Wu, H. Wang, Y. Huo, et al., "Differentiated Embryonic Chondrocyte Expressed Gene-1 Is a Central Signaling Component in the Development of Collagen-Induced Rheumatoid Arthritis," *Journal of Biological Chemistry* 299, no. 3 (2023): 102982, https://doi.org/10.1016/j.jbc.2023.102982.

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ORIGINAL ARTICLE

Rheumatoid Factor Levels Are Associated With Arthritis Exacerbation After Bucillamine Discontinuation

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ABSTRACT

Aim: Bucillamine is a conventional synthetic disease-modifying antirheumatic drug that can be used as a methotrexate alternative. However, which patients with rheumatoid arthritis can benefit from bucillamine treatment has not been established.

Methods: Patients who had taken bucillamine and discontinued it in 2021 due to a nationwide supply shortage were included in this study. We followed up these patients regarding arthritis exacerbation after bucillamine discontinuation until March 2025. Baseline clinical patient characteristics were compared between the exacerbation and non-exacerbation groups.

Results: Thirteen of the 18 patients experienced arthritis exacerbation, whereas five remained exacerbation-free for up to 48 months. The baseline rheumatoid factor levels were significantly higher in the exacerbation group (49 U/mL) than in the non-exacerbation group (6 U/mL). Receiver operating characteristic and Kaplan–Meier analyses showed that baseline RF levels ≥ 28 U/mL predicted arthritis exacerbation after bucillamine discontinuation (sensitivity 76.2% and specificity 80.0%).

Conclusion: Following bucillamine discontinuation, arthritis exacerbations occurred more frequently in patients with rheumatoid factor levels of 28 U/mL or higher, alongside an increase in these levels. Rheumatoid factor levels may serve as a useful biomarker for identifying patients who would benefit from continued bucillamine therapy.

1 | Introduction

Although treatment for rheumatoid arthritis (RA) has significantly improved with the advent of biological disease-modifying antirheumatic drugs, therapeutic options were limited prior to their introduction. Methotrexate (MTX) has been established as an anchor drug and has been commonly used alongside aggressive biological therapies [1]. Current guidelines recommend conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly MTX, for initial therapy, and emphasize personalized treatment decisions based on patient-specific factors such as age, comorbidities, and disease activity [1]. The efficacy of biologics is now well established, as is the importance of tailoring biologic selection to individual patients. Conversely, csDMARDs, which have been in use since before 2000, also demonstrate clinical efficacy; however, they lack clearly defined treatment guidelines and are frequently prescribed based on the clinical experience of specialists [2].

Bucillamine (BUC) is a csDMARD that was developed in Japan in 1975 and has been widely used since its approval in 1987. It has traditionally been employed as a first-line drug alongside sulfasalazine (SSZ) when MTX could not be administered [2]. BUC is a cysteine derivative with two sulfhydryl (–SH) groups and is a structural homolog of D-penicillamine [3]. Multiple studies have reported BUC effectiveness; it is comparable to low-dose MTX, and combination therapy with BUC and SSZ has demonstrated efficacy equivalent to that of tumor necrosis factor-α inhibitors [4]. In addition, case reports have highlighted its role in bone erosion repair and in patients with RA [5–8]. Despite these

positive results, BUC efficacy varies widely among individuals, and predictive markers for clinical benefit remain inadequately defined. Furthermore, the risk of exacerbation following discontinuation also requires further elucidation.

A nationwide supply shortage in 2021 forced many patients with RA in Japan to discontinue BUC therapy. Therefore, we designed a cohort study to analyze the clinical characteristics of patients with and without arthritis exacerbation after BUC discontinuation that would reveal features predictive for the benefit of continued BUC use. Identifying these characteristics is clinically valuable because it can inform individualized decision-making regarding BUC withdrawal.

Thus, this retrospective cohort study investigated the clinical features associated with arthritis exacerbation following unavoidable BUC discontinuation and clarified the patient populations most likely to benefit from continued BUC therapy.

2 | Materials and Methods

2.1 | Study Design and Population

Patients with RA who had taken BUC and discontinued it in 2021 due to a nationwide supply shortage were included in the study. RA was diagnosed according to the 2010 European League Against Rheumatism/American College of Rheumatology criteria [9]. No exclusion criteria were applied. The patients were followed up regarding arthritis exacerbation from BUC discontinuation until March 2025. Arthritis exacerbation was defined as an emergence of swelling or tenderness in at least one joint as determined from physical examination by rheumatologists with a simultaneous increase in the C-reactive protein (CRP) level or serum erythrocyte sedimentation rate, and treatment was changed or strengthened during regular follow-up visits until March 2025.

The baseline clinical characteristics of the patients were retrospectively compared between the exacerbation and non-exacerbation groups. Clinical and laboratory data were obtained from a detailed review of medical records. The RF $\geq$ 16 U/mL was considered positive based on the 95th percentile value from healthy individuals in Japan. The post-discontinuation RF measurement was obtained when arthritis exacerbation was diagnosed or 1 year after discontinuation.

This cohort study was conducted at Takikawa Municipal Hospital, Japan, in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Approval for the study was obtained from the Takikawa Municipal Hospital Ethics Committee (approval number: 25-03). Informed consent was obtained from all the patients using an opt-out procedure.

2.2 | Statistical Analyses

Continuous variables are presented as medians with interquartile ranges (IQR) and compared between groups using the Wilcoxon signed-rank test and Wilcoxon rank-sum test. The categorical variables were compared using the Chi-squared test. Diagnostic accuracy was assessed using the area under the receiver operating characteristic (ROC) curve, expressed as the area under the curve (AUC), as well as sensitivity and specificity. The Kaplan–Meier analysis and the log-rank test were used to assess the significance of the differences between groups. A $p < 0.05$ was considered significant. All analyses were performed using JMP Student Edition software (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Patient Characteristics

This study included 18 patients. Demographic, clinical, and laboratory data at baseline just before BUC discontinuation are summarized in Table 1. Sixteen patients were treated with BUC monotherapy, of which 15 were taking 100 mg daily and 1 was taking 200 mg daily. Two received combination therapy of 100 mg BUC daily and 1000 mg of SSZ daily. None of the patients were treated with MTX. Three patients were concurrently treated with prednisolone (PSL), including one who was taking 1 mg of PSL daily, one who was taking 2.5 mg of PSL daily, and one who was taking 5 mg of PSL weekly. At baseline, 11 patients (61.1%) did not have tender or swollen joints. Of the seven patients with joint symptoms, two had a single tender spot on their wrists, one had swollen knuckles in multiple joints without tenderness, and four had swelling and tenderness in multiple joints. The median serum CRP level was 0.3 mg/dL (IQR: 0–0.9). Thirteen patients tested positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies, and the median serum rheumatoid factor (RF) level was 41.5 U/mL (IQR: 8.2–72) U/mL.

3.2 | Comparisons Between the Exacerbation and Non-Exacerbation Groups

Following BUC discontinuation, arthritis exacerbation was observed in 13 of the 18 patients (72.2%) (Figure 1). The median duration from BUC discontinuation to arthritis exacerbation was 11.5 (range 9–21.8) months.

Although the proportion of patients with anti-CCP antibodies tended to be higher in the exacerbation group, no significant difference was observed (number anti-CCP antibodies: 11 vs. 2, $p = 0.0584$).

Regarding Steinbrocker staging for the patients in the exacerbation and non-exacerbation groups, six and two were in stage I, three and two were in stage II, three and two were in stage III, and one and zero were in stage IV, respectively [10].

No significant differences were observed for age, sex, or disease duration. Significant differences were observed in RF levels between before and after discontinuation (median RF: 41.5 vs. 80 U/mL; $p = 0.0060$; Figure 2A). Compared with the non-exacerbation group, the exacerbation group had significantly higher RF levels both prior to treatment cessation and after discontinuation (before discontinuation: median RF: 49 vs. 6 U/mL;

TABLE 1 | Patient characteristics.

Variable	RA ($n=18$)
Age (years)	70.5 [66–80.2]
Disease duration (years)	10.5 [3.7–16.2]
Women	16 (88.8)
Comorbidity	
Lung disease	
Interstitial lung disease	2 (11.1)
Chronic obstructive pulmonary disease	1 (5.5)
Other lung diseases	3 (16.6)
Chronic kidney disease	
Grade 1–2 (eGFR: > 60)	14 (77.7)
Grade 3 (eGFR: 30–59)	4 (22.2)
Grade 4 (eGFR: 15–29)	0 (0)
Grade 5 (eGFR: < 15)	0 (0)
Other comorbidities[a]	3 (16.6)
Laboratory results	
CRP, mg/dL	0.3 [0–0.9]
Positive RF	13 (72.2)
RF before discontinuation, U/mL	41.5 [8.2–72]
Positive anti-CCP antibodies	13 (72.2)
Steinbrocker stages I/II/III/IV	8/5/4/1
Arthritis symptoms	
No tender or swollen joints before discontinuation	11 (61.1)
Tender joints before discontinuation	6 (33.3)
Tender joints ≤ 1	5 (83.3)
Tender joints > 1	1 (16.6)
Swollen joints before discontinuation	5 (27.7)
swollen joints ≤ 2	4 (80)
swollen joints > 2	1 (20)
DMARDs before discontinuation	
BUC monotherapy	16 (88.8)
100 mg of BUC daily	15 (93.7)
200 mg of BUC daily	1 (6.2)
100 mg of BUC daily +1000 mg of SSZ daily	2 (11.1)
Prednisolone	3 (16.6)
DMARDs after discontinuation	
None	10 (55.5)
1000 mg of SSZ daily	5 (27.7)
50 mg of IGU daily	2 (11.1)
Prednisolone	2 (11.1)

Note: Data are shown as median [quartile] or number (%).
Abbreviations: anti-CCP, anti–cyclic citrullinated peptide; BUC, bucillamine; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; eGFR, estimated glomerular filtration rate; IGU, iguratimod; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulfasalazine.
[a]Other comorbidities were bile duct cancer, stomach cancer, and heart failure.

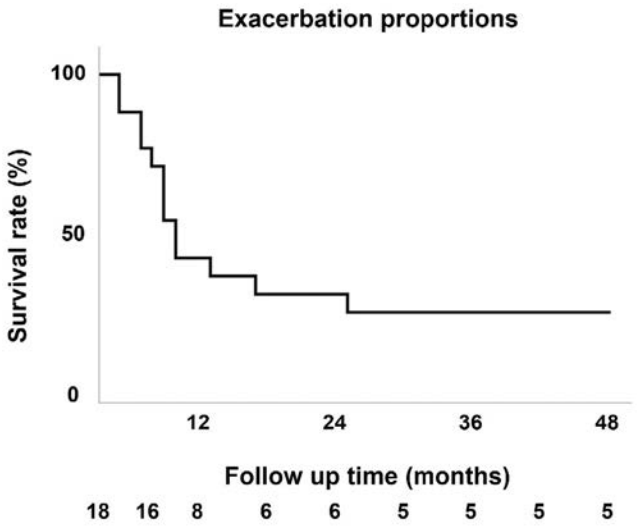

FIGURE 1 | Kaplan–Meier curve showing exacerbation-free survival. Arthritis exacerbation is observed in 13 of the 18 patients (72.2%).

$p=0.0305$) (after discontinuation: median RF: 95 vs. 2 U/mL, $p=0.0190$; Table 2). In both groups, the amount of change in RF levels before and after discontinuation was compared; however, no significant difference was observed (median RF: 48 vs. 0; $p=0.0630$; Figure 2B). In eight patients, treatment was switched to other treatments (SSZ or IGU) after discontinuing BUC, which could have possibly prevented recurrence. Therefore, a similar analysis was conducted on 10 patients, excluding these eight. This subgroup including 10 patients, although there was a slightly higher rate of no tender or swollen joints before discontinuation, had baseline characteristics similar to those of the overall cohort (Table S1). Ten patients took no treatment after discontinuation, and seven of them experienced exacerbation. Significant differences were observed in the RF levels between before and after discontinuation (median RF: 45 vs. 97 U/mL; $p=0.0039$; Figure 2C). The amount of change in RF levels before and after discontinuation was compared, and significant differences were observed (median RF: 64 vs. 0; $p=0.0113$; Figure 2D). Five patients were RF-negative at baseline; of these five patients, two experienced arthritis exacerbation and the RF became positive in one of two.

The ROC curve analysis was performed with all 18 patients, which showed that assessed RF levels at baseline yielded an AUC of 0.80 (95% CI 0.59–1.0) to predict arthritis exacerbation after BUC discontinuation (Figure 3A). Using a cut-off RF level of 28 U/mL, the

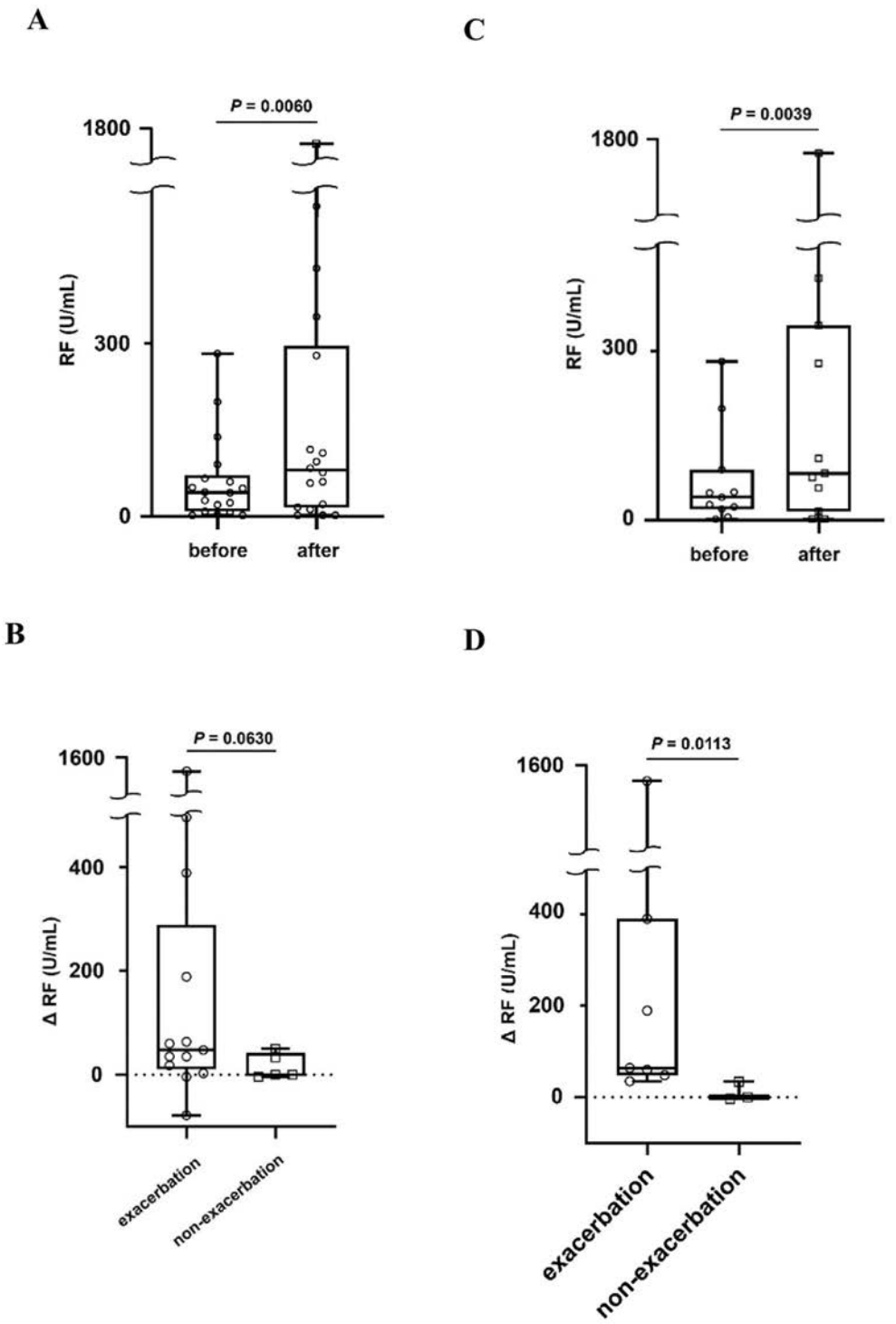

FIGURE 2 | Rheumatoid factor (RF) level alterations upon bucillamine discontinuation. *p*-values are presented above the boxplots. Boxplots indicate the interquartile range. (A) RF level comparisons before and after discontinuation in all patients. The Wilcoxon signed-rank test was used to compare the RF levels. (B) The amount of change in the RF levels before and after discontinuation was compared in both groups. Δ represents the amount of change. The Wilcoxon rank-sum test was used to compare the Δ RF levels between the groups. (C) RF level comparisons before and after the discontinuation for no treatment after discontinuation. The Wilcoxon signed-rank test was used to compare results between groups. (D) The amount of change in the RF levels before and after discontinuation was compared in both groups for no treatment after discontinuation. Δ represents the amount of change. The Wilcoxon rank-sum test was used to compare the Δ RF levels between groups.

sensitivity and specificity were 76.2% and 80.0%, respectively. The Kaplan–Meier analysis revealed a significantly higher exacerbation rate for patients with RF levels ≥28 than for the group with RF levels <28 U/mL (log-rank test, $p = 0.0116$; Figure 3B).

4 | Discussion

This study determined the possibility of discontinuing BUC and the predictors of exacerbation following discontinuation.

TABLE 2 | Factors associated with arthritis exacerbation.

Variable	Exacerbation		*p**
	Yes ($n=13$)	No ($n=5$)	
Age (years)	72 [66–80.5]	67 [65–78.5]	0.3281
Disease duration (years)	13 [2–16.5]	9 [5–16.5]	0.4217
Women	11 (84.6)	5 (100)	0.3522
Laboratory results			
CRP, mg/dL	0.6 [0–0.95]	0.2 [0–0.55]	0.1825
Positive RF	11 (84.6)	2 (40)	0.0584
RF before discontinuation, U/mL	49 [24–114]	6 [2–45]	0.0305
RF at exacerbation or 1-year post discontinuation, U/mL	95 [40.5–388]	2 [2–87]	0.0190
Positive anti-CCP antibodies	11 (84.6)	2 (40)	0.0584
Steinbrocker stages I/II/III/IV	6/3/3/1	2/2/1/0	
Arthritis symptoms			
No tender or swollen joints before discontinuation	7 (53.8)	4 (80)	0.3080
Tender joints before discontinuation	5 (38.4)	1 (20)	0.6977
Swollen joints before discontinuation	5 (38.4)	0 (0)	0.4466
DMARDs before discontinuation			
BUC monotherapy	12 (92.3)	4 (80)	
100 mg of BUC daily	12 (92.3)	3 (60)	
200 mg of BUC daily	0 (0)	1 (20)	
100 mg of BUC daily +1000 mg of SSZ daily	1 (7.6)	1 (20)	
Prednisolone	3 (23)	0 (0)	
DMARDs after discontinuation			
None	7 (53.8)	3 (60)	
1000 mg of SSZ daily	3 (23)	2 (40)	
50 mg of IGU daily	2 (15.3)	0 (0)	
Prednisolone	1 (7.6)	0 (0)	

Note: Data are shown as median [quartile] or number (%).
Abbreviations: anti-CCP, anti–cyclic citrullinated peptide; BUC, bucillamine; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; IGU, iguratimod; RF, rheumatoid factor; SSZ, sulfasalazine.
*p-value, Chi-squared test for categorical variables or Wilcoxon rank-sum test for continuous variables.

BUC is used as an alternative to MTX in patients for whom MTX cannot be administered or is difficult to administer. In our elderly cohort, approximately half of the patients had impaired renal function or lung disease, and some had comorbidities such as liver dysfunction due to bile duct cancer or pleural effusion due to heart failure, in which context MTX was avoided and BUC was selected instead. The strength of this study is that most patients (16 of 18) were treated with BUC alone, and 56% (10 of 18) remained untreated after discontinuing BUC. This indicates that the changes observed after discontinuing BUC were largely unaffected by other DMARDs. We also believe that the results can be used to identify patient groups for whom BUC is likely to be effective. The discontinuation of BUC resulted in arthritis exacerbation in approximately 70% of the patients with significantly increased RF levels. Notably, patients with RF levels of 28 U/mL or higher experienced a significantly higher rate of arthritis exacerbation during the follow-up period.

RF was first discovered in 1940 in the serum of patients with RA and was found to agglutinate rabbit antibody-sensitized sheep erythrocytes [11]. RF is predominantly immunoglobulin M (IgM) that binds to the Fc region of immunoglobulin G (IgG); however, the underlying cause of RF production in RA remains unclear [12]. Currently, no clinical guidelines recommend using RF levels to assess disease activity or guide therapeutic agent selection [1]. Although RF has long been recognized as a laboratory marker, it remains unclear whether it directly contributes to arthritis pathogenesis or simply reflects immunological dysregulation in RA has not been determined [13].

This study found that the discontinuation of BUC led to arthritis exacerbation in more than half of the patients, supporting the concept that BUC potentially helps in controlling RA symptoms and possibly underlying pathophysiology. Notably, exacerbations occurred more frequently in patients with high RF levels. Our results suggest that the mechanism by which BUC suppresses RA may involve correction of underlying immunological abnormalities responsible for RF production.

BUC can exert unique immunomodulatory effects through the formation of an intramolecular disulfide bond [14]. In RA,

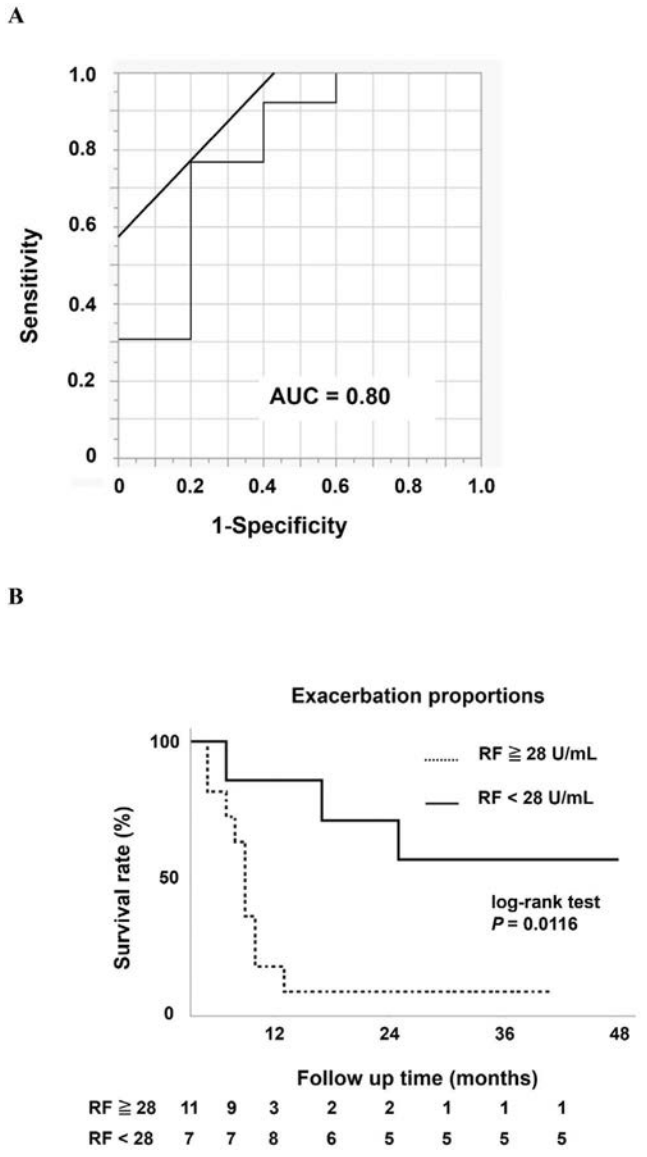

FIGURE 3 | Kaplan–Meier curves showing exacerbation-free survival by baseline rheumatoid factor (RF) levels. (A) Area under the receiver operating characteristic curve (AUC) analysis that assessed rheumatoid factor levels at baseline yielded an AUC of 0.80. Using a rheumatoid factor cut-off level of 28 U/mL, the sensitivity and specificity are 76.2% and 80.0%, respectively. (B) Kaplan–Meier curves show cumulative exacerbation-free survival among patients with rheumatoid arthritis, stratified by baseline RF levels. Patients with a higher RF level at baseline (≥ 28 U/mL) have a significantly higher rate of exacerbation compared to those with RF levels < 28 U/mL ($p = 0.0116$, log-rank test).

aminoacyl-tRNA synthetases (aaRSs) can contribute to the development of the disease by acting as alarmins [15]. Notably, BUC can suppress aaRSs and control the pathology. Unlike MTX, which inhibits cell proliferation via folate antagonism and biological agents, which directly inhibit cytokines, BUC operates through distinct mechanisms [16]. SA981, an active metabolite of BUC, can significantly reduce antibody production via CD40 at lower concentrations than MTX, and inhibit IgM production through inhibition of Akt signaling and direct suppression of B cells' activity [17, 18]. These mechanisms may underlie the observed reduction in RF levels. BUC may represent a viable treatment option for patients with high IgM-type RF levels. Although MTX and biologics remain the mainstay of treatment, BUC may be considered for patients with a high RF or difficult-to-treat RA when conventional options are ineffective. The addition of BUC has also been shown to suppress exacerbation following the suspension of infliximab [19]. Therefore, continuous treatment with BUC could be beneficial for patients with high RF titers unless adverse effects occur. Considering the elevated relapse risk, clinicians should exercise caution before deciding to discontinue BUC in these patients.

This study has a few limitations. First, this study contains data of an exploratory nature with a risk for type I error and statistical uncertainty due to the small sample size. Thus, the RF cut-off value of 28 U/mL derived from this study has limited generalizability. Second, the absence of composite measures from tools such as the Disease Activity Score 28 and Simplified Disease Activity Index limits the interpretation of disease activity and flare severity. Consequently, future prospective studies with larger sample sizes and more complete datasets are required to validate these findings.

5 | Conclusion

Arthritis exacerbation occurred more frequently in patients with RF levels ≥ 28 U/mL following BUC discontinuation. Additionally, RF levels tended to increase after treatment cessation. These findings suggest that RF levels may serve as a useful marker when selecting patients who are likely to benefit from continued BUC therapy.

Author Contributions

Y.O. contributed to the design of the study. 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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Funding

The authors have nothing to report.

Ethics Statement

This study was approved by the Ethics Committee of Takikawa Municipal Hospital (Approval No. 25-03). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent

Informed consent was obtained from all patients via an opt-out procedure.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared by the corresponding author upon reasonable request.

References

1. J. S. Smolen, R. B. M. Landewé, S. A. Bergstra, et al., "EULAR Recommendations for the Management of Rheumatoid Arthritis With Synthetic and Biological Disease-Modifying Antirheumatic Drugs: 2022 Update," *Annals of the Rheumatic Diseases* 82, no. 1 (2023): 3–18, https://doi.org/10.1136/ard-2022-223356.

2. Y. Kawahito, A. Morinobu, Y. Kaneko, et al., "Drug Treatment Algorithm and Recommendations From the 2020 Update of the Japan College of Rheumatology Clinical Practice Guidelines for the Management of Rheumatoid Arthritis-Secondary Publication," *Modern Rheumatology* 33, no. 1 (2023): 21–35, https://doi.org/10.1093/mr/roac017.

3. Y. Nanke, M. Iwatani, T. Kobashigawa, T. Yago, H. Yamanaka, and S. Kotake, "Radiographic Repair in Three Japanese Patients With Rheumatoid Arthritis Treated With Bucillamine," *Modern Rheumatology* 19, no. 6 (2009): 681–686, https://doi.org/10.1007/s10165-009-0209-6.

4. M. Iwatani, E. Inoue, T. Nakamura, et al., "Efficacy Profile of Bucillamine in Rheumatoid Arthritis Patients in a Large Observational Cohort Study, IORRA," *Modern Rheumatology* 16, no. 6 (2006): 376–380, https://doi.org/10.1007/s10165-006-0527-x.

5. H. A. Kim and Y. W. Song, "A Comparison Between Bucillamine and D-Penicillamine in the Treatment of Rheumatoid Arthritis," *Rheumatology International* 17, no. 1 (1997): 5–9, https://doi.org/10.1007/pl00006849.

6. M. Nagashima, T. Matsuoka, K. Saitoh, T. Koyama, O. Kikuchi, and S. Yoshino, "Treatment Continuation Rate in Relation to Efficacy and Toxicity in Long-Term Therapy With Low-Dose Methotrexate, Sulfasalazine, and Bucillamine in 1,358 Japanese Patients With Rheumatoid Arthritis," *Clinical and Experimental Rheumatology* 24, no. 3 (2006): 260–267.

7. H. Matsuno, M. Okada, Y. Sakai, et al., "The Usefulness of a New Triple Combination Treatment Utilising Methotrexate, Salazosulfapyridine, and Bucillamine in Rheumatoid Arthritis," *Modern Rheumatology* 26, no. 1 (2016): 51–56, https://doi.org/10.3109/14397595.2015.1059984.

8. A. Suda, S. Nagaoka, S. Ohono, H. Ideguchi, T. Soga, and Y. Ishigatsubo, "The Efficacy and Safety of Bucillamine as a Second-Line DMARD in the Treatment of Rheumatoid Arthritis: A Retrospective Cohort Study," *Modern Rheumatology* 18, no. 6 (2008): 609–614, https://doi.org/10.1007/s10165-008-0103-7.

9. D. Aletaha, T. Neogi, A. J. Silman, et al., "2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative," *Annals of the Rheumatic Diseases* 69, no. 9 (2010): 1580–1588, https://doi.org/10.1136/ard.2010.138461.

10. O. Steinbrocker, C. H. Traeger, and R. C. Batterman, "Therapeutic Criteria in Rheumatoid Arthritis," *JAMA* 140, no. 8 (1949): 659–662, https://doi.org/10.1001/jama.1949.02900430001001.

11. E. Waaler, "On the Occurrence of a Factor in Human Serum Activating the Specific Agglutintion of Sheep Blood Corpuscles. 1939," *APMIS* 115, no. 5 (2007): 422–439, https://doi.org/10.1111/j.1600-0463.2007.apm_682a.x.

12. K. Aho, M. Heliövaara, J. Maatela, T. Tuomi, and T. Palosuo, "Rheumatoid Factors Antedating Clinical Rheumatoid Arthritis," *Journal of Rheumatology* 18, no. 9 (1991): 1282–1284.

13. E. Pertsinidou, S. Saevarsdottir, V. A. Manivel, et al., "In Early Rheumatoid Arthritis, Anticitrullinated Peptide Antibodies Associate With Low Number of Affected Joints and Rheumatoid Factor Associates With Systemic Inflammation," *Annals of the Rheumatic Diseases* 83, no. 3 (2024): 277–287, https://doi.org/10.1136/ard-2023-224728.

14. S. Hirohata and P. E. Lipsky, "Comparative Inhibitory Effects of Bucillamine and D-Penicillamine on the Function of Human B Cells and T Cells," *Arthritis and Rheumatism* 37, no. 6 (1994): 942–950, https://doi.org/10.1002/art.1780370625.

15. A. Kimura, T. Takagi, T. Thamamongood, et al., "Extracellular aaRSs Drive Autoimmune and Inflammatory Responses in Rheumatoid Arthritis via the Release of Cytokines and PAD4," *Annals of the Rheumatic Diseases* 82, no. 9 (2023): 1153–1161, https://doi.org/10.1136/ard-2023-224055.

16. S. Hirohata, T. Yanagida, T. Tomita, and H. Yoshikawa, "Differential Influences of Bucillamine and Methotrexate on the Generation of Fibroblast-Like Cells From Bone Marrow CD34+ Cells of Rheumatoid Arthritis Patients," *International Immunopharmacology* 9, no. 1 (2009): 86–90, https://doi.org/10.1016/j.intimp.2008.10.007.

17. F. Tsuji, C. Setoguchi, M. Okamoto, I. Seki, M. Sasano, and H. Aono, "Bucillamine Inhibits CD40-Mediated Akt Activation and Antibody Production in Mouse B-Cell Lymphoma," *International Immunopharmacology* 14, no. 1 (2012): 47–53, https://doi.org/10.1016/j.intimp.2012.06.012.

18. S. Hirohata and P. E. Lipsky, "Regulation of B Cell Function by Bucillamine, a Novel Disease-Modifying Antirheumatic Drug," *Clinical Immunology and Immunopathology* 66, no. 1 (1993): 43–51, https://doi.org/10.1006/clin.1993.1006.

19. T. Kurasawa, H. Nagasawa, M. Kishimoto, K. Amano, T. Takeuchi, and H. Kameda, "Addition of Another Disease-Modifying Anti-Rheumatic Drug to Methotrexate Reduces the Flare Rate Within 2 Years After Infliximab Discontinuation in Patients With Rheumatoid Arthritis: An Open, Randomized, Controlled Trial," *Modern Rheumatology* 24, no. 4 (2014): 561–566, https://doi.org/10.3109/14397595.2013.844886.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Characteristics of the 10 patients who did not receive DMARDs after BUC withdrawal.

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EDITORIAL

Editorial: Is CAR T-Cell Therapy the Immunological Reset Autoimmunity Needs?

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1 | From Oncology to Autoimmunity: Expanding Therapeutic Frontiers

The advent of chimeric antigen receptor (CAR) T-cell therapy is redefining therapeutic boundaries in severe, treatment-refractory autoimmune diseases. Originally developed for hematologic malignancies, CAR T-cell therapy is now emerging as a transformative intervention for systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies, and systemic sclerosis. A comprehensive review by Chung et al. aptly synthesizes this evolving field and situates CAR T-cell therapy at the frontier of immune modulation in autoimmunity [1].

2 | Targeting the B-Cell Axis: Beyond CD20

B-cell-directed therapies have long formed the cornerstone of treatment for many autoimmune conditions. However, agents such as rituximab, targeting CD20, achieve only partial B-cell depletion and are often insufficient in inducing sustained remission, especially in tissue-compartmentalized disease [1]. CAR T-cells targeting CD19—expressed across a broader B-cell lineage including plasmablasts—have demonstrated not only profound B-cell depletion but also rapid seroconversion and sustained drug-free remission in early clinical studies [2, 3]. Unlike monoclonal antibodies, CAR T-cells represent a living drug, with the capacity to traffic to inflamed sites and eliminate pathogenic cells with high efficiency.

3 | CAR T-Cells as a Living Drug: Mechanism and Efficacy

CAR T-cells differ fundamentally from passive antibody therapies. Once infused, they expand, persist, and actively target disease-driving B-cells, particularly in sanctuary sites that are often resistant to conventional therapies. Evidence from multiple studies indicates that anti-CD19 CAR T-cell infusion can induce rapid and profound B-cell aplasia, leading to seroconversion to autoantibody negativity and sustained clinical remission in conditions previously resistant to treatment [2, 3]. This durable therapeutic effect underpins the concept of immune reprogramming rather than suppression.

4 | Safety Considerations: Mitigating CRS and Neurotoxicity

The profound efficacy of this "living drug", however, is matched by an equally profound need to understand its safety. Concerns regarding safety, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), persist. However, clinical data from autoimmune populations have thus far demonstrated a more favorable safety profile, potentially due to lower target burden and refined CAR constructs [1, 4]. Design modifications—such as incorporation of CD8α-derived hinge and transmembrane domains in place of CD28-derived motifs—have been shown to reduce

pro-inflammatory cytokine release while preserving cytotoxic efficacy [5]. These engineering advances are essential for applying CAR T-cell therapy in non-malignant diseases, where the therapeutic margin must be wide. Nevertheless, vigilance is paramount. The long-term consequences of profound, albeit transient, B-cell depletion require systematic monitoring, and the potential for rare but serious toxicities cannot be dismissed.

5 | Next-Generation CARs: Dual Targeting and Selectivity

Efforts are also underway to extend the therapeutic reach beyond CD19. Given the persistence of CD19-negative long-lived plasma cells (LLPCs) in autoimmunity, dual-target CAR T-cells directed against both CD19 and B-cell maturation antigen (BCMA) have shown promising preliminary results in SLE [6]. Conversely, more selective approaches such as chimeric autoantibody receptor (CAAR) T-cells, which selectively target autoreactive B-cells via their cognate autoantigens, aim to preserve immune integrity but remain in early development [1, 7]. At present, broader depletion strategies appear to yield more reliable clinical benefit.

6 | Durability and the Immunological Reset Hypothesis

Critical challenges remain. The requirement for lymphodepleting chemotherapy raises concerns regarding toxicity, fertility, and secondary malignancy risk. Trials are underway to assess reduced-intensity or non-myeloablative regimens. Furthermore, the durability of remission—potentially mediated by an immunological reset and reconstitution of a tolerant B-cell repertoire—must be clarified through long-term follow-up [1, 2, 8]. While early results are encouraging, the long preclinical phase of autoimmunity necessitates prolonged observation to determine whether true disease modification or cure has been achieved.

7 | CAR-Tregs and Immune Tolerance Restoration

The development of CAR-engineered regulatory T-cells (CAR-Tregs) introduces a novel concept: restoration of immune tolerance rather than cellular ablation [1]. These cells are designed not to eliminate targets, but to suppress inflammation and restore tissue-specific immune regulation. Although challenges remain in ensuring lineage stability and functional durability, this strategy offers a vision of future therapies focused on immune recalibration rather than deletion.

8 | Conclusion: Towards a New Era in Rheumatology

In summary, CAR T-cell therapy represents a major leap forward in the treatment of refractory autoimmunity. Indeed, the seminal data from Müller et al. [3] has powerfully quantified this potential, demonstrating an unprecedented trifecta of outcomes: deep, durable remission, achieved in the absence of all other immunosuppressants, and with a remarkable safety profile (Figure 1). As clinical trials expand and mechanistic insights deepen, CAR T-cell therapies may fundamentally reshape the landscape of rheumatology, shifting the therapeutic goal from a lifetime of immunosuppression to the possibility of a lasting immunological peace.

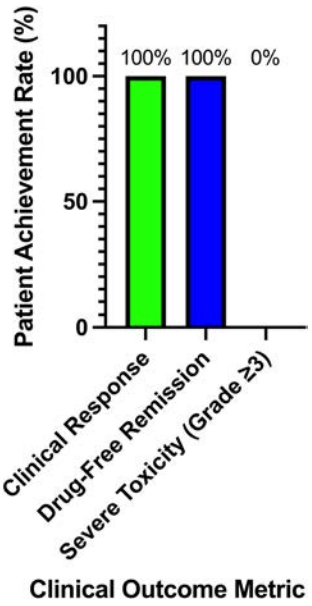

FIGURE 1 | Key clinical outcomes of CD19 CAR-T Therapy. This bar chart summarizes the "trifecta of success" for the 15 patients with severe, refractory autoimmune diseases reported by Müller et al. The therapy achieved a near-perfect result, demonstrating a (A) 100% clinical response rate, (B) enabling 100% of patients to achieve a durable, drug-free remission, and (C) a 0% incidence of severe (Grade ≥3) cytokine release syndrome or neurotoxicity. Data are precise counts derived from the clinical trial report by Müller et al. [3].

Author Contributions

C.-Y.L. drafted the original manuscript. S.-B.Y., L.-C.S., and J.C.W. provided critical review and revised the manuscript. All authors read and approved the final manuscript.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. J. B. Chung, J. N. Brudno, D. Borie, and J. N. Kochenderfer, "Chimeric Antigen Receptor T Cell Therapy for Autoimmune Disease," *Nature Reviews. Immunology* 24, no. 11 (2024): 830–845.

2. A. Mackensen, F. Müller, D. Mougiakakos, et al., "Anti-CD19 CAR T Cell Therapy for Refractory Systemic Lupus Erythematosus," *Nature Medicine* 28, no. 10 (2022): 2124–2132.

3. F. Müller, S. Boeltz, A. Mackensen, D. Mougiakakos, and G. Schett, "CD19 CAR T-Cell Therapy in Autoimmune Disease—A Case Series

With Follow-Up," *New England Journal of Medicine* 390, no. 8 (2024): 687–700.

4. G. Schett, J. Taubmann, W. Rösler, et al., "Safety and Long-Term Efficacy of CD19 CAR-T Cell Therapy in 30 Patients With Autoimmune Disease," *Arthritis and Rheumatology* 76, no. suppl 9 (2024): 3571–3573.

5. J. N. Brudno, N. Lam, D. Vanasse, et al., "Safety and Feasibility of Anti-CD19 CAR T Cells With Fully Human Binding Domains in Patients With B-Cell Lymphoma," *Nature Medicine* 26, no. 2 (2020): 270–280.

6. C. Ding, H. Li, Y. Zhang, et al., "POS0649 Anti-B-Cell Maturation Antigen (BCMA) and Anti-CD19 Chimeric Antigen Receptor (CAR)-T Cell Therapy for Refractory Systemic Lupus Erythematosus," *Annals of the Rheumatic Diseases* 83, no. Suppl 1 (2024): 581–582.

7. C. T. Ellebrecht, V. G. Bhoj, A. Nace, et al., "Reengineering Chimeric Antigen Receptor T Cells for Targeted Therapy of Autoimmune Disease," *Science* 353, no. 6295 (2016): 179–184.

8. T. Alexander, R. Arnold, F. Hiepe, and A. Radbruch, "Depletion of Autoreactive Immunologic Memory Followed by Autologous Hematopoietic Stem Cell Transplantation in Patients With Refractory SLE Induces Long-Term Remission Through de Novo Generation of a Juvenile and Tolerant Immune System," *Blood* 113, no. 1 (2009): 214–223.

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CORRECTION

Correction to "Comparative Effectiveness of TNFα and IL6 Inhibitors on Bone Health Outcomes and Mortality in Rheumatoid Arthritis Patients: A Retrospective Cohort Study"

Wang H. Lee Y. H. Cheng I.H. Wang S. I. Ji J. Huo A. P. Hung Y.M. 2025 Comparative Effectiveness of TNF-α and IL-6 Inhibitors on Bone Health Outcomes and Mortality in Rheumatoid Arthritis Patients: A Retrospective Cohort Study. International Journal of Rheumatic Diseases 28 6 e70204. 10.1111/1756-185X.70204.

The funding section in the above article is incorrect. The correct information is shown below.

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We apologize for this error.

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LETTER TO THE EDITOR

Case Report: Acquired Angioneurotic Edema With Massive Pericardial Effusion as the Harbinger of Systemic Lupus Erythematosus

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Dear Editor,

The global incidence and prevalence of systemic lupus erythematosus (SLE) ranges between 0.28–0.9 and 3.3–8.8 per 100000 children, respectively, with a female preponderance [1]. Pediatric SLE (pSLE) accounts for approximately 20% of all SLE cases and is often characterized by more aggressive disease and lower survival rates [2]. Angioneurotic edema (AE) of the periorbital region and lips is an unusual manifestation, with hereditary AE (HAE) and acquired AE (AAE) associated in fewer than 2% and 1% of SLE patients, respectively [3]. Although pericarditis with pericardial effusion (PE) occurs in up to 25%–50% of SLE patients, massive PE is exceedingly rare and is seen in about 1% of cases [4]. The uniqueness of this case lies in recurrent AE and massive PE serving as the sentinel manifestations of SLE in an adolescent female child.

A 13-year-old girl presented with a five-year history of intermittent and recurrent episodes of lip swelling and anasarca, which used to respond to oral medications for 2 weeks. She also had a recent onset of exertional dyspnea, orthopnoea, and chest pain for the last 4 weeks. There was no history of joint pain, oral ulcers, food allergies, insect bite, urticaria, recent introduction of any new medications or close contact with an index case of tuberculosis (TB) in the last 2 years. Vital parameters showed tachycardia [heart rate 116/min (60–100)], normal SpO_2 (96% on room air) and blood pressure (50-90th centile for age, sex and height). Weight-for-age and height-for-age were −3.34 z and −3.16 z (severe underweight and severe stunting, respectively). Examination showed pallor, lip swelling (Figure 1a), pedal edema, multiple palpable non-discharging posterior cervical and inguinal group lymph nodes (2.5 × 2.5 cm, non-tender, non-matted), raised jugular venous pressure, muffled heart sounds, decreased bilateral breath sounds, with severe hepatomegaly (span 19 cm). The BCG scar was present. Cutaneous examination revealed an erythematous, blanchable, maculopapular rash predominantly involving the neck and extensor surface of limbs (Figure 1b). Fundus examination ruled out the presence of papilledema. Laboratory evaluation revealed hemoglobin 8.8 g/dL (11–14.5), platelets 79×10^9/L (150–400), C-reactive protein 59.1 mg/L (0–6), ESR 88 mm/h (< 20), serum creatinine 0.71 mg/dL (0.4–1.2), and albumin 2.2 g/dL (3.5–5). Peripheral smear was devoid of any atypical cells. Direct Coomb's test was positive (2+, IgG) along with a corrected reticulocyte index 4.83% (normal:< 3%) and high LDH 1243 IU/L (140–280), suggesting autoimmune hemolytic anemia (AIHA). In view of the high endemicity of *Mycobacterium tuberculosis* (MTB) in our region, along with the easy availability of screening methods for TB under a government-approved program, the child was initially worked up extensively for TB. Mantoux was negative. Unavailability of the test obviated investigating for latent TB with interferon-gamma release assays (IGRA). Cartridge-based nucleic acid amplification test (CBNAAT) from gastric aspirate and cervical lymph node fine needle aspirate were negative for MTB. CT thorax performed to look for supportive evidence for disseminated tuberculosis confirmed the presence of a large organized PE and bilateral loculated pleural effusion (right>left) with a normal lung parenchyma (Figure 2a). Electrocardiography showed low-voltage QRS complexes with sinus tachycardia. 2D-echocardiography demonstrated a large pericardial effusion with mobile intrapericardial fibrinous strands (see Video S1). Pericardial fluid analysis by pericardiocentesis revealed total cells 360/mm^3 (95% monomorphs), protein 6.4 g/dL (< 3.1), normal adenosine deaminase, negative CBNAAT and malignant cytology. Pericardial biopsy demonstrated fibrocollagenous tissue with mild chronic inflammation, without any evidence of granuloma or dysplastic cells. Subsequently, in the light of the absence of any definitive

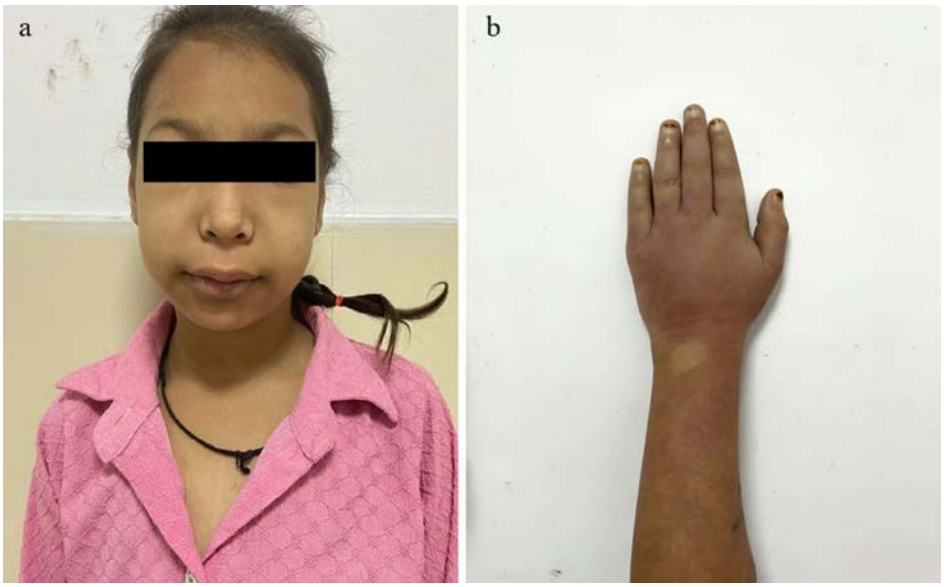

FIGURE 1 | (a) Facial angioedema of the index case; (b) Erythematous, blanchable, maculopapular rash in the extensor surface of left upper limb of the index case.

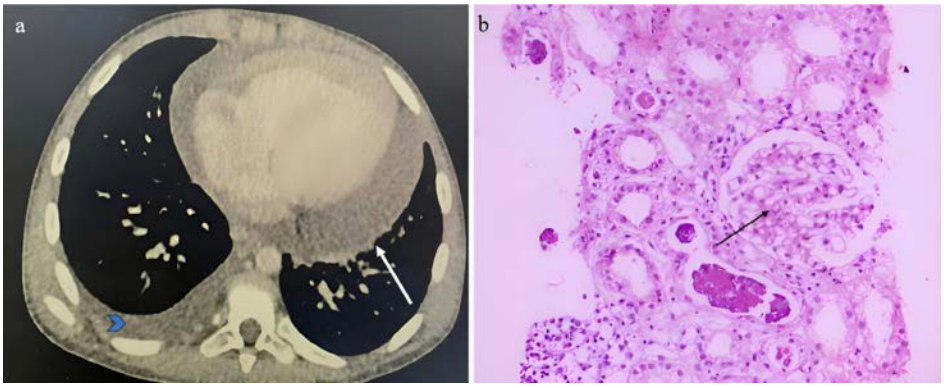

FIGURE 2 | (a) CT thorax image (axial section) showing a large pericardial effusion (white arrow) with right-sided pleural effusion (blue arrowhead); (b) Renal biopsy section of index case showing a non-crescentic class II lupus nephritis with mesangial (black arrow) and endocapillary hypercellularity inside a glomerulus (light microscopy, H&E stain, 40×).

microbiological confirmation of TB, further etiological workup for autoimmunity was considered. Complement levels were markedly reduced (C3: 32 mg/dL [90–180], C4: 2.09 mg/dL [10–40]), and anti-nuclear antibody (ANA) by immunofluorescence was positive (3+ at a 1:100 titre) with a coarse speckled and homogeneous pattern. The extractable nuclear antigen (ENA) profile showed anti-SSA (3+), anti-histone (3+), and anti-ribosomal P protein (2+) positivity. 24-h urine protein was 1.1 g/day, consistent with nephrotic range proteinuria. Renal biopsy confirmed the presence of non-crescentic mesangial glomerulonephritis (Figure 2b) with class II lupus nephritis (LN) with full-house positivity.

SLE was confirmed by European Alliance of Associations for Rheumatology (EULAR) 2019 criteria (score of 27/51) with a SLE disease activity index (SLEDAI) of 13 points (high). In the background of recurrent angioedema likely due to complement consumption, acquired C1–inhibitor (C1–INH) deficiency secondary to SLE was considered. However, the C1–INH level could not be determined due to financial constraints. She was treated with intravenous methylprednisolone (30 mg/kg/day × 3 days) and the first dose of monthly cyclophosphamide pulse (500 mg/m^2), followed by a tapering dose of oral prednisolone (1 mg/kg/day) and maintenance therapy with mycophenolate mofetil (MMF, 750 mg/m^2/day). Due to the persistence of massive PE with cardiorespiratory compromise even after placement of a pericardial drain, a pleuropericardial window (PPW) was surgically created, resulting in hemodynamic stability. Other supportive measures included diuretics and hydroxychloroquine (4 mg/kg/day). The child showed dramatic improvement with immunosuppression, with resolution of the PE and normalization of complement levels over the next 4 weeks. She was discharged on oral prednisolone of 20 mg/day and was planned for monthly doses of 5 more cyclophosphamide pulses in follow-up.

SLE is a multisystem autoimmune disorder that results from the production of diverse autoantibodies, causing immune complex deposition and overactivation of classical and alternate complement pathways, leading to tissue inflammation and damage. The concurrence of AE and massive PE as the first presentation of pSLE is exceptionally rare. The lack of family history and a slightly older age at onset ruled out HAE in our case. SLE patients are at higher risk of developing AAE, with less than 20 cases having

been reported so far in the literature [5, 6]. AAE in lupus may result from autoantibodies against CI-INH (type 2 AAE) or due to complement pathway hyperactivation, transient hypocomplementemia (low levels of C3 and C4, both of which normalize with resolution of AE after immunosuppressive therapy) with normal C1-INH levels and function (type 3 AAE) [3]. This, in turn, leads to unchecked kallikrein–bradykinin activation, increased vascular permeability, and non-pruritic edema- unresponsive to antihistamines. Anti–C1–INH antibodies with hypocomplementemia are detectable in up to 17% of lupus patients, correlating well with disease duration and activity [7]. Luo et al. showed that AAE patients with SLE were associated with a higher predisposition for developing LN, as in our case [5]. Pericardial effusion, meanwhile, occurs in about one-fourth of SLE patients, but massive effusion or tamponade is rare, being reported in about 20 cases of pSLE and tends to correlate with low C4 levels, pleuritis and anti-Ro/SS-A antibody positivity, as in our child [8, 9]. Ours is also the first pediatric case to require the creation of PPW for the treatment of refractory PE in SLE, even after optimal immunosuppression. The management of AAE and massive PE in SLE relies primarily on high-dose corticosteroids and immunosuppressants (cyclophosphamide, MMF, azathioprine, or rituximab). Supportive measures such as fresh frozen plasma or C1-INH concentrate are indicated in airway-threatening episodes [10]. Hydroxychloroquine plays an adjunctive role in disease modulation, while ACE inhibitors should be avoided due to the risk of exacerbating bradykinin accumulation. In our patient, a combination of pulse methylprednisolone, hydroxychloroquine, monthly cyclophosphamide, and maintenance MMF therapy, along with definitive surgical drainage via PPW, resulted in complete remission. One of the limitations of our study was the failure to quantify C1–INH and anti-C1–INH antibody levels in this child, to differentiate between type 2 and 3 AAE.

This case underscores that awareness of lupus-associated AAE can prevent misdiagnosis as an allergic event, allowing timely immunomodulatory therapy. Our case adds novelty in that both bradykinin-mediated angioedema and massive pericardial effusion coexisted as cardinal features in a previously undiagnosed child with SLE.

Author Contributions

Iwa Bhattarai: methodology, data collection, investigations, and resources; **Neethu Ravi:** methodology, data collection, investigations, and resources; **Sarthak Chakrabarti:** framing the manuscript, conceptualisation, data collection, investigations, and resources, reviewing, and editing; **Yash Shrivastava:** conceptualisation, methodology, supervision, reviewing, and editing; **Prashant Kumar Verma:** conceptualisation, methodology, supervision, reviewing, and editing.

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Ethics Statement

The authors have nothing to report.

Consent

Written informed consent was taken from the parents of the case for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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References

1. S. Kamphuis and E. D. Silverman, "Prevalence and Burden of Pediatric-Onset Systemic Lupus Erythematosus," *Nature Reviews Rheumatology* 6 (2010): 538–546.

2. D. M. Levy and S. Kamphuis, "Systemic Lupus Erythematosus in Children and Adolescents," *Pediatric Clinics of North America* 59 (2012): 345–364.

3. T. P. Rasheed, M. Jabeen, S. A. Iqbal, et al., "Angioedema as a Presenting Feature in a Patient With SLE: A Case Report," *Cureus* 16, no. 10 (2024): e71939.

4. M. Kiriakidou and C. L. Ching, "Systemic Lupus Erythematosus," *Annals of Internal Medicine* 172, no. 11 (2020): ITC81–ITC96.

5. Y. Luo, X. Fan, C. Jiang, et al., "Systemic Lupus Erythematosus and Angioedema: A Cross-Sectional Study From the National Inpatient Sample," *Archives of Rheumatology* 34, no. 3 (2019): 301–307.

6. Z. E. Tekin, G. O. Yener, and S. Yüksel, "Acquired Angioedema in Juvenile Systemic Lupus Erythematosus: Case-Based Review," *Rheumatology International* 38, no. 8 (2018): 1577–1584.

7. T. Mészáros, G. Füst, H. Farkas, et al., "C1-Inhibitor Autoantibodies in SLE," *Lupus* 19, no. 5 (2010): 634–638.

8. S. S. Maharaj and S. M. Chang, "Cardiac Tamponade as the Initial Presentation of Systemic Lupus Erythematosus: A Case Report and Review of the Literature," *Pediatric Rheumatology Online Journal* 13 (2015): 9.

9. A. C. Oshiro, S. J. Derbes, A. R. Stopa, and A. Gedalia, "Anti-Ro/SS-A and Anti-La/SS-B Antibodies Associated With Cardiac Involvement in Childhood Systemic Lupus Erythematosus," *Annals of the Rheumatic Diseases* 56 (1997): 272–274.

10. G. Dobson, D. Edgar, and J. Trinder, "Angioedema of the Tongue due to Acquired C1 Esterase Inhibitor Deficiency," *Anaesthesia and Intensive Care* 31, no. 1 (2003): 99–102.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Video S1:** Apical 4-chamber view of 2D-echocardiography of the index case showing massive pericardial effusion.

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LETTER TO THE EDITOR

Comment on: Get OUT: Factors Associated With a Longer Length of Stay in Patients Admitted With an Acute Gout Flare, and the Effects of Anakinra on Length of Stay

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Dear Editor,

The recently published article by Weerawardena et al., "Get OUT: Factors Associated with a Longer Length of Stay in Patients Admitted with an Acute Gout Flare, and the Effects of Anakinra on Length of Stay," represents an important and timely contribution to the clinical management of acute gout [1]. The study elucidates determinants of extended hospitalization and examines the possibility of interleukin-1 receptor antagonism for enhancing inpatient treatment.

The identification of CRP as a strong predictor of LOS is consistent with its role as an objective marker of inflammatory burden. However, the study adds a novel perspective: rather than treating CRP as a passive diagnostic measure, it positions CRP as a potential therapeutic decision point. The identification of CRP and mobility limitation as predictors highlights their potential use in defining high-risk gout and guiding timely therapy.

Several aspects merit discussion and constructive critique. While the authors reasonably propose that anakinra may reduce LOS-related costs, its overall cost-effectiveness remains uncertain [2]. The observed reduction, though statistically significant, may not reach clinical or economic significance across diverse hospital settings [3]. Furthermore, the reported effect size could be over- or underestimated in other clinical environments, as it is highly dependent on local discharge protocols, the timing of anakinra initiation, and specific patient selection criteria. Earlier use of anakinra in patients with high CRP or severe polyarticular disease might further reduce LOS. Combining CRP, joint count, renal function, prior urate-lowering therapy, and functional impairment into a composite index could help clinicians identify those who would most benefit from biologic intervention. Beyond these objective markers, a comprehensive patient selection model should also incorporate contraindications or toxicity risks associated with conventional therapies. For instance, patients with diabetes mellitus (in whom corticosteroids may precipitate hyperglycemia), those with concurrent infection risk (where immunosuppression is hazardous), or individuals with NSAID contraindications (e.g., peptic ulcer disease, advanced chronic kidney disease) represent ideal candidates for early anakinra use. Additionally, prior treatment response history—such as documented failure or intolerance to NSAIDs, colchicine, or corticosteroids—and the duration of the current gout flare (given that colchicine efficacy diminishes beyond 12–24 h of symptom onset) should inform the decision to escalate to biologic therapy. Integrating these clinical nuances into a composite risk-stratification tool would enable more precise, individualized, and cost-justified use of anakinra in hospitalized gout patients. Such a model would allow resource prioritization and provide a clear rationale for high-cost drug use in selected patients. The audit takes place within a single Australian institution, where drug access and hospital funding structures may not mirror other regions. Broader implementation requires clarity regarding reimbursement and inclusion of anakinra on hospital formularies. In healthcare systems with restrictive reimbursement policies, these practical constraints may pose significant challenges to translating such findings into routine care, potentially limiting the use of IL-1 inhibitors to only the most refractory cases. As the authors correctly highlight, the high upfront cost may restrict community use [1]. Although CRP was a significant predictor, the timing of measurement is not fully standardized or reported. Admission versus peak CRP values may differ substantially, and without temporal context, it is challenging to interpret CRP as a predictive or contemporaneous variable [4].

Also, one of the more intriguing findings is that prior allopurinol use correlated with longer LOS, contradicting previous large-scale data showing reduced admissions among patients on urate-lowering therapy. This discrepancy likely reflects confounding by indication—that is, patients on long-term allopurinol may represent a more severe, refractory cohort. Adjusting for tophus burden, disease duration, or baseline urate levels could help clarify whether allopurinol use truly predicts longer hospitalization or simply marks chronic, treatment-resistant disease. An important but unaddressed aspect is whether allopurinol was continued or withheld during the acute flare. Current guidelines recommend continuation of urate-lowering therapy during flares to avoid rebound hyperuricemia; however, clinical practice varies. If allopurinol was discontinued upon admission in this cohort, the observed prolonged LOS may reflect delayed flare resolution due to urate fluctuation rather than a marker of disease severity. Clarifying this practice pattern would strengthen the interpretation and inform future management protocols. The absence of adverse events among anakinra recipients is reassuring. This is consistent with broader real-world evidence and prior hospital-based series, which demonstrate that short courses of anakinra are both effective and well-tolerated in complex, hospitalized patients with multiple comorbidities [5, 6]. Omitting pretreatment infection screening appears safe for a short course, and may even be safer than corticosteroids when the differential diagnosis between a gout flare and soft tissue infection is unclear. While this pragmatic approach supports feasibility, minimal screening remains prudent in high-risk patients to ensure a balance between safety and clinical efficiency [7].

The "Get OUT" study bridges clinical observation and health-economic relevance, illustrating that even modest LOS reductions may offer substantial value. Incorporating CRP and mobility metrics into decision frameworks may help standardize and optimize acute gout management.

Author Contributions

The author takes full responsibility for this article.

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.

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References

1. H. Weerawardena, C. L. Adams, N. Kamalaraj, and K. Pile, "Get OUT: Factors Associated With a Longer Length of Stay in Patients Admitted With an Acute Gout Flare, and the Effects of Anakinra on Length of Stay," *International Journal of Rheumatic Diseases* 28 (2025): e70418.

2. A. So, T. De Smedt, S. Revaz, and J. Tschopp, "A Pilot Study of IL-1 Inhibition by Anakinra in Acute Gout," *Arthritis Research & Therapy* 9 (2007): R28.

3. N. Schlesinger, M. De Meulemeester, A. Pikhlak, et al., "Canakinumab Relieves Symptoms of Acute Flares and Improves Health-Related Quality of Life in Patients With Difficult-To-Treat Gouty Arthritis by Suppressing Inflammation: Results of a Randomized, Dose-Ranging Study," *Arthritis Research & Therapy* 13 (2011): R53.

4. S. HR, Jr. and L. X. Chen, "The Practical Management of Gout," *Cleveland Clinic Journal of Medicine* 75, no. Suppl 5 (2008): S22–S25.

5. P. Ghosh, M. Cho, G. Rawat, P. A. Simkin, and G. C. Gardner, "Treatment of Acute Gouty Arthritis in Complex Hospitalized Patients With Anakinra," *Arthritis Care & Research (Hoboken)* 65 (2013): 1381–1384.

6. S. Ottaviani, A. Molto, H. K. Ea, et al., "Efficacy of Anakinra in Gouty Arthritis: A Retrospective Study of 40 Cases," *Arthritis Research & Therapy* 15 (2013): R123.

7. R. B. Landewe, P. M. Machado, F. Kroon, et al., "EULAR Provisional Recommendations for the Management of Rheumatic and Musculoskeletal Diseases in the Context of SARS-CoV-2," *Annals of the Rheumatic Diseases* 79 (2020): 851–858.

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LETTER TO THE EDITOR

Robotic Ultrasound-Guided Musculoskeletal Injections: The Next Frontier in Precision Medicine

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Dear Editor,

The convergence of artificial intelligence (AI), robotics, and ultrasound (US) imaging is poised to transform musculoskeletal (MSK) interventions, achieving precision comparable to robotic surgery. Although US guidance is superior to landmark-based techniques for joint and soft-tissue injections [1], performance remains highly operator-dependent, with variability in needle placement accuracy. Recent advances suggest that robotic assistance may soon overcome these limitations.

Emerging evidence demonstrates the feasibility of robotic systems for image-guided MSK interventions. These systems typically operate across a spectrum of autonomy levels: from fully operator-controlled (Level 1), through shared-control systems where the robot assists with specific tasks such as needle guidance (Level 2–3), to semi-autonomous systems capable of executing pre-planned trajectories with physician oversight (Level 4). Margalit et al. reported that autonomous robotic systems for spinal injections achieved superior accuracy compared with free-hand techniques, with angular deviation of 5.6 degrees versus 12.0 degrees [2]. Similarly, automated robotic US scanning systems capable of generating three-dimensional (3D) MSK reconstructions are under active development [3]. Most compelling is the AI-GUIDE system from the MIT Lincoln Laboratory, which enables users with minimal US experience to perform vascular access procedures through real-time AI-powered vessel detection and automated needle insertion [4]. These achievements in vascular access directly inform future MSK applications.

Integrating AI with US guidance represents a critical step forward. Deep learning algorithms can now identify anatomical structures in real time, with proven applications in regional anesthesia [5]. Importantly, AI-based sonoanatomy recognition using color-coded maps has been developed by the EURO-MUSCULUS/USPRM expert group, which may boost the educational curve of medical students and could be integrated into robotic systems to plan and perform US-guided procedures [6]. Hybrid position-force control strategies enable adaptive response to tissue deformation [7], while compact body-mounted robotic platforms have demonstrated feasibility for US-guided procedures [8]. Compared with existing adjunctive devices such as passive needle guides, which constrain needle trajectory but lack real-time feedback or active correction, robotic systems offer dynamic adjustment based on tissue movement, automatic trajectory optimization, and integration with imaging data. Notably, many of these systems are compatible with existing commercial US machines, allowing gradual adoption without infrastructure overhaul [9].

The parallels with surgical robotics are instructive. Since Food and Drug Administration (FDA) approval in 2000, the da Vinci Surgical System has transformed surgery through enhanced precision, tremor elimination, and scaled micromovements [10]. Similar benefits for MSK injections could include consistent needle trajectory, accurate depth control, and real-time image feedback confirming proper placement. Beyond precision, robotic systems could mitigate the global

Abbreviations: 3D, three-dimensional; AI, artificial intelligence; EURO-MUSCULUS/USPRM, European musculoskeletal ultrasound study group/ultrasound study group of the international society of physical and rehabilitation medicine; FDA, food and drug administration; MSK, musculoskeletal; US, ultrasound.

TABLE 1 | Key innovations and pitfalls of robotic ultrasound-guided musculoskeletal injections.

Innovations/potential benefits	Pitfalls/challenges
Enhanced accuracy: Reduced angular deviation and improved needle placement precision	High initial costs: Significant capital investment for equipment acquisition and maintenance
Tremor elimination: Removal of physiological hand tremor enabling steadier needle advancement	Limited clinical evidence: Most studies are phantom or cadaveric; true MSK injection trials remain scarce
AI-powered real-time structure identification: Automated recognition of anatomical landmarks	Training requirements: Learning curve for physicians to effectively integrate robotic systems
Standardization: Consistent procedural approach reducing inter-operator variability	Regulatory uncertainty: Evolving FDA pathways and liability frameworks for autonomous devices

Abbreviations: AI, artificial intelligence; FDA, food and drug administration; MSK, musculoskeletal; US, ultrasound.

shortage of trained ultrasonographers, standardize research protocols, and enhance education through simulation-based training. Critically, in current semi-autonomous paradigms, the physician retains ultimate responsibility for patient selection, procedural planning, real-time decision-making, and override capability—serving as the essential supervisor who ensures safety and responds to unexpected anatomical variations or complications.

Early implementation may begin with common procedures such as subacromial or knee joint injections, where anatomy is well defined and movement is limited. Expansion to more complex interventions should follow as experience and safety data accumulate. The educational frameworks and standardized scanning protocols established by organizations such as EURO-MUSCULUS provide a strong foundation for introducing these technologies [11]. It should be acknowledged, however, that true clinical trials of robotic US-guided MSK injections remain limited, with most evidence derived from phantom studies, cadaveric models, and experience extrapolated from adjacent fields such as spinal injections and vascular access. Nevertheless, regulatory pathways must prioritize patient safety, ensure cost-effectiveness in resource-limited settings, and preserve the clinician-patient relationship central to rehabilitation medicine (Table 1).

Robotic-assisted MSK US-guided injections represent not a distant concept but an imminent reality. Just as surgery has been transformed by robotics, interventional MSK medicine now stands at a similar threshold. The question is no longer whether this technology will arrive, but how swiftly and thoughtfully it will be integrated to advance patient care while preserving the clinical judgment that defines our specialty.

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References

1. E. Soh, W. Li, K. O. Ong, W. Chen, and D. Bautista, "Image-Guided Versus Blind Corticosteroid Injections in Adults With Shoulder Pain: A Systematic Review," *BMC Musculoskeletal Disorders* 12 (2011): 137.

2. A. Margalit, H. Phalen, C. Gao, et al., "Autonomous Spinal Robotic System for Transforaminal Lumbar Epidural Injections: A Proof of Concept Study," *Global Spine Journal* 14, no. 1 (2024): 138–145.

3. K. Li, Y. Xu, J. Wang, D. Ni, L. Liu, and M. Q. Meng, "Image-Guided Navigation of a Robotic Ultrasound Probe for Autonomous Spinal Sonography Using a Shadow-Aware Dual-Agent Framework," *IEEE Transactions on Medical Robotics and Bionics* 4 (2022): 130–144.

4. L. J. Brattain, T. T. Pierce, L. A. Gjesteby, et al., "AI-Enabled, Ultrasound-Guided Handheld Robotic Device for Femoral Vascular Access," *Biosensors-Basel* 11, no. 12 (2021): 522.

5. I. Gungor, B. Gunaydin, O. Som, et al., "A Real-Time Anatomy Identification Tool Based on Artificial Intelligence for Ultrasound-Guided Peripheral Nerve Block Procedures: An Accuracy Study," *Journal of Anesthesia* 35, no. 4 (2021): 591–594.

6. L. Ozcakar, F. Tok, V. Ricci, et al., "Artificial Intelligence Featuring EURO-MUSCULUS/USPRM Basic Scanning Protocols," *American Journal of Physical Medicine & Rehabilitation* 101, no. 11 (2022): e174–e175.

7. S. Jiang, P. Li, Y. Yu, J. Liu, and Z. Yang, "Experimental Study of Needle-Tissue Interaction Forces: Effect of Needle Geometries, Insertion Methods and Tissue Characteristics," *Journal of Biomechanics* 47, no. 13 (2014): 3344–3353.

8. C. Kim, D. Chang, D. Petrisor, A. Patriciu, D. Mazilu, and D. Stoianovici, "Ultrasound Probe and Needle-Guide Calibration for Robotic Ultrasound Scanning and Needle Targeting," *IEEE Transactions on Biomedical Engineering* 60, no. 6 (2013): 1728–1734.

9. Z. Jiang, S. E. Salcudean, and N. Navab, "Robotic Ultrasound Imaging: State-Of-The-Art and Future Perspectives," *Medical Image Analysis* 89 (2023): 102878.

10. A. R. Lanfranco, A. E. Castellanos, J. P. Desai, and W. C. Meyers, "Robotic Surgery: A Current Perspective," *Annals of Surgery* 239, no. 1 (2004): 14–21.

11. L. Ozcakar, M. Kara, K. V. Chang, et al., "EURO-MUSCULUS/USPRM Basic Scanning Protocols for Shoulder," *European Journal of Physical and Rehabilitation Medicine* 51, no. 4 (2015): 491–496.