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EDITORIAL

Editorial: From Trained Immunity to Rheumatic Diseases: Updated Evidence

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1 | Introduction

Infectious and rheumatic diseases continue to be major global health concerns, despite the advancements in vaccines that have reduced mortality from many infectious diseases [1]. Trained immunity in rheumatic diseases refers to the innate immune system's ability to develop a form of “memory” after exposure to certain vaccines or artificial stimuli. This enhanced, non-specific immune response may help modulate disease activity by reducing inflammation or preventing infections, potentially offering therapeutic benefits in managing autoimmune conditions [2].

Emerging pathogens highlight the need to improve current vaccinology strategies. Trained immunity (TI) is a novel concept where the innate immune system acquires memory through epigenetic and metabolic changes. This results in enhanced responsiveness to a wide range of pathogens, offering non-specific protection. Trained immunity-based vaccines (TIbV) aim to induce TI and provide broad-spectrum protection, particularly beneficial for vulnerable populations or where conventional vaccines are unavailable. TI has potential applications in both infections and allergic diseases, offering a new avenue for vaccine development [1].

2 | Trained Immunity in Rheumatic Diseases

The mechanisms of trained immunity in rheumatic diseases involve epigenetic and metabolic reprogramming of innate immune cells, such as monocytes and macrophages, after exposure to an initial inflammatory or pathogenic stimulus. Epigenetic changes, such as histone modifications (e.g., H3K4me3), promote the transcription of pro-inflammatory genes in trained cells. These changes are often paired with a shift in metabolism toward glycolysis, enabling cells to meet the energy demands of sustained inflammation [3]. Key metabolic pathways, such as the mTOR pathway, promote glycolysis, driving the enhanced immune responses seen in rheumatic conditions. Sustained mTOR activation perpetuates glycolysis even in the absence of acute stimuli, resulting in chronic energy provision for ongoing cytokine production. This persistent metabolic state supports the survival and activation of pro-inflammatory cells, thereby maintaining low-grade systemic inflammation characteristic of chronic rheumatic diseases [4]. These metabolic and epigenetic alterations result in increased production of pro-inflammatory cytokines like Tumor Necrosis Factor (TNF), Interleukin- 6 (IL-6), and IL-1β, which are central to the pathogenesis of rheumatic diseases. In conditions like rheumatoid arthritis (RA), autoantibodies and immune complexes exacerbate trained immunity, leading to tissue damage and synovial inflammation. Similarly, in Systemic Lupus Erythematosus (SLE), nuclear antigens from apoptotic cells stimulate monocytes, leading to trained immune responses that contribute to disease flares [2]. These molecular adaptations—particularly persistent metabolic reprogramming and histone modification—sustain the hyperinflammatory state seen in RA and SLE, driving disease progression from preclinical immune activation to clinically overt inflammation and tissue damage [3].

3 | Trained Immunity in Rheumatoid Arthritis

The mechanisms behind trained immunity in RA involve metabolic shifts toward glycolysis, which provide the energy needed for sustained inflammation. Additionally, epigenetic changes, such as histone modifications (e.g., H3K4me3), enable these cells to maintain an activated state, ready to produce high levels of inflammatory mediators when re-stimulated. Autoantibodies, especially anti-citrullinated protein antibodies (ACPA), can induce trained immunity in monocytes, enhancing their inflammatory activity [5]. Mechanistically, ACPA immune complexes are taken up by Fcγ receptors on monocytes, leading to inflammasome activation and chromatin remodeling. This cascade reinforces pro-inflammatory gene expression patterns through sustained histone modification and upregulation of glycolytic enzymes [6]. This leads to excessive production of pro-inflammatory cytokines like TNF-α and IL-6, which activate PI3K/AKT signaling. This results in phosphorylation and inactivation of Tuberous sclerosis protein (TSC)1/2, permitting Ras homolog enriched in the brain (Rheb)-GTP to switch on the mTOR complex (mTORC)1 pathway. Likewise, Damage-associated molecular patterns in the joint (e.g., fibronectin fragments, HMGB1) engage Toll-like receptors (TLRs) on macrophages and fibroblast-like synoviocytes (FLS), which trigger MyD88/NF-κB and also recruit PI3K/AKT [7]. The mTOR activation ends up producing more pro-inflammatory cytokines. Trained immunity may begin early in the disease, even before symptoms are evident, especially in individuals with ACPA-positive arthralgia. The hyperresponsiveness of monocytes due to trained immunity could drive the transition from early RA to more established disease, leading to progressive joint damage. This early activation suggests that targeting trained immunity could be a preventive strategy in RA [5, 6].

4 | Trained Immunity in SLE

Trained immunity refers to a state in which innate immune cells undergo long-term changes that enhance their response to future threats. These changes are driven by epigenetic reprogramming, allowing the innate immune system to "remember" past encounters with pathogens or stimuli. Initially studied in infectious disease contexts, trained immunity was observed when certain cells, such as monocytes, macrophages, and natural killer cells, became more responsive after exposure to infections or vaccines. This enhanced immune readiness allows for a stronger and faster response upon subsequent exposure to similar pathogens [8].

Epigenetic modifications in hematopoietic progenitor cells enhance their adaptability to inflammatory and hematopoietic stress, leading to the production of myeloid cells that improve protection against future infections—a concept known as "trained innate immunity." While beneficial against infections, internal stimuli can trigger harmful inflammation. In diseases like systemic lupus erythematosus (SLE) and systemic sclerosis, such inappropriate activation drives chronic inflammation and disease progression [8–10].

SLE pathogenesis is marked by complex immune dysregulation, including defective clearance of immune complexes and nucleic acid debris, leading to overactivation of the innate immune system via Toll-like receptors (TLRs) and type I interferons (IFN) [11]. Type I IFNs, particularly IFN-α, serve as both a consequence and amplifier of trained immunity in SLE. These cytokines further reprogram monocytes and progenitor cells epigenetically, enhancing their responsiveness to inflammatory stimuli and perpetuating the cycle of immune activation and flare-ups [9, 11].

Similar to RA, type I IFN in SLE may augment PI3K/AKT signaling and boost mTORC1 in T cells. This activation occurs through phosphorylation of insulin receptor substrate 1 (IRS1), which binds to the PI3K regulatory subunit p85, leading to activation of the catalytic subunit p110 [11]. This cascade results in the activation of mTORC1. Furthermore, B cell activating factor (BAFF) receptor signaling triggers PI3K/AKT and upregulates mTORC1. BAFF-R signaling also activates NF-κB/NIK, which can phosphorylate mTOR to sustain its activity [7]. Thus, high BAFF in SLE promotes mTOR-driven B-cell proliferation and plasma cell differentiation.

Abnormal lymphocyte activation further exacerbates the condition. Neutropenia is common in SLE, with bone marrow showing reduced granulocyte–macrophage colony-forming units. SLE neutrophils have higher apoptosis rates, impaired phagocytosis, and altered oxidative metabolism, and gene expression studies reveal a granulopoiesis signature in the peripheral blood of these patients [10, 12], suggesting a compensatory response by the body to counteract the increased turnover and apoptosis of neutrophils [13].

This neutrophil dysregulation extends to the patients with active systemic lupus erythematosus (SLE), where bone marrow mononuclear cells exhibit gene expression profiles characteristic of both apoptosis and granulopoiesis. Recent work by Banchereau R. et al. demonstrated a progressive increase in neutrophil-related transcripts in the blood of pediatric SLE patients as lupus nephritis advanced. Among these, low-density granulocytes (LDGs), which are highly inflammatory and play a key role in sustaining the inflammatory subset of neutrophils, exhibit marked demethylation of interferon-related genes, amplifying type I IFN signaling and contributing to the elevated IFN signature observed in SLE. The accumulation and activation of LDGs in SLE highlight the interplay between immune dysregulation, increased neutrophil turnover, and sustained inflammation, underscoring the central role of neutrophils and IFN pathways in the disease's pathogenesis [14].

5 | Future Perspectives

TIbVs represent a novel approach in immunology by harnessing the innate immune system's ability to develop "memory" through metabolic and epigenetic reprogramming. These vaccines offer broad-spectrum protection, extending beyond traditional vaccines that target specific pathogens. Future research will likely expand TIbV applications to not only infectious diseases but also autoimmune and allergic conditions. However, the clinical application of TIbVs remains in early stages. Potential risks include overstimulation of innate immunity leading to excessive inflammation or autoimmune flares, especially in genetically

predisposed individuals. Regulatory challenges also exist, particularly in standardizing manufacturing, defining biomarkers of efficacy, and ensuring long-term safety. These aspects must be addressed in preclinical and phase I/II trials before widespread use [15]. Personalized vaccinology, utilizing epigenetic markers, could further tailor vaccines to individual needs, offering more precise and preventive solutions for diseases like RA and SLE.

Moreover, TIbVs may address vaccine challenges in resource-limited areas by offering long-lasting, broad protection, especially for vulnerable populations. In allergic diseases, next-generation vaccines could reshape immune responses, promoting tolerance instead of sensitization. The potential for epigenetic inheritance also opens new research avenues, with implications for maternal and neonatal health. Overall, TIbVs have the potential to revolutionize vaccine strategies, bridging innate and adaptive immunity to provide more comprehensive disease protection.

Author Contributions

K.-C.C., Y.-H.H., Y.-A.T. drafted the original manuscript. P.-C.S., S.-B.Y. and C.-Y.Y. provided critical review and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Neuro-Ophthalmic-Onset Non-Thrombotic Primary Antiphospholipid Antibody Syndrome: Case Report

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Dear Editor,
A 43-year-old woman presented to our department with fever, impaired vision, and headache.

The patient initially developed a high fever (peak temperature 38.7°C), accompanied by chills, but no respiratory symptoms such as cough or sputum production. A chest CT scan revealed evidence of a pulmonary infection. Although the fever was successfully controlled with antibiotic treatment at a local hospital, she subsequently experienced acute-onset visual loss in the left eye (light perception only, snellen equivalent 0/20), accompanied by a persistent headache. This prompted an emergency referral to our institution. Physical examination: vital signs: Stable. Ophthalmological examination: significant reduction in visual acuity in the left eye. Neurological examination: positive right Babinski sign.

The initial workup revealed leukocytosis (WBC: 10.26×10^9/L), neutrophilia (7.65×10^9/L; 74.5%), a normal platelet count (323×10^9/L) and unremarkable results from routine tests, including biochemical tests, coagulation tests, PCT, ESR and CRP. Immunological profiling showed antiphospholipid antibodies positivity, with elevated anticardiolipin IgM (28.6 MPLU/mL) and anti-β2-glycoprotein I antibodies (155.4 AU/mL; IgM isotype: 141.4 AU/mL), alongside negative IgG and IgA isotypes for both antigens, while ANAs and other autoantibodies were negative. An ophthalmological evaluation revealed absent visual evoked potentials bilaterally, despite normal ocular angiography. Brain MRI scan (Figure 1) revealed left temporo-insular swelling, enhancement of the optic chiasm, and multiple medullary and cerebral ischaemic demyelinating lesions with ventriculomegaly. SWI imaging showed a nodular hypointensity in the right parietal lobe (suggestive of a vascular abnormality or old microbleed), as well as bilateral frontal subcortical hypointensities (possibly arachnoid granulations). However, MRA imaging showed no vascular anomalies. Lumbar puncture revealed normal CSF pressure, mild mononuclear pleocytosis (18×10^6/L), and negative microbiological studies. Autoimmune encephalitis antibody testing was negative; these findings warrant consideration of atypical neuroinflammatory disorders or antibody-negative autoimmune encephalopathy.

On Day 2, the patient developed involuntary limb movements, a choreiform gait, and progressive deterioration of vision in the right eye; ophthalmological examination confirmed a best-corrected visual acuity (BCVA) of 0.3 (Snellen equivalent ~20/60). Given these neurological manifestations, coupled with persistently positive antiphospholipid antibodies, we diagnosed antiphospholipid syndrome involving the central nervous system. Initial immunotherapy comprised intravenous methylprednisolone (1 g daily) and immunoglobulin (20 g daily) pulse therapy, with concurrent dual antithrombotic therapy (aspirin plus rivaroxaban), and addition of low dose rituximab (200 mg every 2 weeks for 2 weeks) for immunomodulatory therapy [1]. At the four-month follow-up, the patient had made a full visual recovery. BCVA improved to 1.0 (Snellen equivalent 20/20) in the left eye and 0.5 (Snellen equivalent ~20/40) in the right eye, and the fever and headache had resolved. Repeat MRI (Figure 1) demonstrated progressive lesion regression, while serial antibody titres showed declining but still high levels. Maintenance therapy was transitioned to mycophenolate mofetil, alongside continued anticoagulation therapy.

APS is an autoimmune disorder characterized by thrombosis and/or pregnancy morbidity, which must be accompanied by persistently positive antiphospholipid antibodies (aPL) [2]. Neurological manifestations (e.g., stroke, epilepsy and cognitive impairment) are relatively common in APS. However, isolated

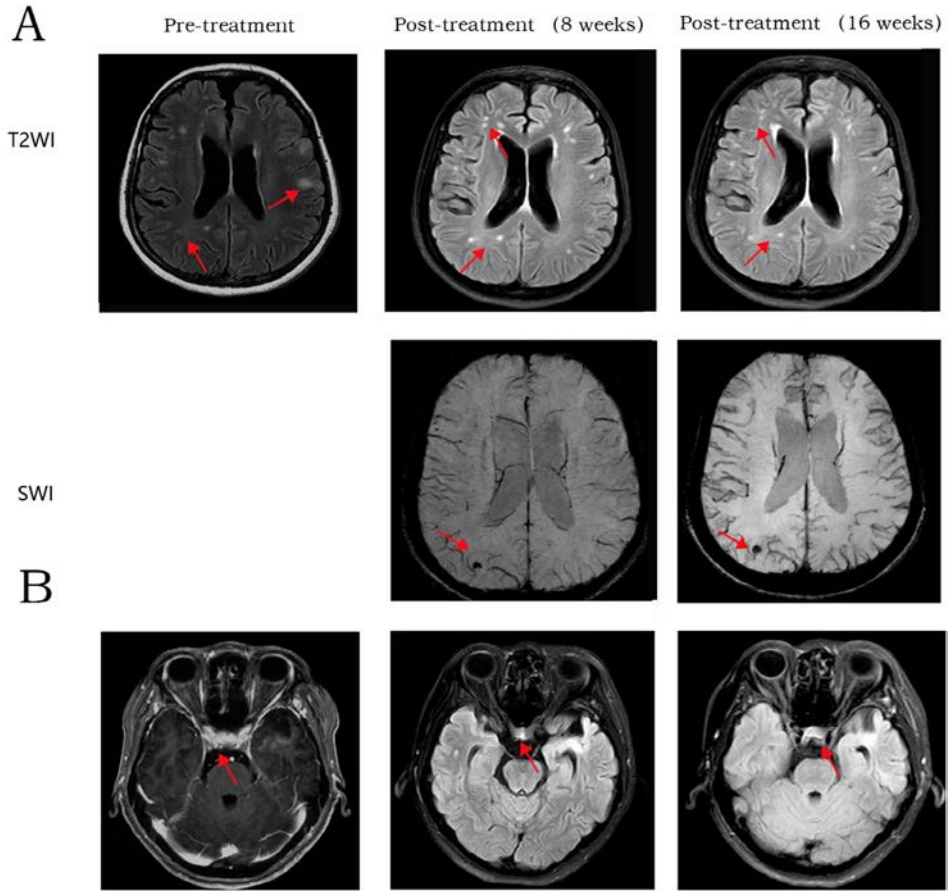

FIGURE 1 | Brain MRI images of the patient. (A) On the left is the T2WI sequence, suggesting multiple demyelinating changes. On the right, the SWI sequences reveal a nodular hypointensity in the right parietal lobe, suggestive of a vascular abnormality or old microbleed. (B) Changes in optic chiasm at 8W and 16W before and after treatment.

visual impairment due to APS-related optic neuropathy or central nervous system (CNS) involvement as the initial presentation is rare. Diagnosing APS in this patient was particularly challenging due to the absence of a typical thrombotic or obstetric history. Following multidisciplinary consultations with specialists in neurology, ophthalmology and radiology, we carefully evaluated the case. The temporal and occipital lobe lesions were consistent with ischaemic changes, while the right parietal lobe findings suggested old microhaemorrhages, indicating possible cerebral microangiopathy. The following conditions should be excluded: (1) Neuromyelitis optica spectrum disorder (NMOSD)—while absence of spinal cord involvement and negative AQP4 antibody; (2) multiple sclerosis (MS)—the patient absence of temporal dissemination and typical MRI findings; and (3) autoimmune encephalitis—the patient's cerebrospinal fluid (CSF) antibody panel was entirely negative, and the clinical presentation lacked characteristic features (e.g., psychiatric symptoms or seizures).

Current research has identified a broad range of non-thrombotic clinical manifestations associated with antiphospholipid antibodies (aPLs). These include cutaneous manifestations such as livedo reticularis and superficial thrombophlebitis; haematological manifestations such as thrombocytopenia and haemolytic anaemia; cardiac manifestations; neurological manifestations such as chorea, cognitive dysfunction and transverse myelitis; and renal manifestations such as aPL-associated nephropathy. While these diverse presentations are distinct from classic vascular thrombotic events, they are increasingly recognised as part of the APS spectrum. It is thought that they arise through alternative pathogenic mechanisms, including direct antibody-mediated endothelial activation, complement pathway dysregulation and tissue-specific inflammatory responses [3]. CNS manifestations constitute one of the most prominent features of APS, encompassing arterial and/or venous thrombotic events, as well as various non-thrombotic neuropsychiatric syndromes. Although the prothrombotic effects of antiphospholipid antibodies (aPLs) are well-established, their relationship with non-stroke neuropsychiatric manifestations (NPMs) remains unclear. Neuroimaging in these patients typically reveals a combination of ischaemic and inflammatory white matter changes, suggesting a complex pathophysiology involving microvascular thrombosis and direct, antibody-mediated neuroinflammation [4]. Reino et al. [5] documented a seminal case involving a middle-aged woman who presented with acute bilateral visual loss. Diagnostic evaluation revealed impaired visual conduction pathways, despite normal retinal architecture. Subsequent immunological testing demonstrated antiphospholipid antibody (aPL) positivity. This case established primary APS as the definitive diagnosis, complete visual recovery was achieved through anticoagulation therapy. A retrospective case series [6] of 23 patients with catastrophic antiphospholipid syndrome (CAPS) and visual impairment revealed that 64% had primary APS, while the remaining 36% were secondary to SLE. The main causes of

vision loss were retinal vascular occlusion (73%), choroidopathy (36%), and ischaemic optic neuropathy (9%). Ischemic optic neuropathy was categorised as either anterior ischemic optic neuropathy (AION), which is caused by ischemia at the optic nerve head (optic disc) and typically presents with optic disc oedema, or posterior ischemic optic neuropathy (PION), which results from impaired blood supply to the retrobulbar, intracanalicular, or intracranial optic nerve segments and is characterised by vision loss without optic disc swelling. Our patient exhibited intracranial ischaemic lesions with optic chiasm enhancement, normal optical coherence tomography results, delayed visual evoked potentials and unremarkable fundus angiography—findings suggestive of PION.

This case highlights APS heterogeneity, emphasizing multidisciplinary evaluation, antibody testing, and imaging in atypical presentations. Further research is needed to elucidate aPL-mediated CNS injury mechanisms and standardize non-thrombotic APS treatment.

Author Contributions

Huiyang Liu: article writing. **Zheng Cui:** data collection. **Dongmei Bao:** data collection. **Yongfu Wang:** data collection and organization.

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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ORIGINAL ARTICLE

Novel Variants in the IL-38 Gene Shape Genetic Susceptibility in Systemic Lupus Erythematosus

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ABSTRACT

Objectives: Available evidence has shown a genetic association with systemic lupus erythematosus (SLE) pathogenesis. Interleukin-38 (IL-38) has been found to correlate with SLE development. However, whether IL-38 gene polymorphisms relate to SLE risk needs clarification.

Methods: A total of 390 age- and sex-matched SLE patients and 390 healthy controls were recruited from the Affiliated Hospital of Southwest Medical University. Blood samples were collected from all the participants. Clinical and laboratory characteristics were collected and evaluated. DNA samples were extracted, and their quality was assessed. Six IL-38 gene polymorphisms (rs3811058, rs3811051, rs3811050, rs28992498, rs28992497, and rs7599662) were screened. Genotyping was performed using KASP methods.

Results: All the six polymorphisms conformed to the Hardy–Weinberg's expectation test. The frequencies of genotypes TT and TT + TC of rs3811058 were lower in SLE patients compared to healthy controls (OR = 1.518, OR = 1.461). Similarly, for rs7599662, the frequencies of genotypes TT, TT + TC, and allele T were lower in SLE patients than in healthy controls (OR = 2.052, OR = 2.494, OR = 1.645). Conversely, the frequency of genotype TC in SLE patients was higher than that in healthy controls (OR = 1.972). Subgroup analysis showed that these gene polymorphisms were associated with various clinical and laboratory features in SLE patients. Notably, the TT + TC genotype of rs3811058 was negatively associated with lupus headache and pyuria. Furthermore, patients with the TT + TC genotype of rs3811058 had higher IgA levels, whereas SLE patients with the CC + CA genotype of rs28992498 showed lower RF and IgG expression.

Conclusion: IL-38 gene polymorphisms (rs3811058 and rs7599662) are associated with SLE susceptibility, and are partially associated with clinical and laboratory features.

1 | Introduction

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease characterized by excessive autoantibody production and imbalanced immune responses [1]. The prevalence of SLE varies widely across different countries. For instance, the global prevalence of SLE is estimated at 43.7/100 000 population [2]. The prevalence of SLE in China is about 47.61/100 000 population [3]. SLE often involves damage to different organs and systems, such as the kidneys, the hematologic system, and the central nervous system. Cardiovascular events are reported in approximately 7.2% of Chinese SLE patients [4]. Neuropsychiatric SLE (NPSLE), affecting both the central nervous system and peripheral nervous system, is observed in about 27%–80% of SLE patients [5]. Lupus nephritis (LN) is considered the most common complication in SLE that resulted from much deposition of immune complex in renal tissues [6]. The prevalence of LN in SLE patients is about 50%–60% in China [7]. Until now, the treatment

of SLE patients mainly relies on immunosuppressants and glucocorticoids. Although several biologics have been used for SLE treatment recently, side effects such as infection, tumor development, pain cannot be ignored [8, 9]. Therefore, identifying potential biomarkers for SLE and investigating the mechanisms by which these markers are involved in SLE pathogenesis will help to identify more precise therapeutic targets in SLE management.

Interleukin-38 (IL-38) is a potent anti-inflammatory member of the IL-1 family, which consists of 11 cytokines, such as IL-1β, IL-36α, IL-1Ra, and IL-37. It was first identified in 2001. IL-38 competitively antagonizes the family member IL-36α, IL-36Ra, and activates downstream signaling such as MAPK, NF-κB [10]. This leads to limited production of pro-inflammatory cytokines and chemokines. IL-38 protein has a molecular weight of approximately 17 kDa, and shares 37% homology with IL-1Ra and 41% homology with IL-36Ra. It is reported that IL-38 can be produced by T cells, monocytes, and macrophages [11]. Several studies have investigated the effects of IL-38 gene polymorphisms and disease risk. Polymorphism rs3811058 in the IL-38 gene was not related to ankylosing spondylitis in Australia population [12]. On the contrary, polymorphism rs3811058 interacted with IL-37 gene polymorphism rs3811047 and IL-36B gene polymorphism rs1562304, and was associated with increased susceptibility in psoriatic arthritis patients from the Canadian population [13]. Based on the above findings, IL-38 gene polymorphism may have a role in the pathogenesis of SLE, an autoimmune rheumatic disease with similar pathogenesis. In the current study, we conducted a case–control study to evaluate whether IL-38 gene polymorphisms were related to SLE risk in the Chinese Han population.

2 | Methods

2.1 | SLE Patients and Healthy Controls

In this study, 390 SLE patients and 390 healthy controls of Chinese Han origin were recruited for analysis. The average age of the SLE patients was 45.00 years (37.00–54.25). The average age of the healthy controls was 44.00 years (34.00–53.00). Age and sex in the two groups were comparable (all $p > 0.05$). SLE patients were diagnosed according to the 1997 American College of Rheumatology clarification criteria [14]. Patients were recruited from the Department of Rheumatology and Immunology, and controls from the Health Management Center, both at the Affiliated Hospital of Southwest Medical University. Healthy controls were free of autoimmune diseases and malignancies. Among the SLE patients, 29.23% had rash, 21.03% had thrombocytopenia, and 27.69% had hematuria (Table 1). This study was approved by the Ethics Research Committee of Affiliated Hospital of Southwest Medical University (KY2020180), and informed consent was collected from each participant.

2.2 | Detection of Inflammatory Indexes

In this study, laboratory parameters from SLE patients, including various autoantibodies, ESR, RF, and CRP were collected. Blood samples were collected from each SLE patient and healthy control. Serum was centrifuged, and the levels of RF and CRP were detected using scattering turbidity (Siemens, Germany). The levels of ANA were examined using indirect immunofluorescence (Omon Medical, Hangzhou, China). The levels of anti-dsDNA were tested using colloidal gold spot filtration (Xitang Biology, Shanghai, China). Other autoantibodies, such as anti-Sm, anti-SSA, anti-SSB, and anti-RNP, were examined by immunoblotting (YHLO, Shenzhen, China). Moreover, the levels of IgG, IgM, IgA, C3, and C4 were measured by DiaSys Diagnostic Systems (Shanghai, China). All the inflammatory factors were detected according to instructions.

2.3 | DNA Extraction and Gene Polymorphisms Detection

DNA was extracted from each blood sample, and its concentration and purity were detected. Qualified samples were used for subsequent genotyping experiments. The selection of IL-38 gene polymorphisms was considered according to the National Center for Biotechnology Information database, the Genome Reference Consortium Human Build 38 project, and the 1000 Genomes Project. Furthermore, we screened these polymorphisms based on several criteria: (1) an allele frequency of each polymorphism higher than 5% in Chinese Han population; (2) a pairing marker r^2 larger than 0.8 in HapMap; (3) polymorphisms located at key functional regions; (4) polymorphisms that had been investigated in inflammatory diseases or rheumatic diseases in previous studies were preferentially selected. Based on these criteria, six polymorphisms (rs3811058, rs3811051, rs3811050, rs28992498, rs28992497, and rs7599662) were included in the study. Genotyping methods were conducted as follows: First, an appropriate amount of DNA was packed into a 96-well plate, and then transferred into a 1536-well plate. Second, the DNA sample was predenatured at 65°C for 30 m. Third, each well was added with 0.5 μL 2× KASP Master Mix, 0.014 μL 72× Assay Mix, and 0.486 μL ddH_2O. Fourth, the wells were sealed and subjected to the following PCR programs: activation, 94°C, 15 m (1 cycle); denaturation, 94°C, 20s and annealing/elongation, 61°C–55°C, 60 s (10 cycles); denaturation, 94°C, 20s and annealing/elongation, 55°C, 60s (26 cycles). Finally, upon completion of the PCR reaction, the products were sequenced, and the resulting fluorescence signals from the FAM and HEX channels were collected for analysis.

2.4 | Statistics

Quantitative indexes were expressed as median (interquartile range) if they were not normally distributed. Qualitative indexes were expressed as percentage or frequency. Quantitative indexes were compared using the Mann–Whitney *U* test. For qualitative indexes, statistical differences among the groups were determined using the chi-square test and Fisher's exact test. The Hardy–Weinberg's expectation (HWE) test was used to evaluate differences in genotype frequencies between two groups. Data analysis was conducted using SPSS 16.0 (Chicago, USA).

TABLE 1 | The demographic and clinical characteristics of SLE patients and controls.

Characteristics	SLE	Healthy controls	*p*
Female (%)/male (%)	82.05/17.95	85.64/14.36	0.173
Age (years)	45.00 (37.00–54.25)	44.00 (34.00–53.00)	0.139
Optic nerve injury [*n* (%)]	14 (3.59)	—	
LN [*n* (%)]	182 (46.67)	—	
Lupus headache [*n* (%)]	23 (5.90)	—	
Vasculitis [*n* (%)]	32 (8.21)	—	
Arthritis [*n* (%)]	196 (50.26)	—	
Myositis [*n* (%)]	47 (12.05)	—	
Rash [*n* (%)]	114 (29.23)	—	
Alopecia [*n* (%)]	76 (19.49)	—	
Oral ulcer [*n* (%)]	25 (6.41)	—	
Fever [*n* (%)]	73 (18.72)	—	
Hypocomplementemia [*n* (%)]	143 (36.67)	—	
Thrombocytopenia [*n* (%)]	82 (21.03)	—	
Reduced leukocyte [*n* (%)]	56 (14.36)	—	
Cylindruria [*n* (%)]	26 (6.67)	—	
Hematuria [*n* (%)]	108 (27.69)	—	
Pyuria [*n* (%)]	43 (12.03)	—	
ANA [*n* (%)]	215 (55.13)	—	
Anti-dsDNA [*n* (%)]	89 (22.82)	—	
Anti-Sm [*n* (%)]	100 (25.64)	—	
Anti-SSA [*n* (%)]	148 (37.95)	—	
Anti-SSB [*n* (%)]	46 (11.79)	—	
Anti-RNP [*n* (%)]	71 (18.21)	—	
C3 [g/L]	0.822 (0.580–1.060)	—	
C4 [g/L]	0.152 (0.078–0.240)	—	
ESR [mm/H]	51.000 (30.000–74.000)	—	
RF [IU/mL]	9.600 (7.000–11.300)	—	
IgA [mg/L]	2.760 (2.050–3.510)	—	
IgM [mg/L]	1.020 (0.720–1.580)	—	
IgG [g/L]	15.300 (11.600–20.430)	—	
CRP [mg/L]	7.600 (1.700–38.150)	—	

Abbreviations: LN, lupus nephritis; SLE, systemic lupus erythematosus.

3 | Results

3.1 | Baseline Characteristics of SLE Patients and Healthy Controls

In this study, 390 SLE patients and 390 age- and sex-matched healthy controls were recruited for analysis. Among the patients, 82.05% of the patients were female, and 17.95% were male. Among the healthy controls, 85.64% of the controls were female and 14.36% were male. In addition, the main clinical and laboratory features in SLE patients were lupus nephritis (46.67%), arthritis (50.26%), hypocomplementemia (36.67%), ANA (55.13%), and anti-SSA (37.95%).

3.2 | Hardy–Weinberg Expectation Test in Healthy Controls of IL-38 Gene Polymorphisms

To prevent population selection bias, we assessed IL-38 gene polymorphisms in healthy controls using the HWE test. Results showed that all the six polymorphisms conformed to the HWE test, with all *p* values higher than 0.05 (Table S1).

3.3 | Power Analysis of IL-38 Gene Polymorphisms

In the current study, we investigated the power of IL-38 gene polymorphisms so as to improve the reliability of the study. We found that the power was 0.900 for rs3811058, 0.895 for rs3811051, 0.894 for rs3811050, 0.918 for rs28992498, 0.911 for rs28992497, and 0.920 for rs7599662 to detect a 1.8-fold increased risk assuming an α value of 0.05. Together, the power for each polymorphism indicated that the sample size in the current study is effective for analysis.

3.4 | Differences in IL-38 Gene Polymorphisms in SLE Patients and Controls

We compared the frequencies of genotypes and alleles in six polymorphisms between patients and controls. For rs3811058, the frequency of TT was lower in SLE patients compared to that in controls (OR = 1.518, 95% CI: 1.005–2.293, $p = 0.047$). The frequency of TT + TC was also lower in SLE patients compared to that in controls as well (OR = 1.461, 95% CI: 1.004–2.125, $p = 0.048$). Similarly, there were reduced frequencies of genotypes TT and TT + TC in SLE patients compared to healthy controls for rs7599662, respectively (OR = 2.052, 95% CI: 1.568–3.707, $p = 0.001$; OR = 2.494, 95% CI: 1.409–3.716, $p = 0.002$). Conversely, the frequency of genotype TC was higher in SLE patients than in healthy controls for rs7599662 (OR = 1.972, 95% CI: 1.073–3.622, $p = 0.029$). Interestingly, the frequency of allele T was significantly different between SLE patients and controls, showing lower frequency of allele T in SLE patients (Table 2). Moreover, the frequencies of alleles or genotypes of the other four polymorphisms (including rs3811051, rs3811050, rs28992498, and rs28992497) were not significantly different between patients and controls (Table 2).

3.5 | Relationship Between IL-38 Gene Polymorphisms and Clinical and Laboratory Features in SLE Patients

Given that the development of SLE is sometimes accompanied by various clinical and laboratory features, we also analyzed association between the six polymorphisms and these features in SLE patients. Our aim was to investigate whether these gene polymorphisms might influence the clinical and laboratory severity in SLE patients. In our study, we found that allele T of rs3811058 was significantly related to optic nerve injury, lupus headache, vasculitis, myositis, alopecia, oral ulcer, fever, thrombocytopenia, reduced leukocyte, cylindruria, pyuria, anti-dsDNA, anti-Sm, anti-SSB, and anti-RNP (all $p < 0.001$). Genotype TT + TC of rs3811058 was significantly related to pyuria in SLE patients ($p = 0.032$). For rs3811051, genotype TT + TG and allele T were significantly related to reduced leukocyte in SLE patients ($p = 0.029$ and $p = 0.007$, respectively). For rs3811050, allele C was significantly related to hypocomplementemia ($p = 0.025$), and genotype CC + CT was related to pyuria in SLE patients ($p = 0.047$). Moreover, genotype CC + CT and allele C were correlated with anti-SSB in SLE patients ($p = 0.042$ and $p = 0.014$). These findings were similar to results for rs28992498, where allele C was related to optic nerve injury ($p < 0.001$), oral ulcer ($p < 0.001$), cylindruria ($p < 0.001$), and genotype CC + CA and allele C were correlated with lupus headache ($p = 0.011$ and $p = 0.002$, respectively). Interestingly, genotype TT + TC of rs7599662 was correlated with alopecia ($p = 0.030$), and genotype TT + TC of rs28992497 was correlated with thrombocytopenia ($p < 0.001$). Other qualitative clinical and laboratory features were not significantly related to IL-38 gene polymorphisms (Tables 3 and 4).

Regarding association between polymorphisms and SLE clinical and laboratory features, we also analyzed the relationship between the six polymorphisms and quantitative laboratory parameters, including C3, C4, ESR, RF, IgA, IgM, IgG, and CRP. Results revealed that genotype TT + TC of rs3811058 was related to higher levels of IgA ($p = 0.032$), and genotype TT + TG was correlated with higher levels of IgG in SLE patients ($p = 0.019$). For rs28992498, genotype CC + CA was significantly correlated with lower levels of RF and IgG in SLE patients ($p = 0.005$ and $p = 0.036$, respectively). Other polymorphisms were not significantly related to quantitative laboratory characteristics (Table 5, Table S2).

4 | Discussion

In this case–control study, we investigated IL-38 gene polymorphisms in 390 age- and sex-matched SLE patients and 390 healthy controls. We found no population selection bias, as evidenced by the six polymorphisms (rs3811058, rs3811051, rs3811050, rs28992498, rs28992497, and rs7599662) being in accordance with the HWE test. These findings suggest that IL-38 gene polymorphisms were propagable in the Chinese Han population. Moreover, the power for the six polymorphisms was near 0.9, suggesting sufficient power in our study and ensuring the reliability of our findings. Furthermore, we showed significant differences in genotypes TT and TT + TC of rs3811058, genotypes TT, TC, and TT + TC, and allele T of rs7599662 between SLE patients and controls. The six polymorphisms were also associated with various clinical and laboratory features in SLE patients. Collectively, our findings revealed that IL-38 gene polymorphisms may correlate with SLE risk in the Chinese Han population.

IL-38 is reported to be a dual inflammatory cytokine. In our previous studies, plasma levels and mRNA expression of IL-38 were elevated in SLE patients, correlating with hematuria, lupus nephritis, and the SLEDAI score [15]. Knockdown of the IL-38 gene in pristane-induced lupus mice resulted in hepatomegaly, splenomegaly, severe kidney damage, and high expression of ANA and anti-dsDNA in serum [10]. In an in vitro study investigating the role of IL-38 in PBMCs from SLE patients, inhibition of IL-38 expression significantly promoted the generation of pro-inflammatory factors IL-6, CCL2, and APRIL [16]. In RA patients, both plasma levels and mRNA expression of IL-38 were elevated compared to healthy controls, and treatment in RA patients downregulated plasma levels of IL-38 [17]. The anti-inflammatory role of IL-38 in RA was demonstrated in collagen-induced arthritis rats, where the wild-type rats were treated with collagen in the presence of recombinant IL-38, showing alleviated joint damage, less inflammatory responses, and low expression of RANKL and RANK [18]. These findings indicated that high expression of IL-38 was observed in autoimmune

TABLE 2 | Allele and genotype frequencies of six single-nucleotide polymorphisms in the IL-38 gene in SLE patients and healthy controls.

Polymorphism	SLE (*n*, %)	Ctl (*n*, %)	OR (95% CI)	*p*
rs3811058				
TT	137 (35.13)	152 (38.97)	1.518 (1.005–2.293)	0.047
TC	175 (44.87)	181 (46.41)	1.415 (0.949–2.111)	0.089
TT + TC	312 (80.00)	333 (85.38)	1.461 (1.004–2.125)	0.048
CC	78 (20.00)	57 (14.62)	—	
T	449 (57.56)	485 (62.18)	1.212 (0.990–1.484)	0.063
C	331 (42.44)	295 (37.82)	—	
rs3811051				
TT	143 (36.67)	155 (39.74)	1.493 (0.981–2.273)	0.062
TG	174 (44.62)	182 (46.67)	1.441 (0.956–2.171)	0.081
TT + TG	317 (81.29)	337 (86.41)	1.464 (0.996–2.153)	0.053
GG	73 (18.71)	53 (13.59)	—	
T	460 (58.97)	492 (63.08)	1.188 (0.969–1.457)	0.097
G	320 (41.03)	288 (36.92)	—	
rs3811050				
CC	220 (56.41)	212 (54.36)	1.065 (0.557–2.037)	0.849
CT	149 (38.21)	159 (40.77)	1.179 (0.610–2.281)	0.624
CC + CT	369 (94.62)	371 (95.13)	1.111 (0.588–2.101)	0.746
TT	21 (5.38)	19 (4.87)	—	
C	589 (75.51)	583 (74.74)	0.960 (0.763–1.207)	0.725
T	191 (24.49)	197 (25.26)	—	
rs28992498				
CC	302 (77.44)	304 (77.95)	1.275 (0.636–2.556)	0.493
CA	69 (17.69)	71 (18.21)	1.303 (0.613–2.769)	0.491
CC + CA	371 (95.13)	375 (96.16)	1.280 (0.641–2.558)	0.484
AA	19 (4.87)	15 (3.84)	—	
C	673 (86.28)	679 (87.05)	1.069 (0.798–1.431)	0.655
A	107 (13.72)	101 (12.95)	—	
rs28992497				
TT	244 (62.56)	253 (64.87)	1.400 (0.765–2.562)	0.275
TC	119 (30.51)	117 (30.00)	1.327 (0.705–2.497)	0.380
TT + TC	363 (93.08)	370 (94.87)	1.376 (0.758–2.497)	0.294
CC	27 (6.92)	20 (5.13)	—	
T	607 (77.82)	623 (79.87)	1.131 (0.887–1.442)	0.321
C	173 (22.18)	157 (20.13)	—	
rs7599662				
TT	219 (56.15)	263 (67.44)	2.502 (1.568–3.707)	0.001
TC	129 (33.08)	109 (27.95)	1.972 (1.073–3.622)	0.029

(Continues)

TABLE 2 | (Continued)

Polymorphism	SLE (*n*, %)	Ctl (*n*, %)	OR (95% CI)	*p*
TT + TC	348 (89.23)	372 (95.39)	2.494 (1.409–3.716)	0.002
CC	42 (10.77)	18 (4.61)	—	
T	567 (72.69)	635 (81.41)	1.645 (1.295–2.090)	< 0.001
C	213 (27.31)	145 (18.59)	—	

Abbreviations: 95% CI, 95% confidence interval; OR, odd ratio.

rheumatic diseases such as SLE and RA, and that IL-38 may inhibit SLE and RA development. To further investigate why IL-38 expression was abnormal in autoimmune rheumatic diseases such as SLE, we analyzed IL-38 gene polymorphisms in SLE and investigate whether the polymorphisms of the IL-38 gene may relate to SLE risk. Our study showed that genotypes TT and TT + TC of rs3811058 were positively related to SLE risk, as were genotypes TT, TC, TT + TC, and allele T of rs7599662. In contrast, polymorphisms rs3811051, rs3811050, rs28992498, and rs28992497 were not significantly related to SLE susceptibility in the Chinese Han population. In a study about IL-38 gene polymorphisms (rs3811050 and rs3811051) and acute myeloid leukemia (AML) in the Iraqi population, rs3811050 was correlated with higher risk of AML, but the association of rs3811051 with AML was not significant [19]. In Kazakhstan population, there were no significant relationship between IL-38 gene polymorphisms (rs3811058 and rs7570267) and thyroid-associated ophthalmopathy (TAO) risk, whereas the CC genotype of rs3811058 was related to higher risk of TAO in Caucasians [20]. For RA patients, there was a reduced risk of RA in the Iraqi population associated with the rs3811050 T allele and CT genotype, whereas there was no relationship of rs3811051 and RA susceptibility [21]. Compared with our findings, difference in findings regarding IL-38 gene polymorphisms and various diseases may be attributed to several reasons. First, sample sizes differs across various diseases, with our study having the biggest sample size. Second, the diseases themselves differ; to date, studies on IL-38 gene polymorphisms have focused on SLE, RA, TAO, and AML, and as different diseases have different pathogenesis, the findings are partly different. Third, ethnicities vary across different studies investigating IL-38 gene polymorphisms. Collectively, in the future, more studies are needed to investigate IL-38 gene polymorphisms and SLE susceptibility, especially in different ethnicities.

In the current study, we found that genotype TT + TC of rs3811058 was significantly associated with vasculitis and cylindruria; genotype CC + CT of rs3811050 was significantly associated with pyuria; and genotype CC + CA of rs28992498 was significantly associated with cylindruria. These findings indicate severe damage of kidneys in SLE patients. As in IL-38 gene knockout mice, imbalanced kidney function was observed after lupus development [10]. Therefore, IL-38 gene mutation may destroy the normal transcription and translation of IL-38, contributing to kidney dysfunction. Similarly, genotype TT + TC of rs3811058 significantly correlated with anti-dsDNA, anti-Sm, anti-SSB, and anti-RNP antibody positivity in SLE patients, and genotype CC + CT and allele C of rs3811050 correlated with anti-SSB positivity in SLE patients. In IL-38 gene knockout mice treated with pristane, a previous study showed increased expression of autoantibodies such as anti-dsDNA. These findings further confirmed our hypothesis that IL-38 gene polymorphisms (rs3811058 and rs3811050) may affect SLE patients presenting with high expression of various autoantibodies. In the future, functional studies are needed to elucidate how IL-38 genetic mutations regulate production of autoantibodies in SLE patients or animal models. It is notable that allele T of rs3811058 closely correlated with optic nerve injury, lupus headache, and alopecia in SLE patients; and genotype CC + CA and allele C correlated with lupus headache as well as genotype TT + TC of rs7599662 associated with alopecia in SLE patients. The findings revealed that IL-38 gene polymorphisms may be associated with brain dysfunction, including optic nerve injury, lupus headache, and alopecia. In a study investigating the association of rs3811058 polymorphism and TAO, there was positive relationship of the polymorphism and TAO [20]. Furthermore, serum levels of IL-38 were higher in patients with intra-axial brain tumors than in patients with extra-axial brain tumors [22]. Abnormal IL-38 levels in brain tissues of ischemic stroke patients and autism spectrum disorder patients may regulate neuromyelitis optica disorder by suppressing Th17 cells differentiation, inhibiting inflammation induction, and inflammatory immune cells infiltration in brain [23]. In the current study, we also found an association between allele C of rs3811050 and hypocomplementemia in SLE patients, an association between allele T of rs3811058 and thrombocytopenia and reduced leukocyte, and an association between allele T of rs3811051 and reduced leukocyte in SLE patients. This suggests that IL-38 genetic mutation may affect hematologic dysfunction. Indeed, SLE is a hematologic disease. However, the mechanisms by which IL-38 gene mutations regulate development of hypocomplementemia, thrombocytopenia, and reduced leukocyte in SLE require further study.

The present study found lower expression of RF and IgG in SLE patients with the CC + CA genotype of rs28992498, higher expression of IgA in SLE patients with the TT + TC genotype of rs3811058, and higher expression of IgG in SLE patients with the TT + TG genotype of rs3811051. In IL-38 gene knockout mice treated with pristane, higher serum levels of IgG were observed [10]. Thus, the IL-38 gene polymorphism rs3811058 may promote IgG expression in SLE. RF is a marker that can be used for monitoring SLE disease activity. High RF expression is related to abnormal immune responses in SLE patients or those with active disease stage [24]. Lower RF expression in SLE patients with the CC + CA genotype of rs28992498 may indicate a possible protective role of this genotype in regulating RF production and subsequently contributing to lower risk of

TABLE 3 | Analysis of IL-38 gene polymorphisms (rs3811058, rs3811051, and rs3811050) in SLE by clinical and laboratory features.

	rs3811058							rs3811051							rs3811050						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
Characteristics	**TT**	**TC**	**CC**	***p***	**T**	**C**	***p***	**TT**	**TG**	**GG**	***p***	**T**	**G**	***p***	**CC**	**CT**	**TT**	***p***	**C**	**T**	***p***
Optic nerve injury																					
Positive	5	7	2		17	11		2	10	1		14	12		6	7	1		19	9	
Negative	132	168	76	0.851[a]	432	320	<0.001[b]	140	164	72	0.060[a]	444	308	0.597[b]	214	142	20	0.581[a]	570	182	0.337[b]
Lupus nephritis																					
Positive	60	75	47		195	169		59	87	36		205	159		106	70	6		282	82	
Negative	77	100	31	0.026[a]	254	162	0.469[b]	84	87	37	0.264[a]	255	161	0.158[b]	114	79	15	0.226[a]	307	109	0.234[b]
Lupus headache																					
Positive	7	9	7		23	23		6	13	4		25	21		10	13	0		33	13	
Negative	130	166	71	0.435[a]	426	308	<0.001[b]	137	161	69	0.462[a]	435	299	0.511[b]	210	136	21	0.123[a]	556	178	0.539[b]
Vasculitis																					
Positive	11	15	6		37	27		13	14	5		40	24		15	16	1		46	18	
Negative	126	160	72	0.968[a]	412	304	<0.001[b]	130	160	68	0.935[a]	420	296	0.550[b]	205	133	20	0.339[a]	543	173	0.480[b]
Arthritis																					
Positive	74	92	30		240	152		67	95	34		229	163		105	82	9		292	100	
Negative	63	83	48	0.064[a]	209	179	0.471[b]	76	79	39	0.306[a]	231	157	0.751[b]	115	67	12	0.304[a]	297	91	0.504[b]
Myositis																					
Positive	20	19	8		59	35		21	19	7		61	33		28	16	3		72	22	
Negative	117	156	70	0.519[a]	390	296	<0.001[b]	122	155	66	0.458[a]	399	287	0.213[b]	192	133	18	0.804[a]	517	169	0.795[b]
Rash																					
Positive	32	61	21		125	103		36	54	24		126	102		68	38	8		174	54	
Negative	105	114	57	0.076[a]	324	228	0.678[b]	107	120	49	0.391[a]	334	218	0.176[b]	152	111	13	0.350[a]	415	137	0.737[b]
Alopecia																					
Positive	26	36	14		88	64		28	35	13		91	61		39	31	6		109	43	
Negative	111	139	64	0.873[a]	361	267	<0.001[b]	115	139	60	0.916[a]	369	259	0.803[b]	181	118	15	0.427[a]	480	148	0.224[b]

(Continues)

TABLE 3 | (Continued)

Characteristics	rs3811058							rs3811051							rs3811050						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
	TT	TC	CC	*p*	T	C	*p*	TT	TG	GG	*p*	T	G	*p*	CC	CT	TT	*p*	C	T	*p*
Oral ulcer																					
Positive	7	15	3		29	21		10	12	3		32	18		12	12	1		36	14	
Negative	130	160	75	0.272[a]	420	310	<0.001[b]	130	162	70	0.660[a]	422	302	0.428[b]	208	137	20	0.577[a]	553	177	0.550[b]
Fever																					
Positive	20	36	16		76	68		24	37	12		85	61		46	26	1		118	28	
Negative	117	139	61	0.342[a]	373	261	<0.001[b]	119	137	61	0.511[a]	375	259	0.837[b]	174	123	20	0.170[a]	471	163	0.098[b]
Hypocomplementemia																					
Positive	47	64	32		158	128		47	69	27		163	123		71	61	11		203	83	
Negative	90	111	46	0.617[a]	291	203	0.792[b]	97	105	46	0.432[a]	299	197	0.368[b]	149	88	10	0.073[a]	386	108	0.025[b]
Thrombocytopenia																					
Positive	29	37	16		95	69		33	34	15		100	64		47	30	5		124	40	
Negative	108	138	62	0.992[a]	354	262	<0.001[b]	110	140	58	0.739[a]	360	256	0.558[b]	173	119	16	0.912[a]	465	151	0.974[b]
Reduced leukocyte																					
Positive	20	24	12		64	48		29	21	6		79	33		30	22	4		82	30	
Negative	117	151	66	0.936[a]	385	283	<0.001[b]	114	153	67	0.029[a]	381	287	0.007[b]	190	127	17	0.783[a]	507	161	0.541[b]
Cylindruria																					
Positive	7	9	10		23	29		9	11	6		29	23		13	12	1		38	14	
Negative	130	166	68	0.051[a]	426	302	<0.001[b]	134	163	67	0.840[a]	431	297	0.627[b]	207	137	20	0.675[a]	551	177	0.672[b]
Hematuria																					
Positive	30	52	26		112	104		40	44	24		124	92		61	41	6		163	53	
Negative	107	123	52	0.143[a]	337	227	0.428[b]	103	130	49	0.475[a]	336	228	0.582[b]	159	108	15	0.995[a]	426	138	0.984[b]
Pyuria																					
Positive	11	17	15		39	47		13	17	13		43	43		31	9	3		71	15	
Negative	126	158	63	0.032[a]	410	284	<0.001[b]	130	157	60	0.067[a]	417	277	0.073[b]	189	140	18	0.047[a]	518	176	0.107[b]

(Continues)

TABLE 3 | (Continued)

Characteristics	rs3811058							rs3811051							rs3811050						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
	TT	TC	CC	*p*	T	C	*p*	TT	TG	GG	*p*	T	G	*p*	CC	CT	TT	*p*	C	T	*p*
ANA																					
Positive	77	94	44		248	182		82	99	33		263	165		128	79	8		335	95	
Negative	60	81	34	0.879[a]	201	149	0.911[b]	61	75	40	0.183[a]	197	155	0.121[b]	92	70	13	0.169[a]	254	96	0.085[b]
Anti-dsDNA																					
Positive	35	31	23		101	77		27	47	15		101	77		54	34	1		142	36	
Negative	102	144	55	0.077[a]	348	254	<0.001[b]	116	127	58	0.201[a]	359	243	0.491[b]	166	115	20	0.119[a]	447	155	0.132[b]
Anti-Sm																					
Positive	36	44	20		116	84		37	50	13		124	76		56	39	5		151	49	
Negative	101	131	58	0.974[a]	333	247	<0.001[b]	106	124	60	0.199[a]	336	244	0.313[b]	164	110	16	0.969[a]	438	142	0.996[b]
Anti-SSA																					
Positive	54	63	31		171	125		53	75	20		181	115		87	58	3		232	64	
Negative	83	112	47	0.773[a]	278	206	0.948[b]	90	99	53	0.065[a]	279	205	0.334[b]	133	91	18	0.071[a]	357	127	0.146[b]
Anti-SSB																					
Positive	18	19	9		55	37		18	24	4		60	32		33	13	0		79	13	
Negative	119	156	69	0.823[a]	394	294	<0.001[b]	125	150	69	0.169[a]	400	288	0.195[b]	187	136	21	0.042[a]	510	178	0.014[b]
Anti-RNP																					
Positive	19	36	16		74	68		23	33	15		79	63		47	22	2		116	26	
Negative	118	139	62	0.264[a]	375	263	<0.001[b]	120	141	58	0.681[a]	381	257	0.371[b]	173	127	19	0.156[a]	473	165	0.058[b]

[a]Patients positive versus patients negative using 3×2 contingency table.
[b]Patients positive versus patients negative using 2×2 contingency table or Fisher's exact test.

TABLE 4 | Analysis of IL-38 gene polymorphisms (rs28992498, rs28992497, and rs7599662) in SLE by clinical and laboratory features.

	rs28992498							rs28992497							rs7599662						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
Characteristics	**CC**	**CA**	**AA**	***p***	**C**	**A**	***p***	**TT**	**TC**	**CC**	***p***	**T**	**C**	***p***	**TT**	**TC**	**CC**	***p***	**T**	**C**	***p***
Optic nerve injury																					
Positive	12	1	1		25	3		11	3	0		25	3		8	5	1		21	7	
Negative	290	68	18	0.550[a]	648	104	< 0.001[b]	233	116	27	0.369[a]	582	170	0.137[b]	211	124	41	0.900[a]	546	206	0.780[b]
Lupus nephritis																					
Positive	144	29	9		317	47		114	58	10		286	78		105	56	21		266	98	
Negative	158	40	10	0.696[a]	356	60	0.541[b]	130	61	17	0.546[a]	321	95	0.637[b]	114	73	21	0.644[a]	301	115	0.822[b]
Lupus headache																					
Positive	14	5	4		33	13		11	10	2		32	14		16	5	2		37	9	
Negative	288	64	15	0.011[a]	640	94	0.002[b]	233	109	25	0.316[a]	575	159	0.165[b]	203	124	40	0.400[a]	530	204	0.224[b]
Vasculitis																					
Positive	26	4	2		56	8		23	8	1		54	10		17	8	7		42	22	
Negative	276	65	17	0.693[a]	617	99	0.768[b]	221	111	26	0.459[a]	553	163	0.188[b]	202	121	35	0.094[a]	525	191	0.185[b]
Arthritis																					
Positive	157	31	8		345	47		122	63	11		307	85		112	63	21		287	105	
Negative	145	38	11	0.438[a]	328	60	0.159[b]	122	56	16	0.515[a]	300	88	0.738[b]	107	66	21	0.917[a]	280	108	0.742[b]
Myositis																					
Positive	41	4	2		86	8		30	14	3		74	20		24	18	5		66	28	
Negative	261	65	17	0.197[a]	587	99	0.118[b]	214	105	24	0.978[a]	533	153	0.822[b]	195	111	37	0.709[a]	501	185	0.565[b]
Rash																					
Positive	92	15	7		199	29		71	33	10		175	53		61	43	10		165	63	
Negative	210	54	12	0.269[a]	474	78	0.602[b]	173	86	17	0.629[a]	432	120	0.645[b]	158	86	32	0.397[a]	402	150	0.896[b]
Alopecia																					
Positive	57	13	6		127	25		49	22	5		120	32		44	30	2		118	34	
Negative	245	56	13	0.394[a]	546	82	0.276[b]	195	97	22	0.929[a]	487	141	0.709[b]	175	99	40	0.030[a]	449	179	0.128[b]
Oral ulcer																					

(Continues)

TABLE 4 | (Continued)

Characteristics	rs28992498							rs28992497							rs7599662						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
	CC	CA	AA	*p*	C	A	*p*	TT	TC	CC	*p*	T	C	*p*	TT	TC	CC	*p*	T	C	*p*
Positive	21	3	1		45	5		14	10	1		38	12		14	9	2		37	13	
Negative	281	66	18	0.712[a]	628	102	<0.001[b]	230	109	26	0.522[a]	569	161	0.749[b]	205	120	40	0.878[a]	530	200	0.830[b]
Fever																					
Positive	53	14	6		120	26		45	23	4		113	31		38	30	5		106	40	
Negative	249	55	13	0.294[a]	553	81	0.111[b]	199	96	23	0.862[a]	494	142	0.835[b]	181	99	37	0.192[a]	461	173	0.979[b]
Hypocomplementemia																					
Positive	109	26	8		244	42		87	44	12		218	68		83	42	18		208	78	
Negative	193	43	11	0.854[a]	429	65	0.550[b]	157	75	15	0.665[a]	389	105	0.605[b]	136	87	24	0.461[a]	359	135	0.987[b]
Thrombocytopenia																					
Positive	64	15	3		143	21		49	28	5		126	38		50	28	4		128	36	
Negative	238	54	16	0.844[a]	530	86	0.702[b]	195	91	22	<0.001[a]	481	135	0.731[b]	169	101	38	0.149[a]	439	177	0.083[b]
Reduced leukocyte																					
Positive	46	9	1		101	11		38	15	3		91	21		34	17	5		85	27	
Negative	256	60	18	0.458[a]	572	96	0.195[b]	206	104	24	0.663[a]	516	152	0.345[b]	185	112	37	0.743[a]	482	186	0.411[b]
Cylindruria																					
Positive	19	7	0		45	7		19	5	2		43	9		15	9	2		39	13	
Negative	283	62	19	0.507[a]	628	100	<0.001[b]	225	114	25	0.432[a]	564	164	0.381[b]	204	120	40	0.871[a]	528	200	0.699[b]
Hematuria																					
Positive	88	17	3		193	23		70	32	6		172	44		60	38	10		158	58	
Negative	214	52	16	0.371[a]	480	84	0.123[b]	174	87	21	0.755[a]	435	129	0.452[b]	159	91	32	0.769[a]	409	155	0.860[b]
Pyuria																					
Positive	32	7	4		71	15		30	10	3		70	16		24	16	3		64	22	
Negative	270	62	15	0.357[a]	602	92	0.287[b]	214	109	24	0.539[a]	537	157	0.398[b]	195	113	39	0.639[a]	503	191	0.703[b]
ANA																					
Positive	171	37	7		379	51		133	65	17		331	99		124	69	22		317	113	

(Continues)

TABLE 4 | (Continued)

Characteristics	rs28992498							rs28992497							rs7599662						
	Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)			Genotype (*n*)				Allele (*n*)		
	CC	CA	AA	*p*	C	A	*p*	TT	TC	CC	*p*	T	C	*p*	TT	TC	CC	*p*	T	C	*p*
Negative	131	32	12	0.234[a]	294	56	0.095[b]	111	54	10	0.698[a]	276	74	0.530[b]	95	60	20	0.792[a]	250	100	0.475[b]
Anti-dsDNA																					
Positive	71	13	5		155	23		61	23	5		145	33		50	29	10		129	49	
Negative	231	56	14	0.659[a]	518	84	0.725[b]	183	96	22	0.414[a]	462	140	0.183[b]	169	100	32	0.984[a]	438	164	0.940[b]
Anti-Sm																					
Positive	74	22	4		170	30		64	30	6		158	42		56	32	12		144	56	
Negative	228	47	15	0.401[a]	503	77	0.514[b]	180	89	21	0.895[a]	449	131	0.641[b]	163	97	30	0.888[a]	423	157	0.799[b]
Anti-SSA																					
Positive	116	28	4		260	36		92	43	13		227	69		87	42	19		216	80	
Negative	186	41	15	0.282[a]	413	71	0.323[b]	152	76	14	0.505[a]	380	104	0.552[b]	132	87	23	0.243[a]	351	133	0.891[b]
Anti-SSB																					
Positive	35	9	2		79	13		28	15	3		71	21		25	12	9		62	30	
Negative	267	60	17	0.930[a]	594	94	0.903[b]	216	104	24	0.946[a]	536	152	0.874[b]	194	117	33	0.103[a]	505	183	0.224[b]
Anti-RNP																					
Positive	53	14	4		120	22		43	21	7		107	35		39	21	12		99	45	
Negative	249	55	15	0.822[a]	553	85	0.497[b]	201	98	20	0.560[a]	500	138	0.434[b]	180	108	30	0.190[a]	468	168	0.240[b]

[a]Patients positive versus patients negative using 3×2 contingency table.
[b]Patients positive versus patients negative using 2×2 contingency table or Fisher's exact test.

TABLE 5 | Association of IL-38 gene polymorphisms (rs28992498, rs28992497, and rs7599662) with clinical features in SLE patients (quantitative variables).

	rs28992498 [Median (P_{25}–P_{75})]				rs28992497 [Median (P_{25}–P_{75})]				rs7599662 [Median (P_{25}–P_{75})]			
Characteristics	**CC**	**CA**	**AA**	***p*[a]**	**TT**	**TC**	**CC**	***p*[a]**	**TT**	**TC**	**CC**	***p*[a]**
C3 [g/L]	0.770 (0.517, 0.991)	0.950 (0.655, 1.185)	0.849 (0.561, 0.998)	0.854	0.793 (0.545, 1.035)	0.780 (0.512, 1.025)	0.777 (0.637, 1.006)	0.666	0.784 (0.538, 1.000)	0.858 (0.570, 1.090)	0.688 (0.468, 1.050)	0.474
C4 [g/L]	0.152 (0.077, 0.239)	0.153 (0.094, 0.241)	0.176 (0.076, 0.248)	0.791	0.151 (0.077, 0.241)	0.165 (0.084, 0.237)	0.153 (0.108, 0.245)	0.913	0.140 (0.074, 0.233)	0.180 (0.091, 0.260)	0.170 (0.071, 0.228)	0.954
ESR [mm/H]	20.000 (10.000, 41.000)	28.000 (16.000, 51.000)	40.000 (11.000, 69.500)	0.315	21.000 (10.000, 45.500)	21.500 (10.000, 41.750)	36.500 (16.500, 45.500)	0.255	28.000 (10.750, 46.000)	19.000 (10.000, 40.000)	17.500 (11.750, 41.750)	0.693
RF [IU/mL]	9.200 (7.800, 11.300)	10.000 (5.000, 11.300)	30.000 (11.550, 52.275)	0.005	9.200 (7.200, 11.300)	10.000 (7.050, 12.500)	9.200 (4.150, 11.550)	0.587	10.600 (6.125, 13.675)	9.200 (7.000, 11.300)	10.100 (8.200, 11.700)	0.712
IgA [mg/L]	2.600 (1.835, 3.420)	2.315 (1.557, 3.292)	3.050 (2.557, 3.682)	0.114	2.620 (1.825, 3.435)	2.515 (1.797, 3.512)	2.180 (1.345, 3.375)	0.151	2.635 (1.865, 3.497)	2.440 (1.620, 3.420)	2.620 (2.050, 3.365)	0.567
IgM [mg/L]	0.970 (0.650, 1.440)	0.930 (0.637, 1.440)	1.085 (0.717, 1.575)	0.487	0.970 (0.625, 1.440)	0.910 (0.677, 1.382)	1.105 (0.907, 1.507)	0.065	0.970 (0.615, 1.467)	0.910 (0.700, 1.380)	0.995 (0.675, 1.490)	0.758
IgG [g/L]	13.000 (10.250, 18.340)	13.400 (9.325, 16.440)	16.550 (13.490, 19.222)	0.036	13.065 (10.287, 17.372)	13.350 (9.535, 18.415)	13.950 (10.657, 18.370)	0.479	13.300 (10.300, 18.340)	12.895 (9.412, 16.807)	13.270 (10.570, 17.370)	0.820
CRP [mg/L]	3.650 (0.707, 19.975)	3.780 (0.950, 13.600)	25.600 (0.200, 108.500)	0.199	3.780 (1.090, 20.350)	5.205 (0.600, 24.445)	3.130 (0.200, 11.300)	0.203	5.700 (1.000, 20.300)	3.460 (1.180, 19.600)	3.130 (0.375, 33.825)	0.292

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factors; SLE, systemic lupus erythematosus.
[a](Wild-type genotypes + heterozygosity) vs. mutant-type genotypes. For example, CC + CA versus AA genotype for rs28992498.

SLE. Nevertheless, the hypothesis needs functional studies for clarification.

There are some limitations in the current study. First, the interaction of different polymorphisms in the IL-38 gene was not investigated. Second, while the study focused on the Chinese Han population, other ethnicities require investigation. Third, although this study included a large number of patients and controls, multicenter studies are necessary for investigating the association between IL-38 gene polymorphisms and SLE susceptibility. Fourth, the interaction of IL-38 gene polymorphisms with other cytokines or chemokines needs to be explored, and their role in other autoimmune diseases also needs to be investigated in the future [25–28]. Moreover, whether IL-38 genetic variations affect IL-38 expression in SLE patients, at both protein and mRNA levels, requires further investigation.

5 | Conclusion

This study showed a significant association between IL-38 gene mutations (rs3811058 and rs7599662) and the risk of SLE, and the six polymorphisms were related to various clinical and laboratory characteristics in SLE patients.

Author Contributions

Study conception and design: Q.S., A.H., and C.H. Acquisition of data, analysis and interpretation of data: Q.S., A.H., and C.H. Drafting the article: Q.S. and C.H. Final approval of the version of the article to be published: all authors, and that all authors 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

Datasets are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Hardy–Weinberg expectation testing of IL-38 gene polymorphisms in healthy controls. **Table S2:** Association of IL-38 gene polymorphisms (rs3811058, rs3811051, and rs3811050) with clinical features in SLE patients (quantitative variables).

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ORIGINAL ARTICLE

Association Between Gout and the Risk of Dementia: A Meta-Analysis of Observational Studies and Biological Mechanisms

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ABSTRACT

Background and Aim: The relationship of gout with the risk of dementia has been a subject of importance in current studies. There is no comprehensive meta-analysis regarding their association. Hence, our team performed a systematic review and meta-analysis to examine the relationship of gout with the risk of dementia.

Methods: We searched PubMed, EMBASE, Scopus, and Web of Science beginning at database commencement till 1 December 2022. For systematic review and meta-analysis, 2 independent reviewers comprised observational researches that assessed the relationship of gout with risk of dementia. This research pursued the Preferred Reporting Items for Systematic reviews and Meta-Analyses summarizing guidelines to extract and synthesize data. Our team applied the random-effects model to determine pooled risk ratios (RRs) with 95% confidence intervals (CIs).

Results: Our study covered 5 observational studies. The pooled RR for the risk of overall dementia was 0.80 (95% CI: 0.58–1.10) with no evidence of publication bias. Moreover, the pooled RR demonstrated lesser risk of Alzheimer's disease (AD) at 0.70 (95% CI: 0.62–0.78) and vascular dementia at 0.68 (95% CI: 0.48–0.95) among patients with gout. An inverse association was observed in Asian people, but there was no relationship of gout with dementia among Western people.

Conclusion: In this meta-analysis of observational studies, gout was not significantly associated with overall dementia risk, although inverse associations were observed for AD and vascular dementia. These findings suggest potential heterogeneity by dementia subtype and population but should be interpreted cautiously given the observational design. Well-designed prospective studies and randomized trials are needed to clarify causality and underlying mechanisms.

Protocol Registration: International Platform of Registered Systematic Review and Meta-analysis Protocols INPLASY2025110018; https://doi.org/10.37766/inplasy2025.11.0018.

1 | Introduction

Dementia, a very usual chronic neurodegenerative disorder and global health problem, affects more than 55 million people [1, 2]. The number of patients with dementia is increasing significantly: it reached 78 million in 2020 and is expected to reach 139 million in 2050 [3, 4]. This huge number of patients has created growing public health concerns with a substantial economic burden; the estimated cost of dementia was 818 billion USD in 2015 [5]. The prevalence of dementia is higher in women than in men. It is also associated with age: the prevalence is about 0.8% in individuals aged over 65 years and 28.5% in individuals aged over 90 years [6]. The etiology of dementia is complex with combined modifiable effects (diabetes, depression, hypertension, obesity, and smoking) [7–10] and genetic factors [11]. Therefore, we aim to determine the potential modifiable risk factors for dementia.

Recent evidence has shown that gout is conversely related to the risk of dementia development. Both diseases share similar pathogenic pathways [12]. Uric acid (UA) might reduce oxidative stress [13, 14] and deplete beta-amyloid [15]. However, the relationship of gout with dementia is conflicting in extensive epidemiological studies, ranging from a positive association [16] to an inverse association [17]. Thus, whether gout increases or decreases the risk of dementia remains unclear.

To address these conflicts, our team used systematic review and meta-analysis to determine the relationship of gout with dementia risk.

2 | Methods

Our research protocol was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (ID: INPLASY2025110018). Our team executed a systematic review with meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines [18, 19]. Details of data information collection are shown in Table S1.

2.1 | Search Strategy

We conducted a comprehensive and systematic literature search of PubMed, EMBASE, Scopus, and Web of Science from database inception through December 1, 2022. The search strategy was developed to maximize sensitivity and minimize the risk of missing relevant studies by combining controlled vocabulary terms (including Medical Subject Headings [MeSH]) with free-text keywords related to gout and dementia.

A stepwise Boolean approach was applied, in which outcome-related terms (including dementia, Alzheimer disease, and cognitive impairment) were first combined using the OR operator and subsequently intersected with exposure-related terms (gout) using the AND operator. Database-specific indexing ensured that studies using alternative terminology were captured through concept mapping during retrieval. The full PubMed search strategy, including Boolean operators and term combinations, is provided in Table S2.

To further enhance completeness, we performed manual searches of reference lists from all eligible articles, relevant reviews, and prior meta-analyses. No language restrictions were applied during the search process.

2.2 | Eligibility Criteria

Eligibility was restricted to observational studies (case–control, cohort, and cross-sectional) which evaluated the relationship of gout with the risk of any kind of dementia as a primary outcome. We included studies if (i) their outcome of interest was the risk of dementia, (ii) they had been published in English, (iii) they included at least 40 participants and provided clear information regarding selection criteria for gout and dementia, and (iv) they provided effect sizes with 95% confidence intervals (CIs) and adjusted risk factors. Our study excluded abstracts, letters to editors, case reports, short communications, and reviews.

2.3 | Selection Process

Two authors screened the titles and abstracts of all recruited articles separately. Connected with the previously developed study selection criteria, these 2 authors separately selected relevant researches. If any disagreement arose in the study selection process, it was settled by consultation with the corresponding author. The very 2 authors established data collection forms to extract the required data from selected studies. Both authors examined the extracted information for duplications by checking the first author's first and last name, publication year, and journal name.

2.4 | Data Extraction

The primary outcome measure was pooled adjusted risk ratios (RRs) with the respective 95% CIs for the relationship of gout with overall dementia risk. We identified adjusted odds ratios (ORs) and hazard ratios (HRs) with 95% CIs and possible confounding factors. We also extracted the name of the first author, study design, publication year, country, data collection period, follow-up time, percentage of male and female participants, age, selection criteria for gout and dementia patients, and study population.

2.5 | Assessment for Risk of Bias

Two authors assessed the risk on the basis of each study applying the Newcastle-Ottawa Scale (NOS) separately [19–21]. They categorized the selected researches into low, moderate, and high risk of bias based on the number of points they received. Moreover, they determined the heterogeneity among study-specific RRs using the Q statistic, the I^2 statistic, and τ^2. We used the Egger's test method to evaluate publication bias.

2.6 | Statistical Analysis

We conducted the meta-analysis by using the relevant studies that provided adjusted ORs/HRs of the relationship of gout with overall dementia. We calculated the pooled adjusted RRs with

95% CIs by using the random-effects method. We drew forest plots to present the overall effect size visually. Moreover, we generated a funnel plot to show publication bias. We performed all analyses by using the meta-analysis software.

3 | Results

3.1 | Study Selection

Initial searches performed in PubMed, EMBASE, Scopus, and Web of Science yielded 1250 studies. After eliminating duplicates and checking titles and abstracts, our team removed 346 articles because of the absence of inclusion criteria. We inspected 9 full-text articles and checked their citation lists for important articles. From this report, our team eliminated four studies due to review and inappropriate study design. Finally, we included five studies in the meta-analysis [12, 16, 17, 22, 23]. Figure 1 demonstrates the flow chart of the systematic literature review.

3.2 | Study Characteristics and Study Quality

We included 5 observational researches in our study (Table 1). The publication year started since 2015 through 2022. Overall, the studies enrolled 227 419 adults with gout who were men and women of all ages. There were five cohort studies [12, 16, 17, 22, 23], which used a standard protocol to select patients with gout and dementia. Two authors determined the quality of the assessed researches by using the NOS, which is suggested by Cochrane to determine non-randomized studies. The NOS scores ranged from 8 to 9 (9 is the highest score), with a mean of 8.2 and a median and mode of 8.

3.3 | Meta-Analysis

3.3.1 | Gout and Dementia Risk

This meta-analysis comprised five studies with 227 419 gout patients. In the pooled analysis, gout and overall dementia association was not significant with an adjusted pooled RR of 0.80 (95% CI: 0.58–1.10, $p = 0.17$). There was significant heterogeneity within these 5 studies ($Q = 541.59$, $I^2 = 99.26$, $\tau^2 = 0.12$, $p < 0.001$) (Figure 2).

3.3.2 | Gout and Alzheimer's Disease Risk

Four studies evaluated the risk of AD in gout patients. There was a negative relationship of gout with AD risk RR of 0.70 (95% CI: 0.62–0.78, $p < 0.001$). There existed moderate heterogeneity in the four studies ($Q = 7.39$, $I^2 = 59.40$, $\tau^2 = 0.008$, $p = 0.06$).

3.3.3 | Gout and Cognitive Impairment Risk

Three studies examined the risk of cognitive impairment in patients with gout. The pooled analysis of the overall gout

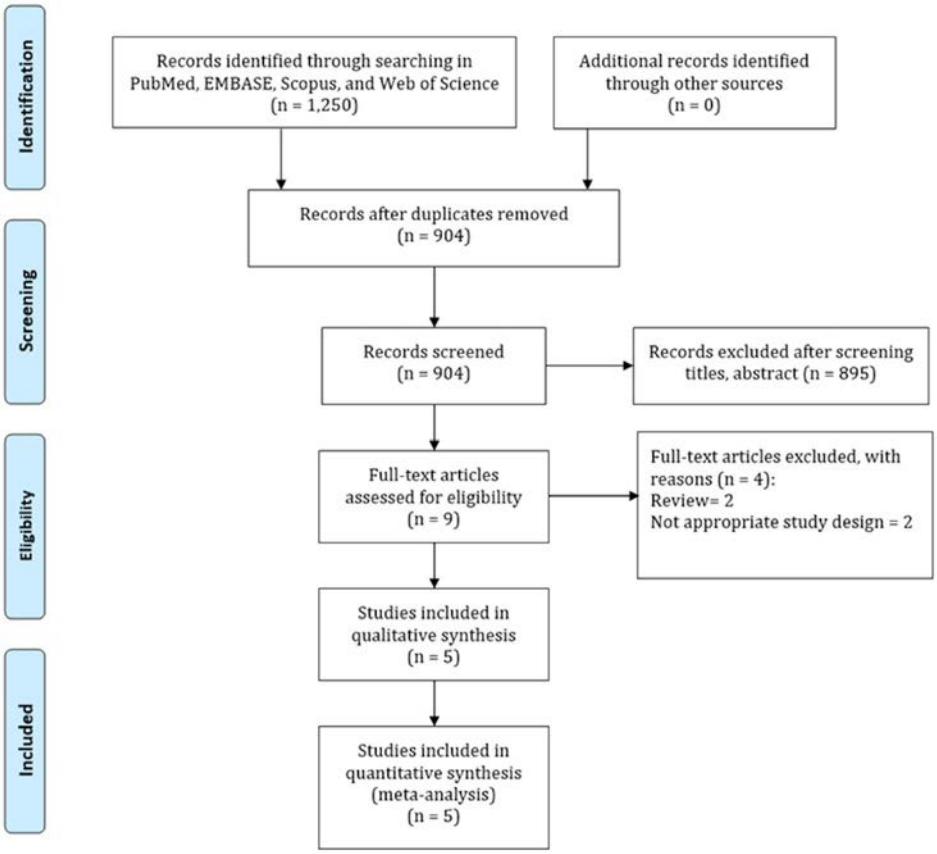

FIGURE 1 | Search strategy for the association between gout and dementia risk.

TABLE 1 | Observational researches involved in the systematic review and meta-analysis.

Author	Year	Country	Study design	Study participant (2 groups)	Age (year in 2 groups)	Gender (% male in 2 groups)	Inclusion criteria for gastric cancer	Adjustment	NOS
Kim	2022	South Korea	Cohort	5052/25 260	Reported as group	92.4/92.4	ICD	Age, sex, income, HTN, DM, dyslipidemia, stroke, depression	9
Min	2021	South Korea	Cohort	22 718/113 590	72.29/72.29	62.5/62.5	ICD	Age, sex, CVDs	8
A.Singh	2018	United States	Cohort	111 656/1 601 165	80.0/74.9	32.9/43.3	ICD	Age, sex, HTN, hyperlipidemia, CAD	8
Lu	2016	United Kingdom	Cohort	59 224/238 805	65.3/65.3	70.8/71.1	ICD	BMI, cardiovascular disease, SDI	8
Hong	2015	South Korea	Cohort	28 769/114 742	63.5/63.5	63.4/63.4	ICD	Age, DM, HTN, COPD	8

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVDs, cardiovascular diseases; DM, diabetes mellitus; HTN, hypertension; ICD, international classification of diseases; NOS, Newcastle-Ottawa Scale; SDI, social deprivation index.

association with cognitive impairment was significant, with a decreased associated risk of 32% for cognitive impairment development RR of 0.68 (95% CI: 0.48–0.95, $p = 0.02$). There existed significant heterogeneity in the three studies ($Q = 23.08$, $I^2 = 91.33$, $\tau^2 = 0.07$, $p < 0.001$).

3.3.4 | Subgroup Analyses

We also carried out subgroup analyses depended on research design along with region (Table 2). No stratifications affected the overall effect size and the observed heterogeneity among the included studies. Gout was related with a decreased risk of dementia in the cohort studies. However, the reduction in risk of dementia was insignificant. Gout was related to a diminished risk of dementia in parts of studies accomplished in Asia. Analogous trend was noted in Western population, although this was insignificant neither.

3.4 | Publication Bias

Figure 3 shows no publication bias significantly, both quantitative by Egger's regression test ($p = 0.34$) and visual representation (funnel plot).

4 | Discussion

Our study provides an up-to-date evaluation of the relationship of gout with the risk of dementia. We found results from population-based observational studies evaluating the potential protective effect of gout on the risk of dementia. Moreover, there was an inverse risk of AD and cognitive impairment in patients with gout. The findings from studies carried out in Asian countries indicated an inverse risk of dementia among people with gout. There was no relationship of gout with dementia risk from studies published in Western countries.

The possible biological mechanisms behind the reported inverse relationship of gout with dementia remain unclear. A previous study mentioned that UA might have antioxidant properties [24], namely potential peroxynitrite and hydroxyl radical scavengers to reduce oxidative stress [25]. The neuroprotective effects of gout can be explained by UA that is linked to suppression of oxyradical accumulation and preservation of mitochondrial function [15]. UA likely inhibits the cytotoxic action of lactoperoxidase [26] as well as stops free radical induced deoxyribonucleic acid destruction [27].

A meta-analysis reported that abnormal oxidative stress in serum, erythrocytes, and circulating lymphocytes is a key factor for AD [28]. UA is related to the elevated accumulation of oxygen and hydroperoxyl radicals, which are able to make iron ions complexes stable [29, 30]. However, the reduced level of UA is linked to weaker protection of oxidative stress, which might lead to an increased risk of cognitive dysfunction. Latourte et al. [31] evaluated the relationship of blood UA with dementia and showed a more powerful relationship with vascular or mixed dementia HR of 3.66 (95% CI: 1.29–10.41) than AD HR of 1.55 (95% CI: 0.92–2.61). Previous studies reported that C-reactive

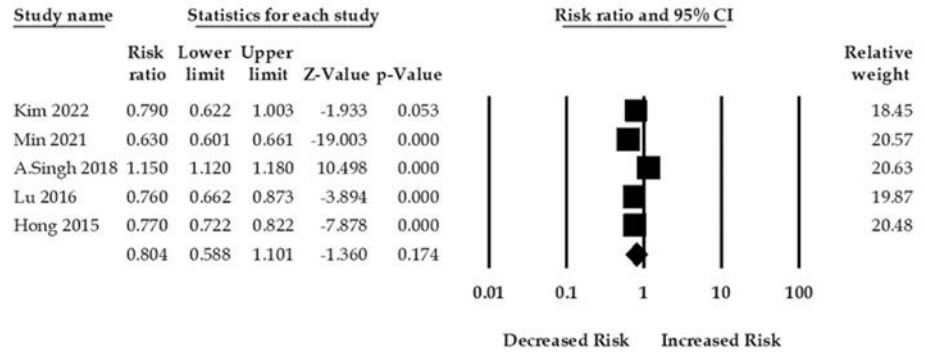

FIGURE 2 | Association between gout and overall dementia risk.

TABLE 2 | Subgroup analyses for the association between gout and dementia risk.

		Pooled estimates		Test of heterogeneity		
Studies	**Number of studies**	**RR (95% CI)**	***p***	***Q***	***p***	I^2 **(%)**
All studies	5	0.80 (0.58–1.10)	< 0.001	541.59	< 0.001	99.26
Study design						
Cohort	5	0.80 (0.58–1.10)	< 0.001	541.59	< 0.001	99.26
Region						
Asian	3	0.71 (0.60–0.84)	< 0.001	25.40	< 0.001	92.12
Western	2	0.94 (0.62–1.41)	0.76	33.35	< 0.001	97.00

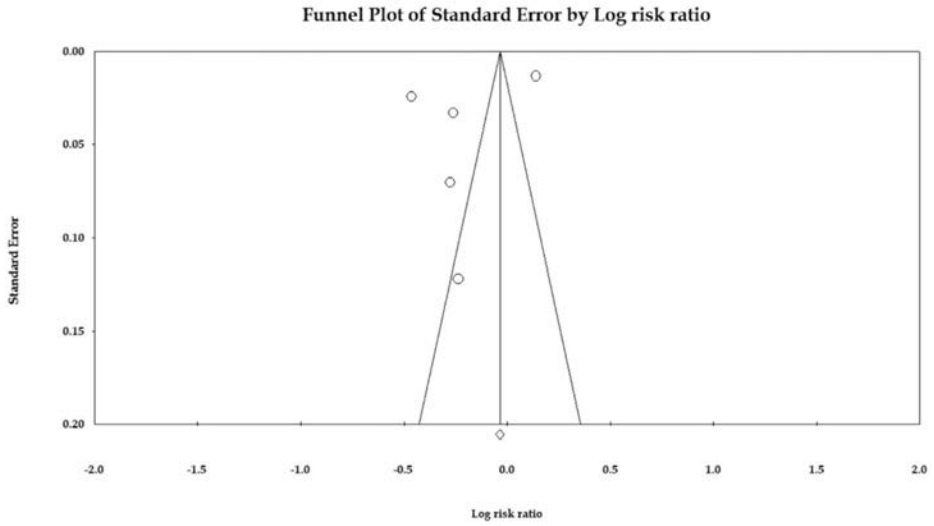

FIGURE 3 | Funnel plot for the association between gout and dementia risk.

protein (CRP) is also a biomarker of inflammation and a higher level of CRP in the brain can lead to all-cause dementia with OR of 3.0 (95% CI: 1.2–7.3) [32]. Moreover, Hsu's research team [33] performed one prospective investigation to examine the relationship of CRP with the risk of dementia in geriatric Asian participants. The investigation showed a 55% higher risk of dementia with HR of 1.55 (95% CI: 1.21–2.00) among patients with a higher CRP level compared to those with a normal CRP level. However, it is reported that gout is related to an elevated level of inflammatory markers including CRP, interleukin (IL)-1, and IL-6 [34, 35].

There are some strengths in our study. First, this is a pioneer systematic review and meta-analysis that has evaluated the relationship of gout with risk of dementia. Second, we found a regional effect regarding the relationship of gout with risk of dementia. Nevertheless, our research has several limitations. First, we included only five articles to assess the risk of dementia among people with gout. Second, we only included observational studies to evaluate the risk of dementia and all the studies were population-based cohort studies. Therefore, there is a limitation to compare differences between the two study designs (case–control and cohort). Case–control studies are needed to

calculate and compare the actual effect size. Third, we could not evaluate the duration of gout and risk of dementia because of data shortage in retrieved articles.

5 | Conclusion

In this systematic review and meta-analysis of observational studies, gout was not significantly associated with overall dementia risk, although inverse associations were observed for certain dementia subtypes. The mechanisms underlying these findings remain uncertain and cannot be established from observational data. Further well-designed prospective studies and randomized clinical trials are needed to clarify causality and to investigate potential biological pathways linking gout and neurodegeneration.

Author Contributions

Yao-Chin Wang: conceptualization, methodology, investigation, writing – original draft. Abel Po-Hao Huang: data curation, resources, validation. Chih-Wei Huang project administration, visualization. Md. Mohaimenul Islam: software, formal analysis. Woon-Man Kung: validation, writing – reviewing and editing, supervision. All authors read and approved the final manuscript.

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Ethics Statement

This article analyzed de-identified individual participant data from previously published studies. Therefore, formal ethical approval and informed consent are not required. No new data involving human participants or animals were collected by any of the authors. We adhere to all relevant data protection standards and ethical guidelines for secondary data analysis.

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 from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Details of data information collection from PRISMA 2020 Checklist. **Table S2:** Search strategy.

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LETTER TO THE EDITOR

Hepatic Lesions With Eosinophilic Granulomatosis With Polyangiitis

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Dear Editor,

Case 1

A 66-year-old male with no previous medical history presented with fever and right upper quadrant pain. Laboratory investigations revealed eosinophilia (1579/μL), elevated C reactive protein [CRP]: 15.81 mg/dL, and elevated serum liver enzymes (aspartate aminotransferase concentration [AST]: 65 U/L, alanine aminotransferase [ALT]: 115 U/L, alkaline phosphatase [ALP]: 412 U, and γ-glutamyl transferase [GTP]: 97 U/L) (Table S1). Contrast CT revealed multiple low-attenuation lesions in the liver (Figure 1A). A liver abscess was initially considered, and antimicrobial therapy was started. However, the fever persisted, and the eosinophil count increased. A liver biopsy revealed multiple foci of hepatocellular necrosis with eosinophilic infiltration (Figure 1B). Bone marrow aspiration revealed a normocellular bone marrow with excess eosinophils. On Day 16, MPO-ANCA was elevated (46 EU), though definitive diagnosis remained elusive. Prednisolone (PSL) 1 mg/kg/day (60 mg/day) was initiated as a therapeutic trial due to suspected secondary hypereosinophilic syndromes, after which the fever subsided and the eosinophil count and CRP levels decreased. The dose of PSL was reduced to 25 mg/day, and the patient was referred to our hospital on Day 29 for further work-up. While gradually reducing PSL to 10 mg/day over 2 weeks, the patient experienced asthma attacks and sensory neuropathy in the upper extremities, alongside recurrent elevations in eosinophils (from 0 to 404 μL) and CRP levels (from 0.03 to 6.46 mg/dL). These findings, alongside eosinophilic infiltration of the liver, led to a diagnosis of EGPA, with a baseline Birmingham Vasculitis Activity Score version 3 (BVAS-3) of 7. We classified the patient as having EGPA with a total of 11 points (≥6), including a history of bronchial asthma (+3), neuropathy (+1), a eosinophil count $\geq 1 \times 10^9$/L (+5), and a biopsy finding of extravascular eosinophilic inflammation (+2) [1]. The patient was discharged after increasing PSL to 30 mg/day and confirming the absence of new organ damage. During steroid tapering, the patient experienced recurrent elevations in eosinophils and hepatobiliary enzymes, indicating relapses. Mepolizumab (300 mg/4 weeks) was given, and the patient has since been maintained on PSL 3 mg/day for more than 2 years (BVAS-3: 0) (Figure S1A).

Case 2

A 39-year-old male with a history of asthma and eosinophilic sinusitis presented with jaundice, right upper quadrant pain, paresthesia, and purpura and plantarflexion impairment in both lower extremities for 1 week. Blood tests on admission showed eosinophilia (11 119/μL) and elevated CRP level (1.89 mg/dL), total bilirubin (7.3 mg/dL), direct bilirubin (5.6 mg/dL), and liver enzymes (AST: 45 U/L, ALT: 71 U/L, ALP: 496 U/L, GTP: 34 U/L). ANCA serology was negative (Table S1). Nerve conduction studies revealed sensorimotor multiple mononeuropathy of the lower extremities. Skin biopsy of the lower leg purpura revealed perivascular eosinophilic infiltration (Figure S2). Liver biopsy revealed portal inflammation and central venulitis with marked eosinophilic infiltration (Figure 1C–E) and was diagnosed with EGPA (baseline BVAS-3: 21). He was classified as having EGPA based on a total score of 10 points, including a history of bronchial asthma (+3), multiple mononeuropathy (+1), an eosinophil count $\geq 1 \times 10^9$/L (+5), biopsy finding of extravascular

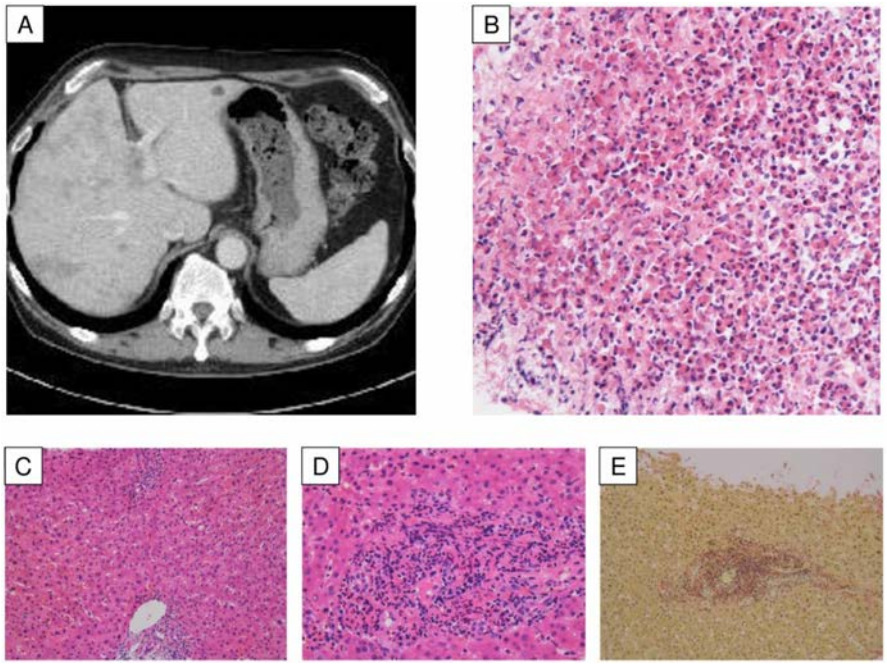

FIGURE 1 | (A) Hepatic involvement of eosinophilic granulomatosis with polyangiitis. Contrast computed tomography scan revealed multiple hepatic hypoattenuations in the liver. (B) Histological examination of the liver specimen obtained via needle biopsy in Case 1. Eosinophilic infiltration of the portal areas, sinusoids, and hepatocytes was seen. Hepatocellular necrosis and fibrin deposition were also observed (Hematoxylin–eosin [H&E] staining; original magnification ×400). (C–E) Histological examination of the liver specimen obtained via needle biopsy in Case 2. Eosinophilic infiltrates were seen in the portal area (C; H&E staining; original magnification ×200). Inflammatory cell infiltration was observed in the hepatic artery, presenting as vasculitis (D, E; H&E staining; original magnification ×400, Elastic Van Gieson staining; original magnification ×200, respectively).

eosinophilic inflammation (+2), and hematuria (−1) [1]. On day 4, a quarter dose of methylprednisolone (mPSL) (250 mg/day for 3 days) was started, followed by 1 mg/kg/day (60 mg/day). After treatment, eosinophil count, CRP level, and hepatobiliary enzymes decreased. The patient achieved remission with mepolizumab (300 mg/4 weeks) and PSL 2 mg/day (BVAS-3: 3) (Figure S1B).

Hepatic involvement in EGPA is highly uncommon, but our cases highlight the importance of recognizing this disease. Several investigators reported newly diagnosed EGPA in which pathological examination of liver biopsy revealed eosinophilic liver infiltration, and we summarized them in Table 1, including our two cases. Clinically, our two cases, along with previously reported cases [2–4, 6], presented with right upper quadrant pain and cholestatic liver dysfunction as the initial symptom of EGPA, which was eventually diagnosed by liver biopsy. Possible mechanisms for right upper quadrant pain in EGPA include periportal eosinophilic inflammation, hepatic capsular distension caused by inflammatory edema, and ischemia resulting from small-vessel vasculitis. In this regard, it is crucial to recognize that EGPA can initially manifest in the liver—preceding systemic hypereosinophilia and neurological involvement—to ensure prompt and accurate diagnosis. EGPA has largely nonspecific imaging findings, such as hepatomegaly or even normal presentations [2, 3, 5, 6]. A previous study demonstrated portal eosinophilic infiltration, fibrinoid necrosis of vessels, and granuloma formation [2–7]. To our knowledge, this is the first reported case of EGPA with pathologically confirmed hepatocellular necrosis and radiologically identified multiple liver mass lesions. Eosinophil-derived cytotoxins, such as major basic protein [8], can cause hepatocyte necrosis, appearing as multiple hepatic hypoattenuations.

Despite being extremely rare, it is important to recognize that EGPA can affect the liver and multiple hepatic hypoattenuations can be observed. Thus, in patients with eosinophilia presenting with right upper quadrant pain and elevated hepatobiliary enzymes, liver biopsy can be a valuable diagnostic tool for identifying EGPA.

TABLE 1 | Summary of case reports on biopsy-proven eosinophilic liver involvement in eosinophilic granulomatosis with polyangiitis.

	Initial clinical findings										
	Abdominal pain	Fever	Cholestatic liver dysfunction	HE	ANCA positivity	Liver imaging findings	Pathological findings	Other organ damage	Treatment	Outcome	Ref.
56/M	−	+	+	−	Negative	Hepatomegaly	Arterial fibrinoid necrosis with a granulomatous reaction and eosinophilic infiltration in the portal area	Asthma, neuropathy	mPSL 1000 mg, followed by PSL 1 mg/kg/day	Remission	[2]
64/M	+, RUQ	+	−	+	MPO-ANCA [150 EU (<10)]	Normal	Eosinophilic infiltrates and fibrinoid necrosis of small-size and medium-sized vessels in the portal triads	Asthma	Steroid and azathioprine	Remission	[3]
27/M	+, RUQ	+	+	+	Negative	NA	Chronic hepatitis of minimal activity with mild portal fibrosis and eosinophilic portal vasculitis	Asthma	Azathioprine 50 mg/day and mPSL 40 mg/day	Remission	[4]
5/M	−	+	NA	+	MPO-ANCA [4 IU/mL]	Mild hepatomegaly	Eosinophilic infiltrates in the portal area, necrotizing granuloma, eosinophil-rich non-necrotizing vasculitis of the portal vein	−	NA	NA	[5]
36/F	−	+	+	+	p-ANCA weakly positive, PR3-ANCA [12 IU/mL (0–10)]	Periportal hypoattenuation	Necrotizing granulomas with infiltration of eosinophils	Asthma, sinusitis	PSL 20 mg/day, reducing by 2.5 mg daily every week to 7.5 mg/day	Remission	[6]
66/F	+	NA	NA	NA	MPO-ANCA	Liver cirrhosis	Eosinophilic infiltrate, granulomatous formation, and vasculitis	Asthma	Cyclophosphamide	Remission	[7]

(Continues)

TABLE 1 | (Continued)

	Initial clinical findings										
	Abdominal pain	Fever	Cholestatic liver dysfunction	HE	ANCA positivity	Liver imaging findings	Pathological findings	Other organ damage	Treatment	Outcome	Ref.
Our Case 1	+, RUQ	+	+	+	MPO-ANCA [46 EU (0–19)]	Multiple hepatic hypoattenuations	Hepatocellular necrosis with eosinophilic infiltration	Asthma, neuropathy	Initial PSL 60 mg/day; 13 years later, PSL 3 mg plus Mepolizumab 300 mg/4 weeks	Remission	
Our Case 2	+, RUQ	+	+	+	Negative	Normal	Portal inflammation and central venulitis, marked eosinophilic infiltration	Asthma, purpura, neuropathy	mPSL 250 mg, followed by PSL 60 mg/day; 2 years later, PSL 2 mg and Mepolizumab 300 mg/4 weeks	Remission	

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; F, Female; HE, Hypereosinophilia; M, Male; MPO-ANCA, myeloperoxidase-specific-antineutrophil cytoplasmic antibodies; mPSL, methylprednisolone; NA, not available; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PR3-ANCA, proteinase-3-antineutrophil cytoplasmic antibodies; PSL, prednisolone; RUQ, right upper quadrant.

Author Contributions

M.W., H.Y., and H.K. were involved in the clinical care of the patients. M.W. and H.Y. contributed to the interpretation of the clinical course of this case. M.W. drafted the manuscript, and the other authors critically revised it for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The authors have nothing to report.

Ethics Statement

All procedures were conducted in accordance with the ethical principles enshrined in the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient for the publication of this case 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.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Clinical course of each patient (A; case 1, B; case 2, respectively). **Figure S2:** Skin biopsy of Case 2. The vascular walls exhibit fibrinoid necrotic degeneration, indicative of fibrinoid vasculitis (A). Extensive eosinophilic infiltration is present throughout the subcutaneous tissue (B). **Table S1:** Laboratory data from the time of admission.

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EDITORIAL

What Is the Role of Alendronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women? - A Cochrane Review Summary With Commentary

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The aim of this commentary is to discuss the Cochrane Review "Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women" [1] by Wells et al.,[a] published in the Cochrane Library. This Cochrane Corner is produced in agreement with *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation with views[b] of the review summary author in the "implications for practice" section.

1 | Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration, leading to increased bone fragility and a higher risk of fractures [2]. Postmenopausal women are particularly vulnerable due to the rapid decline in estrogen levels, which accelerates bone loss [3]. Osteoporotic fractures, especially those of the hip, spine, and wrist, are associated with significant morbidity, mortality, reduced quality of life, and increased healthcare costs [4]. Bisphosphonates such as alendronate are potent inhibitors of osteoclast-mediated bone resorption and are widely considered first-line agents for the prevention and treatment of osteoporosis, as they effectively reduce bone loss and the risk of fragility fractures [5]. This Cochrane systematic review [1] aimed to evaluate the efficacy and safety of alendronate for the prevention of osteoporotic fractures in postmenopausal women categorized into primary or secondary prevention groups based on baseline osteoporosis severity and fracture risk.

2 | Alendronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women [1]

(Wells GA, Hsieh SC, Peterson J, Zheng C, Kelly SE, Shea B, Tugwell P. 2025).

2.1 | What Is the Aim of This Cochrane Review?

The aim of this Cochrane Review [1] was to assess and update the current evidence regarding the efficacy and safety of

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2025, Issue 1, Art. No.: CD001155, DOI: 10.1002/14651858.CD001155.pub3 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.
[b]The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women at lower and higher risk of fracture.

2.2 | What Was Studied in the Cochrane Review?

The population of interest in this review [1] included postmenopausal women without significant underlying diseases, who were at an increased (low or high) risk of osteoporotic fractures and received at least one year of treatment with alendronate, placebo, or other anti-osteoporotic medications.

Eligibility criteria for primary or secondary prevention were based on the presence of a clinical diagnosis of osteoporosis, a history of vertebral fractures, a low bone mineral density (T score ≤ -2.5), or being aged ≥ 75 years.

Participants with lower fracture risk were classified under primary prevention, while those with higher fracture risk were considered under secondary prevention.

The major outcomes assessed were clinical vertebral fractures, nonvertebral fractures, hip fractures, wrist fractures, withdrawals due to adverse events, and serious adverse events.

2.3 | What Was the Search Methodology and Search Date of the Cochrane Review?

The Cochrane review [1] searched for studies published up to February 2023 using a comprehensive strategy that included CENTRAL, MEDLINE, Embase, clinical trial registries (ClinicalTrials.gov, WHO ICTRP), and regulatory agency websites (FDA, EMA, Health Canada), without applying any restrictions on language, date, publication format, or reported outcomes.

2.4 | What Are the Main Results of the Cochrane Review?

The Cochrane review included a total of 119 randomized controlled trials, of which 102 contributed data to the quantitative synthesis. Among these, 34 studies (15 188 participants) focused on primary prevention and 68 studies (29 577 participants) on secondary prevention of osteoporotic fractures in postmenopausal women. Methodological concerns were common; only 20 studies (19%) adequately reported both sequence generation and allocation concealment, and just 8 studies (8%) were assessed as low risk of bias across all seven domains.

The Cochrane review included a total of 34 studies on primary prevention and 68 on secondary prevention. However, the primary analyses were based on a subset of 16 primary prevention studies (10 057 participants, 1–5 years in duration) and 20 secondary prevention studies (7375 participants, 1–3 years in duration). These studies were selected because they provided placebo-controlled data using the standard dose of alendronate (10 mg/day or 70 mg/week), with sufficient follow-up and outcomes appropriate for meta-analysis. Limitations such as indirectness, imprecision, and risk of bias contributed to downgrading the certainty of the evidence across most outcomes.

2.4.1 | Alendronate 10 mg/day Compared to Placebo for the Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women

2.4.1.1 | Vertebral Fractures. Alendronate probably results in a clinically important reduction in clinical vertebral fractures (24 events in 1114 women in the alendronate group versus 51 events in 1055 women in the control group). (Risk Ratio (RR) 0.45, 95% Confidence Interval (CI) 0.28 to 0.73; Absolute Risk Reduction (ARR) 2.7% fewer, 95% CI 3.5% fewer to 1.3% fewer; moderate-certainty evidence).

2.4.1.2 | Nonvertebral Fractures. Alendronate may reduce nonvertebral fracture risk (RR 0.80, 95% CI 0.64 to 0.99; ARR 2.8% fewer, 95% CI 5.1% fewer to 0.1% fewer; low-certainty evidence).

2.4.1.3 | Hip Fractures. Alendronate may reduce hip fracture risk (RR 0.49, 95% CI 0.25 to 0.96), corresponding to 1 fewer hip fracture per 100 women (ARR 1.0% fewer, 95% CI 1.5% fewer to 0.1% fewer; low-certainty evidence).

2.4.1.4 | Wrist Fractures. Alendronate may reduce wrist fracture risk (RR 0.54, 95% CI 0.33 to 0.90; ARR 1.8% fewer, 95% CI 2.6% fewer to 0.4% fewer; low-certainty evidence).

2.4.1.5 | Serious Adverse Events. Alendronate may reduce serious adverse events (RR 0.75, 95% CI 0.59 to 0.96; ARR 3.5% fewer, 95% CI 5.8% fewer to 0.6% fewer; low-certainty evidence).

2.4.1.6 | Withdrawals Due to Adverse Events. The effect of alendronate on treatment discontinuation due to adverse events is very uncertain. (RR 0.95, 95% CI 0.78 to 1.16; ARR 0.4% fewer, 95% CI 1.7% fewer to 1.3% more; very low-certainty evidence).

2.4.2 | | Alendronate 10 mg/day Compared to Placebo for the Primary Prevention of Osteoporotic Fractures in Postmenopausal Women

2.4.2.1 | Vertebral Fractures. Alendronate may reduce clinical vertebral fracture risk (16 events in 1190 women in the alendronate group versus 24 events in 926 women in the control group), with a 55% relative risk reduction (RR 0.45, 95% CI 0.25 to 0.84; ARR 1.4% fewer, 95% CI 1.9% fewer to 0.4% fewer; low-certainty evidence).

2.4.2.2 | Nonvertebral Fractures. Alendronate may reduce nonvertebral fracture risk (RR 0.83, 95% CI 0.72 to 0.97; ARR 1.6% fewer, 95% CI 2.6% fewer to 0.3% fewer; low-certainty evidence).

2.4.2.3 | Hip Fractures. The effect of alendronate on hip fractures is uncertain (RR 0.76, 95% CI 0.43 to 1.32; ARR 0.2% fewer, 95% CI 0.4% fewer to 0.2% more; low-certainty evidence).

2.4.2.4 | Wrist Fractures. The effect of alendronate on wrist fractures is uncertain (RR 1.12, 95% CI 0.84 to 1.49; ARR 0.3% more, 95% CI 0.4% fewer to 1.1% more; low-certainty evidence).

2.4.2.5 | Serious Adverse Events. Alendronate may have little to no effect on serious adverse events (RR 1.08, 95% CI 0.82 to 1.43; ARR 0.5% more, 95% CI 1.2% fewer to 2.8% more; low-certainty evidence).

2.4.2.6 | Withdrawals Due to Adverse Events. Alendronate may have little to no effect on treatment discontinuation due to adverse events (RR 1.03, 95% CI 0.89 to 1.18; ARR 0.2% more, 95% CI 0.9% fewer to 1.5% more; low-certainty evidence).

2.5 | What Did the Authors Conclude?

In this Cochrane review [1], the authors concluded that alendronate 10 mg/day probably results in a clinically important reduction in clinical vertebral fractures in postmenopausal women undergoing secondary prevention. It may also reduce nonvertebral, hip, and wrist fractures, as well as serious adverse events, although the certainty of this evidence is low. However, the effect of alendronate on withdrawals due to adverse events is very uncertain.

For primary prevention, alendronate 10 mg/day may reduce clinical vertebral and nonvertebral fractures, but its effects on hip and wrist fractures, serious adverse events, and treatment discontinuation are likely minimal or uncertain, with wide CIs and low-certainty evidence. The authors emphasized that indirectness, imprecision, and risk of bias in the included studies contributed to downgrading the certainty of the evidence across most outcomes.

3 | What Are the Implications of the Cochrane Evidence for Practice in Rheumatology?

Osteoporotic fractures, particularly those involving the hip and spine, are associated with substantial morbidity, increased mortality, and a significant decline in quality of life. Notably, a significant proportion of these fragility fractures occur in postmenopausal women with osteopenia—defined by reduced bone mineral density that does not reach the diagnostic threshold for osteoporosis. Additionally, the occurrence of a prior osteoporotic fracture significantly elevates the risk of subsequent fractures, with the highest risk observed within the first 2 years following the initial event. These considerations highlight the critical importance of implementing effective strategies to prevent further bone loss and mitigate fracture risk in postmenopausal women [6, 7].

The current Cochrane review assessed alendronate 10 mg/day for fracture prevention in postmenopausal women. In secondary prevention, alendronate likely reduces clinical vertebral fracture risk and also of nonvertebral, hip, and wrist fractures. In primary prevention, it may reduce risk of vertebral and nonvertebral fractures, though effects on hip and wrist fractures remain uncertain. Serious adverse events did not differ significantly from placebo, and no cases of osteonecrosis of the jaw or atypical femoral fractures were reported [1].

Current clinical guidelines recommend bisphosphonates, including alendronate, as first-line therapy for the management of postmenopausal osteoporosis. The National Osteoporosis Guideline Group (NOGG) 2024 advises prescribing oral alendronate (70 mg weekly or 10 mg daily) for at least 5 years, followed by reassessment of fracture risk, with longer treatment durations recommended in women over 70 years or those with prior fragility fractures, ongoing glucocorticoid therapy, or new fractures during treatment [6]. The Bone Health and Osteoporosis Foundation (BHOF) 2022 similarly recommends alendronate as a front-line agent, citing its ability to reduce spine and hip fracture risk by about 50% over 3 years in patients with prior fractures [7]. Meanwhile, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), in collaboration with the International Osteoporosis Foundation (IOF), considers alendronate among the preferred agents for women at high fracture risk, particularly those with a recent fragility fracture, and supports its use in sequential regimens following anabolic therapy [8].

From a rehabilitation perspective, these findings underscore the importance of integrating pharmacological interventions like alendronate into comprehensive management plans for postmenopausal women at risk of osteoporotic fractures. Preventing initial and subsequent fractures is crucial to maintaining functional independence and reducing the burden on rehabilitation services. However, the modest benefits observed in primary prevention highlight the need for individualized risk assessment, considering factors such as bone mineral density, age, prior fracture history, and fall risk [1, 6–8].

In addition to pharmacotherapy, nonpharmacological strategies are integral to osteoporosis management and rehabilitation. Exercise programs focusing on weight-bearing and resistance training can improve bone density and reduce fall risk [9]. Fall prevention measures, including home safety assessments and balance training, are essential components of a holistic approach. Nutritional support, ensuring adequate calcium and vitamin D intake, further complements these interventions [6, 7, 10–12].

Author Contributions

It has been confirmed that the author is solely responsible for the preparation of this article.

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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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ORIGINAL ARTICLE OPEN ACCESS

Can a Targeted Pre-Exercise Education Intervention Enhance the Exercise-Induced Hypoalgesia (EIH) Response in Individuals With Knee Osteoarthritis (OA)?

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ABSTRACT

Objective: Recent evidence suggests that education on the pain-relieving effects of exercise may enhance exercise-induced hypoalgesia (EIH) in healthy individuals. However, its impact in populations with osteoarthritis (OA), where EIH responses are more variable, remains unclear. This study examined whether positive pre-exercise education enhances EIH in individuals with knee OA.

Methods: A double-blind, randomized controlled trial was conducted with 42 participants allocated to either a positive pre-exercise education group ($n = 21$) or a control education group ($n = 21$). Each group received two individual education sessions 24–72 h apart. OA- and EIH-related knowledge and beliefs were assessed pre- and post-education. EIH was evaluated following a single submaximal isometric quadriceps contraction to failure by measuring changes in pressure pain thresholds (PPTs), resting pain, and pain during stepping. Group differences were analyzed using ANCOVA.

Results: The positive pre-exercise education group demonstrated greater improvements in EIH-related knowledge and beliefs compared to the control group ($p = 0.001$, $d = 0.50$, ANCOVA between-group analysis), while OA-related knowledge and beliefs remained unchanged ($p = 0.34$, $d = 0.15$). However, ANCOVA results showed no significant between-group differences in pre- to post-exercise changes in PPTs, resting pain, or pain during stepping (all $p > 0.11$, $d = 0.04–0.25$).

Conclusion: Despite enhancing beliefs about exercise-induced pain relief, positive pre-exercise education did not enhance EIH compared to control education. These findings highlight the need for alternative strategies to optimize exercise-induced pain relief in OA.

1 | Background

Knee osteoarthritis (OA) is a prevalent and disabling condition, incurring substantial healthcare and economic costs [1]. Exercise is recommended as the first line of intervention by international evidence-based guidelines [2], and is one of the most well-documented interventions for alleviating pain and enhancing physical function in people with knee OA [3, 4]. Despite being universally recommended, exercise interventions continue to be underutilized by patients and clinicians [5, 6]. One reason for this is that the pain-relieving effects of exercise are variable across individuals, both initially and over the course of an exercise programme [7, 8]. In particular, at the beginning of an exercise programme some individuals experience exercise-induced flares in pain [9], which can negatively affect exercise adherence [10, 11].

Pain outcomes in knee OA are commonly assessed using a combination of subjective and experimental measures [12, 13]. Subjective pain measures capture the individual's self-reported experience of pain intensity at rest or during movement (i.e., movement-evoked pain) [13], while experimental measures such

Significance and Innovations

- Positive pre-exercise education enhances beliefs about EIH in knee OA but does not increase EIH magnitude compared to control education.
- Cognitive dissonance, arising from conflicting beliefs and lived experiences of pain during exercise, may limit the impact of brief educational interventions on EIH.
- Mechanisms underlying EIH extend beyond psychological factors, suggesting other interventions may be needed to optimize early pain relief with exercise in knee OA.

as pressure pain thresholds provide a quantitative measure of pain sensitivity [14]. These approaches capture complementary aspects of the pain experience and are frequently used to evaluate the effects of exercise on pain [15, 16].

A typical physiological response to exercise is exercise-induced hypoalgesia (EIH), characterized by a short term reduction in pain and/or pain sensitivity that occurs following an acute bout of physical activity and may last for 5–30 min [12, 17]. In contrast, the EIH response is highly variable in individuals with knee OA, with studies demonstrating a normal EIH response [14, 15, 18–19], an increase in pain sensitivity (hyperalgesic response) [13, 14, 20], or unchanged pain sensitivity [21]. The longer-term response to exercise can also be variable in people with OA, with large population studies suggesting that approximately half of participants experience a moderate, clinically important (≥ 30%) improvement in self-reported joint pain intensity, following an 8-week program combining patient education and supervised neuromuscular exercise [22], while the other half do not. It has been suggested that the different pain responses to exercise programs seen in knee OA may be related to impaired EIH [14], with recent evidence demonstrating that reduced EIH, measured at baseline, predicts less improvement in pain and function over the course of 12 exercise sessions in people with knee OA [16].

Despite the potential importance of EIH in the management of pain, studies aiming to enhance EIH are sparse. In healthy, pain-free controls, using brief targeted education (15 min) to positively modify expectations about the beneficial, analgesic, and safe effects of exercise was shown to increase EIH compared to a control education condition [23]. Furthermore, in another study of healthy pain-free controls, negatively manipulating expectations (2–3 min) by suggesting a likely painful response with exercise decreased EIH responses compared to neutral or positive education interventions [24].

The effects of brief pre-exercise education, designed to modify expectations of pain relief, have not been examined in an OA population. Such an intervention may be particularly relevant to knee OA, where negative beliefs, attitudes, and expectations about exercise, such as the belief that if exercise increases pain it will accelerate joint deterioration, are pervasive [25, 26].

Thus, the aim of this study was to investigate the impact of pre-exercise education on EIH in people with knee OA. It was hypothesized that a larger EIH effect would be evident in individuals receiving targeted, positive education emphasizing the safety and pain-relieving benefits of exercise in knee OA compared to a control education condition. Specifically, we hypothesized (1) a larger pre to post-exercise increase in PPT, alongside greater pre to post-exercise reductions in (2) resting pain and (3) movement-evoked pain in the positive education group.

2 | Materials and Methods

This parallel-group, randomized controlled trial was conducted between September and December 2022. The 2010 Consolidated Standards of Reporting Trials (CONSORT) statement [27] and 2017 CONSORT of Non-pharmacological Treatments Extension were used for reporting [28]. All procedures were approved by the Health and Disability Ethics Committee (21STH129) and Auckland University of Technology Ethics Committee (21/241), and written informed consent was obtained. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR 12621000731897). All testing sessions were conducted at Auckland University of Technology's North Campus, Auckland, New Zealand.

2.1 | Participants

Participants were recruited through advertisements and from existing research databases. Additionally, advertisements were left with local knee surgeons, rheumatologists, and physiotherapy clinics.

Inclusion criteria were: met The National Institute for Health and Care Excellence criteria for the diagnosis of knee OA (aged ≥ 45 years with activity-related joint pain and either no morning stiffness or morning stiffness < 30 min), had ongoing knee pain for ≥ 3 months and an average knee pain intensity of ≥ 3/10 in the last week at the time of screening [29]. If participants had bilateral knee OA, the most painful knee was chosen as the index knee for testing. Exclusion criteria were: an inability to speak or write English, medical conditions preventing safe participation in physical activity, an inability to climb 2 flights of stairs, history of knee replacement, knee surgery in the past 6 months, a recent history of lower limb resistance training (≥ 2 times per week for a minimum of 6 weeks within the past 6 months), any other form of arthritis, a history of musculoskeletal pain or injury in the lower limb (other than OA) in the past 6 months, any neurological condition, a current diagnosis of a major psychiatric disorder, or any cognitive impairment.

2.2 | Sample Size

A total of 42 participants were required (21 in each group) to achieve a probability of 80% that the study will detect a difference in EIH between interventions at a one-sided 0.05

significance level, with an effect size of Cohen's $d = 0.8$. This calculation assumed a between-group comparison of the primary outcome (change in PPTs from immediately before to after exercise) between two independent groups (independent-samples *t*-test framework). We utilized a one-sided test as recommended when the alternative hypothesis is specific and directional (i.e., that EIH would improve with positive education compared to control education) [30]. A previous study investigating a similar pre-exercise education intervention on the EIH response in a pain free population demonstrated a very large effect ($r = 0.49$ equating to Cohen's d of 1.12) [23]. We chose a more conservative effect size of Cohen's $d = 0.8$ to account for increased variability in the EIH response in people with OA [14].

2.3 | Randomization

Participants were randomized in a 1:1 ratio using a computer-generated randomization schedule (sealedenvelope.com) with permuted blocks of 2 and 6. To ensure allocation concealment, an independent researcher (not involved in recruitment or data collection) distributed and stored the randomization sequence in sealed, opaque envelopes. Participants, outcome assessors, and the statistician were blinded to treatment. Participants were informed the trial would "compare two different types of education and exercise interventions on knee osteoarthritis pain." The intervention deliverer was not blinded by necessity.

2.4 | Procedures

The experimental procedures are outlined in Figure 1. Each participant attended the laboratory during 2 clinical visits of ~2 h, 24–72 h apart ("visit 1" and "visit 2"). Participants were instructed to avoid vigorous exercise, alcohol, and caffeine for 24 h before testing and to refrain from nicotine use for at least 2 h prior to each testing session. During visit 1, participants provided demographic and clinical data for descriptive purposes, including age, sex, ethnicity, weight (kg), height (m), knee pain duration (years), and current medication use. Questionnaires regarding their pain, mental health, and physical function, as well as knowledge and beliefs related to pain and exercise, were completed. These included the Brief Pain Inventory (BPI) [31], Hospital Anxiety and Depression Scale (HADS) [32], Lower Limb Tasks Questionnaire [33], Pain Catastrophizing Scale (PCS) [34], Tampa Scale of Kinesiophobia (TSK) [35], Knee Osteoarthritis Knowledge Scale (KOAKS) [36] and a single item from Jones et al. [23] specifically related to EIH beliefs: "Pain can be reduced from just a single session of exercise" scored on a 7 point Likert scale from 0 = "strongly disagree" to 6 = "strongly agree."

To standardize exercise intensity for visit 2 EIH testing, participants completed a quadriceps maximum voluntary isometric contraction (MVIC) assessment at the index knee using a Biodex System 3 dynamometer (Biodex Medical Systems, Shirley, NY, USA). Hip and knee flexion were fixed at 85° and 90° respectively. A standardized warm-up included four 5-s isometric contractions at 25%, 50%, 50%, and 75% of perceived maximum effort, followed by three 5-s MVICs with 30-s rests. Consistent verbal encouragement was provided, and MVIC was defined as the peak torque (Nm) achieved during any of the MVICs. Following MVIC testing, participants were familiarized with the upcoming visit 2 EIH testing procedure to obtain pain expectancy scores. They described their current resting knee pain (0–100 NPRS) and were told that in visit 2 they would maintain 25% of their MVIC torque for up to 5 min or until failure. They then performed a 10-s trial at 25% MVIC and rated their expected knee pain (0–100 NPRS) if they held the contraction to failure. Pain expectancy was defined as the expected change in knee pain (expected pain—resting knee pain). All participants were then familiarized with the PPT testing procedures, which involved several practice trials on the dorsum of the hand to ensure understanding of the procedure and consistent reporting of pain onset. After baseline data collection, the envelope with their study number was opened for random allocation to either positive (intervention) or control pre-exercise

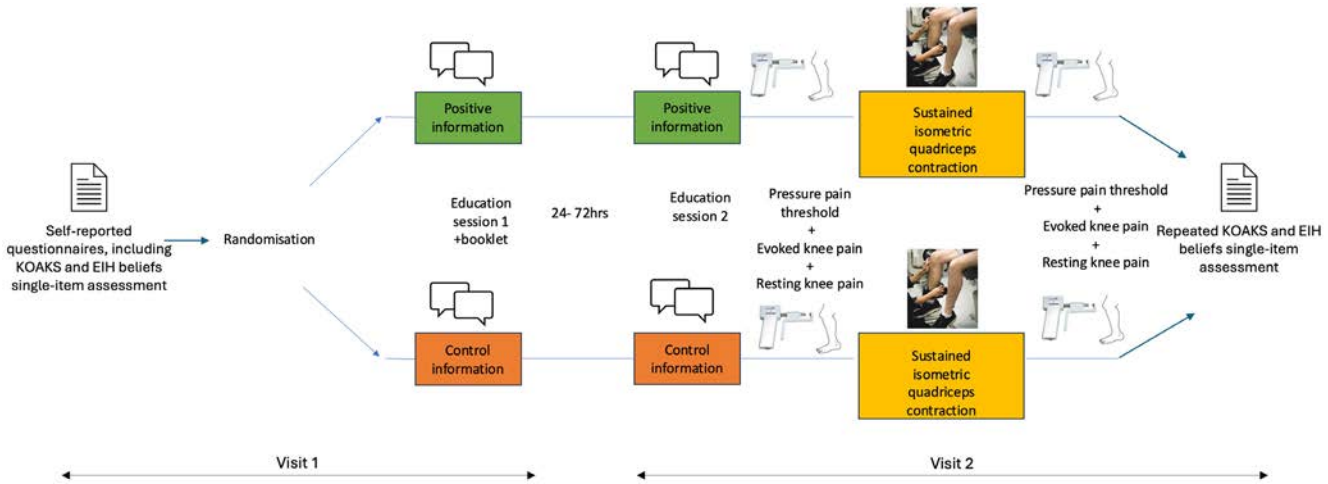

FIGURE 1 | Experimental procedures. Participants were randomized to receive positive education about knee OA and EIH (intervention) or education about knee OA, exercise and pain (control). Each education session for both groups lasted approximately 30 min and participants were given a booklet to take home and read after the 1st visit. At the second visit, following the second education session, EIH was quantified by measuring the participant's pressure pain thresholds (PPTs), evoked knee pain, and resting knee pain before and after performing a sustained isometric quadriceps contraction at 25% of their maximum voluntary isometric contraction for 5 min, or until failure.

education. Participants then completed the first of two education sessions (visit 1).

During visit 2, participants first completed their second education session. Then, to quantify the EIH response, pressure pain thresholds (PPTs), resting and evoked knee pain were collected before and after a single bout of sustained, submaximal isometric quadriceps contraction (25% MVIC). Following the second education session but before exercise and EIH measures, both groups completed the KOAKS and a single-item EIH beliefs questionnaire as a manipulation check for the interventions.

2.5 | Interventions

Two 30-min, one-on-one interactive education sessions ("Session 1" and "Session 2"), 24–72 h apart, were delivered by a postgraduate physiotherapist following standardized, rehearsed scripts (refined via pilot testing for Session 1 and adapted from Jones et al. [24] for Session 2; scripts and resources in Appendix 1). Sessions began with 10 min of rapport building. Participants received printed booklets covering Session 1 content to read between sessions. Engagement was encouraged through questioning to check understanding and relate content to personal experiences.

2.6 | Positive Education

In the intervention group, Session 1 addressed common OA pain and management misconceptions with a biopsychosocial focus [14, 27]. Session 2 provided specific EIH education, describing pain reduction after exercise, effective exercise types, duration, and potential mechanisms, following a script from Jones et al. [24] with minor modifications (Appendix 1).

2.7 | Control Education

In the control group, Session 1 used traditional, largely biomedical OA education from a reputable international website [37], with minor modifications to ensure neutrality regarding exercise and pain. The "Where can I find out more?" page was adapted for UK relevance. Session 2 covered pain ratings and differences in pain perception between athletes and nonathletes, following the control group script from Jones et al. [24].

2.8 | Isometric Exercise

EIH was induced using a single submaximal isometric quadriceps contraction at 25% of MVIC on the Biodex dynamometer. Participants maintained this torque until failure (inability to sustain for ≥ 5 s) or a maximum of 5 min, with visual feedback provided. Rating of perceived exertion (RPE) on Borg's 6–20 scale was recorded every 30 s. Verbal encouragement was given until true failure or the 5-min limit, and time to failure (seconds) was recorded. Participants then rated their maximum knee pain during the contraction (0–100 NPRS). Submaximal isometric exercise to failure was chosen due to its established effectiveness in producing EIH [13].

2.9 | Primary Outcome Measures

The primary outcome was the change in PPTs from immediately before to after exercise. PPTs, a reliable and established measure in EIH research [17], were assessed at the index knee's medial joint line (MJL) (3 cm medial to the midpoint on the medial edge of patella) and the contralateral forearm (5 cm distal to the lateral epicondyle) in a randomized order pre- and post-exercise, using the same order for both [14]. A handheld pressure algometer (SbMedic, Sweden) with a 1 cm rounded tip and a 30 kPa/s ramping rate was used. Participants pressed a button at the first onset of pain, and the pressure (kPa) was recorded. The average of three PPT measurements was taken per site. Both absolute and relative changes in PPTs at local (knee) and remote (forearm) sites were reported and analyzed as there is little consensus on which to report and both are frequently used [37–39]. Relative PPT change was expressed as a ratio of post- to pre-exercise PPT; values > 1.0 indicated hypoalgesia, and < 1.0 indicated hyperalgesia [15].

2.10 | Secondary Outcome Measures

Secondary outcomes included changes in resting and evoked knee pain intensity, assessed before and after exercise. Resting knee pain was measured using a 0–100 NPRS (0 = "no pain," 100 = "worst imaginable"). Evoked pain was measured on the same scale before and after the Staircase-Evoked Pain Procedure (StEPP): stepping up and down a 20 cm platform 24 times, starting with the index knee and alternating limbs [40]. Participants used their normal gait and were encouraged to complete the task without stopping. Time to complete the StEPP was recorded (seconds). Evoked pain was defined as the change in pain (0–100 NPRS) from before to immediately after the StEPP [40].

A fixed order of outcome measure testing was used to try to isolate the effects of exercise (EIH) on the outcome measures. Thus, before exercise, the order of assessment was evoked knee pain (StEPP test), 10 min rest, PPTs, then resting joint pain. A 10-min rest period was given to allow any lingering effects of the StEPP test on pain sensitivity to dissipate before measurement of pre-exercise PPTs. Immediately after exercise, the order was resting joint pain, PPT, and then evoked knee pain. Post-exercise, resting joint pain was assessed immediately after exercise to capture exercise-induced changes in resting pain levels, and because resting pain was quick to measure and would not influence the primary outcome, PPTs. PPTs were then immediately evaluated to determine the EIH response to exercise. Evoked knee pain (StEPP test) was performed last to ensure that any lasting effects of repeated joint loading did not influence the other post-exercise outcomes.

2.11 | Statistical Analysis

Normality of the data was assessed through visual inspection and using the Shapiro–Wilk statistic. As contraction duration (s), maximum knee pain during contraction, and peak RPE were non-normally distributed, these outcomes were compared across groups using Mann–Whitney *U* tests to check that the exercise dose was similar. For each group, Wilcoxon signed rank

tests were undertaken to ensure that the time taken to complete the evoked pain test (StEPP) was similar before compared to after exercise.

For primary and secondary outcome measures, a two-step analysis of covariance (ANCOVA) approach was used. In the first step, a full model regressed post-exercise (or change) scores on pre-exercise scores and all prespecified covariates (age, anxiety subscale of the HADS, and expected change in pain) [41]. These covariates were chosen based on the findings of a large prospective cohort study exploring predictors of EIH in a knee OA population [42]. To account for baseline differences between groups, the baseline single item belief scores were added as an additional covariate. Multicollinearity was evaluated for all the covariates with the variance inflation factor (VIF) [43]. Any variable with a VIF score greater than 10 was excluded. Mean differences across groups (the treatment effect) and mean score or mean change scores within each group (pre- to post-intervention effects), along with 95% confidence intervals (CIs) are reported. To complement these adjusted analyses, unadjusted one-way ANOVAs on pre- to post-exercise change scores were also performed and presented in Appendix S1. These confirm that the pattern of results was unchanged when covariates were not included.

Between group effect sizes were calculated by dividing the mean difference between groups by the pooled standard deviation and interpreted according to Cohen's criteria of 0.2 = small, 0.5 = medium, and 0.8 = large [44]. To examine the potential relationship between beliefs about EIH and the magnitude of EIH, post hoc exploratory correlation analyses were undertaken. These analyses examined the relationship between the primary outcome measure (pre-to-post exercise absolute change in PPT) and: (1) the pre-to-post intervention change in EIH beliefs and (2) the absolute post intervention EIH beliefs score using Spearman's rank correlation coefficient.

The data were analyzed using the R environment for statistical computing [45, 46] and SPSS version 25 (IBM Corp, Armonk, NY). Statistical significance was defined as $p \leq 0.05$ for all analyses.

3 | Results

3.1 | Participant Characteristics

A total of 67 participants were screened for eligibility, of which 25 (39%) were excluded for being ineligible, while 42 participants (65%) (20 females, 22 males) with an average age of 66 ± 7.5 years were recruited (Table 1, Figure 2). Baseline characteristics of the two groups were similar (Table 1). All participants completed the PPT testing, evoked pain testing (StEPP test), and sustained isometric contraction, with no adverse events reported.

3.2 | Similarity of the Exercise Interventions and StEPP Test Performance

There were no significant between-group differences in time to failure ($p = 0.51$), maximum knee pain during exercise ($p = 0.50$), or peak RPE ($p = 0.81$) during the sustained isometric contraction (Table 2). The time taken to complete the StEPP test did not differ before and after isometric exercise in the control group ($p = 0.20$). However, in the intervention group, StEPP test performance was marginally faster post-exercise compared to pre-exercise ($p = 0.05$).

3.3 | Manipulation Checks

The pre- to post-intervention change in EIH-related beliefs was greater in the positive education group compared to the control education group, with a medium effect (mean difference = 1.3, 95% CI [0.5, 2.1], $p = 0.001$, $d = 0.50$; Table 3). In contrast, while the change in OA-related knowledge and beliefs assessed by the KOAKS questionnaire favored the positive education group with a very small effect, this did not reach statistical significance (mean difference = 1, 95% CI [−1, 3], $p = 0.34$, $d = 0.15$). Neither group significantly increased their KOAKS score from pre- to post-intervention (both $p > 0.22$).

3.4 | Primary Outcomes

Analysis of the absolute change in PPT revealed no significant differences between the positive and control education groups at the knee (mean difference 10 kPa [95% CI −40 to 60 kPa]; $p = 0.57$, $d = 0.08$) or the forearm (mean difference −10 kPa [95% CI −50 to 30 kPa]; $p = 0.56$, $d = -0.08$). Similarly, there was no between-group difference in the relative change in PPT at either the knee (mean difference 0 [95% CI −0.2 to 0.19]; $p = 0.97$, $d = 0$) or the forearm (mean difference 0 [95% CI −0.3 to 0.2]; $p = 0.90$, $d = 0$). Unadjusted one-way ANOVA results were consistent with the adjusted analyses, showing no significant between-group differences in pre-to-post changes across all pain outcomes (Appendix S1).

On average, both groups demonstrated a significant increase in knee PPT following isometric exercise, reflecting a local EIH response (knee). Remote EIH (forearm) was smaller, and only statistically significant when expressed as a relative change (Table 4). Despite a significant local EIH response at the knee, the variability in the EIH response was large in both the positive and control education groups (Figure 3).

3.5 | Secondary Outcomes

There was no significant between-group difference in the pre- to post-exercise change in resting pain (mean difference −8 [95% CI −18 to 2]; $p = 0.11$, $d = -0.25$) or evoked pain (mean difference 1 [95% CI −7 to 8]; $p = 0.90$, $d = 0.04$) (Table 4).

3.6 | Relationship Between EIH Beliefs and Primary Outcomes

For the entire sample, there were no significant relationships between absolute or relative EIH (Δ in PPTs) and either the pre-to-post-intervention change, nor the absolute post-intervention score of the single item EIH beliefs question (rho −0.18 to 0.23, all $p > 0.26$).

TABLE 1 | Baseline participant characteristics.

	Intervention group	Control group
Sample size (*n*)	21	21
Age	65 (8.6)	67 (6.2)
Female sex (%)	13 (62%)	9 (43%)
Ethnicity: frequency (%)		
New Zealand European	16 (76%)	16 (76%)
New Zealand Māori	1 (5%)	0 (0%)
Samoan	0 (0%)	1 (5%)
Other European	3 (14%)	3 (14%)
Other ethnicity	1 (5%)	1 (5%)
Height (cm)	170 (7)	174 (10)
BMI (kg/m^2)	28.4 (6.0)	30.1 (5.8)
Duration of knee pain (months)	60 (18–138)	72 (36–120)
LLTQ (0–100)	18 (14–27)	21 (14.5–25)
HADS-depression (0–21)	3 (2–5.5)	4 (1–5.5)
HADS-anxiety (0–21)	5 (2–8.5)	4 (2.5–7)
TSK (11–44)	30 (21–31.5)	29 (25–32.5)
PCS (0–52)	8 (4–10)	5 (4–14)
BPI-Ave (0–10)	3 (1.5–4)	3 (2–4.5)
BPI-worst (0–10)	5 (3–7)	5 (3–7.5)
BPI-least (0–10)	0 (0–1.5)	0 (0–1)
BPI-interference (0–10)	2.6 (1.6–5.1)	2.7 (1.9–5.4)
Peak torque (Nm)	142 (108–175)	160 (120.5–173.5)
Single item EIH beliefs (0–7)	2 (1–4)	3 (1–5)
KOAKS (11–55)	33 (33–34)	36 (34–39)
EIH testing order (knee first (%))	12 (57%)	9 (43%)
Taking any pain medication (%)	3 (14%)	2 (10%)
Types of regular pain medication: frequency (%)		
Paracetamol	1 (5%)	0 (0%)
Anti-inflammatories	1 (5%)	2 (10%)
Opioids	0 (0%)	0 (0%)
Anticonvulsants	1 (5%)	0 (0%)
Antidepressants	0 (0%)	0 (0%)

Note: Data are presented as mean (SD) or median (IQR) unless otherwise stated.
Abbreviations: BMI, body mass index; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile range; KOAKS, Knee Osteoarthritis Knowledge Scale; LLTQ, Lower Limb Task Questionnaire; m, meters; min, minutes; PCS, Pain Catastrophizing Scale; s, seconds; SD, Standard deviation; TSK, Tampa Scale for Kinesiophobia.

4 | Discussion

To our knowledge, this is the first study to investigate the effect of pre-exercise education on EIH in individuals with knee OA. Previous reviews have shown that while EIH is a consistent and robust phenomenon in pain-free populations, its presence and magnitude in chronic pain conditions, including OA, are highly variable [12, 17, 47]. Some studies in people with OA report preserved hypoalgesia following exercise [14, 15, 18–19] whereas others show no change [21], or even hyperalgesic responses [13, 14, 20], mirroring the variability in pain relief observed with exercise in this population.

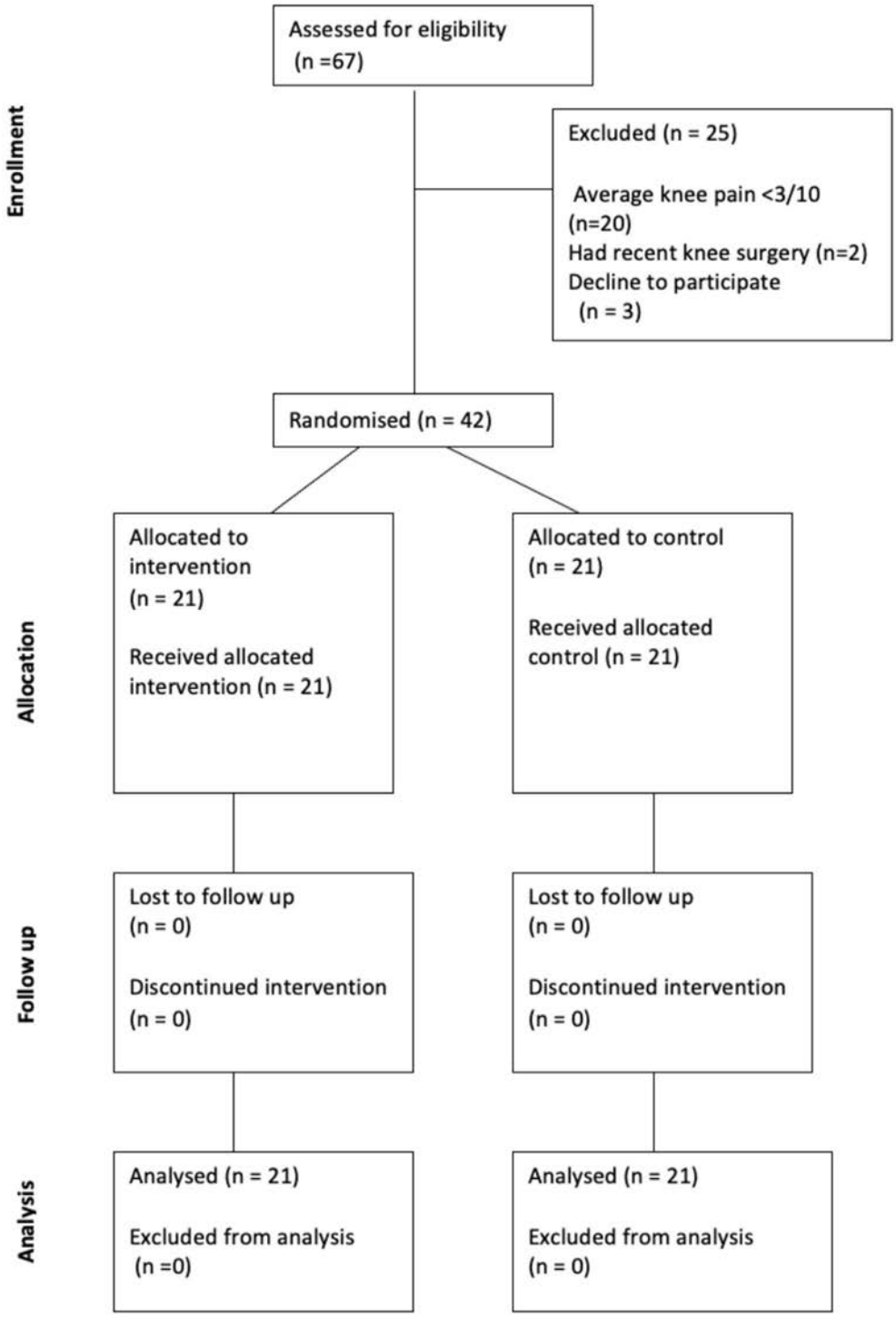

FIGURE 2 | CONSORT flow diagram of the progress through the phases of the randomized trial for each group.

The current study shows that, compared to a control condition, positive pre-exercise education leads to an increase in the belief that a single exercise session can reduce pain but does not affect overall knee OA knowledge as measured by the KOAKS, nor the magnitude of the subsequent EIH response. This includes EIH assessed as the change in PPT (primary outcome) as well as EIH assessed as the change in resting knee pain and evoked knee pain (secondary outcomes). Furthermore, there was no significant association between the change in PPTs and EIH-related beliefs.

Despite utilizing a near-identical script for the education interventions, our results differ from the findings of Jones et al. [23], who observed that in healthy, pain-free control participants, positive pre-exercise education enhanced EIH when compared to a control pre-exercise education, with a large effect size. In addition, a significant positive correlation was observed in their study between the magnitude of the post-intervention EIH response and the degree to which participants agreed with the single item question "pain can be reduced from just a single session of exercise" [23].

TABLE 2 | Expected change in pain, target torque, peak rating of perceived exertion (RPE), time to failure, maximum knee pain during contraction on the Numerical Pain Rating Scale (NPRS), and StEPP time to completion across the intervention and control groups.

Measure	Intervention group	Control group	*p*
Expected change in pain NPRS (0–100)	34.1 (27.2)	28.5 (26.5)	0.50
Target torque (Nm)	36.0 (12.5)	38.4 (10.9)	0.48
Peak RPE (6–20)	20 (19–20)	20 (19–20)	0.81
Time to failure (s)	300 (241.75–300)	300 (251.25–300)	0.51
Maximum knee pain during contraction NPRS (0–100)	27.5 (0.5–47.50)	27.5 (0.0–57.50)	0.50
StEPP time to completion (pre-intervention) (s)	65 (59–75.5)	75.5 (66.75–86.75)	
StEPP time to completion (post-intervention) (s)	63.5 (55.5–74)	70.5 (65.25–88)	

Note: Values are displayed as mean (SD) or median (IQR) unless otherwise stated.
Abbreviations: IQR, interquartile range; NPRS, Numerical Pain Rating Scale; RPE, Rating of perceived exertion; SD, standard deviation.

TABLE 3 | Pre- to post-education intervention change scores in single item exercise-induced hypoalgesia (EIH) beliefs and Knee Osteoarthritis Knowledge Scale (KOAKS).

Measure	Intervention group	Control group	Between group difference (95% CI)	*p*
EIH beliefs (0–7)	2.1 (0.3)*	0.8 (0.3)*	1.3 (0.5, 2.1)	0.001
KOAKS (11–55)	0.9 (0.7)	−0.1 (0.7)	1 (−1, 3)	0.34

Note: Values are displayed as estimated marginal means (standard error) unless otherwise stated.
Abbreviations: CI, Confidence interval; EIH, Exercise Induced Hypoalgesia; KOAKS, Knee Osteoarthritis Knowledge Scale; SE, Standard error.
*Represents significant within group change from pre-to post-intervention $p < 0.05$.

TABLE 4 | Primary and secondary outcome measures across the intervention and control groups.

Measure	Intervention group	Control group	Between group difference [95% CI]	*p*
Knee PPT				
Pre-exercise (kPa)	317 (231)	241 (177)		
Post-exercise (kPa)	370 (266)*	291 (167)*		
Absolute EIH (kPa)	60 (20)	40 (20)	10 [−40, 60]	0.57
Relative EIH (ratio)	1.24 (0.07)*	1.24 (0.07)*	0 [−0.2, 0.19]	0.97
Forearm PPT				
Pre-exercise (kPa)	281 (103)	315 (140)		
Post-exercise (kPa)	309 (205)	319 (152)		
Absolute EIH (kPa)	10 (10)	20 (10)	−10 [−50, 30]	0.56
Relative EIH (ratio)	1.07 (0.08)	1.09 (0.08)	0 [−0.3, 0.2]	0.90
Resting pain (0–100 NPRS)				
Pre-exercise	11.48 (13.32)	8.05 (11.07)		
Post-exercise	9.95 (14.71)	12.95 (18.62)		
EIH (resting pain change)	−2 (3)	6 (3)	−8 [−18, 2]	0.11
Evoked pain (0–100 NRPS)				
Pre-exercise	15.14 (17.69)	12.19 (11.87)		
Post-exercise	11.67 (21.05)	9.00 (11.32)		
EIH (evoked pain change)	−3 (3)	−4 (3)	1 [−7, 8]	0.90

Note: Pre- and post-exercise values are displayed as mean (standard deviation) or median (interquartile range), while change scores are estimated marginal means (standard error) or median (interquartile range).
Abbreviations: CI, Confidence interval; kPa, Kilopascals; NPRS, Numeric Pain Rating Scale; PPT, Pressure Pain Threshold.
*Represents significant within session change from pre-to post-intervention $p < 0.05$.

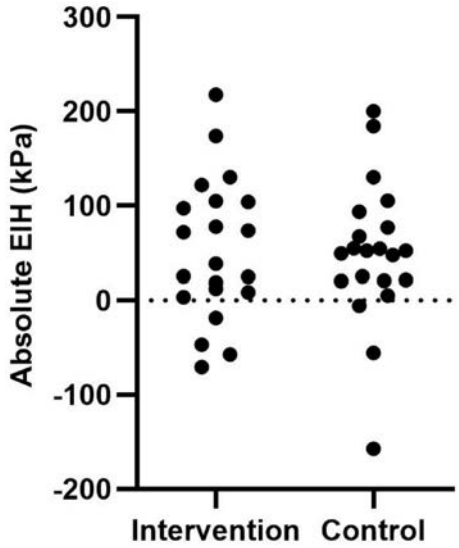

FIGURE 3 | Distribution of the absolute change in knee pressure pain thresholds from pre- to post-isometric exercise for individual participants at the knee (local site) in the intervention and control groups. Positive values indicate hypoalgesia and negative values indicate hyperalgesia, with the dotted line representing no change from baseline.

Our findings are more in line with Vaegter et al. [24], who demonstrated that brief (2–3 min) positive pre-exercise education did not increase EIH in healthy pain-free controls. Conversely, they found that negative pre-exercise education diminished EIH. This observation is consistent with the concept that negative experiences tend to exert a more profound influence on psychological states than positive ones [48], which may in turn influence endogenous pain modulation pathways. It could be that the educational interventions of our study were not sufficiently dissimilar to elicit differential outcomes on EIH. Our decision to avoid a negative intervention, despite its potential to enhance the difference between groups, was based on the ethical consideration to avoid nocebic effects in a clinical population suffering from chronic pain. Furthermore, our focus was on whether providing positive education offers benefits compared to standard biomedical education. This arguably has more clinical relevance than simply establishing its superiority over deliberately nocebic approaches, as it aims to direct treatment strategies toward interventions that do more than avoid harm but rather actively contribute to patient care.

It is well established that people with knee OA commonly have misperceptions about their condition and frequently hold negative attitudes and beliefs about exercise [49]. These may be resistant to change, particularly in the short term. Despite our positive education intervention increasing confidence that "pain can be reduced from just a single session of exercise," this may not have aligned with the personal experiences of participants, especially if they have previously found exercise to be painful or challenging. This mismatch, a form of cognitive dissonance, reflects the complex decision-making process knee OA patients face, as described by Darlow et al. [26], balancing knowledge of the therapeutic role of exercise with the fear of increasing pain or causing further joint damage.

Alternatively, it may be that impaired EIH is only weakly related to expectations in people with knee OA. The mechanisms of EIH remain incompletely understood and are thought to be mediated by a range of different physiological processes [12, 50]. It has been suggested that impaired EIH may reflect maladaptive changes in the function of endogenous pain inhibitory pathways and/or immune system dysfunction [12]. Perhaps, in the presence of such maladaptive changes, cognitive factors such as expectations are less important in determining the overall magnitude of the EIH response. This is supported by a recent systematic review which suggests that cognitive and emotional factors appear to have a stronger association with EIH in pain-free individuals than in those with chronic pain conditions [51].

Strengths of this study include its robust double-blind RCT design and the inclusion of secondary outcome measures of EIH that may have more direct clinical relevance than PPT alone. However, there are also some potential limitations to consider. Notably, an isometric exercise protocol was employed to induce EIH, while Jones et al. [23] used an aerobic exercise protocol. The selection of an isometric protocol is arguably more clinically relevant as local resistance training is routinely prescribed in the management of OA. Previous studies have shown that aerobic and isometric exercise elicit EIH of a similar magnitude, both in healthy controls [17] and knee OA specifically [14]. Thus, it seems unlikely that the type of exercise used to elicit EIH would have affected our results, although this remains a possibility. Importantly, our population of people with OA appeared to have mild to moderate symptoms; we did not collect data on participant comorbidities, and we only examined the immediate effects of an education intervention on EIH after a single bout of exercise. Therefore, our findings may not translate to all people with knee OA or to the longer-term effects with repeated bouts of exercise, which should be examined in future studies. For example, over the course of several sessions, the combination of pain neuroscience education and exercise has been shown to lead to greater improvements in pain than exercise alone [52]. Finally, there was a statistically significant difference in the time taken to perform the StEPP test from pre to post exercise in the intervention group. However, the mean difference was marginal (~1.5 s) and similar to the pre to post exercise difference observed in the control group. As such, it is unlikely to have had an important effect on the findings.

5 | Conclusions

Despite modifying EIH related beliefs, two 30-min sessions of positive pre-exercise education did not enhance the EIH response compared to control pre-exercise education. Different types of interventions, more intensive pre-exercise education interventions, or similar interventions in participants with more severe symptoms should be explored to see if they enhance EIH in people with knee OA. This may minimize exercise-induced flares in pain and increase both efficacy and engagement with exercise-based rehabilitation in the longer-term.

Author Contributions

This study was conceived and designed by D.T., G.L., B.D., U.R., N.T., and D.R. Data collection was performed by D.T. Data analysis and

interpretation were conducted by D.T. and D.R., with input from U.R., D.T. prepared the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Active Control: Script for the education of participants with knee osteoarthritis, utilising the "Versus Arthritis: Osteoarthritis of the knee" handbook, excluding explicit information of exercise induced hypoalgesia.

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LETTER TO THE EDITOR

AI-Powered Detection of Cutaneous Involvement in Familial Mediterranean Fever

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Dear Editor,

Artificial intelligence (AI) has become a transformative tool in dermatology, attaining dermatologist-level precision in the classification of skin malignancies and inflammatory dermatoses when trained on properly structured data sets [1]. However, its specific application to autoinflammatory diseases is mainly unexamined. Familial Mediterranean fever (FMF), the most common monogenic autoinflammatory condition, is characterized by systemic inflammatory attacks and unique dermatological symptoms [2]. Among these, erysipelas-like erythema (ELE) is the characteristic lesion, occasionally accompanied by atypical rashes, including urticarial, panniculitis-like, or Sweet's syndrome–like eruptions in certain patients [2]. These skin findings, though potentially diagnostic, are often underrecognized in clinical practice [3]. I suggest that AI-driven methodologies may significantly enhance the prompt identification of FMF cutaneous involvement and the integration of genetic data to improve diagnostic accuracy.

First, the technical feasibility of AI for dermatologic diagnosis is now well established. Convolutional neural networks (CNNs) and transfer-learning frameworks are increasingly applied beyond oncology, extending into inflammatory and immune-mediated skin diseases [1, 4]. Although no validated models exist for FMF lesions, transfer-learning from existing inflammatory dermatoses could accelerate development. Such models could be trained to discriminate ELE from infectious mimics and to identify atypical rashes with temporal characterization.

Second, recent clinical studies underscore the diagnostic value of cutaneous phenotyping in FMF. In a pediatric cohort, ELE was reported in 7.5% of FMF patients and correlated with subclinical inflammation, acute arthritis, and biallelic MEFV exon 10 mutations [5]. Genotype–phenotype studies further confirm that M694V homozygosity is associated with more severe disease, including higher ELE frequency [6]. Together, these findings highlight cutaneous signs as not merely epiphenomena but important phenotypic markers of systemic disease.

Third, diagnostic challenges remain considerable. ELE commonly mimics cellulitis, which frequently results in hospital stays or needless antibiotics [7]. It can be difficult to identify atypical eruptions because they can mimic allergic or infectious dermatoses. Furthermore, underreporting in non-endemic areas has resulted from a lack of dermatology input into rheumatology cohorts, which delays diagnosis when skin findings are missed [3]. These risks could be lessened with AI-based diagnostic assistance, especially in emergency and primary care settings where FMF is unknown.

Fourth, genomics offers an opportunity for risk stratification when combined with imaging. MEFV variants such as M694V not only influence disease severity but also correlate with skin manifestations [6, 8]. Multi-modal AI systems capable of integrating dermatologic imaging with genetic and clinical features have already been explored in autoimmune and immune-mediated diseases [9]. By applying such frameworks to FMF early diagnosis, high-risk patient stratification, and customized treatment strategies may be made possible.

In summary, cutaneous involvement of FMF is a visible but unexplored diagnostic marker. AI-driven image classifiers,

particularly when combined with MEFV genotype data, may improve recognition, decrease misdiagnosis, and improve precision management. Collaborative initiatives to establish multicenter FMF skin-image repositories with associated genomic data would set the foundation for such advancements. A trial initiative may illustrate feasibility and help with the development of globally scalable AI-driven solutions.

Author Contributions

Kumar Meghwar: conceptualization, writing – original draft preparation, literature review. **Danish Kumar:** writing – review and editing, literature review. **Irfan Ali:** writing – review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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The authors have nothing to report.

Conflicts of Interest

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Data Availability Statement

The authors have nothing to report.

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ORIGINAL ARTICLE

Serum Endocan in Systemic Lupus Erythematosus: Implication for Endothelial Dysfunction and Cardiovascular Risk

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. Endothelial dysfunction is an early change in atherosclerosis. Endocan is a new indicator of endothelial dysfunction and is probably involved in proinflammatory processes in SLE. This study aimed to assess the serum endocan level in SLE patients and its relation to disease activity, endothelial dysfunction, and subclinical atherosclerosis.

Methods: This study included 60 SLE patients and 60 healthy controls. Demographic data were collected, and disease activity was assessed using the SLEDAI score for SLE patients. Functional assessment was done using the Health Assessment Questionnaire (HAQ). Serum endocan level was measured, and subclinical atherosclerosis was assessed using brachial artery flow-mediated dilation (FMD) and carotid intima-media thickness (cIMT).

Results: Endocan levels in the SLE group (632.2 ± 70.58 ng/L) were significantly higher than controls (125.83 ± 16.23 ng/L). cIMT was significantly higher in SLE patients (8.18 ± 1.13 mm) than in controls (6.43 ± 0.54), and the mean flow-mediated dilation value in SLE patients was 9.57 ± 2.59, whereas in the control group, it was 21.8 ± 4.27. The serum level of endocan was significantly correlated with the duration of the disease, triglycerides, and cIMT, and it had a significant negative correlation with flow-mediated dilation. cIMT and flow-mediated dilation were significantly correlated with age, disease duration, and triglycerides.

Conclusions: Elevated serum levels of endocan in SLE patients may be associated with subclinical atherosclerosis and endothelial dysfunction.

1 | Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting mainly women of childbearing age and characterized by antibody production, formation of immune complexes, widespread inflammation, and the involvement of various organs and systems [1].

Cardiovascular disease (CVD) is a well-known complication of SLE and has been demonstrated as a leading cause of morbidity and mortality [2]. Individuals with SLE are at risk of early atherosclerosis, which often progresses silently leading eventually to myocardial infarction [3]. Vascular events are 7–10 times more frequent in SLE patients under 45, with early heart involvement playing a crucial role in their health issues [4].

CVD in SLE is primarily driven by systemic inflammation and autoimmune vascular damage [5]. Chronic inflammation, antibody production, and atherosclerotic risk factors like hypertension, dyslipidemia, central obesity, and glucose intolerance all play a role in the early onset of atherosclerosis [6].

Cardiac involvement in lupus can significantly impact disease classification and severity. Cardiovascular involvement (as pericarditis or myocarditis) in SLE patients can alter the disease activity from mild to moderate or severe [7].

Endothelial dysfunction (ED) is considered an initial step in the pathogenesis of atherosclerosis and can be non-invasively detected as reduced flow-mediated dilation (FMD) in the brachial artery [8].

Carotid intima-media thickness (cIMT) measurement by ultrasonography is a reliable, non-invasive, inexpensive tool that helps to detect subclinical atherosclerosis and plaques in SLE patients [9].

Serum endocan, also known as endothelial cell-specific molecule-1 (ESM-1), is a marker of angiogenesis and endothelial cell activation. It plays a role in the recruitment, adhesion, and migration of leukocytes to the endothelium. The expression, synthesis, and secretion of endocan by endothelial cells are elevated by proinflammatory cytokines and pro-angiogenic growth factors [10]. Additionally, endocan is overexpressed in cancer, sepsis, and chronic autoimmune diseases [11].

To our knowledge, the relation between serum endocan level and endothelial dysfunction has not been investigated yet in SLE patients, and only one study studied the relationship between serum endocan and carotid intima-media thickness (cIMT) in SLE patients [12].

In light of this background, this study aimed to assess the serum endocan level in SLE patients and its relation to disease activity, endothelial dysfunction, and subclinical atherosclerosis.

2 | Methods

It's a case–control study conducted at a single center.

2.1 | Setting

Patients were recruited from the Rheumatology and Rehabilitation Department outpatient clinic, Tanta University Hospitals.

2.2 | Patients

The study included 60 adult patients who fulfilled ACR/EULAR 2019 criteria for SLE [13], and 60 healthy volunteers matched for age and gender. "The sample size was calculated by using MedCalc software version 22.009 package for biomedical research. 40 participants in each group are required to achieve 80% study power at 95% confidence level with a margin of error equal to 5% based on a previous study conducted by Icli et al. [12], and the number of participants was increased to 60 in each group in this study." Patients who had other rheumatological disorders, diabetes, thyroid, a known history of CVDs, acute or chronic kidney disease, lactation, pregnancy, sepsis, or malignancy were excluded from the study.

Duration of the study: 4 months (From August 2024 to November 2024).

2.3 | Ethics Approval and Consent to Participate

This study has been approved by the institution's ethics board with permission number 36264PR788/7/24 and is following the Declaration of Helsinki's ethical principles as well as the ethical standards of the Tanta Faculty of Medicine. Informed consent was taken from each patient according to the local ethical commission.

2.4 | Clinical Assessment

Demographic data and a thorough medication history were recorded. The activity of disease was estimated using Systemic lupus erythematosus disease activity index SLEDAI [14] which measures disease activity within the last 10 days, it includes 24 clinical and laboratory variables. Levels of disease activity were divided into five categories: no activity (SLEDAI = 0), mild activity (SLEDAI = 1–5), moderate activity (SLEDAI = 6–10), high activity (SLEDAI = 11–19) and very high activity (SLEDAI > 20). Functional assessment was done using the Health Assessment Questionnaire (HAQ) which measures disease-related disability, discomfort, and quality of life. It consists of 20 activities grouped in 8 categories. The patient was asked to rate their ability to perform each activity over the last week on a 4-point item scale. The average of the highest score of each category was calculated. The score of HAQ ranges from 0.0 to 3.0. The higher the score, the greater the overall disability [15].

2.5 | Assessment of Subclinical Atherosclerosis and Endothelial Dysfunction

2.5.1 | Carotid Intimal Media Wall Thickness (cIMT) Assessment

The common carotid arteries were assessed using a SAMSUNG MEDISON (UGEO H60) device equipped with a linear transducer (midfrequency 10 MHz). The distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall is known as the cIMT. cIMT of the common carotid artery was measured between 1 and 3 cm proximally to the bifurcation of the carotid artery on the left and right sides. cIMT was measured at the distal wall of the carotid artery on a 10-mm segment [16]. 0.9 mm or higher was considered an increased cIMT. Carotid plaque was described as cIMT ≥ 1.2 mm [17]. Two ultrasonography operators independently examined the recorded scans of the patients and controls.

2.5.2 | Measurement of Brachial Artery Flow

In the brachial artery ultrasound study, all participants were in the supine position, resting for 10 min in a quiet, dark, temperature-controlled room. The measurements of the brachial artery were obtained using a longitudinal scan in the arm, 5–10 cm above the antecubital fossa, without permanent vascular access. The luminal diameter of the artery was measured between the proximal and distal intima. After recording the baseline diameter of the brachial artery (D0), transient ischemia was induced by cuff which was placed around the forearm and inflated to 200 mmHg (or 50 mmHg more than the systolic blood pressure) for 5 min and the cuff was deflated and a second scan for arterial diameter measurements was taken about 40–60 s after deflation (D1), flow-mediated dilatation (FMD) was expressed as a percentage change in the brachial artery diameter from the baseline to ischemia (FMD%) and calculated by the following formula ($D1 - D0/D0 \times 100$), and the higher the percentage value the better the endothelial function [18].

2.6 | Laboratory Assessment

- Routine laboratory assessment: erythrocyte sedimentation rate (ESR) by Westergren method, C-reactive protein (CRP), Complete blood count (CBC), antinuclear antibodies (ANA), Anti-dsDNA, complement (C3, C4), urine analysis, 24 h-Proteinuria, total lipid profile including triglycerides, total cholesterol, low density lipoprotein (LDL) and high-density lipoprotein (HDL).
- Serum endocan level: blood samples were collected from the patient and the control group after 12-h fasting. After appropriate centrifugation, the samples were stored at −20°C until testing. The level of Human Endothelial cell-specific Molecule1 (ECSM1/endocan) in samples was assessed by the enzyme-linked immunosorbent assay (ELISA). The ELISA process was performed according to the manufacturer's instructions. The absorbance was measured spectrophotometrically by the ELISA reader. The absorbance and the concentration of endocan in samples were positively correlated.

2.7 | Statistical Analysis

SPSS version 20 was used for statistical analysis of the data [19]. Numbers and percentages were used to describe the qualitative data. The Kolmogorov–Smirnov and Shapiro–Wilk test was used to verify the normality of distribution. The mean and standard deviation were used to characterize the quantitative data. The categorical data were compared using the chi-square test. Student *t*-test was used to compare two groups for normally distributed quantitative variables. Correlation between variables was done by Pearson's correlation coefficient. Linear regression was done to evaluate the factors associated with cIMT and flow-mediated dilatation. *p* values less than 0.05 were considered statistically significant.

3 | Results

Sixty SLE patients and 60 healthy volunteers completed this study. 54 out of 60 SLE patients were female, with a mean age of 37.07 ± 4.5 years, while 48 out of 60 healthy controls were female, with a mean age of 38.63 ± 4.83 years. Four patients had mild disease activity, 46 had moderate disease activity, while 10 patients had high disease activity. Fifty SLE patients were receiving hydroxychloroquine, 20 patients were receiving mycophenolate mofetil, and 40 patients were treated with corticosteroids during the study. The demographic and clinical data of SLE patients and controls are shown in Table 1.

Endocan levels in the SLE group (632.2 ± 70.58 ng/L) were significantly higher than controls (125.83 ± 16.23 ng/L). cIMT was significantly higher in SLE patients (8.18 ± 1.13 mm) than controls (6.43 ± 0.54). The mean flow-mediated dilatation value in SLE patients was 9.57 ± 2.59, whereas in the control group, it was 21.8 ± 4.27 (*p* value of < 0.0001). laboratory and radiological data of SLE patients and controls are shown in Table 2.

There was a significant positive correlation between the serum level of endocan and duration of the disease, triglycerides, LDL and cIMT and a significant negative correlation with Flow-mediated dilatation. There was a significant correlation between both cIMT and flow-mediated dilatation with age, disease duration, and triglycerides. All correlation analysis results are shown in Tables 3 and 4. On evaluating risk factors associated with cIMT and flow-mediated dilatation, increased age and serum endocan were associated with cIMT. Linear regression analysis results are shown in Table 5.

4 | Discussion

This study evaluated the serum endocan in SLE patients and tried to investigate its relationship with disease activity, endothelial dysfunction, and subclinical atherosclerosis. In this study serum levels of endocan, triglycerides, cholesterol, and LDL were significantly higher in SLE patients than in controls while HDL was significantly lower in SLE patients.

In agreement with our results, Huang et al. reported that serum triglycerides, total cholesterol, LDL, and ApoB were significantly higher in SLE patients, while the serum HDL and ApoA1 were significantly lower in SLE patients [20].

Icli et al. reported that high-density lipoprotein cholesterol was reported to be higher in SLE patients [13]. VLDL and LDL were reported to be lower in patients with SLE than healthy donors, although higher in nephritis patients [21].

In contrast, Blachut et al. demonstrated that triglycerides were significantly higher in SLE patients than in controls while serum cholesterol, HDL, and LDL showed no significant differences between SLE patients and controls [22].

It has been established that VLDL is associated with an elevated risk of cardiovascular disease. VLDL is the main carrier of triglycerides, which are an independent risk factor for cardiovascular disease and VLDL concentrations have been significantly linked with the risk of myocardial infarction [23].

Chronic inflammation can induce reduced serum HDL and increased triglycerides due to increased hepatic VLDL production

TABLE 1 | Demographic and clinical data of SLE patients and controls.

	SLE patients (60)	Controls (60)	
	Mean ± SD	Mean ± SD	*p*
Age (years)	37.07 ± 4.5	38.63 ± 4.83	0.0697
Sex: (male/female)	6\54	12\48	0.125
BMI	27.5 ± 3.39	26.87 ± 2.61	0.256
Duration of disease (years)	5.6 ± 1.69	NA	
Smoking: (yes/no)	6\54	12\48	0.77
Systolic blood pressure	131.33 ± 9.37	118.33 ± 4.97	< 0.0001*
Diastolic blood pressure	81.16 ± 8.06	74 ± 4.43	< 0.0001*
Disease activity (SLEDAI)	8.87 ± 2.13	NA	
Mild disease activity (*N*)	4		
Moderate disease activity (*N*)	46		
High disease activity (*N*)	10		
Functional assessment (HAQ)	1.77 ± 0.25	NA	
Treatment received			
Hydroxychloroquine	50		
Mycophenolate mofetil	20		
Corticosteroid	40		

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, convential synthetic disease-modifying antirheumatic drugs; HAQ, health assessment questionnaire; IQR, interquartile range; *N*, number; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.
*Significant *p* value if < 0.05.

and reduced clearance of triglyceride-rich lipoproteins [24]. It was demonstrated that serum levels of HDL and LDL were correlated with disease activity score in lupus patients [20].

The serum endocan level was reported to be higher in SLE patients than in controls [10, 12].

In this study, SLE patients have significantly higher cIMT, and significantly lower flow-mediated dilatation value compared with controls. There was a significant correlation between both cIMT and flow-mediated dilatation with age, disease duration, triglycerides, and endocan.

Several studies reported that cIMT was elevated in SLE patients as in our study [12, 22, 25]. cIMT was positively correlated with BMI, age, triglyceride, total cholesterol [12, 25], LDL cholesterol, and disease duration [25].

In contrast, Ferrigno et al. reported that cIMT was similar between SLE patients and healthy controls [26, 27].

Several studies demonstrated decreased flow-mediated dilatation in SLE patients compared to controls [28–30]. While other studies found that there was no significant difference regarding flow-mediated dilation, in SLE patients when compared to healthy controls [27, 31]. However, the increased disease duration was associated with worse flow-mediated dilation, which may indicate progressive endothelial dysfunction over time [27].

Flow-mediated dilatation was reported to be correlated with disease activity in SLE patients [32, 33] but Lima et al. reported that the flow-mediated dilatation was not related to disease duration, SLE disease activity score, cumulative steroid dose, antimalarial use, anticardiolipin antibody, Raynaud's phenomenon, hypertension history [34].

Carotid intima thickening occurs late in the process of atherosclerosis [35], but endothelial dysfunction occurs at the initial stage in the pathogenesis of premature atherosclerosis [8]. Endothelial dysfunction can be reversed, unlike established atherosclerosis, If the cardiovascular risk factors are managed [8]. Premature atherosclerosis in SLE may be attributed to chronic inflammation disease activity, treatments, and associated autoimmune diseases, such as antiphospholipid syndrome [36] in addition to traditional risk factors.

In our patients, there was a significant correlation between the serum level of endocan and duration of the disease, triglycerides, cIMT, and flow-mediated dilatation but no significant correlation was found with disease activity, BMI, inflammatory markers, and other lipid profiles.

TABLE 2 | Laboratory and radiological data of SLE patients and controls.

	SLE patients (60)	Controls (60)	
	Mean ± SD	Mean ± SD	*p*
ESR	38.33 ± 8.94	11.67 ± 4.09	< 0.0001*
CRP	11.33 ± 8.94	3.7 ± 1.09	< 0.0001*
Hemoglobin (g/dL)	10.57 ± 0.59	12.5 ± 1.2	< 0.0001*
White blood cells ($\times 10^3/mm^3$)	5.49 ± 1.91	7.1 ± 1.87	< 0.0001*
Platelet ($\times 10^3/mm^3$)	260.17 ± 103.64	320.54 ± 50.2	< 0.0001*
C3 (mg/dL)	105.83 ± 21.46	—	
C4 (mg/dL)	16.6 ± 8.49	—	
Anti ds-DNA		—	
Positive	20		
Negative	40		
Protein in 24 h urine (mg/24 h urine)	383.67 ± 143.6	—	
Triglycerides (mg/dL)	148 ± 53.83	117 ± 27.99	0.0001*
Total cholesterol (mg/dL)	167.17 ± 42.58	137.17 ± 15.41	< 0.0001*
LDL (mg/dL)	30.9 ± 8.06	22 ± 5.02	< 0.0001*
HDL (mg/dL)	42 ± 8.67	49.33 ± 7.85	< 0.0001*
Serum endocan (ng/L)	632.2 ± 70.58	125.83 ± 16.23	< 0.0001*
CIMT	8.18 ± 1.13	6.43 ± 0.54	< 0.0001*
Flow-mediated dilatation	9.57 ± 2.59	21.8 ± 4.27	< 0.0001*

Abbreviations: anti ds-DNA, anti double stranded DNA; C3, complement 3; C4, complement 4; CIMT, carotid intimal media wall thickness; CRP, creactive protein; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; SLE, systemic lupus erythematosus.
*Significant *p* value if < 0.05.

TABLE 3 | Correlation between serum endocan and other parameters in SLE patients.

	Serum endocan	
	r	*p*
Duration	0.439	0.0004*
BMI	0.109	0.405
Disease activity	0.203	0.12
ESR	0.116	0.379
CRP	0.214	0.1
Triglycerides	0.327	0.011*
Total cholesterol	0.2	0.126
LDL	0.258	0.047*
HDL	0.143	0.277
cIMT	0.955	< 0.0001*
Flow-mediated dilatation	−0.745	< 0.0001*

Abbreviations: BMI, body mass index; cIMT, carotid intimal media wall thickness; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; SLE, systemic lupus erythematosus.
*Significant *p* value if < 0.05.

Icli et al. demonstrated that the endocan level was positively correlated with cIMT, ESR, and body mass index [11] in contrast Tokarska et al. reported that there is no relation between endocan and disease activity, duration of the disease, or other laboratory parameters in SLE patients [10].

Several studies demonstrated that endocan was positively associated with cIMT and psoriatic area and severity index in patients with psoriasis [37, 38].

Balta et al. reported that the serum endocan level was elevated in patients with Behçet's disease, and a positive correlation between endocan levels and CRP, ESR, and disease activity [39].

On regression analysis, serum endocan was found to be a predictive factor for cIMT [12] as in our study.

Endocan is released from the vascular endothelium, bronchi, and renal distal tubule epithelial cells. Inflammatory cytokines control their release. Serum endocan was found to be associated with cardiovascular disease [40]. It has been suggested that endocan participates in the development of atherosclerosis mainly through endothelial dysfunction [41]. Endocan stimulates the recruitment of inflammatory cells and the adhesion of leucocytes to the endothelium. These findings indicate that serum

TABLE 4 | Correlation of cIMT and Flow-mediated dilatation with other factors in SLE patients.

	cIMT		Flow-mediated dilatation	
	r	*p*	*r*	*p*
Age	0.754	<0.00001*	−0.419	0.001*
Duration	0.471	0.009*	−0.418	0.001*
BMI	0.195	0.301	−0.053	0.799
Disease activity	0.28	0.029*	−0.226	0.083
ESR	0.006	0.966	0.120	0.361
CRP	0.094	0.473	0.246	0.058
Triglycerides	0.289	0.025*	−0.365	0.004*
Total cholesterol	0.22	0.091	−0.207	0.274
LDL	0.302	0.019*	−0.204	0.118
HDL	0.084	0.522	−0.073	0.581
Serum endocan	0.955	<0.0001*	−0.745	<0.0001*
Flow-mediated dilatation	−0.617	<0.0001*		

Abbreviations: BMI, body mass index; cIMT, carotid intimal media wall thickness; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; SLE, systemic lupus erythematosus.
*Significant *p* value if <0.05.

TABLE 5 | Variables associated with cIIMT and flow-mediated dilatation in SLE patients.

	Beta regression coefficient	*p*	Beta regression coefficient	*p*
	cIMT		Flow-mediated dilatation	
Age	0.067	0.01*	0.058	0.727
BMI	0.023	0.24	0.014	0.915
Duration	0.021	0.628	−0.259	0.397
Disease activity	−0.006	0.872	−0.112	0.667
Triglycerides	−0.001	0.771	−0.010	0.571
Total cholesterol	0.002	0.575	−0.009	0.67
LDL	0.019	0.068	0.017	0.801
HDL	−0.005	0.544	−0.026	0.653
Endocan	0.012	0.0001*	−0.022	0.063

Abbreviations: BMI, body mass index; cIMT, carotid intimal media wall thickness; CRP, creactive protein; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; SLE, systemic lupus erythematosus.
*Significant *p* value if <0.05.

endocan may be related to subclinical atherosclerosis and may be useful as an early predictor for its development [11].

4.1 | Limitations of This Study

The relatively small number of patients, and most of our patients (93.3%) had moderate to severe activity. The cumulative dose of steroid couldn't be calculated, which is considered a risk factor for atherosclerosis. Also, this is a single-center cross-sectional study, so in the future, multicentric, prospective studies are important to support the data in this study.

5 | Conclusion

Elevated serum levels of endocan in SLE patients may be associated with subclinical atherosclerosis and endothelial dysfunction.

Author Contributions

All authors designed the study protocol. Samar abdAlhamed Tabra formulated the idea of the manuscript. Aya A. El Shintenawy and Esraa Elshintenawy monitored the progress and collected the data. Samar AbdAlhamed Tabra formulated the results. All authors contributed to drafting the manuscript and have read and approved the final version of the manuscript.

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The authors have nothing to report.

Ethics Statement

This study has been approved by the institution's ethics board with permission number 36264PR788/7/24 and is in accordance with the Declaration of Helsinki's ethical principles as well as the ethical standards of the Tanta Faculty of Medicine.

Consent

According to the local ethical commission, informed written consent was received from each patient. Every patient file included a code number that incorporated the results of all investigations, ensuring the privacy of all patient data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Osteoporosis and Chronic Inflammation: A Global Bibliometric Analysis Between 1994 and 2025

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ABSTRACT

Background: Osteoporosis is increasingly recognized as a systemic disease influenced by chronic inflammation. The interdisciplinary nature of research in this field necessitates a comprehensive mapping of its evolution, contributors, and thematic trends.

Aim: To perform a bibliometric analysis of global research on osteoporosis and chronic inflammation from 1994 to 2025, identifying publication patterns, key contributors, and emerging research themes.

Methods: Publications were retrieved from Scopus using the terms "chronic inflamm*" and "osteoporo*." Eligible records included original research articles, reviews, conference papers, and editorials. Data were analyzed using bibliometrix (biblioshiny), VOSviewer, and Harzing's Publish or Perish to assess publication trends, geographical contributions, authorship patterns, journal metrics, keyword co-occurrence, and thematic evolution.

Results: A total of 1464 documents from 855 journals were analyzed, authored by 6777 individuals. The average annual growth rate was 13.45%, with a collaboration index of 5.13 and an international collaboration rate of 16.8%. The United States of America led in total citations, while Malaysia, Lebanon, and Austria had the highest average article citations. Most prolific authors and top-cited works were concentrated in academic or governmental institutions, with limited industry-affiliated corresponding author representation identified in the dataset. Osteoporosis-focused journals achieved higher citation impact compared to multidisciplinary journals. Keyword analysis revealed three major thematic clusters: mechanistic/immunological underpinnings, clinical diagnostics/risk factors, and pharmacological interventions/comorbidities, with thematic evolution showing a shift toward interdisciplinary integration since 2014.

Conclusion: Research on chronic inflammation and osteoporosis has expanded rapidly, integrating mechanistic, clinical, and translational perspectives. Our findings indicate that chronic inflammation has increasingly shifted from a peripheral topic toward a central organizing theme within osteoporosis research, reflecting growing integration between immunological and bone-centric research traditions.

1 | Introduction

Osteoporosis is a progressive skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased fracture risk and morbidity, particularly in aging populations. Traditionally regarded as a condition of bone fragility driven mainly by hormonal changes and aging, osteoporosis is now increasingly recognized as a systemic disease influenced by multiple physiological pathways, including immune dysregulation and chronic inflammation [1, 2].

Emerging evidence highlights chronic low-grade inflammation as a key contributor to the pathogenesis of osteoporosis. Inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and receptor activator of nuclear factor kappa-B ligand promote osteoclastogenesis and bone resorption, which in turn link immune activity with skeletal degeneration [3–5]. This intersection of bone biology and immunology has given rise to the concept of "osteoimmunology," which explores how immune signaling pathways regulate bone remodeling and disease progression.

Although the molecular and cellular interdependence between the skeletal and immune systems has been well established, the development of this knowledge has occurred within largely fragmented research traditions. The field of osteoimmunology itself emerged primarily from investigations of inflammatory joint diseases, particularly rheumatoid arthritis, where aberrant immune activation and receptor activator of nuclear factor kappa-B ligand-mediated osteoclastogenesis were shown to drive progressive bone erosion and joint destruction [6]. In contrast, osteoporosis research has historically evolved within a bone-centric and endocrine-oriented paradigm, emphasizing aging, sex hormone deficiency, calcium metabolism, and mechanical loading as principal determinants of bone loss. As a result, immune-mediated mechanisms were long regarded as secondary or context-specific rather than foundational to osteoporosis pathophysiology.

This disciplinary separation has only recently begun to narrow. In recognition of the distinctive immunological contributions to osteoporosis, Srivastava et al. [7] proposed the term "immunoporosis" in 2018 to conceptualize osteoporosis as, at least in part, an immune-regulated disorder. Nevertheless, the integration of chronic inflammation into mainstream osteoporosis research remains uneven. Much of the existing literature on inflammation-related bone loss has focused on acute or localized contexts, such as periprosthetic osteolysis following joint replacement or inflammatory arthritides, rather than on chronic low-grade systemic inflammation as a primary driver of age-related or idiopathic osteoporosis. Consequently, despite accumulating mechanistic evidence, the conceptual position of chronic inflammation within the theoretical framework of osteoporosis and within the intellectual structure of the field remains insufficiently consolidated and empirically mapped.

Building on this gap, the present study aims to make several theoretical contributions to understanding how chronic inflammation, as a core biological process, has been conceptualized and integrated within osteoporosis research. Specifically, it seeks to (i) reconstruct the intellectual structure of the field to assess whether research on chronic inflammation has remained compartmentalized within immunology and rheumatology traditions or has been substantively incorporated into bone-centric osteoporosis research; (ii) examine the temporal evolution of chronic inflammation from a peripheral or context-specific topic (e.g., inflammatory arthritis or post-surgical bone loss) to a potentially central organizing concept in osteoporosis research; and (iii) evaluate the extent to which mechanistic insights into inflammation-mediated bone remodeling have translated into clinically oriented osteoporosis frameworks. By foregrounding chronic inflammation as a unifying analytical lens, this study aims to reframe osteoporosis not merely as a metabolic bone disorder, but as a condition increasingly situated within a broader spectrum of chronic inflammatory diseases.

To operationalize these aims, we conducted a global bibliometric analysis of publications on osteoporosis and chronic inflammation from 1994 to 2025. Using citation-based and network-analytic techniques, we examined publication trends, country-level contributions, author collaboration networks, journal influence, keyword co-occurrence, and thematic evolution. This empirical mapping provides the basis for evaluating how chronic inflammation has been positioned within osteoporosis research over time and across disciplinary boundaries.

2 | Methods

2.1 | Search Strategy and Study Selection

A comprehensive literature search was conducted in the Scopus database on June 8th, 2025, to identify publications related to osteoporosis and chronic inflammation. The full exact search term was ("chronic inflamm*" AND "osteoporo*") to capture relevant variations. The default search field was used. Eligible publication types were restricted to original research articles, review articles, conference papers, and editorials using database filters, followed by manual verification (IHL & LHY). The search period covered 1994 and 2025. All retrieved records were exported in RIS and CSV formats for subsequent bibliometric processing and analysis.

2.2 | Software Tools and Setting

Analyses and visualizations were conducted using multiple platforms. Microsoft Excel 365 was used for certain graphs and tables. VOSviewer (version 1.6.20) was used for network mapping [8], while most bibliometric analyses were performed with the R-based packages bibliometrix and its graphical interface biblioshiny [9]. Citation metrics were supplemented with Harzing's Publish or Perish software (version 8.12) [10].

Bibliometric mapping parameters and preprocessing. Bibliometric networks were constructed using full counting methods for keyword occurrences. Network normalization in VOSviewer employed the association strength method, consistent with standard bibliometric practice. Keyword co-occurrence maps were generated using a minimum occurrence threshold of 15, selected to balance interpretability and network completeness. Manual thesaurus-based keyword merging was also performed to consolidate synonymous terms and spelling variations.

2.3 | Data Synthesis

The bibliometric analysis included the following parameters:

1. Annual Scientific Output: yearly publication counts were assessed to evaluate longitudinal trends in research productivity (Publish or Perish & Biblioshiny & Excel).

2. Geographical Analysis: country-level contributions were determined based on affiliations of corresponding authors, and international collaboration was quantified (Biblioshiny & Excel).
3. Authorship and Collaboration Networks: authors were ranked by publication count, with g-index, h-index, and fractionalized authorship scores calculated (Biblioshiny & Excel). Co-authorship networks were generated to visualize collaborative relationships (VOSviewer).
4. Journal Analysis: journals were ranked by publication volume in the field and assessed using g-index, h-index, and total citation counts (Biblioshiny & Excel).
5. Keyword Co-occurrence: frequently occurring keywords were identified, categorized, and visualized through co-occurrence mapping (VOSviewer).
6. Thematic Evolution: temporal changes in research themes were examined using thematic evolution analysis in relation to annual publication trends (Biblioshiny).

2.4 | Definitions

Lotka's Law describes author productivity patterns, whereby most authors contribute only one publication while a small number produce multiple works and form the core contributors of a research field. This principle was used to assess authorship distribution within the analyzed literature [11].

Bradford's Law describes the distribution of articles across journals within a specific research field, demonstrating that a relatively small core group of journals accounts for a large proportion of publications, while increasingly larger numbers of journals contribute progressively fewer relevant articles [12]. When journals are ranked by productivity and divided into zones, producing approximately equal numbers of articles. These typically consist of a core zone containing the most productive journals, followed by successive zones requiring a greater number of journals to yield similar publication counts. This pattern helps identify core journals central to a research domain.

Thematic maps categorize research themes into four quadrants according to their centrality and density [13]. Motor themes (high centrality and density) represent well-developed and influential topics. Basic themes (high centrality, low density) are fundamental but less internally developed areas. Niche themes (low centrality, high density) correspond to specialized but well-developed topics with limited external connections. Emerging or declining themes (low centrality and density) represent either newly developing or fading research areas.

2.5 | Robustness Check

A sensitivity analysis was performed using PubMed to assess the robustness of publication trends and contribution patterns across databases [14]. Although fewer documents were retrieved from PubMed compared with Scopus, country-level rankings by publication output and multiple country publication (MCP) ratio, as well as journal rankings by publication counts remained broadly consistent.

3 | Results

3.1 | Overview

A total of 1464 documents published between 1994 and 2025 were included in this bibliometric analysis, spanning 855 different journals. The annual scientific production showed an average annual growth rate of 13.45%, with the documents having an average age of 9.73 years. The temporal distribution, stratified by document type, is presented in Figure 1a. During the early period (1994–2001), research activity was limited, with fewer than 10 publications per year. In subsequent years, the volume of literature increased steadily.

By document type, original research articles ($n = 711$) and review articles ($n = 697$) dominated the dataset, with smaller proportions of conference papers ($n = 30$) and editorials ($n = 26$) (Table S1).

3.2 | Contributions of Countries/Regions

Figure 1b and Table 1 summarize the country-level research output and international collaboration based on the corresponding author's affiliation. The USA led with 241 publications, followed by China (156) and Italy (101). However, when examining international collaboration using the MCP ratio, a different pattern emerged. Belgium had the highest MCP ratio (0.571), indicating that more than half of its publications involved international co-authorship, despite a modest total output of 14 articles. Denmark (0.364) and the Netherlands (0.308) also showed high levels of international collaboration relative to their output. Among high-output countries, Germany, Italy, and the UK demonstrated both strong productivity and moderate collaboration ratios (0.247, 0.228, and 0.260, respectively). In contrast, countries such as Japan and Korea had lower MCP ratios (0.053 and 0.121).

Figure 1c,d present country-level citation performance based on total citations and average article citations. The United States of America (USA) led in total citations, followed by the United Kingdom (UK), Germany, and China. However, when ranked by average article citations, a different pattern emerged. Malaysia and Lebanon, despite lower total outputs, exhibited the highest average article citations per article, indicating the presence of a few highly cited publications. Austria also ranked highly by both total and average article citations, suggesting both productivity and impact. Traditional research powerhouses such as France, the UK, and the USA also performed strongly in average article citations.

3.3 | Most Relevant Authors

Table S2 presents the most productive authors in the field of osteoporosis and chronic inflammation research, ranked by the number of publications within the dataset. Georg A. Schett ranked first with 11 publications, followed by Willem F. Lems

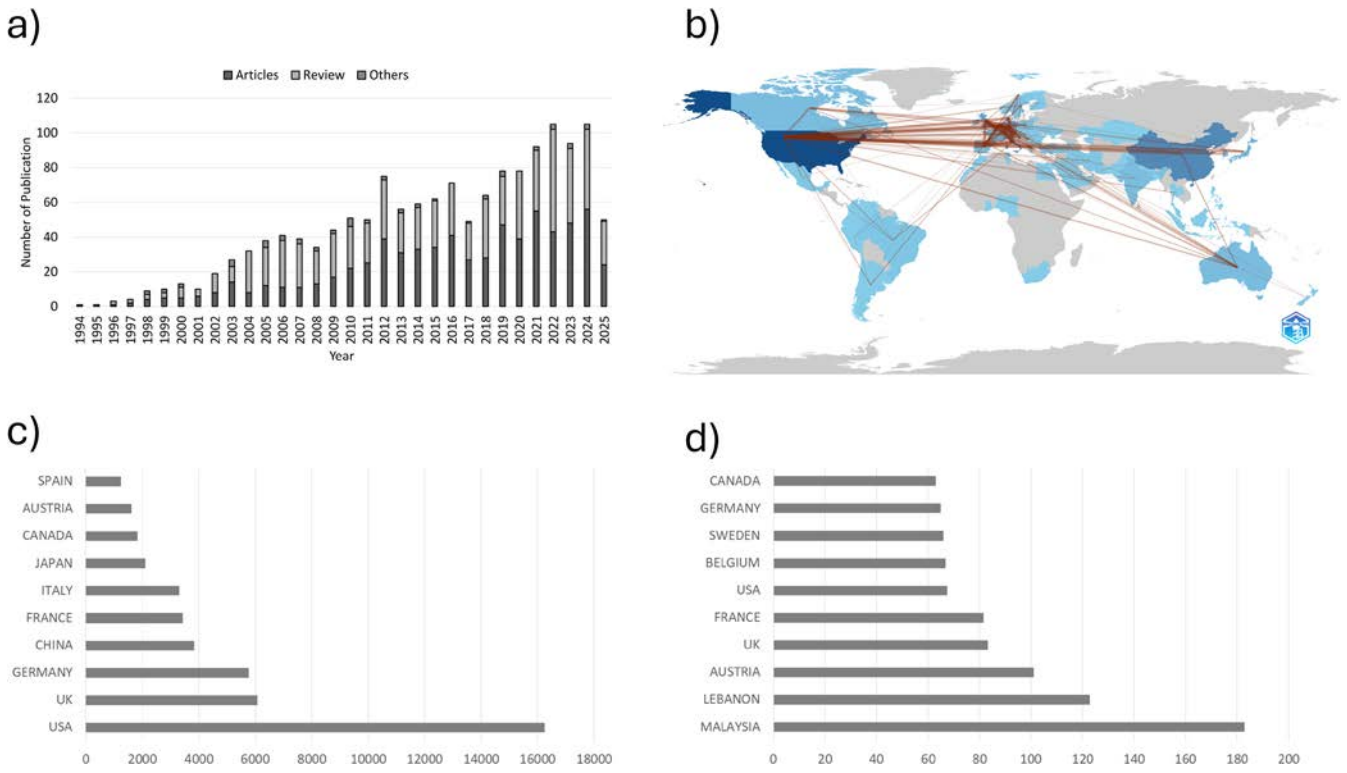

FIGURE 1 | (a) Temporal evolution of research output on osteoporosis and chronic inflammation from 1994 to 2025, stratified by document type (original articles, review articles, and "other" publications such as editorials and conference papers); (b) Country collaboration map based on co-authorship; (c) Country-level research impact based on total citations; (d) Country-level research impact based on average article citations.

with 9. Notably, Peter J. Barnes, despite contributing only five articles, had the highest fractionalized output, suggesting sole authorship in each case. Georg A. Schett and Willem F. Lems also achieved the highest H-indices (H = 8), indicating consistent citation performance across their works. Based on Lotka's Law, around 92.0% of the authors are one-time authors, and 8.0% are core authors in this topic (6.2% with two publications, 1.3% with three publications, and 0.5% with four or more publications), showing significant differences with Lotka's prediction ($p < 0.001$).

Among the most productive authors, several were found to be directly connected through co-authorship (Figure S1). Georg A. Schett, Willem F. Lems, Nancy E. Lane, Rosa Maria Rodrigues Pereira, and Irene E. van der Horst-Bruinsma formed a visible collaboration cluster, suggesting shared research initiatives or co-authored publications. Another distinct co-authorship link was identified between Mark S. Cooper and Rowan S. Hardy. In contrast, the remaining top authors appeared as isolated nodes in the network, indicating that they have not collaborated directly with each other within the scope of this dataset.

3.4 | Most Relevant Sources

A total of 1464 documents were published across 855 journals. According to the Bradford distribution, the journals were divided into three zones of productivity. Zone 1 comprised the top 77 journals, which collectively published 484 documents. Zone 2 included journals ranked 78th to 372nd, accounting for a cumulative total of 497 documents. Zone 3, which encompassed the remaining 483 journals (ranks 373 to 855), produced the final portion of the literature.

Figure 2a,b show the top 10 journals by number of publications, which published 156 papers (10.7% of the dataset) on osteoporosis and chronic inflammation. *International Journal of Molecular Sciences* and *Osteoporosis International* were the most prolific (26 and 25 papers; H = 16 each). Citation influence was greatest for *Journal of Bone and Mineral Research* (1672 citations from 12 papers) and *Frontiers in Pharmacology* (1150 citations from 10 papers), indicating high impact despite lower output. At the opposite end, Clinical Calcium produced 11 papers but garnered only 23 citations (H = 3). These results confirm that both productivity and impact are concentrated in a small core of high-profile, bone-focused journals.

Figure 2c depicts annual publication trajectories for the five leading journals identified. Among the top journals, *Osteoporosis International* was the earliest and sole contributor until 2012 and maintained a steady, near-linear growth thereafter, reaching 25 papers by 2025. In contrast, *International Journal of Molecular Sciences* entered the field only in 2014 but exhibited the most rapid expansion, surpassing *Osteoporosis International* in 2023 and attaining 26 papers by 2025. *Frontiers in Endocrinology* and *Frontiers in Immunology* displayed similar late onset yet steep growth patterns: both journals registered their first publications in 2016 and accelerated sharply after 2018, reaching 18 and 17 papers, respectively, by 2025. *Nutrients* followed a moderate trajectory, commencing in 2015 and increasing to 13 papers in the final year. Collectively, these trends show an early dominance

TABLE 1 | Country-level contributions and international collaboration patterns based on corresponding author affiliation.

Rank by number of articles							Rank by MCP ratio						
Rank	Country	Articles	SCP	MCP	Freq	MCP ratio	Rank	Country	Articles	SCP	MCP	Freq	MCP ratio
1	USA	241	206	35	0.165	0.145	1	Belgium	14	6	8	0.010	0.571
2	China	156	139	17	0.107	0.109	2	Denmark	11	7	4	0.008	0.364
3	Italy	101	78	23	0.069	0.228	3	Netherlands	26	18	8	0.018	0.308
4	Germany	89	67	22	0.061	0.247	4	Germany	89	67	22	0.061	0.247
5	UK	73	54	19	0.050	0.260	5	Italy	101	78	23	0.069	0.228
6	France	42	33	9	0.029	0.214	6	Spain	31	24	7	0.021	0.226
7	Japan	38	36	2	0.026	0.053	7	France	42	33	9	0.029	0.214
8	Korea	33	29	4	0.023	0.121	8	Canada	29	23	6	0.020	0.207
9	Poland	33	30	3	0.023	0.091	9	Greece	16	13	3	0.011	0.188
10	Spain	31	24	7	0.021	0.226	10	Iran	19	16	3	0.013	0.158

Note: Only countries with 10 articles or more were included in the ranking of MCP ratio.
Abbreviations: Freq, frequency, calculated as the number of articles from the country divided by the total number of articles in the dataset; MCP, multiple countries publication; SCP, single country publication.

by a specialty, bone-focused journal, followed by a swift rise of multidisciplinary and open-access platforms after 2015, reflecting a shift toward broader dissemination venues in this research domain.

3.5 | Most Locally Cited Documents

Table S3 presents the most locally cited documents in this research [15–22]. The documents were published between 2005 and 2017, with local citations ranging from 9 to 22. A total of eight publications were reviews discussing osteoporosis in the context of chronic inflammation, while two other documents focused on steroid treatment and its association with osteoporosis. The predominance of review articles among the most locally cited works suggests that conceptual and integrative syntheses, rather than single empirical studies, played a central role in shaping the development of the field. The continued citation of these publications within the dataset indicates that these foundational works remain central reference points for current research, supporting the view that integration between inflammatory and bone-centric research traditions has progressively strengthened over time.

3.6 | Co-Occurrence Network of Keywords

Figure 3 displays the co-occurrence network of keywords, illustrating thematic clustering in research on osteoporosis and chronic inflammation. The network reveals three major clusters: the green cluster centers around chronic inflammation, inflammation, oxidative stress, macrophages, and gene expression, highlighting the mechanistic and immunological underpinnings of inflammation-related bone disorders; the blue cluster revolves around osteoporosis, bone density, bone mineral density, fracture, and calcium, reflecting studies focused on diagnostic tools and bone structural integrity; and the red cluster is dominated by terms associated with disease-related risk factors (e.g., diabetes and hypertension) or pharmacological treatments commonly used in chronic inflammatory diseases (e.g., corticosteroids), which may contribute to osteoporosis as treatment-related adverse effects, representing literature on pharmacological interventions, comorbidities, and treatment-related complications. The presence of terms such as quality of life, diabetes, and hypertension indicates interdisciplinary interest in chronic disease management.

3.7 | Thematic Evolution

Figure 4 illustrates the thematic evolution of research topics over three time periods. In both 1994–2003 (Figure 4a) and 2004–2013 (Figure 4b), "osteoporosis" and "corticosteroids" consistently occupied the basic themes quadrant, reflecting their central role in the literature linking inflammation and bone health. By 2014–2025 (Figure 4c), "osteoporosis" remained a basic theme, but "corticosteroids" shifted into the niche themes quadrant. "Animal" appeared as an emerging or declining theme in the earliest period, then moved into the niche themes quadrant in the latest period. "Chronic inflammation" emerged as a basic theme only in the most recent period.

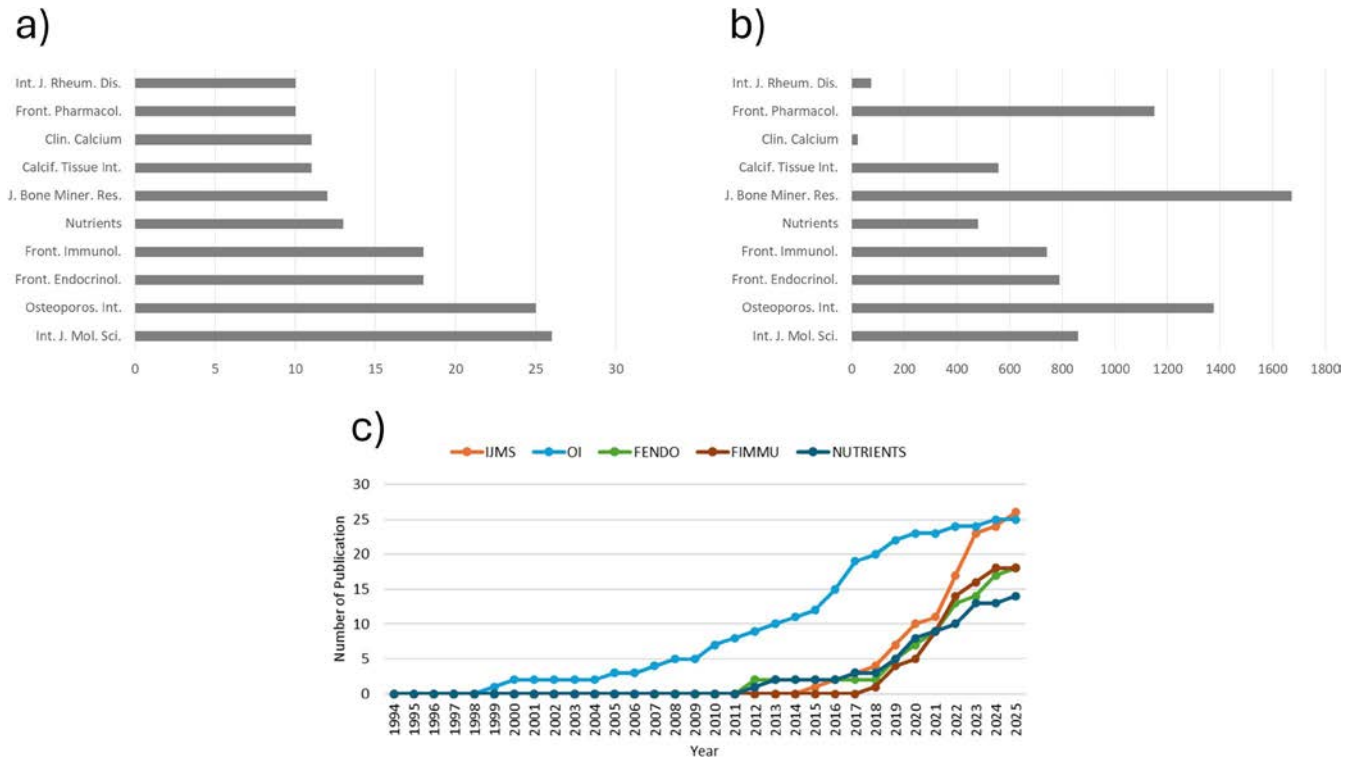

FIGURE 2 | (a) Top journals ranked by number of publication; (b) Top journals ranked by total citation; (c) Annual number of publications from 1994 to 2025 in the top five journals by publication number which published research on osteoporosis and chronic inflammation. FENDO, *Frontiers in Endocrinology*; FIMMU, *Frontiers in Immunology*; IJMS, *International Journal of Molecular Sciences*; OI, *Osteoporosis International*.

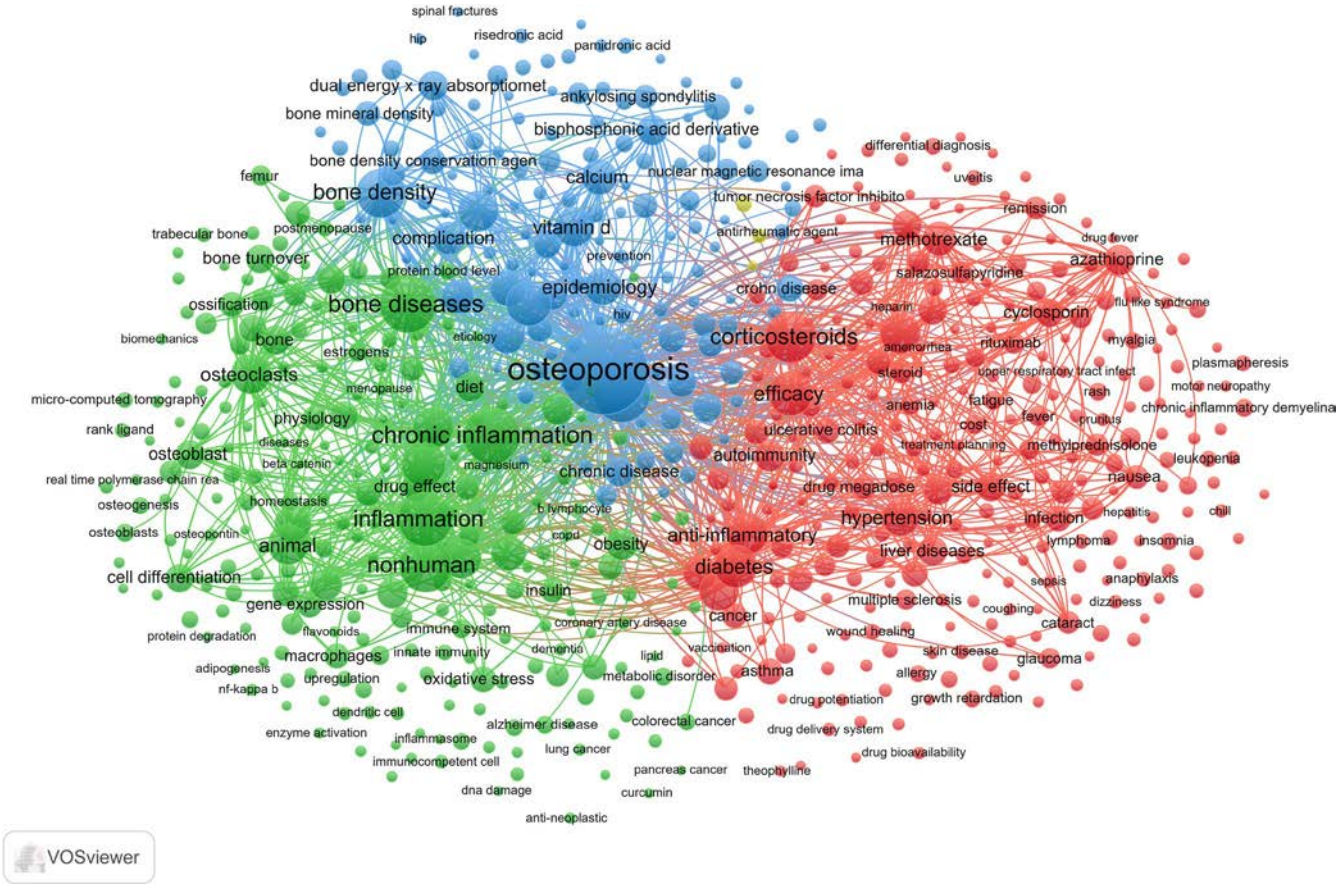

FIGURE 3 | Co-occurrence network of keywords in publications related to osteoporosis and chronic inflammation.

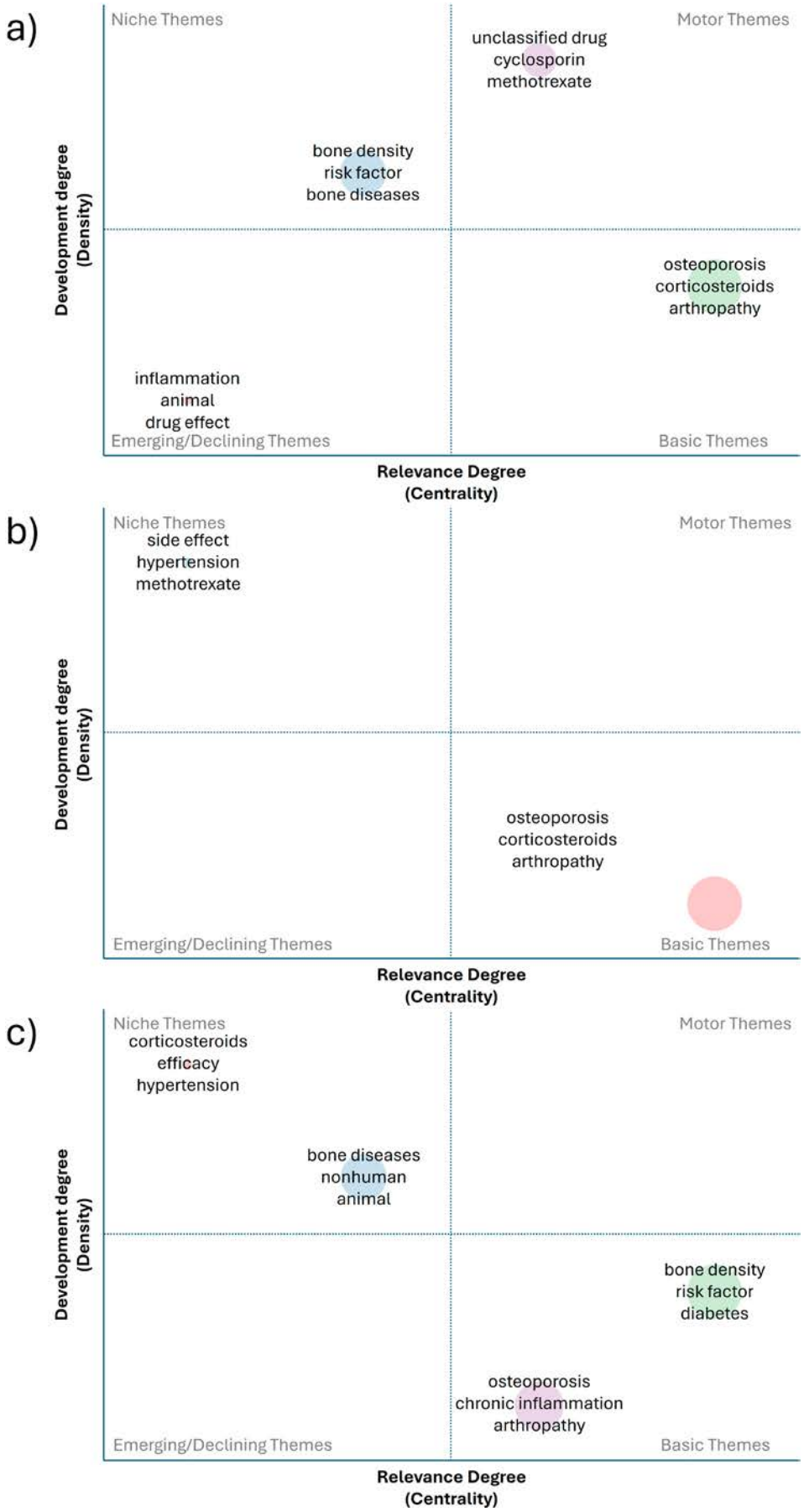

FIGURE 4 | Thematic evolution maps of keywords across three time periods: (a) 1994–2003, (b) 2004–2013, and (c) 2014–2025.

4 | Discussion

A steady increase in publication output was observed between 1994 and 2025, likely reflecting the growing recognition of the connection between inflammation and bone health. Osteoporosis is increasingly regarded not as an isolated skeletal disorder but as a manifestation of broader systemic dysfunction. Accumulating evidence suggests that oxidative stress, inflammation, and cellular senescence act synergistically to disrupt bone homeostasis by enhancing osteoclast activity, suppressing osteoblast function, and promoting bone marrow adiposity [2].

The growing research interest in osteoporosis may be partly attributed to the development and clinical adoption of advanced imaging technologies. Dual-energy X-ray absorptiometry (DEXA), approved by the U.S. Food and Drug Administration in 1988 and reinforced by the Bone Mass Measurements Act of 1998, established itself as the gold standard for measuring bone mineral density, enabling widespread screening and early diagnosis [23]. In parallel, the introduction of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT), provided simultaneous anatomical and metabolic assessment of inflammatory activity, improving clinicians' ability to detect and monitor inflammation-associated bone disorders [24]. As PET/CT became recognized for its utility in evaluating inflammatory and metabolic diseases, it further promoted research into the pathophysiological connections between chronic inflammation and osteoporosis.

The number of original research articles ($n = 711$) and review papers ($n = 697$) was remarkably similar. This balance suggests increasing recognition of the relationship between osteoporosis and chronic inflammation and also highlights a relative paucity of new empirical studies. The field appears to be in a consolidative phase, wherein researchers are systematically synthesizing existing evidence across disciplines to develop unified theoretical and mechanistic frameworks.

When ranked by number of articles, the USA leads with 241 publications, followed by China, Italy, Germany, and the UK. Among the top 10 countries in article count, Europe dominates with six countries (Italy, Germany, UK, France, Poland, and Spain), followed by Asia with three countries (China, Japan, and Korea) and North America with one country (USA). When ranked by MCP ratio, Belgium had the highest proportion of internationally co-authored papers, followed by Denmark and the Netherlands, suggesting strong reliance on global collaboration networks. In the top 10 MCP ratio list, Europe is again the most represented (Belgium, Denmark, Netherlands, Germany, Italy, Spain, France, and Greece), with North America (Canada) and Asia/Middle East (Iran) appearing once each. The absence of the USA, China, Japan, and Korea from the MCP ratio list, despite their high article counts, suggests that their research in this field is more nationally focused compared to European countries that tend to engage in broader international collaborations. The high-density network connections between European countries were observed.

Among the most prolific authors with at least five publications, representation spanned multiple countries, primarily from Australia, Austria, Brazil, the Czech Republic, Germany, Japan, the Netherlands, the UK, and the USA. European researchers accounted for the largest share, followed by those from North America, reflecting the strong concentration of leading academic and research institutions in these regions. The observed proportion exceeds Lotka's original theoretical expectation, possibly reflecting a broad and interdisciplinary interest in the topic from researchers outside the core field.

All identified authors were affiliated with academic institutions or governmental agencies, with no industry-based researchers detected among the top contributors. This pattern suggests that research on osteoporosis and chronic inflammation is predominantly driven by publicly funded or academically oriented initiatives, with limited efforts from the private sector. The absence of industrial participation may reflect the field's current emphasis on fundamental mechanisms and translational research rather than drug development or commercial applications.

Analysis of the co-authorship network among the top corresponding authors revealed that collaborations were generally confined to small, distinct clusters rather than forming a single, interconnected network. For instance, a prominent group comprising Georg A. Schett, Willem F. Lems, Nancy E. Lane, Rosa Maria Rodrigues Pereira, and Irene E. Van Der Horst-Bruinsma indicated close collaborative ties, while other clusters were more isolated. Some authors appeared to work independently without evident collaborative links to other top authors. This pattern suggests that despite the global interest in the field, high-impact research may still be driven by a limited number of regionally concentrated teams, with relatively few cross-cluster collaborations.

Among the top journals, both osteoporosis-focused and non-osteoporosis-focused journals are represented, indicating that the topic attracts interest from multiple disciplinary perspectives. Osteoporosis-specific journals, *Osteoporosis International* (rank 2), *Journal of Bone and Mineral Research* (rank 6), *Calcified Tissue International* (rank 7), and *Clinical Calcium* (rank 8), collectively contributed 49 articles, reflecting the central role of bone health-specialized platforms in disseminating research in this field. However, more than half of the top 10 journals are not osteoporosis-specific, such as *International Journal of Molecular Sciences* (rank 1) and *Frontiers in Immunology* (rank 4), which focus on broader biomedical or immunological topics, as well as nutrition and pharmacology. This distribution highlights that research on osteoporosis and chronic inflammation is inherently multidisciplinary, with substantial contributions from journals addressing molecular biology, immunology, pharmacology, and nutrition, alongside traditional bone health outlets. Osteoporosis-focused journals accounted for 49 articles, while non-osteoporosis-focused journals accounted for 95 articles. Despite the smaller share of total publications, osteoporosis-focused journals demonstrated a higher average citation impact (61.49 citations per article) compared to non-osteoporosis-focused journals (43.11 citations per article), suggesting that research published in osteoporosis-focused outlets may have greater visibility and influence within the scientific community.

Analysis of the time trend for the top five journals revealed distinct publication patterns. *Osteoporosis International* demonstrated the

longest and most consistent record of publications in this field, beginning in the late 1990s and showing steady growth over the years, maintaining a leading position until approximately 2024. In contrast, *International Journal of Molecular Sciences, Frontiers in Endocrinology, Frontiers in Immunology, and Nutrients* began contributing to the field between 2012 and 2018. Among these, *International Journal of Molecular Sciences* showed the most rapid growth, matching *Osteoporosis International* in 2025. These patterns suggest that while osteoporosis-specific journals initially dominated, the field has increasingly attracted multidisciplinary attention in recent years.

The keyword co-occurrence analysis underscores the multidimensional nature of research linking osteoporosis and chronic inflammation. The three distinct clusters reflect complementary yet specialized research streams within the field. The green cluster represents mechanistic and immunological studies that investigate the cellular and molecular pathways through which inflammation influences bone health, demonstrating strong engagement from basic science disciplines. The blue cluster centers on osteoporosis-related diagnostics, risk factors, and bone health assessments, highlighting the contribution of clinical and epidemiological research to understanding disease burden and progression. The red cluster emphasizes pharmacological interventions, comorbidities, and treatment-related complications, underscoring the systemic nature of therapeutic research in this area. Notably, thematic overlaps, such as between inflammatory mechanisms and osteoporosis diagnostics, or between pharmacological treatment and inflammatory pathways, illustrate increasing cross-disciplinary integration. This convergence suggests that future advances are likely to arise from collaborative efforts bridging mechanistic research, clinical evaluation, and therapeutic development.

This thematic diversity is mirrored in the distribution of publications across journals, where both osteoporosis-focused and non-osteoporosis-focused outlets contribute substantially. The active participation of journals in basic science, immunology, and nutrition indicates broad interdisciplinary engagement. Temporal trend analysis further reveals a progressive expansion of research perspectives beyond traditional osteoporosis literature toward more multidisciplinary platforms. This evolution aligns with the cross-cluster linkages observed in the keyword network and underscores the increasing convergence of mechanistic, clinical, and translational research, an integration that may accelerate the development of innovative preventive and therapeutic strategies.

The keyword co-occurrence analysis also identified corticosteroids as a main topic in the field. Corticosteroids, specifically glucocorticoids, are commonly used as anti-inflammatory agents in the treatment of inflammatory and autoimmune diseases; however, their long-term use is a well-established risk factor for secondary osteoporosis. The detrimental skeletal effects of glucocorticoids are multifactorial [24, 25], involving a shift in stromal progenitors toward adipocyte rather than osteoblast differentiation, increased osteoclast-mediated bone resorption, and long-term suppression of bone formation. These changes are compounded by accelerated apoptosis of osteoblasts and osteocytes, and impaired H-type vascular supply, which together undermine bone turnover and structural integrity.

The shift of "corticosteroids" from a basic to a niche theme suggests that research on corticosteroid-induced osteoporosis has become more specialized and potentially less central to the broader field. The evolution of "animal" from an emerging theme to a niche theme indicates that animal models have transitioned from exploratory use to more targeted investigations. The recent emergence of "chronic inflammation" as a basic theme reflects growing recognition of its unifying role in linking immunological mechanisms, metabolic changes, and bone pathology. Overall, these changes highlight a movement from a predominantly pharmacological focus toward a broader, pathophysiology-driven framework that integrates inflammation, comorbidities, and systemic effects into osteoporosis research.

A notable gap in the current literature is the limited investigation of how certain chronic inflammatory diseases, beyond the commonly studied conditions such as diabetes, may be linked to osteoporosis. One underexplored example is the group of hematological malignancies known as myeloproliferative neoplasms (MPN), whose pathogenesis has been proposed to involve chronic inflammation [26–28]. In osteoporosis, activation of the Janus kinase 2 (*JAK2*) signaling pathway has been implicated in bone loss, with both in vitro and in vivo studies demonstrating its role in reducing bone mass and impairing osteoblast function [29–32]. *JAK2* has also been proposed as a potential therapeutic target for osteoporosis [33, 34]. Notably, polycythemia vera (PV), a subtype of MPN driven by the *JAK2*V617F mutation, has been associated with bone loss and reduced osteoblast activity in animal models [35]. Furthermore, higher *JAK2*V617F allelic burden in PV has been linked to more severe symptoms and increased risk of disease progression, potentially reflecting a vicious cycle of inflammation [27, 36]. Given that underlying chronic inflammation can contribute to osteoporosis via the *JAK* pathway, and to MPN development through stem cell mutations, it is plausible that patients with MPN may have an increased risk of osteoporosis. Future research using large-scale databases is warranted to clarify the potential association among *JAK2* mutations, chronic inflammation, and osteoporosis in MPN, building on methodologies from recent population-based studies [37, 38].

To the best of our knowledge, this is the first bibliometric analysis performed regarding the topic of osteoporosis and chronic inflammation. Previous bibliometric research focused on different areas within the field of osteoporosis, including the molecular pathway [39], exploration of global and regional scientific output [40–43], treatment [44–47], and mapping themes and hot spots in subtypes: postmenopausal osteoporosis [48, 49], glucocorticoid-induced osteoporosis [50], and diabetic osteoporosis [51–53].

The latest overall osteoporosis bibliometric analysis identified 10 343 publications [40]. Among the top 10 countries, eight overlapped with those identified in our study. Among the top 10 journals, *Osteoporosis International*, *Frontiers in Endocrinology, Journal of Bone and Mineral Research, Frontiers in Pharmacology*, and *Calcified Tissue International* were also represented in both analyses. In contrast, none of the top 10 authors overlapped, suggesting that the intersection of chronic inflammation and osteoporosis represents a more specialized research niche compared with general osteoporosis research.

This study has several inherent limitations typical of bibliometric analyses. First, the results depend on the selected database and its indexing coverage, which may omit relevant literature from other sources. Second, citation-based metrics are inherently biased; older publications have had more time to accumulate citations, citation counts do not necessarily reflect scientific quality, and self-citations may artificially elevate perceived impact. Third, bibliometric methods quantify publication volume, citation patterns, and collaboration networks, but cannot directly assess the methodological rigor or validity of individual studies. To enhance inclusivity and reduce language bias, this analysis included non-English publications; however, such studies may be disadvantaged in citation counts and underrepresented in text-mining results. As non-English papers constituted approximately 10% of the dataset, their overall influence on the findings is likely minimal.

A list of included articles is available as Table S4.

5 | Conclusion

Research on chronic inflammation and osteoporosis has expanded rapidly, integrating mechanistic, clinical, and translational perspectives. While osteoporosis and corticosteroids remain central themes, the increasing prominence of chronic inflammation in recent years reflects an evolution in scientific focus. Future studies should further explore under-investigated inflammatory conditions to clarify shared pathophysiological pathways and identify novel therapeutic targets for inflammation-related bone loss.

Author Contributions

I-Hsiu Liou: conceptualization, methodology, validation, investigation, resources, writing – original draft, project administration, funding acquisition. **Wan-Yun Huang:** conceptualization, validation, writing – original draft. **Sheng-Hui Tuan:** conceptualization, writing – review and editing. **Wen-Hsin Chang:** conceptualization, validation, writing – review and editing. **Lennex Hsueh-Lin Yu:** methodology, software, formal analysis, investigation, data curation, writing – original draft, visualization, project administration. **Shu-Fen Sun:** conceptualization, resources, writing – review and editing, supervision.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Co-authorship network of authors related to osteoporosis and chronic inflammation. **Table S1:** Summary of bibliometric indicators by publication type in the field of osteoporosis and chronic inflammation research from 1994 to 2025. **Table S2:** Top contributing authors based on number of publications. **Table S3:** Most locally cited documents. **Table S4:** List of publications included.

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ORIGINAL ARTICLE

Classification of Osteoporosis and Detection of Compression Fractures by Implementing Real-Time Object Detection System Upon Medical Radiographs

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ABSTRACT

Aim: Artificial intelligence and machine learning have been increasingly employed in medical image diagnosis, but face the challenge of database acquisition. Hence, this study applies the You Only Look Once (YOLO) technique, a real-time object detection system, to construct the inference model, including the image preprocessing and labeling, model training, and the prediction of unknown data to detect objects.

Methods: We implement the YOLOv4 technique to classify osteoporosis and detect compression fractures. Trabecular characteristics of osteoporosis are extracted from caput femoris in X-ray images, and compression fractures are observed in lateral spine images. All the datasets are derived from the clinical practice of the collaborated teaching hospital.

Results: We construct the YOLOv4 model to classify osteoporosis and detect compression fractures with prediction accuracy of 78.1% and 68.3%, respectively. X-ray could be a screening tool to predict osteoporosis and select patients for DXA, especially in settings where the DXA facility is unavailable.

Conclusion: We find it promising to apply the developed approach to medical diagnosis with an accuracy of near 80%, and this deep learning model could preliminarily help to screen possible positives from abundant radiographs.

1 | Introduction

Recent developments in artificial intelligence (AI) have been inspiring its application in medical domains, such as disease management, health education, and image processing [1–3]. In particular, image classification and the subsequent object detection have become increasingly important to adapt their applications to various fields, such as medical diagnosis, traffic analysis, automated optical inspection, and so on [4, 5].

Most of the deep learning models that classify osteoporosis are based on Convolutional Neural Networks (CNN) [6], such as

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AlexNet, VGG, Inception, and ResNet. So far, the number of neural network layers in the models has grown rapidly to over 100 layers, which requires more input data to train the models.

When employing artificial intelligence measures for medical image diagnosis [7, 8], the acquisition of datasets is sometimes demanding due to limited patient cases. Meanwhile, the detected objects in the input images are prone to being confined within only a few classes. In the digital era, it is important to employ a comprehensive database with the support of digital technologies and a flexible strategy to address the issues [9]. Hence, the advent of the you only look once (YOLO) technique, a real-time object detection system, seems to be a concise way to deal with the mentioned conditions. This approach does not need large-size datasets to train the model, while it derives acceptable output to detect objects with merely several classified types [10]. YOLO has the ability to perform real-time object detection with high speed and accuracy, making it particularly suited for medical imaging where rapid diagnosis is critical. Unlike traditional methods that require multiple passes over the image, YOLO processes the entire image in a single pass, significantly reducing detection time. This efficiency is essential in clinical settings where large volumes of images need to be analyzed quickly. Furthermore, YOLO's ability to detect multiple objects within a single image frame enhances its utility in identifying coexisting conditions or multiple fractures [11].

However, the encountered challenge is that labeling these datasets requires lots of human labor, including technicians and doctors. Thanks to the assistance of the collaborating teaching hospital, Chung Shan Medical University Hospital, these issues have been appropriately addressed.

In this study, we introduce a two-part dataset with different clinical targets: (1) hip X-rays focusing on the caput femoris region to classify osteoporosis, and (2) lateral spine X-rays to detect compression fractures.

In the first part of this study, we classify osteoporosis into three different levels, in accordance with DXA (dual-energy X-ray absorptiometry), BMD (bone mineral density), and T-score. They are normal ($T \geq -1.0$), osteopenia ($-2.5 < T < -1.0$), and osteoporosis ($T \leq -2.5$), where T-scores were calculated by using the BMD data of young females aged from 20 to 40 years old as a reference.

The anteroposterior or lateral view of spines is sometimes used to train neural networks [12]. In more common cases, the fine characteristics of femoral bone trabeculae seem to reveal better information when building the model [13].

In the second part of this study, however, the detected objects of compression fractures are classified into three different types according to their shapes. They are wedge, concave, and crush, respectively. These fractures are labeled in lateral spine X-ray images in this article.

By comparing a high spatial-frequency texture (dense trabecular bone in the femoral head) with a low spatial-frequency feature (vertebral fracture shape), our study provides new insights into how image characteristics affect model performance. Clinically, the proposed YOLOv4 system demonstrates how standard radiographs can be used for opportunistic screening of both osteoporosis and spinal fractures in real-time, which is especially valuable in settings where DXA scans or specialist radiologists are not readily available.

The following statement will elaborate on the procedure of constructing the inference model, which includes image preprocessing and labeling, model training, and the prediction of unknown data.

This work contributes to (1) a two-part, hypothesis-driven radiograph study design that contrasts high spatial-frequency trabecular texture with low spatial-frequency morphological cues (lateral spine images for compression-fracture detection), providing a controlled testbed to examine how feature regimes affect model behavior under a unified pipeline; (2) a deployment-oriented evaluation that goes beyond a single final score by reporting threshold sensitivity and a failure-mode taxonomy to improve transparency and operational decision-making; and (3) a reproducible opportunistic-screening workflow using routine radiographs, clarifying practical design choices and limitations for real-world use cases with constrained data.

2 | Methods

2.1 | Datasets

2.1.1 | First Part

We obtained 192 eligible KUB images from the Department of Nuclear Medicine of Chung Shan Medical University Hospital. The region of interest (ROI) around caput femoris is truncated from each image. Among all, 160 images are used to train the YOLO model, and the remaining 32 images are used to test the inference accuracy.

2.1.2 | Second Part

We also acquired 361 lateral spine images in the same way. In total, 331 images are used for training the YOLO model, and the remaining 30 images are used to test the inference precision.

2.2 | Image Preprocessing

2.2.1 | First Part

Each obtained KUB image is cropped so that only the segment around the caput femoris remains, which is indicated with a red rectangle in Figure 1. The derived image has a dimension of 512×512 pixels.

2.2.2 | Second Part

Each of the obtained lateral spine images is cropped so that only several specific vertebrae still remain in the image. They are L1–L5 and T12, along with parts of T11 and S1, as indicated in Figure 2. The derived image has a dimension of 480×600 pixels.

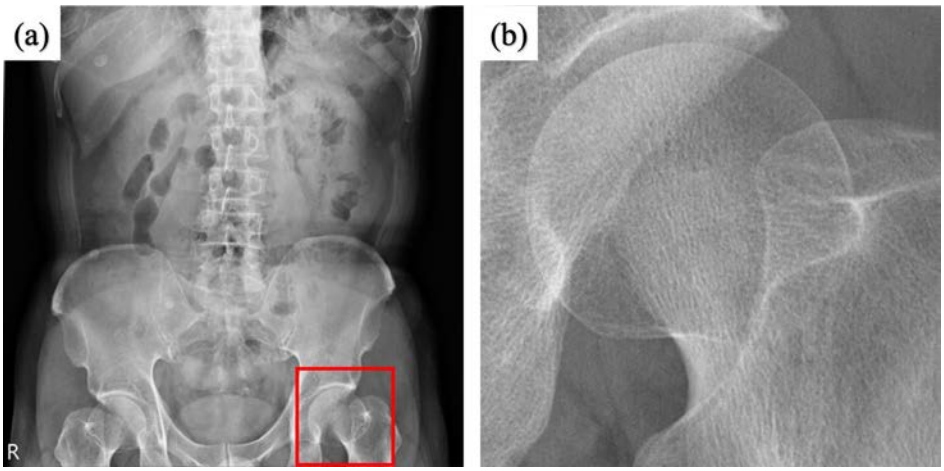

FIGURE 1 | (a) The original KUB image is attached by a red rectangle that will be the truncated area. (b) The cropped image has a dimension of 512×512 pixels, where the dense bone trabeculae are observed inside the caput femoris.

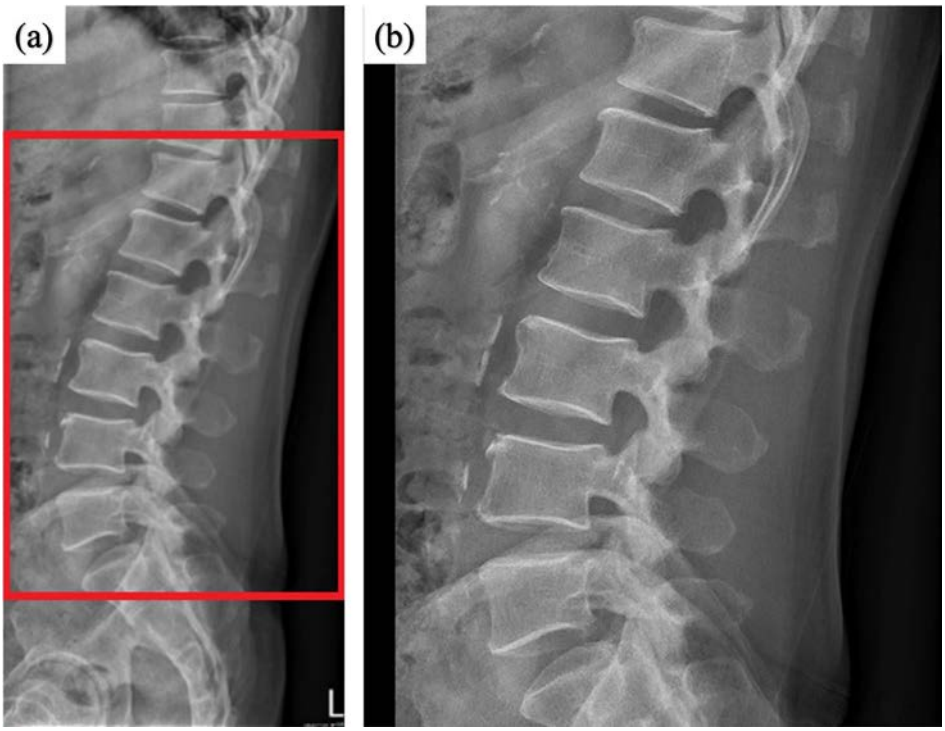

FIGURE 2 | (a) The original lateral spine image. (b) The cropped image has a dimension of 480×600 pixels.

Some original images might not be clear enough to decipher well. In this case, we enhance these images with *Photoshop* software. Most of the enhancements are accomplished by adjusting the brightness or contrast of the images. All radiographs used for training and evaluation were processed through a reproducible, automated preprocessing pipeline implemented programmatically.

2.3 | Image Labeling

2.3.1 | First Part

We performed manual bounding-box annotation using the *labelImage* program with Python 3.7. For the osteoporosis task, the cropped caput femoris ROI was annotated and assigned to one of three classes (normal, osteopenia, osteoporosis). This study does not employ weak-supervision labeling functions or a separate label model; all labels are manually curated. The labeled messages are composed of the location, dimension, and classification, which is indicated in Figure 3a. Only one labeled object exists in each image.

2.3.2 | Second Part

We also use *labelImage* software to label the compression fractures of the vertebrae. The labeled messages comprise their locations, dimensions, and classifications, which are indicated in Figure 3b. Every image could have more than one classified object.

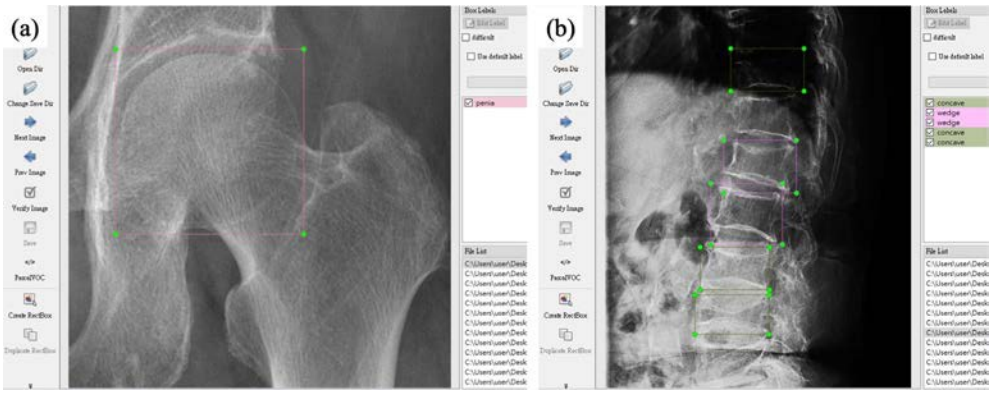

FIGURE 3 | The labeled X-ray image of (a) osteoporosis using labelImage software and (b) compression fractures in the same way.

2.4 | YOLOv4 Architecture

In this study, YOLOv4 was selected as a practical baseline due to its mature implementation and deployment feasibility under our study constraints. Newer YOLO variants can provide incremental improvements in mean average precision, but often at the cost of higher computational demand or less mature software support at the time of our study. Our goal is to demonstrate a reproducible and deployable screening pipeline under limited data and constrained computing resources. We therefore treat YOLOv4 as a stable baseline with widely available implementations.

The YOLOv4 architectures of both the first and second parts are nearly the same, except that they are with different input datasets.

The kernel algorithm of the model is based on CNN, of which the most popular strategy is ResNets (Residual Networks). The CNN calculation is simply performed once when determining the detected objects. Only several rectangles with acceptable confidences and overlapping are finally chosen from hundreds of preliminary ones. The selected rectangles suggest the possible objects' locations and classifications.

For the overall procedure of building the model, once the labeling process is completed, we then have to set up the configuration files. These files constitute the parameters to execute the neural networks, which include the classes, filters, batches, etc.

We afterward upload the related files and directories to the Google Cloud disk, so that the free GPUs of the Colab server can be employed to train our model to derive appropriate weights. Finally, the weights are downloaded to the personal computer to proceed with the consequent inferences.

3 | Results

3.1 | Diagnostic Performance of the YOLOv4 Models

3.1.1 | First Part

The accomplished model eventually infers classifications of osteoporosis of 32 X-ray images, which did not take part in the training. The inference assessment is quite simple because every image can only have one kind of classification. There are 25 images correctly predicted in the experiment, while the remaining 7 images are wrongly predicted. The accuracy is estimated to be around $25/32 = 78.1\%$. Figure 4 shows the forecasted output images with three different types: they are normal, penia (osteopenia), and porosis (osteoporosis).

3.1.2 | Second Part

The model also infers object detection of compression fractures of 30 X-ray images, which did not take part in the training either. The inference assessment here is more complicated than the first one. Because every image is liable to have more than one detected object, as shown in Figure 5. It is then necessary to statistically evaluate the results.

3.2 | Statistical Analysis

3.2.1 | First Part

In addition to the prediction of accuracy, we also establish the confusion matrix to find messages from the statistics. Table 1 shows that porosis vertebrae are seldom mistaken as normal ones, and vice versa. It seems that the misjudgment mainly occurs among spines with neighboring T-scores in this model.

3.2.2 | Second Part

To simplify the evaluation, we only calculate the precision of the inference. The precision is defined as $TP/(TP + FP)$, where TP is the number of true positives and FP is the number of false positives. FP in this study is normal vertebrae mistaken as fractured ones, while TP is the correct determination of fractured spines. The precision with a threshold confidence of 25% is then derived as $28/(28 + 13) = 68.3\%$.

To improve robustness under limited sample size, we propose the repeated stratified random splits (Monte Carlo cross-validation). Specifically, we repeat the train/test partition N times while preserving the class distribution, train the model under the same protocol for each split, and report the mean ± standard deviation of the primary metrics.

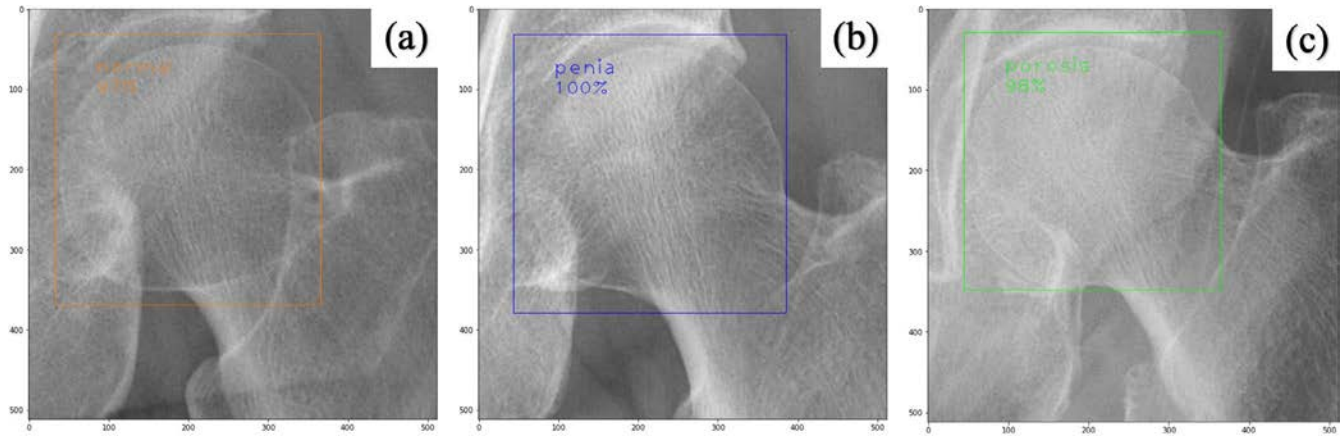

FIGURE 4 | The forecasted images with three different types of osteoporosis. The bounding box also shows its confidence.

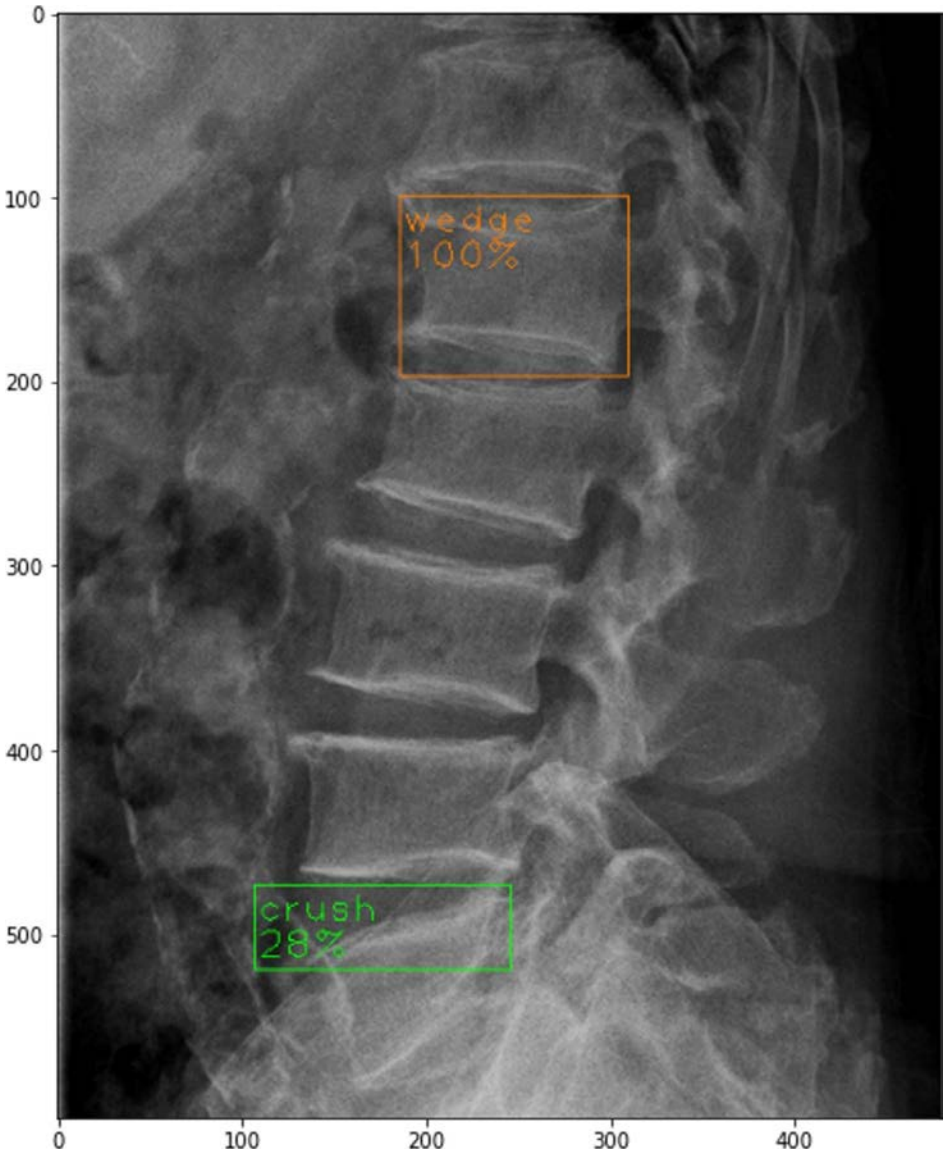

FIGURE 5 | Objects detection of a lateral spine X-ray image. The threshold confidence is chosen 25% as a fixed level in the experiment.

TABLE 1 | The confusion matrix of the first part of the experiment.

Prediction labeled	Normal	Penia	Porosis
Normal	12	1	0
Penia	1	12	0
Porosis	1	4	1

4 | Discussion

This study's two-part design (hip vs. spine X-rays) illustrates a multi-faceted contribution: it not only applies YOLOv4 to new types of radiographic data, but also highlights how trabecular detail and gross anatomical contours influence detection results, providing a deeper understanding of model behavior and clinical applicability.

We deliberately divide this research into two parts to compare the consequences of inputting datasets with different spatial frequencies [14]. The dense bone trabeculae exhibit a high spatial-frequency pattern inside the caput femoris. The fractured vertebrae seem to only contribute their contour messages to the training model, which are considered low spatial frequencies.

Those low spatial frequencies can only offer limited information to the training model. On the contrary, higher spatial frequencies provide more features to compute the model weights. This might be one of the reasons why we just used less than 200 X-ray images in the first part to acquire a sensible forecast result.

In the context of object detection for medical images, one could consider two-stage detectors (e.g., Faster R-CNN with a ResNet-50 backbone) or classification networks (Inception, ResNet) for a similar task. Generally, two-stage detectors could achieve high accuracy on large datasets, but they run slower and require a separate region proposal step. In contrast, our one-stage YOLOv4 approach performs detection and classification in a single forward pass, achieving real-time speed with accuracy that is comparable to modern CNN-based methods.

Moreover, the YOLOv4 model has several advantages compared to CNN. It can precisely select the ROI in the image with an adjustable rectangle; it also makes optimal determinations from hundreds of preliminary feasible choices [15].

Sapthagirivasan et al. [16] used the femoral neck as the ROI to investigate the improvement of osteoporosis diagnosis with support vector machine (SVM) in 2013. The ensuing literature [17] detailed the enhancement measures in the preprocessing. It also compared the results using different ROIs among the hip and calcaneus as well as dental panoramic radiographs, despite the fact that related reports on the adoption of caput femoris are still rarely found. The output of this article recommends the femoral head as a suitable option when applying the deep learning models. The accuracy is possibly elevated to some extent once the enhancement techniques are introduced to the image preprocessing, as we manifested before [18, 19].

It will be intriguing to apply this model to investigate the subchondral insufficiency fracture of the femoral head [20]; it also inspires having this method in conjunction with the research of medication treatment [21, 22].

The adoption of YOLO in medical imaging addresses key challenges in diagnostic radiology by enabling faster and more accurate image analysis [23]. Its application is particularly beneficial in resource-limited environments, where access to specialized radiologists may be scarce. By integrating YOLO into routine screening processes, healthcare providers can automate the detection of various conditions, reducing the workload on radiologists and minimizing the risk of oversight. The model's performance can be influenced by the quality and diversity of the training data, necessitating extensive datasets that reflect a wide range of pathologies and demographic variations.

The reported accuracy (78.1% for osteoporosis classification and 68.3% precision for fracture detection) does not meet the clinical threshold for autonomous deployment. In practice, fracture detection tools are expected to demonstrate sensitivities and specificities above 85%–90%. Our model is intended to assist in preliminary screening or triaging in high-volume or resource-limited environments, rather than to replace radiologist judgment or DXA diagnostics. Improving diagnostic metrics will require larger and more diverse datasets, refined annotation standards, and possibly ensemble or hybrid model approaches.

5 | Limitations

A key limitation is the absence of a cross-architecture benchmark against newer YOLO variants or other classifiers under matched protocols. Hence, this study should be interpreted as a feasibility and baseline study rather than a state-of-the-art comparison. Future work will conduct standardized benchmarking (e.g., YOLOv5/YOLOv8 and a two-stage detector) using repeated splits, threshold sweeps, and metrics.

6 | Conclusion

We demonstrate the procedure of constructing a YOLOv4 model to classify osteoporosis with a prediction accuracy of 78.1%. And we also use a similar model to detect compression fractures with a precision of 68.3%. Clinically, the X-ray could be a screening tool to predict osteoporosis and select patients for DXA, especially in a setting where a DXA facility is unavailable.

Author Contributions

A.-C.C., J.-H.W., C.-W.C., C.-C.Y., and J.C.-C.W. had full access to the study data and verified the underlying study data. A.-C.C. and J.-H.W. contributed to the conception, data analysis, and writing of the original draft of this paper. C.-W.C. contributed to the writing of the original draft of this paper. C.-C.Y. and J.C.-C.W. contributed to the conception and writing with review and editing of this paper. All authors were

involved in study design, data analysis, interpretation, and report writing, and had final responsibility for the decision to submit for publication.

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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.

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LETTER TO THE EDITOR

A Case Report of Relapsing Polychondritis Combined With Lupus Nephritis

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Dear Editor,

This article presents a case of relapsing polychondritis (RP) coexisting with lupus nephritis. Following treatment, the lupus nephritis achieved complete remission, while the polychondritis experienced intermittent relapses. This clinical course offers valuable insights into the potential relationship, as well as the distinguishing features, of these two conditions.

The patient is a 50-year-old female who has experienced recurrent swelling and pain in both auricles over the past 3 months. Each episode typically involves one auricle and is accompanied by erythema and tenderness at the nasal base, with symptoms persisting for approximately 5–7 days before resolving spontaneously without intervention. 10 days prior to presentation, the patient developed redness and swelling of the right auricle again (Figure 1A), along with concurrent swelling and pain in both ankle joints. Laboratory investigations revealed an erythrocyte sedimentation rate (ESR) of 120 mm/h (normal range: 0–20 mm/h), a white blood cell count of 1.9×10^9/L (normal range: 3.8–5.1 $\times10^9$/L), hemoglobin level of 111 g/L (normal range: 115–150 g/L), platelet count of 145×10^9/L (normal range: 125–325 $\times10^9$/L), lymphocyte count of 0.4×10^9/L (normal range: 1.1–3.2 $\times10^9$/L), and neutrophil count of 1.4×10^9/L (normal range: 1.8–6.3 $\times10^9$/L). Cytokine analysis showed elevated levels of IL-6 at 11.06 pg/L (normal range: 0–7 pg/L) and TNF-α at 15.36 pg/mL (normal range: 0–8 pg/mL). The antinuclear antibody titer was 1:3200 with a nuclear granular pattern. Specific autoantibody testing demonstrated positivity for anti-Sm, anti-nucleosome, anti-ribonucleoprotein 70, and anti-RO-52 antibodies, while anti-double-stranded DNA antibody levels were within the normal range at 2.2 IU/mL (normal range: 0–36 IU/mL). Additionally, anti-MPO, anti-PR3, and anti-GBM antibodies were all negative. Biochemical analysis revealed hypoalbuminemia with an albumin level of 26.5 g/L (normal range: 35–52 g/L) and a total protein level of 58.1 g/L (normal range: 65–85 g/L). Elevated inflammatory markers included a C-reactive protein level of 13.1 mg/L (normal range: 0–6 mg/L), complement C3 at 74.6 mg/dL (normal range: 90–180 mg/dL), and complement C4 at 15.1 mg/dL (normal range: 10–40 mg/dL). Urinalysis and urine sediment examination revealed proteinuria (3+), hematuria (2+), with an average of 11.68 red blood cells per high-power field (HPF), and a 24-h urine protein excretion of 2.99 g. No significant abnormalities were detected on chest CT, abdominal color Doppler ultrasound, or cardiac color Doppler ultrasound. A renal biopsy was performed, and the postoperative pathological findings are consistent with lupus nephritis (Class V) (Figure 1C). The patient fulfilled the classification criteria for both relapsing polychondritis according to the 2018 ACR/EULAR guidelines and systemic lupus erythematosus (SLE) based on the 2019 EULAR/ACR criteria, with an SLEDAI-2 K score of 14.

Based on the 2024 APLAR consensus guidelines on the management of lupus nephritis [1], pulse methylprednisolone therapy was not indicated for type V lupus nephritis in this case, and oral glucocorticoid therapy was therefore initiated as an alternative treatment approach. This patient has been diagnosed with lupus nephritis and also exhibits extrarenal manifestations, including leukopenia, arthritis, and chondrositis. After comprehensive evaluation of the clinical profile, tacrolimus was selected as the preferred immunosuppressive agent. Treatment included prednisone 40 mg once daily for anti-inflammatory effects and tacrolimus 1 mg twice daily for immunosuppressive therapy. Subsequently, ESR and CRP levels decreased, while complement and serum albumin levels normalized. The urine protein-to-creatinine ratio (UPCR) continued to decline, indicating complete renal remission 5 months later (UPCR 0.4). During the treatment course, the patient experienced twice episode of

Key Message

RP may coexist with lupus nephritis, with each condition exhibiting distinct clinical features and prognostic outcomes.

auricular and nasal root swelling and pain. The rate of prednisone tapering was reduced, and the symptoms subsequently improved. The patient is currently receiving oral prednisone acetate 7.5 mg once daily and tacrolimus 1 mg twice daily. No complications, such as infections, were observed throughout the treatment period.

RP is a rare autoimmune inflammatory disorder. In addition to affecting cartilaginous tissues, it may also involve multiple organ systems, including the eyes, auditory-vestibular system, cardiovascular system, skin, and nervous system. Renal involvement is less common [2]. RP must be differentiated from several other conditions. VEXAS syndrome, a rare autoinflammatory disorder associated with UBA1 gene mutations and characterized by recurrent chondritis, is typically accompanied by systemic manifestations such as fever, ocular involvement, myelodysplastic syndrome, and pulmonary infiltration. However, this patient does not exhibit these features and therefore does not meet the diagnostic criteria for VEXAS syndrome. Infectious chondritis usually presents with a clear history of infection, clinical signs including fever, cartilage swelling, and pain, along with elevated peripheral white blood cell counts, and demonstrates a favorable response to antimicrobial therapy. IgG4 related disease (IgG4-RD) is a multisystemic fibroinflammatory disease process characterized by multiorgan infiltration of IgG4-positive plasma cells and elevation of serum levels of IgG4 immunoglobulin. This disease can cause pseudotumor-like changes in the ear in a small number of patients, and occasionally cochlear cartilage inflammation occurs [3]. This patient does not meet the above diagnosis.

It is indeed noteworthy that cases of RP co-occurring with systemic lupus erythematosus (SLE) are exceedingly rare. A total of six patients with complete clinical and laboratory data were identified between 1980 and the present. The cohort comprised five females and one male. Among these, four patients developed RP 5–9 years after SLE diagnosis, all during a clinically stable phase of SLE [4–6]. One of these four patients had biopsy-proven membranoproliferative glomerulonephritis. Two patients received concurrent diagnoses of RP and SLE; of these, one had histopathologically confirmed type II lupus nephritis [7, 8]. Serum anti-dsDNA antibodies were positive in three of the six patients. In the index case, RP presented as the initial clinical manifestation and coincided temporally with active SLE and biopsy-confirmed type V lupus nephritis. Notably, cartilage inflammation recurred during renal remission, underscoring the distinct, non-parallel disease trajectory observed in this patient. It is worth mentioning that the patient has active nephritis, but the dsDNA antibody is negative and the antinuclear some antibody is positive. At present, more and more evidence has found that the pathological association between dsDNA antibodies and lupus nephritis is relatively weak, and it has been reported that in lupus nephritis lacking anti-dsDNA antibodies, antinucleosome antibodies, that circulating levels of anti-enolase 1 and anti-histone 2 IgG2 may be the causes of renal damage in patients, which is worthy of further exploration [9].

RP may coexist with SLE, and their clinical manifestations partially overlap, suggesting a potential common pathogenic mechanism between the two diseases. RP is an immune-mediated disorder in which CD4+ T cells serve as central mediators of the immune response. These cells secrete proinflammatory cytokines, including gamma interferon (IFNγ) and interleukin-17 (IL-17), which promote the recruitment and activation of additional immune cells, thereby perpetuating an inflammatory cascade. B cells contribute to disease pathogenesis by producing autoantibodies targeting cartilage components, leading to the formation of immune complexes. These complexes activate the complement system, further exacerbate inflammation, and ultimately result in cartilage degradation. Histopathological analyses of a limited number of patients with both SLE and RP have revealed neutrophil and lymphocyte infiltration, followed by progressive local cellular infiltration and deposition of immunoglobulins and complement component C3 [10, 11]. Although immune-related factors, such as genetic variations and T lymphocyte activation, have been implicated in disease development, the exact mechanisms remain to be elucidated [12]. During the treatment course, the patient experienced recurrence of auricular swelling and pain that was not correlated with the improvement of lupus nephritis. Tracheal involvement, elevated CRP levels prior to treatment, and initial monotherapy with corticosteroids have been identified as risk factors for disease recurrence in patients with RP [13]. Patients often experience a high physical and psychological burden of illness [14]. Combination therapy with corticosteroids and immunosuppressive agents may help delay

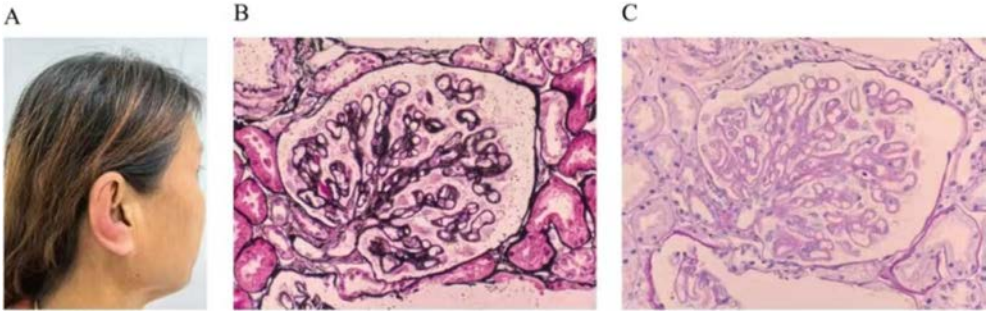

FIGURE 1 | (A) The patient's right auricle exhibits signs of erythema and swelling. (B) PASM-Masson staining (200X). (C) PAS staining (200X) demonstrates diffuse thickening of the glomerular basement membrane with spike formation, the walls of capillaries harden, renal tubules atrophy, and protein casts.

disease relapse. Whether recurrent polychondritis represents an independent entity or a distinct clinical manifestation of systemic lupus erythematosus remains a subject of debate. In this case, the patient achieved a relatively favorable therapeutic response following combination therapy with corticosteroids and tacrolimus. Previous cohort studies have indicated that different clinical phenotypes of RP are associated with varying prognoses [15]. However, further in-depth research is warranted to better understand the long-term prognosis of this specific phenotype in the context of connective tissue disease represented by SLE.

Author Contributions

Fangfang Wang: writing. **Fengmei Ge and Qi Chen:** data collection. **Xuebin Wang:** review and editing.

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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 in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1.** Supporting Informatio

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LETTER TO THE EDITOR

Elevated Serum Levels of β1,4-Galactosyltransferase 1 Have Diagnostic Value in Patients With Dermatomyositis

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Dear Editor,

Dermatomyositis (DM) is a type of idiopathic inflammatory myopathy (IIM) characterized by the presence of distinct skin lesions and diverse clinical manifestations, impacting multiple organ systems, including the pulmonary, cardiac, gastrointestinal, endocrine, and vascular systems [1]. The pathogenesis underlying DM is complex and involves certain genetic and environmental factors. Despite this knowledge, the triggers and mechanisms of autoimmunity in individuals with DM remain unclear [2]. While traditional biomarkers contribute to the early diagnosis of DM, their sensitivity and specificity have limitations [1]. Consequently, there is an ongoing effort among researchers to identify and validate new biomarkers for the improved diagnosis of DM.

β1,4-galactosyltransferase 1 (B4GALT1), which belongs to the B4GALT family, is responsible for transferring galactose to N-acetylglucosamine acceptor sugars through a beta-1,4 linkage and serves as a crucial enzyme in the biosynthesis of N-glycans [3]. Recent studies suggest that B4GALT1 may be involved in the regulation of immune cell functions and the modulation of inflammatory processes. Nonetheless, its potential role in the pathology of DM has yet to be established. Hence, in the present study, we focused on conducting a cross-sectional study to compare the serum levels of B4GALT1 in DM patients against those of healthy controls (HCs), and to assess the diagnostic value of B4GALT1 as a novel biomarker for DM diagnosis.

In this study, we enrolled 48 DM patients who fulfilled both the Bohan and Peter criteria and the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) criteria, along with 50 rheumatoid arthritis (RA) patients meeting the 1987 ACR or the 2010 ACR/EULAR criteria as disease controls, and 40 healthy controls (HCs) from the Department of Rheumatology at West China Hospital of Sichuan University from December 2020 to November 2023. The mean ages were comparable across groups: 47.56 years (standard deviation: 10.43) in the DM group, 47.46 years (standard deviation: 13.18) in the RA group, and 48.18 years (standard deviation: 12.38) in HCs, with no significant intergroup differences (all $p > 0.05$). The proportion of females was also comparable between DM and RA (70.83% vs. 82.00%, $p > 0.05$) and between DM and HCs (70.83% vs. 75.00%, $p > 0.05$). Among those with DM, 38.78% were found to have antibodies against MDA5, while 32.65% had antibodies against Ro52. Furthermore, 24 individuals were diagnosed with interstitial lung disease (ILD). The creatine kinase (CK) levels in DM patients were measured at 59.50 U/L (interquartile range: 42.00–143.50 U/L), whereas the mean levels of LDH and HBDH were 360.15 ± 307.35 U/L and 273.65 ± 191.82 U/L, respectively. The ALT and AST levels in DM patients were observed to be 23.50 U/L (interquartile range: 15.25–47.00 U/L) and 26.00 U/L (interquartile range: 19.00–43.75 U/L), respectively.

Serum levels of B4GALT1 were measured using ELISA in all three groups (DM, RA and HCs). The finding revealed that the serum levels of B4GALT1 were markedly higher in the DM group compared to HCs, registering at 0.154 (0.112, 0.317) ng/mL ($n = 48$) versus 0.037 (0.027, 0.062) ng/mL ($n = 40$), respectively ($p < 0.0001$, Figure 1), but were significantly lower than

Jiaqian Zhang and Zhaodan Li contributed equally to this work.

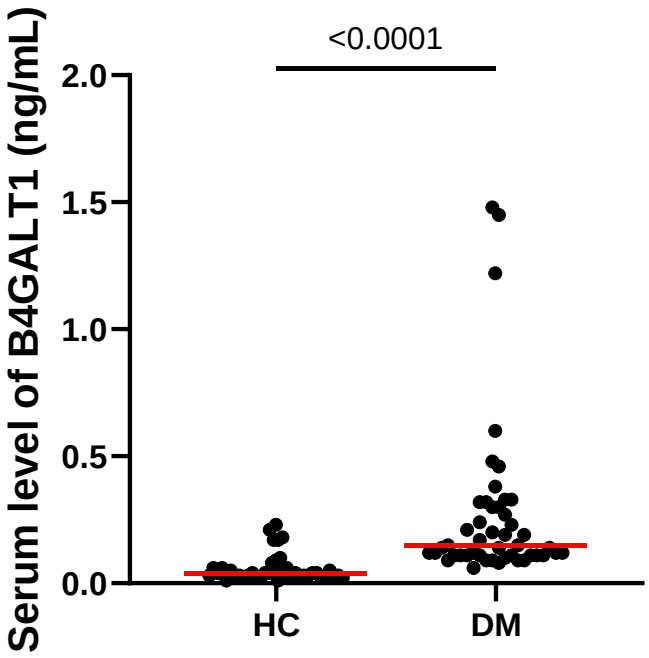

FIGURE 1 | Serum levels of B4GALT1 in HCs and patients with DM. Each dot represents the B4GALT1 level of each individual. The horizontal lines represent the median levels of B4GALT1 in each group. *p*-values were calculated by Mann–Whitney *U* test, and a *p*-value < 0.05 was used to indicate a statistically significant result.

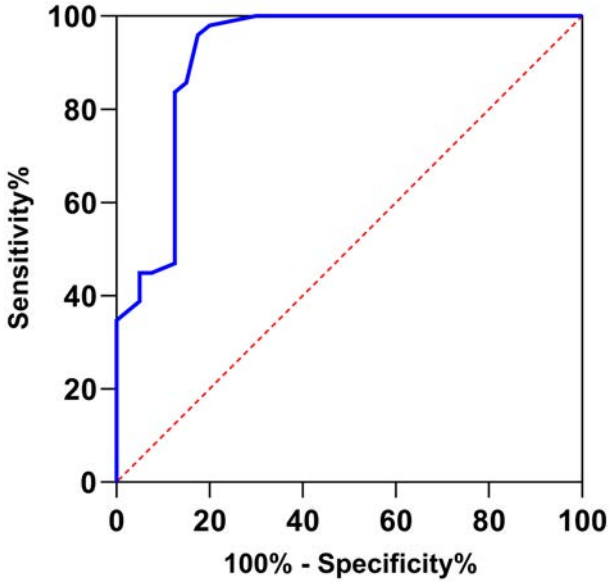

FIGURE 2 | ROC curve of B4GALT1 for distinguishing DM patients from HCs.

those in the RA group (0.527 [0.214, 7.215] ng/mL, $n = 50$, $p < 0.001$), demonstrating a distinct expression profile across autoimmune conditions. Additionally, the diagnostic potential of B4GALT1 in DM patients was evaluated through receiver operating characteristic (ROC) analysis. The results indicated that B4GALT1, with a cutoff value of 0.0815 ng/mL, showed diagnostic capability for DM, achieving a sensitivity of 95.8% and a specificity of 82.5%. The area under the curve (AUC) value for B4GALT1 was 0.920 ($p < 0.001$, 95% CI: 0.857–0.982) (Figure 2). Moreover, B4GALT1 effectively distinguished DM from RA, yielding an AUC of 0.748 ($p < 0.001$, 95% CI: 0.649–0.847), supporting its potential as a differential biomarker in overlapping autoimmune features. Furthermore, Kendall correlation analyses were performed to explore the relationship between serum levels of B4GALT1 and various disease activity or biochemical indicators in DM. The results indicated no significant correlations between B4GALT1 and measures of DM disease activity, including the Myositis Disease Activity Assessment Tool (MYOACT) and the Cutaneous Assessment Tool (CAT). However, the analysis of biochemical indicators demonstrated positive correlations between B4GALT1 and the serum muscle injury enzyme CK ($\tau = 0.289$, $p = 0.005$). Moreover, we examined the serum levels of B4GALT1 in subgroups of DM patients categorized by their ILD, anti-melanoma differentiation-associated gene 5 (anti-MDA5), and anti-Ro52 statuses. Our data showed that the presence of ILD did not alter the serum levels of B4GALT1, and no significant differences were found between DM patients who were positive for MDA5 and those who were negative, nor between those who were positive and those who were negative for Ro52.

Notably, although anti-MDA5-positive DM is classically characterized by milder muscle involvement, our data revealed no significant difference in CK levels between the anti-MDA5-positive and anti-MDA5-negative subgroups ($p > 0.05$), indicating a broader spectrum of muscle involvement within our anti-MDA5-positive population. More importantly, stratified correlation analysis unveiled a strong correlation between the B4GALT1 levels and CK in the anti-MDA5-positive subgroup ($\tau = 0.449$, $p = 0.008$), whereas this correlation was not statistically significant in the anti-MDA5-negative subgroup ($\tau = 0.182$, $p = 0.175$). This suggests that, even with similar CK levels, the relationship between B4GALT1 and myopathy may be particularly relevant in anti-MDA5-positive DM. These findings imply that B4GALT1 may serve as a pathogenetically meaningful biomarker linked to muscle damage in this specific molecular subset.

B4GALT1 is integral to a variety of biological functions, including essential processes such as cell adhesion, cell migration, and immune responses. In the context of immune inflammation, B4GALT1 has been implicated in the pathogenesis of depression through its influence on microglial activation and neuroinflammation [4]. Additionally, B4GALT1 is crucial for the regulation of integrin function and signaling, both of which are vital for the activation and adhesion of immune cells. For instance, in idiopathic pulmonary fibrosis, the overexpression of B4GALT1 in lung tissue is connected to the epithelial–mesenchymal transition pathway, suggesting its involvement in fibrotic processes and immune cell interactions within the lung microenvironment [5]. Moreover, B4GALT1 regulates TGF-β signaling, a pathway central to immune regulation and fibrosis. In colorectal cancer, B4GALT1-mediated glycosylation of the TGF-β receptor Type II inhibits TGF-β-induced epithelial–mesenchymal transition, thereby inhibiting cancer progression [6]. Furthermore, research has revealed that B-cell-specific ablation of B4GALT1 leads to a reduction in hepatocellular carcinoma formation and reverses changes in serum IgG galactosylation levels [7]. Additionally,

B4GALT1 may also mediate muscle damage or protective mechanisms. Platelets deficient in B4GALT1 exhibit heightened adhesion to β1 integrin ligands, potentially affecting the interaction between platelets and muscle tissue during injury and repair processes [8].

Our present study demonstrates that the serum levels of B4GALT1 are considerably elevated in DM patients compared to HCs and correlate with indicators of muscle injury in anti-MDA5-positive patients. Nevertheless, the specific mechanisms and clinical implications of B4GALT1 in DM require further exploration. In conclusion, elevated serum levels of B4GALT1 hold diagnostic value for DM.

Author Contributions

J.Z. conceived and designed the study, conducted experiments, and contributed to manuscript review. Z.L. performed data analysis, drew tables and illustrations, and drafted the manuscript. Y.T. contributed to sample collection and experimental procedures. Y.C. acquired funding and participated in manuscript review. B.W. and H.L. also critically revised the content of the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of West China Hospital, Sichuan University (Chengdu, China, No. 20 in 2021). Informed consent was obtained from all participants involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Association of Mitochondrial DNA Genetic Variants With Depression and Anxiety in Chinese Patients With Systemic Lupus Erythematosus

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ABSTRACT

Objective: To explore the association of mitochondrial DNA (mtDNA) genetic variants, including single nucleotide variants (SNVs), insertions and deletions (InDels), and copy number variations (CNVs), with depression and anxiety in Chinese patients with systemic lupus erythematosus (SLE).

Methods: A two-stage study of 530 patients with SLE was conducted to explore the association between mtDNA genetic variants (SNVs and InDels) and depression and anxiety. A total of 499 patients with SLE were recruited to explore the association between mtDNA CNVs and depression and anxiety. Meanwhile, the patients were followed up for 12 weeks to observe the improvement of depression and anxiety. The levels of reactive oxygen species (ROS), adenosine triphosphate (ATP), interleukin-6 (IL-6), and interleukin-1β (IL-1β) were detected.

Results: Two mtDNA SNVs (C16291T, A16399G) in the displacement loop (D-loop) region were associated with depression in patients with SLE ($P_{BH}=0.003$, $P_{BH}=0.007$). Two mtDNA SNVs (T9950C, T16140C) in the cytochrome c oxidase subunit III (COX3) gene and D-loop region were associated with anxiety in patients with SLE ($P_{BH}=0.001$; $P_{BH}=0.003$). Associations of mtDNA CNVs with depression and anxiety in SLE were observed in several subgroups ($P_{adj}<0.05$). T9950C and T16140C variants were related to the improvement of anxiety in SLE ($P_{BH}<0.05$). An inverse U-shaped non-linear association was observed between mtDNA CNVs and the improvement of anxiety in the body mass index (BMI) ≥ 24 subgroup of SLE ($P_{non\text{-}linear}=0.038$). The levels of ROS ($p=0.040$) and IL-6 ($p=0.039$) were increased and ATP level ($p=0.034$) was decreased in the COX3 gene variation group.

Conclusion: mtDNA genetic variants may be associated with depression and anxiety in Chinese patients with SLE. This study provides a new idea for improving depression and anxiety in SLE.

1 | Introduction

Systemic lupus erythematosus (SLE) is a persistent autoimmune disorder affecting multiple systems with diverse neuropsychiatric manifestations. Depression and anxiety are the most common psychiatric symptoms of the diffuse central nervous system involvement in SLE [1]. A recent systematic review reported a prevalence of 8.7% to 78.6% for depression

Qiqun Zong, Yue Li, Yuxin Wang, Yaping Feng contributed equally to this work and should be considered co-first authors.

Highlights

- mtDNA genetic variants (C16291T, A16399G) were associated with depression in patients with SLE.
- mtDNA genetic variants (T9950C, T16140C) were associated with anxiety in patients with SLE.
- The levels of ROS and IL-6 were increased and ATP level was decreased in the COX3 gene variation group.

and 1.1% to 71.4% for anxiety [2]. Depression and anxiety in SLE have been linked to poor quality of life and high financial burden. In addition, SLE with depression and anxiety can lead to an increased risk of suicide and poor treatment compliance [3, 4]. However, it has not received enough medical attention and treatment.

Mitochondrial DNA (mtDNA) is susceptible to damage with a high mutation rate because of its lack of histone protection and poor DNA repair capacity [5]. Single nucleotide variants (SNVs), insertions and deletions (InDels), and copy number variations (CNVs) are several common types in mtDNA genetic variants, which contribute to mitochondrial dysfunction by affecting oxidative phosphorylation (OXPHOS), adenosine triphosphate (ATP) production, and reactive oxygen species (ROS) production [6, 7]. Mitochondrial dysfunction not only impedes cellular energy production but may also impair neuronal communication and cellular resilience, causing mood disorders and mental disorders [8]. Studies have shown that mitochondrial dysfunction is one of the mechanisms leading to depression [9]. Mitochondrial functions, such as energy metabolism and oxidative stress, were altered in individuals with anxiety [10]. Moreover, mtDNA can bind to Toll-like receptor 9 (TLR9) and activate the expression of proinflammatory cytokines, which played a significant role in depression and anxiety [11–13].

Interestingly, mitochondrial dysfunction is not confined to SLE. It has also been implicated in other autoimmune diseases, such as ankylosing spondylitis [14], rheumatoid arthritis [15], and colitis [16]. In these diseases, mitochondrial dysfunction contributes to the pathophysiology by exacerbating inflammation, oxidative stress, and cellular energy deficits. The shared involvement of mitochondrial dysfunction across these autoimmune diseases underscores its potential as a common pathogenic mechanism, making it a valuable target for therapeutic interventions in both SLE and other autoimmune conditions.

So far, most of the studies on depression and anxiety in SLE have been descriptive studies and the underlying mechanism remains unclear. Studies have shown that inflammatory pathways may interact bidirectionally in depression and anxiety of SLE patients [17]. Direct immunity mediated by autoantibodies could also be involved in the onset of the disease. It has been suggested that depression and anxiety in SLE may be caused by autoimmune, inflammatory, ischaemic and thrombotic pathways [18]. Amygdala damage and microvascular impairment could be associated with emotional disorders in SLE patients [19, 20]. Furthermore, the etiology of psychiatric symptoms in SLE might involve both genetic and environmental factors. However, there have been no studies on depression and anxiety of SLE patients from the mtDNA genetics perspective.

This study was to investigate the relationship of mtDNA genetic variants (SNVs, InDels, and CNVs) with depression and anxiety in individuals with SLE. Meanwhile, the effects of mtDNA genetic variants on mitochondrial function and proinflammatory cytokine levels were explored in SLE. Increased ROS production and decreased ATP generation are hallmarks of mitochondrial dysfunction, so ROS and ATP levels were used to evaluate mitochondrial function. The levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-1β (IL-1β), were elevated in SLE, depression, and anxiety patients [12, 13, 21]. IL-6 and IL-1β levels were used to evaluate proinflammatory cytokine levels. Finally, the relationship between mtDNA genetic variants (SNVs, InDels, and CNVs) and the improvement of depression and anxiety in SLE was also investigated.

2 | Methods

2.1 | Subjects

The study was conducted in two stages to explore the mtDNA genetic variants (SNVs and InDels) with depression and anxiety in SLE. The first stage included 100 samples and the second stage included 430 samples. A total of 499 patients were recruited to investigate the association between mtDNA CNVs and depression and anxiety. All patients were recruited from the First and Second Affiliated Hospitals of Anhui Medical University. Patients were assessed for depression and anxiety. The American College of Rheumatology (ACR) 1997 SLE classification criteria were met by all participants. The exclusion criteria were as follows: (a) With lupus crisis, glucocorticoids (GC) contraindication or allergic to hydroxychloroquine (HCQ), and pregnant or lactating females. (b) With other autoimmune diseases, malignant tumors, central nervous system diseases, and other psychiatric disorders. (c) Refusal to participate in anxiety and depression evaluation and follow-up. A 12-week follow-up research was carried out to evaluate the improvement of depression and anxiety in SLE, and 514 patients (483 patients in CNV analysis) completed the follow-up. There was an overlap between the subjects in this study and our previous study [22, 23].

In addition, to explore the potential mechanism of mtDNA genetic variants and depression and anxiety in SLE, the relationship of mtDNA genetic variants with mitochondrial function and proinflammatory cytokines levels was analyzed. Thirty patients were recruited to detect ROS levels. Thirty patients were recruited to detect ATP levels. Meanwhile, 30 patients were recruited to measure IL-6 and IL-1β levels. These patients had not received GC therapy or low-dose GC maintenance therapy (a maintenance dosage of prednisone ≤ 7.5 mg/day) [24] in the past 3 months before enrollment. And patients with other autoimmune diseases, other mitochondrial diseases, malignant tumors, central nervous system diseases, other psychiatric disorders, and infection-related chronic diseases were excluded.

The Anhui Medical University's ethics committee gave its approval to the study protocol. Informed consent in writing was obtained from each respondent. Quality control measures of the study were provided in the Supporting Information.

2.2 | Depression and Anxiety Assessment

Depression and anxiety in SLE were measured by the 24-item Hamilton Depression Scale (HAMD) and 14-item Hamilton Anxiety Scale (HAMA) in this study. Evidences have shown that HAMD and HAMA scales had good reliability and validity among the Chinese population [25, 26], which have been widely used in the evaluation of anxiety and depression in patients with various diseases. In this study, HAMD and HAMA scales had good reliability and validity (details were provided in the Supporting Information). HAMD score <8 was defined as non-depression (assigned to 0), 8–19 as mild depression (assigned to 1), and ≥ 20 as moderate and severe depression (assigned to 2) [27]. HAMA score <7 was defined as non-anxiety (assigned to 0), 7–14 as mild anxiety (assigned to 1), and ≥ 15 as moderate and severe anxiety (assigned to 2) [28]. The HAMD score and HAMA score were recorded at baseline and Week 12. The improvement of depression and anxiety in SLE was assessed by the score difference between baseline and week 12. The 12 weeks (3 months) is an important assessment point for disease activity in patients with SLE [29], and it is also an important time node to evaluate the condition changes of patients with depression and anxiety [30–32]. Thus, the study set the evaluation time node of improvement at 12 weeks. Patients were also categorized into good improvement group ($>$ median) and poor improvement group ($\leq$ median) of depression and anxiety according to the median of the difference.

2.3 | mtDNA Genetic Variants Detection (SNVs, InDels and CNVs)

Peripheral blood samples from participants were collected using an EDTA anticoagulant tube at baseline. The genomic DNA in peripheral blood leukocytes was extracted by a DNA extraction kit (QIAGEN, Germany). mtDNA genetic variants (SNVs and InDels) were detected by next-generation sequencing on the Illumina Hiseq 2500 platform. In this study, the variation frequency of mitochondrial genome loci >0.9 was considered to be a variation [22]. Quantitative real-time PCR (qPCR) was employed to detect the relative mtDNA copy number (mtDNAcn). mtDNAcn was relatively quantified based on the disparity between mtDNA and nDNA's mean Ct values using nDNA content as the standard. Haplogroups were classified according to the human mtDNA Phylotree [33]. Detailed methods and primer sequences can be found in the method part of the previous study of our research group [22, 23]. Primer sequences for the second stage of mtDNA genetic variants (SNVs and InDels) were shown in Table S1.

2.4 | Detection of Mitochondrial Function-Related Indicators and Proinflammatory Cytokine Levels

Human peripheral blood was centrifuged at $1500 \times g$ for 10 min at 4°C to separate whole blood and plasma. A human ROS ELISA Kit (Enzyme-linked Biotechnology, Shanghai, China) was used to measure ROS levels in plasma. The absorbance at 450 nm was determined. An ATP Assay Kit (Beyotime Biotechnology, Shanghai, China) was used to measure ATP levels in whole blood. The multi-function measuring instrument was used to measure the relative light units (RLU) value. The levels of IL-6 and IL-1β in plasma were detected with human IL-6 ELISA Kit and human IL-1β ELISA Kit (Reed Biotech, Wuhan, China). The absorbance at 450 nm was measured. Experimental procedures were performed according to the manufacturer's guidelines.

2.5 | Statistical Analysis

The differences between the two groups were compared by Student's *t*-test or Mann–Whitney U test as appropriate. The analysis of associations used univariate and multivariate ordinal logistic regression, with adjustments for potential confounding factors. mtDNAcn was analyzed as both a continuous variable (by raw data) and a categorical variable (by median, by tertile, by quartile) (details were provided in the Supporting Information). The association of mtDNAcn with depression and anxiety in SLE was illustrated by a forest plot. Restricted cubic splines (RCS) were employed to analyze the relationship between mtDNAcn and the improvement of depression and anxiety in SLE [33]. Additionally, the combined analysis of discovery stage and validation stage in a two-stage study design has been used in many studies, and the combined analysis can improve the statistical power [34, 35]. Thus, in this study, the pooled approach was utilized to improve statistical power in the final stage for exploring association patterns of SNVs/InDels.

Results with crude p-value <0.1 in the first stage were included in the second stage. For the overall analysis, p-value <0.05 was considered statistically significant. Multiple comparisons were adjusted by the false discovery rate (FDR) approach to reduce false positive errors. Statistical power was calculated with PASS 11 software. The SPSS software (version 23.0) and GMDR software (version 0.7) were used for all statistical analyses.

3 | Results

3.1 | Characteristics of Subjects

This study examined the association between mtDNA genetic variants (SNVs and InDels) and depression and anxiety in 530 SLE patients (non-depression group: 174, mild depression group: 310, moderate and severe depression group: 46; non-anxiety group: 210, mild anxiety group: 263, moderate and severe anxiety group: 57) (Tables S2 and S3). There were 100 cases in the first stage and 430 cases in the second stage. And 514 SLE patients were analyzed for the improvement of depression and anxiety (good improvement of depression: 249, poor improvement of depression: 265; good improvement of anxiety: 219, poor improvement of anxiety: 295) (Table S4).

This study involved 499 SLE patients to explore the association between mtDNA CNVs and depression and anxiety (non-depression group: 163, mild depression group: 286, moderate and severe depression group: 50; non-anxiety group: 201, mild

anxiety group: 246, moderate and severe anxiety group: 52) (Table S5). The characteristics of improvement of depression and anxiety in 483 patients were shown in Table S6 (good improvement of depression: 234, poor improvement of depression: 249; good improvement of anxiety: 203, poor improvement of anxiety: 280).

3.2 | Association Between mtDNA Genetic Variants (SNVs and InDels) and Depression and Anxiety in Patients With SLE

It turns out that 7 loci variants located in the cytochrome c oxidase subunit III (COX3) gene and displacement loop (D-loop) region were associated with depression of SLE patients in the first stage ($p < 0.1$, Table 1). And 6 loci variants located in the COX3 gene and the D-loop region were related to anxiety in SLE patients ($p < 0.1$, Table 1).

Subsequently, we verified the positive loci variants in the second stage in 430 patients with SLE. Two mtDNA SNVs (C16291T, A16399G) located in the D-loop region were associated with a higher risk of depression in SLE patients (C16291T: $OR_{adj} = 7.959$, 95% CI: 1.873–33.810, $P_{adj} = 0.005$; A16399G: $OR_{adj} = 4.563$, 95% CI: 1.132–18.383, $P_{adj} = 0.033$), and significant associations were still observed in the combined sample (C16291T: $P_{adj} = 4.060 \times 10^{-4}$, $P_{BH} = 0.003$; A16399G: $P_{adj} = 0.002$, $P_{BH} = 0.007$) (Table 2). Besides, two mtDNA SNVs (T9950C, T16140C) located in the COX3 gene and the D-loop region were associated with a higher risk of anxiety in SLE patients (T9950C: $OR_{adj} = 4.304$, 95% CI: 1.721–10.767, $P_{adj} = 0.002$; T16140C: $OR_{adj} = 3.804$, 95% CI: 1.216–11.902, $P_{adj} = 0.022$), and significant associations remained in the combined sample (T9950C: $P_{adj} = 2.100 \times 10^{-4}$, $P_{BH} = 0.001$; T16140C: $P_{adj} = 0.001$, $P_{BH} = 0.003$) (Table 2). In addition, we found that mtDNA InDel (CA514-515-) located in the D-loop region was related to anxiety in patients with SLE ($OR_{adj} = 1.643$, 95% CI: 1.110–2.431, $P_{adj} = 0.013$), but no relation was detected in the combined sample ($P_{adj} = 0.184$, $P_{BH} = 0.184$) (Table 2).

3.3 | Association Between mtDNA Copy Number Variations (CNVs) and Depression and Anxiety in Patients With SLE

The relationship between mtDNAcn and depression and anxiety was explored in 499 patients in this study. However, no significant relationship was found between mtDNAcn and depression and anxiety in SLE ($P_{adj} > 0.05$) (Tables S7 and S8).

Then we performed subgroup analyses and obtained some positive results. In the quartile analysis, low mtDNAcn had an increased risk of depression and anxiety than high mtDNAcn in some subgroups ($OR_{adj} > 1$, $P_{adj} < 0.05$) (Figure 1). In the subgroup of SLE patients with body mass index (BMI) ≥ 24, low level of mtDNAcn increased the risk of depression compared to high level ($OR_{adj} = 3.326$, 95% CI: 1.178–9.384, $P_{adj} = 0.023$) (Table S9). In the subgroup of SLE patients with females, non-smoking and non-drinking, low level of mtDNAcn increased the risk of anxiety compared to high level (female: $OR_{adj} = 1.795$, 95% CI: 1.077–2.992, $P_{adj} = 0.025$; non-smoking: $OR_{adj} = 1.733$, 95% CI: 1.054–2.846, $P_{adj} = 0.030$; non-drinking: $OR_{adj} = 1.664$, 95% CI: 1.001–2.765, $P_{adj} = 0.049$) (Table S10).

3.4 | Association Between mtDNA Genetic Variants and Improvement of Depression and Anxiety in Patients With SLE

We analyzed the association between four mtDNA SNVs (C16291T, A16399G, T9950C, T16140C) and the improvement of depression and anxiety in SLE. A16399G variant showed a borderline association with the improvement of depression in SLE patients ($OR_{adj} = 0.229$, 95% CI: 0.062–0.840, $P_{adj} = 0.026$, $P_{BH} = 0.052$) (Table 3). T9950C ($OR_{adj} = 0.172$, 95% CI: 0.061–0.482, $P_{adj} = 0.001$, $P_{BH} = 0.002$) and T16140C ($OR_{adj} = 0.094$, 95% CI: 0.021–0.429, $P_{adj} = 0.002$, $P_{BH} = 0.002$) variants were protective factors for the improvement of anxiety in SLE patients (Table 3).

In addition, RCS was used to analyze the relationship between mtDNAcn and improvement of depression and anxiety in 483 patients with SLE. No significant association was found overall ($P_{overall} = 0.857$; $P_{overall} = 0.277$) (Figure S1). Association was observed in the BMI ≥ 24 subgroup. An inverse U-shaped non-linear dose–response relationship was found between mtDNAcn and improvement of anxiety in BMI ≥ 24 subgroup ($P_{overall} = 0.011$, $P_{non\text{-}linear} = 0.038$) (Figure 2). In the BMI ≥ 24 subgroup, the inflection points were located at 63.50 and 64.73 on the RCS curve. With the increase of mtDNAcn, the risk of poor improvement in anxiety increased first and then decreased to a plateau, reaching the highest risk at 64.11.

3.5 | Association Between mtDNA Genetic Variants and Mitochondrial Function and Proinflammatory Cytokine Levels

The mitochondrial function and proinflammatory cytokine levels of different genotypes of mtDNA C16291T, A16399G, T9950C, and T16140C variants were analyzed. The mtDNA T9950C variant is located in the COX3 gene; mtDNA T16140C, C16291T, and A16399G variants are located in the D-loop region. Thus, the relationship between mitochondrial function and proinflammatory cytokine levels with COX3 gene and D-loop region variants was also analyzed. Variation at any sites on the D-loop region was considered a D-loop region variant. Variation at any sites on the COX3 gene was considered a COX3 gene variant. The frequency distribution of the wild group and the variation group of four sites, COX3 gene and D-loop region variants, was shown in Table S11. The variation frequencies of mtDNA T9950C, T16140C, C16291T, and A16399G variants were too low to analyze. All 30 patients had D-loop region variants and could not be analyzed. Only the COX3 gene variants were available for statistical analysis.

The levels of ROS were significantly higher in the COX3 gene variation group (7.48 ± 1.05) than in the wild group (6.59 ± 1.20) ($p = 0.040$) (Figure 3A). The levels of ATP were lower in the COX3 gene variation group (55.59, 29.31–75.18) than in the wild group (85.99, 45.70–120.64) ($p = 0.034$) (Figure 3B). The levels of IL-6 were higher in the COX3 gene variation group (2.92, 2.58–3.89)

TABLE 1 | mtDNA genetic variants (SNVs and InDels) associated with depression and anxiety in patients with SLE in the first stage.

			Severity						
Sites	**Variation**	**Locus**	**Non *n* (%)**	**Mild *n* (%)**	**Moderate and severe *n* (%)**	**Crude OR (95% CI)**	**Crude *p***	**Adjusted OR (95% CI)**	**Adjusted *p*[a]**
Depression			(*n* = 27)	(*n* = 57)	(*n* = 16)				
9950	T>C	COX3	0 (0)	3 (5.3)	2 (12.5)	4.787 (0.815–28.111)	**0.083**	6.445 (0.962–43.167)	**0.055**
199	T>C	D-loop	4 (14.8)	3 (5.3)	0 (0)	0.225 (0.048–1.063)	**0.060**	0.144 (0.025–0.813)	**0.028**
16 140	T>C	D-loop	0 (0)	3 (5.3)	2 (12.5)	4.787 (0.815–28.111)	**0.083**	7.610 (1.164–49.730)	**0.034**
16 234	C>T	D-loop	0 (0)	1 (1.8)	2 (12.5)	12.487 (1.061–146.912)	**0.045**	11.138 (0.818–151.688)	**0.070**
16 291	C>T	D-loop	0 (0)	2 (3.5)	2 (12.5)	6.652 (0.907–48.770)	**0.062**	11.952 (1.464–97.600)	**0.021**
16 320	C>T	D-loop	0 (0)	1 (1.8)	2 (12.5)	12.487 (1.061–146.912)	**0.045**	17.004 (1.271–227.404)	**0.032**
16 399	A>G	D-loop	0 (0)	3 (5.3)	2 (12.5)	4.787 (0.815–28.111)	**0.083**	4.482 (0.713–28.155)	0.110
Anxiety			(*n* = 35)	(*n* = 50)	(*n* = 15)				
9950	T>C	COX3	0 (0)	3 (6.0)	2 (13.3)	5.520 (0.95–32.079)	**0.057**	5.789 (0.901–37.175)	**0.064**
146	T>C	D-loop	3 (8.6)	7 (14.0)	5 (33.3)	3.097 (1.053–9.104)	**0.040**	2.571 (0.846–7.813)	**0.096**
150	C>T	D-loop	4 (11.4)	10 (20.0)	5 (33.3)	2.425 (0.916–6.423)	**0.075**	2.891 (1.032–8.101)	**0.044**
16 140	T>C	D-loop	0 (0)	3 (6.0)	2 (13.3)	5.520 (0.95–32.079)	**0.057**	7.652 (1.219–48.044)	**0.030**
16 257	C>A	D-loop	1 (2.9)	3 (6.0)	3 (20.0)	4.569 (1.018–20.517)	**0.047**	6.589 (1.371–31.675)	**0.019**
514–515	CA>—	D-loop	15 (42.9)	18 (36.0)	2 (13.3)	0.494 (0.223–1.095)	**0.083**	0.488 (0.210–1.133)	**0.095**

[a]Adjusted for sex, age, BMI, education level, disease duration, SLEDAI score. Bold values indicate statistically significant ($P < 0.1$).

TABLE 2 | Verification of mtDNA genetic variants (SNVs and InDels) associated with depression and anxiety in patients with SLE.

			The second stage					The combined sample					
Sites	**Variation**	**Locus**	**Non *n* (%)**	**Mild *n* (%)**	**Moderate and severe *n* (%)**	**Adjusted OR (95% CI)**	**Adjusted *p*[a]**	**Non *n* (%)**	**Mild *n* (%)**	**Moderate and severe *n* (%)**	**Adjusted OR (95% CI)**	**Adjusted *p*[a]**	**P_{BH}**
Depression			(*n* = 147)	(*n* = 253)	(*n* = 30)			(*n* = 174)	(*n* = 310)	(*n* = 46)			
9950	T>C	COX3	3 (2.0)	15 (5.9)	1 (3.3)	1.776 (0.681–4.627)	0.240	3 (1.7)	18 (5.8)	3 (6.5)	2.354 (1.012–5.472)	0.047	0.110
199	T>C	D-loop	10 (6.8)	19 (7.5)	4 (13.3)	1.485 (0.716–3.079)	0.288	14 (8)	22 (7.1)	4 (8.7)	0.968 (0.508–1.844)	0.921	0.921
16 140	T>C	D-loop	4 (2.7)	8 (3.2)	0 (0)	0.702 (0.220–2.243)	0.551	4 (2.3)	11 (3.5)	2 (4.3)	1.450 (0.541–3.884)	0.460	0.537
16 234	C>T	D-loop	3 (2.0)	10 (4.0)	0 (0)	1.208 (0.391–3.728)	0.743	3 (1.7)	11 (3.5)	2 (4.3)	1.825 (0.656–5.078)	0.249	0.349
16 291	C>T	D-loop	1 (0.7)	4 (1.6)	3 (10.0)	7.959 (1.873–33.810)	**0.005**	1 (0.6)	6 (1.9)	5 (10.9)	8.049 (2.533–25.582)	**4.060×10^{-4}**	**0.003**
16 320	C>T	D-loop	1 (0.7)	0 (0)	0 (0)	—	0.985	1 (0.6)	1 (0.3)	2 (4.3)	5.894 (0.832–41.769)	0.076	0.133
16 399	A>G	D-loop	1 (0.7)	6 (2.4)	2 (6.7)	4.563 (1.132–18.383)	**0.033**	1 (0.6)	9 (2.9)	4 (8.7)	5.405 (1.822–16.035)	**0.002**	**0.007**
Anxiety			(*n* = 175)	(*n* = 213)	(*n* = 42)			(*n* = 210)	(*n* = 263)	(*n* = 57)			
9950	T>C	COX3	1 (0.6)	14 (6.6)	4 (9.5)	4.304 (1.721–10.767)	**0.002**	1 (0.5)	17 (6.5)	6 (10.5)	4.635 (2.060–10.428)	**2.100×10^{-4}**	**0.001**
146	T>C	D-loop	11 (6.3)	25 (11.7)	3 (7.1)	1.537 (0.807–2.927)	0.191	14 (6.7)	32 (12.2)	8 (14.0)	1.877 (1.082–3.257)	0.025	0.038
150	C>T	D-loop	25 (14.3)	31 (14.6)	12 (28.6)	1.570 (0.946–2.608)	0.081	29 (13.8)	41 (15.6)	17 (29.8)	1.733 (1.106–2.715)	0.016	0.032
16 140	T>C	D-loop	1 (0.6)	8 (3.8)	3 (7.1)	3.804 (1.216–11.902)	**0.022**	1 (0.5)	11 (4.2)	5 (8.8)	4.729 (1.821–12.284)	**0.001**	**0.003**
16 257	C>A	D-loop	9 (5.1)	15 (7.0)	3 (7.1)	1.398 (0.648–3.016)	0.393	10 (4.8)	18 (6.8)	6 (10.5)	1.834 (0.925–3.635)	0.082	0.098
514–515	CA>—	D-loop	51 (29.1)	78 (36.6)	21 (50.0)	1.643 (1.110–2.431)	**0.013**	66 (31.4)	96 (36.5)	23 (40.4)	1.267 (0.893–1.798)	0.184	0.184

[a]Adjusted for sex, age, BMI, education level, disease duration, SLEDAI score. Bold values indicate statistically significant (all $P < 0.05$ in the second stage, the combbined samle, and P_{BH}).

than in the wild group (2.20, 1.94–3.38) ($p = 0.039$) (Figure 3C). The levels of IL-1β were higher in the COX3 gene variation group (13.25, 10.65–15.97) than in the wild group (12.08, 9.86–12.39) with a significant trend ($p = 0.091$) (Figure 3D). In addition, the association between mtDNAcn and mitochondrial function and proinflammatory cytokines was analyzed. No significant correlation was observed between mtDNAcn and ROS level ($r = 0.228$, $p = 0.226$), mtDNAcn and ATP level ($r_s = -0.048$, $p = 0.802$), mtDNAcn and IL-6 level ($r_s = 0.201$, $p = 0.287$), mtDNAcn and IL-1β level ($r_s = -0.018$, $p = 0.925$) (Figure S2).

In addition, statistical power analyses for the study were performed, and the results showed that the statistical power was limited. Further validation in larger samples is warranted. Details were provided in the Supporting Information (Tables S19–S21).

4 | Discussion

This study demonstrated that mtDNA SNVs (C16291T, A16399G) in D-loop region were associated with depression in patients with SLE. mtDNA SNVs (T9950C, T16140C) in COX3 gene and D-loop region were related to anxiety in patients with SLE. Meanwhile, low mtDNAcn had an increased risk of depression and anxiety in females, BMI ≥ 24, non-smoking, and non-drinking subgroups of SLE. Interactions between mtDNA genetic variants and environmental factors were also observed. Moreover, A16399G, T9950C, and T16140C variants reduced the risk of poor improvement of depression and anxiety in SLE. A nonlinear dose–response relationship was found between mtDNAcn and improvement of anxiety in the BMI ≥ 24 subgroup. The levels of ROS and IL-6 were higher, and ATP level was lower in the COX3 gene variation group compared with the wild group.

In this study, mtDNA C16291T and A16399G variants were associated with a higher risk of depression in SLE patients. Maggrah et al. [36] indicated that the C16291T variant was linked to the mitochondrial cancerization field effect in breast cancer. Studies have shown that the A16399G variant increased the risk of several cancers and affected their prognosis [37, 38]. C16291T and A16399G variants were located in the displacement loop (D-loop) control region of mitochondrial DNA. Variations in the D-loop region, which participates in the mtDNA replication and transcription, lead to mutations in the coding region and alterations in protein synthesis. It has been reported that ROS levels and apoptosis rates were higher in the mutation group of D-loop region than in the control group in gastric cancer tissue [39]. Reduced copy number and enhanced mutation in the D-loop region might be linked to abnormal mitochondrial membrane potential, reduced ATP production and increased ROS [40]. Mitochondrial dysfunction was associated with depression, possibly due to impaired neuroplasticity, neurogenesis, and signal transduction [8]. Furthermore, it was found that mtDNA D-loop variants have been associated with the development and prognosis of SLE [22]. Thus, C16291T and A16399G variants in D-loop region might contribute to depression with SLE patients.

Mitochondrial DNA T9950C and T16140C variants were associated with a higher risk of anxiety in SLE. The mtDNA T9950C variant locates in the MT-COX3 gene. COX3 gene is a mitochondrially encoded cytochrome c oxidase III gene. COX3 forms the respiratory chain OXPHOS complexes, which pump protons into the inner mitochondrial membrane to drive ATP production. Our results indicated higher ROS levels and lower ATP levels in the COX3 gene variation group compared to the wild group. Similar to our results, Gergely et al. [41] observed an increase in reactive oxygen intermediates (ROIs) and ATP depletion in peripheral blood lymphocytes (PBLs) in SLE patients. Studies have shown that mutations in the COX3 gene occurred frequently within Alzheimer's disease patients' brains, and oxidative damage appeared early in Alzheimer's disease [42, 43]. Mutations in the COX3 gene could affect mitochondrial function by affecting the assembly of the mitochondrial COX subunit and proton translocation thereby reducing the activity of the ATP-synthesizing OXPHOS complexes [44]. ROS was involved in mitochondrial damage-associated molecular patterns (DAMPs) and activated the immune inflammatory system to cause inflammatory responses, which was linked to the risk of SLE, depression, and anxiety [45]. ATP acted as a signal to regulate immune and inflammatory responses and neurotransmitter systems [46]. Mitochondrial DNA damage, increased ROS production, and decreased ATP generation are hallmarks of mitochondrial dysfunction. In this study, the COX3 gene variation group had higher IL-6 levels and a trend towards higher IL-1β levels than the wild group. Studies revealed that the serum and expression levels of pro-inflammatory cytokines, including IL-6 and IL-1β, were significantly elevated in SLE, depression, and anxiety patients [12, 13, 21]. Excessive oxidative stress and decreased ATP levels would increase the levels of proinflammatory cytokines-6 and TNFα, which might be involved in the development of SLE, depression, and anxiety [9]. T16140C variant locates in the mtDNA D-loop region, and variations in the D-loop region may cause mitochondrial malfunction. Mitochondrial dysfunction and oxidative damage have been discovered to be crucial in the pathophysiology of anxiety [47]. Similarly, increasing evidence suggested that mitochondrial dysfunction also played a big part in the pathogenesis of SLE, including effects on mtDNA damage, abnormal energy metabolism, oxidative stress, and inflammatory responses [48]. Given this, we raised the hypothesis that T9950C and T16140C variants might lead to anxiety in patients with SLE by affecting mitochondrial function and proinflammatory factor levels.

Low mtDNAcn had an increased risk of depression and anxiety in females, BMI ≥ 24, non-smoking and non-drinking subgroups of SLE. This study did not find positive results for mtDNAcn with mitochondrial function and proinflammatory factors, probably due to the small sample size. Related studies have found that mitochondrial copy number was lower in depressed patients than in controls [49, 50]. Besides, mtDNAcn in peripheral blood was negatively correlated with anxiety in females [51]. Increased maternal psychosocial stress with reduced placental mtDNAcn [52]. In the cell model with reduced mtDNAcn, it was indicated that the activity of mitochondrial respiratory chain complex and mitochondrial membrane potential decreased, and the level of ATP production reduced [53]. This mitochondrial dysfunction was considered to be associated with the occurrence of depression and anxiety. It was reported that the decrease of mtDNAcn was related to the occurrence and development of SLE [23, 54].

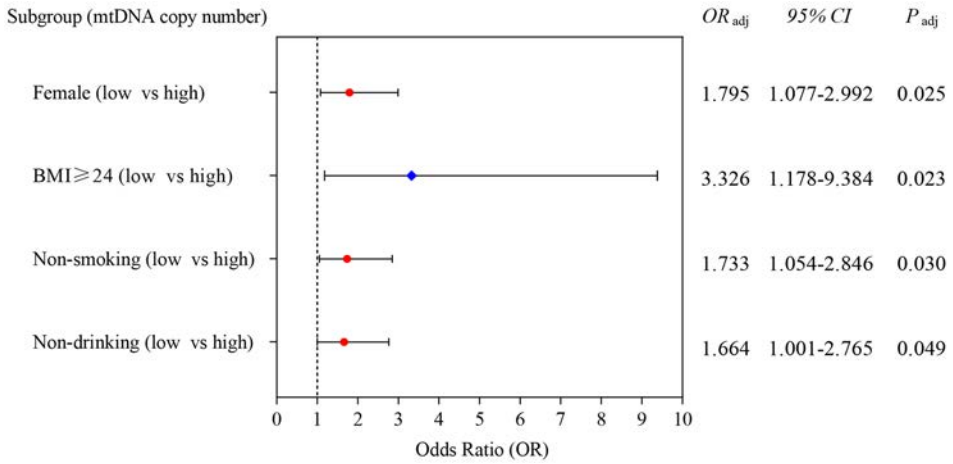

FIGURE 1 | Forest plots of relationship between mtDNA copy number and depression and anxiety in SLE subgroups. Remarks: mtDNA copy number was grouped by quartile. The high group was used as the reference. ◆Relationship between mtDNA copy number and depression in SLE subgroups; •Relationship between mtDNA copy number and anxiety in SLE subgroups.

TABLE 3 | Association between mtDNA genetic variants (SNVs and InDels) and improvement of depression and anxiety in patients with SLE.

Sites	Variation	Locus	Good improvement group *n* (%)	Poor improvement group *n* (%)	Adjusted *OR* (95% CI)	Adjusted *p*[a]	P_{BH}
Depression			(*n* = 249)	(*n* = 265)			
16 291	C>T	D-loop	8 (3.2)	4 (1.5)	0.465 (0.135–1.608)	0.227	0.227
16 399	A>G	D-loop	11 (4.4)	3 (1.1)	0.229 (0.062–0.840)	**0.026**	0.052
Anxiety			(*n* = 219)	(*n* = 295)			
9950	T>C	COX3	18 (8.2)	5 (1.7)	0.172 (0.061–0.482)	**0.001**	**0.002**
16 140	T>C	D-loop	14 (6.4)	2 (0.7)	0.094 (0.021–0.429)	**0.002**	**0.002**

[a]Adjusted for sex, age, BMI, education level, disease duration, GCs dose, difference in SLEDAI score between baseline and Week 12. Bold values indicate statistically significant ($P < 0.05$).

These findings supported our study. Sex, BMI, smoking and drinking were related environmental factors for depression and anxiety in SLE [55, 56]. This may explain the correlation between low mtDNAcn and high risk of depression and anxiety in these SLE subgroups. Multiplicative interactions between mtDNAcn and smoking and drinking for anxiety in patients with SLE were observed. We found a multifactor interaction of T9950C, T16140C, age and BMI on anxiety in patients with SLE. Environmental factors were essential factors affecting anxiety, and mitochondria were closely related to environmental factors [57]. Therefore, mtDNA genetic variants and environmental factors may interact with anxiety in patients with SLE.

A16399G, T9950C and T16140C variants reduced the risk of poor improvement of depression and anxiety in SLE. Similar results have been observed in some patients with cancer. The mutation rate of mtDNA D-loop region was high in patients with oral squamous cell carcinoma, but the mutation of mtDNA D-loop region was related to better survival [58]. Liu et al. observed somatic mutations of the D-loop region in 62.3% patients with squamous

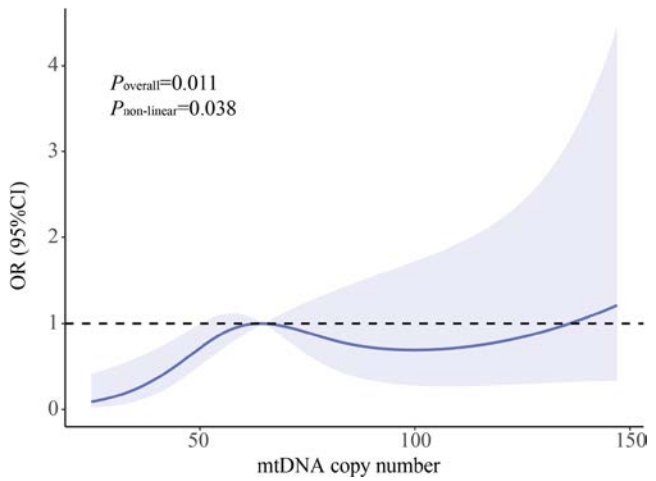

FIGURE 2 | Restricted cubic spline plots of relationship between mtDNA copy number and improvement of anxiety in BMI ≥ 24 subgroup of SLE. Remarks: Four knots (5th, 35th, 65th and 95th percentile) were selected. The solid line and shade indicate the OR and corresponding 95% CI.

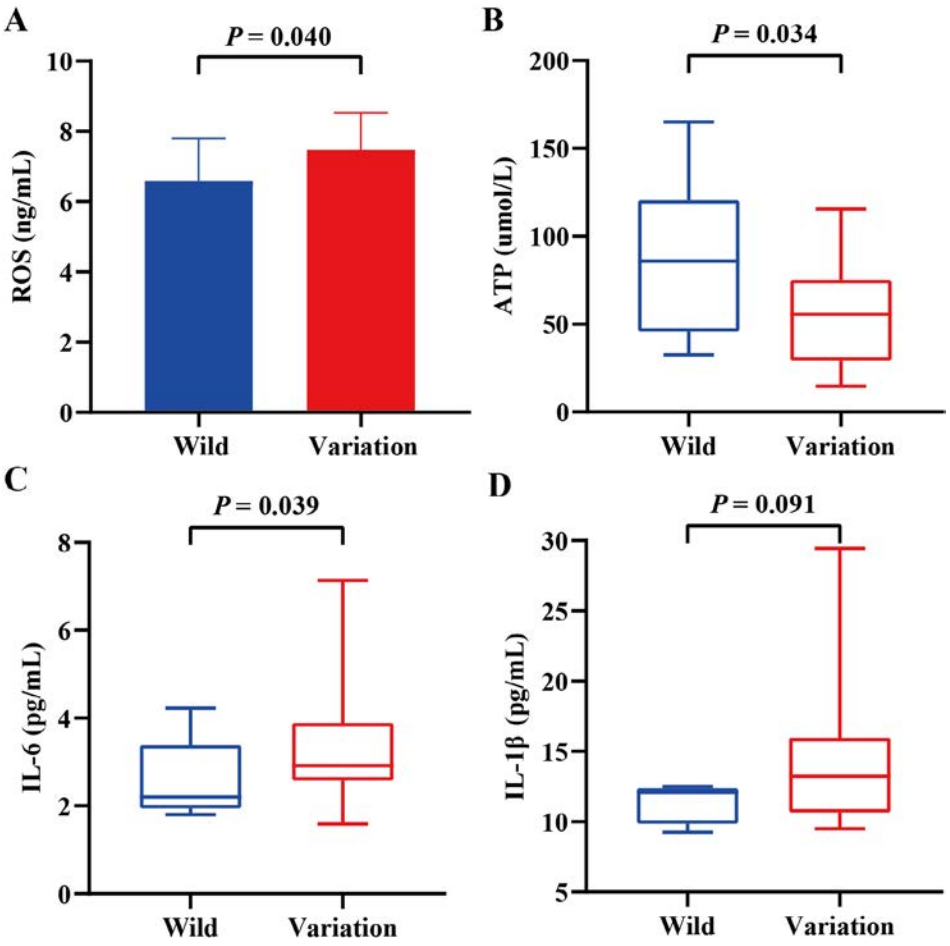

FIGURE 3 | Levels of mitochondrial function-related indicators and proinflammatory cytokines in wild group and COX3 gene variation group. (A) ROS levels in wild group and COX3 gene variation group. (B) ATP levels in wild group and COX3 gene variation group. (C) IL-6 levels in wild group and COX3 gene variation group. (D) IL-1β levels in wild group and COX3 gene variation group.

cell carcinoma in head and neck; patients with D-loop mutations had a higher survival rate [59]. An inverse U-shaped nonlinear dose–response relationship was found between mtDNAcn and improvement in anxiety in two SLE subgroups. Wang et al. [60] found that changes in mtDNAcn were significantly associated with treatment response for depression and anxiety. Two studies suggested that increased mtDNAcn was associated with increased anxiety symptoms [61, 62]. However, a study from the UK Biobank showed an inverse association between mtDNAcn and anxiety in women [51]. It is hypothesized that there may be a threshold effect in the association between mtDNAcn and anxiety, which explains our findings to some extent. The association between mtDNA genetic variants and improvement of depression and anxiety with SLE requires further investigation.

This study was the first to observe an association between mtDNA genetic variations and depression and anxiety and their improvement in patients with SLE. Besides, the interaction between mitochondrial genetic variants and environmental factors was explored. However, there are several limitations in this study. First, the study of improvement in depression and anxiety in SLE patients lost 16 patients to follow-up, which might have a minor effect on the results. Second, 12 weeks of follow-up in the study of improvement of depression and anxiety with SLE was relatively short. We will continue to follow up with patients to observe the subsequent improvement of depression and anxiety in the future. Third, mitochondrial function and proinflammatory cytokine levels were studied in small sample sizes. Future study with larger samples is required to validate these functional observations. Fourth, for loci with extremely low frequencies or minimal inter-group differences, the statistical power was low, and validation in larger samples is warranted.

5 | Conclusion

In summary, this study implicates that mtDNA genetic variants may be associated with depression and anxiety and their improvement in patients with SLE. There may be interactions between mitochondrial genetic variants and environmental factors. This study provides a new idea for the occurrence and improvement of depression and anxiety in SLE patients from the perspective of mtDNA genetics.

Author Contributions

Yanfeng Zou: conceptualization, funding acquisition, methodology, project administration, resources, supervision, writing – review and editing. Qiqun Zong, Yue Li, Yuxin Wang, Yaping Feng: conceptualization, data curation, formal analysis, investigation, methodology,

software, writing – original draft. Liangyu Cui, Lin Cai: investigation, software. Yingying Yu, Mingyi Zhang, Yuqin Tang, Ying Xu, Hongyu Sun, Xingyu Gong, Yuqi Liu: data curation, formal analysis, investigation, software, visualization. Shuang Liu, Yangfan Chen, Wenfei Li: investigation, methodology, resources, validation. Haifeng Pan: funding acquisition, supervision, writing – review and editing. Faming Pan, Hong Su: supervision, writing – review and editing. All authors reviewed and approved the final manuscript.

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Ethics Statement

This study was approved by the Ethical Committee of Anhui Medical University.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Primer sequences for mtDNA genetic variants (SNVs and InDels) in the second stage. **Table S2:** Characteristics of 530 patients with SLE with different levels of depression in the analysis of mtDNA genetic variants (SNVs and InDels). **Table S3:** Characteristics of 530 patients with SLE with different levels of anxiety in the analysis of mtDNA genetic variants (SNVs and InDels). **Table S4:** Characteristics of 514 patients with SLE in depression and anxiety improvement study in the analysis of mtDNA genetic variants (SNVs and InDels). **Table S5:** Characteristics of 499 patients with SLE with different levels of depression and anxiety in the analysis of mtDNA copy number. **Table S6:** Characteristics of depression and anxiety improvement in 483 patients with SLE in the analysis of mtDNA copy number. **Table S7:** The correlation of mtDNA copy number with HAMD score and HAMA score. **Table S8:** Association between mtDNA copy number and depression and anxiety in patients with SLE. **Table S9:** Association between mtDNA copy number and depression in patients with SLE subgroups. **Table S10:** Association between mtDNA copy number and anxiety in patients with SLE subgroups. **Table S11:** Frequency distribution of wild group and variantion group for different sites or genes. **Table S12:** mtDNA genetic variants (SNVs and InDels) associated with depression and anxiety in female patients with SLE in the first satge. **Table S13:** Verification of mtDNA genetic variants (SNVs and InDels) associated with depression and anxiety in female patients with SLE. **Table S14:** Association between mtDNA haplogroups and depression in patients with SLE. **Table S15:** Association between mtDNA haplogroups and anxiety in patients with SLE. **Table S16:** Interactive effects between mtDNA copy number and environmental factors on anxiety in patients with SLE. **Table S17:** MDR interaction of mtDNA genetic variants and environmental factors on anxiety in patients with SLE. **Table S18:** Association between mtDNA genetic variants (SNVs and InDels) and improvement of depression and anxiety in female patients with SLE. **Table S19:** Statistical power of allele frequency for SNV/InDel association analysis. **Table S20:** Statistical power for CNV association analysis. **Table S21:** Statistical power of mitochondrial function-related indicators and proinflammatory cytokines. **Figure S1:** Restricted cubic spline plots of associations between mtDNA copy number and improvement of depression and anxiety in SLE patients. (A) RCS of association between mtDNA copy number and improvement of depression in SLE. (B) RCS of association between mtDNA copy number and improvement of anxiety in SLE. Remarks: Four knots (5th, 35th, 65th and 95th percentile) were selected. The solid line and shade indicate the OR and corresponding 95% CI. Models were adjusted for sex, age, BMI, education level, disease duration, GCs dose, difference in SLEDAI score between baseline and Week 12. **Figure S2:** Correlation between mtDNA copy number and mitochondrial function-related indicators and proinflammatory cytokines. (A) Correlation between mtDNA copy number and ROS level. (B) Correlation between mtDNA copy number and ATP level. (C) Correlation between mtDNA copy number and IL-6 level. (D) Correlation between mtDNA copy number and IL-1β level.

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CLINICAL IMAGE

Recurrent Toe Ulcers in A Patient With Systemic Lupus Erythematosus

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A 31-year-old lady was diagnosed with systemic lupus erythematosus (SLE) and lupus nephritis when she presented with acute symmetric polyarthritis, thrombocytopenia, malar rash, and nephrotic proteinuria with active nephritic urine sediment. She also had recurrent painful ulcers involving the toes of her left foot. There was no accompanying fever, Raynaud's

FIGURE 1 | Dorsal aspect of left foot: Third toe reveals a necrotic ulcer eroding the nail bed and loss of nail.

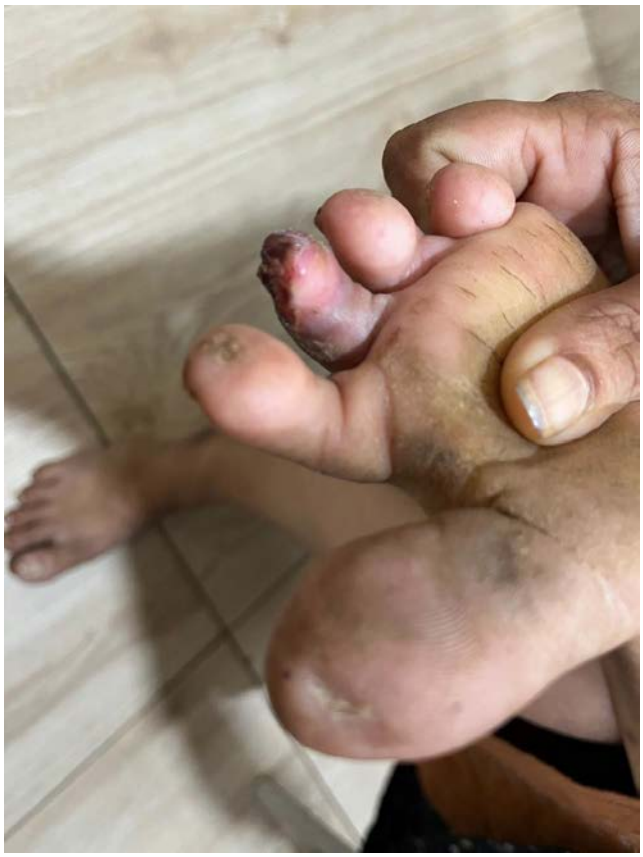

FIGURE 2 | Plantar aspect of left foot: Puckered scars in the first and second toes are evident.

phenomenon or toe gangrene. Clinical examination revealed a tender, necrotic ulcer involving the third toe of the left foot (Figure 1), eroding the nailbed with attendant loss of nail. The first and second toes revealed puckered scars reminiscent of previous ulcerations (Figure 2). Peripheral pulses were intact.

Serum tested positive for antinuclear antibody (1:1000) and anti-dsDNA antibody. Complement component C3 was normal (92 mg/dL, reference: 85–165 mg/dL) while C4 was low (9.5 mg/dL, reference: 15–40 mg/dL). Rheumatoid factor was positive (30 IU/mL, reference < 20 IU/mL). Workup for anti-phospholipid antibodies turned negative. Kidney biopsy revealed class-III lupus nephritis with a full-house immunoglobulin-complement repertoire. Echocardiogram ruled out valvular vegetations and a Doppler ultrasound revealed no obstructive vascular lesions in the affected limb. X-ray of the foot revealed no bony involvement.

The occurrence of a necrotic toe ulcer, absence of antiphospholipid antibodies and Raynaud's phenomenon, positive rheumatoid factor and a low C4 but a normal C3 aroused suspicion of cryoglobulinemia. Upon cooling the serum to 4°C, a cryoprecipitate was obtained (cryocrit 10%). Type-III cryoglobulinemia (polyclonal IgG + polyclonal IgM) was diagnosed based on serum electrophoresis and immunofixation. The hepatitis virus panel was negative. This patient was treated with methylprednisolone pulse and mycophenolate induction, following which toe ulcers healed and proteinuria remitted.

Digital ulcers in patients with SLE could be due to vasculitis, antiphospholipid antibody syndrome (APS), vascular thrombosis, infections, or rarely Raynaud's phenomenon. Purpura, digital ulcers, and ischemia are known cutaneous manifestations of cryoglobulinemia [1]. Cryoglobulinemia is prevalent in 25% to 66% of SLE [1, 2]. The most commonly reported type of cryoglobulinemia is type-III (80%), followed by type-II (19%) [1]. Given the overlapping clinical manifestations of cryoglobulinemia and SLE, treating physicians must be able to delineate manifestations unique to cryoglobulinemia.

Author Contributions

Subrahmanian Sathiavageesan contributed to the study conceptualization, clinical data acquisition, literature review, writing the original draft of the manuscript, and takes full responsibility for the integrity of this work.

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Consent

Consent was obtained from the patient for the publication of their case and images anonymously.

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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EDITORIAL

Current and Future Challenges of Hypogammaglobulinemia in Autoimmune Rheumatic Disease Patients Receiving B-Cell Therapies

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B cell targeted therapies (BCTT) are recognized to be effective in a range of autoimmune rheumatic diseases (AIRD), including systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). BCTT include B-cell depleting therapies (BCDT), for example, rituximab, and those interfering with B-cell activation, for example, belimumab [1]. Despite early smaller studies of short duration indicating otherwise, it is now well recognized that hypogammaglobulinemia is an important side effect, particularly for BCDT. Indeed, physicians looking after AIRD have been ahead of the game recognizing this important side effect. In the June issue of this journal, Tsao et al. published recommendations from the Taiwanese College of Rheumatology for secondary hypogammaglobulinemia in patients with systemic AIRD [2]. Globally, these are only the second published BCTT-related hypogammaglobulinemia recommendations specific to AIRD, though there are sections within other society recommendations, for example, American College of Rheumatology (ACR) and American Academy of Asthma, Allergy and Immunology (AAAAI) applicable to BCTT and hypogammaglobulinemia [3, 4]. Key points from these recommendations are summarized in Table 1.

Mechanistically it was considered that BCDT would have limited effects on serum immunoglobulins, as CD20 is expressed on B-cells but not on plasmablasts or plasma cells, which are responsible for antibody production. However, the effects of prolonged/pronounced B-cell depletion by these agents appear to impact the natural process of B-cell differentiation which normally results in replenishment of plasma cells [1]. Hypogammaglobulinemia can vary in its severity, in terms of the absolute IgG level, the duration of hypogammaglobulinemia (i.e., transient or persistent), and its clinical relevance—i.e. association with increased risk of infection. Undiagnosed hypogammaglobulinemia places AIRD patients at unnecessary risk of infection, with consequent increased morbidity and mortality. Studies have identified a number of risk factors for post-BCTT hypogammaglobulinemia, including baseline IgG level, cumulative rituximab dose, use of certain concomitant or prior immunosuppressive agents, for example, cyclophosphamide, and nature of underlying AIRD [5–7]. Prior to commencing BCTT, it would be useful for physicians to consider such factors in order to stratify the risk of the patient developing hypogammaglobulinemia.

While recognition of BCTT-related hypogammaglobulinemia may have improved over the past few years, monitoring of immunoglobulins both at baseline, during BCTT, and following completion of BCTT can still be improved further [8]. Tsao et al. recommend baseline IgG testing pre-BCTT, and then at 3–6 month intervals following commencement. The concept of baseline and follow-up IgG measurements is supported by Wijetilleka et al., and by several society recommendations; the recommended timing of testing quoted in these articles varies slightly, but the principle remains the same [4, 5]. In the pediatric setting, the concept of inborn errors of immunity (IEI) characterized by immune dysregulation is emerging, so-called primary immune dysregulation disorders. The development of post-BCTT hypogammaglobulinemia may be related to an underlying IEI, giving rise to early onset autoimmunity as well as hypogammaglobulinemia [9]. This is especially true in patients

TABLE 1 | Summary of key recommendations regarding BCTT, IgG monitoring and IgRT in AIRD.

Source	Condition	Date	IgG monitoring	Recommendations IgRT initiation	IgRT discontinuation
AAAAI [4]	SHG, BCTT	2022	Baseline IgG levels before commencing BCTT. Before and/or 4–6 months after each BCTT infusion.	IgRT trial for IgG levels listed below and history of infection. If no history, shared decision making to consider trial. • IgG < 7.0 g/L with associated non-IgG HG and suboptimal vaccine responses, OR • Isolated IgG < 4.0 g/L Isolated IgG < 1.5 g/L without history of infection warrants IgRT trial.	Assessment every 6–12 months, including infection history and IgG. Consider pausing IgRT if immunosuppression stopped (9–12 months after BCTT discontinued). Reevaluate IgG and immune function 3–4 months after pausing IgRT.
ACR/ Vasculitis Foundation [3]	ANCA-Associated Vasculitis	2021		Patients with GPA/MPA and receiving remission maintenance therapy with rituximab. Conditional recommendation of IgRT if HG, e.g., < 3.0 g/L, and recurrent severe infections. Also consider for HG without infections but with impaired vaccine responses.	
Taiwan College of Rheumatology [2]	SARD	2025	Baseline IgG levels pre-BCTT. Follow up monitoring 3–6 months after BCTT infusions; interval shorter if risk factors or prior low IgG.	Initiate IgRT if: • IgG < 3.0 g/L, regardless of infection history • IgG < 4.0 g/L, received appropriate anti-infective therapy, AND severe, recurrent, or persistent infections. • IgG 4.0–6.0 g/L; if at high risk of severe infection, and received appropriate anti-infective therapy AND severe, recurrent, or persistent infections. • IgG < LLN AND overactive immune reactions to infection or life-threatening conditions despite anti-infective therapy	Discontinue IgRT if no infections for 3–6 months AND IgG level returned to normal. Reassess infection risk and IgG level 3–4 months after IgRT discontinuation. Monitor IgG periodically.

Abbreviations: AAAAI, American Academy of Allergy Asthma and Immunology; ACR, American College of Rheumatology; AIRD, autoimmune rheumatic diseases; ANCA, anti-neutrophil cytoplasmic antibody; BCTT, B-cell targeted therapies; GPA, granulomatosis with polyangiitis; HG, hypogammaglobulinemia; IgG, immunoglobulin G; IgRT, immunoglobulin replacement therapy; LLN, lower limit of normal; MPA, microscopic polyangiitis; SARD, systemic autoimmune diseases; SHG, secondary hypogammaglobulinemia.

presenting with autoimmune cytopenia [10]. Hence in pediatric-onset autoimmune patients, it is especially important that the baseline IgG is checked, as this may already be low in IEI patients.

Measurement of immunoglobulins assesses the quantity of the humoral immune response. The use of specific antibody measurements (e.g., to pneumococcus, tetanus) and, if necessary, vaccine challenges represents a measure of the quality of the humoral response [5]. Specific antibody testing is utilized to stratify risk in patients with post-BCTT HG in the ACR AAV and AAAAI secondary immunodeficiency guidance [3, 4]. Although, Tsao et al. do not refer to the usage of this testing, this may also be considered a more pragmatic approach, as BCTT is known to affect post-vaccine antibody responses for many months [4]. Hence, such measurements may be of limited value in this patient group.

While much of the published data concerns rituximab, we need to consider the potential impact of rituximab biosimilars, newer anti-CD20 agents, and novel BCTT's. For example, while obinutuzumab is claimed to induce more potent B-cell depletion, could this therapeutic effect be associated with an increased risk of hypogammaglobulinemia? CAR-T cells targeting B cells have been reported to be effective in patients with refractory SLE. This category of BCTT appears to carry a very high risk of hypogammaglobulinemia, especially in children, and this may need to be specifically addressed in future recommendations [11]. Furthermore, the risk of more complex regimens involving multiple agents such as combining BCDT with belimumab, or BCDT with plasma cell therapies also needs to be considered. Indeed, the risk of hypogammaglobulinemia with the latter combination is likely to be higher. Further assessment regarding the risks and effects of hypogammaglobulinemia needs to be included in future clinical trial design of BCTT. Registry data of AIRD and AAV where BCTT are utilized should include data on immunoglobulin measurements. Interestingly, there appears to be a difference in risk of post-BCTT hypogammaglobulinemia between different AIRD. For example, the risk in SLE and AAV appears to be higher than in rheumatoid arthritis [7]. The reasons behind this need to be further evaluated, but may include factors related to the disease pathogenesis itself, cumulative BCTT dose, as well as other immunosuppressive and corticosteroid use.

The use of immunoglobulin replacement (IgRT) in post-BCTT hypogammaglobulinemia in AIRD is an important management option, but it is important to emphasize that only a minority of patients require IgRT. Roberts et al. reported that IgRT was required in 4.2% of their cohort of 243 rituximab-treated AIRD and systemic vasculitis patients [12]. In a later study from the same center focusing only on the subgroup with hypogammaglobulinemia, Tieu et al. noted that 29/142 (20%) hypogammaglobulinemic patients required IgRT [13]. What has not yet been well established are the specific criteria for introducing IgRT. Tsao et al. propose a range of thresholds for intervention with IgRT dependent on IgG level and infection history/risk of infection. An important concept in these recommendations, also present in the ACR AAV guideline, is the proposed use of IgRT in patients with IgG <300 mg/dL even in the absence of history of infections [2, 3]. This pragmatic approach recognizes that these patients are at high risk of infection, especially with ongoing BCTT/other immunosuppression, and the danger in delaying IgRT while waiting for infections to occur.

Ideally, the applicability of recommendations should be universal, but clearly there may be limitations dependent on the specific healthcare system. For example, Tsao et al. do not discuss the use of subcutaneous immunoglobulin (SCIg) and instead focus only on intravenous immunoglobulin (IVIg) as this is the only administration route available in their healthcare system. SCIg is an excellent alternative, where available, with reduced adverse effects, lower IgG fluctuations, and improved patient convenience [14]. The choice of course has major implications for the patient, who is then committed to either attending the hospital for IVIg infusions or self-infusing with SCIg at home; though the route will be periodically assessed at clinical reviews. The decision also has significant health economic issues, such that we may need to consider the cost of medium or long-term IgRT as part of the overall cost of BCTT. In some healthcare systems, access to any form of IgRT may not be possible or affordable, and alternatives which are less than ideal such as antibiotic prophylaxis might have to be considered. The use of IgRT is not open-ended, and Tsao et al. astutely comment on the criteria for discontinuation of IgRT and the criteria for restarting IgRT should infections recur. Regional disparities mean that some healthcare systems may not have the capabilities or infrastructure to implement regular IgG monitoring or administer IgRT equitably upon recognition of its clinical need. Commercial considerations by pharmaceutical companies may also influence the availability of different IgRT products across the region. Adaptation of guidelines is essential to develop national policies that reflect local realities and health financing systems, particularly in resource-constrained environments.

The issue of post-BCTT hypogammaglobulinemia in AIRD and considering whether to start, continue, or stop IgRT highlights the importance of close working relationships between Rheumatologists, Clinical Immunologists, and Laboratory Immunology. The challenge of post-BCTT hypogammaglobulinemia will only increase with the plethora of novel BCTT being trialed for patients with AIRD.

Author Contributions

Mohammed Yousuf Karim: conceptualization, writing – conceptualization, writing – original draft. **Khadija Karim:** writing – editing and revising, manuscript preparation.

Conflicts of Interest

Professor Karim has undertaken consulting and speaker duties for Takeda Ltd., and speaking duties for CSL Behring Ltd.

Data Availability Statement

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

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LETTER TO THE EDITOR

Outpatient Non-Attendance in Rheumatology Consult and Its Relationship With Depression and Anxiety

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Dear Editor,

Non-attendance, also known as "no-shows" and "lost follow-ups", is defined as the failure to attend a scheduled appointment without prior notification. Non-attendance is a prevalent issue in patients with autoimmune rheumatic diseases (ARD). Several studies have reported its frequency to be 7.1% in first appointments [1]. Lost follow-up frequency may also vary depending on the diagnosis, reported as 23.9% in patients with rheumatoid arthritis (RA) and 25.9% in systemic lupus erythematosus (SLE) [2]. Patients with chronic diseases that lack continuous care may postpone necessary treatment, experience disease flares, and develop disease-related complications. This also affects indirectly other patients by reducing appointment availability and extending waiting times [3].

Patients with ARD tend to have an increased risk of developing anxiety and depression. Depression is one of the most common comorbidities in patients with rheumatic diseases affecting close to 1 in every 5 patients [4]. In RA, the prevalence of depression and anxiety has been reported to be 40.2% and 47.3%, respectively [5]. In other systemic diseases, these psychiatric comorbidities may impact patients' ability to attend medical appointments [6].

Information about the influence of depression and anxiety on the non-attendance of rheumatic patients is limited. This study aims to examine the prevalence of depression and anxiety symptoms among patients with ARD and its relationship with non-attendance at rheumatology appointments.

We conducted an observational retrospective study at an outpatient rheumatology clinic from the University Hospital "Dr. José Eleuterio González" in Monterrey, Mexico. We included patients over 18 years old with an ARD diagnosis and a programmed visit to our rheumatology clinic from March to December 2023. Anxiety and depression symptoms were assessed by a previous Hospital Anxiety and Depression Scale (HADS) evaluation. HADS score was categorized as follows: 0 points for no risk, 1–7 low risk, 8–10 intermediate risk, and ≥11 high risk. We classified patients into attendance and non-attendance groups, whether they missed their programmed appointment or not, and matched them by diagnosis. Sociodemographic data were retrieved from medical records. The institutional ethics committee approved the protocol as part of an integral care program for rheumatologic patients (RE20-00013).

For statistical analysis, qualitative variables are described as frequencies and percentages, while quantitative variables are represented by distributions, including median and interquartile range (IQR). Chi-square was employed to compare differences between groups. Categorical independent groups were compared using Student's *t*-test and/or Mann–Whitney *U* test as appropriate. A $p < 0.05$ was considered statistically significant. The statistical analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

A total of 376 patients were included, 25 (6.64%) were men and 351 (93.36%) were women. The median age for the non-attendance group was 51 (IQR: 39.25–61) years old and for the attendance group was 51 (IQR: 45.25–62). The median years of education were 9 (IQR: 6–12) for the non-attendance group and 9 (IQR: 6–11) for the attendance group. The most common ARD was RA in 268 patients (71.3%), followed by SLE 62 (16.5%) and

Sjogren syndrome 12 (3.2%). Other baseline patient characteristics are outlined in Table 1.

The median HADS score for anxiety was 3 (IQR: 3–8) in the non-attendance group and 1 (IQR: 0–6) in the attendance group. The median HADS score for depression was 0 (IQR: 0–1) for both groups. The risk for anxiety and depression is specified in Table 1. We found that 114 (60.63%) non-attenders and 99 (52.65%) attendees had a risk of developing anxiety. Also, 54 (28.72%) non-attenders and 61 (32.44%) attendees had a risk of developing depression.

We found a statistical difference in HADS anxiety score between attendance and non-attendance groups ($p = 0.04$). No statistical difference was found in HADS depression score ($p = 0.67$).

Regarding sociodemographic factors, there was no statistical difference in age ($p = 0.12$) and years of education ($p = 0.05$) between attendance and non-attendance groups. However, we found a statistically significant difference in patients with ≥9 years of education ($p = 0.026$).

We observed that patients with anxiety symptoms were more likely to miss their medical appointments. Anxiety symptoms in chronic diseases may be related to the fear of receiving bad news, uncertainty, and apprehension regarding treatments, as reported by other authors [6]. Lawson et al. described how not only patients with a high fear of their disease missed their appointments, but also patients with low motivation and fear often felt "well enough controlled not to need to go" and therefore missed clinic appointments [7]. However, information is limited about whether these anxious-depressive symptoms are directly related to rheumatic disease or if it is another proper psychiatric disorder.

In our study, more than 70% of the patients who missed their appointments had ≥9 years of education. We assume that having a higher level of education usually means being formally employed, thus restricting their off-work hours, which often do not align with medical consultation hours. This contrasts with other

TABLE 1 | Demographic characteristics and HADS score in ARD patients.

	Non-attendance $N = 188$	Attendance $N = 188$	p
Sex, *n* (%)			
Men	9 (4.8)	16 (8.5)	0.147
Women	179 (95.2)	172 (91.5)	
Educational level, *n* (%)			
No studies	2 (1.1)	5 (2.7)	0.209
Elementary school	47 (25)	64 (34)	
Secondary	59 (31.4)	52 (27.7)	
High school	51 (27.1)	46 (24.5)	
University	29 (15.4)	21 (11.2)	
Employment status, *n* (%)			
Unemployed	128 (68.1)	143 (76.1)	0.085
Employed	60 (31.9)	45 (23.9)	
HADS-A score, median (IQR)	3 (3–8)	1 (0–6)	**0.04**
Anxiety risk, *n* (%)			
No risk	74 (39.4)	89 (47.3)	0.182
Low	66 (35.1)	61 (2.4)	
Intermediate	24 (12.8)	25 (13.3)	
High	24 (12.8)	13 (6.9)	
HADS-D score, median (IQR)	0 (0–1)	0 (0–1)	0.67
Depression risk, *n* (%)			
No risk	134 (71.3)	127 (67.6)	0.166
Low	42 (22.3)	56 (29.8)	
Intermediate	7 (3.7)	3 (1.6)	
High	5 (2.7)	2 (1.1)	

Abbreviations: ARD, autoimmune rheumatic diseases; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale—Anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression.

findings, which explain that patients with a higher educational level are often more self-aware of their medical condition and the benefits of treatment, leading to better adherence to consultations [8].

In addition to the factors previously mentioned, other studies conducted in the rheumatic population suggest that sex, age, ethnicity, and longer waiting times may also affect the patient's attendance [1]. Patients have reported frequent causes of lost follow-up including moving to another medical institution for convenience, stopping medication due to minimal symptoms, fear of or experience with drug side effects, and lack of trust in the physician [2].

The continuity of care has been demonstrated to improve disease outcomes. A study of patients with SLE indicated that more frequent medical visits could protect against the progression of organ damage. This could be because regular visits enable doctors to detect disease flares early and promptly manage them [9].

Anxiety related to ARD influences the patient's ability and willingness to attend their medical appointments. Proper attendance is crucial for better disease management and control, which may prevent flares of the disease and improve the disease outcome.

Non-attendance at medical appointments is a significant issue for patients with ARD. Our study showed that anxiety symptoms are related to missed appointments, while depression showed no significant difference. Higher educational levels also influence non-attendance, possibly due to work constraints. Addressing mental health factors and practical barriers is essential to improve appointment adherence and continuity of care in rheumatic patients.

This study has some limitations that should be acknowledged. First, only patients with a previously recorded HADS assessment were included, which may introduce selection bias and potentially underestimate the association between anxiety/depression and non-attendance, as patients without HADS scores could represent those at highest risk of psychiatric morbidity or with more limited healthcare access. Second, non-attendance was defined as failure to attend without prior notification, which does not reflect individuals who attempted to cancel but were unable to do so due to language, technological, or administrative barriers, potentially resulting in misclassification. Finally, residual confounding remains a possibility as variables such as socioeconomic status, medication adherence, disease severity, or transportation difficulties were not available and therefore could not be adjusted for.

Author Contributions

Ana Cecilia Bardán-Inchaustegui conceptualized the study, led the project, and provided the original database. Daniela Alejandra Salcedo-Soto contributed to data analysis and drafted the manuscript. Maria Fernanda Ortiz-Nuño participated in data analysis. Anahi Carrazco-Chapa performed the statistical analysis. Angel Kevin Garza-Elizondo, Deynna Monserrat Lara-Mendez, and Miguel Angel Villarreal-Alarcon contributed to data collection and database organization. Jesus Alberto Cardenas-de la Garza and Dionicio Angel Galarza-Delgado supervised the study. Diana Elsa Flores-Alvardo is the corresponding author and oversaw the overall development of the manuscript. All authors critically reviewed 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 from the corresponding author upon reasonable request.

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EDITORIAL

Mitochondrial Energy Metabolism as a Regulator of Immune-Related Diseases

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Autoimmune diseases (AIDs) such as SLE, RA, AS, and pSS arise from dysregulated immune responses, causing self-tissue damage. Beyond genetic and environmental factors, mitochondrial energy metabolism has emerged as a key regulator of immune function. Mitochondria not only produce ATP via oxidative phosphorylation (OXPHOS) but also modulate ROS, calcium signaling, and inflammasome activation. Shifts in mitochondrial metabolism determine immune cell fate and cytokine profiles, while mitochondrial dysfunction—marked by impaired OXPHOS or excess ROS—drives autoantigen release and chronic inflammation. Recent multi-omics studies in the *International Journal of Rheumatic Diseases* further link mitochondrial dysfunction to autoimmune pathogenesis. Luo et al. integrated genetic (SMR, eQTL, mQTL, pQTL) data across multiple AIDs, whereas Chen et al. (2025) combined bulk and single-cell transcriptomics with machine learning to reveal altered OXPHOS pathways in AS. Together, these findings highlight mitochondrial metabolism as a central hub in immune dysregulation and a promising therapeutic target in AIDs.

1 | Causal Inference From Multi-Omics Mendelian Randomization

Luo et al. [1] address a longstanding question: Is mitochondrial dysfunction a cause or consequence of AIDs? Using MR, which leverages genetic variants as instrumental variables to infer causality while minimizing confounding and reverse causation, the authors analyzed data from large-scale genome-wide association studies (GWAS) encompassing 10 AIDs with sample sizes ranging from 303 590 to 456 348 participants. They focused on 1136 mitochondrial-related genes from the MitoCarta database, integrating cis-QTL data: eQTL from 31 684 individuals, mQTL from 1980, and pQTL from 35 559. Key findings reveal four "Grade-II" mitochondrial genes with robust causal associations across AIDs, validated by heterogeneity in dependent instruments (HEIDI) tests and Bayesian colocalization. For MM, ATAD3A expressions were causally linked to increased risk, while UQCRH exerted protective effects. SND1 was associated with OA risk. Notably, TOP1MT showed protective effects against pSS. A striking observation was the dual role of UQCRH in MM, where the variant rs41292543 mediated causal effects via methylation but protection via expression.

These results were bolstered by validation steps, including phenome-wide association studies (PheWAS), bidirectional MR with mtDNA copy number, and multi-omics integration. For example, reduced mtDNA copy number causally increased risks for SLE and RA, aligning with prior observations of mtDNA mutations in AIDs like MS and SLE. The study highlights how epigenetic (mQTL) and transcriptional (eQTL) layers amplify

Su-Boon Yong and Po-Hung Chen contribute equally to this study.

genetic predispositions, suggesting that mitochondrial dynamics, including fission and fusion regulated by genes such as ATAD3A, serve as potential therapeutic nodes. ATAD3A, which participates in mitochondrial membrane organization, may promote inflammation by altering reactive oxygen species levels and mitophagy, whereas TOP1MT, a mitochondrial DNA topoisomerase, could influence autoantigen presentation. This multi-omics approach overcomes limitations of traditional GWAS, which often overlook mitochondrial genes, and provides a framework for precision medicine. The identification of causal variants serves to prioritize candidate genes for subsequent functional verification, as opposed to the direct establishment of pharmacological targets. Although genes like UQCRH emerge as potential focal points for experimental research, genetic causality does not equate to clinical efficacy. Consequently, OXPHOS modulators, such as metformin, represent hypothesis-generating leads that require extensive validation through robust preclinical and clinical trials before their therapeutic potential can be established.

2 | OXPHOS Dysregulation in Ankylosing Spondylitis: A Machine Learning Perspective

Focusing on ankylosing spondylitis (AS), a prototypical HLA-B27-associated and IL-17-driven spondyloarthropathy, Chen et al. [2] applied multi-omics and computational analyses to investigate mitochondrial OXPHOS dysregulation. Bulk RNA-seq of PBMCs from 16 AS patients and 16 controls (GSE25101) identified OXPHOS as a top-enriched pathway by GSEA and PCA. Single-cell RNA-seq revealed cell-type-specific elevation of OXPHOS activity, particularly in monocytes and dendritic cells. WGCNA identified two OXPHOS-related gene modules, and integrated machine learning including SVM-RFE, random forest, and LASSO highlighted three hub genes: LAMTOR2, APBB1IP, and DGKQ, which were validated by RT-PCR and scRNA-seq. LAMTOR2 was enriched in monocytes and dendritic cells and associated with Th17 differentiation through mTOR signaling, linking metabolism and inflammation. These findings suggest that OXPHOS reprogramming and LAMTOR2-mediated signaling are key drivers of AS immune pathology and potential therapeutic targets that complement anti-IL-17 therapy. To further illustrate the interplay between mitochondrial function and immune regulation, the following table summarizes select key genes and pathways implicated in AIDs, drawing from the reviewed studies and broader literature (Table 1). These elements highlight how mitochondrial dynamics, metabolism, and signaling modulate immune cell behavior and disease risk.

3 | Integrating Insights: Mitochondrial Metabolism in Immune Regulation

These studies converge on a central theme: Mitochondrial energy metabolism orchestrates immune tolerance and inflammation in AIDs. Luo et al.'s causal framework complements Chen et al.'s mechanistic dissection, revealing shared pathways. For instance, OXPHOS components like UQCRH overlap with AS-enriched modules, suggesting trans-disease relevance. Broader implications extend to other immune-related diseases. In inflammatory bowel disease (IBD) or psoriasis, often comorbid

TABLE 1 | Key mitochondrial regulators and their implications in autoimmune disorders.

Target	Associated disease	Effect/direction	Evidence type	Proposed mechanism	References
ATAD3A	Multiple Myeloma (MM)	Increased risk	Causal (MR/eQTL)	Regulation of mitochondrial membrane organization and ROS levels	[1]
TOP1MT	Primary Sjögren's Syndrome (pSS)	Protective effect	Causal (MR/pQTL)	mtDNA topoisomerase influencing autoantigen presentation	[2]
UQCRH	Multiple Myeloma (MM)	Protective (via expression)	Causal (MR/eQTL)	Modulates oxidative phosphorylation (OXPHOS) efficiency	[3]
SND1	Osteoarthritis (OA)	Increased risk	Causal (MR)	Linked to epigenetic (mQTL) and transcriptional regulation	[3]
LAMTOR2	Ankylosing Spondylitis (AS)	Hub gene (Upregulated)	Association (scRNA-seq/ML)	Mediates mTOR signaling and Th17 differentiation in monocytes	[4]

with AS, mitochondrial dysfunction exacerbates barrier defects and cytokine storms. Precision medicine could involve mtDNA-targeted therapies or OXPHOS modulators, guided by genetic profiling. Challenges remain: Tissue-specific effects and sex biases in AIDs warrant further scRNA-seq integration with spatial transcriptomics.

4 | Conclusion

The studies by Luo et al. and Chen et al. advance our understanding of mitochondrial energy metabolism as a modifiable regulator in AIDs. By integrating genetic inference with multi-omics analyses, they highlight candidate genes such as TOP1MT, UQCRH, and LAMTOR2 for further mechanistic investigation. These findings provide a conceptual and experimental framework for exploring mitochondrial–immune interactions, rather than immediate therapeutic translation. Before clinical trials of mitochondrial-targeted interventions can be contemplated, additional studies are required to validate these targets in disease-relevant cellular and animal models, clarify tissue- and cell-specific effects, and establish safety and pharmacodynamic profiles. Such a stepwise investigation will be essential to evaluate the feasibility of translating a metabolic–immunologic paradigm into rheumatologic practice.

Author Contributions

S.-B.Y., P.-H.C., and M.-Y.W. conceived and drafted the manuscript, C.-J.L. provided valuable discussion. C.-J.L. and C.-C.W. reviewed and edited of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors do not have permission to share data.

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CLINICAL IMAGE

A Characteristic "Lincoln Sign" in Monostotic Paget's Disease of the Mandible

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Keywords: bone scintigraphy | Lincoln sign | mandible | Paget's disease

A 70-year-old woman with a remote history of breast carcinoma treated 10 years earlier by lumpectomy, adjuvant radiochemotherapy, and hormonal therapy was referred for evaluation of an incidental abnormality detected on routine follow-up bone scintigraphy. She was asymptomatic, with no bone pain, facial swelling, deformity, or functional complaints, and her general condition was preserved. Physical examination was unremarkable.

Laboratory investigations revealed an isolated elevation of alkaline phosphatase (214 U/L; 1.6× the upper limit of normal, reference range 42–121 U/L), while serum calcium and phosphate levels were normal. Whole-body bone scintigraphy using ^{99m}Tc-labeled radiotracers demonstrated a focal, intensely increased uptake confined to the mandible (Figure 1). The tracer distribution followed a linear pattern along the mandibular borders, corresponding to an osteosclerotic area on complementary imaging.

In a patient with a prior history of malignancy, such a finding raises concern for metastatic bone disease. However, the absence of symptoms, the isolated biochemical abnormality, and the highly specific scintigraphic appearance suggested an alternative diagnosis related to focal bone remodeling rather than tumor infiltration. The striking mandibular outline on scintigraphy resembles a dark contour tracing the jaw, prompting recognition of a classic but uncommon imaging sign. What is the diagnosis suggested by this image?

The imaging findings are diagnostic of monostotic Paget's disease of the mandible. The linear, intense uptake outlining the jaw corresponds to the classic "Lincoln sign," also known as the "black beard sign," which reflects increased osteoblastic activity and accelerated bone remodeling along the mandibular cortex [1, 2]. Given the absence of bone pain, deformity, functional impairment, or risk of local complications, no pharmacological treatment was initiated in this patient.

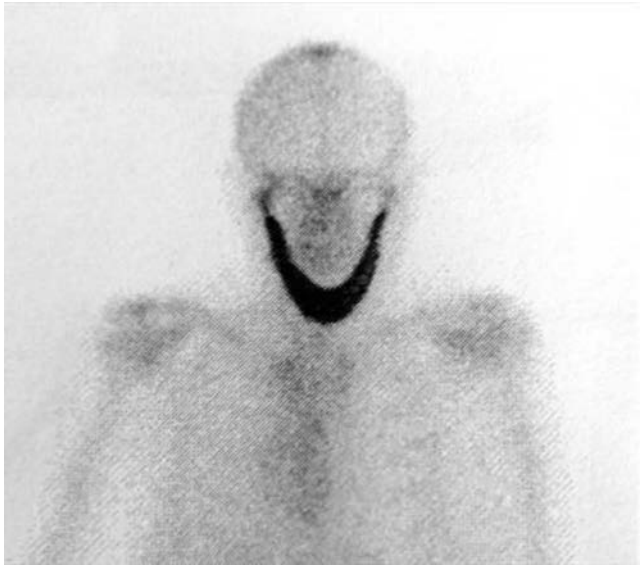

FIGURE 1 | Anterior planar image of ^{99m}Tc-MDP bone scintigraphy showing an intense, well-defined linear tracer uptake outlining the mandible, producing the characteristic "Lincoln sign" or "Black beard" sign.

Paget's disease most commonly involves the pelvis, spine, skull, and long bones, while isolated mandibular involvement is rare [1]. In oncologic patients, this presentation may closely mimic metastatic disease, making recognition of this distinctive scintigraphic pattern essential to avoid misdiagnosis and unnecessary invasive procedures [2].

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection were performed by M.D., visualization and validation by S.B., Z.G., and M.H.K. and supervision by H.F. and S.B. The first draft of the manuscript was written by A.F. All authors read and approved the final manuscript.

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Ethics Statement

Ethical approval was not required for this case report, as it includes only anonymized scintigraphic images obtained as part of routine clinical care; the work was conducted in accordance with ethical standards and patient confidentiality was fully respected.

Consent

Written informed consent was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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REVIEW

Hematopoietic Stem Cell Transplantation in Rheumatic Diseases

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Keywords: autoimmune diseases | hematopoietic stem cell transplantation | juvenile idiopathic arthritis | rheumatic diseases | systemic lupus erythematosus | systemic sclerosis | treatment outcome

ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) is an emerging therapeutic strategy for severe autoimmune rheumatic diseases (AIRD) where conventional therapies often fail to achieve long-term remission. This review focuses on the role of HSCT in specific AIRD, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), deficiency of adenosine deaminase 2 (DADA2), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Takayasu arteritis (TA), and juvenile idiopathic arthritis (JIA).

Objective: The objective was to evaluate the efficacy, immunological mechanisms, patient selection criteria, conditioning regimens, and outcomes of HSCT in the management of these specific AIRD, with a focus on systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Methods: A comprehensive literature review was conducted, analyzing clinical trials, observational studies, and preclinical research on HSCT in the following AIRD: SSc, SLE, RA, DADA2, ANCA-associated vasculitis, TA, and JIA. The review examined pulmonary outcomes, immune reconstitution, CD34+ cell selection, and post-transplant immunosuppression. Keywords used in the search included SSc, SLE, RA, DADA2, ANCA-associated vasculitis, Takayasu arteritis, and JIA.

Results: HSCT has demonstrated promising outcomes, particularly in diffuse cutaneous SSc with ILD improvement and in refractory cases of SLE, RA, and JIA. In DADA2, HSCT can reverse hematological, immunological, and vascular phenotypes. While effective in some cases of ANCA-associated vasculitis and TA, relapses and complications remain a concern. Immunological benefits include the regeneration of a self-tolerant immune system. However, early transplant-related mortality (TRM) necessitates careful patient selection and reduced toxicity conditioning.

Abbreviations: AAV, ANCA-associated vasculitis; ABC, ATP-binding cassette; ADA2, Deficiency of adenosine deaminase 2; AIRD, Autoimmune Rheumatic Diseases; ANCA, Antineutrophil cytoplasmic antibody; ASCT, Autologous stem cell transplantation; ASTIS, Autologous Stem Cell Transplantation International Scleroderma; ATG, Anti-thymocyte globulin; BM, Bone marrow; CLP, Common lymphoid progenitors; CXCR4, C-X-C chemokine receptor type 4; DADA2, Deficiency of adenosine deaminase 2; dcSSc, Diffuse cutaneous systemic sclerosis; DFS, Disease-free survival; DMARDs, Disease-modifying antirheumatic drugs; EBMT, European Group for Blood and Marrow Transplantation; EULAR, European League Against Rheumatism; G-CSF, Granulocyte colony-stimulating factor; GPA, Granulomatosis with polyangiitis; GVHD, Graft-versus-host disease; HCT, Hematopoietic cell transplantation; HSC, Hematopoietic stem cell; HSCT, Hematopoietic Stem Cell Transplantation; ILD, Interstitial Lung Disease; IMIDs, Immune-mediated inflammatory diseases; iPSCs, Induced Pluripotent Stem Cells; JIA, Juvenile Idiopathic Arthritis; MAS, Macrophage activation syndrome; MeSH, Medical Subject Headings; MMF, Mycophenolate mofetil; mRSS, Modified Rodman's Skin Score; NSAIDs, Nonsteroidal anti-inflammatory drugs; OS, Overall survival; PRCA, Pure red cell aplasia; RA, Rheumatoid Arthritis; SCOT, Stem Cell Transplant vs. Cyclophosphamide; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SSc, Systemic Sclerosis; SSc-ILD, Systemic Sclerosis-Associated Interstitial Lung Disease; TA, Takayasu arteritis; TCR, T-cell receptor; TNF, Tumor necrosis factor; Tregs, T regulatory cells; TRM, Transplant-related mortality.

Conclusions: HSCT offers a transformative approach for select patients with refractory SSc, SLE, RA, DADA2, ANCA-associated vasculitis, TA, and JIA, achieving long-term, drug-free remission in some. Future research should optimize conditioning protocols, refine patient selection, and assess long-term outcomes to maximize HSCT benefits and minimize risks.

1 | Introduction

Rheumatic diseases comprise a heterogeneous group of immune-mediated disorders characterized not only by musculoskeletal involvement but, more importantly, by progressive and potentially life-threatening systemic organ damage. Severe manifestations affecting the lungs, heart, kidneys, central nervous system, and vasculature are major contributors to morbidity and mortality, particularly in diseases such as systemic sclerosis, systemic lupus erythematosus, and systemic vasculitides. In these settings, irreversible organ failure rather than joint disease often determines prognosis and survival.

While musculoskeletal symptoms are frequently the most visible and early clinical features, it is the progressive visceral involvement and refractory disease course that necessitate consideration of aggressive therapeutic strategies beyond conventional immunosuppression, including hematopoietic stem cell transplantation (HSCT) [1]. A large subset of rheumatic diseases falls under the umbrella of autoimmune disorders: conditions in which the immune system, rather than defending the body, erroneously targets healthy tissues. Autoimmune diseases encompass more than 100 distinct clinical entities and collectively impact an estimated 5%–8% of the global population. Despite advancements in diagnostics and therapeutics, the etiology and pathogenesis of many of these diseases remain incompletely understood, necessitating continued research into their underlying mechanisms and optimal management strategies [2]. While conventional treatments such as immunosuppressive drugs and biologic agents can help manage symptoms and slow disease progression, they often fall short of providing a cure. As a result, many patients continue to struggle with long-term health challenges, highlighting the pressing need for more effective therapeutic options [3]. HSCT was introduced as a potential therapy for autoimmune diseases based on its ability to eradicate autoreactive immune cells and reconstitute immune tolerance. Advances in transplant techniques, particularly autologous HSCT, have reduced treatment-related mortality and improved outcomes.

1.1 | Types of Stem Cells and the Role of Hematopoietic Stem Cells

Stem cells are undifferentiated cells with the remarkable ability to develop into various specialized cell types. They are classified based on their potency, their ability to differentiate into different cell types, and their source within the body (Table 1).

HSCT primarily sourced from bone marrow, peripheral blood, and umbilical cord blood are responsible for generating all blood and immune cells. They play a critical role in HSCT, where they are used to reset the immune system in patients with severe autoimmune diseases. The ability of HSCs to repopulate the immune system makes them a powerful therapeutic tool in conditions where immune dysregulation drives disease progression [18, 19].

Among the most severe autoimmune rheumatic diseases—such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), deficiency of adenosine deaminase 2 (DADA2), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Takayasu arteritis (TA), and juvenile idiopathic arthritis (JIA), many continue to pose significant therapeutic challenges despite advancements in conventional and biologic treatments. Although immunosuppressants and corticosteroids are widely used for treatment, they are often insufficient, particularly in patients with major organ involvement who are refractory to conventional therapies. Given the limitation of existing treatments, HSCT has emerged as a therapeutic option for severe and refractory autoimmune rheumatic diseases. The concept is based on the ability of HSCT to "reset" the immune system, thereby controlling inflammation and preventing irreversible organ damage. Early registry data and clinical trials have demonstrated encouraging results, particularly in systemic sclerosis, while ongoing studies continue to refine its role in other rheumatic conditions [20].

This review focuses on selected autoimmune rheumatic diseases in which HSCT has demonstrated established or emerging clinical relevance, rather than providing an exhaustive overview of all rheumatic conditions. including SSc, SLE, RA, DADA2, ANCA-associated vasculitis, TA, and JIA. It explores the different types of stem cells, their therapeutic potential, and the latest clinical advancements in HSCT for rheumatic diseases. By critically analyzing recent literature, this review aims to highlight HSCT's efficacy, challenges, and future directions as a transformative treatment option in rheumatology.

2 | Search Strategy

We included studies published from 1990 onwards to capture the full spectrum of experience with HSCT in autoimmune rheumatic diseases. However, given advances in transplant techniques, supportive care, and patient selection, we placed greater emphasis on studies published in the last decade, as these better reflect contemporary practice and outcomes. The search included primary sources, such as MEDLINE via the PubMed interface, Scopus and secondary sources, including Embase. A comprehensive literature search was conducted using the following keywords to identify relevant studies on the role of hematopoietic stem cell transplantation (HSCT) in autoimmune rheumatic diseases: "systemic sclerosis", "SSc", "systemic lupus erythematosus", "SLE", "rheumatoid arthritis", "RA", "deficiency of adenosine deaminase 2", "DADA2", "antineutrophil cytoplasmic antibody-associated vasculitis", "ANCA-associated vasculitis", "Takayasu arteritis", "TA", "juvenile idiopathic arthritis", and "JIA". These terms were combined with "hematopoietic stem

Key Messages for Rheumatologists

- Autoimmune diseases (ADs) are now among the fastest-growing indications for autologous HCT.
- Systemic Lupus Erythematosus (SLE) and systemic sclerosis (SSc) are leading indications, with HCT integrated into treatment algorithms.
- Interest in allogeneic HCT is increasing, especially for ADs with autoinflammatory or immunodeficiency features.
- HCT should be performed in experienced, JACIE-accredited centers with multidisciplinary collaboration.
- Immune reconstitution studies post-HCT offer insights into immune reset and AD pathogenesis.

cell transplantation" and "HSCT" using Boolean operators (OR/AND) to maximize retrieval of relevant articles. MeSH (Medical Subject Headings) terms were utilized to enhance the precision of the search, including "Hematopoietic Stem Cell Transplantation," "Autoimmune Diseases," "Rheumatic Diseases," "Bone Marrow Transplantation," and disease-specific terms such as "Takayasu Arteritis" and "Systemic Lupus Erythematosus." To ensure a comprehensive review, additional literature was manually screened from sources such as Google Scholar, PubMed Central, and ScienceDirect to supplement the primary database findings, as detailed in Appendix S1.

A multi-step selection process was employed, starting with title screening to exclude irrelevant studies, followed by abstract and full-text reviews. Exclusion criteria included editorials, duplicates, non-English publications, and studies lacking relevant outcome data. Inclusion was limited to peer-reviewed articles and clinical trials from the past decade focusing on HSCT in autoimmune diseases—specifically RA, SLE, SSC, ANCA vasculitis, DADA2, and TA. Key study characteristics, treatment outcomes, and safety profiles were extracted and analyzed to identify trends and significant findings. Review articles were also cross-referenced to supplement the literature. Two independent reviewers conducted the selection, resolving discrepancies through discussion or a third reviewer. This structured method enabled the identification of major scientific findings and clinical trial data forming the basis of this review.

2.1 | Concept of Immune Reconstitution With HSCT

HSCT results in partial or complete replacement of the recipient's hematopoietic system by the donor's stem cells. The source of stem cells may be self (autologous HSCT) or from a different donor of the same species (allogeneic HSCT). The stem cells may be harvested from bone marrow, peripheral blood, or cord blood [16].

HSCT can be broadly classified into allogeneic HSCT and autologous HSCT, each with distinct advantages and risks.

- Allogeneic HSCT involves transplanting stem cells from a genetically matched or partially matched donor. This approach offers the potential for long-lasting remission due to the graft-versus-autoimmunity effect, in which the donor's immune system helps eliminate autoreactive cells. However, allogeneic HSCT carries a higher risk of complications, particularly graft-versus-host disease (GVHD), which can lead to significant morbidity and mortality. The need for immunosuppressive therapy post-transplant further complicates the treatment process.
- Autologous HSCT, on the other hand, utilizes the patient's own stem cells, reducing the risk of GVHD and transplant-related mortality. This method is often preferred in autoimmune diseases due to its relatively safer mobilization process and lower risk profile. However, the potential for disease relapse remains a concern, as the underlying immune dysregulation may persist after transplantation.

Current guidelines by the EBMT recommend autologous HSCT with mobilized peripheral blood stem cells for autoimmune rheumatic diseases. Consensus statements by EULAR and EBMT further standardize indications, patient selection, and treatment protocols [21].

TABLE 1 | Types of stem cells.

Stem cell type	Potency	Tissue source	References
Embryonic stem cells	Pluripotent	Blastocyst	Martello and Smith [4], Evans and Kaufman [5], Martin [6], Thomson et al. [7].
Induced pluripotent stem cells	Pluripotent (reprogramed)	Skin fibroblasts, keratinocytes, T cells, hepatocytes, other somatic cells	Takahashi and Yamanaka [8], Takahashi et al. [9], Brouwer [10]
Fetal stem cells	Multipotent	Fetal blood, bone marrow, liver, lung, kidney, pancreas	Leary and Ogawa [11], O'Donoghue and Fisk [12]
Adult stem cells	Multipotent	Hematopoietic stem cells, mesenchymal stem cells: umbilical cord, adult tissues (peripheral blood, bone marrow, synovial membrane, periosteum, adipose tissue, dental pulp)	Till and McCulloch [13], Bryder, Rossi and Weissman [14], Pittenger et al. [15], De Bari, Dell'Accio and Luyten [16], Wang et al. [17]

Steps in HSCT [22, 23]:

1. Mobilization: Hematopoietic stem cells are mobilized from the bone marrow into the peripheral blood, typically using granulocyte-colony-stimulating factor (G-CSF) with or without cyclophosphamide [24].
2. Collection: Peripheral blood stem cells are collected by leukapheresis and cryopreserved until transplantation [24, 25].
3. Conditioning regimen: Conditioning regimens used in HSCT for autoimmune rheumatic diseases are designed to achieve profound immunoablation while minimizing treatment-related toxicity. These regimens may be classified as myeloablative or non-myeloablative, depending on disease severity, organ involvement, and patient-related risk factors. Non-myeloablative or reduced-intensity regimens, most commonly employed in autoimmune diseases, typically consist of high-dose cyclophosphamide combined with anti-thymocyte globulin (ATG). ATG plays a critical role in depleting autoreactive T cells, reducing the risk of immune reconstitution with pathogenic clones, and lowering relapse rates. Myeloablative regimens, used selectively in younger patients with preserved organ function, may incorporate total body irradiation (TBI) in combination with cyclophosphamide or other alkylating agents. While TBI-based regimens have demonstrated durable disease control, particularly in systemic sclerosis, they are associated with higher early toxicity and are therefore reserved for carefully selected patients in experienced transplant centers [18].
4. Stem cell infusion: Following conditioning, cryopreserved autologous hematopoietic stem cells are reinfused intravenously to restore hematopoiesis and immune function. In some protocols, particularly those used in systemic sclerosis and systemic lupus erythematosus, ex vivo $CD34^+$ cell selection is performed prior to reinfusion. This strategy aims to reduce the reinfusion of autoreactive lymphocytes and enhance immune reset. However, the use of $CD34^+$ selection remains variable across centers. While early studies suggested lower relapse rates with $CD34^+$ selection, subsequent registry data have not consistently demonstrated a clear survival advantage, and concerns regarding delayed immune reconstitution and increased infection risk have limited its routine use. As a result, many contemporary protocols favor unmanipulated grafts combined with effective serotherapy (e.g., ATG) to balance efficacy and safety [26, 27].
5. Engraftment and recovery: Hematopoietic recovery is monitored. Supportive care, including infection prophylaxis and transfusions, is provided until neutrophil and platelet engraftment occur [25].
6. Post-transplant care: Patients are followed for immune reconstitution, disease remission, and long-term complications [24].

2.2 | Immune Rewiring Mechanisms Following HSCT

After HSCT, patients can achieve durable, drug-free, and symptom-free remission, primarily through immune rewiring rather than immunosuppression. Several mechanisms are proposed to explain this immune rewiring [28–30]:

1. Depletion of Peripheral Autoreactive T and B Cell Clones: HSCT leads to the reduction of pathogenic T and B cell clones responsible for autoimmune activity.
2. Reduced Pro-Inflammatory Cytokine Production: Peripheral T cells show decreased production of cytokines that drive inflammation.
3. Thrombopoiesis and TCR Repertoire Expansion: Post-conditioning lymphopenia triggers the expansion of surviving T cells, leading to oligoclonal T-cell proliferation. Although these autoreactive clones may resurge, their effector functions are significantly weakened, thereby preventing the reactivation of clinical autoimmunity.
4. Thymopoiesis and Treg Diversification: Thymopoiesis stimulates the development of diverse, polyclonal T regulatory cells (Tregs) with expanded TCR repertoires. Combined with limited effector T-cell activity, these robust, functionally diverse Tregs suppress autoimmunity effectively.
5. Reconstitution of Innate Immune Cells: Post-HSCT, neutrophils and monocytes exhibit a reduced pro-inflammatory signature, though the full pattern of innate immune cell reconstitution in autoimmune conditions remains under investigation [31, 32].

These processes collectively shift the immune system toward a state less prone to autoimmunity, contributing to the clinical improvements observed post-HSCT.

Stem cells' regenerative potential depends on their ability to differentiate into various effector cell types. In the hematopoietic system, hematopoietic stem cells (HSCs) lead a hierarchy that produces nine distinct blood cell types via specialized progenitors. Given the high turnover rate of blood cells, HSCs and progenitors are essential for maintaining homeostasis [33].

Multipotent progenitor cells derived from HSCs retain full lineage potential but have limited self-renewal, making them clinically useful for rapid hematopoietic recovery but less effective for long-term reconstitution [34]. These progenitors further differentiate into common lymphoid progenitors (CLPs) and myeloid progenitors, generating lymphoid and myeloerythroid cells, respectively.

The differentiation from HSCs to mature blood cells is largely irreversible under normal conditions [24]. HSCs primarily remain in the quiescent G0 phase to protect against DNA damage and metabolic stress. They also exhibit high ATP-binding cassette (ABC) transporters, enhancing their cytoprotective roles, which are key to advancing regenerative medicine strategies [7].

2.3 | HSCT in Specific Rheumatic Diseases

The autoimmune rheumatic diseases included in this review were selected based on a combination of clinical severity,

life-threatening organ involvement, refractoriness to conventional and biologic therapies, and the availability of clinical or registry-based evidence supporting the use of hematopoietic stem cell transplantation (HSCT). Systemic sclerosis and systemic lupus erythematosus were prioritized due to the presence of randomized controlled trials and extensive registry data demonstrating HSCT efficacy in improving survival and organ outcomes. Rheumatoid arthritis and juvenile idiopathic arthritis were included as historically important models in which HSCT provided key insights into immune reconstitution, despite a decline in current use following the advent of biologic therapies.

Rare but severe conditions such as deficiency of adenosine deaminase 2, ANCA-associated vasculitis, and Takayasu arteritis were incorporated because they represent high-mortality or treatment-refractory diseases in which HSCT has emerged as a potentially curative or rescue therapy, supported by case series and international registry reports. Collectively, these diseases reflect a spectrum of immune-mediated pathophysiology, disease chronicity, and organ involvement, allowing a comprehensive evaluation of the role of HSCT across rheumatology.

2.4 | Systemic Sclerosis, With Emphasis on Systemic Sclerosis–Associated Interstitial Lung Disease (SSc-ILD)

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by progressive fibrotic changes affecting the skin and internal organ systems. It is classified into diffuse and limited subsets based on the extent of skin involvement, measured using the modified Rodman's Skin Score (mRSS). Higher mRSS values correlate with increased organ involvement and predict poorer outcomes, with severe cases showing a 40%–50% five-year mortality due to cardiac, renal, or pulmonary complications [25].

Conventional immunosuppressive therapies often yield limited success in treating SSc, positioning patients as suitable candidates for autologous HSCT. Early studies by the EBMT/EULAR registry (1996–2002) demonstrated significant benefits of HSCT, including a >25% reduction in skin scores in 80% of patients and durable remission in two-thirds of cases over three years. However, treatment-related mortality (TRM) was approximately 8% [35].

The phase III ASTIS trial compared HSCT with Cyclophosphamide in 156 patients over a median follow-up of 5.8 years. While HSCT was associated with higher mortality during the first year, it offered superior long-term event-free survival. These findings underline the importance of early intervention and careful patient selection to maximize benefits and minimize risks, particularly from the intensive conditioning regimen required for HSCT [36].

The application of HSCT in SSc has shown promising outcomes, particularly in patients with diffuse cutaneous SSc (dcSSc). However, there is currently no substantial evidence supporting its use in other subsets of the disease, such as limited cutaneous SSc, overlap syndromes, or sine scleroderma [31].

Autologous HSCT remains a promising option for remission and improving survival in patients with systemic involvement. Clinical guidelines must balance risks with benefits to optimize its use, emphasizing early-stage intervention and improved procedural safety. The results of the SCOT trial, published in 2018, demonstrated that HSCT led to significantly improved event-free survival and overall survival in patients with severe diffuse cutaneous SSc compared with cyclophosphamide therapy [32]. However, the treatment was associated with a higher early treatment-related mortality, underscoring the need for careful patient selection.

Interstitial lung disease (ILD) represents the leading cause of mortality in systemic sclerosis, accounting for nearly 35%–40% of SSc-related deaths. Progressive pulmonary fibrosis results in irreversible loss of lung function, severely impaired quality of life, and reduced survival, particularly in patients with diffuse cutaneous disease. Conventional immunosuppressive therapies, including cyclophosphamide and mycophenolate mofetil, often slow but rarely halt disease progression, underscoring the need for more effective interventions. HSCT has demonstrated significant and sustained benefits in pulmonary outcomes, particularly in patients with SSc-ILD. In the ASTIS trial, patients receiving HSCT showed stabilization or improvement in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) compared with those treated with cyclophosphamide, with these benefits persisting during long-term follow-up. Similarly, the SCOT trial reported significant improvement in pulmonary function parameters, reduced progression of ILD on imaging, and superior event-free and overall survival among HSCT-treated patients. Importantly, patients with early-stage ILD and preserved baseline lung function derived the greatest benefit, highlighting the importance of early referral and timely transplantation [37, 38].

Collectively, these findings establish HSCT as a disease-modifying therapy capable of altering the natural history of SSc-ILD, offering not only stabilization but also potential improvement in pulmonary function, thereby addressing the principal driver of mortality in systemic sclerosis.

2.5 | Systemic Lupus Erythematosus

Over recent decades, advancements in aggressive immunosuppressive therapies and improved supportive care have significantly reduced mortality in systemic lupus erythematosus (SLE). However, patients with severe visceral organ involvement and suboptimal responses to conventional treatments may benefit from autologous HSCT [25].

Research suggests SLE is associated with bone marrow dysfunction, marked by reduced CD34+ stem cells and increased cell apoptosis, potentially leading to impaired stem cell proliferation. Following autologous stem cell transplantation (ASCT), these abnormalities improve, with fewer apoptotic CD34+ cells and enhanced regenerative potential.

Studies have reported encouraging results:

- The EBMT/EULAR registry recorded 53 cases of SLE treated with ASCT from 1995 to 2023.

- A U.S.-based study from 1997 to 2005 documented 50 cases, showing a 5-year overall survival (OS) rate of 80% and a disease-free survival (DFS) rate of 50%, with a treatment-related mortality (TRM) of 4%.

Secondary analyses revealed stabilization of renal function, improved carbon monoxide diffusion lung capacity, and reductions in disease activity scores (SLEDAI). Serological markers also improved, with lower ANA and anti-dsDNA levels and better complement levels. A smaller study (2001–2008) further confirmed these benefits, demonstrating that ASCT can control disease activity, improve serological profiles, and stabilize or reverse organ dysfunction in refractory SLE cases [39].

HSCT has demonstrated efficacy in achieving clinical remission in patients with severe SLE who are refractory to conventional therapies. However, studies indicate that the relapse/flare rate after HSCT in SLE remains considerably high, with reported relapse rates ranging from 30% to 50%. This underscores the need for careful patient selection and potential post-transplant maintenance strategies to sustain long-term remission [40]. However, HSCT has demonstrated greater promise in SLE with over 300 patients treated worldwide [19].

ASCT shows promise as a treatment for refractory SLE, offering improved survival, reduced disease activity, and organ function stabilization. While preliminary results are encouraging, larger randomized trials, such as the ASTIL study, are needed to establish the role of ASCT as a standard therapeutic option for SLE [41].

Recent studies, including two retrospective analyses from the EBMT/EULAR registry and a Northwestern University study, have evaluated the safety and efficacy of autologous HSCT in patients with treatment-refractory SLE [35]. These studies involved over 100 patients and reported notable improvements in disease activity, better responses to previously ineffective treatments, and a 50% chance of achieving 5-year remission. Additionally, non-myeloablative conditioning regimens appeared to lower the risks of infections and treatment-related complications [39].

Long-term studies have shown that hematopoietic stem cell (HSC) transplantation for treating refractory SSc (SSc) and SLE is safe and correlates with improved disease-free survival [25]. However, none of the trials have reported achieving complete remission, indicating the need for further research to enhance our understanding of HSC biology and the underlying mechanisms of these diseases. Additionally, well-designed randomized controlled trials are essential to validate the efficacy of HSC transplantation against the established standard treatments.

2.6 | Rheumatoid Arthritis

HSCT has shown promising outcomes in patients with rheumatoid arthritis (RA), including reduced mortality, lower infection rates, and improved complication profiles compared with patients without immune-mediated inflammatory diseases (IMIDs). RA patients undergoing HSCT experienced fewer bacteremia and drug-induced opportunistic infections, with a trend toward fewer opportunistic infections in matched comparisons. Subgroup analyses of patients receiving allogeneic HSCT demonstrated reduced mortality, lower graft-versus-host disease (GVHD) rates, and decreased opportunistic drug-induced infections. Hospital metrics, such as length of stay and overall costs, were comparable between RA and non-IMID patients. These findings support HSCT as a viable therapeutic option, particularly for RA patients receiving allogeneic transplants [38].

RA affects approximately 1% of the population and is the most common systemic autoimmune disease. While NSAIDs and DMARDs manage most cases, treatment-resistant disease remains a challenge, leading to severe disability and higher mortality. Early research and clinical observations highlighted the potential of HSCT in RA treatment.

Autologous HSCT, first performed in 1996, has shown efficacy in controlling severe, refractory RA, especially in seronegative cases [42]. While HSCT can provide sustained disease control combined with DMARDs, introducing biological therapies such as anti-TNF agents has reduced demand. However, it remains an option for select, treatment-resistant patients.

Limited evidence from allogeneic HSCT shows durable remission in refractory cases, while syngeneic HSCT outcomes have been mixed. Despite the increasing use of biologics, HSCT retains therapeutic potential for severe, treatment-resistant RA and offers insights into RA's immune system dysfunction through immune system ablation and reconstruction.

In rheumatoid arthritis (RA), autologous HSCT has also been explored for patients not responding to conventional therapies [43]. Retrospective data from the EBMT registry showed that 67% of patients maintained remission at 6 months post-transplant. However, relapse rates were significant due to incomplete T-cell repertoire ablation, requiring the reintroduction of disease-modifying antirheumatic drugs within 6–12 months for many patients. Despite a 94% overall survival rate at 5 years, progression-free survival was only 18%. The emergence of effective new biological agents has decreased interest in HSCT for RA, resulting in a decline in the number of procedures performed [44].

Although early trials confirmed HSCT's feasibility and safety, sustained disease control often depends on post-transplant interventions like DMARDs or rituximab. However, logistical and toxicity barriers limit widespread use, and HSCT remains reserved for rare, refractory cases. Nonetheless, it continues to provide important scientific insights into RA pathophysiology.

2.7 | Deficiency of Adenosine Deaminase 2

Deficiency of adenosine deaminase 2 (DADA2) has been recognized as a rare autosomal recessive immunodeficiency disorder caused by biallelic *ADA2* mutations, with a broadening clinical spectrum that includes vasculopathy, bone marrow failure, and severe immunodeficiency [45, 46]. While anti-TNF agents have been effective in reducing stroke incidence and managing vasculopathy, they failed to provide adequate control over hematological and immune dysfunctions. In such cases, HSCT emerged as the only curative option [47, 48]. By restoring ADA2 enzymatic activity, HCT successfully reversed the hematological, immunological, and vascular phenotypes

of the disease [49, 50]. Among 36 reported patients who underwent 45 HCTs across 24 centers in 15 countries, indications for transplantation included pure red cell aplasia (PRCA), neutropenia, pancytopenia, autoimmune cytopenias, severe aplastic anemia, and immune dysregulation. The majority of these transplants were performed in children with bone marrow failure phenotypes, with bone marrow as the primary graft source and myeloablative conditioning being the predominant regimen [51].

HCT demonstrated an overall survival rate exceeding 95%, with nearly all patients achieving full donor chimerism and disease remission at a median follow-up of 2 years. However, graft failure remained a major challenge, particularly in patients with T-cell-mediated neutropenia, necessitating careful donor selection and post-transplant monitoring [52]. Four cases involved donors with monoallelic *ADA2* mutations, with three showing successful engraftment and sustained remission, while one patient died due to graft failure [46, 53, 54]. Strategies such as serotherapy-containing regimens and close follow-up were suggested to optimize transplant outcomes and minimize complications [55, 56]. Despite these challenges, HCT remained the only definitive cure for patients with severe hematological and immunodeficiency manifestations of DADA2, highlighting the need for continued research into refining transplantation protocols and improving long-term outcomes.

2.8 | ANCA-Associated Vasculitis

ANCA-associated vasculitis is a complex autoimmune disorder characterized by inflammation of blood vessels, leading to tissue damage and multi-organ involvement [57]. ANCA-associated vasculitis (AAV), which includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, often requires aggressive immunosuppressive therapy. Despite advancements in treatment, some patients remain refractory to conventional therapies, necessitating alternative approaches such as HSCT [58]. By resetting the immune system, HSCT offers a potential curative strategy, particularly for severe and treatment-resistant cases. In a Phase 1/2 trial, a 21-year-old male with refractory GPA underwent autologous peripheral blood stem cell transplantation, resulting in a significant reduction in granuloma size and ANCA levels. However, relapse occurred within a year, highlighting the challenge of maintaining long-term remission. Similarly, an international report documented four GPA patients who initially achieved remission post-transplant, but two experienced relapse within 3 years [59].

Complications following HSCT, including secondary autoimmune disorders, further complicate its application in AAV. A notable case involved a 43-year-old male who developed p-ANCA-positive glomerulonephritis after undergoing autologous HSCT for SSc. Despite developing renal complications more than a year post-transplant, the patient responded well to rituximab therapy [58, 60]. These findings underscore the need for careful patient selection, optimization of conditioning regimens, and long-term monitoring to improve HSCT outcomes in vasculitis. While HSCT shows promise in refractory vasculitis, further research is needed to enhance durability of remission and minimize post-transplant complications.

2.9 | Takayasu Arteritis

Takayasu arteritis (TA) is a rare large-vessel vasculitis that primarily affects the aorta and its major branches. Its diagnosis is often challenging due to nonspecific symptoms and the lack of definitive laboratory markers, leading to delays in early detection. The standard treatment approach involves high-dose corticosteroids combined with an immunosuppressive agent to induce remission, followed by maintenance therapy with lower steroid doses alongside drugs such as methotrexate, azathioprine, mycophenolate mofetil (MMF), or cyclophosphamide. While nearly half of patients respond well to steroids, those who are refractory may require additional immunosuppressive options, including biologic agents such as tumor necrosis factor-alpha inhibitors and tocilizumab. Despite these therapies, some cases remain resistant, necessitating alternative treatments like HSCT [61, 62].

Only a few reports describe HSCT in Takayasu arteritis. In one case, a young woman with refractory disease underwent autologous HSCT after failing multiple immunosuppressive therapies, achieving sustained clinical remission with vascular stabilization. While anecdotal, this illustrates the potential of HSCT in otherwise treatment-refractory TA, though robust evidence remains lacking [63, 64].

2.10 | Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a progressive and deforming joint disease in children, often leading to significant morbidity and a reduced quality of life. Many patients experience a chronic disease course with inadequate responses to conventional disease-modifying antirheumatic drugs (DMARDs) and biologic therapies [65, 66]. Systemic JIA is associated with increased mortality, which can be attributed to disease progression as well as treatment-related toxicities [67, 68].

Data from the European Society for Blood and Marrow Transplantation (EBMT) registry highlight the potential role of hematopoietic cell transplantation (HCT) in refractory cases. In a study involving 65 patients with JIA, transplant-related mortality was reported in 7 patients, while progression-free survival at 3 years was observed in 52% of cases. The overall survival rate at 3 years was approximately 85% [19].

A study by Silva [69] (2018) examined outcomes in 16 patients with refractory juvenile arthritis who underwent allogeneic HCT, including those who had previously failed autologous transplantation. Significant clinical improvements were noted, with 11 patients achieving drug-free remission by their last follow-up. However, treatment-related complications were observed, with one patient succumbing to probable sepsis following elective surgery and another to invasive fungal infection, resulting in a treatment-related mortality rate of 12.5%.

A comprehensive review by Saccardi [20] (2008) provided insights into using HCT in JIA and rheumatoid arthritis. Data from the EBMT Registry indicated that over 50 patients with JIA had undergone transplantation, with an approximate drug-free remission rate of 50%. While some late disease relapses were documented, only partial correction of growth impairment was achieved. The frequency of HCT in rheumatoid arthritis has notably declined since 2000, largely due to the availability of advanced biologic therapies. Additionally, many patients who underwent transplantation experienced disease persistence or relapse within six months post-transplant.

Ongoing retrospective analyses by the EBMT Autoimmune Diseases, Pediatric, and Inborn Errors Working Parties aim to provide further insights into the long-term efficacy and safety of HCT in JIA. Despite its potential, HCT remains a treatment option primarily reserved for severe, refractory cases due to its associated risks and variable long-term outcomes [19].

Below is Table 2, which summarizes key clinical trials investigating the role of hematopoietic stem cell transplantation in the treatment of systemic autoimmune rheumatic diseases.

3 | Patient Selection

Patient Selection Criteria for HSCT in Autoimmune Diseases (Table 3)

- Disease Severity and Activity: Candidates for HSCT should have severe, refractory rheumatic autoimmune diseases that have not responded to conventional therapies. The selection criteria often focus on patients with SSc, severe systemic lupus erythematosus, or refractory rheumatoid arthritis [43, 70].
- Timing of Transplantation: The optimal timing for HSCT is crucial. Patients should be selected at a point when their disease is active but not excessively advanced, as the risks of transplant complications increase with more severe disease or organ involvement [79–81].
- Patient Age and Comorbidities: Younger patients generally have better outcomes, so age is critical. Additionally, the presence of significant comorbidities (such as severe heart or lung disease) may preclude patients from being eligible for HSCT, as these factors can increase the risk of complications [73].
- Performance Status: A patient's overall health and functional capacity, often assessed using performance status scales (like the Eastern Cooperative Oncology Group performance status), is considered. Candidates should be in relatively good health to withstand the rigorous HSCT process [74].
- Psychosocial Factors: The psychosocial support system and candidates' mental health are also important considerations. Patients undergoing HSCT need strong support to cope with the psychological stresses associated with the procedure [80].
- HLA Matching: Optimal human leukocyte antigen (HLA) matching between donor and recipient is vital to reduce the risk of complications such as graft-versus-host disease (GVHD).
- Informed Consent and Understanding of Risks: Patients should be informed about HSCT's risks, benefits, and uncertainties. Their ability to understand and consent to the procedure is essential for ethical considerations in patient selection [74].

4 | Clinical Positioning and Guideline Recommendations

International transplant and specialty societies have gradually defined the role of hematopoietic stem cell transplantation (HSCT) in autoimmune rheumatic disease using registry data, randomized trials, and expert consensus. The European Group for Blood and Marrow Transplantation (EBMT) and allied position statements, and the American Society for Transplantation/Blood and Marrow Transplantation (ASBMT) provide practical recommendations for patient selection, conditioning approaches, and center requirements; both emphasize that HSCT should be performed in experienced, JACIE-accredited transplant centers and reserved for carefully selected patients.

4.1 | Systemic Sclerosis (SSc), with Emphasis on SSc-ILD

Autologous HSCT is the best-evidenced HSCT indication in rheumatology and is recommended as a therapeutic option for *selected* patients with early, rapidly progressive diffuse cutaneous SSc and/or SSc-associated interstitial lung disease (SSc-ILD) who have poor prognosis despite optimal conventional therapy and who lack advanced, irreversible cardiopulmonary disease. This recommendation is supported by two randomized trials (ASTIS and SCOT) showing superior event-free and overall survival and by recent EULAR/EBMT guidance endorsing consideration of HSCT within strict selection criteria. Early referral when ILD is progressive but lung function is not yet severely compromised (preserved FVC/DLCO thresholds as per trial criteria) is advised to maximize benefit and minimize TRM [27, 36, 82].

4.2 | Systemic Lupus Erythematosus (SLE)

Autologous HSCT may be considered for patients with severe, organ-threatening, and treatment-refractory SLE (e.g., refractory nephritis, CNS involvement, or life-threatening cytopenias) when there is clinical equipoise and after exhausting standard and biologic options. Evidence is mainly registry analyses and single-center series; guideline statements (EBMT/ASBMT) support use in specialist centers within a clinical-trial or registry framework because relapse rates remain substantial and long-term data are limited [83].

TABLE 2 | Key clinical trials of hematopoietic stem cell transplantation in autoimmune rheumatic diseases.

Study name	Disease	Design	Patients involved	Endpoint	Primary outcome	Results	References
ASTIS (Autologous Stem Cell Transplantation International Scleroderma)	SSc	Randomized controlled trial	156 patients with early diffuse cutaneous SSc	Event-free survival	Improved long-term survival and event-free survival	HSCT led to better long-term outcomes despite higher early treatment-related mortality	Van Laar JM [36]
SCOT (Stem Cell Transplant vs. Cyclophosphamide)	SSc	Randomized controlled trial	Patients with diffuse cutaneous SSc	Global rank composite score	HSCT is superior to Cyclophosphamide in improving clinical outcomes	HSCT showed better outcomes compared with Cyclophosphamide	Keith M [27]
ASSIST (Autologous Stem Cell Transplantation International Scleroderma Trial)	SSc	Randomized controlled trial	Patients with early diffuse cutaneous SSc	Event-free survival	HSCT is superior to Cyclophosphamide in improving clinical outcomes	HSCT showed better outcomes compared with Cyclophosphamide	Burt RK [70]
UPSIDE (UPfront autologous HSCT vs. Immunosuppressive medication in early Diffuse cutaneous SSc)	SSc	Randomized controlled trial	120 patients with early diffuse cutaneous SSc	Event-free survival at 2 years	Evaluating HSCT efficacy vs. standard immunosuppressive therapy	Study is ongoing	Snow [43]
Allogeneic HSCT in Refractory Systemic JIA	Systemic Juvenile Idiopathic Arthritis (sJIA)	Retrospective observational cohort	16 children with severe, refractory sJIA	Disease remission	Achieving disease remission	Allogeneic HSCT led to sustained remission in patients with severe, refractory sJIA	De Kleer IM [71]
Autologous HSCT in Severe RA	Rheumatoid Arthritis (RA)	Analysis of worldwide experience	89 patients with severe RA	Treatment efficacy and safety	Assessing treatment efficacy and safety	Autologous HSCT showed potential benefits in severe RA cases	Snowden et al. [43]

Abbreviations: ASSIST, Autologous Stem Cell Transplantation International Scleroderma Trial; ASTIS, Autologous Stem Cell Transplantation International Scleroderma; HSCT, Hematopoietic Stem Cell Transplantation; SCOT, Scleroderma Cyclophosphamide or Transplantation; SSc, Systemic Sclerosis; UPSIDE, UPfront autologous HSCT vs. Immunosuppressive medication in early Diffuse cutaneous SSc.

TABLE 3 | Recommendations for cell therapy in rheumatic: patient eligibility criteria and contraindications.

Type of disease	Indications	Contraindication
Systemic lupus erythematosus	• Age ≥ 18 years • 2019 EULAR-ACR SLE criteria [72] • Positive for anti-DsDNA, anti-histone, anti-Sm, or anti-nucleosome antibodies • Active disease (not in remission or LLDAS per DORIS) [73–76] • At least one active organ system involved • BILAG A (≥ 1) or BILAG B (> 2) scores • Inadequate response to glucocorticoids and ≥ 2 treatments (≥ 3 months each): cyclophosphamide, MMF, belimumab, azathioprine, anifrolumab, methotrexate, rituximab, obinutuzumab, cyclosporin, tacrolimus, or voclosporin	• Life-threatening organ damage: • FVC < 45% and/or DLCO < 30% (Hb-corrected) • LVEF < 40% (echo) •Pulmonary hypertension: systolic PAP > 50 mmHg • Active liver disease (AST/ALT > 3 × ULN) • History of malignancy (unless disease-free ≥ 2 years, except certain skin/cervical/breast cancers) • Severe cytopenias: • ANC < 0.5×10^9/L • Platelets < 30×10^9/L • Hb < 8 g/dL • Lymphocytes < 100×10^9/L • Uncontrolled infection • Unvaccinated for SARS-CoV-2 (unless previously exposed) • Psychosocial or geographic barriers to treatment adherence [72]
Systemic Sclerosis	• Age ≥ 18 years • SSc diagnosis per ACR/EULAR 2013 criteria • Disease duration ≤ 5 years • Skin involvement: (i) mRSS > 20 with ESR > 25 mm/h and/or Hb < 11 g/dL or (ii) mRSS > 15 with ≥ 1 major organ involvement: • Lung: DLCO and/or FVC < 80% + ILD on X-ray/HRCT • Kidney: History of renal crisis or CKD stage 2/3 (CrCl 30–89 mL/min) • Heart: Reversible CHF, rhythm disturbances, or mild–moderate pericardial effusion • Inadequate response to ≥ 2 of: mycophenolic acid, methotrexate, tocilizumab, rituximab, nintedanib, cyclophosphamide (≥ 3 months each) • Contraindication, poor response, or unwillingness for AHCT (as per clinician/patient decision) [77]	Same as above
Rheumatoid Arthritis	• Age ≥ 18 years • RA per 2010 ACR/EULAR criteria • Moderate to severe activity (DAS28-ESR > 3.2) • Inadequate response to ≥ 3 DMARD classes (tsDMARDs or bDMARDs, ≥ 3 months each) • Seropositivity for RF and/or anti-CCP, or B cells in synovial biopsy (recommended for B cell-targeted therapy) [78]	Same as above
Takayasu arteritis (TA)	Not established	Not established
Deficiency of Adenosine Deaminase 2 (DADA2)		
ANCA-associated vasculitis (AAV)		

Abbreviations: ACR, American College of Rheumatology; AHCT, Autologous Hematopoietic Cell Transplantation; anti-CCP, Anti-Cyclic Citrullinated Peptide Antibody; bDMARDs, Biologic DMARDs; BILAG, British Isles Lupus Assessment Group; CHF, Congestive Heart Failure; CrCl, Creatinine Clearance; DAS28-ESR, Disease Activity Score with 28 joints using ESR; DMARDs, Disease-Modifying Anti-Rheumatic Drugs; DORIS, Definitions of Remission in SLE; EULAR, European Alliance of Associations for Rheumatology; HRCT, High-Resolution Computed Tomography; ILD, Interstitial Lung Disease; LLDAS, Lupus Low Disease Activity State; MMF, Mycophenolate Mofetil; RA, Rheumatoid Arthritis; RF, Rheumatoid Factor; SLE, Systemic Lupus Erythematosus; SSc, Systemic Sclerosis; tsDMARDs, Targeted Synthetic DMARDs.

4.3 | Rheumatoid Arthritis (RA)

HSCT is *not* routine for RA. Early experience informed pathophysiology, but the advent of effective biologic and targeted DMARDs has largely supplanted HSCT; current recommendations reserve HSCT only for very rare, refractory cases or where other therapies are contraindicated, ideally within clinical trials or registries [83, 84].

4.4 | Juvenile Idiopathic Arthritis (JIA), Especially Systemic JIA

HSCT (autologous and in some cases allogeneic) can be considered for severe, refractory systemic JIA with life-threatening features (e.g., refractory MAS or disabling systemic features) after failure of biologics and standard care. Evidence comes from registry series and small cohorts; decisions should be multidisciplinary and undertaken in pediatric transplant centers with long-term follow-up [83].

4.5 | Deficiency of Adenosine Deaminase 2 (DADA2)

For DADA2 with bone-marrow failure, severe cytopenias, or refractory immunodeficiency/vasculopathy, allogeneic HCT is the curative option and is recommended when medical therapy (including TNF-inhibitors) fails to control hematologic or immunologic manifestations. Recent reviews and multi-center series report high rates of donor chimerism and disease reversal after HCT, though graft failure and transplant complications require careful donor selection and peri-transplant planning [51].

4.6 | ANCA-Associated Vasculitis (AAV) and TAKAYASU Arteritis (TA)

Evidence for HSCT in AAV and TA is limited to case reports and small series. Current guidance regards HSCT as an experimental or rescue therapy for refractory, organ-threatening disease when other options have failed; it should be restricted to expert centers and preferably performed in the context of registries or trials [85].

Across diseases, guideline bodies emphasize (1) multidisciplinary evaluation with both disease specialists and transplant physicians, (2) stringent cardiopulmonary screening (ECG, echocardiography, high-resolution CT, pulmonary function tests), (3) the use of JACIE-accredited centers for HSCT delivery, and (4) enrolment in registries (EBMT) or trials to improve evidence and follow-up reporting. For SSc, candidate selection criteria should mirror those used in the RCTs (disease duration, mRSS, FVC/DLCO thresholds), and centers should report outcomes to national and international registries.

5 | Risks and Complication

Despite the promising potential of HSCT in achieving long-term remission in refractory autoimmune rheumatic diseases (AIRDs), its use is limited by significant risks and complications. Transplant-related mortality (TRM) remains a major concern, particularly with high-intensity conditioning regimens, which have shown increased risk in conditions like SSc, SLE. Additional complications include infections (e.g., cytomegalovirus), sepsis, and organ toxicity. While low-intensity regimens may reduce TRM, they can compromise treatment efficacy, underscoring the need for careful patient selection and individualized risk–benefit evaluation [86]. Patient-specific factors like disease severity, age, and organ health significantly impact outcomes.

Risks involve significant organ toxicity, particularly affecting the liver, lungs, and kidneys, stemming from the high-dose chemotherapy and radiation used for conditioning. Immunosuppression increases the risk of serious infections, and there is also a chance of graft-versus-host disease (GVHD) in allogeneic transplants, which can damage organs. Mortality rates are a concern, with the potential for relapse in patients [87]. Here are some key limitations of HSCT in the treatment of autoimmune rheumatic diseases.

5.1 | High Treatment-Related Morbidity and Mortality

One of the major concerns with HSCT is the significant risk of treatment-related morbidity and mortality. The procedure involves high-dose immunoablative therapy, which can lead to life-threatening complications such as infections, sepsis, and organ toxicity. Early transplant-related mortality (TRM) has been reported between 5% and 10%, depending on disease severity and patient selection [88].

5.2 | Risk of Relapse and Incomplete Disease Remission

Although HSCT can achieve disease remission, relapse remains a concern. Studies show that 30%–50% of patients experience disease recurrence within 5 years post-transplant, particularly in conditions such as SSc (SSc) [70]. The effectiveness of HSCT varies among different autoimmune diseases, with some patients requiring additional immunosuppressive therapy post-transplant.

5.3 | Toxicity and Long-Term Complications

The conditioning regimens used in HSCT, which typically include Cyclophosphamide, anti-thymocyte globulin, or total body irradiation, are associated with significant toxicity. Patients are at risk of developing secondary malignancies, infertility, endocrine dysfunction, and cardiovascular complications. Long-term follow-up studies highlight concerns regarding persistent immunodeficiency, increasing susceptibility to infections, and secondary autoimmune disorders [89].

5.4 | Limited Availability and High Costs

HSCT remains highly specialized and resource-intensive, requiring expertise in transplantation, intensive supportive care,

and long-term follow-up. The high costs associated with HSCT, including pre-transplant evaluations, conditioning therapy, hospitalization, and post-transplant care, make it less accessible in many regions [36, 43]. Additionally, the need for specialized centers with transplantation expertise limits availability in developing countries.

6 | Discussion

At the time of writing, over 4000 patients receiving HCT for an AD have been reported to the EBMT, the largest international database, with activity reported to other registries adding substantially to the worldwide numbers of cases documented in the European Society for Blood and Marrow Transplantation (EBMT) registry (Tables 4 and 5). Initially, HSCT was explored as a treatment for rheumatoid arthritis and juvenile idiopathic arthritis, but results were inconsistent, with high relapse rates within six months, necessitating continued disease-modifying therapy. Due to these limitations, its application in these conditions was not pursued further [43, 90].

Clinical data suggest that 50%–66% of patients remain disease-free 5 years post-transplant, often allowing for discontinuation of immunosuppressive therapy [43, 90]. Some patients have even regained seronegativity for antinuclear antibodies—an outcome rarely observed with conventional treatments. Early intervention with HSCT has been linked to improved organ function and overall quality of life [91]. Yet, relapse rates are higher when patients receive unmanipulated grafts or conditioning regimens without serotherapy, likely due to the persistence of autoreactive plasma cells. Addressing this challenge remains a key focus for future treatment strategies [92].

Among rheumatic diseases, rapidly progressive diffuse SSc has emerged as the primary indication for HSCT, given the lack of effective therapies capable of reversing tissue fibrosis and improving lung function. Randomized controlled trials (RCTs) comparing autologous HSCT with cyclophosphamide-based regimens have shown significant improvements in skin fibrosis, pulmonary function, and overall disease burden. Long-term data from the ASTIS and SCOT trials indicate a 5-year progression-free survival of 70%–74%, with benefits extending up to a decade [31, 36, 70]. Despite these encouraging results, HSCT in SSc carries a higher risk of treatment-related complications, particularly in patients with pre-existing cardiac dysfunction [93, 94].

TABLE 4 | Transplant Data Overview (March 2023) [73].

Parameter	Value
Patients	4055
Transplant procedures	4140
Centers/countries	323/44
Autografts/allografts	3854 (93%)/286 (7%)
Median age at autografts/allografts (years)	38 (3–76), 11 (< 1–64)
Male/Female	40/60%

Advances in pre-transplant screening and refined conditioning regimens have helped reduce treatment-related mortality from 10% in earlier studies to as low as 2.4% in recent trials [93]. Based on these findings, autologous HSCT is now considered the standard of care for severe SSc and is endorsed by the EULAR.

Beyond SSc and SLE, HSCT has been explored as a treatment option for rarer autoimmune conditions such as ANCA-associated vasculitis [88], Takayasu arteritis [95], and Behçet's disease [96], with retrospective EBMT studies reporting positive outcomes. As research progresses, further refinements in transplant protocols and patient selection are expected to enhance the safety and efficacy of HSCT, solidifying its role as a viable treatment for refractory autoimmune diseases.

7 | Limitations

This review has several limitations. First, it is not a systematic review, and therefore may be subject to selection bias in the studies discussed. Second, many of the available data on HSCT in rheumatic diseases come from small case series, registry analyses, or single-center experiences, which limits the generalizability of findings. Third, for rarer conditions such as Takayasu arteritis, DADA2, and AAV, the evidence is limited to case reports without prospective clinical trial data. Finally, advances in transplant protocols and supportive care over time may affect comparability between older and more recent studies. Nevertheless, recognizing these limitations, this review synthesizes available evidence and highlights areas where further research and prospective trials are needed.

8 | Future Perspective

HSCT continues to evolve as a promising therapeutic strategy for SSc, SLE, RA, and JIA. As the field matures, several advancements are expected to refine transplantation protocols, improve patient selection, and enhance long-term outcomes. The primary objective remains to reset autoreactive immune responses, offering the potential for sustained remission without continuous immunosuppressive therapy [88].

Beyond hematopoietic stem cell transplantation, the therapeutic landscape in autoimmune rheumatic diseases is expanding with the emergence of advanced cellular therapies, including chimeric antigen receptor (CAR) T-cell therapy and bispecific T-cell engagers (BiTEs). Early clinical experience, particularly with CD19-directed CAR-T cells in refractory systemic lupus erythematosus, has demonstrated rapid and sustained disease remission through targeted immune modulation, potentially avoiding the need for myeloablative conditioning. BiTEs and other immune-redirecting strategies remain investigational in rheumatology but may offer future alternatives or adjuncts for patients unsuitable for HSCT [97, 98].

Despite these advances, HSCT remains unique in its ability to induce a global immune reset and long-term immune tolerance, especially in diseases characterized by complex, multilineage immune dysregulation such as systemic sclerosis. Future treatment paradigms are likely to adopt a personalized cellular

TABLE 5 | Distribution of diagnoses in the EBMT database (March 2023).

Category	Diagnosis	Cases
Multiple sclerosis (MS)	—	2132
Connective tissue diseases	Total	1028
	SSc	835
	Systemic lupus erythematosus	126
	Polymyalgia/dermatomyositis	18
	Sjögren's syndrome	6
	Antiphospholipid syndrome	6
	Other	37
Arthritis	Total	209
	Rheumatoid arthritis	82
Juvenile chronic arthritis (JIA)	Total	115
	Systemic JIA	74
	Other JIA	19
	Articular JIA	22
	Psoriatic arthritis	3
	Other	9
Inflammatory bowel diseases	Total	283
	Crohn's disease	233
	Coeliac disease	18
	Other	32
Hematological diseases	Total	161
	Immune thrombocytopenia purpura (ITP)	42
	Hemolytic anemia	36
	Evans syndrome	24
	Other	60
Vasculitis	Total	67
	Granulomatosis with polyangiitis (GPA)	12
	Behçet's disease	12
	Takayasu's arteritis	3
	Polyarteritis nodosa (PAN)	4
	Eosinophilic granulomatosis with polyangiitis (EGPA)	2
	Other	28
Other neurological diseases	Total	146
	Chronic inflammatory demyelinating polyneuropathy (CIDP)	65
	Neuromyelitis optica	29
	Myasthenia gravis	11
	Other	41
Insulin dependent diabetes mellitus (IDDM)	—	20
Other conditions	—	94

Note: EBMT registry accessed 4 June 2023 [80].
Abbreviations: CIDP, Chronic inflammatory demyelinating polyneuropathy; EBMT, European Society for Blood and Marrow Transplantation; GPA, Granulomatosis with polyangiitis; HSCT, HSCT; HUVS, Hypocomplementemic urticarial vasculitis syndrome; JIA, Juvenile idiopathic arthritis; SLE, Systemic lupus erythematosus.

therapy approach, integrating HSCT and emerging immune-engineering strategies based on disease biology, organ involvement, and patient-specific risk profiles.

Future research will likely focus on optimizing conditioning regimens to reduce toxicity while maintaining efficacy. Incorporating novel agents, such as targeted immunotherapies and less myeloablative conditioning protocols, may minimize transplant-related complications and improve tolerability. Additionally, advancements in graft engineering, including regulatory T-cell infusions or mesenchymal stromal cells, may further enhance immune reconstitution and reduce the risk of disease relapse [99].

With increasing global experience in HSCT for autoimmune diseases, multicenter randomized controlled trials (RCTs) will be crucial to establish standardized protocols and compare HSCT outcomes with emerging biological therapies. As transplantation centers gain expertise and donor availability improves, HSCT may become a more accessible and safer treatment option for carefully selected patients with severe autoimmune diseases refractory to conventional therapy. Ultimately, integrating HSCT into clinical practice will depend on balancing risks, refining protocols, and advancing supportive care strategies to ensure optimal long-term patient outcomes [50].

9 | Conclusion

Hematopoietic cell transplantation (HCT), particularly HSCT, has emerged as a promising therapeutic option for severe and refractory autoimmune rheumatic diseases (AIRDs), including SSc, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA). Extensive research and clinical trials have demonstrated its potential to induce long-term progression-free survival, ameliorate skin thickening, stabilize internal organ function, and improve overall quality of life in select patients. However, its application remains largely investigational for patients who do not meet established clinical criteria and other autoimmune conditions due to insufficient evidence supporting its efficacy in these contexts.

The optimal use of HSCT is currently limited by several challenges, including the need to define regimen intensity to reduce treatment-related mortality (TRM), identify predictive biomarkers or gene profiles for patient selection, monitor long-term adverse events, and explore post-transplant immunosuppression strategies to mitigate disease relapse. Additionally, early treatment-related complications and mortality, particularly in patients with pre-existing organ damage, underscore the importance of careful patient selection and center expertise in achieving favorable outcomes.

While advancements in biological therapies have reduced the reliance on HSCT, it remains a critical option for patients with rapidly progressive disease, high disease activity, and mild initial organ damage. Ongoing research aims to refine patient selection, optimize treatment protocols, and elucidate the interactions between hematopoietic stem cells and their microenvironment. Large-scale, randomized controlled trials are essential to establish HSCT's definitive role in rheumatic disease management and to compare its efficacy with conventional therapies. As the field evolves, HSCT can potentially transform the treatment landscape for severe AIRDs, offering hope for improved outcomes in carefully selected patient populations.

Author Contributions

M.M.: Conceptualization. N.S., D.R.S.R., H.P., and D.A.: Writing – original draft. M.M.: Writing – review and editing. Approval – M.M., N.S., D.R.S.R., H.P., D.A. Responsibility for the integrity and accuracy of all aspects of the work: M.M., N.S., D.R.S.R., H.P., D.A.

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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.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** PRISMA Flow Diagram of Study Selection Process.

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LETTER TO THE EDITOR

Refining Prognostic Assessment in SLE: A Call for Severity Stratification of Thrombocytopenia

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Dear Editor,

Al-Adhoubi et al. [1] report thrombocytopenia in 22.5% of 1160 Omani patients with systemic lupus erythematosus, with striking associations to antiphospholipid antibodies, renal involvement (5.3% vs. 0.6%, $p=0.000$), neuropsychiatric disease (30.9% vs. 17.9%, $p=0.000$), and nearly fourfold higher mortality (11.1% vs. 2.9%, $p=0.000$). Sepsis dominates deaths among thrombocytopenic cases (7.3% vs. 1.7%). Although the study uses the 2019 ACR-EULAR threshold of $<100\times10^9$/L, it treats thrombocytopenia as a single entity, leaving the prognostic impact of platelet nadir depth unexplored.

This binary approach may mask a clinically meaningful severity gradient. Platelet counts of 90×10^9/L and 15×10^9/L differ sharply in bleeding risk, immune dysregulation intensity, and infection susceptibility. Recent large cohorts confirm that severe thrombocytopenia independently predicts higher mortality and faster irreversible organ damage accrual compared with milder forms [2–4]. In the Oman data, where prevalence is similar across pediatric (20.2%) and adult (22.8%) onset ($p=0.490$), stratifying the 262 events by nadir could reveal whether moderate cytopenias preferentially accompany respiratory complications (25.6% vs. 16.4%, $p=0.001$). At the same time, severe thrombocytopenia drives sepsis-related deaths and greater long-term damage.

We respectfully suggest three immediate, low-effort steps using existing records. First, classify the 262 thrombocytopenia episodes by nadir into mild ($50–99\times10^9$/L), moderate ($20–49\times10^9$/L), and severe ($<20\times10^9$/L) categories, then redraw Kaplan–Meier curves with log-rank testing across strata. Second, perform cause-specific Cox regression to estimate sepsis hazard ratios per severity grade, adjusting for antiphospholipid antibody status and concurrent hemolytic anemia or leukopenia. Third, integrate these grades into the published multivariable model alongside age, sex, and organ involvement to derive a refined prognostic index directly comparable to international benchmarks.

These additions require no new data collection yet would transform a valuable prevalence study into a precise risk-stratification tool, helping clinicians identify the highest-risk subset within the 22.5% affected group and potentially informing future iterations of classification criteria. The Oman Lupus Cohort is uniquely positioned to provide this insight for patients in the Middle East.

Author Contributions

Wei Wei and Xuechun Gu drafted the manuscript; Jingjing Liu provided critical revisions.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Defining Inactivity of Juvenile Spondyloarthropathies: Delphi Study Among Pediatric Rheumatology Academy (PeRA) From Türkiye

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ABSTRACT

Introduction: Juvenile spondyloarthropathies (JSpA) are a group of chronic inflammatory diseases that differ in their clinical features and course from adult spondyloarthropathies and other subtypes of juvenile idiopathic arthritis (JIA). Therefore, defining disease inactivity in JSpA requires specific criteria. This Delphi study aimed to establish a national consensus on its core clinical, laboratory, and radiological domains.

Methods: A total of 27 pediatric rheumatologists participated in the Delphi survey, conducted in two rounds. Participants were asked multiple-choice and Likert-type questions regarding their preferences for using domains including anamnesis, laboratory findings, imaging methods, and predefined disease activity scores for assessing inactivity. At the end of each round, the study coordinators determined the "strong consensus" items based on a power analysis of these parameters.

Results: The absence of "pain or tenderness in the peripheral joints, lower back and entheseal regions" in anamnesis domain and "tenderness in the peripheral joints, entheseal areas, and hip examination"; "swelling in the peripheral joints; tenderness on sacroiliac compression testing"; and "no reduction in hip RoM examination" in physical examination domain received the

highest scores and were accepted as strong consensus. Furthermore, normalization of MRI findings of SIJ and hip/peripheral joint and "physician global score = 0" reached the specified thresholds, resulting in strong consensus following the second round. **Conclusions:** This Delphi study highlights the need for a multidimensional approach that integrates clinical, radiological, and physician assessments to define disease inactivity in patients with JSpA. The resulting consensus provides a more specific assessment on inactivity defining JSpA patients and reflects a national consensus.

1 | Introduction

Juvenile Spondyloarthropathies (JSpA) constitute a group of chronic inflammatory disorders characterized by peripheral and axial skeleton involvement, along with enthesitis, which differentiated from the other types of juvenile idiopathic arthritis (JIA) in terms of etiopathogenesis, genetical and immunological basis [1–4]. Additionally, despite its' similarities with adult spondylarthritis from the standpoint of pathophysiological and clinical features, it needs lots of specific aspects on diagnosis, assessment and management due to the dynamic nature of skeletal maturation during childhood and adolescence [5–7].

The definition of disease inactivity in JIA remains controversial. While the inactivity criteria developed by Wallace and colleagues have long been widely used, they are not considered as valid for patients with JSpA as they are for the oligoarticular and polyarticular subtypes [8]. This is because these criteria do not include clinical features specific to JSpA, such as enthesitis, axial skeletal involvement, and extra-articular findings. Similarly, activity or inactivity criteria developed for adult spondyloarthritis, such as the ASAS, BASDAI etc. are of limited use in JSpA because they do not consider specific childhood characteristics such as growth spurts and variable clinical course [9]. Recently, the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) has been introduced as a validated tool specifically designed to measure disease activity in JSpA [2]. Although this score was specifically developed for children, it has certain limitations, such as the exclusion of imaging findings from direct assessment and the inclusion of some subjective parameters (e.g., patient global assessment). Therefore, applying aforementioned criteria directly to JSpA may lead to misclassification of disease activity and underestimation of clinical control.

Consequently, the lack of objective and comprehensive criteria creates an unmet need for clearer definitions in JSpA, often leaving physicians to make solitary and individualized decisions regarding disease inactivity and treatment discontinuation. In this context, this Delphi study conducted among pediatric rheumatologists nationwide aimed to define the core clinical areas and criteria related to the concept of "inactive disease" in JSpA and to establish a national consensus based on expert opinions.

2 | Materials and Methods

2.1 | Participants

This Delphi panel consisted of twenty-seven pediatric rheumatologists from nationwide tertiary hospitals, all actively involved in the management of JSpA. Participants were selected based on their clinical expertise, requiring a minimum of 2 years of independent practice. While the Delphi ratings and clinical decisions were grounded in the participants' extensive field experience, all imaging studies (MRI and USG) in their routine practice are primarily interpreted and reported by dedicated musculoskeletal radiologists. Consequently, the clinicians' evaluations in this study reflect a synthesis of these formal radiological reports integrated with their own longitudinal clinical observations.

2.2 | The Methodology of the First Round Delphi

Prior to first round, an online meeting was held by the Delphi study coordinators to determine the questions which were based on learning about clinical aspects and the common issues in terms of inactivity decisions on JSpA patients. After reaching a consensus on the questions, 50 questions were asked to the participants under 7 main domains (Figure 1):

1. *Anamnesis*: Pain and stiffness on peripheral/hip joints, enthesis, with back and low back regions. In addition, exercise intolerance, morning stiffness, and fatigue upon waking were included in the questionnaire.
2. *Physical Examination*: Tenderness, swelling, and range of motion (RoM) of the peripheral, hip, and sacroiliac joints (SIJ), as well as entheseal tenderness, were examined. The Schober test and SIJ distress tests were also included in the questions.
3. *Predefined Clinical Scoring Systems*: Utilization and perceived importance of standardized instruments such as visual analog score (VAS) (patient/parent), Physician Global Score (PGS), CHAQ, PedQL, BASDAI, JSpADA, ASDAS, and PASS were questioned
4. *Imaging*: Frequency and perceived utility of MRI and ultrasonography findings in decision-making, and the significance of radiological remission in clinical inactivity were assessed. It was also questioned which specific radiological findings in MRI and USG suggested activity.
5. *Diagnostic and Treatment Criteria*: Awareness and use of existing inactivity definitions (Wallace, PRINTO, Physician Global Score and physician judgment) and influencing factors for treatment discontinuation were assessed. Also, the essential criteria for making an inactive disease decision and the criteria taken into consideration when discontinuing treatment were questioned
6. *Demographic and Genetic Factors*: Age at onset, sex, HLA-B27 positivity, and family history in clinical decision-making were considered.

Practitioner Points

1. The strongest predictors for defining inactivity in JSpA were the clinical picture, where the patient's pain and tenderness disappeared and the accompanying normal physical examination findings.
2. Normalization of the SIJ and peripheral/hip MRI was accepted by the panel with strong consensus as essential elements of the inactivity definition, as it reliably demonstrates subclinical inflammation.
3. The limited sensitivity of laboratory markers (ESR/CRP) in reflecting inactivity was emphasized both in the results and in the discussion, demonstrating that decision-making should be based on clinical and radiological data.
4. The Physician Global Score (PGS = 0) emerged as a more accurate measure of inactivity compared to JSpADA = 0 due to its advantage in distinguishing between inflammatory pain and residual pain.

7. *Extra-articular Manifestations*: Influence of uveitis, psoriasis, dactylitis, and gastrointestinal symptoms on remission and follow-up period were examined.

To clearly assess participants' approach, the survey consisted of both Likert-type numerical scales (0–10) and multiple-choice questions, providing both quantitative scoring and qualitative insight. Responses were collected electronically and anonymized to minimize bias. Qualitative responses from multiple-choice and open-ended questions were categorized according to their voting rates, and percentages were calculated. Quantitative data from Likert-type scales were evaluated using descriptive statistics (mean, median, interquartile range, and frequency distributions); vote receiving rates above 8 and 9 points were calculated as well. All results from the first round were evaluated by the study coordinators for defining appropriate cut-off points based on median values, the proportion of responses scoring ≥8 and ≥9, the standard deviation, and the interquartile range (IQR). Only the items with a median score of 10 with a voting rate exceeding 80% above 9 points with 90% above 8 points were generally considered to reflect strong consensus (Figure 1).

2.3 | The Methodology of the Second-Round of Delphi

A total of 27 pediatric rheumatologists participated in the first Delphi round, all of whom were invited to complete the second-round questionnaire. The participants were informed about the first-round results prior to the second round.

The second-round questionnaire was designed to explore and validate areas where weaker consensus was observed in Round 1, including the items with a median score ≥9 was generally considered to reflect consensus. However, certain items with high IQR values (≥1.2) with standard deviation (SD ≥1.2) were considered as weak consensus and referred for re-evaluation in round-2. Besides, with a median value of 9–10 points and more than 60% of participants scored ≥9, and more than 80% scored ≥8 were qualified to the second round as well (Figure 1). It included both open-ended questions and Likert-type (0–10) scales, addressing four major domains:

1. *Anamnesis*: Success in clinically controlling peripheral and low back pain in JSpA patients, considering alternative etiologies of pain, and the influence of residual pain on inactivity decision. Finally, pain symptoms were rated as important in making the decision to inactivate.
2. *Physical Examination*: Items focusing on the role of sacroiliac distraction testing in diagnosis and follow-up, and the extent to which a negative test supports disease inactivity

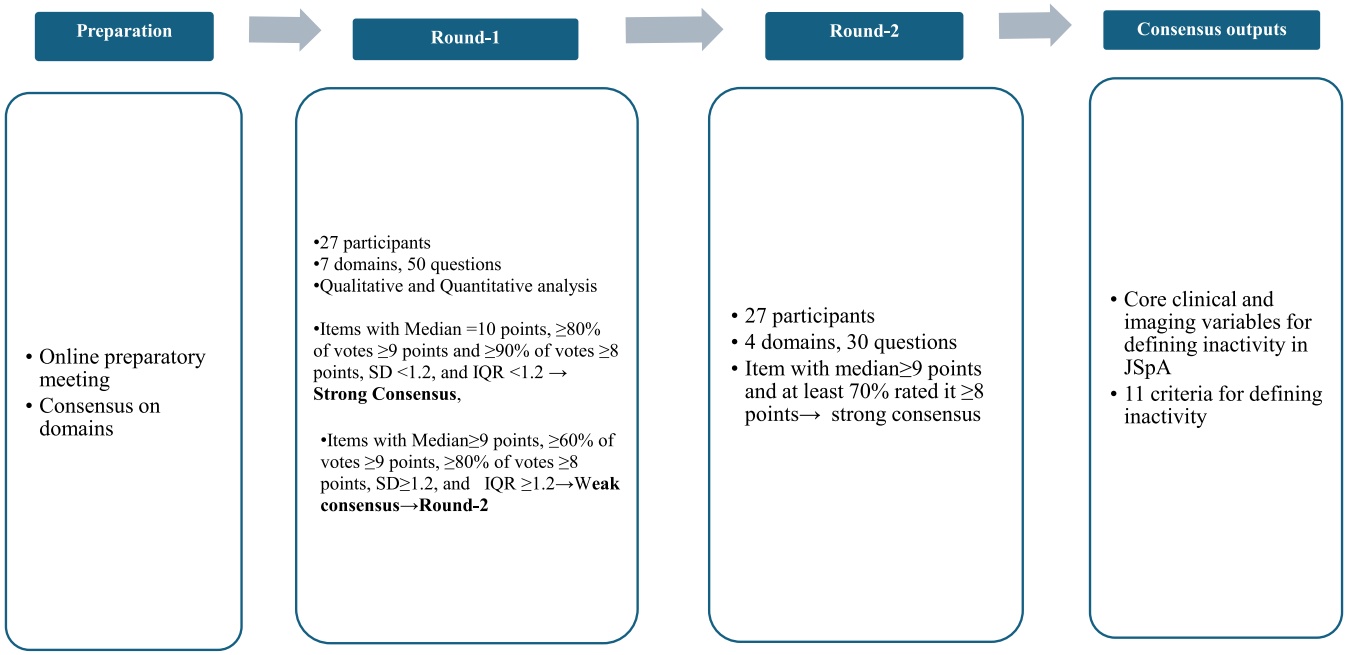

FIGURE 1 | Outline of the consensus process for the defining inactivity criteria of Juvenile Spondyloarthropathies.

3. *Radiological Assessment*: Structured questions including both ultrasonographic (peripheral joints, tendons, entheses, and Doppler findings) and MRI evaluations (sacroiliac, hip, and peripheral joints). Finally, the importance of the method in making the inactivity decision was scored for each radiological method.
4. *Disease Activity Scoring Systems*: Items assessing the extent to which the PGS and JSpADA scores are indispensable in the participant's definition of inactivity and the preference between these two scoring systems in determining remission.

For each variable, median, interquartile range (IQR), standard deviation (SD), and proportions of ≥8 and ≥9 points were calculated, and consensus thresholds defined by the study coordinators were determined based on power analysis of statistical data.

Comparative analyses between Round 1 and Round 2 results were conducted to assess stability and convergence of expert opinion. Items showing improved clustering (narrower IQR or higher ≥9 proportion) were considered to demonstrate strengthened agreement across the expert panel.

2.4 | Statistical Analysis

All analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and results were summarized as frequencies, percentages, and measures of central tendency and dispersion.

3 | Results

3.1 | Participants Data

Twenty-seven pediatric rheumatologists participated in this Delphi survey. Twelve of the participants (44.4%) have 5–10 years, 8 of them (29.6%) have more than 10 years, and 7 of them (25.9%) have 2–4 years' experience in pediatric rheumatology clinics following fellowship education. The number of patients followed annually by the participants was over 50 for nearly one third of them (25.6%) and 26–50 patients for 33.3% of participants.

3.2 | Results of Open-Ended and Multiple Choices Questions

Over 80% of participants reported using MRI (85.2%), their own clinical judgment (81.5%), and the physician global score (81.5%) to decide on disease inactivity in JSpA patients. Further, almost all of them (96.3%) considered that the absence of active arthritis as a prerequisite for inactivity, following that PGS = 0 (66.7%) and no sacroiliitis on SIJ MRI (59.3%) with normal CRP and ESR (49.3%); only half of them considered that the absence of pain is necessary for inactivity (48.1%). Over 70% of the participants considered remission time (88.9%), absence of enthesitis (77.8%), normal MRI findings (74.1%), and adverse drug reactions (70.4%) while tapering the treatments of JSpA patients.

Regarding radiological evaluation for JSpA patient's follow-up, SIJ MRI was the most preferred method (96.3%). Furthermore, USG was voted more frequently than MRI in the radiological evaluation of peripheral/hip joints (81.5% vs. 63%). Conventional X-rays received significantly lower votes (25.9%).

Bone marrow edema (BME) (96.3%), synovitis/increased intra-articular fluid (96.3%), and osteitis (77.8%) were considered the most significant findings in determining active disease on MRI. Furthermore, when determining disease recurrence on ultrasonographic evaluation, participants considered synovitis (88.9%), increased power Doppler (PD) signals (81.5%), entheseal thickening (77.8%), and joint effusion (74.1%), respectively. In another question, all participants selected SIJ-MRI as their most preferred radiological assessment method when monitoring and deciding on inactivity in patients with JSpA (hip joint MRI and peripheral joint MRI were not rated at all).

3.3 | Results of Likert-Type Scale Analysis of Round-1

The results indicating how much importance participants placed on anamnesis, physical examination, laboratory and radiological data when deciding on inactive disease, based on a Likert scale, are given in Table 1.

Following the first round of this Delphi Survey, items were included if they met all of the following thresholds: at least 80% of participants rated the item as ≥9 points, at least 90% rated the item as ≥8 points, with a median score of 10 out of 10, a standard deviation of <1.2, and an interquartile range (IQR) of <1.2 as the rating rank. In the anamnesis domain, the absence of pain or tenderness in the peripheral joints/lower back and entheseal areas was ranked highest. Additionally, in the physical examination domain, the highest-rated options were absence of tenderness in the peripheral joints, entheseal areas, and hip examination; swelling in the peripheral joints; tenderness on sacroiliac compression testing; and no reduction in hip ROM examination. None of the items of the domains including 'Radiologic assessment', "Predefined scoring systems," and "Concomitant factors" reached the threshold required for strong consensus.

3.4 | Results of Multiple-Choice Questions and Likert-Type Scale Analysis of Round-2

Less than half of the participants scored 8 or more on the question about the ability to completely control low back and peripheral joint pain in patients with JSPA (46.4% for low back pain and 40.7% for peripheral joint pain). Furthermore, to the question, "Are you looking for other pathologies in the differential diagnosis?," 77.8% of the participants scored 8 or more for peripheral joint pain and 85.2% for low-back pain. None of the items in anamnesis domain can be reached enough points to be accepted in the second round. Additionally, nearly all participants voted to use SIJ distraction tests in the follow-up of patients with JSPA. However, the importance of normal SIJ distraction tests in determining inactivity was not sufficient to warrant consensus.

TABLE 1 | Detailed results of the responses to the Likert scale type questions in the first round.

1. To what extent do you take the following symptoms into consideration when deciding on inactive disease?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Peripheral joint pain	8.93 ± 1.36	9 (5–10)	8.5–10 (1.5)	85.2	74.1
Lower back pain	9.37 ± 1.24	10 (5–10)	9.5–10 (0.5)	92.6	77.8
Back pain	8.19 ± 1.92	8 (3–10)	7–10 (3)	70.4	48.1
Morning stiffness on peripheral joints/lower back	**9.52 ± 0.89**	**10 (7–10)**	**9–10 (1.0)**	**92.6**	**88.9**
Entheseal regions pain or sensitivity	**9.48 ± 0.9**	**10 (7–10)**	**9–10 (1.0)**	**96.3**	**81.5**
Fatigue in the mornings	7.52 ± 2.12	8 (2–10)	6–9.5 (3.5)	55.6	33.3
Exercise intolerance	7.15 ± 1.81	7 (4–10)	5.5–8 (2.5)	37.0	18.5
2. To what extent do you take the following physical examination findings into consideration when deciding on inactive disease?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Tenderness in peripheral joints	**9.41 ± 0.89**	**10 (7–10)**	**9–10 (1.0)**	**96.3**	**81.5**
Swelling in peripheral joints	**9.56 ± 0.93**	**10 (6–10)**	**9.5–10 (0.5)**	**96.3**	**88.9**
Tenderness in entheseal regions	**9.67 ± 0.78**	**10 (7–10)**	**10–10 (0)**	**96.3**	**88.9**
Sacroiliac compression test tenderness	**9.52 ± 1.09**	**10 (5–10)**	**9.5–10 (0.5)**	**96.3**	**88.9**
Sacroiliac distraction tests tenderness	9.22 ± 1.31	10 (5–10)	8.5–10 (1.5)	88.9	74.1
Reduced hip joint ROM	**9.38 ± 1.02**	**10 (7–10)**	**9–10 (1.0)**	**92.5**	**84.6**
Tenderness in hip examination	**9.33 ± 0.96**	**10 (7–10)**	**9–10 (1.0)**	**92.6**	**81.5**
Limitation in Schober tests	8.11 ± 1.89	8 (4–10)	7.5–10 (2.5)	74.1	44.4
3. To what extent do you use the predefined scoring systems with given cut-off points listed below when making decisions regarding disease inactivity?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Patient-VAS = 0 point	7.93 ± 2.27	8 (1–10)	7–10 (3.0)	66.7	44.4
Parent-VAS = 0 point	7.89 ± 2.22	8 (1–10)	6.5–10 (3.5)	59.3	44.4
Physician global score = 0 point	8.96 ± 1.89	10 (1–10)	9–10 (1.0)	85.2	77.8
CHAQ score ≤ 0.125 points	7.33 ± 2.72	8 (1–10)	6–10 (4.0)	51.9	48.1
PedQL ≥ 80 points	7.04 ± 2.81	8 (1–10)	6–9 (3.0)	51.9	33.3
BASDAI < 2 points	7.04 ± 3.09	8 (1–10)	7–9 (3.0)	63.0	33.3
JSpADA = 0 point	8.27 ± 2.11	9 (1–10)	8–10 (2.0)	81.6	67.5
ASDAS < 1.3 points	6.46 ± 3.02	7 (1–10)	5–9 (4.0)	38.5	34.6
PASS score = 0 point	6.96 ± 2.9	7 (1–10)	5.25–9 (3.75)	50.0	38.5
4. To what extent do you consider each of the following radiological criteria when deciding on disease inactivity in JSpA patients?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Normalization of SIJ MRI on follow-up	9 ± 1.49	10 (4–10)	9–10 (1.0)	85.2	77.8

(Continues)

TABLE 1 | (Continued)

4. To what extent do you consider each of the following radiological criteria when deciding on disease inactivity in JSpA patients?	Mean ± SD	Median (min–max)	Q1–Q3 (IQR)	≥8p (%)	≥9p (%)
Persistent active lesions (BME/osteitis) on follow-up SI-joint MRI despite regression.	7.81 ± 2.15	9 (4–10)	7–9 (2.0)	65.4	46.2
Despite chronic lesions (sclerosis/JSN), follow-up SIJ MRI shows no active inflammation	8.41 ± 1.69	9 (4–10)	8–10 (2.0)	81.8	61.9
Normalization of hip/peripheral joints MRI on follow-up	8.37 ± 1.03	8 (6–10)	6–9 (3.0)	83.3	71.8
Normalization of hip/peripheral joints USG on follow-up	8.89 ± 1.45	10 (5–10)	8–10 (2.0)	81.5	66.7
Normalization of entheseal regions/tendons USG/doppler-USG on follow-up	9.15 ± 1.29	10 (5–10)	8.5–10 (1.5)	88.9	74.1
5. To what extent do you consider each of the following accompanying demographic, clinical and genetic factors when deciding on disease inactivity in JSpA patients?	**Mean ± SD**	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥8p (%)**	**≥9p (%)**
Younger age at onset	6.37 ± 2.95	7 (1–10)	5–8.5 (3.59)	40.7	25.9
Male gender	5.44 ± 3.12	6 (1–10)	2.5–7.5 (5)	25.9	14.8
Positive family history for ankylosing spondylitis	6.07 ± 2.96	7 (1–10)	5–8 (3.0)	44.4	18.5
Accompanying uveitis	8.04 ± 2.43	9 (1–10)	6.5–10 (3.5)	70.4	55.6
Accompanying dactylitis	7.85 ± 1.96	8 (3–10)	7–9 (2.0)	66.7	40.7
Accompanying psoriasis	6.26 ± 2.77	6–1 (10)	5–8 (3.0)	37.0	22.2
Accompanying inflammatory bowel disease	8.78 ± 1.63	9 (5–10)	8–10 (2.0)	81.5	70.4
HLA-B27 positivity	5.7 ± 2.91	6 (1–10)	5–8 (3.0)	10.0	33.3

Note: Parameters considered statistically significant are highlighted in bold.

While weak consensus was achieved for all radiological assessment methods in the first round, it was observed that there was insufficient consensus for USG evaluations (peripheral joints, tendons, entheses, and Doppler findings) after the second round. On the other hand, when the importance placed on MRI follow-ups was evaluated, 88.9% of participants (median score 10) indicated that SIJ and 74.1% (median score 9) of peripheral/hip MRI normalization findings were valuable in identifying inactivity, and this was considered a consensus in the second round of the Delphi.

Whereas a strong consensus was reached on the "PGS = 0 requirement" item, which was one of the items with weak consensus in the first round of predefined disease activity scores (77.8% ≥8 points and median 9 points); the score received by "JSpADA = 0 requirement" was not sufficient for consensus following the second round.

In summary of second round of Delphi survey, "normalization of SIJ-MRI" and "normalization of hip/peripheral joints MRI" with "Physician global score = 0 point" items reached the cut-off points (median ≥9 points and at least 70% rated it ≥8 points) were accepted as strong consensus (Table 2).

Following both of two rounds of this Delphi survey, 11 items reached strong consensus which are given in Table 3.

4 | Discussion

In this complex of Delphi study, we summarized eleven criteria for defining inactivity of JSpA patients including mainly clinical, physical and radiological examination with physician's opinions. These criteria may provide to physician evaluating JSpA patients' inactivity and to plan for discontinuing treatment.

In the first round of the study, the highest level of consensus was achieved with the absence of pain or tenderness in the peripheral joints, entheseal areas, and low back region. This finding demonstrates that symptomatic improvement is considered the primary determinant for defining clinical inactivity. However, the fact that "complete absence of pain" was only considered

TABLE 2 | Detailed analyses of Likert scale responses on Round-2.

1. To what extent do you take the following symptoms that reached weak consensus in first round into consideration when deciding on inactive disease?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
No lower back pain	8.04 ± **2.3**	9 (3–10)	6.5–10 (3.5)	66.7	63.0
No peripheral joint pain	8.44 ± **1.53**	9 (5–10)	7.5–10 (2.5)	69.1	59.3
2. To what extent do you take the following physical examination finding that reached weak consensus in first round into consideration when deciding on inactive disease?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
No sensitivity to sacroiliac distraction tests	7.93 ± **2.25**	9 (3–10)	5.5–10 (4.5)	5.5	10.0
3. To what extent do you take the following radiological findings that reached weak consensus in first round into consideration when deciding on inactive disease?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Normalization of hip/peripheral joints USG on follow-up	7.56 ± **2.5**	8 (1–10)	6–9.5 (3.5)	59.3	44.4
Normalization of entheseal regions/tendons USG/doppler-USG on follow-up	7.52 ± **2.74**	8 (1–10)	6–10 (4.0)	59.3	44.4
Despite chronic lesions (sclerosis/JSN), follow-up SIJ MRI shows no active inflammation	4.26 ± **3.13**	3 (1–10)	1.5–6.5 (5.0)	22.2	14.8
Normalization of SIJ MRI on follow-up	**9.04 ± 1.13**	**10 (7–10)**	**8–10 (2.0)**	**88.9**	**63.0**
Normalization of hip/peripheral joints MRI on follow-up	**8.22 ± 2.17**	**9 (3–10)**	**7.5–10 (2.5)**	**74.1**	**51.9**
4. To what extent do you use the predefined scoring systems with given cut-off points listed below that reached weak consensus in the first round when making decisions regarding disease inactivity?					
	Mean ± SD	**Median (min–max)**	**Q1–Q3 (IQR)**	**≥ 8p (%)**	**≥ 9p (%)**
Physician global score = 0 point	**8.26 ± 2.41**	**9 (2–10)**	**8.5–10 (1.5)**	**77.8**	**74.1**
JSpADA = 0 point	6.93 ± **2.4**	7 (1–10)	5–9 (4.0)	44.4	37.0

Note: Parameters considered statistically significant are highlighted in bold.

necessary for inactivity by half of the participants suggests that low levels of pain are considered clinically tolerable in some patients. This suggests that physicians are taking a cautious approach in assessing subjective symptoms similar to current literature [10–12].

With the advancement of medical technology, the use of MRI has become increasingly widespread in recent years in the Pediatric Rheumatology area, particularly in patients with JSpA, despite higher costs and longer scanning times [13]. Particularly, MRI is the best option for the optimum evaluation method for sacroiliac joints due to the difficulty of clinical evaluation of this joint and its importance in evaluating subclinical inflammation [14, 15]. Given its frequent use by clinicians in daily practice, this finding emphasizes that SIJ-MRI deserves to be formally incorporated into the criteria for defining disease inactivity [16, 17]. Our findings on imaging present a critical nuance regarding the roles of MRI and USG. The panel achieved a strong consensus for the normalization of both SIJ and peripheral/hip MRI as formal criteria for inactivity. Conversely, USG normalization for both peripheral joints and entheseal regions failed to meet the consensus threshold. This is particularly noteworthy given that our results also show USG is more frequently preferred than MRI for the *general* radiological evaluation of peripheral/hip joints (81.5% vs. 63%).

We interpret this apparent paradox as a clear distinction between routine, practical monitoring and the strict, formal definition of

TABLE 3 | The items that reached consensus following Round 1 and 2 for defining inactive JSpA patients.

Anamnesis	Radiological assessment
1. Absence of Morning stiffness on peripheral joints/ lower back	9. Normalization of SIJ MRI on follow-up
2. Absence of entheseal regions pain or sensitivity	10. Normalization of hip/peripheral joints MRI on follow-up
Physical examination	**Disease activity assessment**
3. Absence of tenderness in peripheral joints	11. Physician global score = 0 point
4. Absence of swelling in peripheral joints	
5. Absence of tenderness in entheseal regions	
6. Absence of sacroiliac compression test tenderness	
7. Absence of reduced hip joint ROM	
8. Absence of tenderness in hip examination	

inactivity. While USG is valued as an accessible tool for day-to-day follow-up, the panel's consensus endorses MRI as the 'gold standard' modality required for the critical decision of defining inactivity. This preference is likely driven by MRI's superior capacity to detect subclinical inflammation, such as bone marrow edema (BME) and osteitis, which our experts overwhelmingly (96.3% and 77.8%, respectively) recognized as significant findings of active disease.

A significant outcome of this Delphi consensus is the panel's clear skepticism regarding the definitive value of acute-phase reactants. Despite their frequent use in daily practice [2, 18, 19], normal ESR and CRP levels were considered a prerequisite for inactivity by less than half of our participants (49.3%). This finding strongly suggests that physicians do not rely on these markers alone for inactivity decisions. Such an opinion, as reflected in the literature, is likely based on the limited sensitivity and specificity of these markers for disease activity in JSpA. Notably, a significant proportion of patients may exhibit normal ESR and CRP levels despite ongoing subclinical inflammation detected by MRI [20–23]. Therefore, our findings reinforce that the definition of inactivity in JSpA should be anchored in robust clinical evidence (our eight Round 1 criteria) and objective radiological normalization (MRI criteria), rather than relying on potentially misleading laboratory markers.

The resulting consensus included MRI findings in the assessment, considering not only peripheral joints but also JSpA-specific features such as enthesitis and axial skeleton involvement. In this respect, the study provides a more specific and comprehensive assessment of inactivity compared to the criteria described by Wallace et al. [8]. Moreover, it is more useful than the criteria that describe disease inactivity in adult SpA such as ASAS, ASDAS and BASDAI scoring systems [16, 24–26]. Adult scoring systems are based on axial involvement by the majority and do not consider the clinical nature of JSpA such as involvement in entheseal and peripheral joint areas.

Perhaps the most striking finding of this study is the clear preference for subjective physician assessment over a validated, objective score for defining inactivity. The panel reached a strong consensus for the "Physician Global Score (PGS) = 0" item yet simultaneously rejected the "JSpADA = 0" criterion. Given that JSpADA is a validated tool specifically for JSpA, this discrepancy suggests that while JSpADA may be valuable for *monitoring* disease activity, our experts find a strict cut-off of zero to be insufficient for *defining* true inactivity [14].

This paradox is likely explained by the panel's nuanced view of pain. Our results show that only half of the participants (48.1%) considered the 'complete absence of pain' to be a prerequisite for inactivity. Moreover, less than half of the experts believed that low back pain (46.4%) or peripheral joint pain (40.7%) could be *completely* controlled in JSpA patients. This aligns with the rejection of the "no lower back pain" and "no peripheral joint pain" items in Round 2. Taken together, these findings imply that the panel trusts the clinician's ability (via PGS = 0) to differentiate true inflammatory pain (which must be absent, e.g., entheseal pain) from low-level, non-inflammatory residual pain, a distinction that a JSpADA = 0 score cannot make [27].

The consensus that pain may not be fully controlled in all JSpA patients points to a multifactorial etiology of pain in this cohort. Beyond active inflammation, mechanical stress in enthesal areas, structural damage developing in the chronic process, and secondary central sensitization can cause residual pain even when the disease is biologically inactive. This explains why experts prioritize objective MRI findings and physical examination over subjective pain reports when defining true disease inactivity. This nuanced understanding highlights the difference between 'active inflammatory pain' and 'chronic residual pain,' which subjective scoring systems like JSpADA may fail to adequately distinguish.

This study has several limitations. Due to the nature of the Delphi method, the findings are based on expert opinions and are not supported by actual patient data. The small number of participants and the inclusion of only pediatric rheumatologists may limit the generalizability of the results. Furthermore, despite the prominence of MRI in inactivity assessment, accessibility and interpretation differences may pose practical limitations. Another significant shortcoming is that the study was not validated with long-term clinical outcomes. Therefore, the findings must be supported by multicenter, patient-based studies. Furthermore, these findings represent a valuable *national consensus* based on the opinions of PeRA members from Türkiye. This national scope is a limitation, as practice patterns, particularly regarding the routine accessibility of MRI and the clinical adoption of scoring systems like JSpADA, may vary significantly in other regions (e.g., North America vs. Europe). Therefore, the generalizability of these criteria remains to be established, and we recommend that future efforts aim to replicate this Delphi study with a larger,

international panel (e.g., through PRINTO or CARRA) to pursue a global consensus.

5 | Conclusion

In summary, this study, based on the opinions of pediatric rheumatologists, has revealed the prominent criteria for assessing inactivity in JSpA. The findings indicate that physicians rely primarily on clinical evaluation and SIJ-MRI findings in the decision-making process, while laboratory markers such as ESR and CRP play a limited role. The results emphasize the need for a multidimensional approach to defining inactivity in JSpA and the development of standardized criteria that integrate clinical, radiological, and physician assessments.

Author Contributions

Study coordinators: Serkan Türkuçar, Betül Sözeri, Hafize Emine Sönmez, and Nihal Şahin. Participants: All of the 27 authors. Statistical analysis: Serkan Türkuçar. Writing: Serkan Türkuçar, Hafize Emine Sönmez, Belde Kasap Demir and Selçuk Yüksel. Critical review: Betül Sözeri, Mukaddes Kalyoncu, Erbil Ünsal, Belde Kasap Demir, Sevcan Bakkaloğlu and Selçuk Yüksel.

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The authors have nothing to report.

Ethics Statement

Ethical approval was not obtained as it was not needed in the Delphi survey study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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REVIEW

Therapeutic Potential of Spermidine in Rheumatoid Arthritis: Mechanisms and Future Directions

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease that not only severely impairs joint function but also leads to various systemic complications, significantly reducing patients' quality of life. Furthermore, RA imposes a substantial economic burden on healthcare systems globally. Current clinical treatments primarily consist of non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs, which effectively control symptoms and delay joint damage. However, achieving a complete cure remains a considerable challenge. Consequently, therapeutic strategies aimed at joint protection and the prevention of systemic complications have become central to research efforts. Spermidine (SPD), a naturally occurring polyamine in the human body, has garnered significant attention due to its multifaceted effects as anti-aging, cardiovascular protection, neuroregulation, and anti-inflammation. Notably, SPD has shown significant therapeutic effects in mouse models of various inflammatory diseases, including inflammatory bowel disease, psoriasis, osteoarthritis and RA. The exploration of the role of SPD in RA may provide new targets and effective therapeutic approaches for the treatment of RA. This review provided a comprehensive overview of the potential mechanisms of SPD in the pathological progression of RA, including the inhibition of inflammatory cytokines expression, reduction of oxidative stress, modulation of immune cell functions, and maintenance of bone metabolism homeostasis. Through these mechanisms, SPD shows potential as a promising novel candidate for RA therapy. However, its precise efficacy and safety must be validated through large-scale clinical trials. This article aimed to provide theoretical insights and future research directions for understanding the pathological mechanisms of RA and developing novel therapeutic agents.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease. Epidemiological data indicate that its global prevalence ranges from 0.5% to 1%, with the incidence in women being 2–3 times higher than in men. The regulatory effect of estrogen on immune function is considered a major factor contributing to this gender difference [1]. RA primarily presents with inflammation of the synovial membrane, accompanied by joint pain, swelling, and dysfunction. It commonly affects small joints, such as the fingers and wrists, in a symmetrical distribution. Pathological features include fibroblast-like synoviocytes (FLS) proliferation, inflammatory cell infiltration, and damage to joint cartilage and bone [2–4]. RA not only affects the joints but can also result in systemic complications, including pulmonary fibrosis, cardiovascular diseases, and metabolic syndrome, substantially

affecting patients' quality of life and shortening life expectancy [5]. Although the exact etiology of RA remains incompletely understood, studies suggest that genetic susceptibility (such as the HLA-DR4 gene) and environmental factors (such as smoking and infections) may jointly trigger abnormal immune responses, leading to autoimmune inflammation [1, 6–8]. Currently, available treatment options for RA are limited, primarily focusing on alleviating symptoms, controlling inflammation, and preventing joint damage.

In recent years, spermidine (SPD), a polyamine (PA) compound, has garnered increasing attention as research deepens. Experimental evidence suggests that it demonstrates significant therapeutic potential in various diseases, including the inhibition of renal fibrosis [9], delaying the progression of nonalcoholic steatohepatitis [10], alleviating inflammation in RA [11], improvement of multiple sclerosis (MS) [12], and relieving ulcerative colitis [13]. Furthermore, studies have shown that SPD can modulate immune responses, improve inflammatory conditions, and maintain bone metabolism homeostasis, which suggests that it could serve as a potential therapeutic target for RA [11, 14–16]. Therefore, investigating the role of SPD in the pathological progression of RA, especially its potential impact on joint inflammation and bone destruction, is crucial for understanding the disease's pathogenesis and identifying new therapeutic targets. This review aims to explore the current research on SPD's role in RA.

Although prior studies have reported therapeutic effects of SPD in a range of inflammatory disorders, a systematic synthesis of its involvement in the pathogenesis of RA remains lacking. Existing work has predominantly emphasized the effects of SPD within a single pathogenic facet (anti-inflammatory effects or immunomodulation), without an integrated appraisal of its roles in RA. In this review, we provide the first systematic consolidation of the mechanisms through which SPD engages four key pathological processes in RA (inhibition of inflammatory cytokine expression, reduction of oxidative stress, modulation of immune cell function, and maintenance of bone metabolism homeostasis), thereby offering a new perspective on its multitarget therapeutic effects. This integrative analysis not only deepens understanding of the pleiotropic protective actions of SPD during RA progression but also provides a theoretical rationale for the development of innovative, SPD-based therapeutic strategies for RA, highlighting its potential for clinical translation.

2 | Fundamental Characteristics and Natural Sources of SPD

SPD is a naturally occurring polyamine that plays a vital role in maintaining cellular homeostasis, regulating immune function, promoting cell proliferation, and providing antioxidant protection [17]. It is widely found in natural diets, with major sources including aged cheese, wheat germ, nuts, and fermented legume products. In addition to dietary intake, SPD can also be synthesized intracellularly or produced by gut microbiota to meet the physiological needs of mammals [18]. The intracellular synthesis of SPD is a highly regulated process involving multiple enzymatic reactions, which catalyze the stepwise conversion from ornithine to putrescine (PUT) and then to SPD. Precise regulation of SPD metabolism is essential for normal cellular function, and its dysregulation is linked to the development of various diseases. Key enzymes involved in SPD synthesis include ornithine decarboxylase (ODC) and spermidine/spermine N1-acetyltransferase (SSAT1) [19, 20]. In this pathway, ornithine serves as a crucial substrate, converted to PUT by ODC. Ornithine can be sourced from plasma or produced through the hydrolysis of arginine by arginase 1 (Arg1), making arginine the first step in PA biosynthesis. Arg1 hydrolyzes arginine to generate ornithine, which is then catalyzed by spermidine synthase, where PUT reacts with decarboxyspermidine from S-adenosylmethionine to form SPD. Subsequently, spermine synthase catalyzes the conversion of SPD to spermine (SPM). SPM can be converted into N1-acetylspermine by SSAT1, which is then re-converted into SPD via an oxidative reaction mediated by acetylpolyamine oxidase [19–21].

3 | The Multiple Mechanisms of Action of SPD in RA

With the continuous advancement of research, we speculate that SPD may play a key role in the treatment of RA through the synergistic action of multiple mechanisms. These mechanisms primarily include inhibiting the expression of inflammatory cytokines, decreasing oxidative stress, modulating the function of immune cells, and maintaining the homeostasis of bone metabolism.

3.1 | SPD Inhibits the Expression of Inflammatory Cytokines

Inflammatory cytokines play a central regulatory role in the inflammatory response of RA. Excessive expression of these factors significantly exacerbates joint inflammation, promotes FLS proliferation, and leads to the destruction of cartilage and bone tissue [3]. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are central to its pathogenesis, while excessive expression of other inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-17 (IL-17), interleukin-21 (IL-21), interleukin-23 (IL-23), and granulocyte-macrophage colony-stimulating factor, also plays a significant role in disease progression [3, 22]. The overexpression of these pro-inflammatory cytokines is closely linked to several critical signaling pathways, including nuclear factor-kappa B (NF-κB), NLRP3 inflammasome, mitogen-activated protein kinases (MAPK), and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), all of which are key to RA pathogenesis [23–26].

Multiple studies have demonstrated that exogenous supplementation of SPD can significantly inhibit the production of inflammatory cytokines in both cell and animal models [27–29]. Xiaocheng Guo et al. [27] showed that SPD reduces the release of inflammatory cytokines by inhibiting the NF-κB and NLRP3/caspase-1/GSDMD pathways. Specifically, SPD works as follows: (1) it inhibits the activation of the NLRP3 inflammasome, reduces caspase-1 activation, and prevents GSDMD cleavage and membrane pore formation, thereby decreasing IL-1β release; (2) SPD inhibits the phosphorylation of p65 and IκBα in the NF-κB pathway, blocking NF-κB nuclear translocation

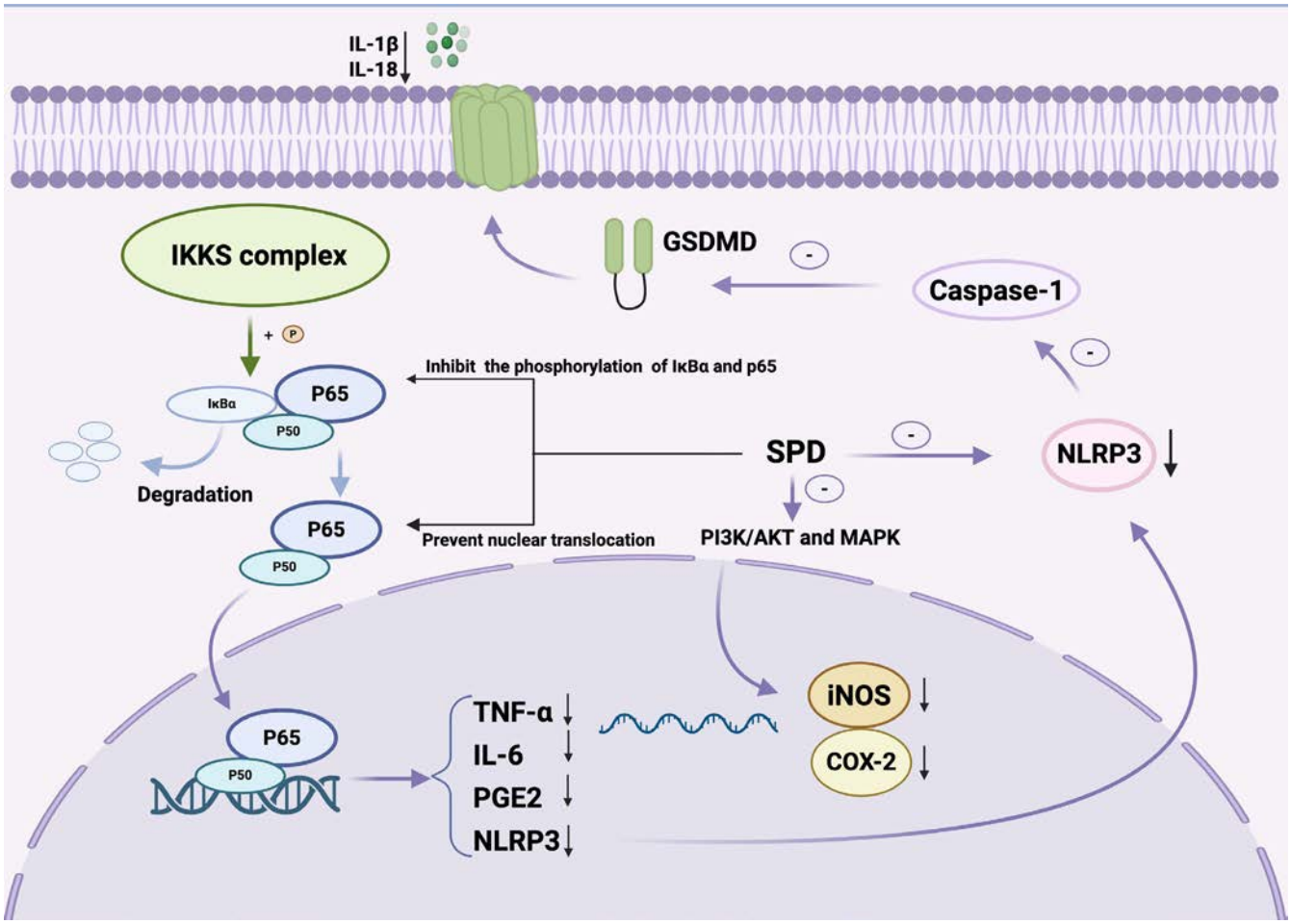

FIGURE 1 | Mechanisms of SPD inhibition of inflammatory signaling pathways and inflammatory cytokine secretion. First, suppression of NF-κB signaling pathway: SPD blocks NF-κB nuclear translocation by inhibiting the phosphorylation of IκBα and p65, ultimately downregulating the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and PGE2, as well as NLRP3 expression. Second, modulation of NLRP3 Inflammasome Pathway: SPD suppresses NLRP3 inflammasome assembly and activation, reduces caspase-1 activity, prevents GSDMD protein cleavage and membrane pore formation, consequently decreasing IL-1β and IL-18 release. Third, blockade of PI3K/AKT and MAPK Pathways: SPD synchronously inhibits PI3K/Akt and MAPK signaling transduction, downregulates the expression of iNOS and COX-2, and reduces the production of inflammatory mediators such as NO and PGE2.

and ultimately downregulating TNF-α expression, while also reducing the release of pro-inflammatory cytokines like IL-6 and Prostaglandin E2 (PGE2). Similarly, SPD can suppress the NF-κB signaling pathway mediated by mitochondrial reactive oxygen species (ROS), significantly inhibiting the activation of the NLRP3 inflammasome under high glucose conditions. This reduces the secretion of pro-inflammatory cytokines IL-1β and IL-18, alleviating the inflammatory response [28]. In addition, in a lipopolysaccharide (LPS)-stimulated BV2 microglial cell model, SPD simultaneously blocks the PI3K/Akt and MAPK signaling pathways, inhibiting the mRNA transcription and protein expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). This reduces the excessive synthesis of inflammatory mediators, such as nitric oxide and PGE2 [29].

In summary, SPD inhibits the production of multiple key pro-inflammatory cytokines (Figure 1) by targeting multiple signaling pathways such as NF-κB, NLRP3 inflammasome, MAPK, and PI3K/Akt, providing potential molecular targets for anti-inflammatory therapy of RA. However, inflammatory cytokines and oxidative stress mutually promote each other in the pathological process of RA, forming a vicious cycle. Excessive ROS can not only directly damage tissues, but also activate inflammatory pathways such as NF-κB and NLRP3, while the release of inflammatory cytokines further aggravates oxidative stress. Therefore, in addition to directly inhibiting inflammatory signaling pathways, the regulatory effect of SPD on oxidative stress is equally worthy of in-depth investigation.

3.2 | SPD Decreases Oxidative Stress

Oxidative stress is a key component of the inflammatory response, resulting from the imbalance between ROS generation and endogenous antioxidant defenses. While low concentrations of ROS are essential for cellular homeostasis, excessive ROS production exacerbates inflammation and causes tissue and cellular damage [30, 31]. In RA patients, ROS levels in synovial tissue, synovial fluid, and blood are significantly elevated, leading to oxidative damage in joint tissues and amplifying the inflammatory response [32]. Oxidative stress has been shown to contribute to the progression of RA by damaging cellular DNA,

lipids, and proteins, ultimately resulting in synovial inflammation [33]. Importantly, oxidative stress-induced cellular damage is not limited to local joint tissues; its systemic effects are also closely associated with the onset of complications such as cardiovascular diseases and pulmonary interstitial fibrosis in RA patients [34].

The potential of antioxidant therapy in RA has been validated through evidence-based research. A meta-analysis of 30 randomized controlled trials revealed that antioxidant intervention significantly improved clinical symptoms and laboratory markers in RA patients, with a moderate effect size (Cohen's $d = 0.525$), suggesting that modulating oxidative stress may be a key strategy in RA treatment [35]. This demonstrates the clear clinical relevance of antioxidant interventions for RA and supports the use of bioactive molecules with antioxidant properties, such as SPD, in therapeutic interventions.

Mitochondria are not only the main source of cellular energy but also the primary source of ROS. In RA patients, FLS often exhibit mitochondrial dysfunction. Mitochondrial dysfunction leads to disruption of the tricarboxylic acid cycle, resulting in excessive ROS production and can activate pro-inflammatory pathways such as NF-κB and NLRP3 inflammasome, ultimately causing a pathological cascade of oxidative damage and inflammation amplification [23]. The transcriptional co-activator peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), a key regulator of mitochondrial biogenesis, is dynamically regulated by sirtuin 1 (SIRT1). SIRT1 deacetylates PGC-1α, enhancing mitochondrial DNA transcription and the assembly of electron transport chain complexes, thereby maintaining oxidative phosphorylation efficiency and inhibiting excessive ROS production [36, 37].

Junying Wang et al. [38] has shown that in the cardiac tissue of aging rats, SPD activates the SIRT1/PGC-1α pathway, enhancing the expression of mitochondrial biogenesis-related genes such as mitochondrial transcription factor A (TFAM) and Nuclear factor erythroid 2-related factor 2 (NRF2), increasing the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), significantly reducing intracellular ROS levels, boosting antioxidant capacity, reducing oxidative stress, protecting mitochondrial function, and delaying cardiomyocyte aging. Additionally, activation of SIRT1 inhibits the NF-κB signaling pathway, reducing the production of pro-inflammatory cytokines such as TNF-α and IL-1β, further reducing inflammation induced by oxidative stress [39]. D. J. Puleston et al. [40] also demonstrated that SPD promotes mitophagy, selectively removing damaged mitochondria, thereby improving mitochondrial quality and quantity while reducing ROS accumulation. In a zebrafish model [41], SPD supplementation reduced pro-inflammatory mediators and cytokines production, inhibited NF-κB pathway activation, and decreased ROS accumulation, thus alleviating inflammation. Moreover, SPD can directly scavenge various free radicals and protect DNA from oxidative damage in vitro.

NRF2 is a core transcriptional regulator in cellular responses to oxidative stress. It plays a critical role in maintaining cellular redox homeostasis by promoting the transcriptional activation of antioxidant proteins through binding to antioxidant response elements (ARE) [42, 43]. When cells experience oxidative damage, NRF2 is released from its cytoplasmic Kelch-like ECH-associated protein 1 (KEAP1) and translocates to the nucleus, triggering the transcription of antioxidant enzymes such as SOD and glutathione peroxidase (GPx), thereby reducing ROS levels and inhibiting inflammation [44, 45]. Evidence suggests that SPD acts as a non-classical NRF2 inducer by enhancing Microtubule-associated protein 1S (MAP1S) expression, which stabilizes NRF2 in two ways: first, by binding to KEAP1, reducing KEAP1's inhibition of NRF2, and second, by promoting the degradation of KEAP1 via a p62-dependent autophagy pathway [46]. This regulation forms a positive feedback loop: NRF2 enhances SPD synthesis by increasing ODC activity, establishing an "NRF2-SPD" antioxidant synergistic pathway [47]. However, in human dermal fibroblasts, although SPD treatment increases SOD activity, NRF2 expression decreases, suggesting that NRF2-independent antioxidant pathways may exist, which require further investigation [34].

Oxidative stress plays an important role in the pathological process of RA, and excessive ROS can aggravate inflammatory responses and lead to joint tissue damage. SPD can regulate oxidative stress through the multiple mechanisms (Figure 2) mentioned above. Although the effect of SPD in antioxidation is relatively significant, its specific mechanisms still need further exploration. Furthermore, the pathological process of RA involves not only excessive production of inflammatory cytokines and oxidative stress but also the dysfunction of immune cells, which is equally a key factor driving the occurrence and development of the disease. Therefore, investigating the regulatory effect of SPD on immune cell function is crucial for comprehensively understanding its therapeutic potential in RA.

3.3 | SPD Modulates the Function of Immune Cells

Immune cells play a crucial role in the onset and progression of RA, with T cells, B cells, macrophages, and dendritic cells (DCs) being key players. Abnormal activation of these cells can lead to excessive production of pro-inflammatory cytokines, osteoclast differentiation, and the proliferation of FLS, ultimately resulting in the destruction of bone tissue and cartilage [48, 49] SPD plays a key role in regulating the immune system and holds therapeutic potential in modulating immune cell functions [14, 50–53].

Multiple studies have shown that the onset of RA is closely linked to an imbalance between regulatory T cells (Treg) and T helper type 17 cells (Th17), with Treg numbers and function often suppressed, while the activity and number of Th17 are abnormally increased [54–56]. Tregs play a crucial role in maintaining immune tolerance and homeostasis by suppressing autoimmune and other pathological immune responses. It is through various mechanisms that inhibit the excessive activation, proliferation, and function of effector CD4+ T cells. For instance, first and foremost, Tregs express high levels of cytotoxic T lymphocyte-associated protein 4 (CTLA-4), which competitively binds to CD80/CD86 on antigen-presenting cells (APCs), thereby inhibiting the CD28 co-stimulatory signal. In addition, they express high levels of the IL-2 receptor α-chain (CD25), enabling them to absorb large amounts of IL-2. Finally, Tregs secrete

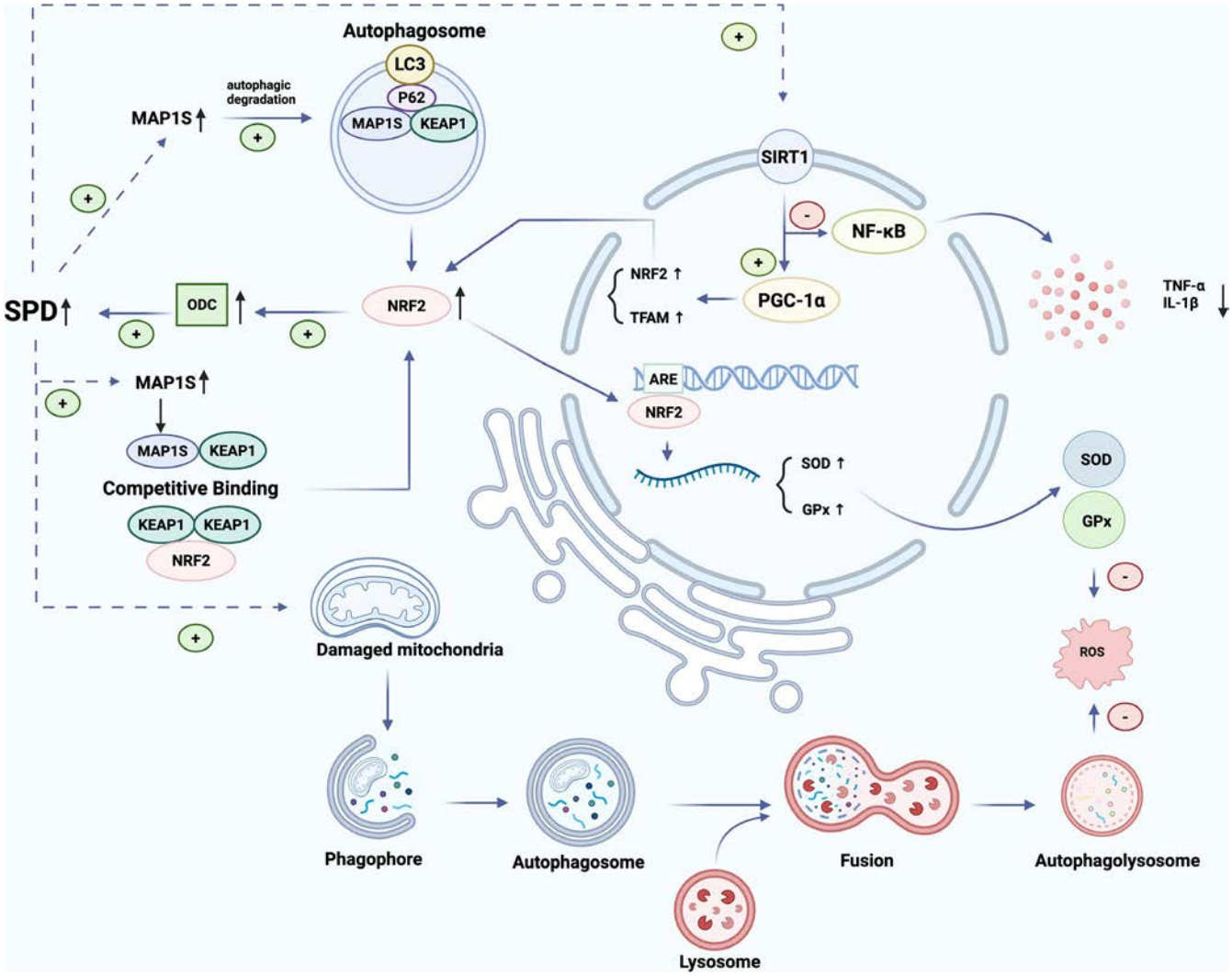

FIGURE 2 | SPD alleviates oxidative stress and mitochondrial damage through multi-pathway synergistic mechanisms: First, SPD activates the SIRT1/PGC-1α pathway, thereby upregulating mitochondrial biogenesis-related genes including TFAM and NRF2. Concurrently, SIRT1 activation suppresses NF-κB signaling, consequently reducing the release of pro-inflammatory cytokines such as TNF-α and IL-1β, which indirectly attenuates oxidative stress. Second, SPD upregulates MAP1S expression. On one hand, MAP1S competitively binds to KEAP1 to release NRF2; on the other hand, MAP1S promotes p62-mediated autophagic degradation of KEAP1. Together, these mechanisms stabilize and activate NRF2, subsequently inducing the expression of antioxidant enzymes such as SOD and GPx, thereby enhancing cellular antioxidant responses. Additionally, activated NRF2 augments ODC activity, promoting endogenous SPD biosynthesis and further reinforcing antioxidant defense mechanisms. Third, SPD promotes mitophagy to eliminate damaged mitochondria, consequently reducing ROS generation.

anti-inflammatory cytokines such as TGF-α and IL-10 [57, 58]. In RA, Th17 secrete pro-inflammatory cytokines (INF-α, IL-17, IL-6, IL-21, IL-22) and promote the accumulation of immune cells, such as macrophages, in the joints, exacerbating synovial inflammation. Additionally, Th17 either directly express receptor activator of nuclear factor kappa B ligand (RANKL) or secrete IL-17, which stimulates FLS to express RANKL, leading to the differentiation and activation of osteoclasts, ultimately resulting in bone destruction [59–62]. It has been reported that Th17 and Treg show heterogeneous distribution in RA patients at different stages. In early-stage RA, the numbers of Th17 and Treg are similar to those in healthy controls, indicating that immune homeostasis has not been completely disrupted. Early intervention may prevent the development of RA [63]. Studies suggest that SPD promotes Treg differentiation and function while inhibiting the activation of Th17, thus restoring the balance of T cell subsets. This mechanism involves the induction of autophagy and regulation of the mTOR signaling pathway, thereby restoring immune tolerance and reducing inflammation [50].

In the inflammatory milieu of RA, M1 macrophages (M1) predominate. M1 are activated through Toll-like receptor (TLR) and interferon (IFN) signaling pathways, producing a high level of pro-inflammatory cytokines. These cytokines promote the differentiation of osteoclast precursor cells and the proliferation of FLS via paracrine signaling, resulting in osteoclast formation, bone erosion, and joint destruction. Conversely, M2 macrophages (M2) contribute to the anti-inflammatory response by secreting growth factors and anti-inflammatory cytokines [64, 65]. The imbalance between M1 and M2 in the synovial tissue of RA patients is closely associated with disease activity. In the colitis mouse model, SPD supplementation in a

dose-dependent manner enhances M2 function, maintains a balanced gut microbiome, and preserves epithelial barrier integrity, thereby mitigating intestinal inflammation. These findings highlight SPD's potential clinical applications in treating autoimmune diseases such as inflammatory bowel disease [52]. Moreover, Hao Yuan et al. [14] demonstrate that SPD may protect collagen-induced arthritis (CIA) mice from arthritis by inhibiting the polarization of M1 in synovial tissue. This reduces the release of pro-inflammatory cytokines, including IL-6 and IL-1β, while increasing levels of the anti-inflammatory cytokine IL-10. A higher concentration of SPD (50 mg/kg) shows better therapeutic effects on CIA mice compared to 2 mg/kg SPD. In experimental autoimmune encephalomyelitis (EAE) models of MS, SPD further demonstrated immunomodulatory capacity by inducing M2 polarization through upregulation of Arg1 and by reprogramming macrophage oxidative phosphorylation and tricarboxylic acid cycle metabolism via eIF5A hypusination. These coordinated effects inhibited the infiltration of autoimmune T lymphocytes into the central nervous system, thereby reducing demyelination and neuroinflammation [12]. Additionally, multiple studies have confirmed that SPD increases M2 polarization and decreases M1 polarization through various mechanisms [66–68]. These results suggest that exogenous SPD supplementation can alleviate RA pathology by influencing macrophage polarization, thereby reducing synovial tissue inflammation and slowing disease progression.

DCs are specialized APC that play a crucial role in bridging the innate and adaptive immune responses. DCs are highly accumulated in the synovial fluid and tissues of RA patients. They not only express high levels of MHC class II molecules (HLA-DR) and co-stimulatory molecules (CD40, CD80, CD86) that trigger T cell activation, but also secrete pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IL-23) that induce CD4+ T cell differentiation into activated Th1 and Th17 subsets. Additionally, it promotes the pathological progression of RA through various mechanisms, such as presenting self-antigens to stimulate the production of autoantibodies and attracting inflammatory cells [69–71]. In the imiquimod (IMQ)-induced psoriasis-like mouse model, SPD activates the FOXO3 pathway, which reduces the expression of MHC II and co-stimulatory molecules (CD86, CD40), inhibits the activation of IFN-DCs, and the production of pro-inflammatory cytokines. Ultimately, this exerts anti-inflammatory effects and alleviates the skin inflammation symptoms in the mouse [51]. Furthermore, a study by Marcin Wawrzyniak et al. [53] showed that SPM and SPD can suppress the secretion of pro-inflammatory cytokines (TNF-α, I1L-6) in LPS-induced human DCs in vitro. They also reduce the expression of co-stimulatory molecules (CD80, CD86) and co-inhibitory molecules (PDL1, PDL2) on the surface of DCs, thereby interfering with T cell activation.

Within the synovial microenvironment of RA, FLS interact with B cells through the secretion of IL-6 and the expression of CD40 ligand (CD40L). Alt-hough CD40L signaling is critical for B-cell survival and antibody production, its persistent activation paradoxically suppresses terminal B-cell differentiation. However, memory B cells exhibit resistance to this inhibitory effect and are therefore preferentially driven by FLS toward plasma cell differentiation, ultimately leading to excessive autoantibody production [72]. B cells play multiple roles in the pathogenesis of RA: on one hand, by producing autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which form immune complexes. These immune complexes not only activate innate immune cells to exacerbate inflammation, but also directly promote osteoclast differentiation. On the other hand, B cells express RANKL, thereby directly inducing osteoclast differentiation. In addition, B cells are involved in antigen presentation, T cell activation, and the secretion of pro-inflammatory cytokines, which further aggravate synovial inflammation and ultimately lead to bone destruction [54, 73]. While B cells play a critical role in the pathogenesis of RA, there have been no reports on the regulatory effects of SPD on B cells. While B cells play a pivotal role in the pathogenesis of RA, SPD's regulatory effects on B cell function remain unexplored. Given SPD's demonstrated anti-inflammatory and immunomodulatory properties across multiple immune cell types, we hypothesize that SPD may confer therapeutic benefits in RA by suppressing autoantibody production, downregulating RANKL expression, attenuating antigen presentation, and reducing pro-inflammatory cytokine secretion. Nevertheless, these postulated mechanisms require rigorous validation through comprehensive preclinical investigations and subsequent clinical trials.

These findings indicate that aberrant activation of T cells, B cells, macrophages, and DCs plays an important role in the occurrence of RA. SPD can exert anti-inflammatory effects by regulating multiple immune cells, thereby alleviating joint inflammation (Figure 3). Although the regulatory effect of SPD on B cells has not yet been clarified, its comprehensive regulation of immune cells provides new insights for RA treatment. It is noteworthy that chronic inflammation caused by immune cell dysfunction may exacerbate the most destructive pathological outcome of RA—imbalance of bone metabolic homeostasis. In the sustained inflammatory microenvironment, excessive activation of osteoclasts and suppressed function of osteoblasts jointly drive irreversible bone destruction. Therefore, exploring the regulatory effect of SPD on bone metabolic homeostasis may make it another key link in the treatment of RA.

3.4 | SPD Maintains the Homeostasis of Bone Metabolism

In healthy individuals, there is a balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. In RA patients, however, this balance is disrupted, resulting in excessive bone resorption and inhibition of bone repair processes [74].

Osteoclasts are multinucleated cells formed by the fusion of precursor cells from the monocyte/macrophage lineage and are responsible for degrading bone matrix proteins through the secretion of various proteolytic enzymes. Their differentiation relies on macrophage colony-stimulating factor and RANKL signaling. RANKL is a critical factor for osteoclast differentiation and activation. It binds to the nuclear factor kappa B (RANK) receptor on pre-osteoclasts, thereby initiating osteoclast differentiation. Additionally, various cytokines, such as TNF-α, IL-1β, and IL-6, regulate osteoclastogenesis and function through different signaling pathways [62, 75–76]. In RA patients, osteoclasts are activated within the synovium, contributing to bone destruction [77]. This

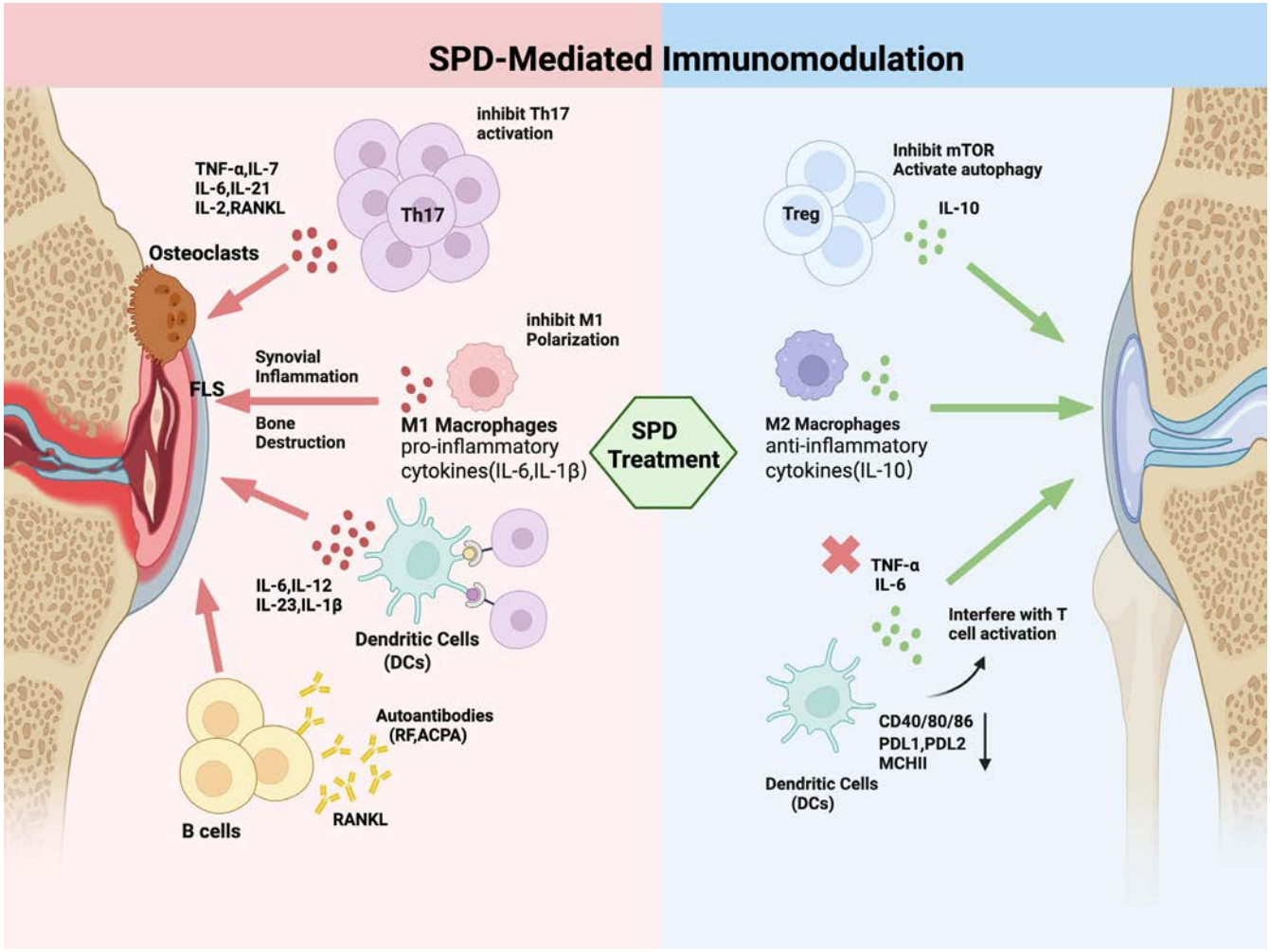

FIGURE 3 | In RA, Th17 secrete pro-inflammatory cytokines (TNF-α, IL-6, etc.) and express RANKL or promote RANKL expression in FLS; M1 secrete multiple pro-inflammatory cytokines, including IL-6 and IL-1β; DCs express high levels of MHC class II molecules (HLA-DR) and co-stimulatory molecules (including CD40, CD80, and CD86) to activate T cells, and secrete pro-inflammatory cytokines that induce Th1/Th17 cell differentiation and activation; B cells produce pathogenic autoantibodies (RF, ACPA) and express RANKL. The aberrant activation of these multiple immune cell subsets synergistically exacerbates synovial inflammation and bone destruction. SPD supplementation inhibits mTOR signaling and subsequently activates autophagy, thereby enhancing Treg cell differentiation and functional capacity, suppressing Th17 cell activation, and promoting IL-10 secretion by Tregs; inhibits M1 macrophage polarization, facilitates M2 macrophage polarization with secretion of anti-inflammatory cytokines such as IL-10; reduces the expression of MHC II, costimulatory molecules (CD40/80/86), and PDL1/PDL2 on DCs, consequently suppressing T cell activation and decreasing the production of TNF-α and IL-6. Through modulating multiple immune cells population, SPD ultimately alleviates synovial inflammation and prevents bone destruction in RA.

bone destruction is one of the primary causes of joint dysfunction and deformity. As early as 2014, studies demonstrated that natural PA (such as PUT, SPD, and SPM) inhibit the migration of pre-osteoclasts by suppressing the Ca2+-PYK2-Src-NFATc1 signaling axis, thereby exerting an inhibitory effect on osteoclastogenesis [15]. Tomomi Yamamoto et al. [78] reported that adding SPD and SPM to the drinking water of ovariectomized (OVX) mice significantly inhibited osteoclast differentiation and maturation, effectively preventing OVX-induced bone loss. In vitro experiments further confirmed that SPD and SPM exert concentration-dependent inhibitory effects on RANKL-induced osteoclast differentiation and markedly reduce NF-κB transcriptional activity and p65 phosphorylation, suggesting that they may act by interfering with the RANKL/NF-κB signaling pathway, although the exact molecular mechanisms remain to be further explored. Recent studies have also shown that treatment with the SSAT1 inhibitor Berenil in OVX mice significantly increases osteoclast apoptosis and reduces osteoclast numbers, thereby decreasing bone resorption [79]. This effect is likely due to an increase in SPD levels resulting from SSAT1 inhibition. Takanori Yamada et al. [80] demonstrated that intervention with S631 yeast, enriched in SPD and SPM, effectively prevents bone loss by inhibiting osteoclast activation. Overall, current evidence suggests that SPD has potential anti-bone destruction effects by modulating osteoclast differentiation, maturation, and apoptosis through multiple targets, contributing to the maintenance of bone metabolic balance.

Osteoblasts are specialized cells derived from mesenchymal stem cells and are essential for bone formation and maintenance [81]. Osteogenic genes, including Runt-related transcription factor 2 (Runx2), alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OC), play critical roles in regulating osteoblast

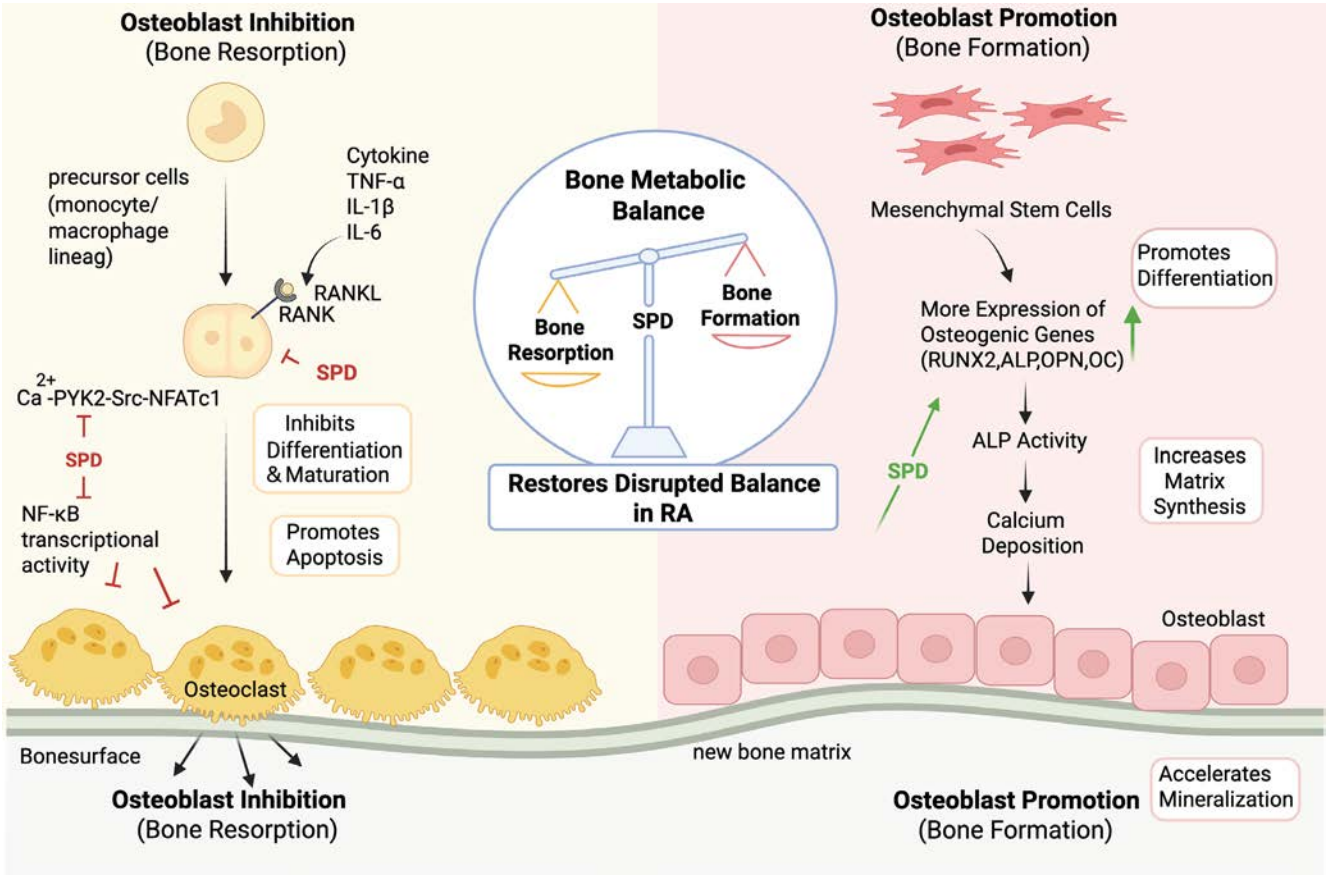

FIGURE 4 | SPD restores the disrupted bone metabolic homeostasis in RA through bidirectional regulation of bone resorption and bone formation. Regarding bone resorption, pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) promote osteoclast differentiation by increasing RANKL expression. However, SPD inhibits osteoclast differentiation and maturation while promoting their apoptosis through reducing pro-inflammatory cytokines production, suppressing the Ca2 + -PYK2-Src-NFATc1 signaling axis, and decreasing NF-κB transcriptional activity. Regarding bone formation, SPD promotes the differentiation of mesenchymal stem cells (MSC) into osteoblasts and upregulates the expression of osteogenic genes (including RUNX2, ALP, OPN, and OC), consequently enhancing ALP activity and accelerating calcium deposition, which ultimately augments bone matrix synthesis and promotes mineralization.

differentiation and bone matrix formation. Runx2, as the core transcription factor in osteoblast differentiation, is pivotal in the early stages of osteoblast development. It promotes osteoblast differentiation and mineralization by regulating the expression of downstream genes [82]. In vitro studies have shown that, compared to the untreated control group, treatment with exogenous PA (such as PUT, SPD, and SPM) not only significantly increases ALP activity in human bone marrow-derived mesenchymal stem cells but also promotes the upregulation of osteogenic genes such as Runx2, ALP, OPN, and OCN mRNA levels, as well as enhances calcium deposition [16]. The study by Zhi-Qing Du et al. [83] found that, compared to the ferric ammonium citrate (FAC) group, SPD treatment significantly improved the bone microstructure in aged rats. For example, bone volume per total volume, bone trabecular thickness, trabecular number, and bone mineral density all increased, while trabecular spacing decreased. Additionally, SPD significantly enhanced the bone mineralization rate in rats treated with FAC. This suggests that exogenous supplementation of SPD not only stimulates early osteogenesis but also accelerates the synthesis and mineralization of the bone matrix, which is of great importance for developing therapeutic approaches aimed at promoting bone formation.

In summary, SPD exerts a dual effect on bone metabolism regulation (Figure 4): it inhibits osteoclast differentiation, maturation, and activation, thereby reducing pathological bone resorption; at the same time, it promotes osteoblast differentiation and bone matrix synthesis, accelerating bone mineralization and enhancing bone formation. This bidirectional modulation of bone resorption and formation suggests that SPD may restore the disrupted bone metabolic balance, offering potential therapeutic applications in the treatment and prevention of bone-destructive diseases, such as RA and osteoporosis.

4 | The Current State of RA Treatment and New Research Directions

Currently, the treatment of RA primarily focuses on alleviating symptoms and slowing disease progression. The main therapeutic options include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs). NSAIDs are commonly used during the acute phase of RA and help reduce inflammation and pain by inhibiting COX and PGE synthesis. However, their use can lead to adverse reactions, such as bleeding, ulcers, and

kidney damage [7, 84]. GCs have a dual role in RA treatment: first, as "bridge therapy" before the onset of DMARDs' effects; second, as adjunctive therapy for active lesions that are poorly controlled by DMARDs. The adverse effects of GCs are closely related to their dosage and duration of use, and can include cardiovascular diseases, infections, gastrointestinal issues, psychological disorders, endocrine diseases, skin problems, musculoskeletal diseases (e.g., osteoporosis), and ocular diseases [7, 85]. While long-term GC use remains controversial, some studies suggest that long-term low-dose GC therapy for RA does not significantly increase the risk of adverse events and can alleviate disease progression. However, the increased risk of infections still requires careful monitoring [86].

DMARDs are a class of drugs that alleviate the condition by inhibiting autoimmune activity and delaying or preventing joint damage. They are classified into conventional synthetic (csDMARDs), biologics (bDMARDs), and targeted synthetic (tsDMARDs). Due to the slow onset of action, typically requiring 6 weeks to 6 months, treatment should be initiated as early as possible to achieve better efficacy [7, 87].

However, current treatment options for RA still face several challenges, including the safety concerns associated with NSAIDs and GCs, the delayed onset of action of DMARDs, and the high cost of biologic therapies. These issues highlight the need for safer and more effective therapeutic targets.

In recent years, the multifaceted biological functions of exogenous SPD supplementation have garnered significant attention, with its mechanisms of action gradually becoming clearer in the fields of anti-aging, cardiovascular protection, neuroregulation, and anti-inflammation. Research has confirmed that SPD intervention can alleviate arthritis inflammation in CIA mouse [14], inhibit IMQ-induced psoriatic skin inflammation in mouse [51], improve intestinal mucosal damage in the mouse model of colitis [52], and reduce joint inflammation and cartilage damage in osteoarthritis mouse [88]. Furthermore, in cardiovascular and neurological disease models, SPD has shown protective effects by delaying cardiomyocyte aging [38] and improving cognitive function in vascular dementia rats [89]. Notably, SPD exhibits high biological safety and low toxicity [90].

If SPD is applied to the treatment of RA in the future, it may delay disease progression through multiple targets. Its potential advantages lie in reducing adverse events associated with traditional drugs and alleviating economic burden, offering an innovative approach for personalized treatment of RA.

5 | Translational Challenges and Therapeutic Potential of SPD

Although extensive in vitro and animal studies have demonstrated that SPD exerts multiple beneficial effects, its translation from preclinical research to clinical practice faces substantial barriers. Therefore, despite accumulating evidence providing a robust mechanistic rationale for SPD therapy in RA, establishing its clinical utility requires rigorously designed translational research, particularly well-designed clinical trials to validate its efficacy, safety profile, and optimal therapeutic strategies in patients with RA.

After exogenous SPD supplementation, it can enter the blood circulation through intestinal microbial metabolism or direct absorption [90, 91]. The biological half-life of SPD in the body is relatively short, and its clearance mainly depends on biotransformation and renal excretion. Biotransformation pathways include: (1) polyamine oxidase (PAO)-mediated oxidative deamination reaction; (2) SSAT1-mediated acetylation reaction, ultimately excreted through the kidneys [90]. In the study by Anna Niechcial et al. [52], mice reached peak serum concentration approximately 30 min after oral SPD administration. However, human metabolism differs from this. A randomized crossover clinical trial including 12 healthy volunteers showed that after 5 consecutive days of oral SPD 15 mg/day, neither plasma nor salivary pharmacokinetic analyses revealed significant elevations in SPD levels, contrasting sharply with murine experimental findings. Conversely, the plasma exposure of its metabolite SPM increased significantly (AUC_0-tlast↑, $p = 0.0282$). This species difference indicates that orally administered SPD undergoes more extensive first-pass metabolism, with partial conversion to SPM prior to entering systemic circulation where it exerts biological effects, while mice tend to directly absorb SPD [92]. In addition, SPD may directly enter the blood and be rapidly taken up by tissues to exert effects inside cells, rather than being reflected in plasma concentrations [93]. This metabolic difference suggests that when applying animal experimental data to humans, species-specific metabolic characteristics need to be carefully considered. It is worth noting that SPD and SPM in the body are not simply in a precursor-product relationship but rather work synergistically in the PA metabolic network. Therefore, the in vivo process of oral SPD may involve multifactorial regulation such as first-pass metabolism and tissue-selective uptake, and its plasma exposure is insufficient to fully reflect the actual systemic exposure and biological activity. This finding provides important pharmacokinetic evidence for subsequent exploration of SPD transformation and metabolic mechanisms.

A randomized controlled trial demonstrated that 100 healthy participants were randomly assigned to receive SPD supplementation (derived from wheat germ extract, 0.9 mg daily) or placebo for 12 months. During the observation period, SPD was well-tolerated and exhibited potential anti-inflammatory properties, with no SPD-related serious safety concerns or renal injury identified [94]. In another 3-month clinical trial, daily supplementation with 1.2 mg SPD was safe and well-tolerated in the elderly population, with no significant clinical adverse events observed [95]. However, these two trials had certain limitations, including low dosages, short study duration, and enrollment of exclusively healthy participants. Furthermore, a clinical study employing a higher dosage regimen found that supplementation with 40 mg/day of high-purity spermidine (hpSPD) for 28 consecutive days was safe and well-tolerated in healthy elderly men. In this study, compared with the placebo control group, no significant effects of hpSPD on clinical chemistry, hematology, high-sensitivity C-reactive protein (hsCRP), lipid profiles, body weight, or blood pressure were observed in the treatment group. This study represents the first assessment of hpSPD supplementation safety in humans and provided important evidence for future investigations on the potential health impacts of SPD

supplementation [96]. It is important to note that although current clinical studies have established the safety profile of SPD in healthy individuals, investigations involving RA patients are still in the preclinical phase. The safety, tolerability, and therapeutic effectiveness of SPD in this specific population remain to be validated through rigorous clinical trials.

Regarding routes of administration, SPD can be delivered not only orally but also via local intra-articular application. Studies by Pape Elise et al. [97] and Songbai Zhang et al. [98] provide methodological frameworks for local SPD delivery. In the study by Pape Elise et al., rapamycin-loaded poly (lactic-co-glycolic acid) nanoparticles (Rapamycin-PLGA NPs) were fabricated and their in vitro cytotoxicity and inflammatory effects on human chondrocytes and FLS were systematically evaluated, establishing safe dosage parameters and formulation rationale for subsequent intra-articular injection therapy in osteoarthritis (OA). The Alg-PBA/Spd viscoelastic hydrogel developed by Songbai Zhang et al. represents an intelligent inflammation-responsive delivery system. This system exhibits inflammatory microenvironment responsiveness and can autonomously modulate drug release kinetics based on local inflammation levels, achieving on-demand release through intelligent local delivery. This inflammation-responsive design not only enhances therapeutic efficiency but also mitigates toxicity risks associated with sustained high-concentration exposure. Therefore, similar local administration strategies may achieve an optimized balance between high intra-articular drug exposure and minimal systemic toxicity.

A recent study reported a novel discovery in a continuous cohort spanning the entire disease trajectory of RA, revealing that RA patients had already exhibited downregulation of peripheral blood autophagy-related genes ATG7 and LAMP1 prior to diagnosis (during the arthralgia/undifferentiated arthritis stage), accompanied by expansion of T/B cell senescence phenotypes [99]. This finding suggests that autophagy dysfunction and immune cell senescence may emerge at early stages of RA pathogenesis. SPD has been previously demonstrated to promote hypusination modification of eIF5A, thereby enhancing translation of the master autophagy regulator (TFEB), which activates autophagy and restores senescent T cell function [100]. Therefore, RA patients may benefit from early SPD supplementation to activate autophagy, potentially blocking inflammatory progression during the arthralgia/undifferentiated arthritis stage. Considering these multiple potential mechanisms, SPD holds promise as an adjunctive or combination therapy with csDMARDs, biologics, or JAK inhibitors. By attenuating or blocking autoimmune inflammatory responses, this approach could achieve dual therapeutic objectives: primary prevention of RA and dose-reduction maintenance therapy following disease remission, thereby providing a novel strategy for early intervention and precision treatment of RA.

Although existing studies demonstrate that SPD exhibits a favorable safety profile, its potential adverse effects and contraindications warrant careful attention and continued investigation. Evidence suggests that SPD concentrations exceeding cellular binding capacity result in free SPD accumulation, which directly oxidizes Fe^{2+} to generate superoxide anions (O_2^-), thereby triggering oxidative stress and iron homeostasis disruption that ultimately lead to cytotoxicity [101]. Additionally, elevated SPD concentrations in the tumor microenvironment are closely associated with immune evasion, tumor progression, and therapeutic resistance, indicating that targeting SPD metabolism rather than supplementation may represent a safer approach in cancer patients or high-risk populations [102]. Available clinical evidence indicates that SPD demonstrates good tolerability in healthy populations without observed adverse reactions; however, animal studies have confirmed that high-dose SPD administration induces electrolyte disturbances, elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels, weight loss, and altered organ weights [103]. These preclinical findings underscore the necessity of closely monitoring electrolytes, hepatic and renal function, and body weight in future high-dose SPD clinical trials. Notably, clinical data for patients with RA, hepatic or renal impairment, pregnancy or lactation remain limited, and the safety, tolerability, and efficacy in these special populations require validation in clinical trials. SPD should be considered relatively contraindicated in pregnant and lactating women. Therefore, clinical application of SPD should be guided by individualized risk–benefit assessment, with tailored dosing regimens developed for distinct patient populations.

Based on the limitations of existing research, we propose designing a 12-month randomized, double-blind, placebo-controlled trial to systematically evaluate the safety and efficacy of varying doses of SPD supplementation in RA patients across different disease stages. Regarding the dosing strategy, SPD groups with different dose levels should be established, and at the same time, experimental groups in combination with csDMARDs, biologics, and JAK inhibitors should also be set up to evaluate the effectiveness, safety, drug interactions, and optimal therapeutic regimens for these combination regimens. Regarding assessment parameters, during the study period, serial laboratory assessments should be performed at predefined time points (serum electrolytes, hepatic and renal function parameters (ALT, AST, creatinine, etc.), complete blood count (CBC), and inflammatory biomarkers), and the 28-joint Disease Activity Score (DAS28) will be employed to assess disease activity. In addition, body weight and blood pressure will also be monitored at each follow-up visit. More importantly, this trial will systematically evaluate the pharmacokinetic characteristics of SPD in RA patients, including absorption, distribution, metabolism, and excretion, clarifying the correlation between plasma drug concentration and clinical efficacy and adverse reactions. It should be particularly pointed out that, given the complexity of clinical trial methodology and the need to formulate rigorous protocols that comply with Good Clinical Practice (GCP), the framework presented in this paper represents only a preliminary conceptual framework and still requires thorough validation and refinement by multidisciplinary expert teams before actual implementation.

6 | Summary and Outlook

Collectively, this study provides critical innovative insights into RA therapeutics. First, we systematically elucidate for the first time the mechanistic roles of SPD across four core pathological processes in RA, thereby transcending the constraints of previous literature that focused solely on single pathological

events and isolated signaling pathways. This systematic framework offers novel theoretical foundations for understanding the multi-target therapeutic potential of SPD. Second, we highlight the unique advantage of SPD in achieving bidirectional regulation of "inflammation relief–bone repair", a characteristic infrequently observed among current anti-RA therapeutics. csDMARDs mainly focus on immune regulation, biologics target specific immune targets, and JAK inhibitors have broad-spectrum anti-inflammatory effects, but these drugs still have limitations in simultaneously balancing anti-inflammation and promoting bone repair. By contrast, SPD can not only effectively inhibit inflammatory cascade reactions but also promote osteoblast function and inhibit excessive osteoclast activation, achieving the dual goals of disease modification and structural protection. Based on the above mechanism characteristics, SPD shows great potential as an adjuvant and combination therapy for existing anti-RA treatment regimens. In addition, as a natural product-derived compound, SPD has significant advantages in pharmacoeconomics compared to costly biologics and novel small-molecule drugs and holds promise for reducing the economic burden of long-term treatment for patients.

Nevertheless, current research is mainly based on in vitro cell experiments and animal models, lacking clinical trial data in patients with RA. Regarding the potential adverse reactions of SPD supplementation, although existing studies show overall good safety, there are still several preliminary observation signs that need attention. In animal experiments, high-dose SPD administration showed electrolyte disturbances, elevated ALT/AST, weight loss, and organ weight changes. In vitro investigations reveal that SPD exhibits cytotoxicity at high concentrations; while this phenomenon has not been observed within the therapeutic concentration range, vigilance is still needed for the potential risks of long-term large-dose use. Therefore, implementation of comprehensive pharmacovigilance systems is imperative for advancing clinical translation of SPD. With the progressive development of translational medicine research and the systematic development of multi-center clinical trials, SPD holds promise as an important adjunctive therapeutic option for RA treatment. Especially when used as an adjuvant or combination therapy for existing first-line and second-line treatment regimens, SPD may significantly enhance disease remission rates, ameliorate osteoarticular structural damage, reduce treatment-related adverse events, and ultimately achieve the clinical goal of improving patients' long-term outcomes and quality of life, thereby paving novel avenues for precision and individualized RA therapeutics.

Author Contributions

Yi Chen: Writing – original draft, Methodology, Investigation, Data curation. Yi-Feng Zhou: Writing – original draft, Methodology, Investigation. Zhen-Yi Long: Writing – original draft, Investigation. Ya-Meng Peng: Methodology, Investigation. Si-Xian Wu: Data curation. Fang Peng: Supervision, Methodology. Ming-Hao Yuan: Methodology. Yi-Zhao Zhou: Writing – original draft. Lei Wang: Writing – review and editing. Hao Yuan: Writing – review and editing, Investigation, Funding acquisition.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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EDITORIAL

Strengthening Rheumatology Services in Low-Income Countries: Lessons From Tajikistan's COPCORD Experience

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Rheumatic diseases (RDs) encompass more than 100 conditions, ranging from osteoarthritis to systemic disorders; they remain a neglected burden in low-income countries, with shortages of specialists and fragmented systems undermining early diagnosis and disability prevention. Tajikistan, with a population exceeding 10 million but only 31 rheumatologists, exemplifies this challenge. The country's experience over the past 3 years demonstrates both the scale of the problem and the potential for modest, well-targeted interventions to catalyze systemic change [1].

1 | The Burden of Rheumatic Diseases in Tajikistan

In Tajikistan, as in many low-income settings, these conditions are often underdiagnosed, misclassified, or recorded only when disability compensation is sought. Family doctors identify most cases, but their limited training in rheumatology leads to frequent misdiagnosis [2].

Official statistics from the Ministry of Health and Social Protection of the Population (MoHSPP) show that between 2020 and 2022, the number of registered RD cases fluctuated between 7600 and 9600 annually. Rheumatoid arthritis, osteoarthritis, and gout were consistently the most prevalent conditions, while systemic lupus erythematosus and ankylosing spondylarthritis were leading causes of disability. These numbers capture only part of the burden; many patients rely on self-medication until disability forces care [3].

2 | The COPCORD Initiative: A Catalyst for Change

In 2022, the Asia-Pacific League of Associations for Rheumatology (APLAR) awarded a COPCORD (Community-Oriented Program for Control of Rheumatic Diseases) grant to Tajikistan [4]. The grant supported a pilot survey at Primary Health Center (PHC) in Dushanbe. Conducted early in 2023, the survey followed the COPCORD framework, with trained 38 nurses conducting door-to-door interviews and 11 rheumatologists providing diagnostic confirmation.

Among 1190 volunteered participants, 327 reported musculoskeletal complaints. Osteoarthritis was the leading condition (46.8%), followed by rheumatoid arthritis (17.7%) and post-traumatic complaints (8.9%). None had received disability support, underscoring the gap between burden and protection.

Beyond its immediate findings, the COPCORD survey revealed systemic weaknesses: poor healthcare-seeking behavior due to economic constraints, lack of awareness among family doctors, and absence of clinical guidelines for common rheumatic conditions. These insights were reported on the official event and reached policymakers, triggering broader action.

3 | From Pilot to National Policy

In October 2023, the MoHSPP issued Order #317, mandating all PHCs to record rheumatologic indicators. This directive expanded the COPCORD framework from a single-center pilot to a nationwide monitoring system. By the end of 2023, 85 health centers had reported data, registering 12 143 patients with rheumatic diseases. Of these, 11.3% had confirmed disability.

This represents the first comprehensive national dataset on rheumatic diseases in Tajikistan. It also demonstrates how a modest grant, when strategically implemented, and reported on a higher level can catalyze systemic reform. As it is presented in Figure 1,

the COPCORD initiative not only provided epidemiological data but also stimulated the development of updated clinical guidelines, quarterly meetings of the Tajikistan Rheumatologist Association, and training courses for family doctors.

4 | Challenges in Sustaining Reform

Despite notable achievements, sustaining COPCORD-driven reforms in Tajikistan remains a complex task. The establishment of a national registry across 84 PHCs is a milestone, yet its long-term effectiveness depends on continuous monitoring, mentoring, and high-level communication. Progress in shifting policymakers' attitudes is encouraging, but without dedicated personnel and institutional support, momentum risks fading. The small group of rheumatologists is balancing clinical duties with advocacy, training, and collaboration with family doctors, while also engaging younger researchers to modernize the registry through digital tools and data protection standards.

5 | Policy and Practice Recommendations

Tajikistan's COPCORD experience highlights several strategies that can guide both national sustainability and replication in other low-income countries. First, capacity-building must extend beyond rheumatologists: short training modules for general practitioners and mentorship networks can improve early detection. Second, sustainability of the registry requires digital integration, local ownership, and diversified funding, ensuring that data collection remains consistent and valuable. Finally, replication in other countries should begin modestly, embedding simple indicators into primary care and leveraging international partnerships for technical support. These steps demonstrate that even small investments, when strategically implemented, can catalyze systemic reform and improve patient outcomes. The trajectory from evidence to policy impact is clear, but maintaining reform will require resilience, investment, and integration of rheumatology into primary care to prevent regression.

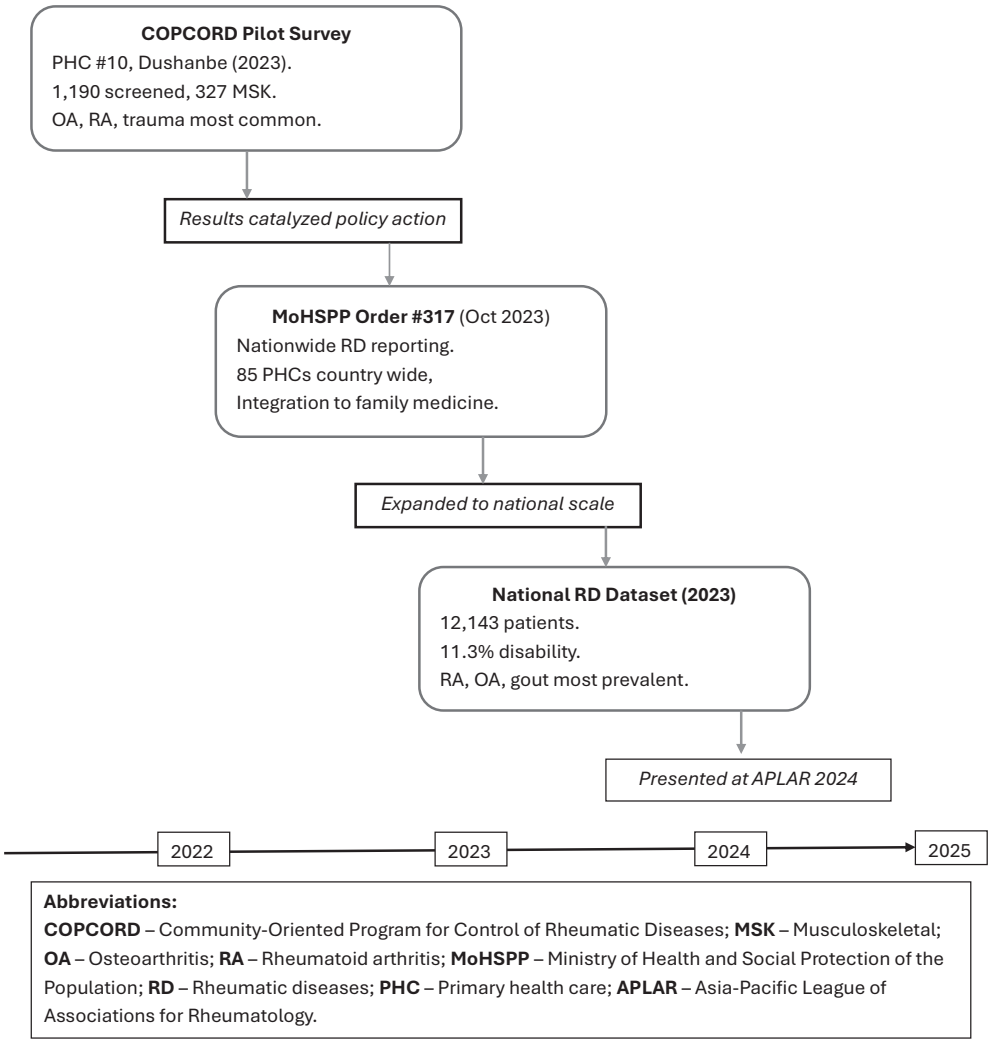

FIGURE 1 | Flow from COPCORD pilot survey to national policy and dataset in Tajikistan, 2022–2024. The pilot survey at PHC#10 in Dushanbe identified musculoskeletal conditions, which catalyzed national policy action (MoHSPP Order #317, October 2023). By the end of 2023, 85 PHC institutions reported data on 12 143 patients with rheumatic diseases, including 11.3% with disability.

6 | A Call for Global Support

In low-income countries, where patients may remain invisible until disability strikes, the need for early detection and prevention is urgent. Tajikistan's COPCORD experience shows that progress is possible. What is needed now is sustained international support, such as APLAR Academy provides through training, research collaboration, and funding, to ensure that these gains are consolidated and expanded. The trajectory from evidence to policy impact is clear, but maintaining reform will require resilience, investment, and integration of rheumatology into primary care to prevent regression.

7 | Conclusion

This editorial documents how a pilot COPCORD survey in Dushanbe catalyzed national reform, leading to the first comprehensive dataset on rheumatic diseases in Tajikistan. It closes the COPCORD grant cycle by demonstrating tangible outcomes: improved awareness, policy action, and systemic change. This experience illustrates the importance of sustained collaboration to ensure rheumatology services in low-income countries are no longer invisible.

Author Contributions

Zumrad Khamroeva: principal Investigator, COPCORD Grant awardee, and lead author. Prepared all reports and drafted this publication. **Suraiyo Shukurova:** professor and Chief Rheumatologist of Tajikistan, ensured that the COPCORD study results were widely disseminated at decision-making levels, enabling nationwide joint syndrome enquiry and supporting the development of the national rheumatology database. **Firuzajon Zoidova:** co-researcher, collected data from primary healthcare centers across the country, standardized the information for analysis, and created the dataset repository.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Risk of Cancer in Patients With Primary Sjögren's Disease and Their Relatives

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ABSTRACT

Objectives: Familial clustering and HLA haplotype association studies suggest that genetic factors disrupting the regulation of the immune system may predispose to risk of both neoplasms and autoimmune diseases, potentially leading to an increased frequency of cancer development in patients with primary Sjögren's disease (SjD), as well as their relatives. In this study, we aimed to assess the risk of cancer in patients with primary SjD and their close relatives.

Methods: Primary SjD patients who were actively followed-up in the rheumatology outpatient clinic at Gazi University Hospital and who met the 2016 ACR-EULAR classification criteria for primary SjD were included in the study. Data on cancer history in patients and their relatives were collected through direct face-to-face interviews and telephone surveys with the patients. The risk of developing cancer was calculated by comparing it with the general population of Turkey obtained from the Global Cancer Observatory of the World Health Organization International Agency for Research on Cancer (GLOBOCAN).

Results: A total of 323 primary SjD patients (F/M: 313/10, mean age: 56 ± 11) and their 1750 close relatives (parents, siblings, and children) were studied. Among SjD patients, 29 (9%) had a history of malignancy. Of these, 19 (5.9%) were solid organ and 10 (3.1%) were hematological malignancies. Breast cancer was the most common solid tumor. The median follow-up was 3.6 years, and the calculated standardized incidence ratio (SIR) for all cancers was 3.3 (95% CI: 2.2–4.7, $p < 0.001$). Leukemia or lymphoma cases had an SIR of 22.5 (95% CI: 10.8–41.4, $p < 0.001$). Among 313 women, seven cases of breast cancer had an SIR of 3.8 (95% CI: 1.5–7.9, $p < 0.001$). Risk of malignancy in patients with SjD did not differ based on age, gender, smoking history, Schirmer test result, laboratory parameters including anti-SSA, anti-SSB, ANA, complement levels, ESSDAI status, or Focus score, but it was higher in the presence of a cancer among close relatives. A total of 128 (43.3%) patients with SjD had at least one close relative with cancer (176 cancer cases in total), giving an SIR of 3.5 (95% CI: 3.0–4.1, $p < 0.001$). The average age of close relatives with cancer was 58 ± 10 years; 56% were male, and 7.4% were active smokers.

Conclusion: Our results suggest that not only patients with primary SjD but also their close relatives have an increased risk of developing cancer compared with the general population.

1 | Introduction

Sjögren's disease (SjD) is a chronic, systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands [1]. Sjögren's disease may occur as a primary condition or in association with other systemic autoimmune diseases [2]. Although the salivary and lacrimal glands are the primary targets of SjD, in at least one-third of patients, several different organs and

systems may be affected during the course of the disease, leading to various systemic clinical manifestations, serological abnormalities, and complications. The clinical presentation can vary significantly, ranging from classic sicca symptoms, like dry eyes and dry mouth, to constitutional symptoms (e.g., fatigue, weakness, and joint pain) and systemic symptoms (e.g., neuropathy and vasculitis) [1]. One of the well-known complications of SjD is non-Hodgkin's lymphoma, which occurs in approximately 5% of patients and significantly worsens the disease prognosis [3]. Factors such as, gender, ethnicity, dysfunctional exocrine glands, and immune dysregulation play a role in the development of malignancy [4]. Studies conducted to date have investigated the increased cancer risk in individuals with autoimmune diseases. It has been shown that patients diagnosed with SjD have an increased risk for both solid and hematological malignancies compared to the general population, with significant heterogeneity except for Hodgkin lymphoma andleukemia. Although the overall risk for solid tumors is not significant, when looking at site-specific cancers, an increased risk has been reported for oral, laryngeal, thyroid, skin (non-melanoma), liver, lung, prostate, and kidney cancers [5].

The tendency of autoimmune diseases to cluster in families is well known. The familial clustering tendency of SjD suggests that factors such as shared genes and common environmental influences play a role in the pathogenesis of the disease. Efforts to define the pathogenesis of SjD have focused on genetic factors, and susceptibility regions for SjD have been identified in various studies [6]. However, it is still unknown whether a personal history of autoimmune disease, which is associated with increased cancer incidence, shares familial susceptibility. The contribution of shared environmental or genetic factors to familial clustering has not been determined [5]. However, more recent population-based studies have begun to explore familial cancer susceptibility in the context of autoimmunity. In a nationwide Swedish cohort study using multigeneration and cancer registry data, Ji et al. demonstrated an increased risk of gastric cancer among individuals with siblings affected by various autoimmune diseases, supporting the concept of shared genetic susceptibility beyond individual disease status [7].

In a more recent and population-based study, Ekström et al. evaluated the risk of malignant lymphoma in RA patients and their first-degree relatives using Swedish registry data. While RA patients exhibited a markedly increased risk of lymphoma, their first-degree relatives did not show a significant increase in overall lymphoma risk. However, a threefold increased risk of Hodgkin lymphoma was found in children (aged 0–14) of RA patients [8]. In the present study, we aimed to investigate the risk of cancer in patients with primary Sjögren's disease and their family members.

2 | Materials and Methods

2.1 | Study Design and Subjects

Patients followed-up in the Gazi University Hospital Rheumatology outpatient clinic with a diagnosis of SjD were screened. Those whose records, including history, physical examination, and laboratory analysis were accessible, met the 2016 ACR-EULAR classification criteria, and gave informed consent to participate were included in the study. The study cohort consisted exclusively of patients with primary Sjögren's disease. Three hundred twenty-three consecutive patients were studied. The study was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment, and the consent process included permission to collect patient-reported information regarding the health and cancer history of biological family members. Patients were contacted through face-to-face interviews and via the phone numbers registered in the hospital's operating system when needed.

Patients whose health records were inaccessible or contained insufficient data in Gazi University Hospital's database, those under the age of 18, and those who did not sign the informed consent form or did not agree to participate in the study were excluded from the study.

The demographic characteristics of the patients were investigated. Data on smoking status, duration of smoking (pack-years), alcohol consumption, and the number of glasses consumed per week, if applicable, were obtained from the patients themselves.

During interviews with patients diagnosed with Sjögren's disease, data were collected on patient comorbidities, history of malignancies, number of children (including birth dates and sex), number of siblings (including birth dates and sex), history of connective tissue diseases among relatives (and specific diagnoses, if present), and history of malignancies among relatives. First-degree relatives were defined as biologic parents and children only and were considered the primary group for the assessment of familial cancer risk. Close relatives were defined as biologic parents, children, and siblings; analyses including siblings were performed to evaluate broader familial aggregation.

The case registry of the Gazi University Hospital Automation System included records on the type of SjD, the date of diagnosis, the date of the last follow-up at our hospital, medical treatments applied for the disease, the pathological diagnosis of patients with a history of malignancy, the date malignancy diagnosed, and the treatments applied for the malignancy.

History of malignancies in close relatives was obtained from the SjD patients. The following information was obtained regarding their relatives: birth dates, gender, occupation, place of residence, education level, date of death if deceased, smoking status, duration of smoking (pack-years), alcohol consumption and the number of glasses consumed per week if applicable, presence of comorbidities, presence of connective tissue diseases (diagnosis and diagnosis date, if present), and the presence of malignancy (pathological diagnosis, date of malignancy, and malignancy treatment, if present). Family history of cancer was obtained from the patients themselves through structured face-to-face interviews and/or telephone surveys. Cancer diagnoses among relatives were not independently verified using national cancer registry systems or medical records.

The follow-up duration of patients with SjD was specified in years as the time elapsed between the initial diagnosis date and

the date of the last visit. The follow-up duration for malignancy in patients was specified in months as the time elapsed between the date of SjD diagnosis and the date of malignancy diagnosis.

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), designed to measure disease activity in patients with primary SjD, was used [9]. A disease activity index of ≥ 1 was considered indicative of active disease. Schirmer test result was considered positive when it was ≤ 5 mm/5 min. ANA antibodies were considered positive at a titer of $> 1/160$.

2.2 | Statistical Evaluation

In the analysis of the data obtained from the descriptive study, the SPSS v.23 program was used. Whether the numerical data followed a normal distribution was determined by examining the histogram graph, skewness, and kurtosis values and by conducting the Shapiro–Wilk test (p-value < 0.01 was found). Since the data did not show a normal distribution, nonparametric tests were applied. The nonparametric Mann–Whitney U test was used since the patients' ages did not show a normal distribution. Descriptive statistical methods were used to evaluate the research data, calculating values such as count, percentage, minimum, maximum, mean, standard deviation, first quartile, third quartile, and median. The chi-square test (Pearson and Fisher's exact test) was used to compare categorical variables. In cases where groups could not be combined in Rxc tables, Fisher's exact test developed by Mehta and Patel was used [10]. The Mann–Whitney U test was used to compare continuous variables. Analyses were conducted with a 95% confidence interval, and a p-value < 0.05 was considered statistically significant.

The standardized incidence ratio (SIR) is the ratio of observed cancer cases to expected cancer cases. In observational studies, it is used to determine the incidence rate of a disease in a cohort compared to a reference population, such as the general population of a specific region. The risk of developing all cancers and organ-specific cancers in patients with SjD and their first-degree relatives was calculated by comparing it with the general population of Turkey. The cancer incidence data for the general population of Turkey were obtained from the International Agency for Research on Cancer's Global Cancer Observatory (GLOBOCAN). Furthermore, standardized incidence ratios were calculated using age- and sex-specific population incidence rates. Expected counts were obtained by applying these rates to the corresponding age and sex strata of the study population. The most recent available GLOBOCAN data were used as reference rates. The 95% confidence intervals for the SIR were calculated according to the Poisson distribution.

3 | Results

A total of 323 patients diagnosed with SjD were included in the study. 97% ($n = 313$) of 323 patients were female and 3.0% ($n = 10$) were male. The age of the patients did not show a normal distribution, and the mean age + standard deviation (mean ± SD) was 56 ± 11 (minimum: 25; maximum: 80; 1st quartile = 49.00; median = 57.00; 3rd quartile = 64.00) years. Among patients with SjD, 45.8% ($n = 148$) had hypertension (HT), 27.6% ($n = 89$) had hypothyroidism, 17% ($n = 55$) had coronary artery disease, 13.9% ($n = 45$) had diabetes mellitus, 9% ($n = 29$) had malignancy, 3.1% ($n = 10$) had chronic kidney disease, and 2.2% had interstitial lung disease. While ANA positivity was found in 69.0% of patients diagnosed with SjD, anti-SSA positivity was present in 58%, and anti-SSB positivity was found in 28.3%.

Among the 29 (9%) SjD patients diagnosed with a malignancy, 19 (5.9%) had solid organ, and 10 (3.1%) had hematological malignancies. The most commonly observed solid organ cancer was breast cancer (2.2%) (Table 1). In 5 cases (17.2%), SjD and cancer were diagnosed simultaneously (within 1 year). In 9 cases (31%), SjD was diagnosed more than 1 year before the diagnosis of malignancy, and in 15 cases (51.7%), SjD was diagnosed more than 1 year after the diagnosis of malignancy.

The median follow-up duration of the cohort was relatively short, at 3.6 years (IQR: 1.77–4.87). The SIR for all 29 cancers was calculated to be 3.3 (95% CI: 2.2–4.7, $p < 0.001$). For the 10 cases of hematological malignancies (leukemia or lymphoma), the SIR was found to be 22.5 (95% CI: 10.8–41.4, $p < 0.001$). Among 313 women, seven cases of breast cancer were observed, with an SIR of 3.8 (95% CI: 1.5–7.9, $p < 0.001$). For three thyroid cases, the SIR was determined to be 5.5 (95% CI: 1.1–16.2, $p < 0.01$). No statistically significant increased risk was observed for other types of cancer.

TABLE 1 | Distribution of cancer types among patients with primary Sjögren's disease and their close relatives.

Cancer type	SjD patients ($n = 323$) n (%)	Close relatives ($n = 1750$) n (%)
Lung	2 (0.6)	41 (2.3)
Breast	7 (2.2)	25 (1.4)
Colon	—	20 (1.1)
Gastric	—	16 (0.9)
Prostate	—	12 (0.6)
Leukemia	5 (1.5)	11 (0.6)
Lymphoma	5 (1.5)	1 (0.06)
Brain	—	8 (0.4)
Endometrial	—	7 (0.4)
Laryngeal	—	7 (0.4)
Liver	—	5 (0.3)
Kidney	—	5 (0.3)
Thyroid	3 (0.9)	4 (0.2)
Pancreas	—	4 (0.2)
Skin (non-melanoma)	2 (0.6)	1 (0.06)
Other[a]	5 (1.5)	9 (0.5)
Total cancer cases	29[b] (9.0% of patients)	176[b] (10% of close relatives)

[a]"Other" includes rare malignancies such as rhabdomyosarcoma, testicular, tongue, adrenal, ovarian, osteosarcoma, and cholangiocarcinoma.
[b]Represents the total number of relatives with cancer**.

Cancer risk estimates were presented separately for first-degree relatives and close relatives. First-degree relatives constituted the main analytic group, whereas analyses including siblings were additionally performed to examine broader patterns of familial aggregation. Among the 295 SjD patients who had complete family history, 128 patients (43.3%) had a history of cancer in at least one of the parents, children, or siblings. The distribution of the types of these cancers is shown in Table 1.

In 1750 close relatives for whom data were available, a total of 176 cancer cases were observed, and the SIR was calculated as 3.5 (95% CI: 3.0–4.1, $p < 0.001$). The three most common cancer types were lung cancer observed in 41 relatives with an SIR of 2.66 (95% CI: 1.9–3.6, $p < 0.001$), breast cancer observed in 25 relatives with an SIR of 4.6 (95% CI: 2.95–6.86, $p < 0.001$), and colon cancer observed in 20 relatives with an SIR of 3.7 (95% CI: 2.3–5.7, $p < 0.001$). The distribution of other cancers is shown in Table 2. When considered alongside the patient cohort, individuals with Sjögren's disease exhibited an approximately 4.6-fold higher standardized incidence ratio for hematological malignancies (95% CI: 1.67–12.62) compared with their close relatives.

Fifty-nine patients had at least one sibling with cancer, with a total of 69 cancer cases seen among siblings. Detailed distributions of cancer types among siblings are provided in Table S1.

Mean ± SD age of the close relatives with cancer was 58 ± 10 years (minimum: 27; maximum: 80; 1st quartile = 53; median = 57; 3rd quartile = 65). Of the relatives diagnosed with cancer, 56% were men and 7.4% were active smokers.

When comparing SjD patients with and without relatives with cancers, there was no significant difference in terms of Schirmer result, focus score, or laboratory parameters, including SSA, SSB, ANA, RF, complement levels, serum IgA, IgM, IgG levels, as well as ESSDAI status. However, there was a significant difference in the malignancy status of the close relatives based on whether the SjD patients themselves had a malignancy. The frequency of malignancy among SjD patients without a history of cancer in close relatives was 4.2%, compared to 15.0% among those with at least one close relative affected by malignancy. There were no significant differences in gender distribution, smoking status, or alcohol consumption between patients with and without a close relative cancer history. The proportion of female patients was similarly high in both groups ($p = 0.308$). Likewise, smoking status ($p = 0.799$) and alcohol consumption ($p = 0.106$) did not differ significantly between the groups.

A total of 97 cancer cases have been observed in the parents of patients with SjD, with an SIR calculated as 5.6 (%95 CI: 4.5–6.8, $p < 0.001$). The three most common cancer types were lung, colon, and breast; for 27 cases of lung cancer, the SIR was 4.75 (%95 CI: 3.1–6.9, $p < 0.001$); for 11 cases of colon cancer, the SIR was 6.4 (%95 CI: 3.2–11.5, $p < 0.001$); for nine cases of breast cancer, the SIR was 4.75 (%95 CI: 2.2–9, $p < 0.001$).

A total of 107 cancer cases were identified among the first-degree relatives (parents and offspring) of patients with SjD, with a calculated SIR of 4.46 (95% CI: 3.63–5.34, $p < 0.001$). The three most common cancer types were lung cancer observed in 27 relatives with an SIR of 3.97 (95% CI: 2.5–5.59, $p < 0.001$), gastric cancer observed in 13 relatives with an SIR of 14.13 (95% CI: 6.52–22.83, $p < 0.001$), colon cancer observed in 11 relatives with an SIR of 6.88 (95% CI: 3.13–11.25, $p < 0.001$), and breast cancer observed in 10 relatives with an SIR of 2.19 (95% CI: 0.88–3.73, $p < 0.001$). Detailed site-specific risk estimates for first-degree relatives are presented in Table S2.

TABLE 2 | Number of cases observed in close relatives, standardized incidence ratios (SIR), 95% confidence intervals, and P values by cancer type.

Cancer Type	Number of Cases	SIR	95% Confidence Interval	*P*-value
Lung	41	2.66	1.90–3.60	< 0.001
Breast	25	4.60	2.95–6.86	< 0.001
Colon	20	3.70	2.30–5.70	< 0.001
Gastric	16	4.30	2.50–7.10	< 0.001
Prostate	12	2.80	1.40–4.80	< 0.01
Brain	8	4.60	1.70–10.00	< 0.01
Laryngeal	7	7.80	3.10–16.00	< 0.001
Endometrial	7	5.50	2.20–11.30	< 0.001
ALL	6	4.90	1.80–10.70	< 0.01
Liver	5	4.10	1.30–9.60	< 0.05
Kidney	5	4.60	1.50–10.80	< 0.05

Note: 95% CI, 95% confidence interval; SIR, standardized incidence ratio.

4 | Discussion

In this study, we demonstrated that individuals with Sjögren's disease and their close relatives have an increased risk of malignancy compared with the general population. The elevated risk observed among patients was largely attributable to hematological malignancies, which is consistent with the well-established association between Sjögren's disease and lymphoproliferative disorders. Notably, the detection of an increased cancer risk among close relatives suggests that, in addition to disease-specific mechanisms, shared genetic and environmental factors may also contribute to familial cancer clustering. Therefore, in our study, cancer risk was assessed separately for first-degree relatives and for a broader group of close relatives; this approach was adopted in accordance with methodologies used in population-based familial cancer studies [11].

Sjögren's disease has been reported to be significantly associated with an increased risk of all malignancies, including NHL, Hodgkin lymphoma, multiple myeloma, leukemia, and solid cancers, such as lung cancer, thyroid cancer, non-melanoma skin cancer, kidney cancer, liver cancer, and prostate cancer [12–15]. The increased risk of cancer in these patients can be partially explained by the involvement of similar environmental factors (such as viruses, smoking, and gender) in the etiology of both disease groups. Additionally, shared pathogenic

mechanisms between these diseases may also contribute to the elevated cancer risk.

In patients with Sjögren's disease, the risk of lymphoma increases with systemic involvement of the disease. Additionally, this association is correlated with lymphoid structures containing B-cell aggregates in salivary gland biopsies. Moreover, chronic B-lymphocyte activation not only elevates the salivary gland focus score but is also associated with an increased risk of lymphoma [16–18]. These markers have been consistently validated in large-scale studies, including those by Theander and colleagues and in the Nocturne cohort [14, 17].

However, in our study, no significant association was observed between these parameters and the development of overall malignancy. This finding may be explained by several factors. First, our primary endpoint was overall malignancy, encompassing both hematological and solid tumors rather than lymphoma alone; therefore, biological markers that are specific to lymphoma may not be expected to predict the risk of solid tumors. In addition, the predictive value of these markers has mainly been demonstrated in large, multicenter cohorts with long-term follow-up, and the relatively limited sample size and follow-up duration in our study may have reduced the statistical power to detect such associations.

In a study conducted by Zhong et al., the relationship between primary SjD and cancer risk was explored, and SjD was reported to be significantly associated with an increased risk of all malignancies, including NHL, Hodgkin lymphoma, multiple myeloma, leukemia, and solid cancers such as lung cancer, thyroid cancer, non-melanoma skin cancer, kidney cancer, liver cancer, and prostate cancer [19]. In our study, the overall cancer risk was comparably elevated in both patients with Sjögren's syndrome and their first-degree relatives. However, this result points to a striking divergence when the malignancy profiles observed between relatives and patients are considered together. Whereas patients with SjD demonstrated a predominance of hematologic malignancies, particularly lymphoma and leukemia, their close biological relatives exhibited markedly elevated risks for a much broader spectrum of solid tumors such as gastric, colon, brain, and laryngeal cancers. This divergence suggests that while SjD pathology strongly predisposes affected individuals to lymphoproliferative malignancies, shared familial risk may extend more broadly to diverse solid tumors, implicating genetic or environmental susceptibility beyond disease-specific mechanisms. Importantly, while the malignancy spectrum partially overlapped between patients and their relatives, the magnitude of cancer risk was consistently highest in patients with Sjögren's syndrome, followed by lower levels in first-degree and close relatives. This risk gradient suggests that the excessive cancer burden in Sjögren's syndrome reflects a combination of disease-related factors and shared familial predisposition.

Studies investigating the relationship between familial autoimmunity and malignancy suggest that genetically determined dysregulation of the immune system may predispose individuals to both autoimmune diseases and lymphoid neoplasms. In particular, reported associations between chronic lymphocytic leukemia and autoimmune diseases have highlighted the role of shared HLA haplotypes and $CD5^+$ B cells [20, 21].

Similarly, studies reporting a higher prevalence of rheumatoid arthritis and other autoimmune diseases among first-degree relatives of patients with multiple myeloma indicate the presence of a shared genetic background underlying both autoimmunity and malignancy [22].

To our knowledge, there is no study investigating the incidence of cancer in first-degree or close relatives of SjD patients. Limited data are available in the form of case presentations regarding the association between SjD and family history of cancer [23]. In the literature, a distinct study by Mellemkjaer et al. investigated the risk of developing NHL in patients with NHL and their families, considering the development of autoimmune diseases and lymphoma. This study, which included 24 728 lymphoma patients and 55 632 controls, found that a family history of systemic autoimmune diseases was modestly and nonsignificantly associated with NHL OR(h) 1.31 [95% CI 0.85–2.03] [24]. Similarly, studies examining the association between maternal autoimmune diseases and childhood hematological malignancies have not demonstrated a significant increase in risk for Sjögren's disease [25].

In this context, the finding of a 3.5-fold increased risk for all cancer types among close biological relatives of patients with Sjögren's disease in our study is noteworthy. Marked increases in risk were observed particularly for laryngeal and endometrial cancers, as well as for hematological malignancies. These findings suggest that genetic and environmental factors associated with Sjögren's disease may increase cancer risk not only in affected patients but also in healthy individuals within the same family.

Our observation of a significantly elevated frequency of both hematologic and solid malignancies among close relatives of patients diagnosed with SjD holds profound implications for clinical practice and future scientific inquiry. These findings strongly advocate for the integration of comprehensive family cancer history into the clinical assessment of individuals with SjD and underscore the potential utility of implementing proactive screening strategies and enhanced surveillance protocols for their at-risk relatives. Such measures could facilitate earlier detection of malignancies, potentially leading to improved treatment outcomes and reduced morbidity within these families.

Our study has several limitations. Its single-center design and conduct in a tertiary care rheumatology clinic may limit the generalizability of the findings. Cancer history among family members was obtained through patient self-report and was not validated against national cancer registries, introducing a potential risk of recall bias. Nevertheless, the inclusion of only first-degree and close biological relatives is likely to enhance the accuracy of recall for serious diagnoses. Nevertheless, due to the family history reported by the patient, potential subtype misclassification may affect the accuracy of organ-specific risk estimates; therefore, region-specific SIR predictions should be interpreted with caution. Furthermore, site-specific SIRs based on small case counts (e.g., gastric cancer) should be interpreted with caution. The wide confidence intervals reflect imprecision and statistical uncertainty, and these findings require confirmation in larger cohorts. Another important limitation is the relatively short median follow-up duration of the cohort, which may have led to underestimation of cancer

incidence, particularly for malignancies with longer latency periods. Although patient and relative SIRs were not directly compared analytically, this underestimation could make the relative magnitude of familial risk appear larger when the two estimates are presented concurrently. In addition, the absence of an internal control group limits direct comparisons beyond population-based reference rates; however, the use of standardized incidence ratios based on national cancer statistics is a well-established approach in epidemiological studies. Finally, considering that cancer incidence rates may change over time, the use of a single reference period may have introduced some degree of uncertainty, particularly in analyses involving long follow-up durations. However, owing to the historical limitations of continuous and standardized national datasets on an annual basis for Turkey, the most recent and refined GLOBOCAN data were adopted as a fixed reference to ensure methodological consistency. This approach was chosen to minimize potential systematic errors arising from historical variability in registry quality and to preserve internal comparability throughout the entire cohort.

In this study, patients under the age of 18 were excluded because pediatric Sjögren's disease represents a distinct clinical entity with different diagnostic challenges, disease phenotype, and follow-up considerations compared with adult-onset disease [26]. The apparent underrepresentation of individuals aged 18–25 years reflects the well-established epidemiology of Sjögren's disease, which predominantly affects middle-aged adults, with peak incidence reported between the fourth and sixth decades of life [27]. Consequently, the age distribution observed in our cohort is consistent with previously reported large epidemiological and registry-based studies of primary Sjögren's disease.

In conclusion, within a median follow-up period of 3.6 years, our study demonstrates an increased risk of both hematological and solid malignancies in patients with primary Sjögren's disease, with a similarly pronounced elevation in risk among their family members. This familial clustering points to the presence of shared pathogenic pathways linking autoimmunity and malignancy. Our findings underscore the importance of systematically obtaining a detailed family history of cancer during the clinical evaluation of patients with primary Sjögren's disease and highlight the potential benefit of targeted surveillance and screening strategies for at-risk relatives. Larger studies with longer follow-up are needed to further elucidate the biological mechanisms underlying this association.

Author Contributions

Tuba Uğur Tuzcu was responsible for the study design, patient recruitment, data collection, and manuscript writing. İbrahim Karaduman assisted in manuscript preparation and writing. Rıza Can Kardaş performed the statistical analysis. Hamit Küçük contributed to manuscript revision and critical editing. Mehmet Akif Öztürk contributed to interpretation of the results and manuscript review. Berna Göker conceived the study idea and supervised the study. All authors read and approved the final manuscript.

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The authors have nothing to report.

Ethics Statement

This study is approved by the local ethics committee (24.10.2022/786) and conducted according to 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 on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Types of cancer observed in siblings of patients diagnosed with primary Sjögren's disease. Table S2. Number of cancer cases observed among first-degree relatives of patients with primary Sjögren's disease, standardized incidence ratios (SIRs), 95% confidence intervals, and *P*-values by cancer type.

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ORIGINAL ARTICLE

Inflammatory Bowel Disease in Patients With Atopic Dermatitis and Allergic Rhinitis: A Nationwide Case–Control Study

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ABSTRACT

Introduction: Inflammatory bowel disease (IBD) has been associated with several allergic diseases, including atopic dermatitis, allergic rhinitis, and asthma. However, the correlations between these conditions vary—some are positively correlated, and some are negatively correlated. To address these discrepancies, this study explored the risk of IBD in patients with allergic diseases.

Methods: Data were collected from the Taiwan National Health Insurance Research Database, which contains data on approximately 99% of Taiwan's population. Patients with new-onset IBD and matched controls were enrolled. Data on comorbidities, demographics, and corticosteroid use were collected. Statistical analysis included conditional logistic regression analysis.

Results: In total, 300 patients with IBD and 2400 patients without IBD were enrolled. Atopic dermatitis (OR: 5.73, 95% CI: 1.69–19.48), allergic rhinitis (OR: 1.72, 95% CI: 1.06–2.79), chronic kidney disease (OR: 3.04, 95% CI: 1.15–8.04), and ischemic heart disease (OR: 1.97, 95% CI: 1.20–3.26) were associated with an increased risk of IBD. Among patients with atopic dermatitis or allergic rhinitis, the risk of IBD was higher for those aged < 65 years, men, or those not using corticosteroids.

Conclusion: This study highlights an associated risk of IBD in patients with atopic dermatitis and allergic rhinitis.

1 | Introduction

Inflammatory bowel disease (IBD) encompasses ulcerative colitis and Crohn's disease, both of which are characterized by symptoms such as diarrhea, abdominal pain, and bloody stool. Diagnosis can be confirmed through endoscopy with biopsy or radiographic imaging [1]. The incidence of IBD is higher in adolescents and adults than in older adults and children. Men and women are equally affected by IBD [2]. Incidence as high as 20.2 and 12 per 100 000 person-years has been reported in North America and Europe [3], respectively. In Asia, the incidence of IBD is low [4]. According to data from the Taiwan National Health Insurance Research Database, the incidence of Crohn's disease increased from 0.17 to 0.47 per 100 000 person-years between 2001 and 2015; the incidence of ulcerative colitis increased from 0.54 to 0.95 per 100 000 person-years between 2001 and 2015 [5]. IBD is primarily characterized by chronic inflammation of the intestinal mucosa. The etiology of IBD is

unknown. Genetic susceptibility, host immunity deregulation, intestinal microbiota dysbiosis, and environmental factors such as diet and stress contribute to a cycle of chronic inflammation in the intestine [6, 7]. Patients with IBD are at increased risk of asthma according to data from the Taiwan National Health Insurance Research Database [8]. Patients with atopic dermatitis are at increased risk of rheumatic arthritis and IBD [9]. According to a nationwide population-based study in Korea, patients with atopic dermatitis, allergic rhinitis, or asthma are at increased risk of Crohn's disease and ulcerative colitis [10]. However, a study found no association between atopic dermatitis and IBD [11]. Whether atopic dermatitis is associated with IBD remains unclear. The present study investigated the risk of IBD in patients with allergic diseases.

2 | Materials and Methods

2.1 | Data Source

This retrospective nested case–control study used data from the Taiwan National Health Insurance Research Database. Approximately 99% of Taiwan's approximately 23 million residents are enrolled in the National Health Insurance program [12]. The database consists of the health insurance claims data of outpatients, emergency department patients, and hospitalized individuals. One million participants from 1999 to 2013 were enrolled. Data were identified. The study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (No. CS15134).

2.2 | Study Group

This study enrolled patients with new-onset IBD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 555 and 556), defined as follows: 1. Patients were identified as having inflammatory bowel disease (IBD) if they had ≥3 outpatient visits or ≥1 hospital admission with a diagnosis of IBD and 2 patients received ≥4 prescriptions for IBD-related medications within 1 year during the study period (2002–2013). IBD medications were identified using Anatomical Therapeutic Chemical (ATC) codes, as detailed in Table S2. The Taiwan National Health Insurance Research Database has been used in other studies on IBD [13]. Patients without IBD from 1999 to 2013 were enrolled into the control cohort. The index date was the first date of receiving a diagnosis of IBD.

Initially, 302 patients with IBD were enrolled. These patients were matched by age and sex with patients without IBD at a ratio of 1:8. In total, 300 patients with IBD and 2400 patients without IBD were enrolled (Figure 1).

2.3 | Covariates

Data on baseline characteristics (age, sex, and comorbidities) were collected. Comorbidities were atopic dermatitis (*ICD-9-CM* code 691), allergic rhinitis (*ICD-9-CM* code 477), asthma (*ICD-9-CM* code 493), hypertension (*ICD-9-CM* codes 401 and 405), hyperlipidemia (*ICD-9-CM* codes 272.0 to 272.4), chronic liver disease (*ICD-9-CM* code 571), chronic kidney disease (*ICD-9-CM* code 585), diabetes (*ICD-9-CM* code 250), chronic obstructive pulmonary disease (*ICD-9-CM* codes 491, 492, and 496), autoimmune disease (*ICD-9-CM* codes 710, 714, and 720), ischemic heart disease (*ICD-9-CM* codes 410 to 414), stroke (*ICD-9-CM* codes 430 to 438), and gout (*ICD-9-CM* code 274). Comorbidities were included if they were identified within 2 years before the index date and were accompanied by records of ≥3 outpatient visits or hospitalization once. Use of oral or intravenous corticosteroids was defined as prescriptions for ≥30 days within 2 years before the index date. Corticosteroid exposure was identified using Anatomical Therapeutic Chemical (ATC) codes, as detailed in Table S1.

2.4 | Statistical Analysis

Categorical characteristics were compared using Chi-square or Fisher's exact tests. Continuous variables were compared using

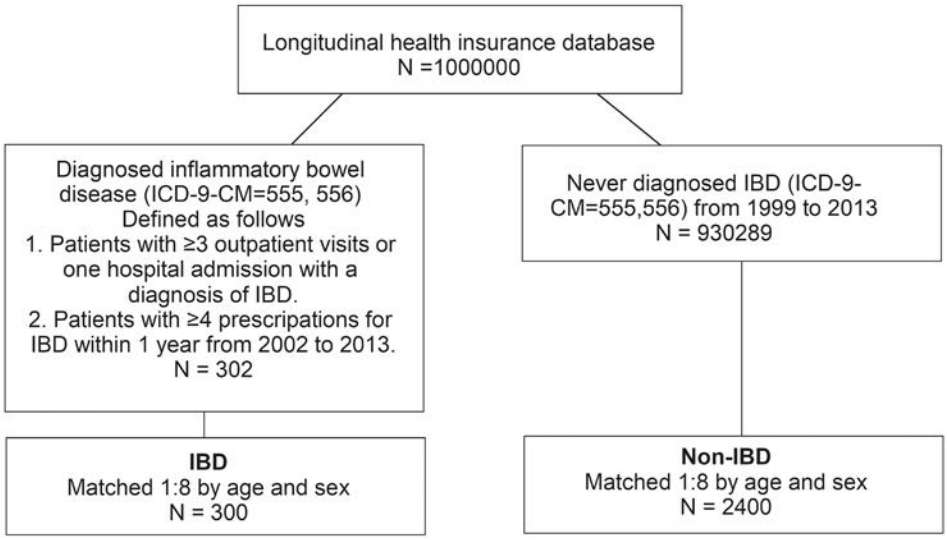

FIGURE 1 | Patient enrollment process.

Student's *t*-test. Conditional logistic regression was used to estimate the odds ratio for each comorbidity. Subgroup analyses by age, sex, and corticosteroid use were performed. Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was indicated by $p < 0.05$.

3 | Results

Patient demographic characteristics are presented in Table 1. A total of 300 patients with IBD were enrolled. Most patients were aged between 40 and 64 years. The mean age of patients was 48.6 years. Most patients (65.7%) were men. The incidence rates of chronic kidney disease, ischemic heart disease, chronic obstructive pulmonary disease, atopic dermatitis, and allergic rhinitis significantly differed between the groups.

After adjusting for comorbidities, atopic dermatitis (OR: 5.73, 95% CI: 1.69–19.48), allergic rhinitis (OR: 1.72, 95% CI: 1.06–2.79), chronic renal disease (OR: 3.04, 95% CI: 1.15–8.04), ischemic heart disease (OR: 1.97, 95% CI: 1.20–3.26), and corticosteroid use (OR: 3.13, 95% CI: 2.05–4.78) were associated with an increased risk of IBD (Table 2). Asthma, hypertension, hyperlipidemia, chronic liver disease, diabetes, chronic obstructive pulmonary disease, autoimmune disease, stroke, and gout were not significantly associated with IBD.

According to subgroup analysis, atopic dermatitis (OR: 5.40, 95% CI: 1.05–27.86) and allergic rhinitis (OR: 2.02, 95% CI: 1.15–3.55) were associated with an increased risk of IBD in patients aged < 65 years. Furthermore, atopic dermatitis (OR: 5.69, 95% CI: 1.2.-27.00) and allergic rhinitis (OR: 1.97, 95% CI: 1.12–3.49) were associated with a significantly increased risk of IBD in men. Atopic dermatitis (OR: 8.91, 95% CI: 2.08–38.08) and allergic rhinitis (OR: 1.89, 95% CI: 1.12–3.22) were associated with a significantly increased risk of IBD in patients not using corticosteroids (Table 3).

TABLE 1 | Patient demographic characteristics.

	IBD ($N = 300$)		Non-IBD ($N = 2400$)		
Factor	***n***	**%**	***n***	**%**	***p***
Age					1
< 40	103	34.3	824	34.3	
40–64	131	43.7	1048	43.7	
≥ 65	66	22.0	528	22.0	
Mean ± SD	48.6 ± 18.7		48.6 ± 18.7		1
Sex					1
Female	103	34.3	824	34.3	
Male	197	65.7	1576	65.7	
Hypertension	70	23.3	469	19.5	0.121
Hyperlipidemia	31	10.3	183	7.6	0.102
Chronic liver disease	21	7.0	116	4.8	0.107
Chronic kidney disease	7	2.3	16	0.7	0.010[a]
Diabetes	30	10.0	199	8.3	0.317
COPD	19	6.3	86	3.6	0.020
Autoimmune disease	6	2.0	25	1.0	0.147[a]
Ischemic heart disease	30	10.0	124	5.2	0.001
Stroke	8	2.7	96	4.0	0.258
Gout	17	5.7	102	4.3	0.260
Atopic dermatitis	6	2.0	7	0.3	0.002[a]
Allergic rhinitis	25	8.3	112	4.7	0.006
Asthma	10	3.3	58	2.4	0.339
Corticosteroids	43	14.3	116	4.8	< 0.001

Note: Chi-square or Fisher's exact tests were used for categorical variables, and Student's *t*-test was used for continuous variables.
Abbreviation: COPD, chronic obstructive pulmonary disease.
[a]Fisher's exact test.

4 | Discussion

IBD is a chronic inflammatory disease of the digestive system. In Taiwan, the crude incidence of IBD is relatively rare (approximately 1.5 per 100 000 person-years in 2015); however, the condition is gradually becoming more prevalent [5]. Between 2002 and 2013, 302 patients developed IBD. This result is consistent with the actual incidence in Taiwan [5]. Half of the patients in our study were aged 40 to 64 years. The average age of patients with IBD in our study was higher than that in a similar study conducted in Germany [14]. The male:female sex ratio in our study was 3:2; this ratio differed from that in a Western study [2].

The present study investigated associations between several allergic conditions and the risk of IBD. Atopic dermatitis was associated with an increased risk of IBD, which is consistent with the results of other studies [9, 15–18]. Allergic rhinitis was also associated with an increased risk of IBD, which is consistent with the results of other studies [16, 19]. The possible mechanism can be explained by T-cell-mediated chronic inflammation (T helper 17 cells, which secrete interleukin 17). These T helper 17 cells have been implicated in both IBD and atopic disease [20–23]. Specific single-nucleotide polymorphisms of atopic dermatitis were associated with several immune-mediated inflammatory diseases, including IBD [24, 25]. The hygiene hypothesis, originally associated with allergic diseases, has evolved into the microflora hypothesis [26–28]. The human microbiome has evolved in response to industrialization, which has disrupted our environment. Dysbiosis has been observed in patients with allergic diseases [29] or IBD [30].

Several studies have observed an association between asthma and the increased incidence of IBD [31–34]. Our study found no such association, which is consistent with the finding of

TABLE 2 | Conditional logistic regression for the risk of IBD.

Factor	Crude OR (95% CI)	*p*	Adjusted OR[a] (95% CI)	*p*
Atopic dermatitis	7.49 (2.40–23.38)	< 0.001	5.73 (1.69–19.48)	0.005
Allergic rhinitis	1.86 (1.18–2.92)	< 0.001	1.72 (1.06–2.79)	0.029
Asthma	1.39 (0.70–2.77)	0.341	0.67 (0.31–1.44)	0.304
Hypertension	1.38 (0.98–1.95)	0.066	1.03 (0.70–1.53)	0.876
Hyperlipidemia	1.42 (0.94–2.14)	0.096	1.15 (0.72–1.82)	0.562
Chronic liver disease	1.48 (0.92–2.40)	0.109	1.41 (0.85–2.33)	0.180
Chronic kidney disease	3.67 (1.47–9.16)	0.005	3.04 (1.15–8.04)	0.026
Diabetes	1.27 (0.82–1.95)	0.287	1.06 (0.66–1.69)	0.810
COPD	1.96 (1.13–3.39)	0.016	1.21 (0.65–2.23)	0.545
Autoimmune disease	1.96 (0.79–4.87)	0.147	1.19 (0.44–3.22)	0.731
Ischemic heart disease	2.25 (1.43–3.55)	< 0.001	1.97 (1.20–3.26)	0.008
Stroke	0.64 (0.30–1.36)	0.245	0.54 (0.25–1.18)	0.123
Gout	1.37 (0.80–2.34)	0.255	1.11 (0.63–1.96)	0.720
Corticosteroids	3.54 (2.40–5.24)	< 0.001	3.13 (2.05–4.78)	< 0.001

Abbreviation: COPD, chronic obstructive pulmonary disease.
[a]Adjusted for atopic dermatitis, allergic rhinitis, asthma, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, autoimmune disease, ischemic heart disease, stroke, gout, and corticosteroids.

another study [35]. Asthma usually occurs in young children or adolescents. In total, 80% of patients with new-onset asthma are aged ≤ 20 years [36]. The average annual remission rate of asthma in Italy from 1940 to 2010 was 43.2 per 1000 patients. This rate remained relatively stable over time, specifically across different birth cohorts [36]. Symptoms of asthma are rare after adulthood. In the present study, 65.7% of patients with IBD were aged ≥ 40 years. It is very possible that patients with IBD had not visited the outpatient department for asthma within the 2 years preceding their diagnosis. If comorbidities such as asthma could be traced back further than 2 years before the index date of IBD, an association between IBD and asthma might be revealed.

This study found a significant association between chronic kidney disease and IBD. We were unable to determine the underlying reason for this association through a literature review. Chronic kidney disease was found to be more prevalent in patients with IBD than in those without IBD [37]. Our study also found a significant association between ischemic heart disease and IBD. Patients with IBD and ischemic heart disease experienced attacks with a frequency of ≥ 2 times within 2 years before their IBD diagnosis than those without IBD. The pathophysiology of ischemic heart disease is complex and multifactorial and involves atherosclerosis, coronary microvascular dysfunction, inflammation, and vasospasm [38]. The pathological mechanisms of IBD and atherosclerotic cardiovascular disease are similar, both involving inflammatory cytokines, the innate immune system, the adaptative immune system, gene variants, and gut microbiota [39]. Further research is required to elucidate the main reason for these associations. Individuals who used corticosteroids for > 30 days within 2 years before the index date were more likely to develop IBD than were those who did not use corticosteroids. This observation might be explained by the fact that this population may already have some form of inflammatory disease, such as an allergic or autoimmune disease.

Atopic dermatitis and allergic rhinitis were significantly associated with an increased risk of IBD in patients aged < 65 years. This finding may be because the majority (78%) of IBD cases occurred in this age group. Furthermore, patients with atopic dermatitis and allergic rhinitis tend to experience more severe symptoms during their younger years. Therefore, the association between allergic disease and age at the onset of IBD is significant. Additionally, the associations of atopic dermatitis and allergic rhinitis with IBD were stronger in men than in women [10].

Atopic dermatitis and allergic rhinitis were associated with a significantly increased risk of IBD in patients not using corticosteroids. Corticosteroids may lead to an anti-inflammatory response [40], potentially delaying or reducing the occurrence of IBD.

4.1 | Limitations

First, the low incidence of IBD in the general population meant that we could only enroll a small number of patients, which might have led to statistical bias that could affect our results. Second, this timeframe was chosen on the basis of the data collection period and the study design. If the database had a longer coverage period, more accurate results may have been obtained. Third, metagenomic and multi-omic studies of gut microbiota are required to gain deeper insights into how

TABLE 3 | Subgroup analysis of the association between allergic diseases and the risk of IBD.

Factor	*N*	No. of IBD	OR (95% CI)	*p*
Age < 65[a]				
Atopic dermatitis	7	3	5.40 (1.05–27.86)	0.044
Allergic rhinitis	99	19	2.02 (1.15–3.55)	0.014
Asthma	33	4	0.46 (0.14–1.48)	0.191
Age ≥ 65[b]				
Atopic dermatitis	6	3	5.82 (0.83–40.69)	0.076
Allergic rhinitis	38	6	1.24 (0.46–3.34)	0.675
Asthma	35	6	0.96 (0.32–2.87)	0.943
Female[c]				
Atopic dermatitis	4	2	6.50 (0.80–52.69)	0.080
Allergic rhinitis	40	5	1.29 (0.46–3.56)	0.628
Asthma	23	3	0.68 (0.17–2.77)	0.595
Male[c]				
Atopic dermatitis	9	4	5.69 (1.20–27.00)	0.029
Allergic rhinitis	97	20	1.97 (1.12–3.49)	0.020
Asthma	45	7	0.63 (0.25–1.64)	0.346
Non-corticosteroids[c]				
Atopic dermatitis	8	4	8.91 (2.08–38.08)	0.003
Allergic rhinitis	117	19	1.89 (1.12–3.22)	0.018
Asthma	41	3	0.41 (0.12–1.44)	0.163
Corticosteroids[c]				
Atopic dermatitis	5	2	1.75 (0.27–11.43)	0.558
Allergic rhinitis	20	6	1.13 (0.34–3.73)	0.846
Asthma	27	7	1.17 (0.38–3.61)	0.783

[a]Adjusted for atopic dermatitis, allergic rhinitis, asthma, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, autoimmune disease, ischemic heart disease, gout, and corticosteroid use.
[b]Adjusted for atopic dermatitis, allergic rhinitis, asthma, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, stroke, gout, and corticosteroid use.
[c]Adjusted for atopic dermatitis, allergic rhinitis, asthma, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, autoimmune disease, ischemic heart disease, stroke, gout, and corticosteroid use.

interactions with the immune system occur in individuals with atopic conditions. Fourth, detailed information on socioeconomic status, urbanization level, health-care-seeking behavior, lifestyle factors (e.g., diet and smoking status), and family history was not available; this may have introduced residual confounding. However, the universal coverage of Taiwan's National Health Insurance, which includes more than 99% of the population, helps minimize disparities in health-care access. Fifth, corticosteroid use was defined as taking corticosteroids for ≥ 30 days within a 2-year period, which may not fully reflect usage patterns related to disease severity, lifestyle, or family history. This definition may have also introduced "immortal time" bias because patients must survive to accumulate exposure, potentially affecting odds ratio estimates. Additionally, prospective cohort studies at the population level are warranted.

5 | Conclusion

This study highlights an associated risk of IBD in patients with atopic dermatitis and allergic rhinitis.

Clinicians should be vigilant for early symptoms of IBD in individuals with atopic dermatitis and allergic rhinitis. Further research is required to elucidate the pathophysiological mechanisms underlying the relationship between allergic diseases and IBD.

Author Contributions

Chung-Fang Tseng, Chih-Jung Yeh, and Jame Cheng-Chung Wei: conceptualization. Chung-Fang Tseng, Chih-Jung Yeh, Yu-Hsun Wang, Jing-Yang Huang, and Jame Cheng-Chung Wei: methodology. Chung-Fang Tseng, Hsiao-Chen Lin, Te-Chia Tseng, and Meng-Che Wu: writing – Review and Editing. Meng-Che Wu, Jame Cheng-Chung Wei, Chih-Jung Yeh, and Jing-Yang Huang: supervision. Yu-Hsun Wang, Jame Cheng-Chung Wei, and Jing-Yang Huang: formal analysis, data curation. Jing-Yang Huang: editing. Chih-Jung Yeh and Jame Cheng-Chung Wei: project administration.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this research are derived from the National Health Insurance Research Database (NHIRD) in Taiwan, which is managed by the National Health Research Institutes (NHRI).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **TABLE S1:** Code for corticosteroids. **TABLE S2:** Code for IBD medications.

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LETTER TO THE EDITOR

Regarding the Prognostic Value of the HALP Score in Giant Cell Arteritis and Polymyalgia Rheumatica

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Dear Editor,

We read with great interest the article by Ulutaş et al. entitled "Can HALP score predict the prognosis of patients with giant cell arteritis and polymyalgia rheumatica?" [1]. In this study, the authors enrolled 169 elderly patients (mean age: 72.17 ± 8.29 years) with giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR) to investigate the prognostic value of the HALP score for glucocorticoid (GC) dependence and mortality. They found that a lower HALP score was significantly associated with maintenance GC therapy at doses ≥ 5 mg/day and with increased mortality.

The HALP score (Hemoglobin × Albumin × Lymphocyte count/Platelet count) integrates four key peripheral blood indices. Initially proposed by Chen et al., it was developed to predict prognosis in patients with gastric cancer [2]. Subsequent systematic reviews and meta-analyses have demonstrated that the HALP score holds prognostic value across various malignancies [3]. It reflects immune status, nutritional condition, and systemic inflammatory burden. Given that chronic inflammation and immune dysregulation are central pathological features of GCA and PMR, incorporating the HALP score into prognostic assessment of these diseases has a sound biological rationale and potential clinical relevance.

While the study was well-designed, we would like to offer several suggestions for improvement. First, repeated measurements of the four components of the HALP score during follow-up may help capture their dynamic changes and potentially enhance prognostic performance. Second, although the authors have acknowledged the limitations of their single-center retrospective design, multicenter prospective studies with larger sample sizes are still required to validate the optimal cutoff value of the HALP score in patients with GCA and PMR.

A low HALP score is typically associated with a poorer prognosis, potentially linked to systemic inflammation, compromised immunonutritional status, and endothelial dysfunction. Hemoglobin reflects bone marrow hematopoietic function and tissue oxygen delivery, while albumin indicates disease-induced inflammatory burden and nutritional reserves. Lymphocyte count represents T cell reserves, and platelets function as key mediators of inflammation, including the release of pro-inflammatory cytokines such as interleukin-1β [4].

First, in chronic inflammatory diseases such as GCA and PMR, sustained inflammation suppresses hepatic albumin synthesis while simultaneously enhancing its catabolism [5]. Hypoalbuminemia typically reflects a high inflammatory burden and nutritional depletion. This compromised state can attenuate the therapeutic response to GCs and increase susceptibility to infection, potentially necessitating higher maintenance doses of GCs and thereby elevating the risk of mortality.

Second, anemia is a common consequence of chronic inflammation. Research indicates that the key pro-inflammatory cytokine IL-6 disrupts iron metabolism, suppresses erythropoiesis, and shortens erythrocyte lifespan, ultimately impairing tissue oxygen delivery [6]. Chronic hypoxia exacerbates systemic damage, impairs cardiovascular function, and hinders tissue repair, thereby contributing to reduced GC responsiveness and adverse survival outcomes.

Third, both chronic inflammation and long-term GC therapy contribute to lymphopenia. Functional impairment of lymphocytes, particularly regulatory T cells (Tregs), may result in unchecked inflammation [7]. In this context, lymphopenia often reflects immune exhaustion or dysregulation. This weakened immune control hinders disease remission and fosters GC

dependence. Furthermore, the resulting immunocompromised state significantly heightens the risk of severe infections, subsequently contributing to mortality [8].

Finally, sustained systemic inflammation and platelet activation have been demonstrated to co-mediate endothelial dysfunction [9]. The convergence of thrombocytosis, inflammation, and potential malnutrition promotes a pro-thrombotic milieu. This elevates the risk of cardiovascular events, such as myocardial infarction and stroke, which are significant contributors to fatal outcomes in patients with GCA.

In summary, a low HALP score may reflect severe chronic inflammation, malnutrition, immune exhaustion, and vascular endothelial dysfunction. These factors together complicate disease management and may necessitate higher GC doses. However, exposure to high-dose GCs may further exacerbate immune dysfunction and inflammatory dysregulation, increase the risk of infection, and ultimately contribute to GC dependence and increased mortality.

Author Contributions

All authors participated in the conception and drafting of this manuscript. All authors have read and approved the final version for submission.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Yan Zhang
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LETTER TO THE EDITOR

Factors Associated With Oral Frailty in Patients With Rheumatoid Arthritis: A Cross-Sectional Observational Study

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Dear Editor,

This cross-sectional observational study aimed to identify factors associated with oral frailty in patients with rheumatoid arthritis (RA). Oral frailty, characterized by a decline in oral function involving chewing, swallowing, and speech, is increasingly recognized as a component of overall frailty and is closely linked with physical decline, cognitive impairment, and mortality [1, 2]. As Japan faces rapid population aging, understanding oral frailty in RA is important because both patients with RA and the general population are becoming older, and RA itself may increase the risk of oral health deterioration.

A total of 597 patients with RA meeting established classification criteria underwent comprehensive assessments, including oral frailty evaluation using the Oral Frailty Index-8 (OFI-8), physical frailty assessment using the Kihon Checklist (KCL), and clinical profiling. Oral frailty was defined as an OFI-8 score ≥ 4 [3, 4]. Clinical data included demographics, RA disease duration, BMI, smoking status, income, RA-related medications, Clinical Disease Activity Index (CDAI), physical function (HAQ-DI), bone mineral density, vitamin D levels, and frailty according to KCL assessment.

Univariate analysis compared characteristics between the oral frailty (+) and (−) groups. Variables with $p < 0.05$ based on univariate analysis were included in multivariate logistic regression analysis. The model showed good discrimination (AUC, 0.772) and calibration.

The prevalence of oral frailty was 36.7%. Patients with oral frailty were significantly older (Figure 1) and more likely to

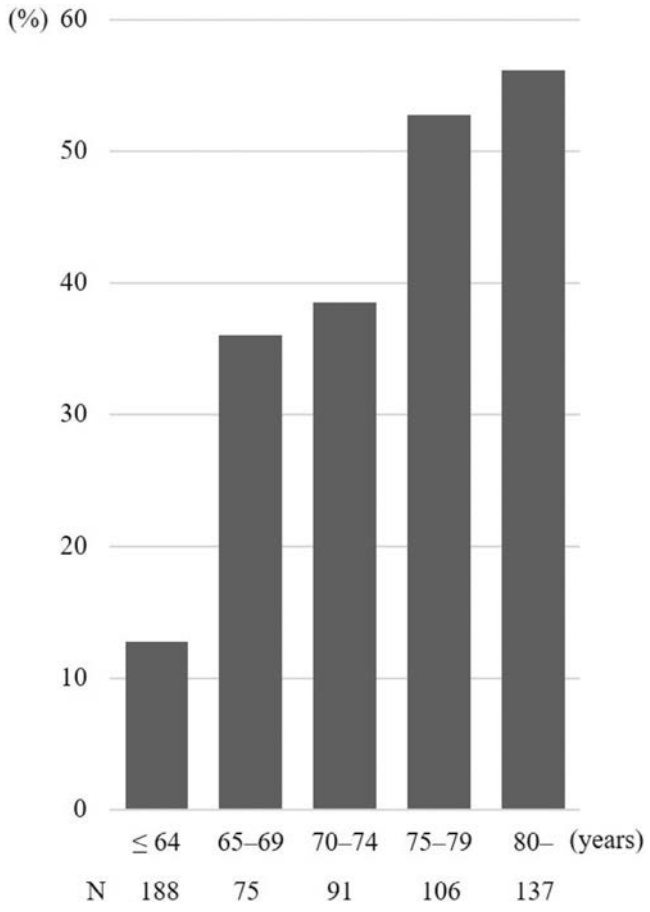

FIGURE 1 | Prevalence of oral frailty by age.

TABLE 1 | Patient characteristics and clinical data.

	All ($n=597$)	Oral frailty (+). ($n=219$).	Oral frailty (–) ($n=378$)	p-value (uni)	p-value (multi)	Odds ratio (95% CI)
Age, years	69.2 ± 13.1	75.5 ± 8.9	65.6 ± 13.7	< 0.001	< 0.001	1.06 (1.04–1.09)
Female, *n* (%)	499 (83.6)	183 (83.6)	316 (83.6)	1.000		
Body mass index	22.3 ± 4.7	22.0 ± 4.6	22.5 ± 4.8	< 0.001	0.478	1.02 (0.97–1.06)
Duration of RA, years	16.0 ± 11.2	17.9 ± 12.1	14.8 ± 10.4	< 0.001	0.643	1.00 (0.99–1.02)
Anti-CCP Ab positive, *n* (%)	456 (76.4)	163 (74.4)	293 (77.5)	0.424		
Smoker, *n* (%)	176 (29.5)	68 (31.1)	108 (28.6)	0.576		
Low income, *n* (%)	325 (54.4)	138 (63.0)	187 (49.5)	0.002	0.084	0.71 (0.49–1.05)
b- or tsDMARDs use, *n* (%)	336 (56.3)	131 (59.8)	205 (54.2)	0.200		
MTX use, *n* (%)	344 (57.6)	113 (51.6)	231 (61.1)	0.026	0.702	1.08 (0.73–1.60)
Glucocorticoid use, *n* (%)	92 (15.4)	37 (16.9)	55 (14.6)	0.481		
CDAI	4.2 ± 4.2	4.8 ± 4.5	3.8 ± 4.0	< 0.001	0.126	1.04 (0.99–1.09)
HAQ-DI	0.40 ± 0.66	0.63 ± 0.78	0.26 ± 0.53	0.178		
Serum 25-hydroxyvitamin D, ng/mL	16.2 ± 7.4	15.8 ± 7.9	16.4 ± 7.1	< 0.001	0.348	0.99 (0.96–1.01)
BMD in lumbar spine, g/cm^2	1.11 ± 0.22	1.10 ± 0.23	1.12 ± 0.21	< 0.001	0.664	0.80 (0.29–2.22)
BMD in total hip, g/cm^2	0.79 ± 0.14	0.75 ± 0.13	0.81 ± 0.14	< 0.001	0.752	0.59 (0.02–14.97)
BMD in femoral neck, g/cm^2	0.75 ± 0.13	0.71 ± 0.12	0.77 ± 0.13	< 0.001	0.551	0.37 (0.02–9.89)
BMD in hand, g/cm^2	0.29 ± 0.06	0.28 ± 0.06	0.30 ± 0.06	< 0.001	0.394	6.42 (0.09–461.92)
Presence of frailty according to the KCL, *n* (%)	208 (34.8)	124 (56.6)	84 (22.2)	< 0.001	< 0.001	2.68 (1.78–4.04)

Abbreviations: anti-CCP Ab, anti-cyclic citrullinated peptide antibody; bDMARDs, biological disease-modifying antirheumatic drugs; BMD, bone mineral density; CDAI, Clinical Disease Activity Index; CI, confidence interval; HAQ-DI, Health Assessment Questionnaire Disability Index; KCL, Kihon Checklist; MTX, methotrexate; multi, multivariate logistic regression; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; uni, univariate analysis.

exhibit frailty according to the KCL assessment. In the multivariate analysis, age ($p<0.001$) and frailty according to KCL ($p<0.001$) were independently associated with oral frailty (Table 1). The prevalence of frailty according to the KCL in the oral frailty (+) group was compared with that in the oral frailty (–) group (56.6% vs. 22.2%).

Comparisons with previous studies showed that oral frailty is relatively common in patients with RA, similar to or higher than rates seen in older community-dwelling adults [5, 6]. Prior studies have also linked oral frailty with adverse outcomes such as physical frailty, diminished recovery capacity, and increased vulnerability [6–8]. Because patients with RA are at a higher risk of physical frailty due to chronic inflammation and functional limitations, assessing oral frailty in this population is particularly important.

Although methotrexate (MTX) use and RA disease activity appeared significant in univariate analysis, these associations disappeared after multivariate adjustment, suggesting confounding effects. Prior research indicates limited direct impact of MTX on periodontal disease, while high RA disease activity is associated with poorer oral health, including increased periodontitis and dental caries [9, 10]. The lack of significance in adjusted models suggests overlapping influences with age or physical frailty. These factors are widely recognized in general populations. This study specifically demonstrates that traditional frailty determinants continue to play a dominant role in patients with RA, suggesting that general geriatric mechanisms may outweigh disease-specific factors. This has important implications for clinical management, highlighting the need for comprehensive geriatric assessment in RA care.

The study has several limitations. First, oral frailty was defined using OFI-8, which, although validated, may not fully align with other oral health assessment tools. The OFI-8 score ≥ 4 demonstrated a sensitivity of 80% and a specificity of 80% for identifying individuals at risk of oral frailty [3]. Second, other known risk factors for oral health decline, such as diabetes, history of cancer, malnutrition, oral interventions, and cognitive impairment, were not evaluated. Third, being a single-center, cross-sectional study relying partly on self-reported assessments, it may be subject to selection and reporting biases and cannot establish causality. Nonetheless, it adds valuable data to the limited literature on the relationship between RA and oral frailty.

In conclusion, a substantial proportion of patients with RA exhibit oral frailty, and its presence is strongly associated with older age and frailty according to the KCL. Because oral frailty can affect nutrition, activities of daily living, and mortality, routine evaluation and early management, especially in older patients with RA or those exhibiting frailty, are essential. Multidisciplinary collaboration among medical, dental, and rehabilitation professionals may help improve outcomes. Future longitudinal studies are needed to clarify causal pathways and examine changes in oral frailty over time in RA populations.

Author Contributions

Study concept and design: Takeshi Mochizuki, Katsunori Ikari, and Ken Okazaki. Acquisition of subjects and the data: Takeshi Mochizuki. Analysis and interpretation of the data: Katsunori Ikari and Koichiro Yano. Preparation of the manuscript: Takeshi Mochizuki, Katsunori Ikari, and Ken Okazaki.

Ethics Statement

This study was conducted in accordance with the principles stated in the Declaration of Helsinki, and written informed consent was obtained from all the patients (approval number: TGE00652-064).

Conflicts of Interest

T. Mochizuki received honoraria for lectures from AbbVie, Asahi Kasei, Astellas, Bristol-Myers, Eisai, Eli Lilly, Pfizer, Mochida, and UCB. K. Yano received honoraria for lectures from AbbVie, Chugai, Eisai, Gilead Sciences, Janssen, Kaken, Pfizer, and UCB. K. Ikari received honoraria for lectures from Asahi Kasei, Astellas, AbbVie, Ayumi, Bristol Myers, Chugai, Eisai, Eli Lilly, Janssen, Kaken, Mitsubishi Tanabe, Pfizer, Takeda, Teijin, and UCB. The other authors declare that they have no conflicts of interest.

Data Availability Statement

Research data are not shared.

Takeshi Mochizuki
Koichiro Yano
Katsunori Ikari
Ken Okazaki

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LETTER TO THE EDITOR

TAP1 Deficiency Masquerading as Granulomatosis With Polyangiitis: A Case Report Highlighting the Importance of Genetic Evaluation in Atypical Presentations

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Dear Editor,

The *TAP1* gene (OMIM #170260) encodes a subunit of the transporter associated with the antigen processing (TAP) complex, which facilitates the translocation of cytosolic peptides into the endoplasmic reticulum for loading onto MHC class I molecules. The TAP complex, comprising TAP1 and TAP2, is essential for MHC class I assembly and antigen presentation to $CD8^+$ T cells [1–3]. Biallelic pathogenic variants in *TAP1*, *TAP2, TAP Binding Protein (TAPBP)*, or *Beta-2-microglobulin (B2M)* result in MHC class I deficiency (Bare Lymphocyte Syndrome type I, OMIM #604571), a rare autosomal recessive immunodeficiency. Affected individuals typically present in childhood or adolescence with recurrent sinopulmonary infections that may progress to bronchiectasis, nasal polyps,

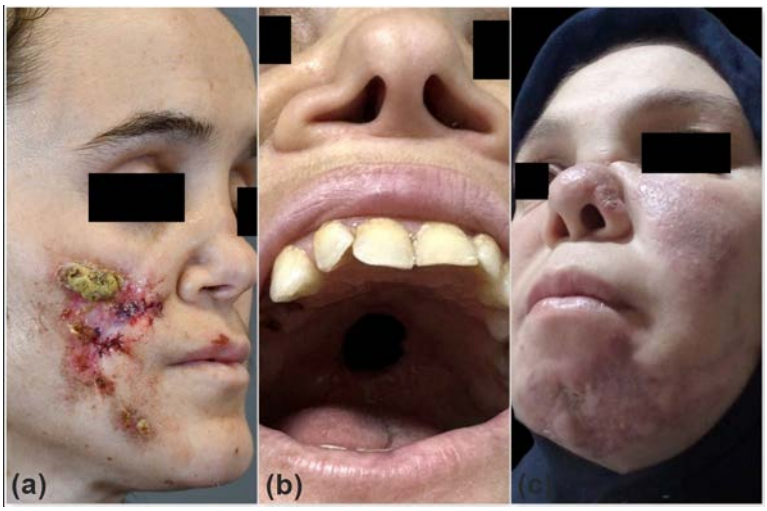

FIGURE 1 | (a) Chronic lesion on the patient's right cheek showing crusting, induration, focal atrophy, and hemorrhagic areas. Saddle-nose deformity is also apparent. (b) Intraoral examination revealing a sharply demarcated perforation of the palate. (c) Patient's sister demonstrating facial scarring on the nose, left malar region, and chin, and saddle-nose deformity.

Learning Points

1. TAP1 deficiency is a rare autosomal recessive immunodeficiency characterized by defective MHC class I expression and reduced CD8+ T cell function.
2. Clinical features such as granulomatous skin lesions, palatal perforation, and saddle-nose deformity may mimic autoimmune vasculitides (e.g., granulomatosis with polyangiitis), leading to potential misdiagnosis.
3. The combination of ANCA negativity, early-onset symptoms, and strong familial clustering in patients with granulomatous disease should raise suspicion of an underlying primary immunodeficiency.

and chronic granulomatous lesions involving the nasal cavity, upper respiratory tract, and/or skin. Immunologically, these patients show markedly reduced or absent HLA class I surface expression [3, 4]. Given overlapping clinical features, *TAP1* deficiency may be misdiagnosed as autoimmune vasculitis, particularly granulomatosis with polyangiitis (GPA) [5]. We present a case initially diagnosed as GPA but later confirmed as *TAP1* deficiency through genetic testing.

A 30-year-old female was referred to the dermatology clinic at Ankara University School of Medicine with a chronic facial lesion. She had previously been diagnosed with GPA and was treated with 5 mg/day prednisolone and 2.5 mg methotrexate on alternate days. Examination revealed a 3 × 5 cm yellowish, crusted lesion on her right cheek (present for 5 years), a palatal perforation of similar duration, and a saddle-nose deformity noted since childhood (Figure 1). Her medical history included hyposmia, recurrent respiratory infections, otitis media, and longstanding bilateral hearing loss. She had undergone tympanostomy and reported persistent nasal discharge and postnasal drip. Family history was significant: four siblings died perinatally, one sister died during childbirth, and one sibling was reportedly healthy. Another sister, also diagnosed with GPA, exhibited similar clinical features—facial lesion with scarring, saddle-nose deformity, palatal perforation, recurrent respiratory infections, and hearing impairment (Figure 1). The parents reported no known consanguineous relationship; however, both originated from a small neighboring geographic region, raising the possibility of unrecognized inbreeding.

Laboratory investigations, including anti-neutrophil cytoplasmic antibody (ANCA) and an extended immunologic panel, were unremarkable. Infectious causes such as leprosy, leishmaniasis, syphilis, and tuberculosis were ruled out via serologic tests and cultures. Thoracic CT revealed bronchiectasis and chronic infection; temporal bone CT showed findings consistent with mastoiditis. Audiometry confirmed bilateral profound mixed hearing loss. Histopathology from the facial lesion showed dermal granulomatous inflammation with central fibrinoid necrosis, surrounded by epithelioid histiocytes and lymphocytes. This, combined with the clinical history and familial presentation, raised suspicion for a primary immunodeficiency. Whole-exome sequencing (WES) was performed using the QIAGEN QIAseq Targeted DNA Panel on the Illumina NextSeq platform. Data were aligned to the GRCh38/hg18 reference genome and analyzed via QIAGEN software. A homozygous nonsense variant was identified in *TAP1* (NM_000593.6:c.1963C>T; p.R655*), predicted to cause loss of function. According to ACMG 2015 criteria, this variant was classified as likely pathogenic (PVS1, PM2) [6]. The variant is reported in gnomAD Exomes (version 4.1) with a frequency of 0.00001442 (https://gnomad.broadinstitute.org; accessed 02, 2026) [7]. The variant has been submitted to ClinVar under accession number SUB15997302. Segregation analysis revealed that the affected sibling carried the same homozygous variant, while both parents were heterozygous. The segregation analysis of the TAP1 c.1963C>T (p.Arg655*) variant, including the pedigree and IGV visualization, is shown in Figure S1.

TAP1 deficiency is a rare autosomal recessive immunodeficiency characterized by markedly reduced surface expression of MHC class I molecules. Fewer than 20 cases have been reported worldwide, and clinical recognition remains limited [8]. Clinical presentations vary widely, from recurrent respiratory tract infections to chronic granulomatous skin or mucosal lesions. A summary of reported cases is presented in Table 1 (adapted from Bhattarai et al.), highlighting clinical heterogeneity and known pathogenic variants [8]. While some patients present early in life with severe infections, others—like our patient—may have a delayed diagnosis due to overlap in clinical features with autoimmune vasculitides, particularly ANCA-negative GPA.

In this case, both the patient and her sibling were initially misdiagnosed with GPA due to chronic granulomatous lesions, saddle-nose deformity, and palatal perforation. Notably, both were ANCA-negative, had early-onset symptoms, and shared a strong familial pattern—features atypical for classical GPA and suggestive of an underlying primary immunodeficiency. ANCA negativity, in particular, should raise suspicion in cases with granulomatous disease and familial clustering.

The diagnostic clue came from histological features consistent with granulomatous inflammation, in combination with bronchiectasis, hearing loss, and the presence of similar findings in a sibling. The absence of ANCA and a non-supportive infectious workup further directed investigations toward a genetic etiology. Identification of a homozygous nonsense variant in *TAP1* confirmed the diagnosis.

Treatment of *TAP1* deficiency remains supportive, focusing on prompt management of infections and surveillance for complications. The efficacy of immunosuppressive therapy is questionable and may pose additional risks in these patients. While IVIG may offer benefit in some cases, its role is not yet well defined. Hematopoietic stem cell transplantation has been attempted in select cases but is associated with high risk due to the immunologic mismatch introduced by donor-derived MHC class I-expressing cells [2, 3].

Greater awareness of rare immunodeficiencies such as *TAP1* deficiency is essential in dermatology and rheumatology, where chronic granulomatous lesions may be the presenting feature. Multidisciplinary collaboration between dermatology,

TABLE 1 | Reported cases with TAP1 Deficiency, TAP1 gene variant, and clinical findings (adapted from Bhattarai, D. et al. [8]).

Reference	Tap1 Gene Variant	Age, Sex	Respiratory Findings	Otorhinolaryngological Findings	Dermatologic Findings	Treatment
Maeda et al., 1985, Japan	{c.599-1G > A, p.E201Rfs*28}	33, F	Diffuse panbronchiolitis	Sinusitis, nasal polyp, septal deviation	Ichthyosis vulgaris, leg ulcers, subcutaneous nodules, necrobiotica lipoidica, cutaneous granulomas	Polypectomy & deviatomy
Plebani et al., 1996, Italy	{c.639delC, p.W214Gfs*15}	16, M	Pulmonary emphysema, bronchiectasis	Pansinusitis, nasal polyps	Leg ulcers	Antibiotic prophylaxis, chest physiotherapy, and topical therapy
Moins-Teisserenc et al., 1999, UK	Undetermined	N/A, F	Bronchitis, bronchiectasis	Recurrent purulent rhinitis	Granulomas on legs, cutaneous granulomas	Antimicrobial prophylaxis
Moins-Teisserenc et al., 1999, UK	Undetermined	20, F	Recurrent purulent bronchopulmonary infections	Nasal granuloma, septal perforation	Granulomas on legs, cutaneous granulomas	Antimicrobial prophylaxis
Moins-Teisserenc et al., 1999, UK	Undetermined	27, F	None	None	Leg plaque, cutaneous granulomas	Antibiotics and steroids
Parissidiasis et al., 2005, France	{c.1564 C > T, p.Q522*}	14, M	None	None	None	Sulfadiazine, pyrimethamine, steroids, pars plana vitrectomy
Parissidiasis et al., 2005, France	{c.1564 C > T, p.Q522*}	N/A, M	Bronchial obstruction	None	None	Bronchodilators
Dogu et al., 2006, Turkey	{c.1132 C > T, p.R378*}	14, M	Respiratory distress, frequent pulmonary infections, bronchiectasis	Sinus infections	Recurrent scar-forming skin lesions around the nose/nostrils and mouth, cutaneous granulomas	Antimicrobials, anti-Toxoplasma therapy, IVIg
Dogu et al., 2006, Turkey	{c.1132 C > T, p.R378*}	21, F	Recurrent lower airway disease, bronchiectasis	Not Specified	Not Specified	TMP-SMX and symptomatic treatment

(Continues)

TABLE 1 | (Continued)

Reference	Tap1 Gene Variant	Age, Sex	Respiratory Findings	Otorhinolaryngological Findings	Dermatologic Findings	Treatment
Caversaccio et al., 2008, Switzerland	{c.639delC, p.W214Gfs*15}	31, F	Bronchitis	Rhinosinusitis, pharyngitis, nasal polyps, septal deviation, rhinolalia, bilateral tympanosclerosis, mastoiditis, hearing loss	None	High-dose steroids, nasal septal corrective surgery
Caversaccio et al., 2008, Switzerland	{c.639delC, p.W214Gfs*15}	40, F	Pulmonary infections, bronchiectasis	Dried nasal mucosae, nasal polyps, septal deviations and perforation, bilateral tympanosclerosis, mastoiditis, hearing loss	Necrotizing lesions, cutaneous granulomas	High-dose steroids
Villa-Forte et al., 2008, USA	Undetermined	20, F	Recurrent bacterial pneumonia, bronchiectasis	Pansinusitis	Multiple leg skin lesions, cutaneous granulomas	Cyclophosphamide, steroids, methotrexate, azathioprine
Gao et al., 2016, UK	{deletion from exon 3 of TAP1 to exon 11 of TAP2}	6, F	Recurrent chest infections, bronchiectasis	Otitis media with effusion	Skin ulcers at elbows, severe eczema	Antibiotics, HSCT (9/10 MUD)
Hanalioglu et al., 2017, Turkey	{c.1924dupC, p.Q642Pfs*27}	15, F	Recurrent cough, right lung atelectasis, bronchiectasis	Pansinusitis, purulent postnasal discharge	None	Bronchodilators, IVIg, TMP-SMX, tenofovir
Hanalioglu et al., 2017, Turkey	{c.1924dupC, p.Q642Pfs*27}	33, M	Recurrent pulmonary infections, bronchiectasis	Sinusitis	None	Supportive drugs
Law-Ping-Man et al., 2018, France	{c.1699 A > T, p.K567*}	4, F	Recurrent pneumonia, spastic bronchitis, bronchiectasis	Sinusitis	Skin ulcers at the bottom, extremities, and cheek, cutaneous granulomas	Chloroquine, clarithromycin
Tsilifis et al., 2021, UK	{deletion from exon 3 of TAP1 to exon 11 of TAP2}	11, F	Cavitary pulmonary tuberculosis, bronchiectasis	Not Specified	Skin ulcers in limbs, midface, and trunk, cutaneous granulomas	Anti-tubercular drugs, HSCT (9/10 MUD)
Wang et al., 2024, China	{c.971 C > G, p.S324*}	34, F	None	None	Non-painful plaques and ulcers over the right leg, cutaneous granulomas	Surgical resection, intralesional interferon α-2b, imiquimod

(Continues)

TABLE 1 | (Continued)

Reference	Tap1 Gene Variant	Age, Sex	Respiratory Findings	Otorhinolaryngological Findings	Dermatologic Findings	Treatment
Bhattarai et al., 2024, Nepal	{c.297dupA, p.A100Sfs*28}	7, F	Upper respiratory tract infections, bronchitis, pulmonary infections, bronchiectasis	None	Pyoderma gangrenosum-like cutaneous ulcers, cutaneous granulomas	Antimicrobial therapy, IVIg, antiviral therapy
Our Case, 2025, Turkey	{c.1963C>T p.R655}	30, F	Pulmonary tuberculosis, bronchiectasis, recurrent upper-lower respiratory tract infections	Palatal perforation, saddle-nose deformity, chronic mastoiditis, bilateral profound mixed hearing loss, recurrent otitis media, hyposmia, postnasal drip	Persistent necrotizing granulomatous lesion	Monthly IVIg therapy (Planned)

immunology, and genetics is crucial for early diagnosis and improved outcomes in these patients.

Author Contributions

Bengü Nisa Akay: conceptualization, writing – original draft, writing – review and editing, supervision. **Simge Gürpınar Kılıç:** conceptualization, writing – original draft. **Şule Altıner:** data analysis, visualization. **Aylin Okçu Heper:** data analysis, visualization. **Nihal Kundakcı:** supervision.

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Ethics Statement

The authors have nothing to report.

Consent

The patient and family members provided written informed consent for genetic analysis and publication of their case details and 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 from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Segregation of the TAP1 NM_000593.6:c.1963C>T (p.R655) variant in the family. (a) Simplified pedigree. (b) Integrative Genomics Viewer (IGV) visualization of sequencing reads at the TAP1 locus. Homozygous variant alleles are observed in the proband (II.6) and affected sibling (II.7), while the father (I.1) and mother (I.2) exhibit heterozygous read distributions consistent with carrier status. The variant results in a premature termination codon at residue p.Arg655*.

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LETTER TO THE EDITOR

Can Colchicine Be a Therapeutic Option for Patients With Ankylosing Spondylitis?

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Dear Editor,

Ankylosing spondylitis (AS) is characterized by chronic inflammation of the axial skeleton, sacroiliac joints, and entheses, often presenting in early adulthood and its pathogenesis remains incompletely understood and appears to involve a complex interplay between autoinflammatory and autoimmune mechanisms [1, 2].

Genetic susceptibility plays a central role in AS. Beyond the strong association with HLA-B27, several molecular pathways, including the IL-17/IL-23 axis, endoplasmic reticulum aminopeptidases (ERAP1/2), have been implicated in disease development [2]. Variants of the MEFV gene, classically associated with Familial Mediterranean Fever (FMF), have also been linked to an increased frequency of spondyloarthritis in FMF patients and their relatives [3]. In particular, the M694V mutation has been associated with heightened inflammatory activity and increased disease susceptibility [4].

FMF is considered a prototype autoinflammatory disorder driven by innate immune dysregulation and excessive IL-1–mediated inflammation [5]. Colchicine, the mainstay of FMF treatment, suppresses inflammation through inhibition of microtubule polymerization and downstream inflammasome activation [5]. Despite overlapping inflammatory pathways between FMF and AS, colchicine has not been systematically evaluated as a treatment option for AS and has only been reported in isolated cases, such as AA amyloidosis secondary to AS [6].

We included 28 patients with established diagnoses of AS and FMF. AS was diagnosed according to the 1984 Modified New York Criteria, and FMF diagnosis was based on the Tel-Hashomer criteria [4, 5]. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Visual Analogue Scale (VAS) for back pain before and after colchicine treatment. Genetic data, including MEFV mutation status, and treatment histories were obtained from medical records.

The mean age of the patients was 44.89 ± 10.9 years with disease duration of AS and FMF being 12.35 ± 6.95 years and 17.71 ± 7.72 years, respectively. Colchicine treatment was associated with improvement in both BASDAI (6.17 ± 2.56 to 5.05 ± 2.26, $p = 0.068$) and VAS back pain scores (6.69 ± 3.65 to 5.48 ± 2.65, $p = 0.145$) without reaching statistical significance. Similarly no significant improvement was observed in patients carrying heterozygous M694V mutations ($n = 9$) for either parameter. In contrast, patients with homozygous M694V mutation ($n = 6$), both BASDAI and VAS improvement was found significant (Table 1).

Our findings suggest a genotype-specific response to colchicine in AS patients with coexisting FMF. AS is increasingly recognized as a disease with overlapping autoinflammatory and autoimmune features [2]. Its classification as an MHC class I–opathy and the evidence linking inflammasome activation to enhanced MHC class I expression further support this concept [7].

Colchicine inhibits NLRP3 inflammasome activation and IL-1 secretion, pathways that are central to FMF pathogenesis and may also contribute to AS, particularly in genetically susceptible individuals [8]. Additionally, interactions between IL-1, TNF, and the IL-17/IL-23 axis may play a role in amplifying inflammation [9]. IL-1–mediated suppression of IL-2 and FOXP3 expression may further impair regulatory T-cell function, providing a potential mechanistic link between autoinflammatory and autoimmune processes [10].

TABLE 1 | Patient's scores before and after the treatment.

	Before colchicine therapy	After colchicine therapy	*p*
Average VAS scores (total back pain), mean ± SD	6.69 ± 3.65	5.48 ± 2.65	0.145
Average BASDAI scores, mean ± SD	6.17 ± 2.56	5.05 ± 2.26	0.068
Average VAS scores of M694V heterozygous, mean ± SD	6.88 ± 3.51	5.77 ± 2.22	0.217
Average BASDAI scores of M694V heterozygous, mean ± SD	5.64 ± 3.16	5.24 ± 2.27	0.47
Average VAS scores of M694V homozygous, mean ± SD	8.33 ± 1.96	4.5 ± 2.88	0.011
Average BASDAI scores of M694V homozygous, mean ± SD	6.68 ± 1.94	4.38 ± 2.38	0.048

The significant improvement observed exclusively in M694V homozygous patients suggests that effective control of FMF-related inflammation may also modulate AS disease activity in this subgroup. In contrast, the absence of benefit in heterozygous patients highlights the importance of genetic stratification. Previous studies evaluating IL-1 inhibitors in AS have reported inconsistent results, likely due to small sample sizes [11, 12].

This study has limitations, including its retrospective design, reliance on patient recall for BASDAI and VAS scores, and potential confounding related to FMF disease activity. In addition, the number of patients included in this study needs to be increased in future, larger prospective studies. Nevertheless, it represents the first systematic evaluation of colchicine's effect on AS disease activity and identifies a clinically meaningful response in a genetically defined subgroup.

Colchicine may reduce disease activity in AS patients carrying homozygous MEFV M694V mutations, suggesting a genotype-specific therapeutic effect and reinforcing the role of autoinflammatory mechanisms in AS pathogenesis. Prospective, genotype-stratified studies are needed to confirm these findings and further clarify the contribution of MEFV variants to AS.

Author Contributions

Muhammed Bahaddin Ates: writing – review and editing, writing – original draft, visualization, methodology, formal analysis, data curation, conceptualization. **Bugra Han Egeli:** writing – review and editing. **Serdal Ugurlu:** writing – review and editing, supervision, methodology, conceptualization.

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Ethics Statement

The study was approved by the Istanbul University–Cerrahpaşa Ethical Committee (reference code: nq09KzAR).

Consent

Verbal informed consent was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Muhammed Bahaddin Ates
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