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ORIGINAL ARTICLE

A Comprehensive Analysis of Differential Protein Expression in the Plasma of Rheumatoid Arthritis Patients Utilizing Data-Independent Acquisition (DIA) Proteomics Technology

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Keywords: data-independent acquisition (DIA) proteomics | differential proteomics analysis | rheumatoid arthritis (RA) | SERPINA3

ABSTRACT

Background: Rheumatoid Arthritis (RA) is a Prevalent Autoimmune Disorder Affecting Millions of People Worldwide. A Thorough Understanding of Its Clinical and Pathological Features Is Essential to Improve Patient Outcomes.

Methods: This Study Combined Data-Independent Acquisition Proteomics and Enzyme-Linked Immunosorbent Assay (ELISA) to Identify and Validate Potential Plasma Protein Biomarkers for the Early Diagnosis of RA.

Results: Differential Proteomic Analysis Identified Differentially Expressed Proteins Between Patients With RA and Healthy Controls and Characterized Their Functions. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Enrichment Analyses Were Performed to Explore Protein Functions and Associated Biological Pathways. The STRING Database and the Metascape Platform Were Used to Conduct an in-Depth Analysis of the Protein–Protein Interaction Network, Highlighting the Functional Attributes and Interconnections of Upregulated Proteins and Identifying Key Protein Complexes Involved in RA. ELISA Analysis of Plasma Samples Revealed Significantly Elevated SERPINA3 Levels in Patients With RA, Which Were Positively Correlated With Disease Activity Indicators—Including Erythrocyte Sedimentation Rate, C-Reactive Protein, and Disease Activity Score 28—But Were Not Correlated With Rheumatoid Factor or Its Subtypes.

Conclusions: This Study Provides New Insights and Identifies Potential Biomarkers for the Early Diagnosis of RA.

1 | Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder primarily characterized by symmetrical polyarthritis, predominantly affecting individuals aged 30–55 years [1, 2]. Despite extensive research, the precise pathogenesis of RA remains unclear, and its global prevalence is estimated to range from 1% to 3%. In China alone, approximately 5 million individuals are affected by this condition, imposing significant economic and social burdens [3, 4]. RA is a complex disease involving dysregulation of the immune system and is characterized by chronic, symmetrical, and progressive polyarthritis, accompanied by symptoms such as joint pain, stiffness, and swelling. Pathologically, the synovium undergoes extensive changes, including chronic inflammation, hyperplasia, vascular proliferation, and invasion into articular cartilage, subchondral bone, ligaments, and tendons [5]. These pathological changes ultimately lead to the destruction of articular cartilage, bone, and joint capsules, resulting in irreversible joint deformities and functional

Yang Zhao and Yuan Li contributed equally to this work and are considered co-first authors.

impairment. Consequently, the disability rate among patients with RA can reach up to 50%. A thorough understanding of the clinical manifestations and pathological processes associated with RA is essential for advancing research and improving patient outcomes [6].

Proteins serve as the primary effectors of biological processes, and alterations in plasma protein levels may indicate pathological conditions in the body. As essential components of human cells and tissues, proteins play pivotal roles in signal transduction, catalysis of metabolic reactions, and maintenance of cellular structure [7]. Plasma proteins are crucial for maintaining immune function, reflecting nutritional status, and supporting cell regeneration [8]. In recent years, rapid advances in mass spectrometry have significantly accelerated progress in proteomics, establishing it as a critical methodological approach in protein research. Proteomics enables the large-scale identification and quantification of proteins in biological samples, as well as the analysis of post-translational modifications. Additionally, it facilitates the extraction of meaningful information and patterns from high-throughput data, thereby providing a foundation for investigating functional mechanisms.

Serine protease inhibitors (SERPINs) constitute a superfamily of proteins that regulate diverse physiological processes, including fibrinolysis, hemostasis, extracellular matrix remodeling, cellular proliferation and differentiation, inflammatory responses, and immune regulation [9]. SERPINA3, a prominent member of the SERPIN family, has been implicated in multiple inflammatory diseases [10, 11]. As a prominent member of the serpin superfamily, SERPINA3 may exert regulatory effects in RA by inhibiting proteases involved in the complement and coagulation cascades, as well as immune activation. Excessive proteolysis is a hallmark of RA and contributes to cartilage degradation and synovial inflammation. Although SERPINA3 has been reported in other inflammatory diseases, its expression pattern, correlation with disease activity, and clinical relevance in RA remain largely unexplored. Moreover, in contrast to nonspecific acute-phase proteins such as SAA1 and SAA2, SERPINA3 may represent a pathway-specific biomarker reflecting protease imbalance and immune dysregulation in RA. Proteomic advances have uncovered vital evidence explaining RA pathogenesis, such as modified protein lactylation, matching proteomic features in synovial fluid and plasma, and autoantibody changes specific to disease stages, supporting disease prediction and precise treatment.

Data-independent acquisition (DIA) [12] is a mass spectrometry acquisition method that has emerged in recent years and represents a major advancement in quantitative proteomics [13, 14]. DIA proteomics is a quantitative approach that utilizes unbiased acquisition for the systematic analysis of proteins in biological samples. Compared with conventional label-free methods, tandem mass tag labeling, and other techniques, DIA-based quantitative proteomics offers several advantages, including high throughput, improved precision, enhanced sensitivity, and greater reproducibility. Immunological detection methods, such as enzyme-linked immunosorbent assay (ELISA) and Western blotting, have been widely used to validate candidate protein biomarkers identified through DIA proteomics [15]. In this study, DIA proteomics was integrated with ELISA to identify and validate differentially expressed proteins in the plasma of patients with RA, with the aim of exploring potential biomarkers for early diagnosis.

2 | Materials and Methods

2.1 | Research Participants and Sample Collection

From January to June 2023, Tianjin First Central Hospital recruited six patients with RA and six age- and sex-matched healthy volunteers for a preliminary DIA proteomics study. From August to October 2024, based on the findings of the first phase, the hospital recruited an additional 47 patients with RA and 28 age- and sex-matched healthy volunteers for the validation cohort (Table 1). ELISA was used to validate and further confirm the expression levels of key proteins. The inclusion criteria were based on the RA classification criteria established by the American College of Rheumatology and the European League Against Rheumatism. Patients with concurrent other autoimmune diseases, infectious diseases, malignancies, or severe dysfunction of the heart, liver, or kidneys were excluded. Additionally, during the same period, healthy volunteers with no history of autoimmune diseases, infectious diseases, or malignancies were recruited. All patients and volunteers involved in this study strictly adhered to the ethical guidelines of the World Medical Association Declaration of Helsinki. Blood samples were collected into tubes containing ethylenediaminetetraacetic acid as an anticoagulant. The samples were centrifuged at 4°C at 3 000 rpm for 10 min. The supernatant plasma was aspirated, aliquoted into appropriate containers, and stored at −80°C for subsequent analysis.

2.2 | Sample Preparation

Plasma samples were lysed with 400 μL of 8 M urea lysis buffer (supplemented with 1× Roche protease inhibitor cocktail). Following centrifugation at 20 000 × g for 20 min, the

TABLE 1 | Demographic and clinical characteristics of patients with RA and healthy controls.

Characteristic	RA Patients ($n = 47$)	Healthy Controls ($n = 28$)	p-value
Age (years)	54.89 ± 8.54	60.02 ± 12.74	> 0.05
Sex			
Male, *n* (%)	12 (25.5%)	9 (32.1%)	> 0.05
Female, *n* (%)	35 (74.5%)	19 (67.9%)	> 0.05
Disease Duration (months)	24.96 ± 13.78	N/A	—
Disease Activity Score			
DAS28	5.86 ± 1.74	N/A	—

supernatant was collected, and 5 μL was reserved for the BCA assay. DTT was added to a final concentration of 10 mM, and the samples were incubated in a 37°C water bath for 1 h. Subsequently, IAA was added to a final concentration of 20 mM, and the samples were incubated in the dark for 30 min. For each sample, 150 μg of protein was digested with trypsin at a protein-to-enzyme ratio of 50:1 and incubated at 37°C for 14–16 h. The resulting peptides were desalted using Waters solid-phase extraction cartridges and then dried under vacuum. The peptide fractions were reconstituted in 0.1% FA and stored at −20°C for further analysis.

2.3 | LC–MS/MS Analysis

Peptides were analyzed using liquid chromatography–tandem mass spectrometry (LC–MS/MS) in DIA mode (LC Bio Technology Co. Ltd.) with mass spectrometer settings optimized for DIA analysis. The dried peptide samples were reconstituted in 0.1% FA and centrifuged at 20 000 × g for 10 min. The resulting supernatant was collected and loaded onto a self-packed C18 column (100 μm internal diameter, 1.8 μm particle size, approximately 35 cm in length). Peptide separation was performed using a Thermo Scientific EASY-nLC 1200 system at a flow rate of 300 nL/min with the following gradient: 4%–27% solvent B (98% acetonitrile, 0.1% FA) from 0 to 103 min; 27%–40% solvent B from 103 to 111 min; 40%–90% solvent B from 111-113 min; and 90% solvent B maintained until 120 min. The separated peptides were ionized by nano-electrospray ionization and introduced into an Orbitrap Exploris 480 mass spectrometer (Thermo Fisher Scientific, San Jose, CA) configured for DIA. The mass spectrometry parameters included a scan range of m/z 350–1 500 with a resolution of 120 000 and a normalized automatic gain control (AGC) target of 300%. In DIA mode, the m/z range of 400–1 200 was divided into 53 isolation windows for sequential fragmentation and signal acquisition. Higher-energy collisional dissociation was used for ion fragmentation with a normalized collision energy of 32%. Fragment ions were detected in the Orbitrap at a resolution of 30 000, with a normalized AGC target of 200%.

2.4 | Database Search

DIA-NN was used to analyze the DIA data using a library-free method. MS/MS data were searched against protein sequences downloaded from the UniProt database with the following parameters: Enzyme specificity, trypsin/P; maximum missed cleavages, 2; fixed modification, carbamidomethyl (C); variable modifications, oxidation (M) and acetyl (protein N-terminus); precursor mass tolerance, 20 ppm; and fragment mass tolerance, 0.05 Da. The results were filtered at an FDR of 1%, and only protein groups that passed this filtering criterion were included in downstream analyses.

2.5 | ELISA Detection of Rheumatoid Factor (RF)-IgA, RF-IgG, and SERPINA3

According to the manufacturer's instructions provided with the ELISA kit, plasma samples were diluted to the required concentration. The diluted samples were then aliquoted into a 96-well plate, followed by the addition of the corresponding antibodies and substrates according to the protocol. Incubation and colorimetric reactions were performed in strict accordance with the manufacturer's guidelines. Absorbance values were measured using an ELISA plate reader, and the data were analyzed to determine the concentrations of the target proteins in the samples.

2.6 | Statistical Analysis

Statistical analysis was performed using R (version 4.0.0). Raw protein intensities were normalized using the "median" method. Hierarchical clustering was conducted using the pheatmap package. Analysis of significantly differentially expressed proteins was performed using the metaX package. A *t*-test was used for differential expression analysis, and proteins with a *p*-value ≤ 0.05 and a fold change ≥ 1.2 were considered statistically significant. Hypergeometric-based enrichment analyses of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Gene Ontology (GO) terms, and Reactome pathways were performed to annotate protein sequences. Subcellular localization was predicted using WoLF PSORT. For datasets that conformed to a normal distribution, data were expressed as the mean ± standard deviation, and comparisons between groups were performed using the independent-samples *t*-test. For datasets that did not conform to a normal distribution, data were expressed as the median and interquartile range, and the Mann–Whitney U test was used. Correlation analysis was performed using Spearman's rank correlation coefficient. A *p*-value < 0.05 was considered statistically significant.

3 | Results

3.1 | Differential Protein Expression Analysis

A statistical analysis was conducted to determine the number of differentially expressed proteins between patients with RA and healthy controls. Upregulated proteins are shown in red, whereas downregulated proteins are shown in blue. A volcano plot was generated with log2(fold change, FC) on the x-axis and −log10(*p*-value) on the y-axis to visualize the results of the differential expression analysis. In this plot, red dots represent significantly upregulated proteins, blue dots represent significantly downregulated proteins, and gray dots indicate proteins that were not significantly differentially expressed. Additionally, a heatmap was generated with samples on the x-axis and selected differentially expressed proteins on the y-axis. The color gradient represents relative protein expression levels, ranging from blue (low expression) to white and red (high expression). Furthermore, the subcellular localization of the differentially expressed proteins was analyzed and is presented in Figure 1. To illustrate variability in protein expression within and between groups, box plots were constructed to depict the expression levels of the nine proteins with the lowest *p*-value. This analysis revealed significant differences in the expression of these key proteins between patients with RA and healthy controls and provided a foundation for subsequent functional studies.

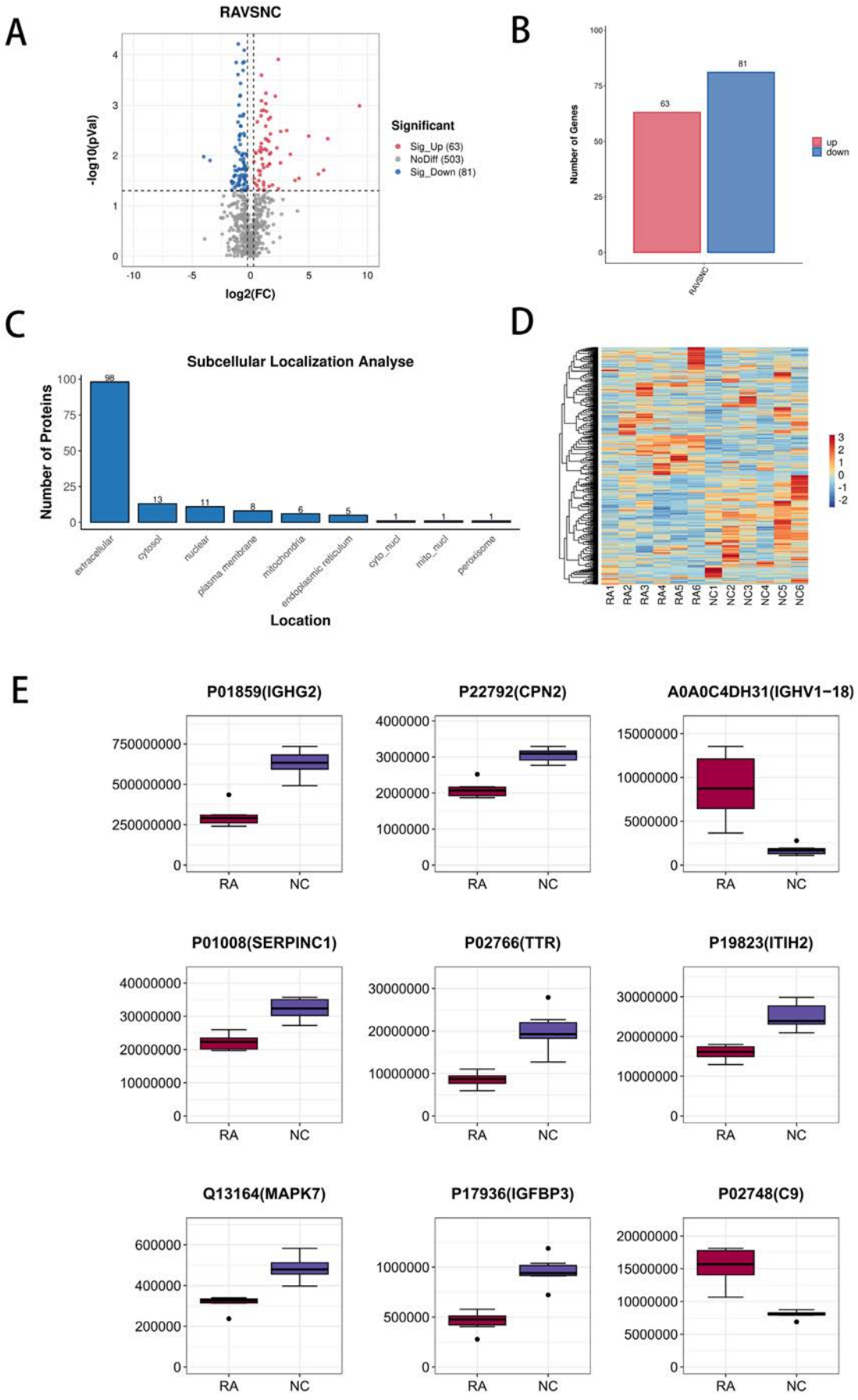

FIGURE 1 | Legend on next page.

FIGURE 1 | Differential Protein Expression Analysis: (A) Volcano plot of differentially expressed proteins; (B) summary of differentially expressed proteins; (C) subcellular localization of differentially expressed proteins; (D) heatmap of differentially expressed proteins; (E) box plots of the top nine proteins with the smallest *p*-value.

3.2 | Enrichment Analysis of Differential Proteins

To gain further insight into the functional roles of the differentially expressed proteins, GO enrichment analysis was performed. Three visualization methods—bar plots, circular plots, and scatter plots—were used to present the results. The bar plot highlights the number of enriched proteins in each pathway. For Biological Process, enrichment was primarily observed in GO:0002250 | adaptive immune response, GO:0006955 | immune response, and GO:0006953 | acute-phase response. For Cellular Component, enrichment was mainly associated with GO:0005576 | extracellular region, GO:0005615 | extracellular space, and GO:0070062 | extracellular exosome. For Molecular Function, enrichment was concentrated in GO:0003823 | antigen binding, GO:0046872 | metal ion binding, and GO:0042802 | identical protein binding.

The circular plot emphasizes the classification and overall distribution of enriched pathways. For Biological Process, enrichment was mainly observed in GO:0002250 | adaptive immune response, GO:0007596 | blood coagulation, and GO:0006953 | acute-phase response. For Cellular Component, enrichment was primarily associated with GO:0005886 | plasma membrane, GO:0005576 | extracellular region, and GO:0005788 | endoplasmic reticulum lumen. For Molecular Function, enrichment was mainly concentrated in GO:0042802 | identical protein binding, GO:0005102 | signaling receptor binding, and GO:0008201 | heparin binding.

The scatter plot provides a comprehensive visualization of multidimensional enrichment information. Certain GO terms exhibit high enrichment factors and are associated with a relatively large number of proteins, appearing as larger points in the plot. For example, GO terms related to the extracellular region (GO:0005576 | extracellular region) and antigen binding (GO:0003823 | antigen binding) demonstrate significant enrichment.

Additionally, KEGG enrichment analysis was performed on the differentially expressed proteins. The bar plot shows that, for Cellular Processes, enrichment was primarily observed in hsa04810 | regulation of actin cytoskeleton, hsa04216 | ferroptosis, and hsa04115 | p53 signaling pathway. For Environmental Information Processing, enrichment was mainly associated with hsa04066 | HIF-1 signaling pathway, hsa04068 | FoxO signaling pathway, and hsa04014 | Ras signaling pathway. For Genetic Information Processing, enrichment was concentrated in hsa04141 | protein processing in endoplasmic reticulum and hsa04120 | ubiquitin-mediated proteolysis. For Human Diseases, enrichment was primarily observed in hsa05200 | pathways in cancer, hsa05171 | coronavirus disease–COVID-19, and hsa05143 | African trypanosomiasis. For Metabolism, enrichment was centered in hsa01100 | metabolic pathways, hsa01200 | carbon metabolism, and hsa00780 | biotin metabolism. For Organismal Systems, enrichment was mainly associated with hsa04610 | complement and coagulation cascades, hsa04918 | thyroid hormone synthesis, and hsa04935 | growth hormone synthesis, secretion, and action.

Furthermore, for Cellular Processes, enrichment was also observed in hsa04510 | focal adhesion, hsa04218 | cellular senescence, and hsa04810 | regulation of actin cytoskeleton. For Environmental Information Processing, enrichment was observed in hsa04010 | MAPK signaling pathway, hsa04014 | Ras signaling pathway, and hsa04064 | NF-κB signaling pathway. For Genetic Information Processing, enrichment was identified in hsa04120 | ubiquitin-mediated proteolysis and hsa04141 | protein processing in endoplasmic reticulum. For Human Diseases, enrichment was observed in hsa05171 | coronavirus disease–COVID-19, hsa05146 | amoebiasis, and hsa05144 | malaria. For Metabolism, enrichment was detected in hsa00563 | glycosylphosphatidylinositol-anchor biosynthesis, hsa00670 | one carbon pool by folate, and hsa00340 | histidine metabolism. For Organismal Systems, enrichment was observed in hsa04935 | growth hormone synthesis, secretion, and action, hsa04610 | Complement and coagulation cascades, and hsa04918 | Thyroid hormone synthesis.

In the scatter plot, enrichment was primarily concentrated in hsa04610 | complement and coagulation cascades, hsa05143 | African trypanosomiasis, and hsa05144 | malaria (Figure 2).

Structural domain enrichment analysis of the differentially expressed proteins revealed that upregulated proteins were mainly enriched in domains such as IPR013106 |Immunoglobulin V-set domain, IPR036179|Immunoglobulin-like domain superfamily, and IPR007110 |Immunoglobulin-like domain. In contrast, downregulated proteins were predominantly enriched in domains including IPR013783 |Immunoglobulin-like fold, IPR023795 |Serpin conserved site, IPR023796 |Serpin domain, and IPR036186 |Serpin superfamily. Reactome enrichment analysis demonstrated that these differentially expressed proteins were primarily enriched in R-HAS-109582 |Hemostasis, R-HAS-166658 |Complement, and R-HAS-166663 |Initial triggering of complement pathways, regardless of upregulation or downregulation. Disease Ontology (DO) enrichment analysis showed that upregulated proteins were mainly associated with pathways related to DOID:1621|cancer, DOID:7148| rheumatoid arthritis, and DOID:18481|arthritis, whereas downregulated proteins were primarily associated with terms including DOID:1621|cancer, DOID:2251|syndrome, and DOID:4|disease (Figure 3).

3.3 | Analysis of Differential Protein–Protein Interaction (PPI) Networks

To investigate protein interactions, the complete set of differentially expressed proteins—both upregulated and downregulated—was imported into the STRING database [16] for network

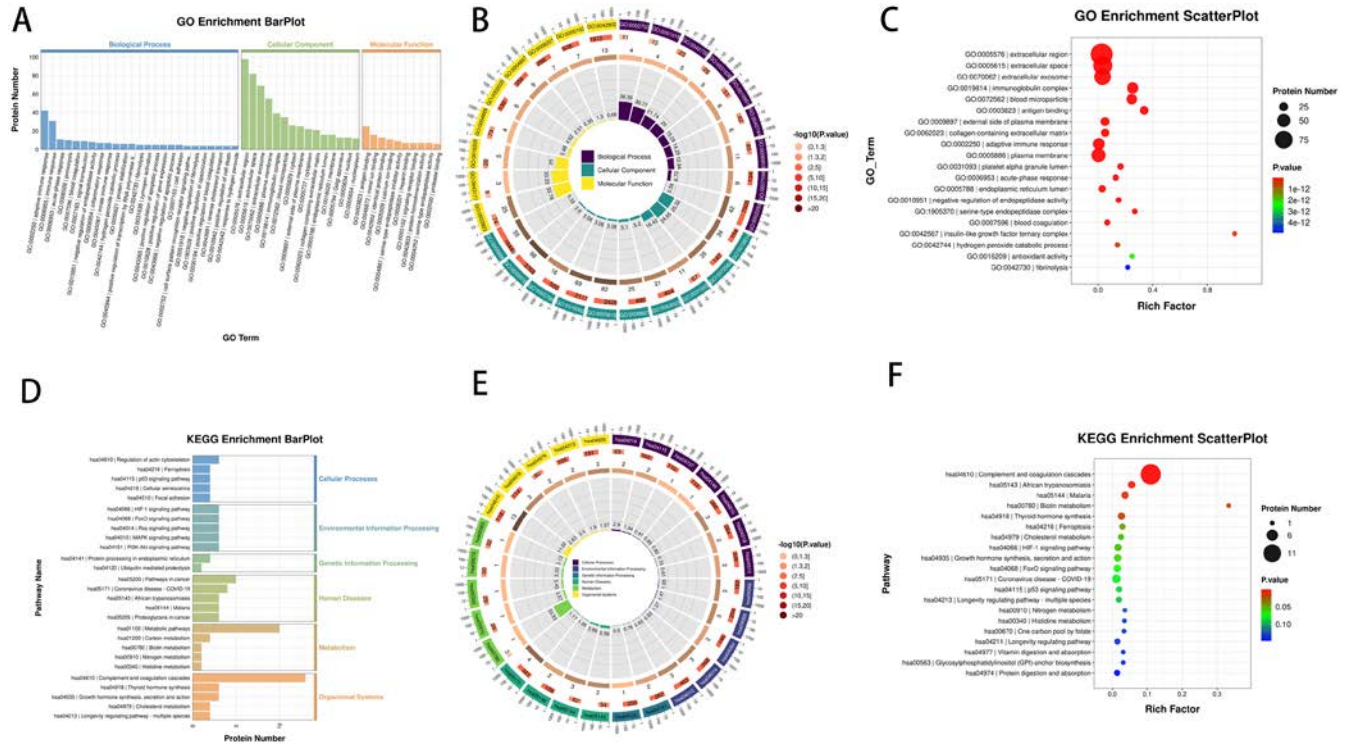

FIGURE 2 | GO and KEGG enrichment analysis: (A) GO enrichment bar chart; (B) circular plot of GO enrichment; (C) GO enrichment scatter plot; (D) KEGG enrichment bar chart; (E) circular plot of KEGG enrichment; (F) KEGG enrichment scatter plot.

interaction analysis. The results revealed complex interconnections among these proteins, providing insight into their coordinated functions in the context of RA.

In this study, a comprehensive analysis of the upregulated proteins was first conducted. To further characterize their functional roles, the bioinformatics platform Metascape [17] was used to perform GO enrichment analysis. The GO results showed that the upregulated proteins were significantly enriched in several biological processes, including adaptive immune response, immunoglobulin production, acute-phase response, neutrophil degranulation, defense response to bacteria, and complement activation.

Furthermore, Metascape was used to construct a PPI network of the upregulated proteins to identify potential functional associations. Within this PPI network, the MCODE (Molecular Complex Detection) algorithm was applied to identify densely connected protein clusters. In the MCODE1 cluster, several key proteins were identified, including SERPINA1, SERPINA3, HP (haptoglobin), CP (ceruloplasmin), and ORM1 (orosomucoid 1, also known as α-1-acid glycoprotein 1). These proteins exhibited high connectivity within the PPI network and may collectively contribute to the regulation of the biological processes described above (Figure 4).

3.4 | Analysis of SERPINA3 Expression Levels

In this study, ELISA was used to analyze plasma samples from patients with RA and healthy controls. Receiver operating characteristic (ROC) analysis was performed, and the Youden index was maximized to determine an optimal cutoff value of 16.32 for distinguishing elevated plasma SERPINA3 levels in patients with RA from those in healthy controls. This cutoff yielded a sensitivity of 68.09% and a specificity of 75.00% (AUC = 0.7629, 95% CI: 0.6534–0.8724). Compared with the healthy control group, plasma SERPINA3 levels were significantly elevated in patients with RA. In patients with low and moderate disease activity, plasma SERPINA3 levels were 16.36 (12.38, 19.78), which differed significantly from those in healthy controls [7.585 (3.575, 16.41); $p = 0.0256$]. In patients with high disease activity, plasma SERPINA3 levels further increased to 22.34 (13.80, 34.21), and the difference compared with healthy controls was highly significant ($p < 0.0001$). Moreover, patients with high disease activity exhibited higher plasma SERPINA3 levels than those with low and moderate disease activity ($p = 0.0154$).

Correlation analysis was further performed to evaluate the association between SERPINA3 levels and RA disease activity indicators. SERPINA3 levels were positively correlated with erythrocyte sedimentation rate (ESR) ($r = 0.3903$, $p = 0.0067$), C-reactive protein (CRP) ($r = 0.3254$, $p = 0.0256$), tender joint count ($r = 0.2939$, $p = 0.0450$), swollen joint count ($r = 0.2877$, $p = 0.0499$), and Disease Activity Score 28 (DAS28) ($r = 0.3990$, $p = 0.0055$). However, no significant correlation was observed between SERPINA3 levels and RF ($r = 0.0040$, $p = 0.9828$), RF-IgG ($r = 0.0938$, $p = 0.6036$), or RF-IgA ($r = 0.2390$, $p = 0.1484$).

In a subgroup analysis, patients with RA were stratified into three groups according to RF levels: < 20, 20–100, and > 100. Comparison of SERPINA3 levels among these RF-based subgroups revealed no statistically significant differences ($p > 0.05$). Similarly, patients were stratified according to anti-cyclic citrullinated peptide (ACCP) antibody levels

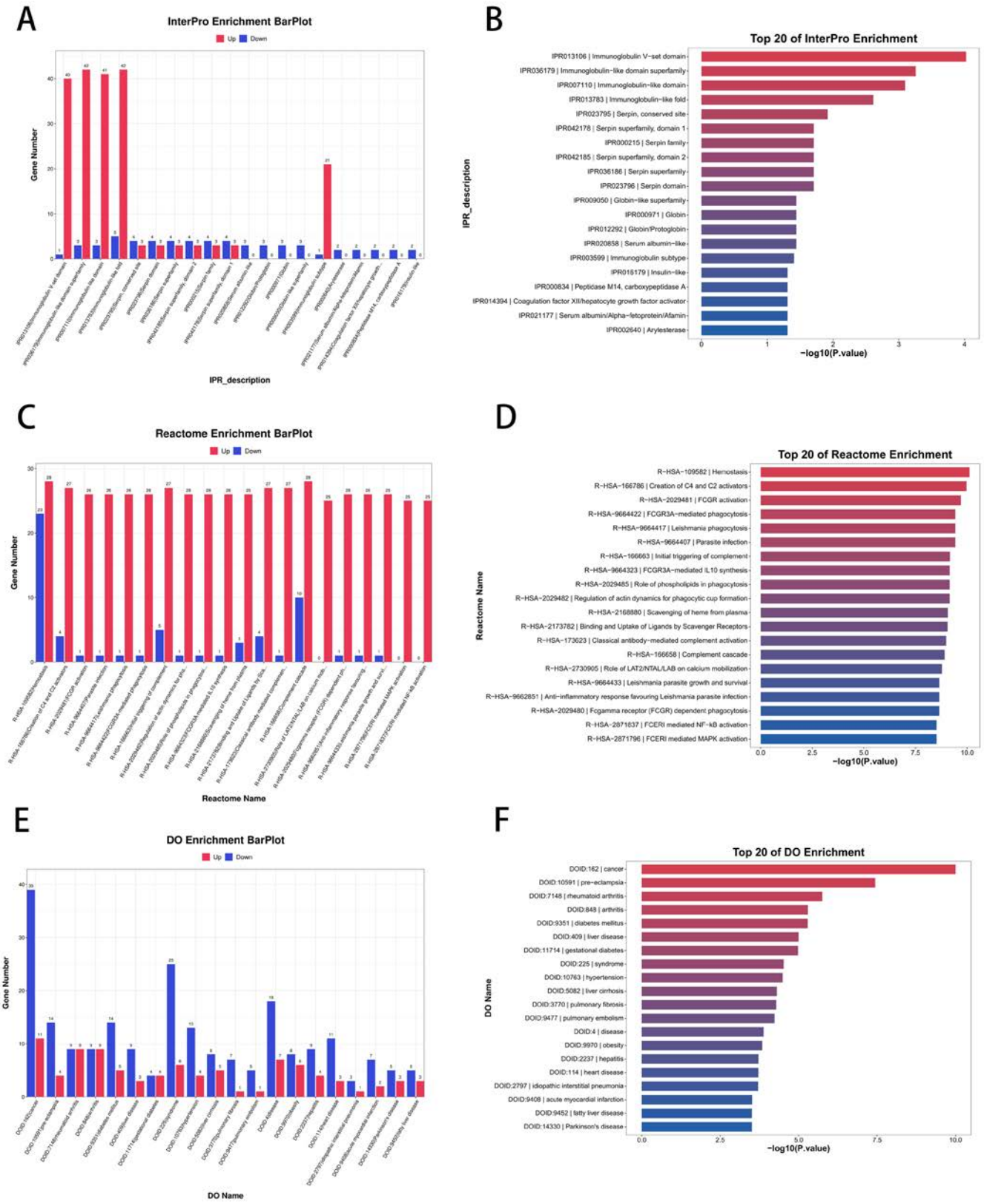

FIGURE 3 | Domain, Reactome, and DO Enrichment Analysis: (A) InterPro enrichment bar plot; (B) top 20 InterPro enrichment terms; (C) Reactome enrichment bar plot; (D) top 20 Reactome enrichment terms; (E) DO enrichment bar plot; (F) top 20 DO enrichment terms.

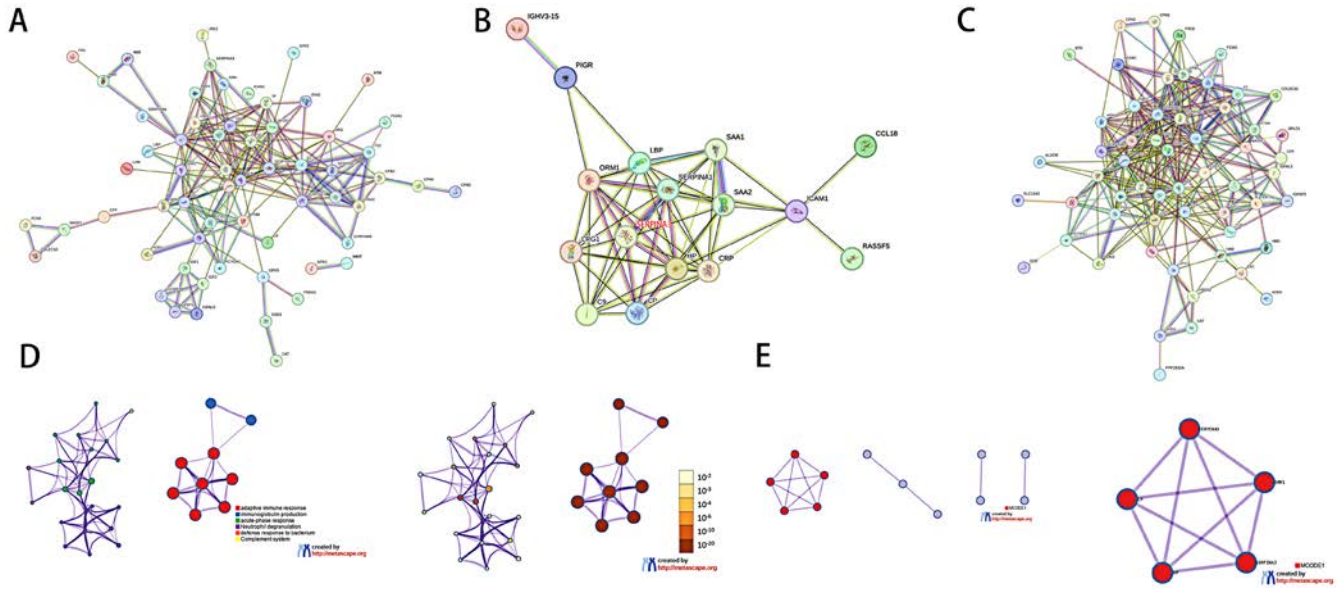

FIGURE 4 | Analysis of Differential PPI Networks: (A) total differential PPI network; (B) upregulated PPI network; (C) downregulated PPI network; (D) GO enrichment analysis of upregulated proteins using Metascape; (E) MCODE analysis of upregulated proteins using Metascape.

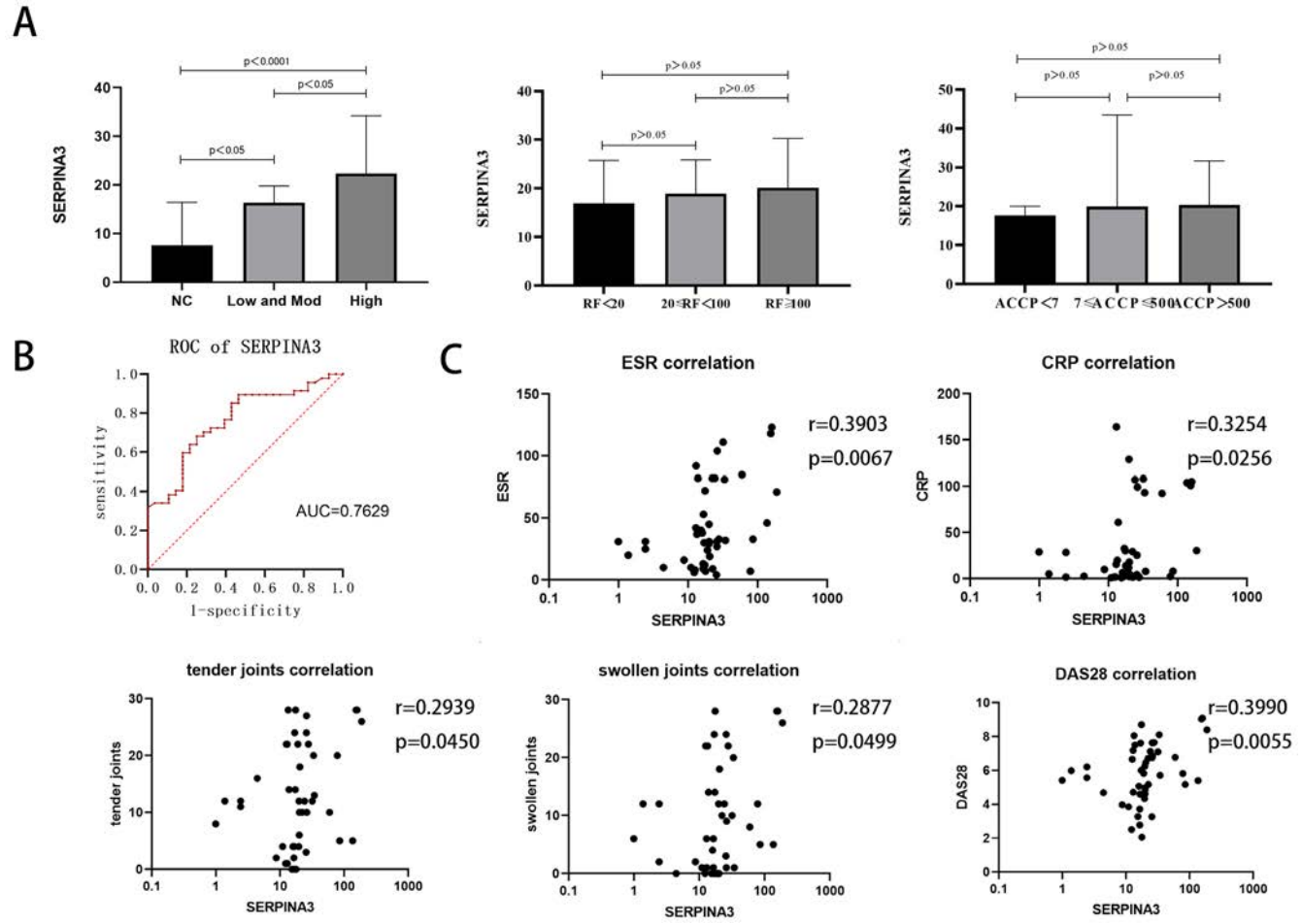

FIGURE 5 | Expression Analysis of SERPINA3: (A) SERPINA3 levels stratified by DAS28, RF, and ACCP status; (B) ROC curve evaluating the diagnostic performance of SERPINA3; (C) correlation analysis of ESR, CRP, tender joint count, swollen joint count, and DAS28.

into three groups: < 7, 7–500, and > 500. Comparative analysis of SERPINA3 levels among these ACCP-based subgroups also showed no statistically significant differences ($p > 0.05$) (Figure 5).

4 | Discussion

This study focused on RA and identified SERPINA3 as a potential biomarker for both diagnosis and prognosis. Recent proteomic studies have provided important insights into RA pathogenesis, including alterations in protein lactylation, concordance between synovial fluid and blood proteomes, and stage-specific autoantibody changes, all of which facilitate disease prediction and precision therapy [18, 19]. These findings have laid the foundation for exploring novel RA biomarkers and therapeutic targets.

Using comprehensive bioinformatics analyses—including GO, KEGG, Reactome, domain enrichment, DO, and PPI network analysis—we systematically characterized plasma proteomic differences between patients with RA and healthy controls to identify potential diagnostic and prognostic biomarkers. We observed that the plasma levels of several proteins, including SAA1, SAA2, haptoglobin, ceruloplasmin, ORM1, LRG1, ICAM1, LBP, SERPINA1, and SERPINA3, were significantly elevated in patients with RA compared with healthy controls. These proteins may be closely associated with inflammatory pathways, cartilage degradation, and autoimmune mechanisms involved in RA. We also observed downregulation of proteins such as GPX3, PON1, APOA2, and ITIH2 in the plasma of patients with RA. These proteins are primarily involved in maintaining physiological homeostasis but may be suppressed or dysregulated during RA pathogenesis.

Notably, domain enrichment analysis demonstrated that the differentially expressed proteins were predominantly enriched in serpin-type peptidase inhibitor domains, suggesting that an imbalance between proteases and serpins may constitute a key molecular mechanism underlying RA pathogenesis. These findings further support the critical role of SERPINA3 in regulating proteolytic activity, which is essential to the pathophysiological progression of RA. Consistent findings from KEGG and Reactome pathway analyses demonstrated significant enrichment of RA-related pathways, including complement and coagulation cascades, endoplasmic reticulum protein processing, ubiquitin-mediated proteolysis, hemostasis, complement activation (C4/C2 activation), and FCGR-mediated immune activation. These pathways are closely associated with autoantibody-dependent immune complex formation and chronic inflammation in RA, and their aberrant activation exacerbates immune cell infiltration, synovial damage, and local microthrombosis within the joints. SERPINA3 may fine-tune local immune activation by modulating the proteolytic processing of antibodies, Fc receptors, or complement components. Specifically, it may regulate proteases involved in C4/C2 activator formation, thereby directly influencing complement activation. In addition, SERPINA3 may inhibit key proteases within the complement and coagulation cascades, thereby modulating pathway activation and progression and influencing host immune responses and hemostatic balance in patients with RA. Furthermore, SERPINA3 was identified as a central hub gene in the MCODE1 module of the PPI network, exhibiting strong interactions with multiple inflammation- and protease-related proteins. This hub status suggests that SERPINA3 may participate in the assembly of functional protein complexes to coordinately regulate critical processes in RA pathogenesis, including proteolysis, immune responses, and inflammatory amplification. Notably, the potential compensatory role of SERPINA3 in RA remains to be fully elucidated. Although our data indicate that SERPINA3 may mitigate excessive tissue damage by inhibiting proteolysis, its upregulation may also contribute to RA pathogenesis by disrupting hemostasis or impairing immune complex clearance, reflecting a dual functional role similar to that observed in other inflammatory diseases.

The central role of SERPINA3 in the PPI network suggests that it may function as a key regulator of the pathways described above. Among the top upregulated proteins, SERPINA3 was selected for experimental validation in the present study based on multiple lines of evidence. Our proteomic data demonstrated markedly elevated plasma levels of SERPINA3 in patients with RA. In addition, domain enrichment, KEGG, and Reactome analyses consistently associated SERPINA3 with core pathological processes of RA, including serpin dysfunction, dysregulated complement and coagulation cascades, and aberrant immune-inflammatory pathways. Furthermore, the identification of SERPINA3 as a hub protein in the PPI network supports its potential regulatory role within this interaction network. Accordingly, SERPINA3 was prioritized for validation using ELISA to characterize its expression profile, verify its involvement in RA pathogenesis, and evaluate its potential as a diagnostic and prognostic biomarker.

The study findings revealed a significant difference in SERPINA3 levels between patients with RA and healthy controls, highlighting its potential as a diagnostic biomarker. Further analysis demonstrated markedly elevated plasma SERPINA3 levels in patients with RA. Notably, plasma SERPINA3 levels in patients with low disease activity were already higher than those in healthy individuals and increased further in patients with high disease activity, showing a strong correlation with disease activity. In addition, SERPINA3 levels were correlated with RA disease activity indicators, including ESR, CRP, tender joint count, swollen joint count, and the DAS28, suggesting that elevated SERPINA3 levels may reflect enhanced inflammatory responses in patients with RA. However, no significant correlation was observed between SERPINA3 levels and RF or its subtypes (RF-IgG and RF-IgA). Although RF is a common autoantibody detected in the plasma of patients with RA, its association with disease activity remains inconsistent. These findings indicate that the mechanism by which SERPINA3 contributes to RA pathogenesis may differ from that involving RF. Compared with previous studies, the present investigation is the first to systematically characterize the plasma expression profile of SERPINA3 in RA and its association with disease activity. Although prior research has reported aberrant SERPINA3 expression in other inflammatory conditions, including neurodegenerative disorders and inflammatory bowel disease, its relationship with disease activity has not been thoroughly examined [20, 21]. This study extends these findings by clarifying the distinct role of SERPINA3 in RA, demonstrating that plasma SERPINA3 levels

may serve as a dynamic indicator of inflammatory burden and overall disease activity. Notably, RF and anti-citrullinated protein antibodies are RA-specific autoantibodies primarily used for diagnostic and classification purposes. Although both are commonly detected in patients with RA, their titers do not consistently correlate with disease activity. In contrast, SERPINA3 appears to play a regulatory role more directly related to the dynamic balance of inflammatory responses. Consequently, a direct linear correlation may not exist between SERPINA3 levels and RF or ACCP titers. The variation in SERPINA3 levels across different stages of disease activity, together with its lack of association with RF and ACCP, suggests a distinct mechanism underlying its involvement in inflammation and immune regulation. These findings deepen our understanding of RA pathogenesis and indicate that SERPINA3 holds promise as a novel biomarker for disease diagnosis, therapeutic monitoring, and prognostic assessment.

In addition, CRP and ESR, which are widely used inflammatory markers, play important roles in the diagnosis and monitoring of RA. However, their specificity is relatively limited, as their levels may increase in a wide range of inflammatory and non-inflammatory conditions. In contrast, our findings suggest that SERPINA3 demonstrates greater specificity, indicating that it may provide additional value in distinguishing RA from other disease states and reducing false-positive results. The higher specificity of SERPINA3 supports its potential as a supplementary biomarker. Combining SERPINA3 with CRP or ESR may improve diagnostic accuracy by integrating complementary information. Moreover, SERPINA3 may offer unique insights into the pathogenesis and progression of RA. Given its regulatory role in inflammatory and immune processes, further investigation of its signaling pathways and molecular mechanisms may help identify key factors involved in disease initiation and progression. In the future, SERPINA3 may represent a promising therapeutic target and provide a rationale for the development of more specific and effective treatments for RA.

Although this study employed DIA proteomics, which offers advantages such as high throughput, enhanced sensitivity, and reliable data quality, several limitations should be acknowledged. First, the relatively small sample size may have limited the statistical power, particularly for subgroup analyses (e.g., comparisons among patients with different levels of disease activity). Second, as a cross-sectional study, it could not establish a causal relationship between SERPINA3 levels and RA progression. Third, the absence of patients with other autoimmune diseases as disease controls limited the ability to determine whether elevated SERPINA3 levels are specific to RA. Finally, the molecular mechanisms regulating SERPINA3 expression were not investigated, which restricts understanding of its precise role in RA pathogenesis. Several issues remain unresolved. The specific mechanism by which SERPINA3 contributes to RA remains unclear, and the combined diagnostic value of SERPINA3 with other established biomarkers has not been evaluated. To address these limitations, future studies should include larger sample sizes, adopt longitudinal designs to monitor dynamic changes in SERPINA3 levels in patients with RA, and assess its combined diagnostic performance with other biomarkers. Furthermore, the use of gene-editing approaches, such as CRISPR/Cas9-mediated knockout or overexpression of SERPINA3, may help clarify its role in RA-related inflammation and joint destruction.

In summary, using DIA proteomics and bioinformatic analyses, this study identified SERPINA3 as a novel plasma biomarker elevated in patients with RA. SERPINA3 is closely associated with disease activity and is involved in multiple core pathways implicated in RA pathogenesis. These findings provide new insights into RA pathogenesis and support the potential clinical utility of SERPINA3 in diagnosis, therapeutic monitoring, and prognostic assessment.

Author Contributions

Yang Zhao took charge of conceptualizing and designing the study. Junhua Xu and Fengwei Ji were responsible for collecting the data. Yuan Li and Meng Qi conducted the analysis of the collected data. Yan Kan and Chunyu Kong interpreted the results derived from the data analysis. All authors participated in drafting the article and critically revising it for important intellectual content, ultimately approving the final version for submission and publication.

Acknowledgments

Yang Zhao and Yuan Li have contributed equally to this paper and are considered co-first authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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CLINICAL IMAGE

Chronic Non-Bacterial Osteitis Initially Attributed to Knee Osteoarthritis in an Older Adult: Bone Scintigraphy and MRI Findings

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A 62-year-old woman presented with a 10-year history of recurrent knee pain and functional limitation. Plain radiographs demonstrated bilateral degenerative changes, leading to initial treatment for degenerative knee disease with oral etoricoxib and local therapy, without meaningful improvement. Whole-body 99mTc-MDP bone scintigraphy showed focal increased radiotracer uptake in

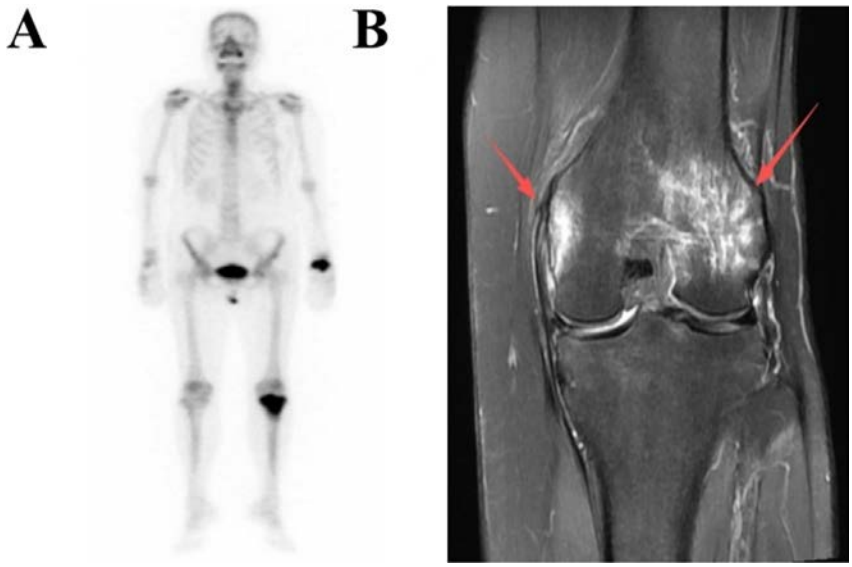

FIGURE 1 | Imaging findings of the patient. (A) Whole-body bone scintigraphy with ^{99m}Tc-MDP showing increased radiotracer uptake in the left knee joint; (B) MRI demonstrating bone marrow edema in the distal left femur.

Cen Chang, Zhimin Lin contributed equally to this study.

the left knee (Figure 1A), whereas MRI revealed bone marrow edema-like signal in the distal left femur (Figure 1B).

Although imaging findings initially supported a diagnosis of osteoarthritis, the relapsing clinical course, inadequate response to conventional treatment, and osseous abnormalities not fully explained by osteoarthritis prompted further clinical reassessment. Following evaluation, chronic nonbacterial osteitis (CNO) was clinically favored. Intravenous bisphosphonate therapy resulted in marked pain relief and restoration of independent ambulation. CNO should be differentiated from osteoarthritis by considering its relapsing bone-pain course, discordance between symptoms or osseous lesions and degenerative changes, and appropriate evaluation for alternative diagnoses, including infection and malignancy [1–4].

Author Contributions

Chen Li and Dongyi He designed this study. Cen Chang and Zhimin Lin wrote the manuscript and processed images. Jingchen Yang, Naigang Chen, Cheng Xu, and Fanzhang Meng contributed to the content of the manuscript. All authors approved the final manuscript.

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Consent

Informed consent to publication was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets analyzed for this study are available from the corresponding author, Dr. Chen Li (casio1981@163.com) upon reasonable request.

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ORIGINAL ARTICLE

Efficacy and Safety of Ultra-Low Starting Dose Febuxostat Titration in Male Patients With Primary Gout

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ABSTRACT

Background: Since gout is a common metabolic arthritis caused by urate crystal deposition, urate-lowering therapy (ULT) is clearly indicated, but the initiation of ULT frequently causes paradoxical acute flares that in turn impair patient adherence.

Objective: This study sought to assess the effectiveness and safety of an ultra-low-dose initiation strategy for febuxostat (10 mg/day) compared to the standard starting dose (20 mg/day) in reducing initiation-related flares while maintaining long-term urate control.

Methods: 120 male patients with primary gout presenting with acute arthritis were randomly assigned to initiate febuxostat at 10 mg/day (Group A) or 20 mg/day (Group B), with protocol-mandated biweekly titration. The primary outcomes were gout flare frequency over 24 weeks (assessed using Poisson regression), serum uric acid (SUA) target attainment, and the incidence of adverse events.

Results: Although both groups achieved comparable target SUA levels by week 24, Group A demonstrated a significantly lower overall flare incidence (36.7% vs. 70.0%; $p < 0.001$), along with a greater percentage of flare-free patients (70.0% vs. 46.7%; $p = 0.016$). Multivariable Poisson regression revealed that Group B had an approximately twofold higher risk of flares compared to Group A (Incidence Rate Ratio = 1.95; $p = 0.012$), with obese patients deriving the most pronounced benefit from the ultra-low-dose approach. To avert one additional flare, the calculated number needed to treat was 4.3. Additionally, the occurrence of clinically significant liver injury (ALT/AST > 3× ULN) was low in both groups, with 3.3% in Group A and 1.7% in Group B. Multivariable regression analysis confirmed that LDL-C is an independent predictor of ALT ($\beta = 12.90$, $p = 0.009$), while febuxostat dosage was not linked to hepatotoxicity.

Conclusion: Initiating febuxostat at a dose of 10 mg/day with gradual titration demonstrates a superior safety profile by effectively reducing early acute flares without compromising long-term urate control, which is particularly advantageous for high-risk cohorts, including obese patients.

Abbreviations: ALT, alanine aminotransferase; ARD, absolute rate difference; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cys-C, cystatin C; FBG, fasting blood glucose; GGT, glutamyl aminotransferase; HCY, homocysteine; HDL-c, high-density lipoprotein cholesterol; IRRs, incidence rate ratios; LDL-c, low-density lipoprotein cholesterol; MSU, monosodium urate; NNT, number needed to treat; PLT, platelet count; sCr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; ULT, urate-lowering therapy; WBC, white blood cells.

Sun Huizhen and Li Yadi contributed equally to this work.

1 | Introduction

Gout, a prevalent metabolic arthropathy characterized by the accumulation of monosodium urate crystals, manifests as severe arthritis and tophaceous deposits, thereby threatening joint integrity and renal function [1]. The worldwide burden of this condition is rising, particularly within industrialized regions, where it is strongly associated with comorbidities such as obesity and hypertension [2]. While acute exacerbations significantly diminish patient quality of life and increase medical expenditures, the associated systemic inflammation further increases cardiovascular risk, underscoring the urgent need for robust, sustained therapeutic strategies [3].

The treatment of gout is divided into the management of acute attacks and long-term urate-lowering therapy to dissolve crystals and prevent disease progression [2, 4]. Acute flares are managed with colchicine, NSAIDs, or corticosteroids, whereas chronic management relies on urate-lowering therapy with xanthine oxidase inhibitors [5]. Guidelines advocate a treat-to-target approach, keeping serum urate below 360 μmol/L to avoid acute flares, or below 300 μmol/L to dissolve crystal deposits [6]. A challenge arises when starting therapy: paradoxical acute flares, or "mobilization flares," occur due to rapid urate reduction destabilizing crystals, triggering inflammation [7, 8]. This can reduce patient adherence, as flares are mistaken for treatment failure [9]. A key focus in current gout management is the "start low, go slow" principle when initiating urate-lowering therapy [10]. This involves a low initial dose with gradual titration to avoid acute flares [11].

Febuxostat, a selective xanthine oxidase inhibitor, is an alternative for patients who are intolerant to allopurinol [12]. Guidelines often recommend starting at 40 mg/day with possible titration to 80 mg/day, though optimal dosing to balance efficacy and flare risk is debated [13]. Starting doses such as 20 mg/day may be employed to enhance tolerability, typically alongside prophylactic agents like colchicine, NSAIDs, or corticosteroids to prevent flares without compromising efficacy [14, 15]. However, these prophylactic agents carry risks: colchicine can cause bone marrow suppression and potential toxicity, NSAIDs may lead to gastrointestinal and renal problems, and corticosteroids can disrupt glucose homeostasis. The effectiveness and safety of starting therapy at low doses, particularly comparing 10 mg/day versus 20 mg/day, have not been thoroughly examined. This study aims to define a refined regimen balancing early tolerability, long-term urate control, and metabolic health for more precisely tailored gout management.

2 | Materials and Methods

2.1 | Study Subjects

This study enrolled 120 male patients diagnosed with primary acute gouty arthritis presenting to the Northern Theater Command General Hospital between January and March 2025. The inclusion criteria were as follows: (1) fulfillment of the "2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Gout" [16]; (2) age between 18 and 70 years; (3) no use of medications for preventing or treating gouty arthritis in the past month; (4) intact cognitive function, with the ability to comprehend the study material and provide appropriate responses. The exclusion criteria were as follows: (1) coexisting acute or chronic infectious diseases; (2) autoimmune disorders, hematologic diseases, malignancies, or secondary gout caused by medications; (3) significant abnormalities in cardiovascular, hepatic, or renal function tests; (4) previous use of urate-lowering drugs such as febuxostat or benzbromarone within the past month; and (5) known allergy or severe adverse reactions to the study medications [17]. The study protocol was approved by the Ethics Committee of the Northern Theater Command General Hospital (Approval No. 2025-145); informed written consent was obtained from all participants.

2.2 | Experimental Design

Eligible participants were randomly assigned (1:1) to either the ultra-low-dose febuxostat titration group (Group A) or the conventional-dose group (Group B) using a permuted block randomization scheme with variable block sizes of 4. An independent statistician, uninvolved in patient enrollment or outcome assessment, computer-generated the randomization sequence. Allocation concealment was ensured via sequentially numbered, opaque, and sealed envelopes (SNOSE). After confirmation of eligibility and informed consent, the enrolling physician opened the subsequent sequentially numbered envelope to determine the participant's treatment assignment.

Participants in Group A ($n = 60$) began treatment with febuxostat at a dosage of 10 mg/day, while those in Group B ($n = 60$) initiated treatment with 20 mg/day. Urate-lowering therapy (ULT) was commenced 2 weeks after the resolution of acute gout attacks. In Group A, dosages were increased by 10 mg every 2 weeks, while in Group B, the increase was 20 mg every 2 weeks. Dosages of febuxostat were adjusted according to clinical signs and symptoms, as well as hepatic and renal function, alongside serum uric acid (SUA) levels. The target SUA level was set at 200–360 μmol/L for patients without tophi or gouty nephropathy, and 200–300 μmol/L for those with these conditions. Patients achieving target SUA levels continued maintenance therapy with a maximum febuxostat dosage of 80 mg/day.

All patients underwent systematic evaluation starting from treatment initiation, with in-person visits scheduled at weeks 4, 8, 12, and 24 for comprehensive biochemical assessment, physical examination, and dose adjustment based on SUA levels and tolerability. Additionally, telephone follow-ups were conducted by a dedicated research nurse to assess symptoms, adverse events, and confirm dose escalation at weeks 2, 6, 10, 14, 18, and 22. Between in-person visits, dose escalation followed a fixed algorithm unless contraindicated: (1) In the absence of flares, ALT levels $> 3 \times$ ULN, or SUA levels < 200 μmol/L, the dose was escalated according to the protocol. (2) If a flare occurred: flare treatment per protocol, dose maintained (not increased) until 2 weeks post-resolution. (3) If SUA < 200 μmol/L at any in-person visit: dose reduced by one step. (4) If ALT levels exceeded 3×ULN, febuxostat was discontinued until resolution. Patients maintained a medication diary recording daily febuxostat intake, flare occurrences,

and any symptoms. This diary was reviewed at each in-person visit.

All patients were provided with health education and instructed to adhere to a low-purine diet. Non-cardiovascular hyperlipidemic patients were managed with dietary intervention alone (low-fat diet), whereas those with cardiovascular disease maintained their ongoing statin therapy (atorvastatin or rosuvastatin). Patients with hyperhomocysteinemia received daily oral supplementation of 0.8 mg folic acid, 10 mg vitamin B6, and 25 μg vitamin B12. During gout flares, patients received oral etoricoxib (60–120 mg/day) or prednisone (10–30 mg/day for refractory cases) for up to 1 week, without interruption of the febuxostat regimen. Concomitant use of colchicine and other nonsteroidal anti-inflammatory drugs was withheld. The dose titration schedule resumed as protocolized 2 weeks after the resolution of acute symptoms.

2.3 | Data Collection

2.3.1 | General Information

During the first visit, we gathered information on the patient's age, height, weight, duration of illness, location and number of swollen or painful joints, presence of tophi, frequency of previous gout attacks, comorbidities (such as diabetes, dyslipidemia, hypertension, and coronary heart disease), prior medication use (including urate-lowering drugs and anti-inflammatory analgesics), and family history. The Body Mass Index (BMI) was calculated using the formula BMI = weight (kg)/height^2 (m^2).

2.3.2 | Biochemical Indicators

Venous blood samples were obtained after an overnight fast to evaluate the following parameters: complete blood count (including white blood cells [WBC] and platelets [PLT]), serum uric acid (SUA), liver function markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma-glutamyl transferase [GGT]), renal function parameters (serum creatinine [sCr], cystatin C [Cys-C], and blood urea nitrogen [BUN]), fasting blood glucose (FBG), lipid profile (total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol [LDL-C]), and homocysteine (HCY). Additionally, midstream clean-catch urine samples were collected for routine urinalysis, including the recording of urine pH.

2.3.3 | Imaging Data

Ultrasonography of the urinary system and affected joints was performed.

2.3.4 | Observation Indicators

The main outcome measure was the frequency of gout attacks. Secondary outcomes included alterations in SUA levels, liver and kidney function parameters, lipid profiles, and the incidence of adverse events. The CONSORT flow diagram for this study is presented in Figure 1.

2.4 | Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Python (version 3.x with the StatsModels package). The normality of continuous variables was evaluated through the Shapiro–Wilk test and by visually inspecting Q-Q plots. Normally distributed continuous variables were reported as the mean ± standard deviation (SD), and intergroup differences were assessed using independent-samples *t*-tests. For within-group comparisons of pre- and post-treatment measurements, paired-samples *t*-tests were utilized. Non-normally distributed continuous variables were presented as the median (interquartile range [IQR]), with intergroup comparisons carried out using the Mann–Whitney *U* test. Categorical variables were summarized as frequencies and percentages [*n* (%)], and group comparisons were performed using the chi-square test or Fisher's exact test when any cell had an expected frequency of < 5.

The primary outcome was analyzed using Poisson regression. Negative binomial regression was performed as a sensitivity analysis to account for potential overdispersion. A zero-inflated Poisson (ZIP) model was additionally fitted to distinguish between "structural zeros" and "sampling zeros" and to evaluate the robustness of the findings. Quasi-Poisson regression was further employed to obtain robust standard errors in the presence of mild overdispersion. Multivariable Poisson and negative binomial regression models were constructed to adjust for potential confounders. Subgroup analyses were performed based on predefined stratification variables. Interaction terms between the treatment group and each stratification variable were tested within the multivariable Poisson model to assess effect modification. Absolute rate difference (ARD) and number needed to treat (NNT) were calculated to translate the relative effect estimates into clinically interpretable measures. To assess the statistical power of the primary outcome analysis, a post hoc power analysis was performed using the observed effect size and sample size.

All statistical tests were two-sided. A p value < 0.05 was considered statistically significant. Results were reported as incidence rate ratios (IRRs) with 95% confidence intervals (CIs) unless otherwise specified.

3 | Results

3.1 | Comparison of Baseline Clinical Characteristics and Laboratory Indicators

As shown in Table 1, the baseline characteristics of the two groups were comparable, showing no statistically significant differences in age, disease duration, family history, BMI, annual frequency of gout attacks, number and location of affected joints, or prevalence of tophi and nephrolithiasis (all $p > 0.05$). Approximately 60% of patients in both groups presented with dyslipidemia and hyperhomocysteinemia, and about 36% were

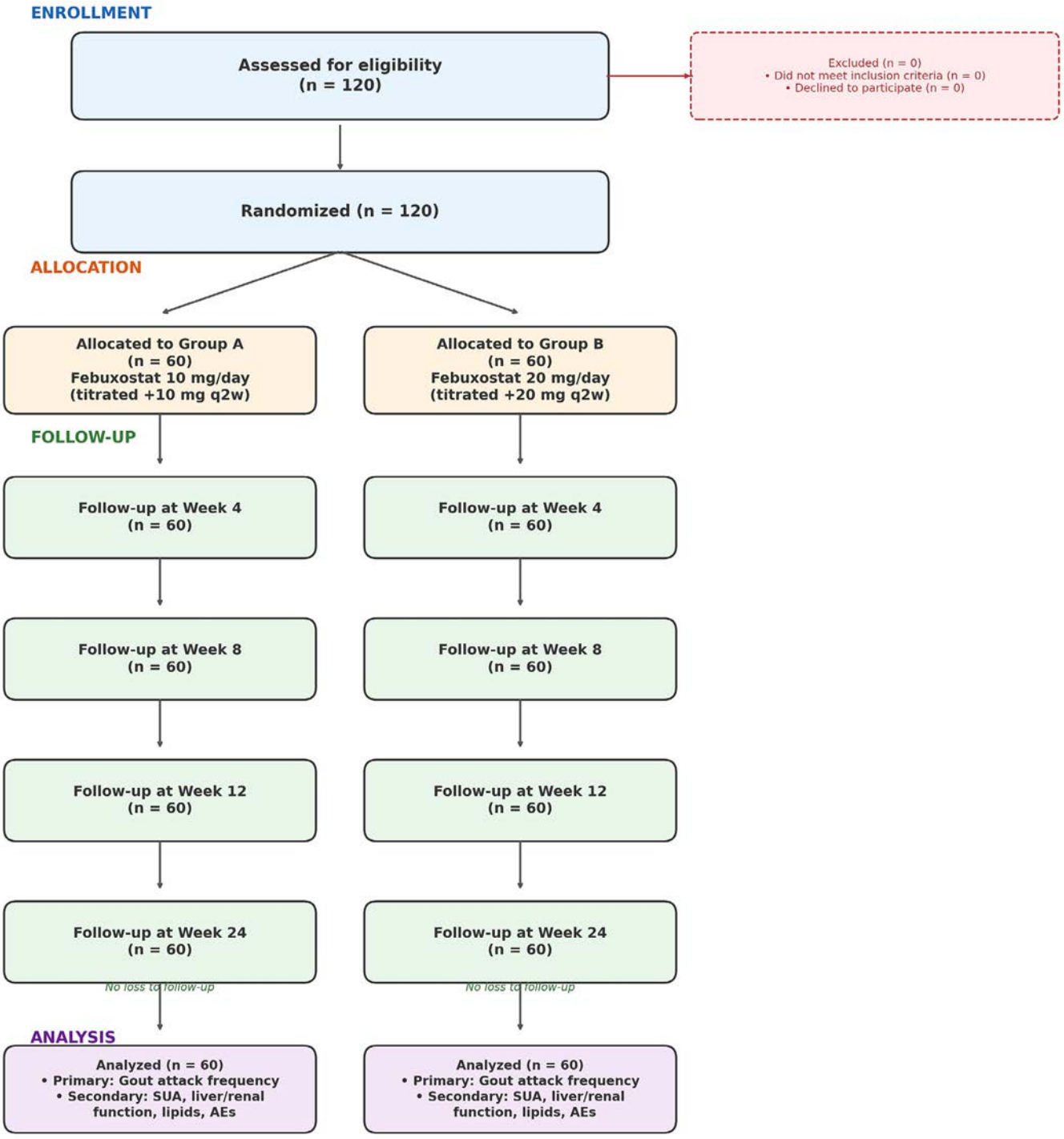

FIGURE 1 | CONSORT flow diagram of efficacy and safety of ultra-low starting dose febuxostat titration in primary gout.

obese, with no significant intergroup differences (all $p > 0.05$). The prevalence of diabetes, hepatic steatosis, and cardiovascular diseases was not significantly different between the groups (all $p > 0.05$). Prior medication histories showed no significant differences between the groups. There were no significant differences among the groups (all $p > 0.05$). Additionally, 60% of the patients had previously used febuxostat, although inappropriate use resulted in acute gout attacks. Baseline laboratory tests (Table 1), including complete blood count (WBC, Hb, PLT), liver function (ALT, AST, GGT), renal function (SCR, BUN, CYS-C), fasting glucose, and lipid profile (TC, TG, LDL-C, HDL-C), were assessed. No significant differences were found between the two groups for these parameters, nor for serum uric acid (SUA) and homocysteine (HCY) (all $p > 0.05$).

3.2 | Longitudinal Changes in BMI and Biochemical Markers Posttreatment

As indicated in Table 2, BMI decreased significantly in both groups relative to baseline after treatment ($p < 0.05$). Levels of SUA, TC, LDL-C, and homocysteine were also considerably

TABLE 1 | Baseline clinical characteristics and laboratory parameters of the two gout groups.

Variables	Group A ($n=60$)	Group B ($n=60$)	$t/z/\chi^2$	p
General information				
Age (years)	35.0 (25.3, 43.8)	33.0 (30.0, 41.0)	−0.131	0.896
Duration (years)	4.0 (2.0, 7.0)	4.0 (2.3, 6.0)	−0.235	0.814
Family history, *n* (%)	5 (8.3%)	6 (10.0%)	0.100	0.752
BMI (kg/m^2)	27.2 (25.8, 29.7)	27.1 (25.2, 28.9)	−0.294	0.769
Attacks per year	3.0 (2.0, 4.0)	2.0 (2.0, 4.0)	−0.225	0.822
Number of joints involved	2.0 (1.0, 4.0)	2.0 (1.0, 3.8)	−0.479	0.632
Affected joints				
Metatarsophalangeal joint	49 (81.7%)	51 (85.0%)	0.240	0.624
Ankle	27 (45.0%)	31 (51.7%)	0.534	0.465
Knee	11 (18.3%)	13 (21.7%)	0.208	0.648
Other	31 (51.7%)	33 (55.0%)	0.134	0.714
Comorbidities				
Tophus, *n* (%)	10 (16.7%)	11 (18.3%)	0.058	0.810
Nephrolithiasis, *n* (%)	15 (25.0%)	9 (15.0%)	1.875	0.171
Cardiovascular disease, *n* (%)	15 (25.0%)	8 (13.3%)	2.636	0.104
Diabetes, *n* (%)	8 (13.3%)	5 (8.3%)	0.776	0.378
Dyslipidemia, *n* (%)	34 (56.7%)	41 (68.3%)	1.742	0.187
Hepatic steatosis, *n* (%)	8 (13.3%)	9 (15.0%)	0.069	0.793
Obesity, *n* (%)	23 (38.3%)	22 (36.7%)	0.036	0.850
Hyperhomocysteinemia, *n* (%)	45 (75.0%)	35 (58.3%)	3.750	0.053
Previous medication history				
Allopurinol, *n* (%)	1 (1.7%)	1 (1.7%)	0.000	1.000
Febuxostat, *n* (%)	34 (56.7%)	40 (66.7%)	1.269	0.260
Benzbromarone, *n* (%)	7 (11.7%)	11 (18.3%)	1.046	0.306
NSAIDs, *n* (%)	59 (98.3%)	58 (96.7%)	0.000	1.000
Colchicine, *n* (%)	34 (56.7%)	33 (55.0%)	0.034	0.854
Glucocorticoids, *n* (%)	4 (6.7%)	6 (10.0%)	0.436	0.509
Laboratory indicators				
WBC ($\times10^9$/L)	7.14 ± 1.62	7.52 ± 2.18	−1.069	0.287
Hb (g/L)	158.33 ± 12.32	157.8 ± 11.7	0.228	0.820
PLT ($\times10^9$/L)	266.37 ± 62.10	270.8 ± 56.9	−0.408	0.684
ALT (U/L)	29.94 (17.73, 39.30)	29.2 (22.5, 42.4)	−0.821	0.411
AST (U/L)	22.48 (17.79, 26.62)	22.3 (18.7, 28.4)	−0.420	0.675
GGT (U/L)	35.93 (23.15, 47.07)	32.5 (23.1, 49.3)	−0.459	0.646
BUN (mmol/L)	4.68 (3.70, 5.29)	4.19 (3.68, 4.97)	−1.289	0.198
sCr (μmol/L)	89.85 (80.02,98.82)	86.59 (78.26, 98.80)	−0.588	0.557
eGFR (mL/min/1.73m^2)	97.99 (87.99, 112.35)	103.05 (87.28, 113.50)	−0.299	0.765

(Continues)

TABLE 1 | (Continued)

Variables	Group A ($n=60$)	Group B ($n=60$)	$t/z/\chi^2$	p
Cys-C (mg/L)	0.88 (0.79, 1.08)	0.88 (0.79, 1.08)	−0.307	0.759
Glu (mmol/L)	5.22 (5.00, 5.55)	5.11 (4.82, 5.61)	−1.270	0.204
TC (mmol/L)	5.07 ± 0.87	5.08 ± 1.02	−0.075	0.940
TG (mmol/L)	1.76 (1.24, 2.17)	2.02 (1.60, 2.47)	−1.934	0.053
HDL-C (mmol/L)	1.08 (0.92, 1.27)	1.01 (0.91, 1.15)	−1.161	0.246
LDL-C (mmol/L)	3.09 ± 0.79	3.10 ± 0.74	−0.088	0.930
UA (μmol/L)	611.50 (557.25, 654.75)	595.50 (566.25, 659.00)	−0.580	0.562
HCY (μmol/L)	18.24 (14.47, 31.29)	15.47 (13.26, 23.44)	−1.506	0.132

lowered in both groups ($p<0.05$). Serum creatinine (sCr) levels dramatically decreased, while the estimated glomerular filtration rate (eGFR) increased in both groups ($p<0.05$), indicating a significant improvement in renal function. Conversely, liver enzyme levels (ALT and AST) moderately increased in both groups posttreatment, suggesting that febuxostat affected liver function ($p<0.05$).

3.3 | Febuxostat Dose Comparison of Group A and Group B

Figure 2A shows the distribution of final febuxostat doses. Group A received a significantly lower mean dose (47.3 ± 18.7 mg) compared to Group B (56.0 ± 17.6 mg; $t=-2.617$, $p=0.010$). The median dose was 40.0 mg in Group A versus 50.0 mg in Group B.

The percentage distribution of dosages across both groups is shown in Figure 2B.

Group A showed a broader distribution, spanning 20–80 mg, whereas Group B was concentrated in the 40–80 mg range, with no patients receiving ultra-low doses.

Figure 2C presents dose stratification analysis ($\chi^2=17.255$, $p<0.001$). Group A had 13.3% (8/60) of patients maintained on 20 mg, 38.3% (23/60) on 30–40 mg, 21.7% (13/60) on 50–60 mg, and 26.7% (16/60) on 70–80 mg. Conversely, Group B had no patients in the 20 mg category; 25.0% (15/60) received 30–40 mg, 35.0% (21/60) received 50–60 mg, and 40.0% (24/60) received 70–80 mg. Figure 2D shows dose stratification by uric acid target achievement (≤360 μmol/L at 24th week). In Group A, patients who achieved the target had a significantly lower mean dose compared to non-achievers (44.9 ± 17.2 mg vs. 74.0 ± 13.4 mg; $p=0.001$), suggesting that ultra-low-dose titration was sufficient for most patients. Group B showed comparable doses between achievers and non-achievers, although the number of non-achievers was small ($n=2$).

3.4 | Rates of Achieving Target Serum Uric Acid Levels

As shown in Table 3, in patients without tophi, Group B demonstrated a significantly higher rate of reaching target SUA levels compared to Group A at week 4 (22.4% vs. 6.0%, $p=0.019$). However, no statistically significant differences in target attainment were found between the two groups at weeks 8, 12, and 24 (all $p>0.05$). In the subgroup of patients with tophi, while the target achievement rate in Group A was numerically lower than that in Group B at each follow-up time point, these differences were not statistically significant (all $p>0.05$).

3.5 | Incidence of Acute Gout Flares During Titration

At the 0–4, 4–8, 8–12, and 12–24 week intervals, the incidence of acute gout flares in Group B was 33.3% (20/60), 20.0% (12/60), 13.3% (8/60), and 3.3% (2/60), respectively. Although these rates were higher than those in Group A [18.3% (11/60), 11.7% (7/60), 5.0% (3/60), and 1.7% (1/60)], the differences at each individual time point did not reach statistical significance (all $p>0.05$). However, over the cumulative 24-week period, Group A demonstrated a 33.3% reduction relative to Group B (36.7% vs. 70.0%; $\chi^2=13.39$, $p<0.01$). These findings are summarized in Figure 3.

Gout flare outcomes during the 24-week follow-up are shown in Figure 4. There were notable differences in the distribution of acute gout flares between the two groups ($\chi^2=6.765$, $p=0.034$). The proportion of patients who remained flare-free was significantly higher in Group A than in Group B (70.0% vs. 46.7%; $\chi^2=6.720$, $p=0.010$). Conversely, Group B exhibited a greater frequency of recurrent flares across all categories: ≥1-flare rate [53.3% vs. 30.0%, $\chi^2=5.794$, $p=0.016$] and ≥2-flare rate [13.3% vs. 6.7%, $p=0.042$].

3.6 | Poisson Regression Analysis of Gout Flare Frequency

Poisson regression analysis revealed that patients in Group B exhibited an approximately twofold higher risk of experiencing gout flares compared with those in Group A, with an incidence rate ratio (IRR) of 1.95 (95% CI: 1.16–3.27, $p=0.012$; Figure 5A) after multivariable adjustment for age, disease duration, number of joints involved, pre-study flare frequency, BMI, and baseline serum uric acid. This result remained robust across all other statistical models, including unadjusted Poisson regression (IRR = 1.91, 95% CI: 1.14–3.20, $p=0.014$),

TABLE 2 | Comparative analysis of BMI and biochemical parameters pre- and posttreatment across the two gout cohorts.

	Group A				Group B			
	Pretreatment	**Posttreatment**	***t*/*z***	***p***	**Pretreatment**	**Posttreatment**	***t*/*z***	***p***
BMI (kg/m^2)	27.6 ± 3.8	26.3 ± 3.1	7.790	0.000	27.1 (25.2, 28.9)	26.3 (24.9, 27.7)	5.685	0.000
UA (μmol/L)	611.50 (557.25, 654.75)	324.50 (292.50, 338.00)	28.351	0.000	595.50 (566.25, 659.00)	319.00 (279.503, 36.50)	26.096	0.000
Scr (μmol/L)	89.85 (80.02, 98.82)	84.57 (74.78, 90.31)	5.628	0.000	86.59 (78.26, 98.80)	83.51 (74.36, 92.68)	3.684	0.000
eGFR ($mL/min/1.73\,m^2$)	97.99 (87.99, 112.35)	104.33 (95.53, 119.00)	−5.706	0.000	103.05 (87.28, 113.50)	108.24 (94.54, 118.55)	−4.377	0.000
BUN (mmol/L)	4.68 (3.70, 5.29)	4.60 (3.99, 5.49)	−0.410	0.684	4.19 (3.68, 4.97)	4.45 (3.82, 5.15)	−1.820	0.074
ALT (U/L)	29.94 (17.73, 39.30)	33.42 (23.24, 50.47)	−2.203	0.032	29.16 (22.47, 42.40)	43.10 (36.03, 51.79)	−3.931	0.000
AST (U/L)	22.48 (17.79, 26.62)	26.64 (21.29, 32.95)	−3.329	0.002	22.33 (18.68, 28.36)	31.44 (23.03, 37.05)	−4.838	0.000
GGT (U/L)	35.93 (23.15, 47.07)	35.41 (22.45, 53.81)	−0.855	0.396	32.50 (23.09, 49.25)	38.85 (27.35, 55.85)	−2.033	0.047
Glu (mmol/L)	5.22 (5.00, 5.55)	5.08 (4.90, 5.40)	2.416	0.019	5.11 (4.82, 5.61)	5.01 (4.76, 5.33)	1.762	0.083
TC (mmol/L)	5.07 ± 0.87	4.61 ± 0.86	6.069	0.000	5.08 ± 1.02	4.62 ± 0.82	4.583	0.000
TG (mmol/L)	1.76 (1.24, 2.17)	1.49 (1.16, 1.98)	1.611	0.113	2.02 (1.60, 2.47)	1.79 (1.34, 2.14)	1.236	0.221
HDL-C (mmol/L)	1.08 (0.92, 1.27)	1.05 (0.94, 1.24)	1.762	0.083	1.01 (0.91, 1.15)	1.01 (0.88, 1.24)	−1.351	0.182
LDL-C (mmol/L)	3.09 ± 0.79	2.70 ± 0.68	4.632	0.000	3.10 ± 0.74	2.70 ± 0.72	5.166	0.000
HCY (μmol/L)	18.24 (14.47, 31.29)	12.32 (11.00, 14.01)	4.304	0.000	15.47 (13.26, 23.44)	12.48 (10.89, 14.61)	−4.408	0.000

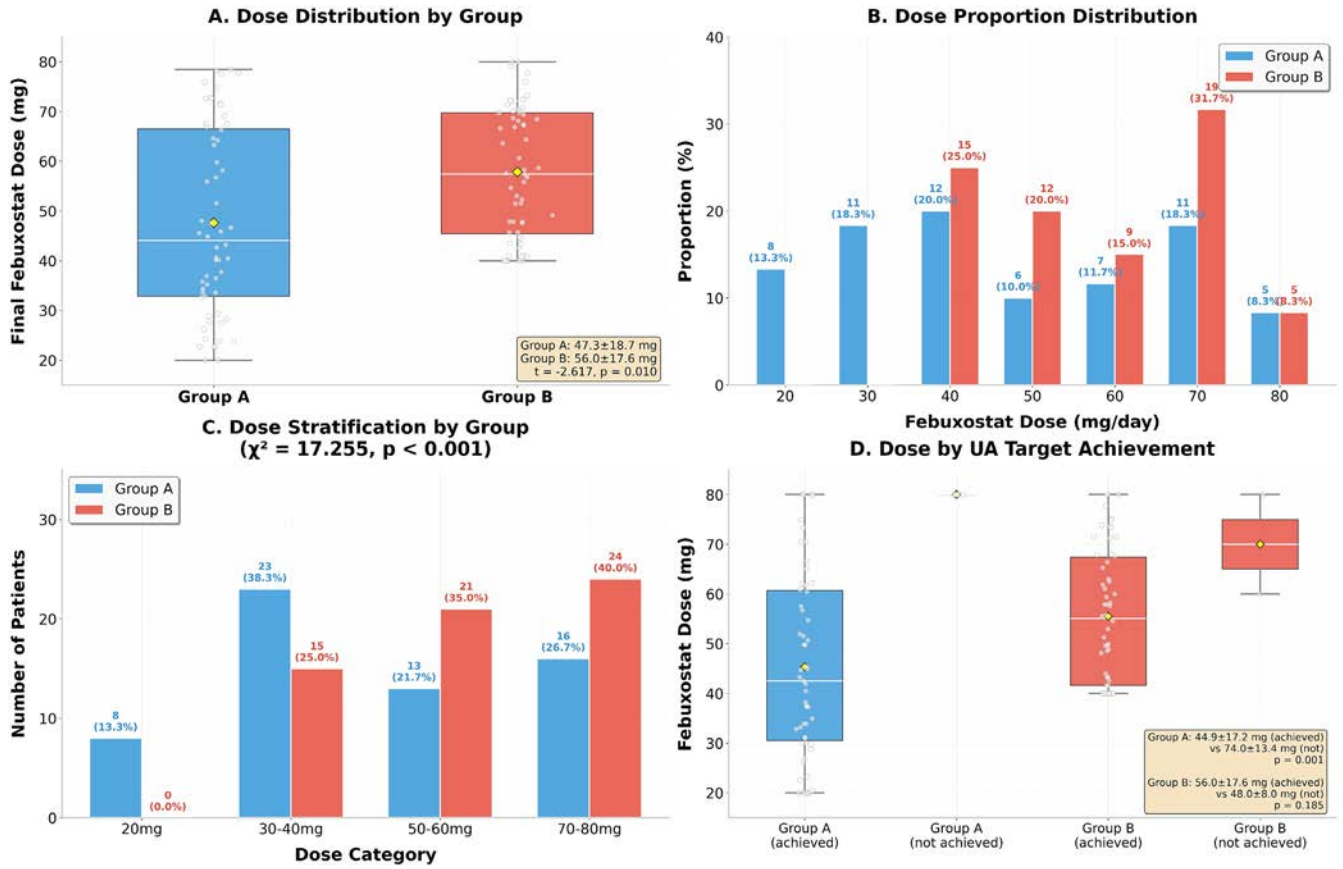

FIGURE 2 | Febuxostat dose comparison between Group A and Group B at week 24. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 | Proportion of patients achieving target serum uric acid levels in the two gout groups [% (*n*)].

Subgroup	*n*	Week 4	Week 8	Week 12	Week 24
Group A without tophi	50	6.0% (3)	46% (23)	76% (38)	96.0% (48)
Group B without tophi	49	22.4% (11)	65.3% (32)	87.8% (43)	98.0% (48)
χ^2		5.515	3.736	2.299	0.323
p		0.019	0.053	0.129	0.570
Group A with tophi	10	0% (0)	20.0% (2)	30.0% (3)	70.0% (7)
Group B with tophi	11	36.4% (4)	36.4% (4)	45.5% (5)	90.9% (10)
χ^2		2.443	0.119	0.078	0.439
p		0.090	0.635	0.659	0.311

adjusted and unadjusted negative binomial regression (adjusted IRR = 1.97, 95% CI: 1.03–3.75, $p = 0.040$; unadjusted IRR = 1.91, 95% CI: 1.02–2.53, $p = 0.044$), and Zero-inflated Poisson regression (ZIP; IRR = 1.68, 95% CI: 1.00–2.84, $p = 0.051$). The marginal significance observed in the latter model may be attributable to the high proportion of zero-flare patients in Group A (70.0% vs. 46.7%). The deviance-to-degrees-of-freedom ratio was 0.975 (≈1), indicating no substantial overdispersion. The Poisson model yielded a lower Akaike information criterion (AIC = 227.14) compared with the negative binomial model (AIC = 237.58). Consequently, Poisson regression was selected as the primary analytical approach.

Stratified subgroup analyses based on baseline characteristics revealed consistent directional trends in therapeutic effects across the majority of patient cohorts (Figure 5B). Notably, individuals with obesity (defined as BMI ≥ 28 kg/m^2) derived the greatest benefit from the ultra-low-dose initiation protocol, yielding an incidence rate ratio (IRR) of 5.18 (95% confidence interval: 1.76–15.23; $p = 0.003$). These findings indicate that a gradual titration approach may offer distinct clinical benefits, particularly for this high-risk population.

Similarly, significant benefits were observed in patients of younger age (< 40 years; IRR = 2.30, 95% CI: 1.21–4.36, $p = 0.011$), those with elevated baseline sUA (≥ 600 μmol/L;

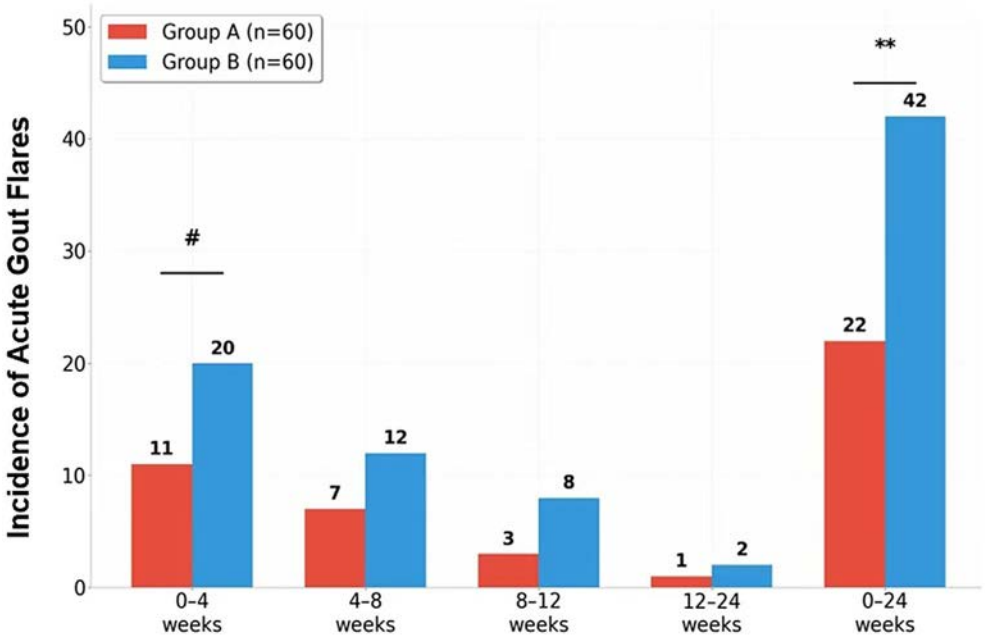

FIGURE 3 | Acute gout flare incidence during consecutive treatment intervals (0–24 weeks) in Two Groups. #indicates a trend toward significance ($p = 0.061$); **$p \leq 0.001$; ns $p > 0.05$.

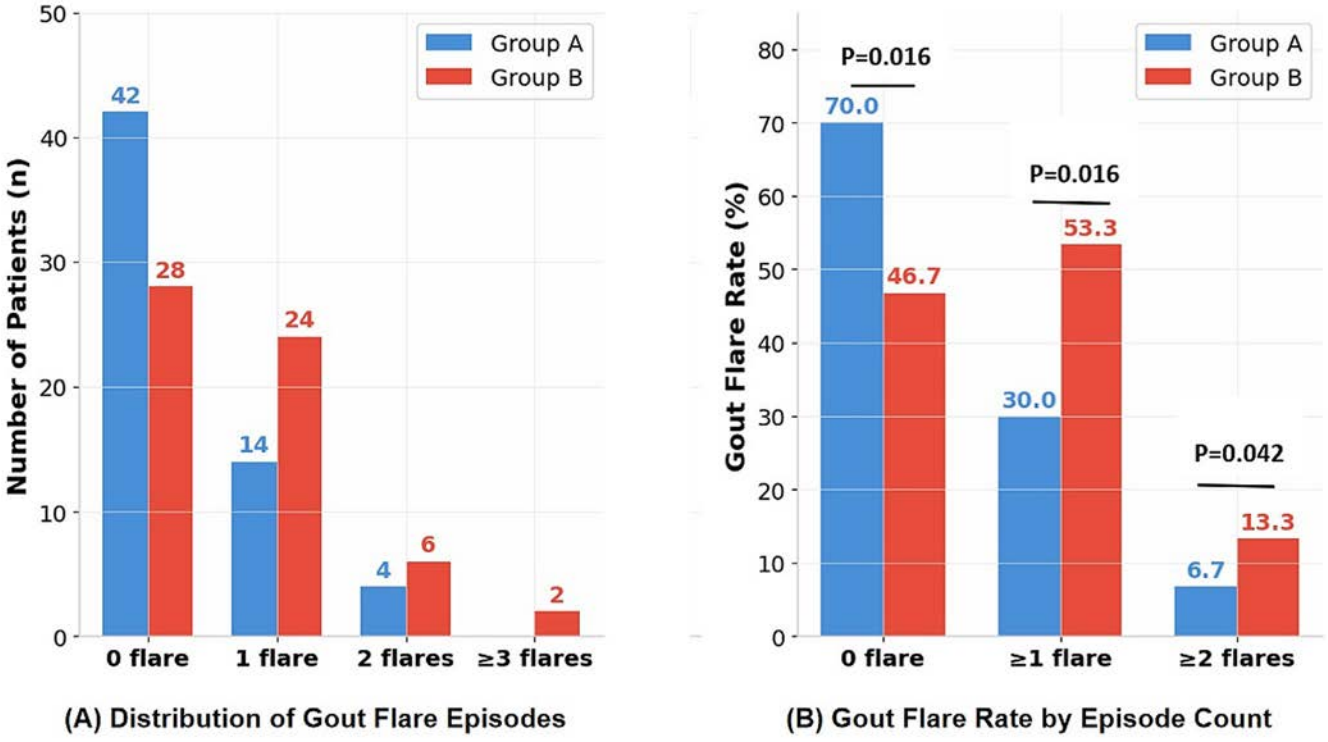

FIGURE 4 | Gout flare outcomes of the two groups during the 24-week follow-up.

IRR = 2.04, 95% CI: 1.03–4.05, $p = 0.041$), and those with lower pre-study flare frequency (< 4 episodes/year; IRR = 2.13, 95% CI: 1.07–4.25, $p = 0.031$). In contrast, no significant interaction was found among patients aged 40 years and older (IRR = 1.22, 95% CI: 0.48–3.08, $p = 0.670$). No statistically significant differences were observed in patients with a BMI of less than 28 kg/m^2 (IRR = 1.21, 95% CI: 0.65–2.24, $p = 0.544$) or those with baseline sUA < 600 μmol/L (IRR = 1.79, 95% CI: 0.82–3.94, $p = 0.146$), although the point estimates were directionally consistent with a benefit for Group A.

In Group A, the percentage of patients who remained flare-free was considerably higher than in Group B (70.0% vs. 46.7%), as shown in Figure 6 ($p = 0.016$). Among patients who experienced at least one flare, the mean flare count was comparable between the two groups (1.2 vs. 1.3, $p = 0.074$). However,

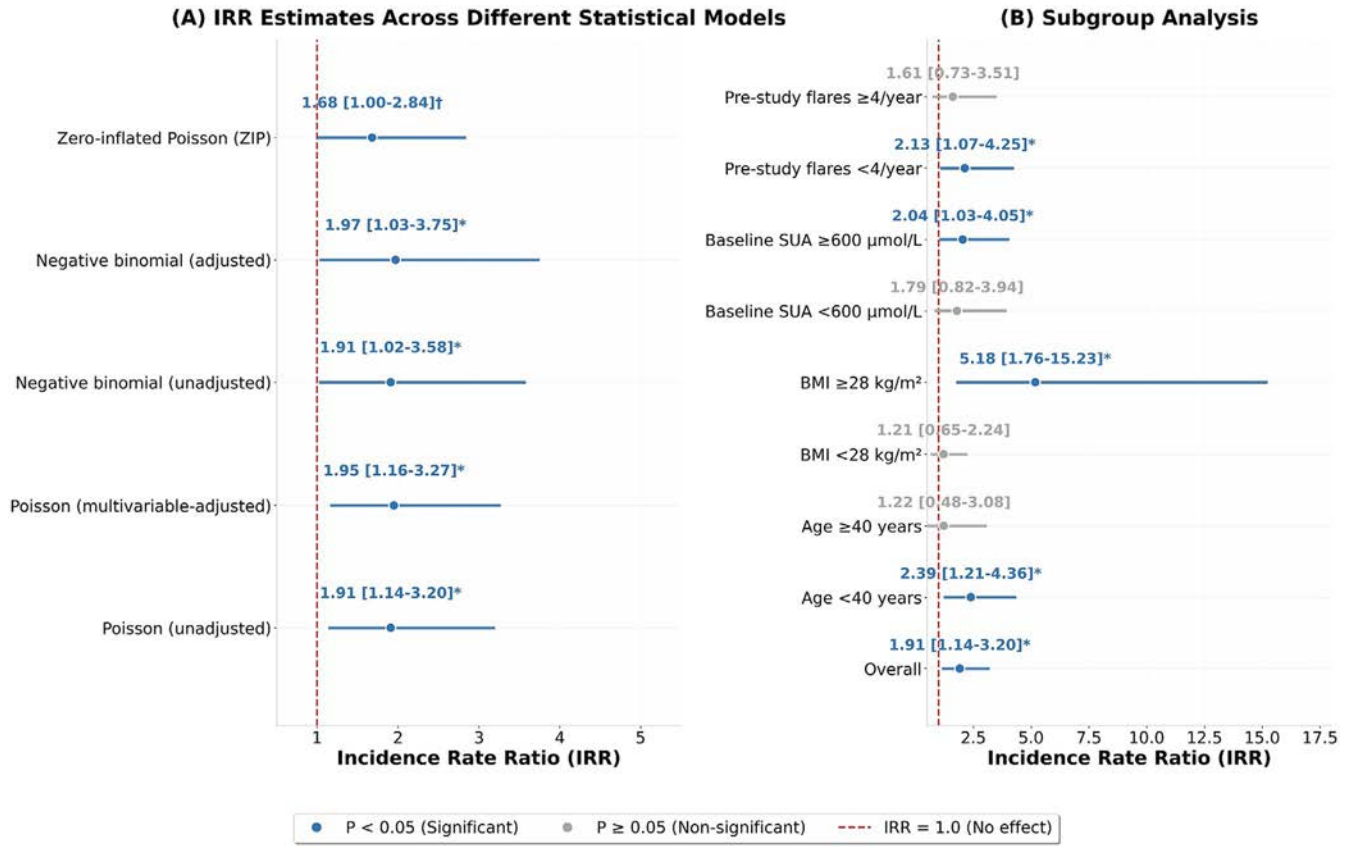

FIGURE 5 | Forest plot of incidence rate ratios (IRRs) for gout flare frequency comparing Group B and Group A.

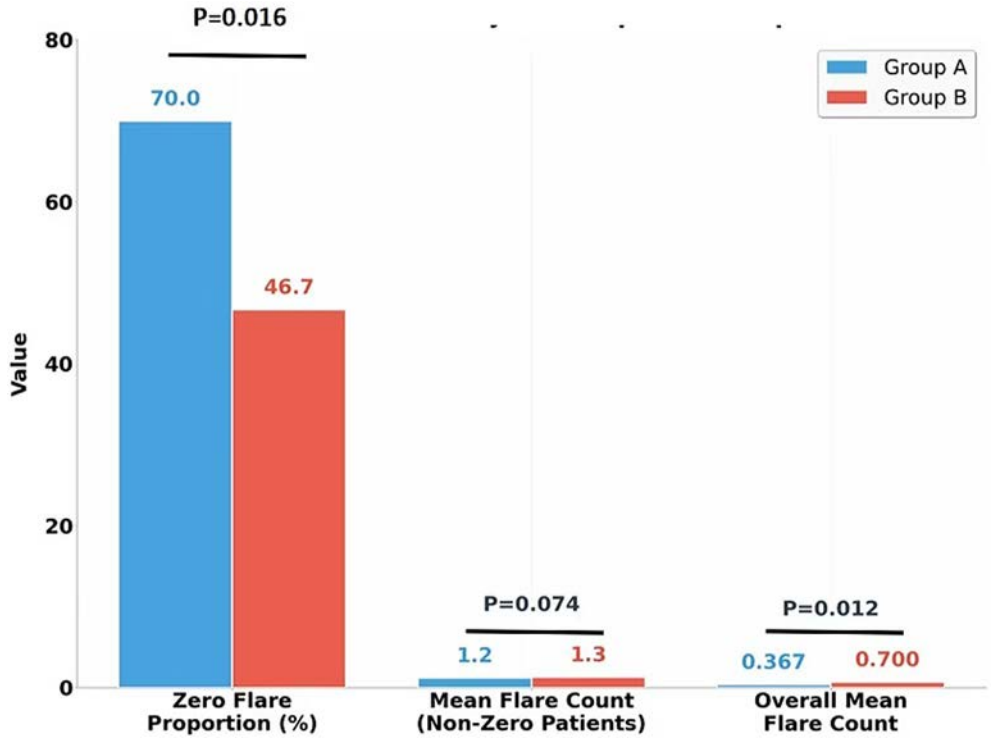

FIGURE 6 | Zero-inflation analysis of gout flare outcomes comparing Group A and Group B during 24-week follow-up.

Group A had a considerably lower overall mean flare count than Group B (0.367 vs. 0.700) in all patients ($p = 0.012$). The absolute rate difference was 0.33 flares per 24 weeks, yielding a number needed to treat (NNT) of 4.3 to prevent one additional gout flare episode. These findings indicate that the core advantage of the ultra-low-dose initiation strategy lies

in enabling a significantly higher proportion of patients to achieve zero flares, rather than merely reducing recurrence frequency among those who do flare.

Table 4 shows that the Number Needed to Treat (NNT) is 4.3, indicating that for approximately four patients treated with the 10-mg ultra-low-dose initiation strategy, one additional gout flare can be prevented relative to the 20-mg conventional strategy. The NNT is 15, meaning that for every 15 patients treated with this strategy, one additional patient with multiple flares can be prevented compared with the conventional 20-mg strategy.

TABLE 4 | Clinical translation metrics.

Metric	Group A	Group B	Difference	NNT
Flare rate (≥1 episode)	30.0%	53.3%	23.3%	4.3
Multiple flare rate (≥2 episodes)	6.7%	13.3%	6.7%	15.0

3.7 | Incidence of Adverse Drug Reactions

3.7.1 | Liver Safety and Tolerability

As seen in Figure 7, (A–C) Box plots comparing baseline and 24th week liver enzyme levels for ALT (A), AST (B), and GGT (C) in Group A and Group B. The upper limit of normal (ULN) reference lines are indicated: 1× ULN (40 U/L for ALT, 40 U/L for AST, 60 U/L for GGT) and 2× ULN (80 U/L for ALT, 80 U/L for AST, 120 U/L for GGT). (D) Changes in liver function parameters from baseline to 24th week. Rates of abnormal liver function at week 24 (E). For ALT ($p = 0.589$), AST ($p = 0.507$), and GGT ($p = 0.383$), no significant differences were found between Group A and Group B. Group B had a greater proportion of patients with ALT > 40 U/L (63.3%) than Group A (38.3%), while ALT > 80 U/L rates were similar (6.7% vs. 6.7%). Group A had a slightly higher rate (26.0%) than Group B (21.7%) for GGT > 60 U/L. (F) Baseline ALT status subgroup analysis. Group B demonstrated a significantly greater increase in ALT levels among patients with normal baseline ALT compared to Group A ($p = 0.003$). Nevertheless, there was no statistically significant difference between the groups in patients with increased baseline ALT ($p = 0.332$).

Shown in Figure 8A, significant positive correlations between baseline liver enzymes and lipid profile parameters were

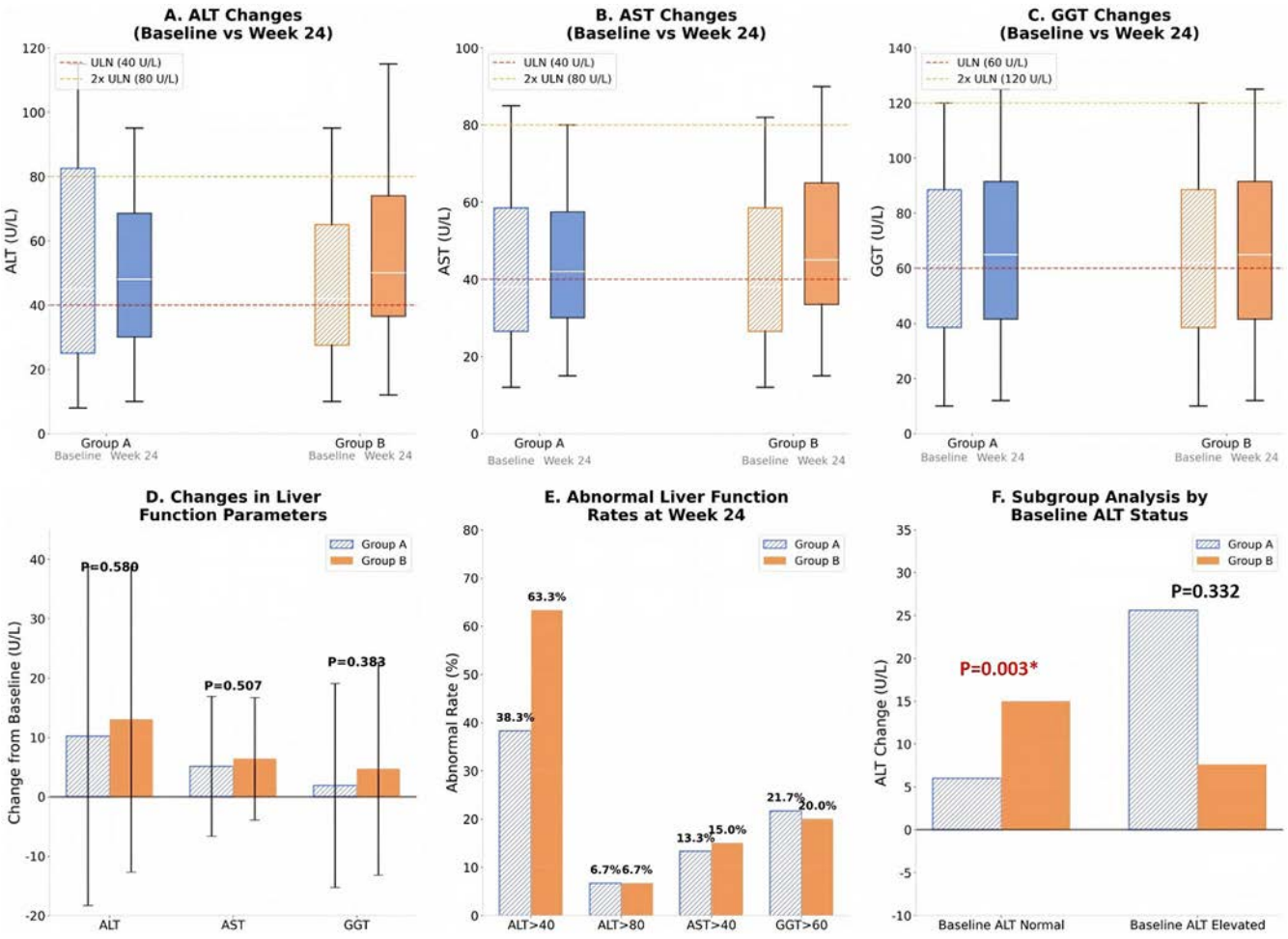

FIGURE 7 | Liver function changes and safety assessment in patients receiving febuxostat titration therapy. ULN, upper limit of normal; *$p < 0.05$.

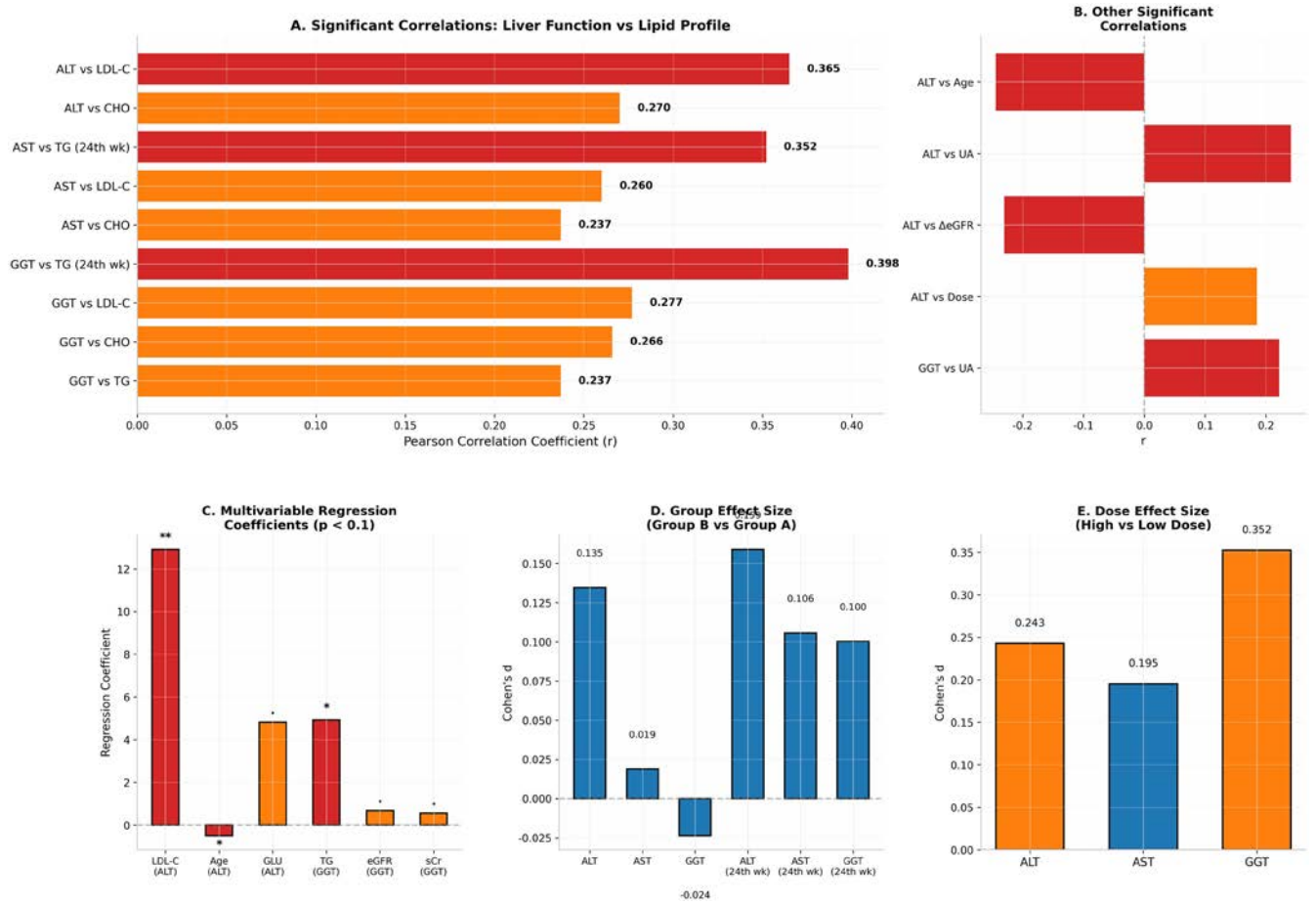

FIGURE 8 | Integrated assessment of hepatic function in patients receiving dose-adjusted febuxostat treatment.

identified. ALT showed the strongest correlation with LDL-C ($r = 0.365$, $p < 0.001$), followed by GGT with TG at the 24th week ($r = 0.398$, $p < 0.001$) and AST with TG at the 24th week ($r = 0.352$, $p < 0.001$). (B) Other significant correlations included negative associations of ALT with age ($r = -0.244$, $p = 0.007$) and ΔeGFR ($r = -0.230$, $p = 0.012$), and positive associations with uric acid ($r = 0.241$, $p = 0.008$) and febuxostat dose ($r = 0.185$, $p = 0.045$). (C) Multivariable linear regression coefficients ($p < 0.1$) identified independent predictors of liver function. LDL-C was the strongest predictor of baseline ALT ($\beta = 12.90$, $p = 0.009$); meanwhile, TG predicted GGT levels ($\beta = 4.92$, $p = 0.040$). Age was negatively correlated with ALT ($\beta = -0.49$, $p = 0.036$). (D) Effect sizes (Cohen's d) were assessed for group comparisons (Group B vs. Group A). All effect sizes were small ($d < 0.2$), suggesting no clinically significant differences in liver function between the ultra-low-dose titration (Group A) and standard-dose (Group B) strategies at either baseline or the 24th week. (E) Dose-effect sizes were compared between high-dose (60–80 mg) and low-dose (20–30 mg) febuxostat. No dose-dependent hepatotoxicity was observed, with all effect sizes remaining below 0.5.

3.7.2 | Cardiovascular Diseases Safety

No major cardiovascular events (such as angina pectoris, myocardial infarction, and heart failure) occurred during the entire follow-up period; however, there were 2 cases of palpitations (3.3%) and 6 cases of blood pressure fluctuations (5.0%), specifically comprising 1 case of palpitations and 3 cases of blood pressure fluctuations in Group A, and 3 cases of palpitations and 3 cases of blood pressure fluctuations in Group B.

A robustness assessment of the model in Figure 9 showed that the primary finding was consistent across all multivariable adjustments. In the basic model (Model 1), Group B exhibited a significantly higher flare incidence (IRR = 1.91; 95% CI: 1.14–3.20; $p = 0.014$). After adjusting for age, BMI, and disease duration (Model 2), the effect estimate remained largely unchanged (IRR = 1.99; 95% CI: 1.18–3.35; $p = 0.010$). The sequential inclusion of hyperhomocysteinemia (HHCY; HCY > 15 μmol/L; Model 3: IRR = 1.96; 95% CI: 1.16–3.33; $p = 0.012$) and high cardiovascular risk (composite score ≥ 2; Model 4: IRR = 1.99; 95% CI: 1.18–3.36; $p = 0.010$) did not materially alter the treatment effect. The fully adjusted model (Model 5), incorporating all covariates, yielded an IRR of 1.94 (95% CI: 1.15–3.29; $p = 0.013$), confirming the robustness of the primary finding.

HCY-Stratified Subgroup Analysis. Among patients with normal baseline homocysteine (≤ 15 μmol/L; $n = 40$), Group B demonstrated a markedly elevated flare incidence (IRR = 3.46; 95% CI: 1.18–10.20; $p = 0.024$). Conversely, in the high-HCY subgroup (> 15 μmol/L; $n = 80$), the treatment effect was attenuated and nonsignificant (IRR = 1.65; 95% CI: 0.88–3.11; $p = 0.119$). The formal interaction test between the treatment

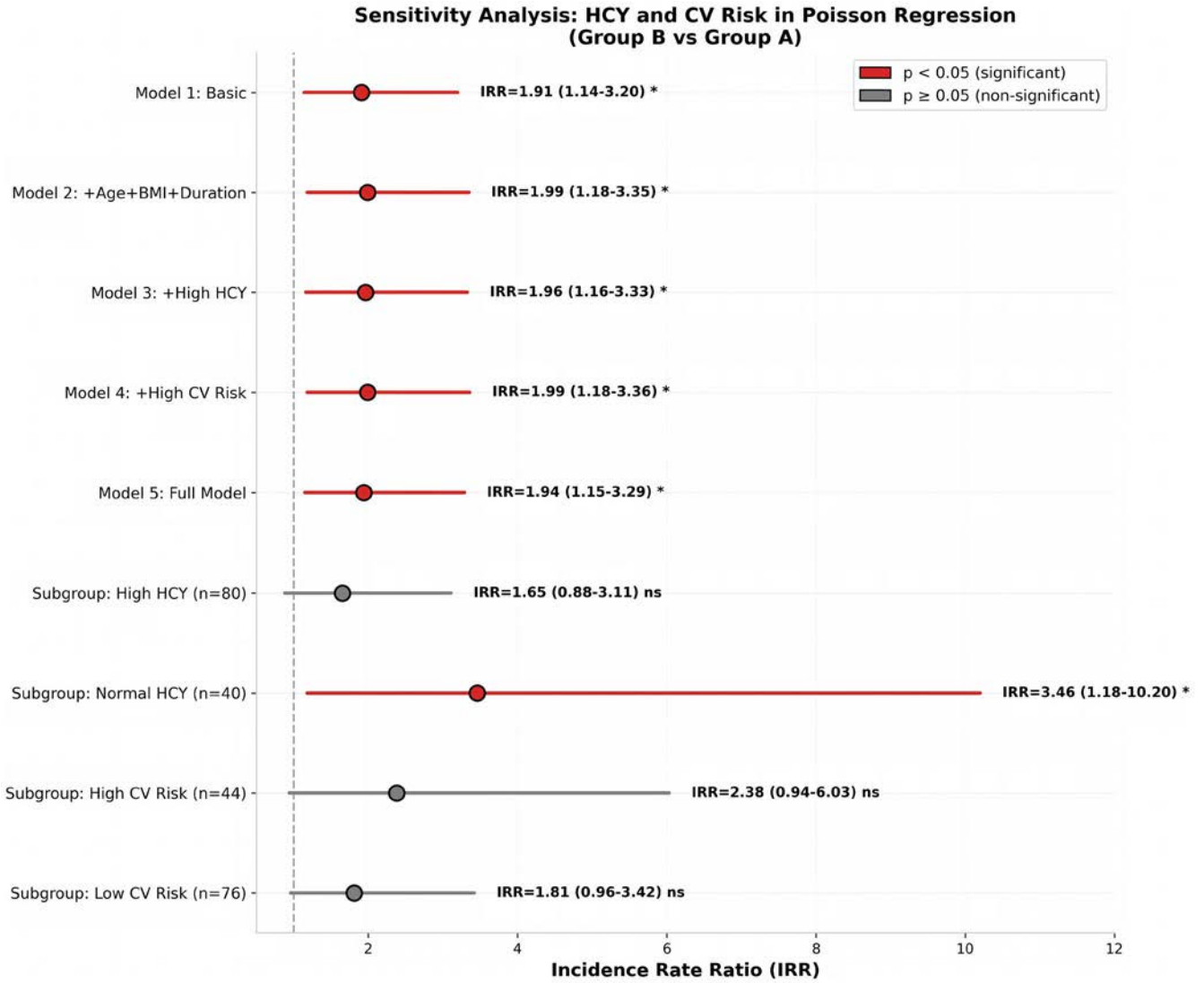

FIGURE 9 | Forest plot of incidence rate ratios (IRRs) comparing Group B with Group A across progressively adjusted Poisson regression models and predefined subgroups.

group and HHCY status was nonsignificant ($p = 0.301$), suggesting this observed difference may reflect limited statistical power in the smaller normal-HCY subgroup rather than true effect modification.

CV Risk-Stratified Subgroup Analysis. Neither the high-CV-risk subgroup ($n = 44$; IRR = 2.38; 95% CI: 0.94–6.03; $p = 0.067$) nor the low-CV-risk subgroup ($n = 76$; IRR = 1.81; 95% CI: 0.96–3.42; $p = 0.067$) achieved statistical significance, although both demonstrated consistent effect directions favoring Group A. The treatment-by-CV risk interaction was nonsignificant ($p = 0.632$), indicating no evidence of effect modification by cardiovascular risk profile.

The ultra-low-dose febuxostat titration strategy (Group A) consistently showed a reduced incidence of gout flares in comparison to the standard-dose initiation (Group B) across all model specifications, with incidence rate ratio (IRR) estimates consistently ranging from 1.9 to 2.0. This treatment effect was particularly pronounced in patients with normal homocysteine levels.

3.8 | Post Hoc Analysis and A Priori Calculation

Figure 10 depicts the correlation between sample size, effect size, and statistical power within the study parameters.

In Panel A, the power curve illustrates that with an actual sample size of 60 participants per group (total $n = 120$), the study achieved a statistical power of 73.6% to detect the observed incidence rate ratio (IRR = 1.91) for the primary endpoint (shown by the blue line). Although this figure is slightly below the conventional threshold of 80% (represented by the dashed orange line), it remains within acceptable limits for identifying clinically significant effects. To attain a 90% power (indicated by the purple dashed line), a projected sample size of 78 participants per group was estimated.

Panel B presents the sensitivity analysis for effect size: The required sample size demonstrated a strong relationship with the magnitude of the assumed effect size (IRR). For the observed IRR of 1.91, a calculated sample size of 60 participants per group (indicated by the red dashed line) falls within the acceptable range

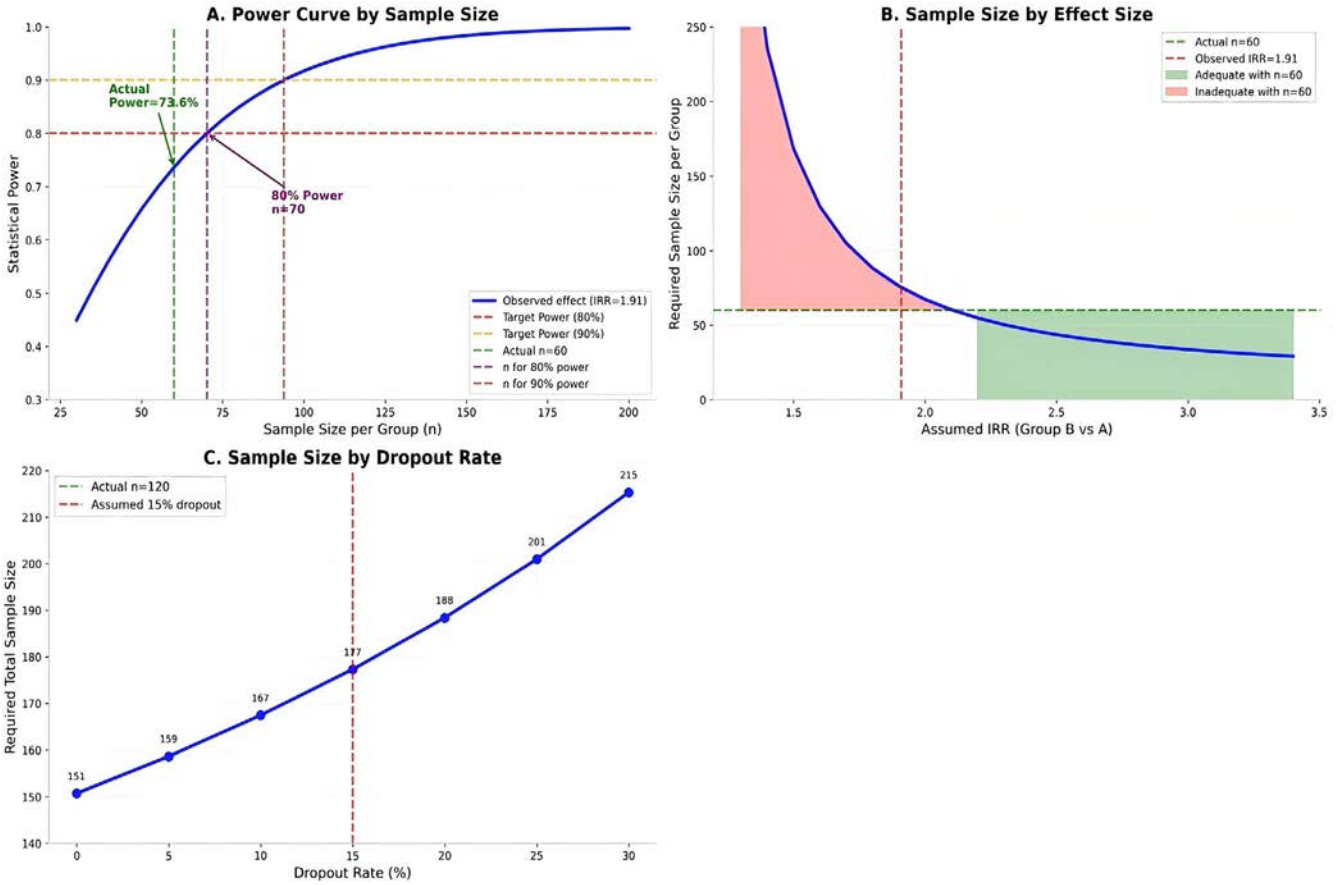

FIGURE 10 | The relationship between sample size, effect size, and statistical power across the study parameters.

(green shaded area, 60–80 participants per group). However, if the true effect size were to increase to an IRR of 2.0 or higher (shown by the vertical red dashed line), the needed sample size would decrease significantly, indicating that our study was sufficiently powered to identify moderate to large treatment effects.

Panel C addresses dropout rate considerations: To mitigate the potential impact of attrition, we calculated the required total sample size across varying attrition scenarios. Our analysis demonstrates that with an actual enrollment of 120 subjects (indicated by the green dashed line), the study maintains sufficient statistical power even under a projected 15% dropout rate (red dashed line), which corresponds to a required initial cohort of 141 individuals. This strategic buffer ensures that the final analytic sample will satisfy target power specifications, despite anticipated losses during the follow-up phase.

4 | Discussion

4.1 | Principal Findings and Clinical Implications

This study demonstrates that initiating febuxostat at an ultra-low dose of 10 mg/day followed by gradual titration significantly reduces the incidence of acute gout flares during the critical early phase of urate-lowering therapy (ULT) compared to the conventional 20 mg/day starting regimen. Over the 24-week observation period, the cumulative flare rate in Group A (10 mg/day) was 30.0%, significantly lower than 53.3% in Group B (20 mg/day) ($p = 0.016$). This finding challenges the conventional paradigm that rapid urate reduction is universally advantageous, instead supporting a "steady and safe reduction" strategy that prioritizes early tolerability without compromising long-term efficacy [18, 19]. The clinical significance of this risk reduction is further underscored by the zero-inflated distribution of flares: 70.0% of patients in Group A remained completely flare-free throughout the study, compared to only 46.7% in Group B ($p = 0.016$). Poisson regression analysis confirmed that Group B carried a 1.95-fold higher risk of gout flares (adjusted IRR = 1.95, 95% CI: 1.16–3.27, $p = 0.012$), a finding robust across negative binomial and zero-inflated Poisson models. The number needed to treat (NNT = 4.3) indicates that for every 4–5 patients treated with the ultra-low dose strategy, one additional gout flare can be prevented—an effect size of substantial clinical relevance [20]. These results align with the established pathophysiological concept of the "trigger effect," wherein rapid declines in serum urate (SUA) destabilize synovial fluid homeostasis, promoting monosodium urate (MSU) crystal shedding and activating innate immune pathways, particularly the NLRP3 inflammasome-mediated IL-1β cascade [21, 22]. The 10 mg/day regimen, with 10 mg increments every 2 weeks, likely achieved a more gradual SUA reduction, minimizing the acute biochemical perturbation that provokes crystal-induced inflammation. This mechanism is consistent with prior evidence that initial high-dose febuxostat without preventive medications significantly increases flare risk (HR 3.08; 95% CI: 1.34–7.07) [7], whereas stepwise dose escalation can effectively suppress attacks [23].

Despite the superior flare profile, the ultra-low dose regimen did not compromise long-term urate-lowering efficacy. Although Group B demonstrated significantly higher target attainment rates at weeks 4 and 8 in patients without tophi (22.4% vs. 6.0%, $p = 0.019$, 65.3% vs. 46%, $p = 0.053$), this early advantage dissipated by week 24, when both groups achieved comparable target attainment rates (96.0% vs. 98.0%). This "early heterogeneity, later convergence" pattern emphasizes that while higher starting doses accelerate initial SUA reduction, both strategies ultimately achieve equivalent therapeutic goals [24, 25].

Notably, the final maintenance dose in Group A (47.3 ± 18.7 mg/day) was significantly lower than in Group B (56.0 ± 17.6 mg/day; $p = 0.010$), with 13.3% of Group A patients successfully maintained at 20–30 mg/day—a range not observed in Group B. This dose-sparing effect has important pharmacoeconomic implications, as minimizing febuxostat exposure may reduce both direct medication costs and the cumulative risk of dose-dependent adverse effects [26]. The ability to identify patients highly sensitive to xanthine oxidase inhibition—potentially influenced by fractional urate excretion or baseline metabolic profiles—opens avenues for refined individualized treatment strategies [27, 28].

4.2 | Safety Profile: Hepatic and Cardiovascular Considerations

4.2.1 | Hepatic Safety

Our study found that both ultra-low (10 mg/day) and low (20 mg/day) starting doses of febuxostat demonstrated acceptable hepatic safety over 24 weeks. The incidence of clinically significant liver injury (ALT/AST > 3× ULN) was low in both groups (3.3% and 1.7%), consistent with or lower than rates reported in large febuxostat safety trials (typically 4%–6%) [29]. Although univariate analysis showed a weak correlation between dose and ALT ($r = 0.185$), this relationship was no longer observed in the multivariable model ($p = 0.323$). Dose-stratified ANOVA demonstrated no evidence of dose-dependent hepatotoxicity across the prescribed range. These findings align with and extend prior observations that febuxostat-induced liver enzyme elevations are generally mild, transient, and reversible [12]. Based on its pharmacokinetic profile, febuxostat, which is primarily metabolized hepatically via oxidation and glucuronidation, does not appear to induce cumulative hepatic stress at lower initiation doses [12]. These findings are particularly encouraging given the growing interest in individualized, low-dose urate-lowering strategies to minimize early treatment flares while maintaining long-term efficacy.

The present study identified lipid metabolism parameters as the principal factors associated with hepatic enzyme elevations in gout patients undergoing febuxostat therapy. LDL-C and TG demonstrated significant positive correlations with ALT, AST, and GGT [30]. Multivariable regression further confirmed that LDL-C was an independent predictor of ALT ($\beta = 12.90$, $p = 0.009$), even after adjusting for treatment group, body weight, and other metabolic parameters. This finding suggests that gout is frequently comorbid with metabolic syndrome, and hepatic steatosis is prevalent in this population [31]. Elevations in liver enzymes may reflect underlying metabolic dysregulation rather than direct drug hepatotoxicity.

Collectively, our findings support the integration of this methodology as a tailored, low-risk therapeutic option into clinical practice. This is especially pertinent for individuals diagnosed with metabolic syndrome, where the dual imperative of minimizing polypharmacy while preserving potent urate-lowering effects represents a key clinical goal.

4.2.2 | Cardiovascular Safety

During the 24-week follow-up period, no major adverse cardiovascular events (MACE) occurred in either group, and the incidence of cardiovascular-related adverse events, including palpitations and blood pressure fluctuations, remained low (3.3% vs. 5.0%). While these short-term outcomes are encouraging, they must be interpreted with caution. The cardiovascular implications of urate-lowering therapy (ULT) remain a topic of ongoing debate [32]. The CARES trial demonstrated increased cardiovascular mortality associated with febuxostat in patients with established cardiovascular disease [33, 34]; however, the FAST trial showed that febuxostat is non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and its long-term use is not associated with an increased risk of death or serious adverse events compared with allopurinol [35]. Some Asian studies also don't indicate increased risk, but effects depend on disease status, with increased heart failure risk in some groups and protective effects in advanced CKD [36–38]. Cardiovascular risk appears dose-dependent, with higher doses leading to worse outcomes [37]. Our ultra-low-dose regimen (10–20 mg/day with gradual escalation) may reduce this risk by limiting effective dose exposure and enabling early detection of individual responses. Our young, low-risk cohort had no major adverse events over 24 weeks, but the study was not designed for cardiovascular endpoints; our study population exhibited a high prevalence of hyperhomocysteinemia, an independent cardiovascular risk factor [39], received daily oral supplementation of 0.8 mg folic acid, 10 mg vitamin B6, and 25 μg vitamin B12, which may partially reduce the risk of major adverse cardiovascular events. So, our results suggest short-term tolerability. Future RCTs are needed to confirm whether ultra-low dosing maintains efficacy while reducing cardiovascular concerns.

4.3 | Subpopulation Effects and Precision Medicine Implications

Subgroup analyses revealed that obese patients (BMI ≥ 28 kg/m^2) derived the greatest benefit from the ultra-low-dose strategy (IRR = 5.18, 95% CI: 1.76–15.23, $p = 0.003$). This finding may reflect the pro-inflammatory adipokine profile and higher baseline SUA levels characteristic of obesity, which amplify the destabilizing effects of rapid urate reduction [40]. Additionally, the effect size was more pronounced in patients with normal baseline homocysteine levels (IRR = 3.46, 95% CI: 1.18–10.20, $p = 0.024$), suggesting that the metabolic context modulates treatment response. These observations support the broader paradigm of precision medicine in gout management, where individual metabolic phenotypes and genetic polymorphisms (e.g., HLA-B*5801, urate transporter variants), and comorbidity profiles should inform starting dose selection and titration algorithms [21, 28, 41].

4.4 | The "Re-Initiation Paradox" and Its Clinical Implications in Real-World Settings

A salient observation within our study cohort is that nearly 60% of participants experienced acute gout flares precipitated by preceding febuxostat exposure. This finding underscores a well-documented clinical challenge known as the "re-initiation paradox" associated with urate-lowering therapy (ULT) [42]. It is widely acknowledged that the initiation of ULT or rapid dose escalation—particularly with xanthine oxidase inhibitors such as febuxostat—can paradoxically induce acute inflammatory episodes, especially during the initial weeks to months of treatment [43]. The pathophysiological basis of this phenomenon lies in the rapid mobilization and dissolution of monosodium urate crystals, which results in a transient surge in crystal shedding and consequently provokes an inflammatory cascade [44]. Suboptimal dosing regimens, frequently encountered in real-world clinical practice due to patient self-medication or inconsistent medical guidance, may further exacerbate this complication. Existing evidence strongly supports the implementation of a gradual, stepwise dose-titration strategy to attenuate this early pro-inflammatory response and enhance long-term adherence to ULT protocols [11].

Moreover, insufficient counseling regarding the transient nature of flares upon commencing urate-lowering therapy (ULT), coupled with a lack of emphasis on concurrent anti-inflammatory prophylaxis, is a significant driver of adverse clinical outcomes [7]. The substantial proportion of participants with prior febuxostat exposure in our cohort highlights a pivotal deficiency in current practice: the suboptimal implementation and communication of safe re-initiation protocols. This finding corroborates evidence supporting nurse-led, standardized frameworks for dose escalation and patient instruction, which have demonstrated efficacy in safely accelerating the attainment of target serum uric acid (SUA) concentrations [45]. For individuals who previously discontinued ULT due to intolerance or perceived lack of benefit, a cautious re-challenge employing an ultra-low initial dose, followed by a gradual, structured titration schedule, may offer a more tolerable and safe route for therapy reintroduction. This approach is especially pertinent given that alternatives such as allopurinol also pose hypersensitivity risks, while febuxostat retains its status as a vital second-line agent [46]. The principle of a "restart" strategy, previously investigated in contexts involving agents like pegloticase, underscores the necessity of meticulous monitoring and incremental re-exposure to balance safety and efficacy [47]. Consequently, our identification of widespread prior suboptimal febuxostat use not only validates a tangible real-world challenge but also reinforces the clinical justification for assessing low-dose initiation strategies as a viable solution for this complex patient population [7].

4.5 | Renal Function Outcomes

Both treatment groups demonstrated a notable improvement in renal function following a 24-week period of ULT, characterized by a reduction in serum creatinine levels and an increase in creatinine clearance. This observation aligns with the well-established link between hyperuricemia and renal impairment, where elevated serum uric acid contributes to renal injury through mechanisms such as endothelial dysfunction and oxidative stress [48]. The decline in serum uric acid achieved by febuxostat is associated with the preservation of renal function, a benefit supported by studies highlighting the role of ULT in slowing the progression of chronic kidney disease [49]. Moreover, the ability of febuxostat to reduce serum uric acid levels effectively is a critical factor in mitigating the adverse renal effects of hyperuricemia, such as those mediated by the downregulation of urate transporters, enhancement of reabsorption, or inhibition of excretion [12]. This therapeutic effect is clinically relevant, as even modest reductions in serum urate can improve renal outcomes [50]. The observed renal benefits in our study corroborate the conclusions of previous studies that verify the safety and effectiveness of febuxostat in patients with different degrees of renal function, where dose adjustment is guided by clinical response rather than solely by creatinine clearance, although the differential effects of starting dose strategies on renal protection require further investigation [23].

4.6 | Integration With Contemporary Evidence and Guidelines

Our results are consistent with the evolving treat-to-target (T2T) framework for gout care. The 2026 GO TEST Overture trial demonstrated that T2T protocols yield significantly higher remission rates than symptom-based approaches (39.4% vs. 24.0% at 18–24 months) [51], while the 5-year NOR-Gout follow-up confirmed persistent crystal clearance via sustained serum urate (SUA) control [52]. Nevertheless, these pivotal investigations primarily employed conventional initial dosing regimens (febuxostat $\geq$ 20 mg/day). Our study extends these findings by showing that a more cautious initiation strategy can optimize the critical early stage of urate-lowering therapy (ULT)—a phase characterized by peak flare susceptibility and the highest rates of patient discontinuation.

The FORTUNE-1 trial provided direct precedent for our strategy, showing that stepwise febuxostat escalation (10 $\rightarrow$ 40 mg/day) achieved flare rates comparable to fixed-dose febuxostat plus colchicine prophylaxis (20.8% vs. 18.9%), both significantly lower than fixed-dose without prophylaxis (36.0%) [53]. Our study advances this concept by isolating the 10 mg/day starting dose as an independent variable, confirming its superiority over 20 mg/day initiation and establishing it as a viable alternative for patients with contraindications or intolerance to colchicine or nonsteroidal anti-inflammatory drugs.

4.7 | Limitations and Future Directions

Several limitations warrant acknowledgment. First, the sample size (60 per group), while adequate for the primary endpoint, provided 73.6% statistical power—marginally below the conventional 80% threshold. Post hoc sensitivity analysis indicated that for true effect sizes $\geq$ 2.0, the required sample size would decrease substantially, suggesting adequate power for moderate-to-large effects. Second, the study included only male patients, which restricts the applicability of the findings to female patients with gout, representing a significant limitation [54]. There is a gap due to the established sex-based differences in the pathophysiology of gout and responses to treatment [55]. Third, the 24-week follow-up period, while sufficient to capture early titration-related flares, may not be

long enough to assess long-term outcomes such as tophus regression, cardiovascular events, or sustained urate-lowering effects [56]. Prior research has demonstrated that longer treatment durations are necessary to fully evaluate the benefits of ULT on cardiovascular risk [57]. Fourth, the single-center design may introduce institutional biases, and the results require validation in multi-center, diverse populations. Furthermore, approximately 40% of the study cohort received supplementation with folic acid and B vitamins for hyperhomocysteinemia; although homocysteine levels were adjusted for in sensitivity analyses, the potential independent effect of these supplements on inflammatory pathways or gout flare incidence cannot be completely excluded [58]. Finally, the study cohort had a relatively low median age and excluded patients with significant comorbidities, so extrapolation to older populations or those with multiple conditions must be approached with caution, as aging is often linked to a decrease in renal function, a key determinant of both the efficacy and safety profile of urate-lowering agents like febuxostat [59].

Future investigations should include larger, adequately powered trials with extended follow-up, include female participants, and incorporate hard endpoints such as cardiovascular events and renal function decline to confirm and extend these findings. Specifically, future research should prioritize the design of multicenter, large-scale non-inferiority trials with each group comprising 70–100 patients and a follow-up duration of at least 12 months, ensuring the inclusion of female patients, elderly individuals, and those with renal insufficiency, as these populations have been historically underrepresented in gout trials [60].

Author Contributions

S.H. and L.P. prepared the initial draft of this manuscript; S.H., G.L., L.Y., G.X., and S.R. recruited participants; S.H. and L.Y. did data analysis; L.P. and L.Y. edited subsequent drafts; Sun H and Li P prepared and submitted the final draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Methodological Considerations on Relative Handgrip Strength and Cancer Risk in Older Adults

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Dear Editor,

Lian and Luo [1] examined the association between relative handgrip strength and cancer risk in older adults using harmonized multinational cohort data from HRS, ELSA, and SHARE. This work addresses an important question in aging research. However, because cancer diagnosis and mortality are both frequent and interrelated outcomes in older populations, several aspects of the analytic approach warrant further clarification.

In this setting, death may occur before cancer is diagnosed or recorded. Standard time-to-event analyses may therefore overestimate or misrepresent cancer risk if mortality is not explicitly handled as a competing event [2]. A competing-risk framework would help determine whether the observed association remains consistent after accounting for the possibility that death precludes subsequent cancer ascertainment.

Reverse causation is another concern. Although the authors excluded participants with follow-up shorter than 2.5 years, the preclinical interval differs substantially across cancer types [3]. Some cancers may influence muscle strength, weight, systemic inflammation, or general functional status several years before diagnosis. Sensitivity analyses excluding cancers diagnosed within the first 3 and 5 years of follow-up would provide a stricter assessment of whether the association persists after reducing the influence of occult malignancy.

Finally, the description of follow-up time appears to require clarification. The manuscript seems to define time as extending from the estimated diagnosis time or last participation year to baseline handgrip measurement, which could be read as a reversed temporal interval. A more explicit explanation of how follow-up was calculated and whether cancer diagnosis timing was treated as interval-censored [4], would improve reproducibility and help readers interpret the temporal structure of the analysis.

Author Contributions

Chung-Chu Tung: writing – original draft. **Hui-Yuan Chen:** writing – original draft. **Renin Chang:** conceptualization, writing – review and editing. **Sun-Lin Huang:** conceptualization, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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ORIGINAL ARTICLE

Efficacy and Safety Assessment of Upadacitinib for SAPHO Syndrome: A Retrospective Study of 35 Patients

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of upadacitinib administered over a short-term period in patients with SAPHO syndrome.

Methods: In this 12-week retrospective observational study, eligible SAPHO syndrome patients diagnosed within the past year and treated with upadacitinib were enrolled. Efficacy was assessed using the Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP) and the Palmoplantar Pustulosis Area and Severity Index (PPPASI). Safety was evaluated based on the incidence of adverse events during the treatment period.

Results: A total of 35 eligible patients were included. Both ASDAS-CRP and PPPASI scores decreased rapidly by Week 4 (−1.01 and −11.41, respectively; both $p < 0.001$) and showed further significant improvements at Week 12 (−1.50 and −14.69, respectively; both $p < 0.001$) compared to baseline. Similar improvements were observed in the Visual Analogue Scale for overall musculoskeletal pain, the Bath Ankylosing Spondylitis Disease Activity Index, and other quality-of-life measures. Upadacitinib was well tolerated, with no serious adverse events reported. The most common adverse event was upper respiratory tract infection (20%). Other mild adverse events included elevated alanine aminotransferase, nausea, mild headache, and sore throat.

Conclusion: Upadacitinib demonstrated a rapid onset of action, significant efficacy, and a favorable safety profile in the treatment of SAPHO syndrome, supporting its potential as a therapeutic option in clinical practice.

1 | Introduction

SAPHO syndrome (synovitis, acne, pustulosis, osteophytosis, and osteitis) is a rare, chronic autoimmune disorder [1]. Clinical manifestations typically involve skeletal and joint lesions in the anterior chest wall and spine, alongside skin lesions such as pustules on the palms and soles and facial acne [2]. The pathogenesis of SAPHO syndrome remains unclear, though it is widely considered an autoinflammatory disorder triggered by multiple factors including infection, genetics, immunity, and

Fanzhang Meng, Yuqing Zhang, and Yuan Chen contributed equally and should be the co-first author.

Highlights

- This is the first retrospective observational study evaluating upadacitinib for the treatment of SAPHO syndrome.
- Upadacitinib rapidly improved both musculoskeletal and cutaneous lesions of SAPHO syndrome within 4 weeks, achieving rapid disease remission by Week 12.
- Upadacitinib demonstrated rapid onset of action in treating SAPHO syndrome without serious adverse reactions.

environment [3, 4]. The recurrent nature of its musculoskeletal and cutaneous symptoms often leads to depression in patients, significantly impairing their quality of life [5, 6].

There is currently no unified standard for treating SAPHO syndrome. Clinical options include nonsteroidal anti-inflammatory drugs, corticosteroids, conventional disease-modifying antirheumatic drugs, and biologics [7]. However, some patients exhibit poor response to these treatments or cannot tolerate their side effects. For example, TNF-α antagonists may induce paradoxical rashes [8]. Furthermore, treatments previously explored by our team, such as intravenous bisphosphonates [9] and *Tripterygium wilfordii* Hook F (TwHF) [10, 11], have demonstrated efficacy but face limitations due to infusion-related acute reactions and potential long-term toxicity, respectively. Consequently, there is an urgent clinical need for novel therapeutic options that offer rapid onset of action and superior safety profiles.

In recent years, inhibitors targeting Janus kinase signaling and transcription activation pathways have provided novel therapeutic strategies for various autoimmune diseases. Upadacitinib, as a novel, highly selective JAK1 inhibitor, precisely suppresses signaling of multiple proinflammatory cytokines and theoretically controls the abnormal immune inflammation underlying SAPHO syndrome at its source [12]. A growing body of clinical trials has demonstrated the efficacy and safety of upadacitinib in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis [13]. Currently, evidence of upadacitinib's efficacy in SAPHO syndrome patients is limited to case reports [12], with no clinical studies of sufficient sample size available.

Therefore, we conducted this retrospective observational study to evaluate the efficacy and safety of upadacitinib in treating SAPHO syndrome within real-world clinical practice.

2 | Research Methods

2.1 | Research Design and Patients

This study is a single-center, retrospective, observational investigation. We retrospectively screened and enrolled adult patients with SAPHO syndrome who visited the Rheumatology

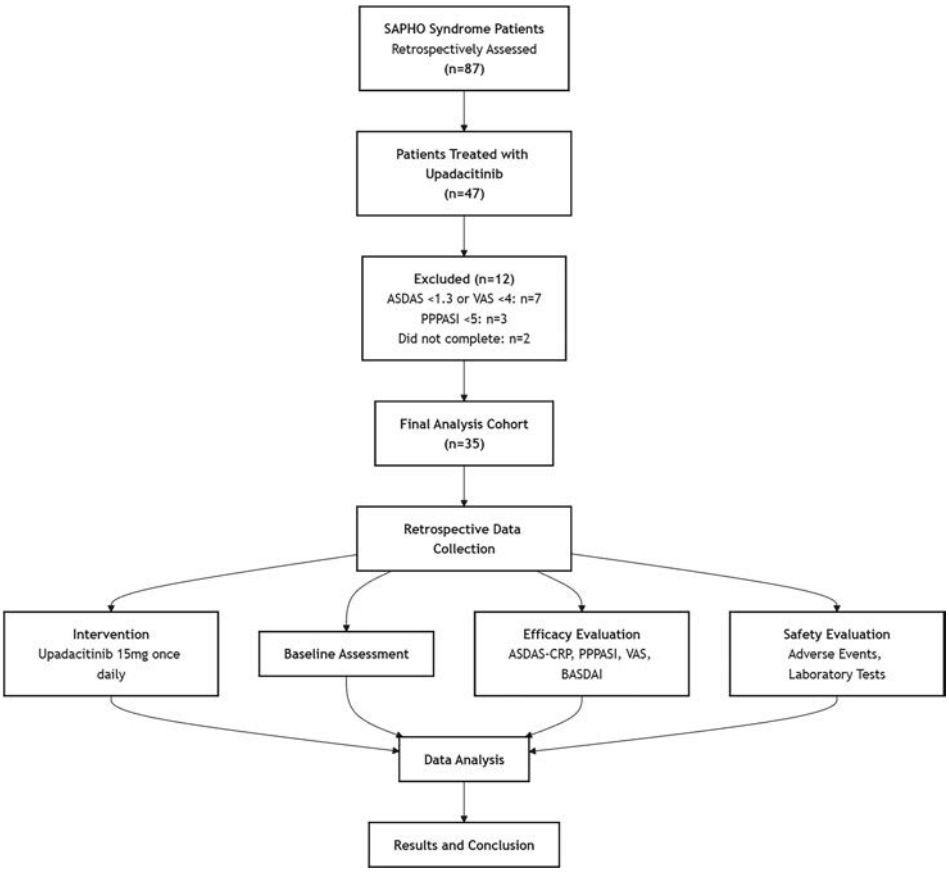

FIGURE 1 | Analysis flowchart for this retrospective study.

Department of Beijing University of Chinese Medicine Fangshan Hospital between October 2023 and October 2024 and received treatment with upadacitinib. The patient recruitment process for this retrospective study is illustrated in Figure 1. Included patients met the following criteria: (1) met the diagnostic criteria for SAPHO syndrome proposed by Kahn et al. [14]; (2) age 18–70 years; (3) active disease prior to initiating upadacitinib treatment, defined as Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) ≥ 1.3, Visual Analogue Scale (VAS) score for total musculoskeletal pain ≥ 4, concurrently presenting with active palmoplantar pustulosis (PPPASI) ≥ 5; (4) Received at least 12 weeks of upadacitinib treatment; (5) Possessed complete baseline and post-treatment follow-up clinical data. Exclusion Criteria: (1) Pregnant or lactating women; (2) Lack of baseline data or incomplete clinical information.

2.2 | Research Ethics

This study was approved by the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine (Approval: No. FZJ JS-2021-002) and exempted from obtaining individual informed consent from patients. All data were anonymized. The research was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

2.3 | Treatment Protocol

In actual clinical practice, all treating physicians prescribed upadacitinib (15 mg once daily) based on their clinical judgment of each enrolled patient's condition. Treatment decisions were independent of the study design.

2.4 | Data Collection

We retrospectively extracted patient data at baseline (prior to initiating upadacitinib treatment) and at follow-up visits at weeks 4, 8, and 12 after treatment initiation. Clinical and demographic data collected prior to starting upadacitinib treatment included age, sex, body mass index (BMI), comorbidities, prior exposure to biologic agents, and bone and skin involvement. The primary efficacy endpoints at baseline and each follow-up (Weeks 4, 8, 12) were the change from baseline in ASDAS-CRP and PPPASI at week 12. Secondary efficacy endpoints included the change from baseline in VAS and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), as well as achieving ASDAS2.1 (ASDAS < 2.1), ASDAS 1.3 (ASDAS < 1.3), ASDAS-CII (ASDAS ≥ 1.1 reduction from baseline), VAS50 (VAS ≥ 50% reduction), PPPASI50 (PPPASI ≥ 50% reduction), and BASDAI50 (BASDAI ≥ 50% improvement) at Week 12. Additional efficacy assessments included the BASFI, HAQ-S, ASQoL, EQ-5D, the Short Form 36 (SF-36), and inflammatory markers (erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP)). All efficacy measures were collected at baseline and at each follow-up visit (Weeks 4, 8, and 12). These widely used patient-reported outcomes and laboratory tests for axial spondyloarthritis have also been demonstrated to reflect functional status and disease activity in SAPHO patients [15, 16].

2.5 | NSAIDs Usage

This retrospective study does not restrict the use of NSAIDs usage during the trial period was recorded at Week 12.

2.6 | Safety and Tolerability Assessment

Blood samples for laboratory analysis (complete blood count, ALT, and creatinine) were collected at baseline and at each follow-up visit. The occurrence of any adverse events (AEs), including serious AEs and AEs leading to discontinuation of upadacitinib, was recorded using a self-reporting model during treatment.

2.7 | Statistical Analysis

Data were summarized using descriptive analysis. For continuous variables, mean, median, standard deviation (SD), and interquartile range (Q2, Q4) were calculated. For categorical variables, absolute values and frequency (%) were calculated. For data distribution analysis, the Shapiro–Wilk test ($\alpha = 0.1$ to reduce Type II error) assessed normality. For continuous data, independent samples *t*-tests (normally distributed data) or non-parametric Wilcoxon signed-rank tests (non-normally distributed data) and chi-square tests were used. All analyses were performed using IBM SPSS Statistics for Windows Version 25.0. $p < 0.05$ was considered statistically significant.

3 | Result

3.1 | Participants Characteristics

From October 2023 to October 2024, this study enrolled 35 patients with SAPHO syndrome who received upadacitinib treatment. The mean age of these patients was 43.71 ± 12.47 years, including 9 males and 26 females. Thirty-three patients (94.29%) had anterior chest wall involvement, and 23 patients (65.71%) had axial joint involvement. The baseline ASDAS score was 2.65 (2.28, 3.04). Twenty-two patients (62.86%) primarily presented with palmo-plantar pustulosis (PPP), while 10 patients (28.57%) primarily presented with coexisting PPP and psoriasis vulgaris (PV). with a baseline PPPASI of 12.20 (7.60, 16.80). All subjects had received one or more nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the study. Five patients (14.29%) had received disease-modifying antirheumatic drugs (DMARDs), and 14 patients (40%) had received biologic disease-modifying antirheumatic drugs (bDMARDs). Table 1 summarizes detailed patient characteristics, including clinical features and prior treatments.

3.2 | Treatment Outcomes

This study demonstrates that upadacitinib exhibits rapid onset of action in patients with SAPHO syndrome, with the most significant improvement in disease activity scores occurring within the initial 4 weeks (ASDAS: −1.01, $p < 0.001$; PPPASI: −11.41, $p < 0.001$), followed by a sustained gradual decline throughout

TABLE 1 | Baseline demographic and clinical characteristics of participants.

Characteristics	Participants ($n = 35$)
Age (years)	43.71 (12.47)
Gender (female/male)	26/9
Weight (kg)	67.79 (12.55)
BMI (kg/m^2)	24.81 (2.99)
Overweight (BMI: 25–29.9 kg/m^2)	14 (40)
Obesity (BMI ≥ 30 kg/m^2)	3 (8.57)
Smoking	21 (60.0)
Alcohol intake	10 (28.57)
Past medical history	
Hypertension	2 (5.71)
Diabetes mellitus	2 (5.71)
Hyperlipidemia	8 (22.86)
CAD	0 (0)
Disease duration (months)	24 (12.36)
Clinical characteristics	
Skin manifestations	
None	1 (2.86)
PPP only	22 (62.86)
PPP and PV	10 (28.57)
Nail lesion	14 (40)
Osteoarticular pain	
Anterior chest wall	33 (94.29)
Axial skeleton	23 (65.71)
Spine	19 (54.29)
Cervical region	5 (14.29)
Thoracic region	14 (40)
Lumbosacral region	10 (28.57)
Sacroiliac joints	12 (34.29)
Peripheral bones and joints	12 (34.29)
ASDAS	2.65 (2.28, 3.04)
VAS	7 (6.8)
BASDAI	4.2 (3.4, 5.4)
PPPASI	12.20 (7.60, 16.80)
hsCRP (mg/L)	5.00 (1.00, 8.70)
ESR (mm/h)	15.00 (6.00, 25.00)
BASFI	3.8 (2.8, 4.2)
ASQoL	13 (12, 15)
EQ-5D	0.641 (0.431, 0.813)
SF-36	59.33 (41.28, 70.72)
DLQI	11 (7, 15)
Laboratory tests	
ANA positivity	0 (0)
RF positivity	0 (0)
HLA-B27 positivity	0 (0)
Prior medication	
NSAIDs	35 (100.0)
GCs	3 (8.57)
cDMARDs	5 (14.29)
bDMARDs	14 (40)
Bisphosphonates	3 (8.57)

Note: Data are presented as mean (SD), Median (Q2, Q4) or *n* (%).
Abbreviations: ANA, antinuclear antibody; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; cDMARDs, conventional disease-modifying anti-rheumatic drugs; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol five dimensions questionnaire; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ-S, Health Assessment Questionnaire for the Spondylarthropathies; HLA-B27, human leukocyte antigen B27; hsCRP, high-sensitivity C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; PPP, palmoplantar pustulosis; PPPASI, Palmoplantar Pustular Psoriasis Area and Severity Indices; PV, psoriasis vulgaris; RF, rheumatoid factor; SF-36, short from-36; TNFi, tumor necrosis factor-α inhibitors; VAS, Visual Analogue Scale.

the remainder of the study. After 12 weeks of upadacitinib treatment, patients demonstrated substantial improvement in both musculoskeletal and skin lesion symptoms (ASDAS: −1.50, $p < 0.001$; PPPASI: −14.69, $p < 0.001$). A substantial proportion of patients achieved ASDAS2.1, ASDAS1.3, ASDAS-MI, and PPPASI50 (Week 4 vs. Week 12) (ASDAS1.3: 17.14% vs. 74.29%; ASDAS2.1: 82.86% vs. 94.29%; ASDAS-CI: 31.43% vs. 85.71%; PPPASI50: 74.29% vs. 88.57%) (Figure 2). Concurrently, other efficacy measures including VAS, VAS50, BASDAI, BASDAI50, BASFI, and inflammatory markers (ESR and hsCRP) demonstrated comparable improvement patterns across both groups during the trial period (Figure 3). Regarding quality of life measures, DLQI scores rapidly decreased within the initial 4 weeks and maintained a steady decline thereafter. HAQ-S, ASQoL, SF-36, and EQ-5D scores all demonstrated sustained improvement (Figure S1).

3.3 | NSAIDS Use

All 35 patients (100%) required regular or on-demand NSAIDs for bone pain prior to receiving upadacitinib. However, only five patients intermittently used NSAIDs for pain relief during the study. Overall NSAID exposure during follow-up is summarized in Table S1.

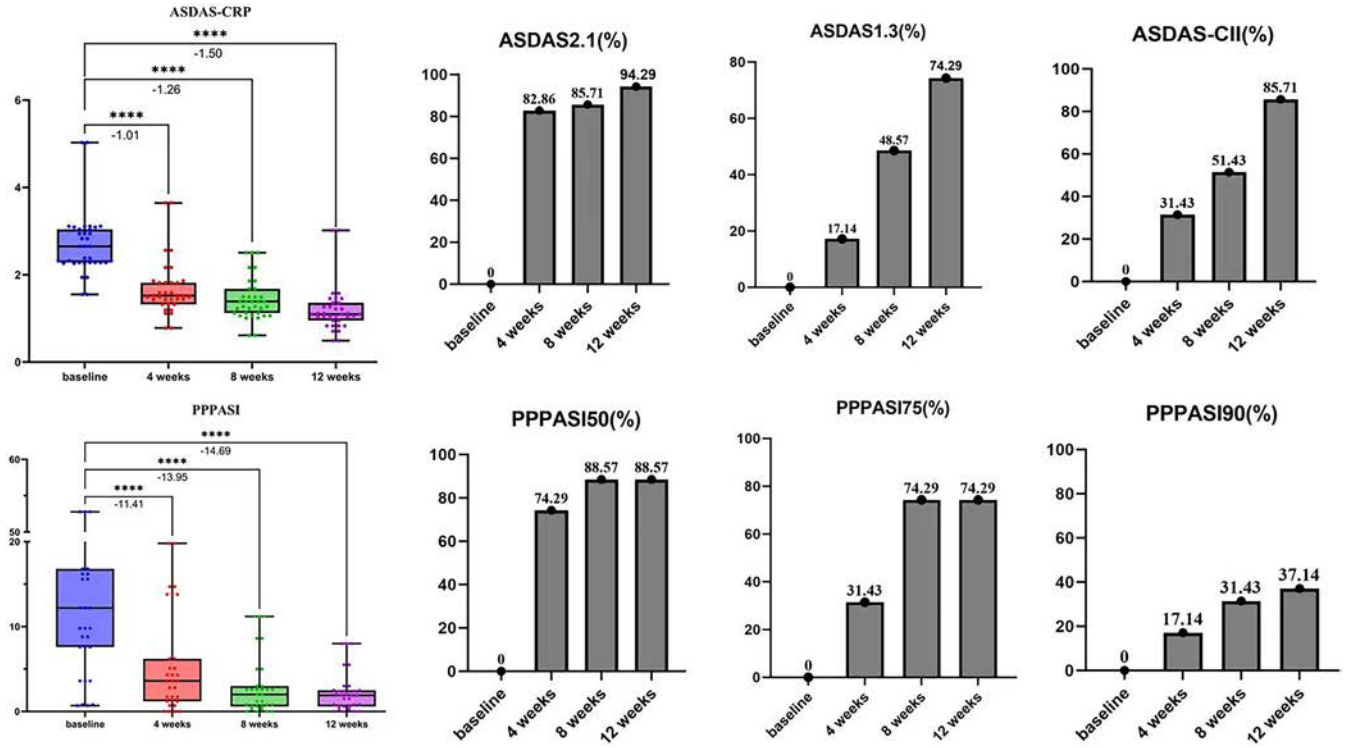

FIGURE 2 | Changes in major osteoarticular and skin lesion outcome metrics in patients with SAPHO syndrome; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$. ASDAS-CRP indicates ankylosing spondylitis disease activity score which incorporates C-reactive protein levels. PPPASI indicates the palmoplantar psoriasis area and severity index.

3.4 | Safety and Tolerability

Fourteen patients (40%) experienced adverse events, and no patients discontinued the study due to adverse events. The most common adverse event in this study was upper respiratory tract infection (20%), which resolved with symptomatic treatment and did not impact upadacitinib use. Additionally, mild elevations in ALT, nausea, mild headache, and sore throat were observed. No other serious adverse events were recorded. All adverse events occurring during the trial are listed in Table 2.

4 | Discussion

To our knowledge, this is the first retrospective observational study investigating the efficacy and safety of upadacitinib in patients with SAPHO syndrome. Our study found that 12 weeks of upadacitinib treatment was effective and well-tolerated in these patients. Furthermore, upadacitinib demonstrated a rapid onset of action, significantly improving disease activity within the first 4 weeks of treatment initiation.

We have previously conducted clinical trials on bisphosphonates and Tripterygium wilfordii Hook F (TwHF) for SAPHO syndrome [9, 10]. Patients receiving bisphosphonates (zoledronic acid 4 mg or pamidronate disodium 1 mg/kg for 3 days) showed significantly lower post-treatment bone pain VAS, BASDAI, and BASFAI scores compared to baseline, with good tolerability. Zoledronic acid was associated with significantly fewer adverse events than pamidronate. Similarly, both dosage groups of TwHF (1.0 and 1.5 mg/kg/day) were effective and well-tolerated over 12 weeks, also exhibiting rapid efficacy, achieving maximal therapeutic effect within 2–4 weeks of treatment initiation. The present study found that, analogous to TwHF, upadacitinib also demonstrated rapid efficacy regarding osteoarticular and cutaneous manifestations in SAPHO patients. Within the initial 4 weeks of treatment, ASDAS-CRP, BASDAI, bone pain VAS, and PPPASI scores decreased rapidly, and disease activity for both bone pain and skin lesions remained at a stably low level after 3 months. Concurrently, upadacitinib demonstrated a favorable safety profile; the incidence of adverse events observed with upadacitinib was notably lower than that reported for bisphosphonates and TwHF in previous studies. However, owing to disparities in study design, enrollment criteria, and eras, direct comparisons are inappropriate. Consequently, the absolute efficacy and safety advantages of upadacitinib require final confirmation through head-to-head randomized controlled trials.

Upadacitinib is a Janus kinase (JAK) inhibitor that exerts anti-inflammatory and immunomodulatory effects by broadly inhibiting multiple cytokines via the JAK–STAT signaling pathway [12]. Unlike tofacitinib, upadacitinib is a novel, highly selective JAK1 inhibitor, offering a potentially improved safety and tolerability profile. It is currently approved for the treatment of various immune-mediated diseases [17], including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), atopic dermatitis (AD), ulcerative colitis (UC), and Crohn's disease (CD). Upadacitinib has demonstrated efficacy in improving both osteoarticular and cutaneous lesions. In the SELECT-AXIS study of axial spondyloarthritis, it rapidly reduced bone pain and disease activity in refractory AS, with sustained efficacy over 2 years, low radiographic progression,

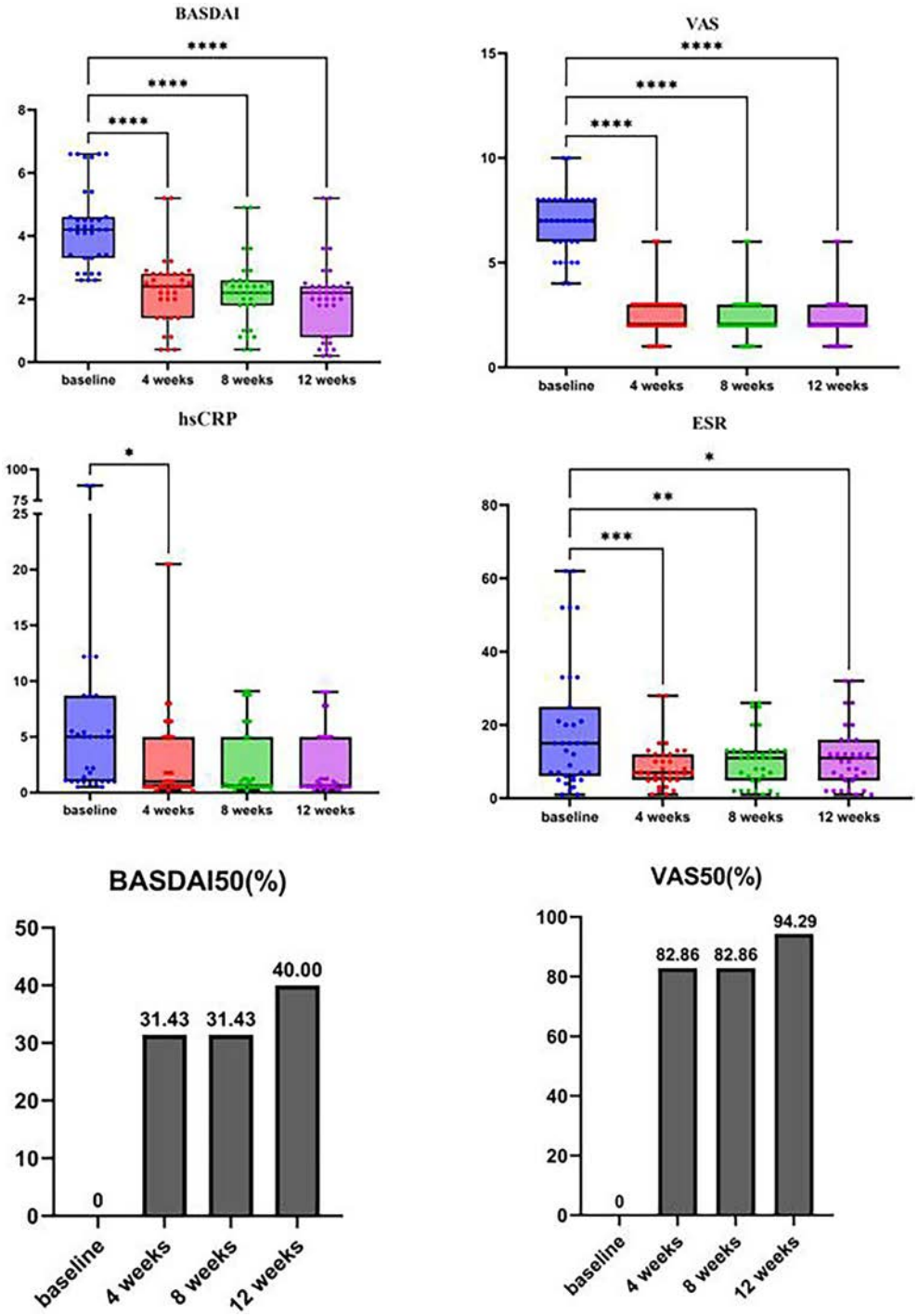

FIGURE 3 | Changes in activity of other diseases in SAPHO syndrome; *Indicates a significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.05$; **Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.01$; ***Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.001$; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$. BASDAI, bath ankylosing spondylitis disease activity index; ESR, erythrocyte sedimentation rate; hsCRP, indicates hypersensitive C-reactive protein; VAS indicates visual analogue scale.

and good tolerability [18, 19]. Similarly, the SELECT-PsA study in psoriatic arthritis showed rapid improvement in PASI scores, joint pain, and enthesitis, with stable efficacy and favorable safety over 3 years [20]. SAPHO syndrome is a chronic relapsing autoimmune disorder involving both bones/joints and skin. Similar to axial spondyloarthritis and psoriatic arthritis, the osteoarticular and cutaneous manifestations of SAPHO syndrome impose not only a significant physical pain burden but also a psychological burden, severely impairing quality of life. Therefore, actively controlling disease activity in SAPHO syndrome is crucial.

Our study found that upadacitinib significantly improved the quality of life in SAPHO patients over 12 weeks. We observed that upadacitinib also displayed a rapid onset of effect on disease-specific quality of life measures, namely the

TABLE 2 | Adverse events in all participants.

Adverse event	Participants ($n = 35$)
All	14 (40.0)
Gastrointestinal event	4 (11.43)
ALT elevation	2 (5.71)
Nausea	2 (5.71)
Abdominal distention	0
Diarrhea	0
Infection	7 (20.0)
Upper respiratory infection	7 (20.0)
Pulmonary infection	0
Urinary tract infection	0
Thrombosis	0
Cardiovascular event	0
Malignant tumor	0
Others (headache, earache)	5 (14.29)

Note: Data expressed as *n* (%).

Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) and the Dermatology Life Quality Index (DLQI), with rapid improvement within the first 4 weeks, consistent with the improvement in disease activity. For other generic quality of life instruments, such as the SF-36 and EQ-5D, improvements were more evenly distributed over the 12-week period. It is recognized, however, that the primary contextual factors interpreted by ASQoL/DLQI versus EQ-5D/SF-36 differ [21]. The EQ-5D and SF-36 are comprehensive quality of life assessments not solely focused on skin and joint manifestations, which may explain the differential patterns of improvement observed across these instruments. Despite varying degrees of improvement, this preliminary study indicates that upadacitinib unequivocally improves quality of life over 12 weeks, further highlighting its beneficial role.

The frequency of NSAID use during the trial period can also be considered a reflection of clinical efficacy. SAPHO syndrome patients often experience intolerable bone and joint pain, leading many to use NSAIDs for relief. However, some patients continue to have uncontrolled pain and disease activity even with maximum NSAID doses, and NSAIDs are associated with various side effects. Therefore, alternative treatments are needed to allow for NSAID dose reduction or discontinuation. The Assessment of SpondyloArthritis international Society (ASAS) recommends the collection, analysis, and reporting of NSAID intake in clinical trials for axial spondyloarthritis and has developed the ASAS-NSAID score as a standardized method for this assessment [22]. In our study involving 35 SAPHO patients treated with upadacitinib, only 5 patients required NSAIDs due to intolerable pain, and all 5 discontinued NSAIDs by week 4 until the end of the trial. The marked reduction in NSAID use observed indirectly supports the efficacy of upadacitinib in alleviating osteoarticular pain. However, the protocol's allowance for NSAID use as needed during the initial treatment phase may have confounded the magnitude of early pain score improvement. Future prospective studies should use the ASAS-NSAID scoring system to assess the intake scores of NSAIDs at baseline and follow-up nodes to more precisely evaluate upadacitinib's efficacy. Among the 35 patients, 14 experienced adverse events during the trial, with no serious adverse events recorded. The most common events were mild gastrointestinal reactions and upper respiratory tract infections, which resolved with symptomatic treatment and did not necessitate upadacitinib discontinuation. This safety profile is consistent with previous reports on upadacitinib, further confirming its clinical safety.

This study has several limitations. First, this study is a single-center, retrospective and observational study that explored the efficacy and safety of upadacitinib, without a placebo or active control, and the evidence is limited. Since SAPHO syndrome is a rare disease without standard treatment, it may be impractical and unethical. Future studies should conduct multicenter prospective clinical trials to compare the efficacy of upadacitinib with that of validated drugs. Second, there are no validated scales or scoring systems available in clinical practice to assess therapeutic outcomes in patients with SAPHO syndrome. Since the primary osteoarticular involvement in SAPHO syndrome is the anterior chest wall and the spine, sacroiliac joints, our efficacy evaluation primarily references clinical scores for axial spondylitis and patient-reported outcomes [9, 11]. However, the lack of imaging evidence such as MRI [23] and CT [24] hinders the objective confirmation of the endpoint for inflammatory resolution. Future research should focus on developing a validated disease activity score tailored for the osteoarticular involvement in SAPHO syndrome, along with the application of various imaging modalities to evaluate therapeutic changes in this condition. Finally, this was a short-term, small-sample, retrospective trial with only 12 weeks of follow-up. We plan to expand the sample size and follow-up duration for this cohort to investigate the long-term efficacy and safety of upadacitinib in SAPHO syndrome patients.

5 | Conclusion

In summary, this 12-week retrospective observational study found that upadacitinib rapidly and significantly improved osteoarticular and cutaneous symptoms, enhanced quality of life, and was well-tolerated. Our conclusions preliminarily indicate that upadacitinib is a highly promising novel therapeutic option for SAPHO syndrome, laying a solid foundation for subsequent prospective controlled clinical trials.

Future research directions should focus on addressing the limitations of the present study: conducting multicenter prospective trials with active comparators to confirm the absolute efficacy and safety advantages of upadacitinib; developing a validated disease activity scale specific to SAPHO syndrome and incorporating imaging modalities (such as MRI and CT) for objective efficacy assessment; and expanding the sample size and extending follow-up duration to explore the long-term therapeutic effects and safety profile of upadacitinib in patients with SAPHO syndrome.

Author Contributions

Fanzhang Meng designed and wrote this article. Yuqing Zhang and Yuan Chen collected data and helped to write this article. Zhimin Lin helped to write this article and visualized it. Yuanhao Wu, Xiujuan Hou and Chen Li reviewed and edited the manuscript.

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Ethics Statement

This study was approved by the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine (Approval: No. FZJ JS-2021-002) and exempted from obtaining individual informed consent from patients. All data were anonymized. The research was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Consent

All patients gave written informed consent for the retrospective retrieval of anonymized data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Changes in quality of life in SAPHO syndrome; ns indicates that there is no significant decrease

in outcome metric scores after treatment compared with baselin, $p > 0.05$; ***Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.001$; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$.ASQOL, dermatology life quality index; BASFI, Bath Ankylosing Spondylitis Functional Index; DLQI, visual analogue scale; Q-5D, euroqol five dimensions questionnaire; SF-36, MOS 36-item short-form health survey. **Table S1:** Concurrent use of NSAIDs during the trial period.

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ORIGINAL ARTICLE

Efficacy and Safety Assessment of Upadacitinib for SAPHO Syndrome: A Retrospective Study of 35 Patients

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of upadacitinib administered over a short-term period in patients with SAPHO syndrome.

Methods: In this 12-week retrospective observational study, eligible SAPHO syndrome patients diagnosed within the past year and treated with upadacitinib were enrolled. Efficacy was assessed using the Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP) and the Palmoplantar Pustulosis Area and Severity Index (PPPASI). Safety was evaluated based on the incidence of adverse events during the treatment period.

Results: A total of 35 eligible patients were included. Both ASDAS-CRP and PPPASI scores decreased rapidly by Week 4 (−1.01 and −11.41, respectively; both $p < 0.001$) and showed further significant improvements at Week 12 (−1.50 and −14.69, respectively; both $p < 0.001$) compared to baseline. Similar improvements were observed in the Visual Analogue Scale for overall musculoskeletal pain, the Bath Ankylosing Spondylitis Disease Activity Index, and other quality-of-life measures. Upadacitinib was well tolerated, with no serious adverse events reported. The most common adverse event was upper respiratory tract infection (20%). Other mild adverse events included elevated alanine aminotransferase, nausea, mild headache, and sore throat.

Conclusion: Upadacitinib demonstrated a rapid onset of action, significant efficacy, and a favorable safety profile in the treatment of SAPHO syndrome, supporting its potential as a therapeutic option in clinical practice.

1 | Introduction

SAPHO syndrome (synovitis, acne, pustulosis, osteophytosis, and osteitis) is a rare, chronic autoimmune disorder [1]. Clinical manifestations typically involve skeletal and joint lesions in the anterior chest wall and spine, alongside skin lesions such as pustules on the palms and soles and facial acne [2]. The pathogenesis of SAPHO syndrome remains unclear, though it is widely considered an autoinflammatory disorder triggered by multiple factors including infection, genetics, immunity, and

Fanzhang Meng, Yuqing Zhang, and Yuan Chen contributed equally and should be the co-first author.

Highlights

- This is the first retrospective observational study evaluating upadacitinib for the treatment of SAPHO syndrome.
- Upadacitinib rapidly improved both musculoskeletal and cutaneous lesions of SAPHO syndrome within 4 weeks, achieving rapid disease remission by Week 12.
- Upadacitinib demonstrated rapid onset of action in treating SAPHO syndrome without serious adverse reactions.

environment [3, 4]. The recurrent nature of its musculoskeletal and cutaneous symptoms often leads to depression in patients, significantly impairing their quality of life [5, 6].

There is currently no unified standard for treating SAPHO syndrome. Clinical options include nonsteroidal anti-inflammatory drugs, corticosteroids, conventional disease-modifying antirheumatic drugs, and biologics [7]. However, some patients exhibit poor response to these treatments or cannot tolerate their side effects. For example, TNF-α antagonists may induce paradoxical rashes [8]. Furthermore, treatments previously explored by our team, such as intravenous bisphosphonates [9] and *Tripterygium wilfordii* Hook F (TwHF) [10, 11], have demonstrated efficacy but face limitations due to infusion-related acute reactions and potential long-term toxicity, respectively. Consequently, there is an urgent clinical need for novel therapeutic options that offer rapid onset of action and superior safety profiles.

In recent years, inhibitors targeting Janus kinase signaling and transcription activation pathways have provided novel therapeutic strategies for various autoimmune diseases. Upadacitinib, as a novel, highly selective JAK1 inhibitor, precisely suppresses signaling of multiple proinflammatory cytokines and theoretically controls the abnormal immune inflammation underlying SAPHO syndrome at its source [12]. A growing body of clinical trials has demonstrated the efficacy and safety of upadacitinib in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis [13]. Currently, evidence of upadacitinib's efficacy in SAPHO syndrome patients is limited to case reports [12], with no clinical studies of sufficient sample size available.

Therefore, we conducted this retrospective observational study to evaluate the efficacy and safety of upadacitinib in treating SAPHO syndrome within real-world clinical practice.

2 | Research Methods

2.1 | Research Design and Patients

This study is a single-center, retrospective, observational investigation. We retrospectively screened and enrolled adult patients with SAPHO syndrome who visited the Rheumatology

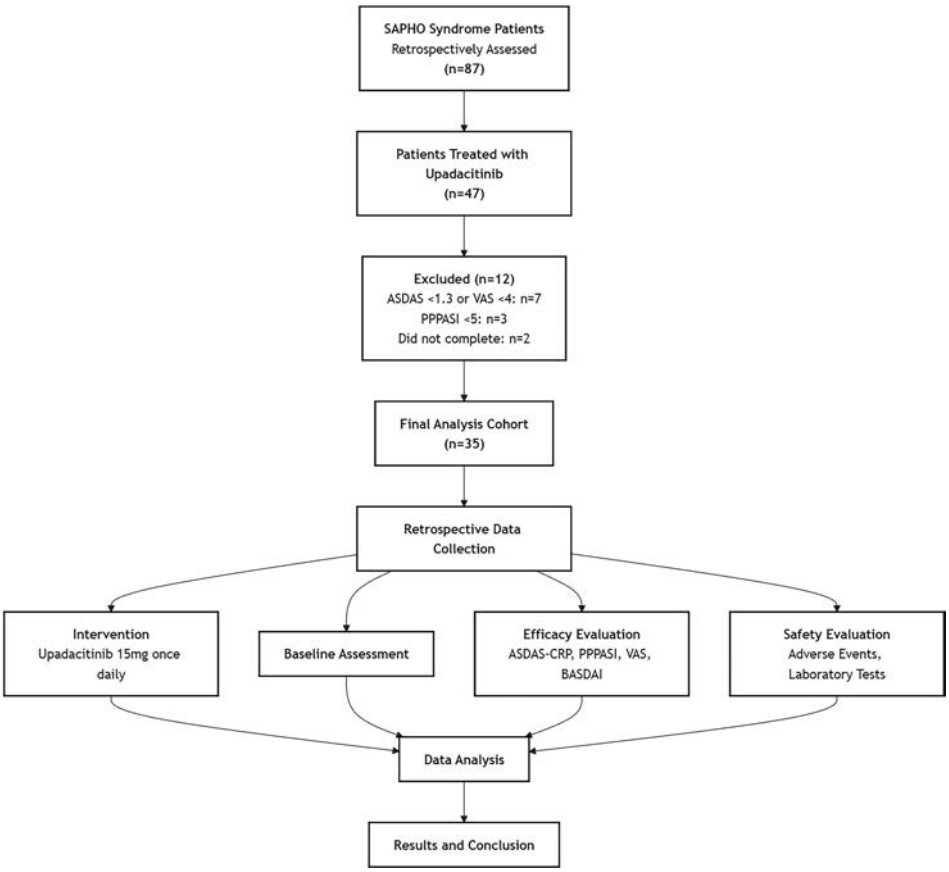

FIGURE 1 | Analysis flowchart for this retrospective study.

Department of Beijing University of Chinese Medicine Fangshan Hospital between October 2023 and October 2024 and received treatment with upadacitinib. The patient recruitment process for this retrospective study is illustrated in Figure 1. Included patients met the following criteria: (1) met the diagnostic criteria for SAPHO syndrome proposed by Kahn et al. [14]; (2) age 18–70 years; (3) active disease prior to initiating upadacitinib treatment, defined as Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) ≥ 1.3, Visual Analogue Scale (VAS) score for total musculoskeletal pain ≥ 4, concurrently presenting with active palmoplantar pustulosis (PPPASI) ≥ 5; (4) Received at least 12 weeks of upadacitinib treatment; (5) Possessed complete baseline and post-treatment follow-up clinical data. Exclusion Criteria: (1) Pregnant or lactating women; (2) Lack of baseline data or incomplete clinical information.

2.2 | Research Ethics

This study was approved by the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine (Approval: No. FZJ JS-2021-002) and exempted from obtaining individual informed consent from patients. All data were anonymized. The research was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

2.3 | Treatment Protocol

In actual clinical practice, all treating physicians prescribed upadacitinib (15 mg once daily) based on their clinical judgment of each enrolled patient's condition. Treatment decisions were independent of the study design.

2.4 | Data Collection

We retrospectively extracted patient data at baseline (prior to initiating upadacitinib treatment) and at follow-up visits at weeks 4, 8, and 12 after treatment initiation. Clinical and demographic data collected prior to starting upadacitinib treatment included age, sex, body mass index (BMI), comorbidities, prior exposure to biologic agents, and bone and skin involvement. The primary efficacy endpoints at baseline and each follow-up (Weeks 4, 8, 12) were the change from baseline in ASDAS-CRP and PPPASI at week 12. Secondary efficacy endpoints included the change from baseline in VAS and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), as well as achieving ASDAS2.1 (ASDAS < 2.1), ASDAS 1.3 (ASDAS < 1.3), ASDAS-CII (ASDAS ≥ 1.1 reduction from baseline), VAS50 (VAS ≥ 50% reduction), PPPASI50 (PPPASI ≥ 50% reduction), and BASDAI50 (BASDAI ≥ 50% improvement) at Week 12. Additional efficacy assessments included the BASFI, HAQ-S, ASQoL, EQ-5D, the Short Form 36 (SF-36), and inflammatory markers (erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP)). All efficacy measures were collected at baseline and at each follow-up visit (Weeks 4, 8, and 12). These widely used patient-reported outcomes and laboratory tests for axial spondyloarthritis have also been demonstrated to reflect functional status and disease activity in SAPHO patients [15, 16].

2.5 | NSAIDs Usage

This retrospective study does not restrict the use of NSAIDs usage during the trial period was recorded at Week 12.

2.6 | Safety and Tolerability Assessment

Blood samples for laboratory analysis (complete blood count, ALT, and creatinine) were collected at baseline and at each follow-up visit. The occurrence of any adverse events (AEs), including serious AEs and AEs leading to discontinuation of upadacitinib, was recorded using a self-reporting model during treatment.

2.7 | Statistical Analysis

Data were summarized using descriptive analysis. For continuous variables, mean, median, standard deviation (SD), and interquartile range (Q2, Q4) were calculated. For categorical variables, absolute values and frequency (%) were calculated. For data distribution analysis, the Shapiro–Wilk test ($\alpha = 0.1$ to reduce Type II error) assessed normality. For continuous data, independent samples *t*-tests (normally distributed data) or non-parametric Wilcoxon signed-rank tests (non-normally distributed data) and chi-square tests were used. All analyses were performed using IBM SPSS Statistics for Windows Version 25.0. $p < 0.05$ was considered statistically significant.

3 | Result

3.1 | Participants Characteristics

From October 2023 to October 2024, this study enrolled 35 patients with SAPHO syndrome who received upadacitinib treatment. The mean age of these patients was 43.71 ± 12.47 years, including 9 males and 26 females. Thirty-three patients (94.29%) had anterior chest wall involvement, and 23 patients (65.71%) had axial joint involvement. The baseline ASDAS score was 2.65 (2.28, 3.04). Twenty-two patients (62.86%) primarily presented with palmo-plantar pustulosis (PPP), while 10 patients (28.57%) primarily presented with coexisting PPP and psoriasis vulgaris (PV). with a baseline PPPASI of 12.20 (7.60, 16.80). All subjects had received one or more nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the study. Five patients (14.29%) had received disease-modifying antirheumatic drugs (DMARDs), and 14 patients (40%) had received biologic disease-modifying antirheumatic drugs (bDMARDs). Table 1 summarizes detailed patient characteristics, including clinical features and prior treatments.

3.2 | Treatment Outcomes

This study demonstrates that upadacitinib exhibits rapid onset of action in patients with SAPHO syndrome, with the most significant improvement in disease activity scores occurring within the initial 4 weeks (ASDAS: −1.01, $p < 0.001$; PPPASI: −11.41, $p < 0.001$), followed by a sustained gradual decline throughout

TABLE 1 | Baseline demographic and clinical characteristics of participants.

Characteristics	Participants ($n = 35$)
Age (years)	43.71 (12.47)
Gender (female/male)	26/9
Weight (kg)	67.79 (12.55)
BMI (kg/m^2)	24.81 (2.99)
Overweight (BMI: 25–29.9 kg/m^2)	14 (40)
Obesity (BMI ≥ 30 kg/m^2)	3 (8.57)
Smoking	21 (60.0)
Alcohol intake	10 (28.57)
Past medical history	
Hypertension	2 (5.71)
Diabetes mellitus	2 (5.71)
Hyperlipidemia	8 (22.86)
CAD	0 (0)
Disease duration (months)	24 (12.36)
Clinical characteristics	
Skin manifestations	
None	1 (2.86)
PPP only	22 (62.86)
PPP and PV	10 (28.57)
Nail lesion	14 (40)
Osteoarticular pain	
Anterior chest wall	33 (94.29)
Axial skeleton	23 (65.71)
Spine	19 (54.29)
Cervical region	5 (14.29)
Thoracic region	14 (40)
Lumbosacral region	10 (28.57)
Sacroiliac joints	12 (34.29)
Peripheral bones and joints	12 (34.29)
ASDAS	2.65 (2.28, 3.04)
VAS	7 (6.8)
BASDAI	4.2 (3.4, 5.4)
PPPASI	12.20 (7.60, 16.80)
hsCRP (mg/L)	5.00 (1.00, 8.70)
ESR (mm/h)	15.00 (6.00, 25.00)
BASFI	3.8 (2.8, 4.2)
ASQoL	13 (12, 15)
EQ-5D	0.641 (0.431, 0.813)
SF-36	59.33 (41.28, 70.72)
DLQI	11 (7, 15)
Laboratory tests	
ANA positivity	0 (0)
RF positivity	0 (0)
HLA-B27 positivity	0 (0)
Prior medication	
NSAIDs	35 (100.0)
GCs	3 (8.57)
cDMARDs	5 (14.29)
bDMARDs	14 (40)
Bisphosphonates	3 (8.57)

Note: Data are presented as mean (SD), Median (Q2, Q4) or *n* (%).
Abbreviations: ANA, antinuclear antibody; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; cDMARDs, conventional disease-modifying anti-rheumatic drugs; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol five dimensions questionnaire; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HAQ-S, Health Assessment Questionnaire for the Spondylarthropathies; HLA-B27, human leukocyte antigen B27; hsCRP, high-sensitivity C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; PPP, palmoplantar pustulosis; PPPASI, Palmoplantar Pustular Psoriasis Area and Severity Indices; PV, psoriasis vulgaris; RF, rheumatoid factor; SF-36, short from-36; TNFi, tumor necrosis factor-α inhibitors; VAS, Visual Analogue Scale.

the remainder of the study. After 12 weeks of upadacitinib treatment, patients demonstrated substantial improvement in both musculoskeletal and skin lesion symptoms (ASDAS: −1.50, $p < 0.001$; PPPASI: −14.69, $p < 0.001$). A substantial proportion of patients achieved ASDAS2.1, ASDAS1.3, ASDAS-MI, and PPPASI50 (Week 4 vs. Week 12) (ASDAS1.3: 17.14% vs. 74.29%; ASDAS2.1: 82.86% vs. 94.29%; ASDAS-CI: 31.43% vs. 85.71%; PPPASI50: 74.29% vs. 88.57%) (Figure 2). Concurrently, other efficacy measures including VAS, VAS50, BASDAI, BASDAI50, BASFI, and inflammatory markers (ESR and hsCRP) demonstrated comparable improvement patterns across both groups during the trial period (Figure 3). Regarding quality of life measures, DLQI scores rapidly decreased within the initial 4 weeks and maintained a steady decline thereafter. HAQ-S, ASQoL, SF-36, and EQ-5D scores all demonstrated sustained improvement (Figure S1).

3.3 | NSAIDS Use

All 35 patients (100%) required regular or on-demand NSAIDs for bone pain prior to receiving upadacitinib. However, only five patients intermittently used NSAIDs for pain relief during the study. Overall NSAID exposure during follow-up is summarized in Table S1.

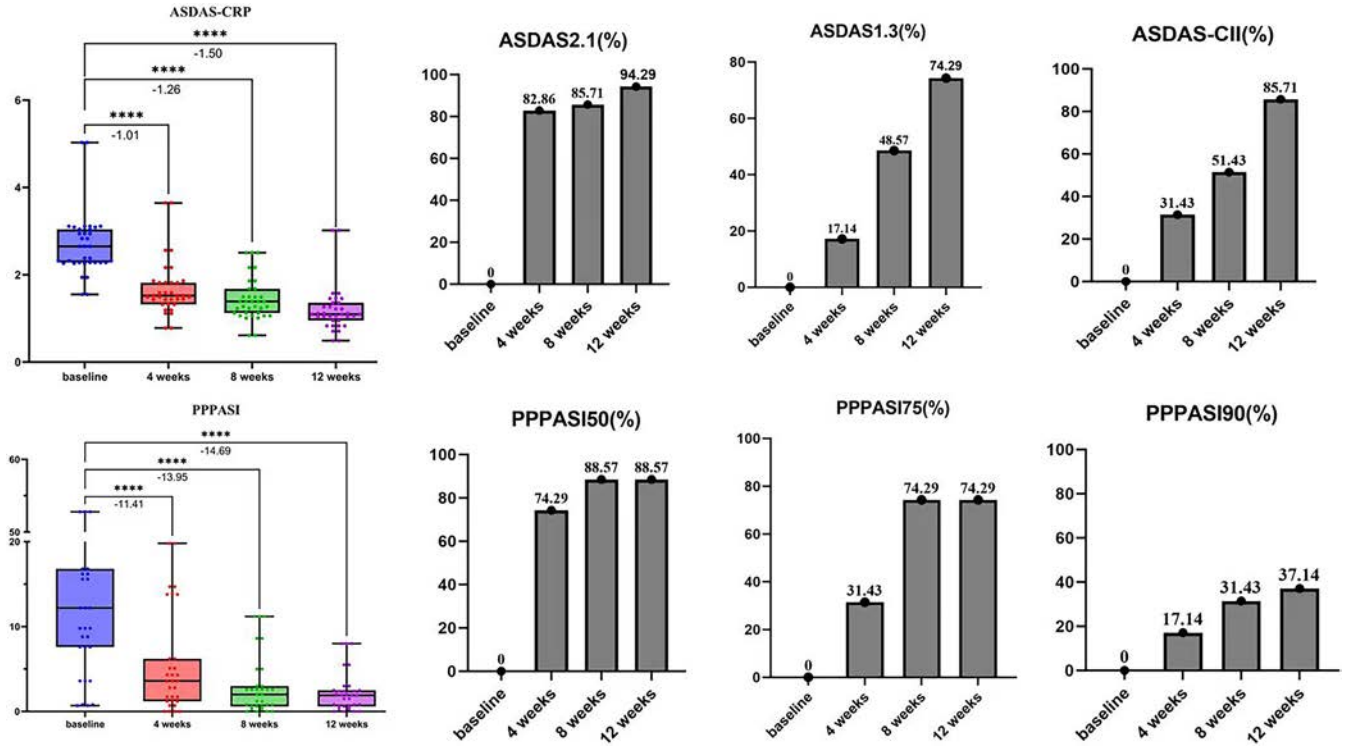

FIGURE 2 | Changes in major osteoarticular and skin lesion outcome metrics in patients with SAPHO syndrome; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$. ASDAS-CRP indicates ankylosing spondylitis disease activity score which incorporates C-reactive protein levels. PPPASI indicates the palmoplantar psoriasis area and severity index.

3.4 | Safety and Tolerability

Fourteen patients (40%) experienced adverse events, and no patients discontinued the study due to adverse events. The most common adverse event in this study was upper respiratory tract infection (20%), which resolved with symptomatic treatment and did not impact upadacitinib use. Additionally, mild elevations in ALT, nausea, mild headache, and sore throat were observed. No other serious adverse events were recorded. All adverse events occurring during the trial are listed in Table 2.

4 | Discussion

To our knowledge, this is the first retrospective observational study investigating the efficacy and safety of upadacitinib in patients with SAPHO syndrome. Our study found that 12 weeks of upadacitinib treatment was effective and well-tolerated in these patients. Furthermore, upadacitinib demonstrated a rapid onset of action, significantly improving disease activity within the first 4 weeks of treatment initiation.

We have previously conducted clinical trials on bisphosphonates and Tripterygium wilfordii Hook F (TwHF) for SAPHO syndrome [9, 10]. Patients receiving bisphosphonates (zoledronic acid 4 mg or pamidronate disodium 1 mg/kg for 3 days) showed significantly lower post-treatment bone pain VAS, BASDAI, and BASFAI scores compared to baseline, with good tolerability. Zoledronic acid was associated with significantly fewer adverse events than pamidronate. Similarly, both dosage groups of TwHF (1.0 and 1.5 mg/kg/day) were effective and well-tolerated over 12 weeks, also exhibiting rapid efficacy, achieving maximal therapeutic effect within 2–4 weeks of treatment initiation. The present study found that, analogous to TwHF, upadacitinib also demonstrated rapid efficacy regarding osteoarticular and cutaneous manifestations in SAPHO patients. Within the initial 4 weeks of treatment, ASDAS-CRP, BASDAI, bone pain VAS, and PPPASI scores decreased rapidly, and disease activity for both bone pain and skin lesions remained at a stably low level after 3 months. Concurrently, upadacitinib demonstrated a favorable safety profile; the incidence of adverse events observed with upadacitinib was notably lower than that reported for bisphosphonates and TwHF in previous studies. However, owing to disparities in study design, enrollment criteria, and eras, direct comparisons are inappropriate. Consequently, the absolute efficacy and safety advantages of upadacitinib require final confirmation through head-to-head randomized controlled trials.

Upadacitinib is a Janus kinase (JAK) inhibitor that exerts anti-inflammatory and immunomodulatory effects by broadly inhibiting multiple cytokines via the JAK–STAT signaling pathway [12]. Unlike tofacitinib, upadacitinib is a novel, highly selective JAK1 inhibitor, offering a potentially improved safety and tolerability profile. It is currently approved for the treatment of various immune-mediated diseases [17], including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), atopic dermatitis (AD), ulcerative colitis (UC), and Crohn's disease (CD). Upadacitinib has demonstrated efficacy in improving both osteoarticular and cutaneous lesions. In the SELECT-AXIS study of axial spondyloarthritis, it rapidly reduced bone pain and disease activity in refractory AS, with sustained efficacy over 2 years, low radiographic progression,

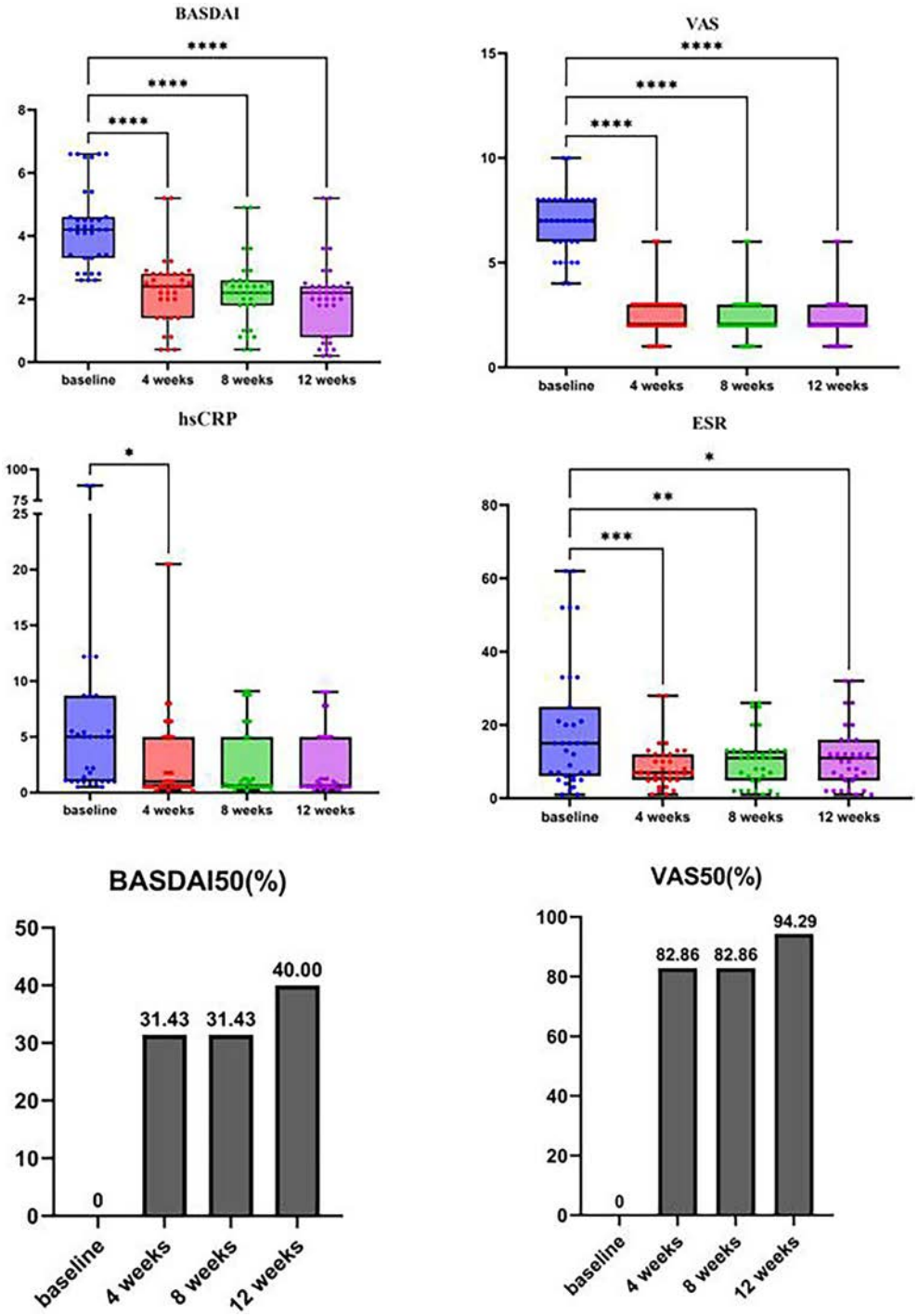

FIGURE 3 | Changes in activity of other diseases in SAPHO syndrome; *Indicates a significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.05$; **Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.01$; ***Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.001$; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$. BASDAI, bath ankylosing spondylitis disease activity index; ESR, erythrocyte sedimentation rate; hsCRP, indicates hypersensitive C-reactive protein; VAS indicates visual analogue scale.

and good tolerability [18, 19]. Similarly, the SELECT-PsA study in psoriatic arthritis showed rapid improvement in PASI scores, joint pain, and enthesitis, with stable efficacy and favorable safety over 3 years [20]. SAPHO syndrome is a chronic relapsing autoimmune disorder involving both bones/joints and skin. Similar to axial spondyloarthritis and psoriatic arthritis, the osteoarticular and cutaneous manifestations of SAPHO syndrome impose not only a significant physical pain burden but also a psychological burden, severely impairing quality of life. Therefore, actively controlling disease activity in SAPHO syndrome is crucial.

Our study found that upadacitinib significantly improved the quality of life in SAPHO patients over 12 weeks. We observed that upadacitinib also displayed a rapid onset of effect on disease-specific quality of life measures, namely the

TABLE 2 | Adverse events in all participants.

Adverse event	Participants ($n = 35$)
All	14 (40.0)
Gastrointestinal event	4 (11.43)
ALT elevation	2 (5.71)
Nausea	2 (5.71)
Abdominal distention	0
Diarrhea	0
Infection	7 (20.0)
Upper respiratory infection	7 (20.0)
Pulmonary infection	0
Urinary tract infection	0
Thrombosis	0
Cardiovascular event	0
Malignant tumor	0
Others (headache, earache)	5 (14.29)

Note: Data expressed as *n* (%).

Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) and the Dermatology Life Quality Index (DLQI), with rapid improvement within the first 4 weeks, consistent with the improvement in disease activity. For other generic quality of life instruments, such as the SF-36 and EQ-5D, improvements were more evenly distributed over the 12-week period. It is recognized, however, that the primary contextual factors interpreted by ASQoL/DLQI versus EQ-5D/SF-36 differ [21]. The EQ-5D and SF-36 are comprehensive quality of life assessments not solely focused on skin and joint manifestations, which may explain the differential patterns of improvement observed across these instruments. Despite varying degrees of improvement, this preliminary study indicates that upadacitinib unequivocally improves quality of life over 12 weeks, further highlighting its beneficial role.

The frequency of NSAID use during the trial period can also be considered a reflection of clinical efficacy. SAPHO syndrome patients often experience intolerable bone and joint pain, leading many to use NSAIDs for relief. However, some patients continue to have uncontrolled pain and disease activity even with maximum NSAID doses, and NSAIDs are associated with various side effects. Therefore, alternative treatments are needed to allow for NSAID dose reduction or discontinuation. The Assessment of SpondyloArthritis international Society (ASAS) recommends the collection, analysis, and reporting of NSAID intake in clinical trials for axial spondyloarthritis and has developed the ASAS-NSAID score as a standardized method for this assessment [22]. In our study involving 35 SAPHO patients treated with upadacitinib, only 5 patients required NSAIDs due to intolerable pain, and all 5 discontinued NSAIDs by week 4 until the end of the trial. The marked reduction in NSAID use observed indirectly supports the efficacy of upadacitinib in alleviating osteoarticular pain. However, the protocol's allowance for NSAID use as needed during the initial treatment phase may have confounded the magnitude of early pain score improvement. Future prospective studies should use the ASAS-NSAID scoring system to assess the intake scores of NSAIDs at baseline and follow-up nodes to more precisely evaluate upadacitinib's efficacy. Among the 35 patients, 14 experienced adverse events during the trial, with no serious adverse events recorded. The most common events were mild gastrointestinal reactions and upper respiratory tract infections, which resolved with symptomatic treatment and did not necessitate upadacitinib discontinuation. This safety profile is consistent with previous reports on upadacitinib, further confirming its clinical safety.

This study has several limitations. First, this study is a single-center, retrospective and observational study that explored the efficacy and safety of upadacitinib, without a placebo or active control, and the evidence is limited. Since SAPHO syndrome is a rare disease without standard treatment, it may be impractical and unethical. Future studies should conduct multicenter prospective clinical trials to compare the efficacy of upadacitinib with that of validated drugs. Second, there are no validated scales or scoring systems available in clinical practice to assess therapeutic outcomes in patients with SAPHO syndrome. Since the primary osteoarticular involvement in SAPHO syndrome is the anterior chest wall and the spine, sacroiliac joints, our efficacy evaluation primarily references clinical scores for axial spondylitis and patient-reported outcomes [9, 11]. However, the lack of imaging evidence such as MRI [23] and CT [24] hinders the objective confirmation of the endpoint for inflammatory resolution. Future research should focus on developing a validated disease activity score tailored for the osteoarticular involvement in SAPHO syndrome, along with the application of various imaging modalities to evaluate therapeutic changes in this condition. Finally, this was a short-term, small-sample, retrospective trial with only 12 weeks of follow-up. We plan to expand the sample size and follow-up duration for this cohort to investigate the long-term efficacy and safety of upadacitinib in SAPHO syndrome patients.

5 | Conclusion

In summary, this 12-week retrospective observational study found that upadacitinib rapidly and significantly improved osteoarticular and cutaneous symptoms, enhanced quality of life, and was well-tolerated. Our conclusions preliminarily indicate that upadacitinib is a highly promising novel therapeutic option for SAPHO syndrome, laying a solid foundation for subsequent prospective controlled clinical trials.

Future research directions should focus on addressing the limitations of the present study: conducting multicenter prospective trials with active comparators to confirm the absolute efficacy and safety advantages of upadacitinib; developing a validated disease activity scale specific to SAPHO syndrome and incorporating imaging modalities (such as MRI and CT) for objective efficacy assessment; and expanding the sample size and extending follow-up duration to explore the long-term therapeutic effects and safety profile of upadacitinib in patients with SAPHO syndrome.

Author Contributions

Fanzhang Meng designed and wrote this article. Yuqing Zhang and Yuan Chen collected data and helped to write this article. Zhimin Lin helped to write this article and visualized it. Yuanhao Wu, Xiujuan Hou and Chen Li reviewed and edited the manuscript.

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Ethics Statement

This study was approved by the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine (Approval: No. FZJ JS-2021-002) and exempted from obtaining individual informed consent from patients. All data were anonymized. The research was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Consent

All patients gave written informed consent for the retrospective retrieval of anonymized data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Changes in quality of life in SAPHO syndrome; ns indicates that there is no significant decrease

in outcome metric scores after treatment compared with baselin, $p > 0.05$; ***Indicates a statistically significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.001$; ****Indicates an extremely significant decrease in outcome metric scores after treatment compared to baseline, $p < 0.0001$.ASQOL, dermatology life quality index; BASFI, Bath Ankylosing Spondylitis Functional Index; DLQI, visual analogue scale; Q-5D, euroqol five dimensions questionnaire; SF-36, MOS 36-item short-form health survey. **Table S1:** Concurrent use of NSAIDs during the trial period.

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EDITORIAL

Beyond Inflammation: Breaking the Vicious Cycle of Matrix Stiffness and Mechanotransduction in Systemic Sclerosis

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Keywords: extracellular matrix | fibrosis | matrix stiffness | mechanotransduction | systemic sclerosis

1 | The Limitations of the Immunological Lens

Systemic sclerosis (SSc) remains a formidable challenge in clinical rheumatology, characterized by progressive tissue fibrosis that often resists conventional immunosuppressive therapies [1]. Managing this disease frequently presents a frustrating clinical bottleneck: while initial inflammatory phases may be mitigated with current therapeutic arsenals, the relentless progression of fibrosis often continues unchecked. The systemic burden of SSc—ranging from profound cutaneous induration to life-threatening interstitial lung disease and major adverse cardiovascular events—highlights an urgent need to rethink our approach to fibrogenesis [2]. Traditionally, the rheumatology community has viewed the pathogenesis of SSc predominantly through an immunological lens, focusing on how autoantibodies and inflammatory cytokines continuously activate fibroblasts [3]. However, recent breakthroughs suggest that extracellular matrix (ECM) stiffness is not merely an endpoint of the disease but a plausible feed-forward amplifier. This editorial explores the clinical implications of identifying mechanosensitive fibroblast progenitor populations and targeting mechanical stiffness to better understand the self-sustaining cycle of fibrosis in SSc.

2 | Matrix Stiffness as a Plausible Feed-Forward Amplifier

Recent original research published in the Annals of the Rheumatic Diseases by Ueberall et al. provides a compelling perspective: the physical rigidity of the ECM itself acts as a signal that may further amplify disease progression [4]. This builds upon an existing, broader mechanobiology paradigm involving integrin-mediated mechanotransduction, YAP/TAZ signaling, TGF-beta activation, LOX-dependent matrix crosslinking, and FAK signaling. The recent work challenges the classical "chicken-or-egg" dilemma in fibrosis by demonstrating in experimental contexts that once the tissue stiffens, this mechanical signal becomes a plausible feed-forward amplifier for further deterioration.

3 | Mechanosensitive Fibroblast Progenitor Populations and the Fibrotic Feedback Loop

The identification of specific cellular populations provides a mechanistic link for this phenomenon. A subset of fibroblast progenitor cells, defined as PI16+, possess specialized

Tang-Kai Cheng and Durga Prasanna Misra contributed equally to this article.

mechanoreceptors like PIEZO1/2 that allow them to continuously monitor matrix rigidity [4]. In a rigid microenvironment, these precursor cells appear driven to differentiate into SFRP2+ COMP+ myofibroblasts, which act as a key profibrotic myofibroblast subset responsible for excessive collagen production. This creates a vicious, self-sustaining feedback loop: a stiffened ECM "educates" precursor cells to become fibrotic effectors, which in turn secrete more matrix, further increasing tissue stiffness within the localized environment [4].

4 | Speculative Links Between Local Mechanics and Systemic Morbidities

For clinicians and researchers investigating the epidemiological and systemic impact of SSc—such as the significantly increased risks of cardiovascular comorbidities [2] or premature ovarian insufficiency [5] frequently observed in extensive real-world data analyses—one might speculatively hypothesize that this localized mechanical feedback loop plays a role. It is possible that localized fibrotic niches, where PI16+ and COMP+ cells highly co-localize, contribute broadly to the disease burden. However, it is essential to acknowledge that these systemic morbidities and epidemiologic associations [6] may alternatively reflect vascular injury, underlying immune dysregulation, specific treatment exposures, age, ascertainment biases, or other confounding factors, rather than being solely attributable to tissue stiffness.

5 | Therapeutic Horizons: Cautious Optimism for "Anti-Stiffness" Strategies

The translational potential of this mechanobiology framework is an active area of investigation. If matrix stiffness functions as an amplifier of SSc, future therapeutic horizons may eventually expand from being solely "anti-inflammatory" to incorporating "anti-stiffness" approaches. Preclinical experimental models have shown that mechanical stress-induced myofibroblast activation can be mitigated by blocking mechanotransduction pathways, such as through the use of focal adhesion kinase (FAK) inhibitors [4]. However, transitioning these preclinical findings into clinical reality requires careful navigation. Targeting FAK, PIEZO, and extracellular matrix remodeling, or attempting to directly inhibit progenitor cells raises significant challenges regarding pathway specificity, systemic safety, efficient tissue delivery, and potential adverse effects on essential wound healing and vascular integrity.

6 | Conclusion: Re-Evaluating the Vicious Cycle

The integration of cellular biomechanics into rheumatology offers valuable insights into the pathophysiology of SSc for patients severely restricted by tissue fibrosis [1]. As the field moves forward, the development of pharmacological agents that carefully target mechanotransduction pathways may represent a future therapeutic direction. To ultimately improve patient outcomes and safely reduce the severe systemic comorbidities associated with SSc, researchers must carefully define plausible biomarkers and clinical endpoints for anti-stiffness strategies, moving beyond inflammation to understand how to structurally manage the fibrotic microenvironment [3].

Author Contributions

Tang-Kai Cheng: conceptualization, literature search and data analysis, writing – original draft. **Durga Prasanna Misra:** conceptualization, literature search and data analysis, writing – original draft. **James Cheng-Chung Wei:** conceptualization, writing – 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 on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

Comparative Safety Analysis of Targeted Synthetic and Biologic Disease-Modifying Antirheumatic Drugs Among Patients With Rheumatoid Arthritis: A Nationwide Cohort Study in Japan

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ABSTRACT

Aim: To compare risks of malignancy, opportunistic infections, and venous thromboembolism between the targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) and biologic DMARDs (bDMARDs) at the 2nd and 3rd lines of therapy (LOT).

Methods: We conducted a cohort study using the National Database of Health Insurance Claims (2013–2021). Patients with rheumatoid arthritis (RA) initiating tsDMARDs or bDMARDs after conventional synthetic DMARDs (csDMARDs) were identified at the 2nd LOT or 3rd LOT. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox models weighted by inverse probability of treatment weighting.

Results: Among 498 813 csDMARD initiators, 66 638 and 4177 initiated bDMARDs and tsDMARDs at 2nd LOT; 14 085 and 1757 initiated bDMARDs and tsDMARDs at 3rd LOT. For malignancy, HRs (95% CIs) for tsDMARDs versus bDMARDs were 0.92 (0.60–1.43) at 2nd LOT and 0.94 (0.53–1.65) at 3rd LOT. HRs (95% CIs) for pneumocystis pneumonia (PCP) and deep vein thrombosis (DVT) were as follows: PCP, 0.98 (0.75–1.29) at 2nd LOT and 1.12 (0.81–1.54) at 3rd LOT; DVT, 1.13 (0.64–1.99) at 2nd LOT

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CT, computed tomography; DVT, deep vein thrombosis; EULAR, European Alliance of Associations for Rheumatology; ICD-10, International Classification of Diseases, 10th Revision; IPT, inverse probability of treatment; IQR, interquartile range; IR, incidence rate; KM, Kaplan–Meier; LOT, line of therapy; MRI, magnetic resonance imaging; MTX, methotrexate; NDB, National Database of Health Insurance Claims and Specific Health Checkups; NMSC, nonmelanoma skin cancer; NTM, nontuberculous mycobacterial infection; ORAL, Oral Rheumatoid Arthritis Trial; PCP, pneumocystis pneumonia; PE, pulmonary embolism; PMS, post-marketing surveillance; RA, rheumatoid arthritis; SD, standard deviation; SMD, standardized mean differences; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; VTE, venous thromboembolism.

and 0.96 (0.52–1.78) at 3rd LOT. In contrast, herpes zoster (HZ) risk was consistently higher with tsDMARDs (2nd LOT: HR, 2.61 [95% CI, 2.24–3.05]; 3rd LOT: HR, 2.90 [95% CI, 2.38–3.53]).

Conclusions: In the nationwide Japanese cohort, tsDMARDs did not show increased malignancy risk compared to bDMARDs, and PCP risk had no clear difference at 2nd and 3rd LOTs, whereas the risk of HZ was higher with tsDMARDs.

1 | Introduction

Rheumatoid arthritis (RA) is the most prevalent autoimmune disease; the estimated prevalence of RA in Japan was 1.24 million, corresponding to 1.0% of the population [1]. Patients with RA are at elevated risk of developing malignancies, particularly lymphoma, leukemia, and lung cancer [2–5]. This increased risk is attributed to chronic immune dysregulation and inflammation, which can promote oncogenesis via enhanced cell proliferation, DNA damage, and angiogenesis [6, 7].

Current clinical guidelines recommend conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), particularly methotrexate (MTX), as the initial treatment for DMARD-naïve patients with active RA [8–10]. For patients with an inadequate response to MTX, subsequent treatment options include adding other csDMARDs or escalating to biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), either in combination with MTX or, in selected patients, as monotherapy [9–12].

The tsDMARDs, such as tofacitinib and baricitinib, have prompted additional safety concerns, particularly regarding cancer, venous thromboembolism (VTE), and infection risk [13–17]. Global trials of tofacitinib reported a malignancy incidence rate of approximately 0.85 per 100 person-years [18]. Infections, especially pneumonia and herpes zoster, were also common [19]. Japanese post-marketing data have shown similar safety profiles, although the data remain limited [20, 21]. Of note, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance was a randomized safety trial that enrolled patients with active RA who had an inadequate response to MTX, were aged ≥ 50 years, and had at least one cardiovascular risk factor. The trial reported higher rates of malignancy and major adverse cardiovascular events with tofacitinib than with tumor necrosis factor (TNF) inhibitors [22]. However, many of these studies were limited by small sample sizes, short follow-up periods, and a lack of real-world comparative data, especially in Japanese clinical settings. This gap has resulted in a limited understanding of the real-world safety of tsDMARDs among Japanese RA patients. This study aimed to compare the incidence of malignancies, serious infections, and venous thromboembolism between RA patients treated with tsDMARDs and those treated with bDMARDs at the 2nd or 3rd line of therapy (LOT), using nationwide administrative claims data from Japan.

2 | Methods

2.1 | Study Design and Data Source

This cohort study used data from the National Database of Health Insurance Claims (NDB), a nationwide administrative database maintained by the Ministry of Health, Labor and Welfare in Japan. The study period was between July 2013 and March 2021. The NDB includes 98% of all health insurance claims and health checkup records for individuals covered by Japan's universal health insurance system, including information on diagnoses, procedures, and prescriptions [23]. This study was approved by the Institutional Review Board of the University of Tokyo (approval no. 2020282NI-[2]).

2.2 | Study Population

We included patients with a diagnosis of RA who initiated treatment with csDMARDs and were aged ≥ 18 years at csDMARD initiation. RA diagnosis was identified using the International Classification of Diseases, 10th Revision (ICD-10) codes M05 and M06, excluding M06.0, M06.1, and M06.4. We excluded patients with a malignancy in the prior 12 months and those with psoriasis diagnosed within a month before or after csDMARD initiation. The detailed Japanese claims codes for the included drugs are provided in Table S1.

2.3 | Post-First-Line csDMARD Treatment Group

We grouped patients by the targeted agent initiated as the 2nd LOT. Initiating a tsDMARD (monotherapy or in combination with csDMARDs) defined the 2nd LOT-tsDMARD initiator group; initiating a bDMARD (monotherapy or in combination with csDMARDs) defined the 2nd LOT-bDMARD initiator group. Line-of-treatment transitions were defined using prescription records. A LOT was considered to be continuing when the same eligible DMARD was recorded again within 180 days of the preceding record. When no subsequent record for the same DMARD was observed within this 180-day grace period, we assessed whether another eligible bDMARD or tsDMARD was initiated within the same 180-day grace period. If another eligible DMARD was initiated during this grace period, the patient was classified as having switched treatment. The initiation date of the new agent was used as the index date of the next LOT. If no eligible alternative DMARD was observed during this window, the episode was classified as discontinuation without switch. The patient flowchart is shown in Figure 1.

For malignancy assessments, sub-cohorts were created for each treatment group by excluding patients with a recorded diagnosis of any malignancy (ICD-10 codes: C00–C97 [except C76–C80] and D00–D09) within 1 year prior to the initiation of each respective LOT (Figure S1A,B).

2.4 | Covariates

We assessed baseline characteristics at the index date and during the 12 months preceding the initiation of the 2nd and 3rd LOTs. Variables included age, sex, duration of the prior line of therapy,

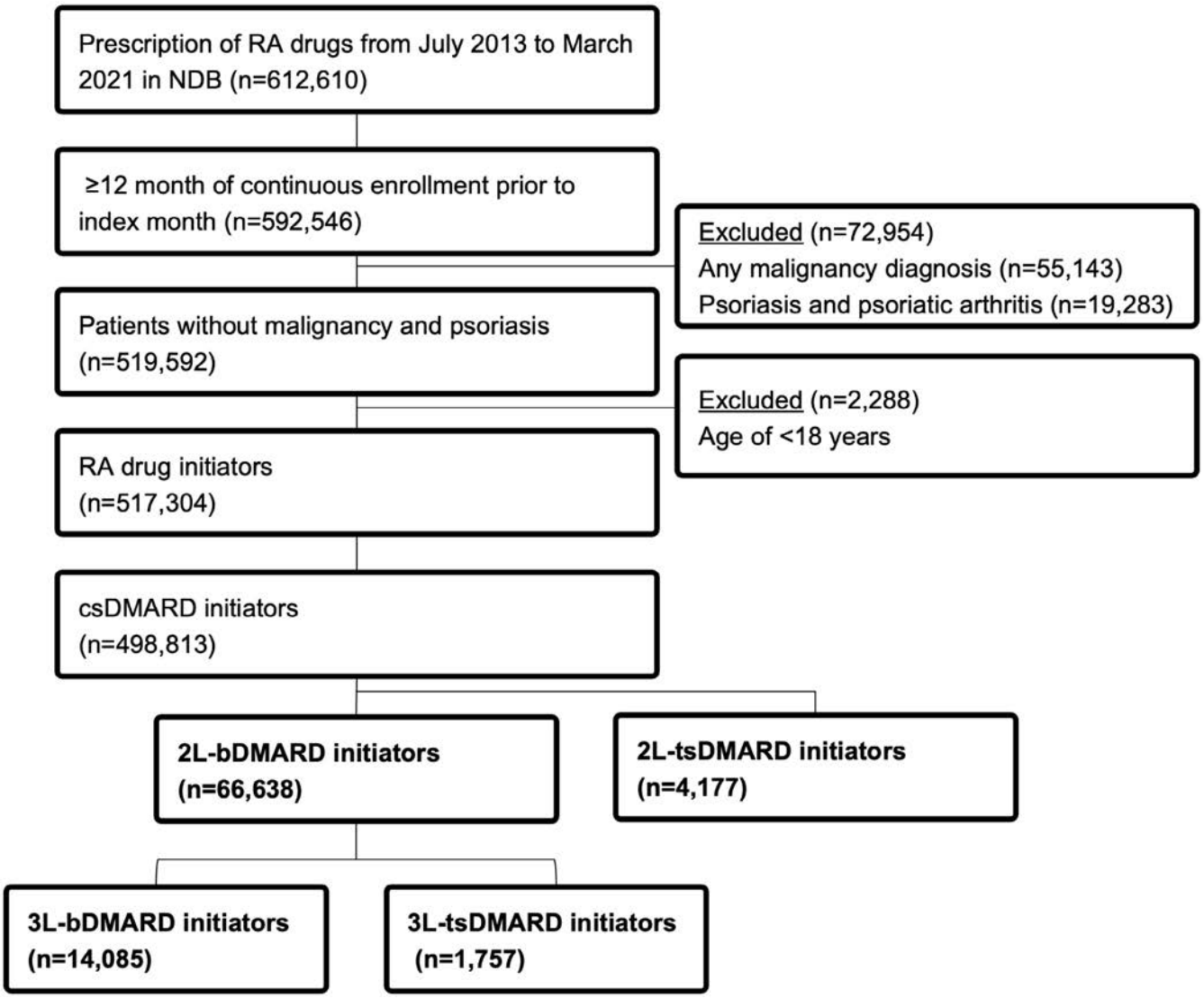

FIGURE 1 | Patient flow chart.

proxies for disease severity (e.g., inflammatory marker testing, RA-related surgical procedures, intra-articular injections, and extra-articular manifestations of RA), comorbid conditions, concomitant medication use, hospitalization history, imaging procedures, and year of treatment initiation. Detailed Japanese disease codes and claims codes are provided in Table S2.

2.5 | Follow-Up and Outcomes

Follow-up started on the index date and continued until the earliest of the following: occurrence of the study outcome, initiation of an alternative eligible DMARD, treatment discontinuation without a switch, switch, death, or the end of the study period (March 31, 2021). Switching was assessed before assigning discontinuation. For patients who switched treatment, follow-up for the preceding LOT continued until the initiation date of the alternative DMARD, and the next LOT started on that date. For patients who did not switch, discontinuation was assigned to the last prescription date of the current LOT drug after confirming that no subsequent prescription for the same drug or eligible alternative DMARD occurred within 180 days.

The incidence of the following 14 outcomes was evaluated: all malignancies defined using disease and procedure codes (e.g., oncology testing and care management) (both excluding and including nonmelanoma skin cancer [NMSC]) and the following outcomes—breast, lung, gastric, pancreatic, and colorectal cancers; lymphoma; pneumocystis pneumonia (PCP); tuberculosis (TB); nontuberculous mycobacterial infection (NTM); herpes zoster (HZ); pulmonary embolism (PE); and deep vein thrombosis (DVT)—defined using disease, drug, and procedure codes. For malignancy and infectious outcomes, the definitions were adapted from previously validated claims-based algorithms, with modifications according to the available NDB claims data [24, 25]. The definitions of outcomes are listed in Table S3.

For non-malignancy outcomes, 3-month event-free windows were used to distinguish incident episodes from ongoing claims

related to the same clinical episode. These windows were selected based on clinical judgment and expert consensus because standardized, validated event-free windows for these outcomes in the NDB are not available.

2.6 | Statistical Analyses

To address confounding due to non-randomized treatment allocation, we applied stabilized inverse probability of treatment (IPT) weighting to estimate the average treatment effect in the cohort. Treatment probabilities of initiating tsDMARDs compared with initiating bDMARDs at each line of therapy were estimated using multivariable logistic regression including all prespecified covariates listed above. The distribution of estimated treatment probability was evaluated graphically using histograms. Baseline characteristics were summarized using means with standard deviations (SDs) and medians with interquartile ranges (IQRs) for continuous variables and counts and proportions for categorical variables. Covariate balance before and after weighting was assessed using standardized mean differences (SMDs).

Crude outcome risks were evaluated using incidence rates (IRs) and cumulative incidence, with the latter estimated via the Kaplan–Meier (KM) method, both with and without IPT weighting. Cumulative incidence functions were plotted for the entire follow-up. Hazard ratios (HRs) between treatment type and outcomes were estimated using IPT-weighted and unweighted Cox proportional hazards models, with treatment as the sole covariate in the model. Robust 95% confidence intervals (CIs) were calculated using the sandwich variance estimator. Per the NDB data-use agreement, we could not disclose any cell counts < 10; such values were suppressed or aggregated as required. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | Results

3.1 | Patient Characteristics and IPT Weighting

Among 498 813 patients who initiated csDMARDs between July 2013 and March 2021 (Figure 1), 66 638 patients initiated bDMARDs as the 2nd LOT (median [IQR] age: 63 [53–74] years; 74.5% women) (2nd LOT-bDMARD group) and 4177 patients initiated tsDMARDs as the 2nd LOT (median [IQR] age: 65 [53–74] years; 72.2% women) (2nd LOT-tsDMARD group). Among the 2nd LOT-bDMARD group, 14 085 patients initiated another bDMARD with a distinct active ingredient (median [IQR] age: 63 [49–73] years; 76.3% women) as 3rd LOT (3rd LOT-bDMARD group) and 1757 patients initiated tsDMARDs as 3rd LOT (median [IQR] age: 64 [52–74] years; 74.0% women) (3rd LOT-tsDMARD group) (Tables 1 and 2). Note that those initiating tsDMARDs were predominantly from the later years, with 72% initiating treatment in 2019 or later.

Baseline characteristics before and after IPT weighting are presented in Tables 1 and 2. Before weighting, compared with the 2nd LOT-bDMARD group, the 2nd LOT-tsDMARD group was older, had a longer duration of csDMARD treatment, initiated 2nd LOT more recently, and was more likely to use calcineurin inhibitors. In contrast, the 2nd LOT-tsDMARD group was less likely to have received intra-articular injections, had ankylosing spondylitis, or used NSAIDs. Similarly, compared with the 3rd LOT-bDMARD group, the 3rd LOT-tsDMARD group was older, had a longer duration of prior bDMARD treatment, initiated 3rd LOT more recently, and had a higher prevalence of diabetes. The prevalence of systemic glucocorticoid use was slightly higher in the bDMARD group at both the 2nd and 3rd LOTs. The malignancy assessment subgroup showed similar baseline characteristics to the overall study population (Tables S4 and S5).

The distributions of estimated treatment probability before and after weighting for the bDMARD group and the tsDMARD group at each treatment line are presented in Figures S3 and S4. The treatment probability models showed good discrimination, with C-statistics of 0.75 and 0.68 for the 2nd and 3rd LOT cohorts, respectively, in both the overall study population and the malignancy assessment sub-cohort. After applying stabilized IPT weighting, absolute values of all SMDs for baseline covariates were below 0.1 across both LOTs for the overall study population and the malignancy assessment sub-cohort, supporting the covariate balance between treatment groups.

3.2 | Outcomes at the 2nd LOT

3.2.1 | Malignancy

During a median follow-up of 534 days (IQR, 218–853) in the tsDMARD group and 1096 days (IQR, 574–1741) in the bDMARD group, 41 and 993 cases of all malignancies excluding NMSC were identified, respectively. Before weighting, the IRs of all malignancies excluding NMSC were 0.80 (95% CI, 0.56–1.05) and 0.85 (95% CI, 0.80–0.91) per 100 person-years in the tsDMARD and bDMARD groups, respectively (weighted IRs: 0.81 [95% CI, 0.61–1.00] and 0.86 [95% CI, 0.80–0.91]) (Table S6 and Table 3). The weighted 5-year cumulative incidence of all malignancies excluding NMSC was 2.5% (95% CI, 1.5%–4.2%) in the tsDMARD group and 4.5% (95% CI, 4.1%–4.9%) in the bDMARD group (Table 3; Figure 2). After IPT weighting, no clear increase in the risk of all malignancies excluding NMSC was observed with tsDMARDs compared with bDMARDs (HR, 0.92 [95% CI, 0.60–1.43]) (Table 3). Results of all malignancies and for specific cancer types (breast, lung, gastric, pancreatic, colorectal, and lymphoma) are shown in Figure S5 and Table S6. For all malignancies (including NMSC), the results were consistent with those excluding NMSC. However, due to the very low incidence of specific malignancy types in the tsDMARD group, event rarity limited the precision of incidence rate and HR estimates (Table S7; Figure S5).

3.2.2 | Infectious Disease and Venous Thromboembolism

During a median follow-up of 522 days (IQR, 217–849) in the tsDMARD group and 1092 days (IQR, 570–1736) in the bDMARD

TABLE 1 | Baseline characteristics of 2L-tsDMARD group and 2L-bDMARD group (all eligible patients).

Variable	Unweighted			IPT-weighted[a]		
	2L-tsDMARDs ($n=4177$)	2L-bDMARDs ($n=66638$)	Standardized mean difference	2L-tsDMARDs ($n=4084.5$)	2L-bDMARDs ($n=66640.9$)	Standardized mean difference
Women, sex	3016 (72.2)	49673 (74.5)	0.05	3016.9 (73.9)	49580.7 (74.4)	0.01
Age, years, median (IQR)	65 (53, 74)	63 (53, 74)	0.18	63 (51, 72)	63 (50, 73)	0.03
No. of hospital days, mean (SD)	1.3 (10.5)	2.2 (12.3)	−0.08	2.2 (18.3)	2.2 (12.0)	0.00
Duration to second-line, days, median (IQR)	310 (107, 874)	200 (80, 507)	0.35	234 (87, 584)	204 (81, 522)	0.00
Disease severity						
Marker of inflammation test	4135 (> 99.0)[b]	66522 (99.8)	0.00	> 4043.7 (> 99.0)	66525.1 (99.8)	0.02
RA-related surgeries	113 (2.7)	1565 (2.3)	−0.02	106.2 (2.6)	1579.0 (2.4)	−0.01
Any intraarticular injection	1286 (30.8)	23756 (35.6)	0.10	1513.9 (37.1)	23566.0 (35.4)	−0.04
Extra-articular manifestation of RA	1128 (27.0)	16958 (25.4)	−0.04	1089.4 (26.7)	17023.1 (25.5)	−0.03
Comorbidities						
Ischemic heart disease	483 (11.6)	7326 (11.0)	−0.02	475.0 (11.6)	7350.0 (11.0)	−0.02
COPD	544 (13.0)	7707 (11.6)	−0.04	539.1 (13.2)	7767.8 (11.7)	−0.05
Interstitial lung disease	895 (21.4)	13006 (19.5)	−0.05	854.0 (20.9)	13085.1 (19.6)	−0.03
Cerebrovascular disease	460 (11.0)	6870 (10.3)	−0.02	432.4 (10.6)	6898.1 (10.4)	−0.01
Fracture	382 (9.1)	5798 (8.7)	−0.02	357.3 (8.7)	5816.1 (8.7)	0.00
Diabetes	687 (16.4)	9498 (14.3)	−0.06	592.8 (14.5)	9584.5 (14.4)	0.00
Hypertension	1773 (42.4)	25750 (38.6)	−0.08	1595.5 (39.1)	25900.5 (38.9)	0.00
Hyperlipidemia	1724 (41.3)	25224 (37.9)	−0.07	1525.5 (37.3)	25361.5 (38.1)	0.01
Emphysema	125 (3.0)	1472 (2.2)	−0.05	120.5 (3.0)	1505.4 (2.3)	−0.04
Sjogren syndrome	325 (7.8)	5079 (7.6)	−0.01	327.7 (8.0)	5086.6 (7.6)	−0.01
Systemic lupus erythematosus	175 (4.2)	2403 (3.6)	−0.03	155.5 (3.8)	2426.7 (3.6)	−0.01
Mixed connective-tissue disease	61 (1.5)	686 (1.0)	−0.04	45.0 (1.1)	702.8 (1.1)	0.00
Systemic sclerosis	59 (1.4)	1158 (1.7)	0.03	65.8 (1.6)	1145.8 (1.7)	0.01
Pneumocystis pneumonia	238 (5.7)	4535 (6.8)	0.05	252.0 (6.2)	4490.1 (6.7)	0.02
Tuberculosis	198 (4.7)	3679 (5.5)	0.04	236.5 (5.8)	3649.7 (5.5)	−0.01

(Continues)

TABLE 1 | (Continued)

Variable	Unweighted			IPT-weighted[a]		
	2L-tsDMARDs ($n = 4177$)	2L-bDMARDs ($n = 66638$)	Standardized mean difference	2L-tsDMARDs ($n = 4084.5$)	2L-bDMARDs ($n = 66640.9$)	Standardized mean difference
Nontuberculous mycobacteriosis	46 (1.1)	827 (1.2)	0.01	43.9 (1.1)	821.0 (1.2)	0.01
Herpes zoster	133 (3.2)	2059 (3.1)	−0.01	146.8 (3.6)	2063.0 (3.1)	−0.03
Pulmonary embolism	12 (0.3)	192 (0.3)	0.00	13.6 (0.3)	191.8 (0.3)	−0.01
Deep vein thrombosis	157 (3.8)	2491 (3.7)	0.00	153.0 (3.7)	2491.4 (3.7)	0.00
Heart failure	551 (13.2)	8410 (12.6)	−0.02	521.3 (12.8)	8433.9 (12.7)	0.00
Asthma	633 (15.2)	10872 (16.3)	0.03	672.2 (16.5)	10827.9 (16.2)	−0.01
Ankylosing spondylitis	< 10[b]	1008 (1.5)	0.14	27.8 (0.7)	956.0 (1.4)	0.08
Autoimmune hemolytic anemia	< 10[b]	37 (0.1)	0.02	< 10	35.8 (0.1)	0.00
Mixed cryoglobulinemia	< 10[b]	60 (0.1)	0.01	< 10	59.3 (0.1)	0.01
Inflammatory bowel disease	26 (0.6)	628 (0.9)	0.04	27.3 (0.7)	615.1 (0.9)	0.03
Colon polyps	194 (4.6)	2969 (4.5)	−0.01	189.9 (4.6)	2976.9 (4.5)	−0.01
H-pylori associated chronic gastritis	108 (2.6)	1723 (2.6)	0.00	133.5 (3.3)	1723.6 (2.6)	−0.04
Hepatitis C virus	165 (4.0)	2061 (3.1)	−0.05	141.8 (3.5)	2097.7 (3.1)	−0.02
Hepatitis B virus	158 (3.8)	2958 (4.4)	0.03	184.9 (4.5)	2932.3 (4.4)	−0.01
Medication use						
Opioids	805 (19.3)	13614 (20.4)	0.03	857.3 (21.0)	13570.0 (20.4)	−0.02
Systemic glucocorticoids	2343 (56.1)	39438 (59.2)	0.06	2455.1 (60.1)	39320.3 (59.0)	−0.02
Non-steroidal anti-inflammatory agents (non-selective and COX-2 selective)	2517 (60.3)	43424 (65.2)	0.10	2616.1 (64.0)	43232.6 (64.9)	0.02
Calcineurin inhibitor	609 (14.6)	7355 (11.0)	−0.11	445.8 (10.9)	7492.6 (11.2)	0.01
Methotrexate	3546 (84.9)	56401 (84.6)	−0.01	3538.1 (86.6)	56417.9 (84.7)	−0.05
Image inspections						
CT	2539 (60.8)	43391 (65.1)	0.09	2597.0 (63.6)	43225.3 (64.9)	0.03
MRI	1281 (30.7)	22690 (34.0)	0.07	1347.9 (33.0)	22559.7 (33.9)	0.02
X-rays	3969 (95.0)	64378 (96.6)	0.08	3913.5 (95.8)	64317.4 (96.5)	0.03
Mammography	156 (3.7)	2466 (3.7)	0.00	141.5 (3.5)	2466.6 (3.7)	0.01
Index year			0.28			0.01

(Continues)

TABLE 1 | (Continued)

Variable	Unweighted			IPT-weighted[a]		
	2L-tsDMARDs (*n* = 4177)	2L-bDMARDs (*n* = 66 638)	Standardized mean difference	2L-tsDMARDs (*n* = 4084.5)	2L-bDMARDs (*n* = 66640.9)	Standardized mean difference
2013	< 10[b]	967 (1.5)		45.7 (1.1)	917.5 (1.4)	
2014	< 60[b]	5296 (7.9)		275.6 (6.7)	5032.5 (7.6)	
2015	116 (2.8)	7642 (11.5)		447.1 (10.9)	7300.4 (11.0)	
2016	149 (3.6)	8520 (12.8)		485.1 (11.9)	8157.5 (12.2)	
2017	265 (6.3)	9853 (14.8)		593.8 (14.5)	9521.4 (14.3)	
2018	585 (14.0)	11 129 (16.7)		681.6 (16.7)	11022.7 (16.5)	
2019	1197 (28.7)	10 896 (16.4)		702.1 (17.2)	11377.8 (17.1)	
2020	1323 (31.7)	9764 (14.7)		671.4 (16.4)	10437.2 (15.7)	
2021	482 (11.5)	2571 (3.9)		182.1 (4.5)	2873.9 (4.3)	

Note: Data are numbers (%) of patients unless stated otherwise.
Abbreviations: 2L, 2nd line; bDMARD, biologic DMARD; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; CT, computed tomography; *H.-pylori*, *Helicobacter pylori*; IPT, inverse probability of treatment; IQR, interquartile range; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; SD, standard deviation; tsDMARD, targeted synthetic DMARD.
[a]Weights were truncated at the 99.5th percentile.
[b]Counts were suppressed in accordance with disclosure control requirements when the cell count or complementary cell count was < 10.

group, the crude IRs per 100 person-years (95% CIs) in the tsDMARD and bDMARD groups were as follows: for PCP, 2.16 (1.76–2.56) and 1.84 (1.76–1.92) (weighted IRs [95% CIs], 1.75 [1.45–2.04] and 1.84 [1.77–1.92]); for NTM, 0.23 (0.10–0.36) and 0.21 (0.19–0.24) (weighted IRs [95% CIs], 0.29 [0.17–0.40] and 0.21 [0.19–0.24]); and for HZ, 6.45 (5.74–7.17) and 2.47 (2.38–2.56) (weighted IRs [95% CIs], 6.41 [5.82–6.99] and 2.47 [2.38–2.56]) (Table S6; Table 3). The weighted 5-year cumulative incidences (95% CIs) in the tsDMARD and bDMARD groups were as follows: for PCP, 6.2% (4.5%–8.5%) and 6.8% (6.4%–7.1%); for NTM, 1.0% (0.5%–2.1%) and 0.8% (0.7%–1.0%); and for HZ, 24.0% (19.5%–29.3%) and 10.7% (10.2%–11.1%), respectively (Table 3 and Figure 2). The use of tsDMARDs at the 2nd LOT did not increase the risk of PCP (HR, 0.98 [95% CI, 0.75–1.29]) or NTM (HR, 1.39 [95% CI, 0.69–2.80]) compared with bDMARDs. However, the risk of HZ was higher in the tsDMARD group (HR, 2.61 [95% CI, 2.24–3.05]) (Table 3). The number of TB events in the tsDMARD group was insufficient to estimate the incidence rates and the HR for the outcome (Table S7; Figure S5).

For PE, the crude IRs per 100 person-years (95% CIs) were 0.14 (0.04–0.23) in the tsDMARD and 0.08 (0.07–0.10) in the bDMARD groups; weighted IRs (95% CIs) were 0.13 (0.05–0.20) and 0.09 (0.07–0.10), respectively. For DVT, the crude IRs (95% CIs) were 0.48 (0.29–0.67) and 0.38 (0.34–0.41), and the weighted IRs (95% CIs) were 0.42 (0.28–0.57) and 0.38 (0.35–0.42) (Table S6; Table 3). After weighting, the 5-year cumulative incidence (95% CIs) of PE was 0.4% (0.1%–1.0%) in the tsDMARD group and 0.3% (0.3%–0.5%) in the bDMARD group; for DVT, 1.3% (0.7%–2.3%) vs. 1.5% (1.4%–1.7%), respectively (Table 3; Figure 2). No clear increased risks of PE or DVT were observed with tsDMARDs compared with bDMARDs (PE: HR, 1.55 [95% CI, 0.46–5.25]; DVT: HR, 1.13 [95% CI, 0.64–1.99]) (Table 3).

3.3 | Outcomes at the 3rd LOT

3.3.1 | Malignancy

The median follow-up duration [IQR] was 656 [319–995] days in the tsDMARD group and 1008 [571–1573] days in the bDMARD group, during which 18 and 164 cases of any malignancy excluding NMSC were identified, respectively. The unweighted incidence rates were 0.71 (95% CI, 0.38–1.04) and 0.75 (95% CI, 0.64–0.87) per 100 person-years in the tsDMARD and bDMARD groups, respectively (weighted IRs [95% CIs], 0.71 [0.42–1.01] and 0.76 [0.65–0.88]) (Table S6; Table 3). The weighted 5-year cumulative incidence (95% CIs) of all malignancies excluding NMSC was 4.7% (1.7%–12.2%) in the tsDMARD group vs. 3.5% (2.9%–4.3%) in the bDMARD group (Table 3; Figure 3). After weighting, treatment with tsDMARDs did not show an increased risk of all malignancies excluding NMSC compared with bDMARDs (HR, 0.94 [95% CI, 0.53–1.65]). The results for overall malignancies were consistent with those for malignancy excluding NMSC. Many of the site-specific malignancy outcomes—such as breast, lung, gastric, pancreatic, colorectal cancer, and lymphoma—had limited event counts, precluding stable estimation of incidence rates HRs (see Table S7; Figure S6).

3.3.2 | Infectious Disease and Venous Thromboembolism

The crude IRs per 100 person-years (95% CIs) in the tsDMARD and bDMARD groups were as follows: for PCP, 2.54 (1.92–3.16) and 2.17 (1.97–2.36) (weighted IRs [95% CIs], 2.36 [1.83–2.90] and 2.20 [2.00–2.39]); for NTM, 0.15 (0.00–0.31) and 0.17 (0.12–0.22) (weighted IRs [95% CIs], 0.10 [0.00–0.21]

TABLE 2 | Baseline characteristics of 3L-tsDMARD group and 3L-bDMARD group (all eligible patients).

Variable	Unweighted			IPT-weighted[a]		
	3L-tsDMARDs ($n=1757$)	3L-bDMARDs ($n=14085$)	Standardized mean difference	3L-tsDMARDs ($n=1742.0$)	3L-bDMARDs ($n=14085.6$)	Standardized mean difference
Women, sex	1301 (74.0)	10742 (76.3)	0.05	1298.6 (74.5)	10705.3 (76.0)	0.03
Age, years, median (IQR)	64 (52, 74)	63 (49, 73)	0.10	62 (51, 72)	63 (50, 73)	−0.01
No. of hospital days, mean (SD)	2.3 (11.0)	2.7 (13.3)	−0.03	2.4 (11.3)	2.7 (13.2)	−0.02
Duration to second-line, days, median (IQR)	224 (106, 549)	185 (96, 398)	0.21	193 (94, 408)	189 (97, 412)	0.00
Disease severity						
Marker of inflammation test	>1739 (>99.0)[b]	14063 (99.8)	−0.01	>1724.6 (>99.0)[b]	14064.3 (99.8)	−0.01
RA-related surgeries	44 (2.5)	321 (2.3)	−0.01	44.4 (2.5)	324.8 (2.3)	−0.02
Any intraarticular injection	583 (33.2)	4786 (34.0)	0.02	588.9 (33.8)	4773.0 (33.9)	0.00
Extra-articular manifestation of RA	581 (33.1)	4200 (29.8)	−0.07	523.8 (30.1)	4250.8 (30.2)	0.00
Comorbidities						
Ischemic heart disease	189 (10.8)	1581 (11.2)	0.01	201.8 (11.6)	1574.9 (11.2)	−0.01
COPD	204 (11.6)	1822 (12.9)	0.04	209.7 (12.0)	1800.7 (12.8)	0.02
Interstitial lung disease	457 (26.0)	3346 (23.8)	−0.05	419.7 (24.1)	3381.3 (24.0)	0.00
Cerebrovascular disease	205 (11.7)	1388 (9.9)	−0.06	180.0 (10.3)	1416.9 (10.1)	−0.01
Fracture	157 (8.9)	1340 (9.5)	0.02	147.7 (8.5)	1329.9 (9.4)	0.03
Diabetes	341 (19.4)	2188 (15.5)	−0.10	295.5 (17.0)	2250.3 (16.0)	−0.03
Hypertension	732 (41.7)	5495 (39.0)	−0.05	677.5 (38.9)	5536.3 (39.3)	0.01
Hyperlipidemia	733 (41.7)	5324 (37.8)	−0.08	661.9 (38.0)	5384.6 (38.2)	0.00
Emphysema	35 (2.0)	325 (2.3)	0.02	38.4 (2.2)	320.1 (2.3)	0.00
Sjogren syndrome	158 (9.0)	1152 (8.2)	−0.03	138.7 (8.0)	1164.3 (8.3)	0.01
Systemic lupus erythematosus	83 (4.7)	595 (4.2)	−0.02	65.9 (3.8)	601.4 (4.3)	0.02
Mixed connective-tissue disease	24 (1.4)	131 (0.9)	−0.04	17.1 (1.0)	137.5 (1.0)	0.00
Systemic sclerosis	30 (1.7)	261 (1.9)	0.01	36.4 (2.1)	258.6 (1.8)	−0.02

(Continues)

TABLE 2 | (Continued)

Variable	Unweighted			IPT-weighted[a]		
	3L-tsDMARDs ($n=1757$)	3L-bDMARDs ($n=14085$)	Standardized mean difference	3L-tsDMARDs ($n=1742.0$)	3L-bDMARDs ($n=14085.6$)	Standardized mean difference
Pneumocystis pneumonia	194 (11.0)	1481 (10.5)	−0.02	184.6 (10.6)	1490.4 (10.6)	0.00
Tuberculosis	110 (6.3)	962 (6.8)	0.02	120.4 (6.9)	953.4 (6.8)	−0.01
Nontuberculous mycobacteriosis	31 (1.8)	204 (1.4)	−0.03	24.2 (1.4)	208.8 (1.5)	0.01
Herpes zoster	82 (4.7)	612 (4.3)	−0.02	76.0 (4.4)	616.9 (4.4)	0.00
Pulmonary embolism	13 (0.7)	53 (0.4)	−0.05	< 10[b]	58.7 (0.4)	0.00
Deep vein thrombosis	84 (4.8)	590 (4.2)	−0.03	68.4 (3.9)	598.1 (4.2)	0.02
Heart failure	218 (12.4)	1838 (13.0)	0.02	220.4 (12.7)	1828.1 (13.0)	0.01
Asthma	308 (17.5)	2402 (17.1)	−0.01	303.1 (17.4)	2410.2 (17.1)	−0.01
Ankylosing spondylitis	10 (0.6)	195 (1.4)	0.08	16.2 (0.9)	182.2 (1.3)	0.04
Autoimmune hemolytic anemia	< 10[b]	11 (0.1)	−0.01	< 10[b]	11.3 (0.1)	0.01
Mixed cryoglobulinemia	< 10[b]	17 (0.1)	0.02	< 10[b]	16.1 (0.1)	−0.03
Inflammatory bowel disease	21 (1.2)	143 (1.0)	−0.02	15.4 (0.9)	145.5 (1.0)	0.01
Colon polyps	85 (4.8)	626 (4.4)	−0.02	76.0 (4.4)	632.3 (4.5)	0.01
H-pylori associated chronic gastritis	49 (2.8)	375 (2.7)	−0.01	49.6 (2.8)	376.8 (2.7)	−0.01
Hepatitis C virus	58 (3.3)	414 (2.9)	−0.02	57.4 (3.3)	420.9 (3.0)	−0.02
Hepatitis B virus	89 (5.1)	727 (5.2)	0.00	95.7 (5.5)	726.4 (5.2)	−0.02
Medication use						
Opioids	365 (20.8)	3038 (21.6)	0.02	373.3 (21.4)	3026.8 (21.5)	0.00
Systemic glucocorticoids	1068 (60.8)	8780 (62.3)	0.03	1070.7 (61.5)	8755.6 (62.2)	0.01
Non-steroidal anti-inflammatory agents (non-selective and COX-2 selective)	1020 (58.1)	8432 (59.9)	0.04	1042.4 (59.8)	8405.3 (59.7)	0.00
Calcineurin inhibitor	261 (14.9)	2035 (14.4)	−0.01	263.8 (15.1)	2042.6 (14.5)	−0.02
Methotrexate	1424 (81.0)	11 579 (82.2)	0.03	1455.6 (83.6)	11562.8 (82.1)	−0.04
Image inspections						

(Continues)

TABLE 2 | (Continued)

Variable	Unweighted			IPT-weighted[a]		
	3L-tsDMARDs ($n=1757$)	3L-bDMARDs ($n=14085$)	Standardized mean difference	3L-tsDMARDs ($n=1742.0$)	3L-bDMARDs ($n=14085.6$)	Standardized mean difference
CT	1076 (61.2)	8552 (60.7)	−0.01	1048.9 (60.2)	8561.3 (60.8)	0.01
MRI	521 (29.7)	4355 (30.9)	0.03	549.3 (31.5)	4337.8 (30.8)	−0.02
X-rays	1634 (93.0)	13179 (93.6)	0.02	1628.9 (93.5)	13171.5 (93.5)	0.00
Mammography	55 (3.1)	562 (4.0)	0.05	77.1 (4.4)	549.2 (3.9)	−0.03
Index year			0.28			0.01
2013	< 10[b]	35 (0.2)		< 10[b]	31.1 (0.2)	
2014	14 (0.8)	597 (4.2)		64.8 (3.7)	543.2 (3.9)	
2015	58 (3.3)	1390 (9.9)		158.2 (9.1)	1287.4 (9.1)	
2016	92 (5.2)	1900 (13.5)		215.2 (12.4)	1771.0 (12.6)	
2017	153 (8.7)	2251 (16.0)		264.5 (15.2)	2137.4 (15.2)	
2018	347 (19.7)	2590 (18.4)		323.7 (18.6)	2610.9 (18.5)	
2019	576 (32.8)	2957 (21.0)		390.8 (22.4)	3140.6 (22.3)	
2020	513 (29.2)	2350 (16.7)		322.8 (18.5)	2547.0 (18.1)	
2021	< 10[b]	15 (0.1)		< 10[b]	16.9 (0.1)	

Note: Data are number (%) of patients unless stated otherwise.

Abbreviations: 3L, 3rd line; bDMARD, biologic DMARD; COPD, chronic obstructive pulmonary disease; CT, computed tomography; *H. pylori*, *Helicobacter pylori*; IPT, inverse probability of treatment; IQR, interquartile range; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; SD, standard deviation; tsDMARD, targeted synthetic DMARD; COX-2, cyclooxygenase-2.

[a]Weights were truncated at the 99.5th percentile.

[b]Counts were suppressed in accordance with disclosure control requirements when the cell count or complementary cell count was < 10.

TABLE 3 | IPT-weighted incidence rates, 5-year cumulative incidence, and hazard ratios for safety outcomes at the 2nd and 3rd LOTs.

Outcome	2L-tsDMARDs			2L-bDMARDs			Hazard ratio (95% CI)
	Number of patients with incident event	Incident rate (/100 person-years)	Cumulative incidence at 5-year, % (95% CI)	Number of patients with incident event	Incident rate (/100 person-years)	Cumulative incidence at 5-year, % (95% CI)	
All malignancies, excluding NMSC	63.5	0.81 (0.61–1.00)	2.5 (1.5–4.2)	977.5	0.86 (0.80–0.91)	4.5 (4.1–4.9)	0.92 (0.60–1.43)
Pneumocystis pneumonia	136.6	1.75 (1.45–2.04)	6.2 (4.5–8.5)	2102.9	1.84 (1.77–1.92)	6.8 (6.4–7.1)	0.98 (0.75–1.29)
Nontuberculous mycobacterial infection	22.9	0.29 (0.17–0.40)	1.0 (0.5–2.1)	247.4	0.21 (0.19–0.24)	0.8 (0.7–1.0)	1.39 (0.69–2.80)
Herpes zoster	458.7	6.41 (5.82–6.99)	24.0 (19.5–29.3)	2763.4	2.47 (2.38–2.56)	10.7 (10.2–11.1)	2.61 (2.24–3.05)
Pulmonary embolism	10.1	0.13 (0.05–0.20)	0.4 (0.1–1.0)	99.1	0.09 (0.07–0.10)	0.3 (0.3–0.5)	1.55 (0.46–5.25)
Deep vein thrombosis	33.9	0.42 (0.28–0.57)	1.3 (0.7–2.3)	444.2	0.38 (0.35–0.42)	1.5 (1.4–1.7)	1.13 (0.64–1.99)
Outcome	**3L-tsDMARDs**			**3L-bDMARDs**			**Hazard ratio (95% CI)**
	Number of patients with incident event	**Incident rate (/100 person-years)**	**Cumulative incidence at 5-year, % (95% CI)**	**Number of Patients with incident event**	**Incident rate (/100 person-years)**	**Cumulative incidence at 5-year, % (95% CI)**	
All malignancies, excluding NMSC	22.7	0.71 (0.42–1.01)	4.7 (1.7–12.2)	162.3	0.76 (0.65–0.88)	3.5 (2.9–4.3)	0.94 (0.53–1.65)
Pneumocystis pneumonia	74.7	2.36 (1.83–2.90)	8.7 (5.9–12.7)	473.4	2.20 (2.00–2.39)	7.5 (6.7–8.4)	1.12 (0.81–1.54)
Nontuberculous mycobacterial infection	< 10	0.10 (0.00–0.21)	0.3 (0.1–0.9)	38.1	0.17 (0.12–0.23)	0.6 (0.4–1.0)	0.64 (0.20–2.03)
Herpes zoster	212.8	7.30 (6.32–8.28)	28.2 (22.1–35.6)	538.2	2.53 (2.32–2.75)	9.7 (8.7–10.8)	2.90 (2.38–3.53)
Pulmonary embolism	< 10	0.06 (0.00–0.15)	0.2 (0.0–1.3)	23.4	0.11 (0.06–0.15)	0.4 (0.2–0.6)	0.62 (0.18–2.15)
Deep vein thrombosis	15.0	0.46 (0.22–0.69)	2.2 (0.8–6.4)	107.1	0.49 (0.40–0.58)	2.4 (1.8–3.1)	0.96 (0.52–1.78)

Abbreviations: 2L, 2nd line; 3L, 3rd line; bDMARD, biologic DMARD; CI, confidence interval; IPT, inverse probability of treatment; NMSC, nonmelanoma skin cancer; tsDMARD, targeted synthetic DMARD.

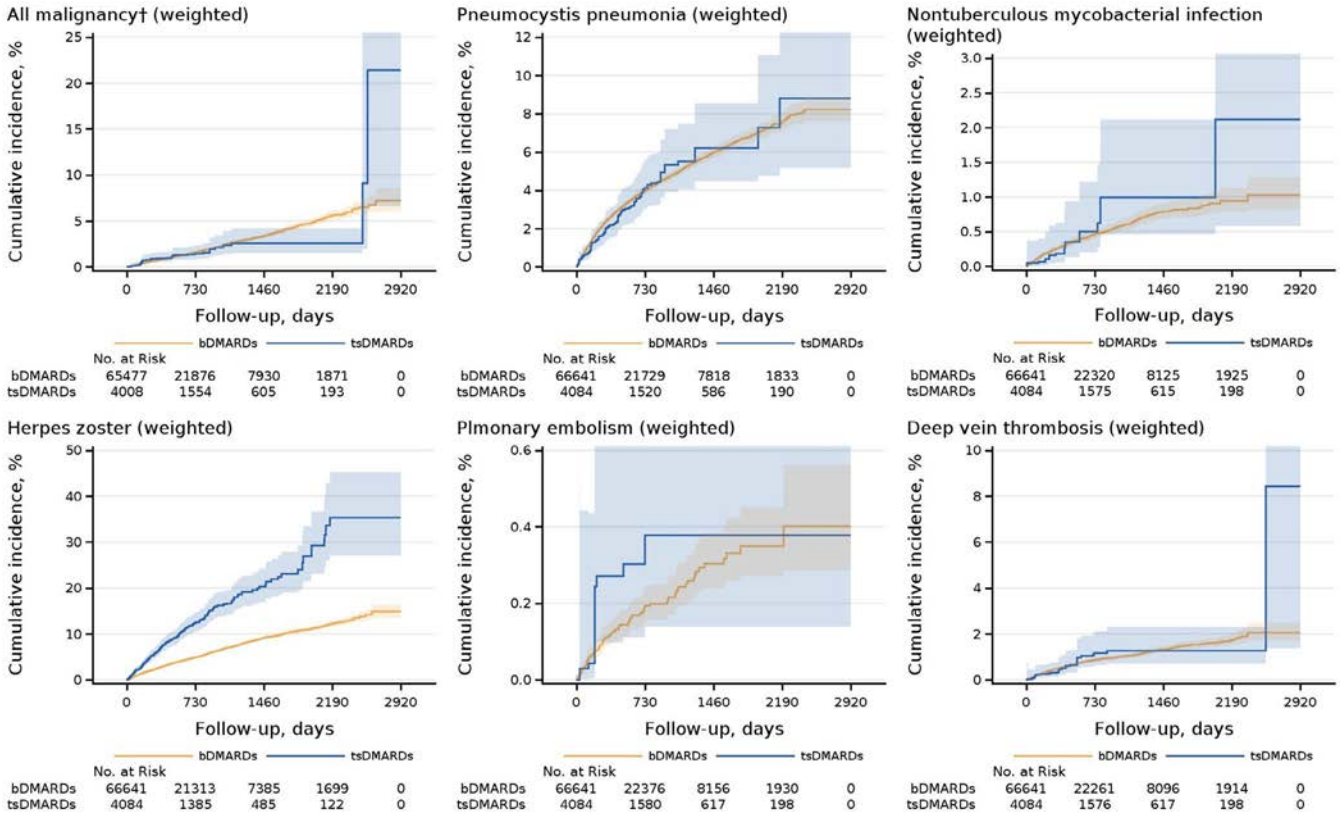

FIGURE 2 | IPT-weighted cumulative incidence of adverse events in 2nd LOT: tsDMARDs vs. bDMARDs. †All malignancy excluding NMSC. bDMARD, biologic DMARD; IPT, inverse probability of treatment; tsDMARD, targeted synthetic DMARD.

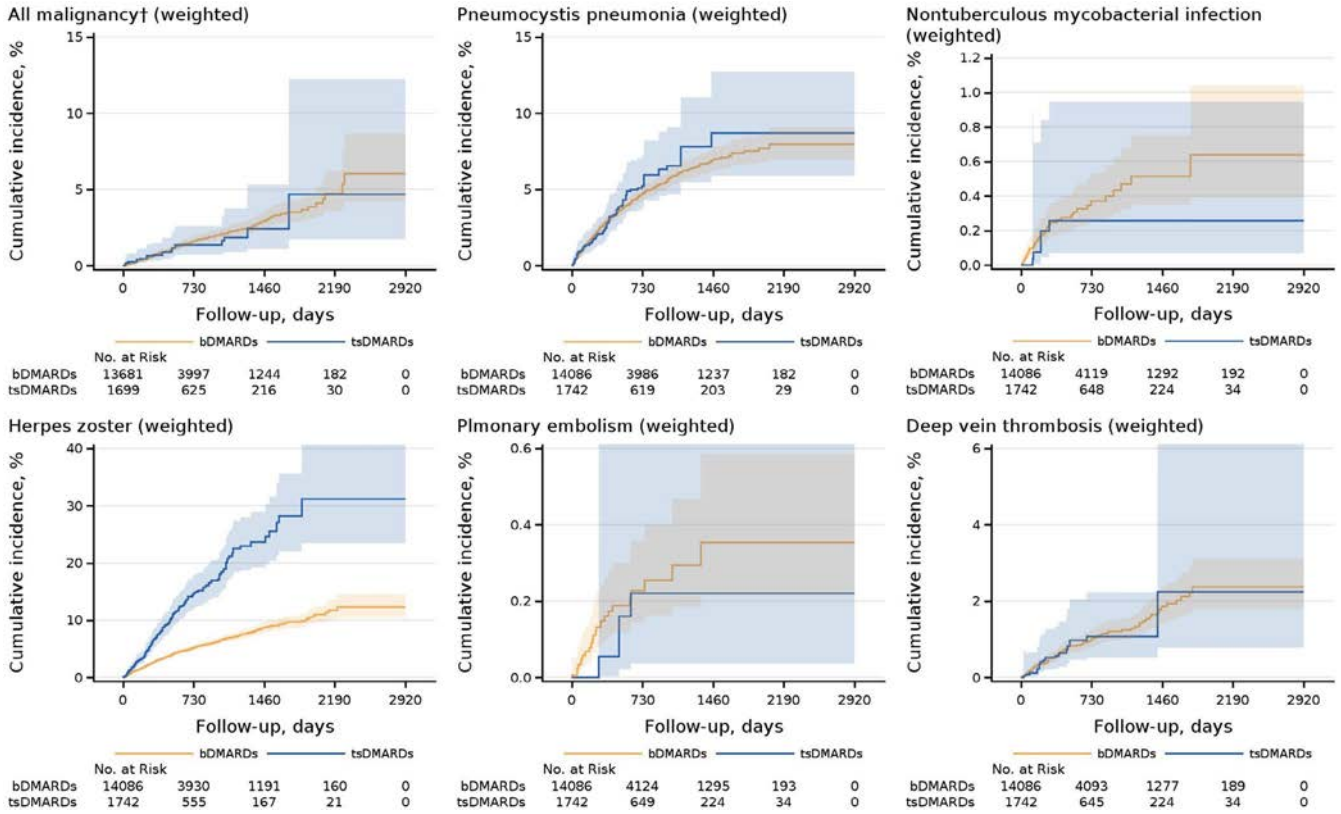

FIGURE 3 | IPT-weighted cumulative incidence of adverse events in 3rd LOT: tsDMARDs vs. bDMARDs. †All malignancy excluding NMSC. bDMARD, biologic DMARD; IPT, inverse probability of treatment; tsDMARD, targeted synthetic DMARD.

and 0.17 [0.12–0.23]); and for HZ, 7.25 (6.17–8.34) and 2.52 (2.31–2.73) (weighted IRs [95% CIs], 7.30 [6.32–8.28] and 2.53 [2.32–2.75]) (Table S6; Table 3). The weighted 5-year cumulative incidence (95% CIs) for PCP was 8.7% (5.9%–12.7%) in the tsDMARD group and 7.5% (6.7%–8.4%) in the bDMARD group. For NTM, it was 0.3% (0.1%–0.9%) vs. 0.6% (0.4%–1.0%), and for HZ, 28.2% (22.1%–35.6%) vs. 9.7% (8.7%–10.8%), respectively (Table 3; Figure 3). After weighting, tsDMARD use at the 3rd LOT did not increase the risk of PCP (HR, 1.12 [95% CI, 0.81–1.54]) and NTM (HR, 0.64 [95% CI, 0.20–2.03]) compared to bDMARDs. However, the risk of HZ remained elevated in the tsDMARD group (HR, 2.90 [95% CI, 2.38–3.53]) (Table 3). The number of TB events in the tsDMARD group was too small to yield reliable incidence rate estimates or hazard ratios (Table S7; Figure S6).

For PE, the crude IRs per 100 person-years (95% CIs) were 0.12 (0.00–0.25) in the tsDMARD and 0.10 (0.06–0.14) in the bDMARD groups, and weighted IRs (95% CIs) were 0.06 (0.00–0.15) and 0.11 (0.06–0.15), respectively. For DVT, the crude IRs (95% CIs) were 0.58 (0.29–0.88) and 0.48 (0.39–0.58), and the weighted IRs (95% CIs) were 0.46 (0.22–0.69) and 0.49 (0.40–0.58), respectively (Table S6; Table 3). The weighted 5-year cumulative incidence (95% CIs) of PE was 0.2% (0.0%–1.3%) in the tsDMARD group and 0.4% (0.2%–0.6%) in the bDMARD group; for DVT, the corresponding cumulative incidence was 2.2% (0.8%–6.4%) vs. 2.4% (1.8%–3.1%) (Table 3; Figure 3). Treatment with tsDMARDs did not show increases in the risks of PE (HR, 0.62 [95% CI, 0.18–2.15]) or DVT (HR, 0.96 [95% CI, 0.52–1.78]) compared with bDMARDs (Table 3).

4 | Discussion

In this large, real-world cohort of patients with rheumatoid arthritis initiating tsDMARDs or bDMARDs at the 2nd and 3rd LOTs, initiation of tsDMARDs did not show a clear increase in overall malignancy risk compared with bDMARDs. At both treatment lines, PCP risk appeared comparable between tsDMARDs and bDMARDs, and an increased VTE risk was not observed. In contrast, HZ occurred more frequently among tsDMARD users, highlighting the need for preventive strategies in clinical practice.

The ORAL Surveillance trial was a randomized, open-label, phase IIIb/IV, non-inferiority, safety end-point study analyzed by intention-to-treat. It compared tofacitinib 5 mg twice daily or 10 mg twice daily with a TNF inhibitor in patients with rheumatoid arthritis who had an inadequate response to methotrexate and were aged ≥ 50 years with at least one cardiovascular risk factor. The risk of malignancy was higher with tofacitinib than with TNFi (HR, 1.47 [95% CI, 1.00–2.18] for 5 mg BID; HR, 1.48 [95% CI, 1.00–2.19] for 10 mg BID), and non-inferiority was not met [22, 26]. In a subgroup analysis, tofacitinib increased the risk of malignancy excluding NMSC among patients ≥ 65 years with a history of smoking (HR, 2.42 [95% CI, 1.21–4.82]), whereas no clear increase was observed in < 65-year-old never-smokers [27]. In contrast, our Japanese nationwide claims-based cohort included a broader age and cardiovascular-risk distribution, evaluated class-level use of tsDMARDs and bDMARDs, and relied on claims-based outcome definitions under a per-protocol follow-up framework. These differences in patient risk profile, including the prevalence of concomitant MTX use, exposure scope, and outcome ascertainment, likely explain the weaker malignancy risk observed in our study.

The Japanese all-case post-marketing surveillance (PMS) program for tofacitinib enrolled patients initiating the drug and a contemporaneous control cohort receiving methotrexate or other DMARDs [20, 21]. In the 3-year PMS analysis, the IRs were 6.86 (95% CI, 5.96–7.86) per 100 person-years for serious infections and 1.40 (95% CI, 1.18–1.66) for malignancy, with herpes zoster being the most frequent serious infection (IR, 4.82 [95% CI, 4.47–5.20]). In our claims-based, active-comparator analysis of tsDMARDs versus bDMARDs, which applied an on-treatment risk window and algorithm-defined outcomes, the malignancy IR was slightly lower at 0.81 (95% CI, 0.61–1.00) per 100 person-years, whereas the herpes zoster IR was more similar at 6.41 (95% CI, 5.82–6.99), among the 2nd LOT. These differences likely reflect both population and methodological factors: PMS followed patients throughout a predefined observation period irrespective of treatment persistence and relied on investigator-reported outcomes, whereas our study used administrative claims with high specificity but incomplete event capture, and ascertainment accuracy may vary by outcome type and data source.

Several observational studies have evaluated the safety of tsDMARDs, including the risks of malignancy, infection, and venous thromboembolism (VTE). Among RA patients with an inadequate response to csDMARDs, comparative risks versus bDMARDs have shown nuanced patterns. A pooled analysis of the tofacitinib clinical development program (total 12 664 patient-years of exposure) reported an overall malignancy incidence rate excluding NMSC of 0.85 per 100 PY (95% CI, 0.70–1.02) [18]. This value is similar to rates reported for bDMARDs in the literature; however, the pooled program is largely single-arm, so it does not provide a direct comparative estimate. The standardized incidence ratio (SIR) for all malignancies (excluding NMSC) versus the US SEER population was 1.17 (95% CI, 0.96–1.41), consistent with expectations for moderate-to-severe RA [18].

Direct real-world head-to-head studies comparing tofacitinib/JAK inhibitors with TNF inhibitors have shown mixed results, ranging from no difference [28, 29] to a moderately higher risk in some settings [30]. For example, a nationwide Korean cohort comparing JAK inhibitors (tofacitinib, baricitinib, upadacitinib) with TNFi found an increased malignancy risk (HR, 1.61 [95% CI, 1.08–2.41]) after adjustment [30]. In contrast, the multidatabase STAR-RA study observed no risk with tofacitinib versus TNFi (pooled weighted HR, 1.01 [95% CI, 0.83–1.22]), with results varying by subgroup (e.g., sex, age, prior bDMARD use) and data source (Optum, MarketScan, Medicare) [28]. Our finding of no overall increase in malignancy with tsDMARDs versus bDMARDs at later treatment lines complements prior routine-care comparisons while highlighting that population risk profiles, exposure patterns, and study design can substantially influence absolute risk estimates.

Opportunistic infections—including HZ, PCP, and NTM—occur in patients treated with both tsDMARDs and bDMARDs.

HZ is consistently more frequent with tsDMARDs/JAK inhibitors, and our findings are aligned with prior reports [22, 31–34]. The HZ vaccine could help prevent the onset of events among patients receiving tsDMARDs and bDMARDs and may be an important confounder in safety assessments. However, vaccination data are not included in Japanese claims data due to a lack of coverage by the national health insurance. As a result, the distribution of HZ vaccine coverage could not be obtained. Moreover, the HZ vaccine was introduced in December 2020, and the national immunization program (NIP) for it began in April 2025. This suggests that the majority of patients in our study population did not receive the vaccine. These considerations also imply that HZ is a preventable adverse event and that the implementation of the NIP may reduce HZ incidence, thereby lessening concerns regarding HZ.

In a Japanese nationwide cohort, the IR of PCP with bDMARDs was approximately 0.11–0.21 per 100 person-years (95% CI, 0.09–0.14 to 0.16–0.28), which was similar to the IR with tofacitinib (0.22 per 100 person-years [95% CI, 0.07–0.63]) [34]. To our knowledge, comparative evidence for PCP risk between tsDMARDs and bDMARDs remains limited. In our study, PCP risk was comparable between treatment classes (HR, 0.98 [95% CI, 0.75–1.29] at 2nd LOT; HR, 1.12 [95% CI, 0.81–1.54] at 3rd LOT), adding head-to-head data to an area with sparse prior evidence. In addition, studies have assessed PCP prophylaxis in rheumatic diseases, including populations treated with bDMARDs or tsDMARDs [35, 36]. Prophylaxis—particularly in patients receiving prolonged high-dose glucocorticoids—had a lower incidence of PCP without new safety concerns [35].

The association between glucocorticoid therapy and serious infections has been well documented in observational studies [37, 38]. In our analysis, we adjusted for systemic glucocorticoid use to account for its potential confounding effects. Notably, the prevalence of concomitant glucocorticoid use was slightly higher in the bDMARD group at both 2nd and 3rd LOTs. Taken together, our 2nd and 3rd LOT findings support risk-adapted selection: tsDMARDs are a reasonable choice when malignancy and VTE profiles are acceptable, with enhanced HZ vaccination, optimal systemic glucocorticoid use, and monitoring.

There were no increased risks of malignancy excluding NMSC, PCP, and NTM infections, or VTE observed with tsDMARDs compared with bDMARDs at the 2nd and 3rd LOTs. These results were generally similar to the 5-year results of the CORRONA RA registry [29]. However, a cautious approach to the use of tsDMARDs is warranted. In line with the European Alliance of Associations for Rheumatology (EULAR) Recommendations [10], patient-specific risks should be carefully assessed, and the decision to administer tsDMARDs should be made after patients have been adequately informed.

This study had several limitations. First, as an analysis of administrative claims, residual confounding cannot be excluded despite extensive covariate adjustment and IPT weighting; important factors such as disease activity measures or proxies of inflammation (e.g., DAS28), BMI, smoking, HZ vaccination status, and clinician-related factors (e.g., physician prescribing preferences) are not directly captured. These factors may influence both treatment selection and outcomes. Although the study period preceded the introduction of Japan's national routine HZ vaccination program in April 2025 and vaccination uptake under municipal subsidy programs was reportedly low [39], individual vaccination status was unavailable, precluding assessment of differential uptake between treatment groups. Second, misclassification of exposures, covariates, and outcomes is possible. RA and comorbidities were identified by diagnosis codes, and LOTs were algorithmically defined using claims records and a 180-day grace period. This LOT-based exposure definition does not fully capture temporary treatment interruptions, dose adjustments, delayed prescriptions, or true pharmacologic exposure in routine RA care. Post-index time-varying exposure and cumulative drug exposure were also not explicitly modeled, which may be particularly relevant for outcomes such as malignancy and VTE. Third, outcome ascertainment was based on claims-based algorithms. Although malignancy and infectious outcomes were defined using algorithms adapted from prior validation studies [24, 25], the outcome definitions were not directly validated within the NDB, and sensitivity analyses using alternative definitions were not conducted. Therefore, outcome misclassification, including under- or over-ascertainment, may have affected hazard ratio estimates, particularly for low-frequency outcomes such as NTM infection, PE, DVT, and site-specific malignancies. Fourth, a small proportion of patients in the RA cohort had ankylosing spondylitis (AS)-related claims. AS-related claims were more frequent than expected and may have reflected diagnostic misclassification or suspected diagnoses. Although residual confounding related to treatment selection cannot be excluded, their low prevalence suggests that any impact on the overall estimates was likely limited. Fifth, as there are currently no validated definitions or standardized time frames for event-free windows for these outcomes, including those described in existing literature and clinical guidelines, a 3-month event-free window was defined based on prior clinical experience and expert opinion. Sixth, follow-up duration differed between treatment classes and was relatively short in some patients, particularly among tsDMARD users. Given the long latency of many malignancies and the low event counts for several site-specific cancers and rare safety outcomes, some estimates were imprecise with wide CIs, especially in subgroup/3rd LOT analyses. The absence of clear differences in several outcomes, particularly malignancy, should not be interpreted as evidence of equivalent risk. Further studies with longer follow-up are warranted. Finally, because the NDB mainly represents Japanese insured populations under the Japanese healthcare and insurance system during 2013–2021, generalizability to populations outside Japan may be limited, particularly given differences in background infection risks, such as herpes zoster and nontuberculous mycobacterial infection.

In conclusion, in this nationwide Japanese real-world RA cohort, no increased risk of malignancy or PCP was observed with tsDMARDs compared with bDMARDs at 2nd and 3rd LOTs, whereas the risk of HZ was higher with tsDMARDs. An increased VTE risk was not evident. Given the limitations in follow-up duration and event accrual, particularly for malignancy, individualized risk assessment and shared decision-making remain warranted when initiating tsDMARDs.

Author Contributions

S.N. contributed to the conceptualization and methodology of the study, investigation, interpretation of the results, formal analysis, software, visualization, and preparation of the original draft. T.H. contributed to conceptualization, investigation, interpretation of the results, funding acquisition, project administration, and review and editing of the manuscript. S.S. contributed to conceptualization, methodology, investigation, interpretation of the results, funding acquisition, supervision, and review and editing of the manuscript. H.M. contributed to conceptualization, data curation, investigation, software, resources, and review and editing of the manuscript. Y.T. (Yoshinori Takeuchi) contributed to conceptualization, methodology, data curation, investigation, funding acquisition, and review and editing of the manuscript. Y.I. (Yasushi Inoue), Y.T. (Yoshiya Tanaka), and K.Y. contributed to conceptualization, investigation, interpretation of the results, and review and editing of the manuscript. Y.I. (Yoichi Ii) and S.H. contributed to conceptualization, methodology, investigation, interpretation of the results, and review and editing of the manuscript. M.H. and N.S. contributed to conceptualization, investigation, interpretation of the results, funding acquisition, and review and editing of the manuscript. Y.M. contributed to conceptualization, funding acquisition, supervision, and review and editing of the manuscript. H.K. contributed to conceptualization, methodology, investigation, supervision, interpretation of the results, and review and editing of the manuscript. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Ethics Statement

This study was approved by the Institutional Review Board of the University of Tokyo (approval no. 2020282NI-[2]).

Consent

The authors have nothing to report.

Conflicts of Interest

S.N., H.M., Y.T. (Yoshinori Takeuchi), Y.M., and H.K. have received funding from Pfizer Japan Inc. in connection with this study through their university. S.S. received research funding from Pfizer Inc., Pfizer Japan, BMS, and Daiichi Sankyo and served as a consultant for Pfizer Inc., Pfizer Japan, Merck Co. Inc., and Regeneron Inc. Y.T. (Yoshinori Takeuchi) had received consultant fees from Pharmaceuticals and Medical Devices Agency, EPARK Inc., and EPS Corporation. M.H. and T.H. are employees of Pfizer Japan Inc. Y.I. (Ii Yoichi) and S.H. are employees of Pfizer R&D Japan G.K. Y.T. (Yoshiya Tanaka) has received speaking fees and/or honoraria from Chugai, UCB, Abbvie, AstraZeneca, Eli-Lilly, Behringer-Ingelheim, GlaxoSmithKline, Eisai, IQVIA, Daiichi-Sankyo, Otsuka, Taisho, Gilead, Bristol-Mayers. Y.I. (Yasushi Inoue) has received honoraria from Pfizer Japan Inc. K. Yamaoka has received honoraria from Pfizer, Chugai Pharma, Takeda Industrial Pharma, Astellas Pharma Inc., AbbVie, Bristol-Myers Squibb, Mitsubishi-Tanabe Pharma, GlaxoSmithkline, Eli lilly Japan K.K., Janssen Pharma, Eisai Pharma, Actelion Pharmaceuticals Japan, Asahikasei Pharma Corp, Ono Pharma, Otsuka Pharma, Nippon Shinyaku, Gilead G.K, Daiichi-Sankyo, Behringer Ingelheim Japan, Japan Tobacco Inc., Hisamitsu Pharma Co, MSD, Sanofi, AYUMI Pharma Co, NIPPON KAYAKU, Bayer Yakuhin Ltd., UCB Jaoan Co Ltd., Amfeb Inc., Taisho Pharmaceutical Co. Ltd., and KYOWA KIRIN. N.S. is an employee of Bristol-Myers Squibb K.K. Y.M. received research funding from EPS Corporation. H.K. has received consulting fees from Mitsubishi Tanabe Pharma and speakers' fees from Pfizer Japan Inc. and Johnson & Johnson K.K. S.N. and H.K. are affiliated with the Department of Healthcare Quality Assessment at The University of Tokyo. This department is a social collaboration department supported by the National Clinical Database, Johnson & Johnson K.K., Nipro Corporation, and Intuitive Surgical Sàrl.

Data Availability Statement

In accordance with the regulations governing Japan's National Database of Health Insurance Claims and Specific Health Checkups (NDB) and our Data Use Agreement with the Ministry of Health, Labour and Welfare, we are not permitted to share the study dataset.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Code list of DMARDs. **Table S2:** Code list of baseline comorbidities and medications. **Table S3:** Code list of outcome definition. **Table S4:** Baseline characteristics of 2L-tsDMARD group and 2L-bDMARD group (malignancy assessment cohort). **Table S5:** Baseline characteristics of 3L-tsDMARD group and 3L-bDMARD group (malignancy assessment cohort). **Table S6:** Unweighted incidence rates, 5-year cumulative incidence, and hazard ratios for all safety outcomes at the 2nd and 3rd LOTs. **Table S7:** IPT-weighted incidence rates, 5-year cumulative incidence, and hazard ratios for additional safety outcomes at the 2nd and 3rd LOTs. **Figure S1:** (A) Flow diagram of 2nd line cohorts and malignancy-assessment subcohorts. (B) Flow diagram of 3rd line cohorts and malignancy-assessment subcohorts. **Figure S2:** Outcome definition of incident case. **Figure S3:** (A) Distribution of estimated treatment probability (unweighted) of 2L-tsDMARD group and 2L-bDMARD group (all eligible patients). (B) Distribution of estimated treatment probability (weighted) of 2L-tsDMARD group and 2L-bDMARD group (all eligible patients). (C) Distribution of estimated treatment probability (unweighted) of 2L-tsDMARD group and 2L-bDMARD group (malignancy assessment cohort). (D) Distribution of estimated treatment probability (weighted) of 2L-tsDMARD group and 2L-bDMARD group (malignancy assessment cohort). **Figure S4:** (A) Distribution of estimated treatment probability (unweighted) of 3L-tsDMARD group and 3L-bDMARD group (all eligible patients). (B) Distribution of estimated treatment probability (weighted) of 3L-tsDMARD group and 3L-bDMARD group (all eligible patients). (C) Distribution of estimated treatment probability (unweighted) of 3L-tsDMARD group and 3L-bDMARD group (malignancy assessment cohort). (D) Distribution of estimated treatment probability (weighted) of 3L-tsDMARD group and 3L-bDMARD group (malignancy assessment cohort). **Figure S5:** IPT-weighted cumulative incidence of adverse events in second-line therapy: tsDMARDs versus bDMARDs. **Figure S6:** IPT-weighted cumulative incidence of adverse events in third-line therapy: tsDMARDs vs. bDMARDs.

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LETTER TO THE EDITOR

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

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Dear Editor,

We read with interest the study by Wang and colleagues examining resting-state functional connectivity alterations of the anterior cingulate cortex (ACC) and its subdivisions in patients with fibromyalgia [1]. The focus on dorsal ACC subregional specificity and its association with pain and affective symptoms addresses an important mechanistic gap in the neurobiology of fibromyalgia and offers a refined network-based perspective on central sensitization.

A key consideration relates to the operationalization of functional connectivity findings as putative markers of pain–emotion integration. While statistically significant rsFC differences were demonstrated between dorsal ACC subregions and limbic structures, the clinical interpretability of these effect sizes warrants further scrutiny. The reported correlations with symptom scales, although directionally consistent, remain modest and cross-sectional, raising questions about whether the observed connectivity alterations reflect primary drivers of symptom severity or secondary network adaptations to persistent pain. Without anchoring these associations to clinically meaningful thresholds—such as minimal clinically important differences for WPI, FIQ, or SDS—translation into patient-relevant stratification or prognostication remains uncertain. Future work may benefit from embedding connectivity metrics within multivariable clinical models to evaluate their incremental explanatory value beyond established symptom measures.

The reliance on seed-based rsFC using predefined ACC subregions also introduces conceptual constraints. While atlas-driven parcellation enhances reproducibility, it may insufficiently capture individual-level functional heterogeneity, particularly in disorders characterized by network-level plasticity [2]. Interindividual variability in ACC functional boundaries could lead to partial averaging of distinct neural phenotypes within fibromyalgia, potentially attenuating subgroup-specific effects [3]. Complementary data-driven approaches, such as independent component analysis or subject-specific parcellation, may help determine whether the reported supACC- and aMCC-centered networks represent stable disease-related circuits or context-dependent configurations.

Another aspect concerns the asymmetry of findings predominantly involving left-sided ACC–limbic connectivity. The lateralization of affective and nociceptive processing is biologically plausible [4]; however, its robustness remains unclear without explicit hemispheric interaction analyses. Given prior evidence of bilateral and sex-dependent ACC involvement in chronic pain

syndromes, systematic testing of lateralized effects and their behavioral correlates may refine interpretation and improve external validity across heterogeneous fibromyalgia populations.

The interpretation of enhanced connectivity as maladaptive hypercoupling also merits cautious framing. Increased rsFC does not uniformly imply pathological overactivation and may, in some contexts, represent compensatory engagement of cognitive–affective control circuits [5]. Distinguishing maladaptive sensitization from adaptive regulation would benefit from integration with task-based fMRI paradigms probing cognitive control, emotion regulation, or pain modulation, thereby linking intrinsic connectivity states to functional capacity rather than symptom burden alone.

Finally, the study's implications for neuromodulatory interventions, such as rTMS targeting ACC subregions, are conceptually appealing but remain inferential. Network-informed stimulation strategies would require demonstration that modulation of the identified circuits produces predictable and durable changes in both connectivity patterns and clinically meaningful outcomes [6]. Prospective mechanistic trials incorporating pre–post connectivity assessments could help bridge this translational gap.

In summary, this work provides valuable subregional insight into ACC–limbic network alterations in fibromyalgia and advances the discussion of affective–nociceptive integration at a systems level. Addressing the clinical anchoring, individual variability, and functional interpretation of these connectivity findings may further enhance their relevance for precision neurobiological models and targeted interventions in fibromyalgia.

Author Contributions

Palavardhan Peddapalegani: validation, writing – original draft, writing – review and editing. **Raghav Gupta:** supervision, project administration, writing – original draft, writing – review and editing. **Priyanka Bansal:** conceptualization, methodology, writing – original draft, writing – review and editing. **Pankaj Nainwal:** writing – original draft, writing – review and editing. **Hariharan Srinivasan:** writing – original draft, writing – review and editing. All authors reviewed and approved the manuscript.

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Conflicts of Interest

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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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LETTER TO THE EDITOR

Yinlian Tongfeng Granules: A Promising Clinical Treatment Option for Gouty Arthritis

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Dear Editor,

Gouty arthritis (GA) is a chronic immune-metabolic disease characterized by recurrent flares and progressive joint damage [1]. Sustained serum urate control during the intercritical period is central to relapse prevention [2]. Although febuxostat is effective for urate lowering [3], its long-term use may be limited by adverse effects and recurrence after discontinuation. Yinlian Tongfeng (YLTF) granules, a Traditional Chinese Medicine formulation composed of *Artemisia capillaris* Thunb. (Yinchenhao), *Glechoma longituba (Nakai) Kupr.* (Lianqiancao), and *Lycopodium japonicum* Thunb. (Shenjincao), have shown favorable efficacy and tolerability in prior studies [4]. However, their optimal role across different degrees of hyperuricemia remains unclear. We therefore conducted a stratified randomized clinical trial to evaluate the efficacy and safety of YLTF in intercritical GA.

This single-center, assessor-blinded, randomized controlled trial (ITMCTR2025001026) enrolled 220 patients with intercritical GA (recruited from the outpatient clinic of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine) who met the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [5] for gout and a serum uric acid level $>420\,\mu mol/L$, and who had no acute flare within the preceding month, no other inflammatory arthritides, and no severe hepatic or renal impairment. Participants were stratified by baseline blood uric acid (BUA) into a mild subgroup ($\leq 480\,\mu mol/L$, $n=80$) [6] and a moderate-to-severe subgroup ($>480\,\mu mol/L$, $n=140$). Within each stratum, patients were randomized 1:1 using block randomization to receive YLTF monotherapy versus febuxostat 20 mg daily (mild subgroup), or YLTF combined with febuxostat 40 mg daily versus febuxostat 40 mg daily alone (moderate-to-severe subgroup). The primary outcome was the relapse rate at week 12 of treatment. Response rate and changes in BUA levels after the 12-week treatment period were also recorded, as well as relapse status at follow-up weeks 12 and 24 (off treatment). BUA levels were monitored before and after the 12-week treatment cycle. Lipid profiles, hepatic and renal function, electrocardiogram findings, and other adverse reactions were assessed as safety outcomes. The study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Approval No. 2025-085). Statistical analyses were performed using SPSS version 27.0 and R (4.4.1). For descriptive statistics, qualitative data were presented as frequencies and percentages, and quantitative data as mean ± SD or median (range). Group comparisons used *t*-tests (with Satterthwaite correction for unequal variances) or Wilcoxon rank-sum tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables; repeated measures were analyzed by ANOVA. All tests were two-sided and $p<0.05$ was considered statistically significant.

Baseline characteristics, including sex ratio, age, and disease duration, did not differ significantly between the mild and moderate-to-severe subgroups ($p>0.05$). In the mild

Mengji Xie, Xiaojie Ding and Xiangfei Zhai contributed equally to this work.

Trial Registration: This protocol was registered with the International Clinical Trial Registry Platform for Traditional Medicine (ITMCTR2025001026).

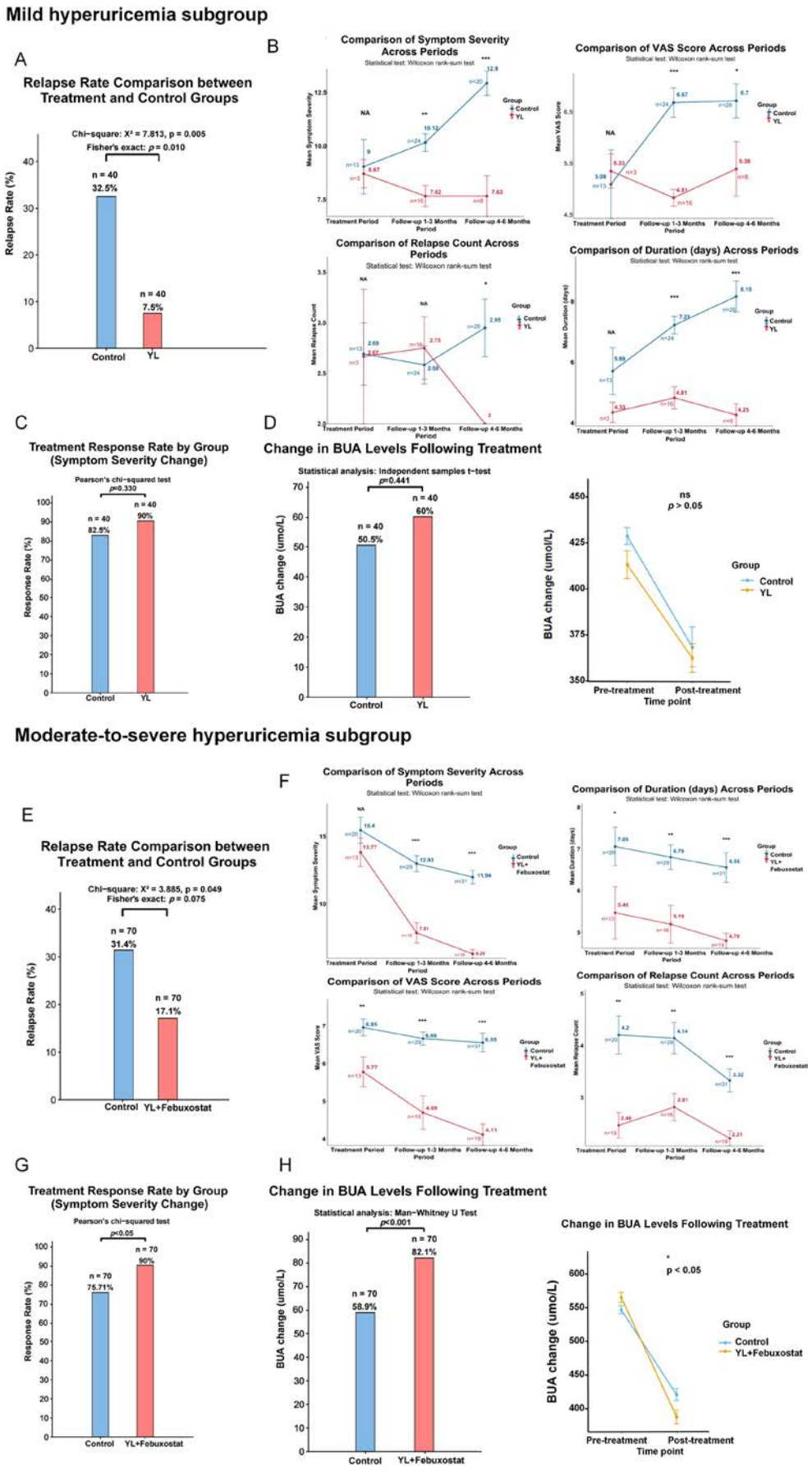

FIGURE 1 | Legend on next page.

FIGURE 1 | Efficacy outcomes stratified by baseline uric acid level. (A) Relapse rate at week 12 in the mild hyperuricemia subgroup (BUA ≤480 μmol/L). (B) Relapse characteristics during follow-up in the mild subgroup. (C) Response rate based on symptom improvement in the mild subgroup. (D) Change in blood uric acid (BUA) after the 12-week treatment in the mild subgroup. (E) Relapse rate at week 12 in the moderate-to-severe hyperuricemia subgroup (BUA >480 μmol/L). (F) Relapse characteristics during follow-up in the moderate-to-severe subgroup. (G) Response rate based on symptom improvement in the moderate-to-severe subgroup. (H) Change in BUA after the 12-week treatment in the moderate-to-severe subgroup. Data are presented as mean ± SD or percentage. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ns, not significant.

TABLE 1 | Baseline characteristics and adverse events.

	Mild Hyperuricemia Group (BUA ≤480 μmol/L)		Moderate to severe Hyperuricemia Group (BUA >480 μmol/L)	
	YL ($n = 40$)	Febuxostat 20 mg ($n = 40$)	YL + Febuxostat ($n = 70$)	Febuxostat 40 mg ($n = 70$)
Baseline characteristics				
Male (%)	82.5%	82.5%	80%	78.75%
Age (years, Mean ± SD)	58.53 ± 2.23	59.43 ± 2.13	57.80 ± 1.68	55.36 ± 1.54
Disease duration (months)	62.35 ± 10.75	66.50 ± 8.22	63.27 ± 4.99	60.41 ± 4.31
Adverse events (AV)				
Cardiovascular disease	0	0	0	0
Arrhythmia	0	0	0	1 (1.43)
Angina pectoris	0	0	0	0
Myocardial infarction	0	0	0	0
Cerebral infarction	0	0	0	0
Stroke	0	0	0	0
Dyslipidemia	0	0	0	0
Abnormal blood pressure	0	0	0	0
Abnormal blood glucose	0	0	0	0
Hepatic dysfunction	0	0	2 (2.86)	6 (8.57)
Renal dysfunction	0	0	0	0
Lower limb edema	0	0	0	0
Dizziness	0	0	0	0
Gastrointestinal discomfort	0	1 (2.50)	2 (2.86)	4 (5.71)
Rash/Pruritus	0	0	1 (1.43)	3 (4.29)

Note: Adverse Events: Data are from the treatment and follow-up period.
Abbreviation: YL, Yinlian Tongfeng Granules.

hyperuricemia subgroup, the 12-week relapse rate was significantly lower with YLTF monotherapy than with febuxostat 20 mg (7.5% vs 32.5%, $p < 0.05$) (Figure 1A). During the 4–6 month follow-up period, patients receiving YLTF experienced fewer mean relapses (2.00 vs 2.95, $p < 0.05$), shorter flare duration (4.15 vs 8.15 days, $p < 0.001$), and lower symptom severity and visual analog scale scores ($p < 0.001$ and $p < 0.05$, respectively) (Figure 1B). The response rate, defined by symptom improvement, was 90.00% in the YLTF group versus 82.50% in the febuxostat group ($p < 0.05$) (Figure 1C). YLTF monotherapy achieved urate-lowering efficacy comparable to febuxostat 20 mg, with no significant between-group difference in BUA reduction ($p > 0.05$) (Figure 1D). In the moderate-to-severe hyperuricemia subgroup, YLTF-febuxostat combination therapy was associated with a lower 12-week relapse rate than febuxostat 40 mg monotherapy (17.1% vs 31.4%, $p < 0.05$) (Figure 1E). The combination group also demonstrated fewer relapses, shorter flare duration, and reduced symptom severity and pain scores throughout the treatment and follow-up periods (all $p < 0.05$) (Figure 1F). The response rate, based on symptom improvement, was significantly higher with combination therapy than with monotherapy (90.00% vs 75.71%, $p < 0.05$) (Figure 1G). In addition, BUA reduction was greater in the combination group ($p < 0.001$) (Figure 1H).

Yinlian Tongfeng-containing regimens were well tolerated, with no serious adverse events or major cardiovascular events reported. In the mild subgroup, no adverse events occurred with YLTF monotherapy. In the moderate-to-severe subgroup, YLTF-febuxostat combination was associated with a lower incidence of hepatic dysfunction (2.86% vs 8.57%) and gastrointestinal discomfort (2.86% vs 5.71%) compared with febuxostat monotherapy (Table 1). Furthermore, groups receiving YLTF exhibited lower triglyceride levels and higher high-density lipoprotein cholesterol compared with those not receiving YLTF ($p < 0.001$).

Our findings revealed comparable urate-lowering efficacy between YLTF monotherapy and febuxostat in the $\leq 480\,\mu$mol/L subgroup, with superior recurrence prevention by YLTF. For patients with BUA $> 480\,\mu$mol/L, YLTF-febuxostat combination therapy demonstrated enhanced BUA reduction and greater relapse prevention compared with febuxostat alone. These results underscore the clinical value of BUA-stratified management in intercritical GA.

This study clarifies the clinical positioning of YLTF granules in gout management. First, YLTF may serve as an alternative monotherapy for mild hyperuricemia (BUA $\leq 480\,\mu$mol/L), particularly in patients intolerant to conventional urate-lowering agents or those with hepatic or renal impairment. Prior studies have reported that Traditional Chinese Medicine formulations achieve comparable urate reduction with fewer adverse events than conventional therapy [7, 8]. However, unlike these reports focusing on acute-phase symptom control [9, 10], our study specifically addresses the intercritical phase and introduces a BUA-stratified strategy that positions YLTF as either monotherapy or an adjunct to febuxostat depending on baseline uric acid burden, which refines its clinical application beyond general anti-inflammatory or urate-lowering effects [11]. Second, in moderate-to-severe hyperuricemia (BUA $> 480\,\mu$mol/L), YLTF acts as an effective adjunct to febuxostat, accelerating symptom resolution and enhancing relapse prevention. This aligns with evidence that staged integrated Traditional Chinese and Western medicine strategies, specifically YLTF granules during the intercritical phase combined with conventional urate-lowering and anti-inflammatory therapy, achieve superior clinical response rates compared with conventional treatment alone (96.81% vs 73.63%, $p < 0.05$) [12]. Third, YLTF may be considered as transitional therapy during dose reduction or post-treatment maintenance to stabilize BUA levels and prolong intercritical periods. The importance of maintaining urate control during treatment de-escalation is well recognized, as BUA fluctuation is strongly associated with recurrent flares [13]. Notably, YLTF-containing regimens were also associated with improved lipid profiles, specifically lower triglyceride levels and elevated high-density lipoprotein cholesterol ($p < 0.001$). This observation is biologically plausible, as prior studies have demonstrated that Artemisia capillaris and *Glechoma longituba*, the principal constituents of YLTF, possess lipid-regulating properties [14, 15]. These findings underscore the substantial clinical value of YLTF in the management of gouty arthritis. Driven by an unmet clinical need, namely the lack of safe and effective relapse-preventive agents during the intercritical phase of GA, this study proposes a novel BUA-stratified therapeutic strategy and validates its efficacy through a randomized controlled trial. As a key Traditional Chinese Medicine formulation for intercritical intervention, YLTF holds considerable promise for further translational development [16].

Several limitations should be acknowledged. The single-center, small-sample cohort design may carry a certain risk of bias in patient enrollment. The short duration of both the intervention and follow-up periods has resulted in limited data on the long-term efficacy and potential adverse effects of YLTF granules.

In summary, this study supports a BUA-stratified management strategy for intercritical gouty arthritis, positioning YLTF granules as monotherapy for mild hyperuricemia and as a synergistic adjunct for moderate-to-severe disease, with validated efficacy in reducing relapse. These findings highlight the potential of YLTF to improve long-term outcomes in hyperuricemia management.

Author Contributions

Mengji Xie: methodology, investigation, and writing-original draft. **Xiaojie Ding and Xiangfei Zhai:** methodology, data curation, and writing-original draft. **Miao Li:** visualization, writing-review and editing. **Mi Zhou:** conceptualization, writing-review and editing, validation, and funding. All the authors approved the final version.

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Ethics Statement

The study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Approval No. 2025-085). And written informed consent was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Case Report: Effectiveness of Abatacept for Palindromic Rheumatism Followed by Rheumatoid Factor-Positive Polyarticular Juvenile Idiopathic Arthritis

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Dear Editor,

Palindromic rheumatism (PR) is an acute arthritis lasting from a few hours to days, followed by recurrent attacks at intervals of several days to months. In adults, some cases of PR progress to rheumatoid arthritis (RA) [1, 2]; however, reports in children are rare, and the pediatric incidence is unclear. We report a pediatric case of PR that preceded anti-cyclic citrullinated peptide (CCP) antibody-positive polyarticular juvenile idiopathic arthritis (JIA).

A 14-year-old girl presented with an 8-month history of recurrent painful swelling of her shoulders, wrists, and small hand joints, occurring approximately weekly and resolving spontaneously within 1 to 2 days. At the time of presentation, several areas of the body were swollen, and the pain intensity had increased; therefore, the patient sought care locally and was referred to our hospital for admission. She had no significant prior or family history of RA. The patient weighed 51 kg. Physical examination revealed swelling and tenderness in the bilateral shoulders, right elbow, bilateral wrist, bilateral second to fifth metacarpophalangeal (MCP) joints, and bilateral third proximal interphalangeal (PIP) joints. There was no noted skin or ophthalmologic involvement. Laboratory results revealed the following: C-reactive protein (CRP): 2.03 mg/dL; matrix metallopeptidase 3 (MMP-3): 159 ng/mL; rheumatoid factor (RF): 14.3 IU/L (reference range: < 14.0 IU/L) and remained positive when retested 3 months later (16.8 IU/L); and anti-CCP antibody: 604 U/mL. HLA-B27 was negative. Reactive arthritis and infection-associated arthritis were considered less likely because there was no preceding gastrointestinal or genitourinary infection, and bacterial cultures of the throat, stool, and urine were negative. Serological testing did not indicate acute Epstein–Barr virus or cytomegalovirus infection, and the T-SPOT.TB test was negative. Contrast-enhanced, fat-suppressed, T1-weighted magnetic resonance imaging of the right shoulder showed synovial hypertrophy, joint effusion, and contrast enhancement, suggesting active synovitis (Figure 1). Two days after admission, the swelling and pain in all joints resolved, and the patient was discharged. However, after discharge, swelling and pain, which had improved within 2 days, began to recur in various joints. Ultrasonography and magnetic resonance imaging were not performed during the intercritical periods. Arthritis in each joint improved within 1 or 2 days, but at the time of the patient's visit, arthritis had developed in one of the joints, and CRP had not yet become negative. The episodes leading up to referral to our hospital were characterized by cyclical paroxysmal joint symptoms, and subjective symptoms fully resolved during the intercritical periods. As clinical findings of arthritis had completely resolved between attacks, we considered a diagnosis of PR. Genetic testing revealed a *MEFV* variant L110P-E148Q heterozygous mutation. Naproxen was initiated but was ineffective. Although the arthritis did not persist, it appeared and disappeared repeatedly, and the interval between episodes became shorter. Because anti-CCP antibody levels were elevated, the onset of polyarticular JIA was suspected. Methotrexate (MTX) at 8 mg/week was initiated (Figure 2), but no improvement was observed. The dose was increased to 12 mg/week, and prednisolone was administered at 15 mg/day (0.3 mg/kg/day), then tapered to 10 mg/day (0.2 mg/kg/day) and 5 mg/day (0.1 mg/kg/day). Thereafter, the interval between episodes in each joint shortened, and neither MTX nor 15 mg/day PSL was deemed effective. Hydroxychloroquine and colchicine, which have been reported to be effective in PR, were also

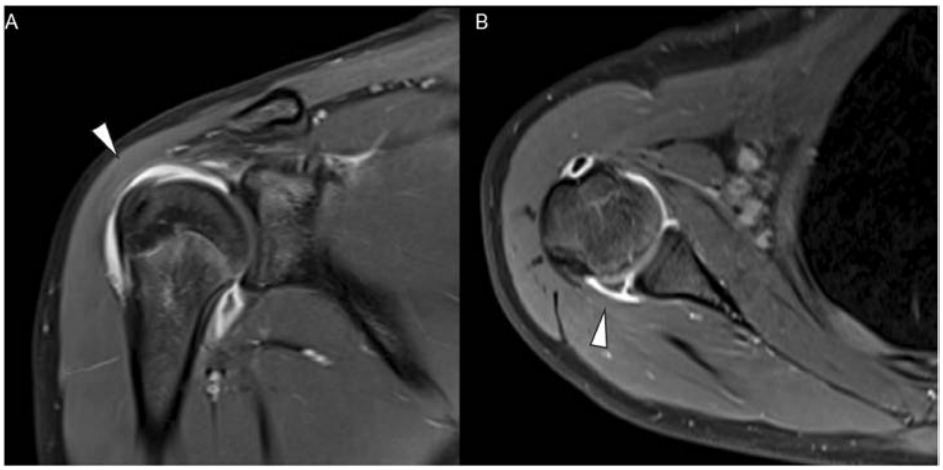

FIGURE 1 | Right shoulder magnetic resonance imaging. Right shoulder contrast-enhanced, fat-suppressed, T1-weighted magnetic resonance imaging revealing synovial hypertrophy, joint effusion, and contrast enhancement, suggesting active synovitis (white arrow). (A) Coronal; (B) Axial.

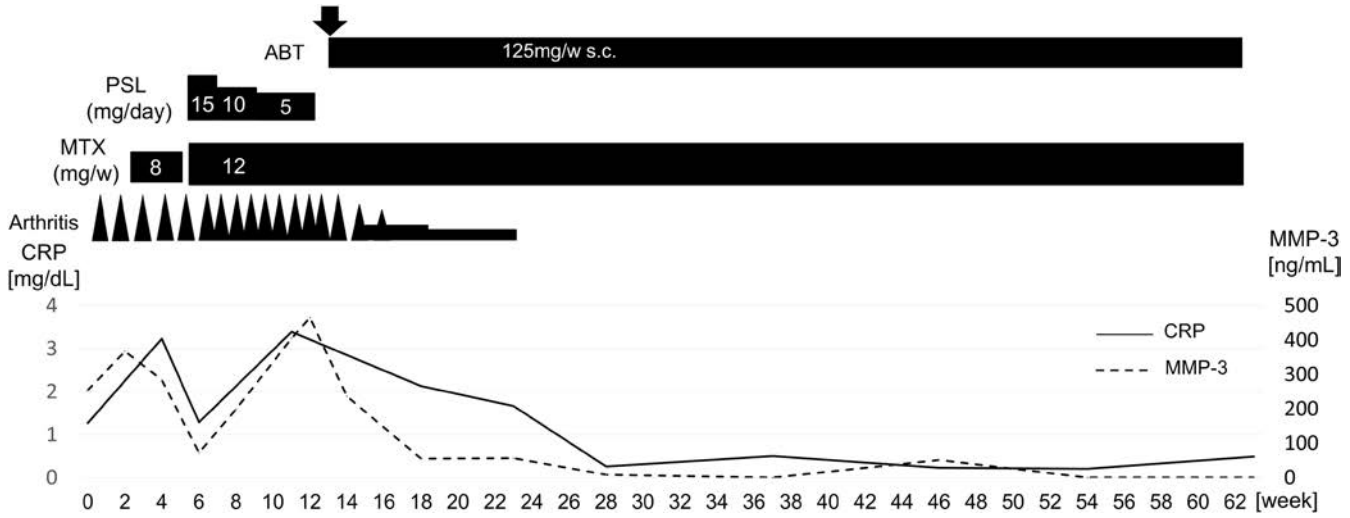

FIGURE 2 | Clinical course. Naproxen, methotrexate, and prednisolone did not improve the patient's periodic arthritis. Abatacept treatment improved the periodic and subsequently persistent arthritis symptoms in the right shoulder, left wrist, and left third MCP joints, and the CRP and MMP-3 levels, as shown. ABT, abatacept; CRP, C-reactive protein; MCP, metacarpophalangeal; MMP-3, matrix metallopeptidase-3; MTX, methotrexate; PSL, prednisolone; S.C., subcutaneous injection.

considered treatment options. However, the patient was anti-CCP antibody-positive and at high risk of developing JIA. The intervals between periodic attacks of arthritis gradually shortened (from every 2 weeks to every 3 days), and serum markers such as CRP and MMP-3 did not become negative, suggesting progression from PR to JIA. Thus, additional treatment with biologic agents was initiated. The patient prioritized safety when selecting medication and preferred abatacept over adalimumab and tocilizumab. She was RF- and CCP-positive and was thus at high risk for developing JIA. We also referred to a study on the effectiveness of abatacept in CCP-positive pre-clinical RA [3], although this study was conducted in adults, rather than in children. At the time of selecting abatacept, we were unaware of the existence of clinical trials evaluating abatacept for seropositive PR. Taking these factors into consideration, we chose abatacept after consultation with the patient and her guardian. After discontinuing PSL and initiating abatacept, the periodic attacks of arthritis resolved; however, 3 weeks after starting abatacept, arthritis in the right shoulder, left wrist, and left third MCP joints persisted. Subsequently, arthritis of the left third MCP, right third MCP, and PIP joint also developed. The arthritis improved 16 weeks after starting abatacept, as did serological biomarkers such as CRP and MMP-3. Arthritis in more than five joints persisted for more than 6 weeks, and RF remained positive from the first visit up to 3 months, and anti-CCP antibodies also remained consistently positive. Therefore, the patient was diagnosed with RF-positive polyarticular JIA.

Adults with PR have positive RF and anti-CCP antibody rates of approximately 30%–60% [1, 2, 4–6]. Studies have shown that patients with positive RF and anti-CCP antibodies are more likely to exhibit disease progression to RA [1, 2, 4, 5]. There are few reports on progression to JIA in children. One case series examining the clinical course of 10 pediatric patients diagnosed with PR found that 3/10 patients experienced long-term remission, 6/10 experienced episodic attacks, and 1/10 progressed to JIA [7]. In addition, the RF was positive in 2/9 cases; however, the RF levels of the patient who developed JIA were not recorded.

PR in children is rare, and it is unclear whether RF-positive PR, like in adults, is at high risk for progression to JIA, and further investigation is needed.

RA is an autoimmune disease, whereas PR is an autoinflammatory condition. A study on the *MEFV* gene in 65 patients with PR in Spain found that 12.3% (8/65) had *MEFV* gene mutations [8]. *MEFV* mutations were more common in anti-CCP-negative than in anti-CCP-positive cases (22.2% vs. 5.3%, $p = 0.058$), suggesting that anti-CCP-negative PR may have an autoinflammatory component. There has been one report of a pediatric patient with PR progressing to JIA in Japan [9]. This patient had negative RF and anti-CCP, but genetic testing revealed an *MEFV* variant L110P-E148Q heterozygous mutation. Our patient also exhibited an *MEFV* variant L110P-E148Q heterozygous mutation. Although our patient did not receive colchicine, the other patient reportedly did not respond to colchicine [9]. In this case, both RF and anti-CCP antibody were positive, and abatacept was effective; therefore, the *MEFV* variant in our case was considered to have limited pathological significance, and the disease process was thought to have minimal autoinflammatory involvement. The clinical significance of *MEFV* in the pathogenesis of PR remains uncertain, and further investigation is needed into the role of autoinflammatory components.

There is no standard management for PR; however, various treatments have been investigated. Non-steroidal anti-inflammatory drugs have been effective in 68% of patients, although they were not effective for our patient [10]. Because PR is thought to be an autoinflammatory disease with a periodic nature, colchicine may be effective [11]. Hydroxychloroquine has also been demonstrated to treat PR and prevent the progression of PR to RA [12, 13]. MTX has been administered to patients with PR who experienced an inadequate benefit from hydroxychloroquine [14], but MTX was ineffective for our patient. There are no data demonstrating the efficacy of tumor necrosis factor, interleukin-6, or Janus kinase inhibitors for PR, all of which have been effective against RA and JIA. Rituximab has been effective in controlling periodic attacks in conventional synthetic disease-modifying antirheumatic drug (csDMARD)-refractory PR [15].

In an ongoing multicenter randomized trial for patients with seropositive PR, abatacept is reported to be effective for the clinical remission of PR and the prevention of progression to RA compared with hydroxychloroquine [16]. We were unaware of the existence of this clinical trial when selecting abatacept, but the periodic attacks disappeared after abatacept was started, suggesting that it may have been effective in treating the periodic arthritis attacks of seropositive PR in this pediatric case. To our knowledge, this is the first case report to demonstrate these results, and further investigation of the utility of abatacept in pediatric patients with PR is required.

A limitation of this case report is the lack of laboratory findings in intermittent periods, which are important in diagnosing PR. To diagnose PR, it is important to confirm that not only clinical findings but also imaging findings, such as blood tests, ultrasonography, and magnetic resonance imaging, are improving during the intermittent period. However, in this case, only the disappearance of clinical arthritis was confirmed, so we considered it appropriate to diagnose this case as PR.

Author Contributions

Yuji Fujita collected and analysed the data and drafted the manuscript. All other authors contributed to data collection and interpretation and critically revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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Consent

Written informed consent was obtained from the patient's parents for publication of this case report.

Conflicts of Interest

Kei Ikeda has received speaker's fee from AbbVie, Eisai, Eli Lilly, Gilead Sciences, Novartis, AstraZeneca, and Asahi Kasei. The other authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

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

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Dear Editor,

We read with great interest the original article by Haroon et al., reporting a 70.9% lower rate of acute anterior uveitis (AAU) flares in certolizumab pegol (CZP)-treated patients from the C-VIEW study compared with those receiving standard non-biologic care, using an overlap-weighting propensity score approach [1]. The study addresses a genuine evidence gap—direct comparative data for monoclonal tumor necrosis factor inhibitors (TNFi) versus non-biologic treatment for AAU prevention in axial spondyloarthritis (axSpA) have been largely absent [2]. However, three interpretive concerns temper the clinical translation of these findings.

The analysis employs overlap weighting (OW), which estimates the Average Treatment Effect for the Overlap population (ATO)—the treatment effect in patients at genuine clinical equipoise for whom either CZP or non-biologic care would be equally appropriate [3]. This is a methodologically defensible choice, but the ATO is a narrower estimand than the Average Treatment Effect (ATE), and the two are not interchangeable. The authors report a sensitivity analysis incorporating six additional covariates, but this re-applies the same overlap-weighting design and therefore yields a re-specified ATO rather than an average treatment effect. No subgroup or stratified analysis by disease activity, sex, age, or radiographic status is presented, and the only unweighted estimate available is the pre-weighting comparison, which remains confounded by the very baseline imbalances that weighting was applied to correct. Readers are therefore left with no basis on which to infer effect sizes for patients outside the overlap population. The reported effective sample size—38 for the comparator and 66 for the CZP group, against 162 patients analyzed—indicates how substantially narrower the overlap population is than the enrolled cohort. This distinction matters clinically: most patients with high disease activity (ASDAS $\geq$ 2.1), recurrent AAU, and prior NSAID failure are already designated biologic candidates and are not at genuine equipoise. Extrapolating the reported rate ratio of 0.29 (95% CI: 0.18–0.47) to the broader high-risk population conflates these distinct estimands, with direct implications for how this effect size should inform guideline interpretation.

A second concern relates to flare ascertainment. In C-VIEW, AAU episodes were captured prospectively, with scheduled ophthalmological assessments throughout a 96-week follow-up [2]. Comparator patients from the UCSF and UHN registries were identified retrospectively, where flares would be recorded only upon clinical presentation. Mild or rapidly self-resolving episodes managed by a community ophthalmologist outside the rheumatology registry would go unrecorded in the comparator arm. This constitutes differential outcome misclassification: flare ascertainment is systematically less complete in the comparator arm than in the trial arm, and the misclassification is non-random with respect to treatment allocation. The direction of this bias is not neutral—it inflates the observed treatment effect. The 70.9% relative reduction should therefore be interpreted as a probable upper-bound estimate, rather than a stable

treatment effect generalisable to routine care settings where flare capture is similarly inconsistent.

Third, C-VIEW was conducted across five European countries, and both comparator cohorts are North American. The analysis provides no data on HLA-B27-positive axSpA in South or East Asian populations—precisely the populations that this journal primarily serves. Pooled data across 143 studies have shown geographical area to be independently associated with the prevalence of extra-articular manifestations in ankylosing spondylitis, supporting the concern that findings from European and North American cohorts may not transfer directly [4]. Whether the magnitude of benefit observed here is reproducible in Asian cohorts therefore remains unknown [5, 6]. To our knowledge, no prospective trial or registry study evaluating TNFi therapy for AAU prevention in an Asian axSpA population has been registered or published to date; this absence, rather than any contrary evidence, is the basis for our call for regionally representative data. Beyond epidemiological considerations, CZP is not widely accessible across South and Southeast Asia owing to cost and the limited availability of biosimilar certolizumab pegol. Future studies should explicitly enroll Asian populations and report cost-effectiveness data alongside efficacy outcomes.

Nevertheless, Haroon et al. address an important comparative gap in the AAU evidence base. The choice of OW over inverse probability of treatment weighting is appropriate for structurally disparate cohorts, and the consistency between the primary and sensitivity analyses strengthens confidence in the direction of effect.

In summary, the ATO estimand constrains generalisability to patients at genuine clinical equipoise; differential outcome misclassification between a prospective trial and retrospective registries likely inflates the observed effect size; and the evidence base currently offers no applicability data for Asia-Pacific populations. Prospective, registry-based studies in ethnically diverse cohorts—with standardized ophthalmological outcome ascertainment—represent the logical next step.

Author Contributions

Bodhisatwa Choudhuri: conceptualisation, critical analysis of the index article, drafting the letter, final approval. **Jay Prakash:** critical review of methodology and statistical arguments, revision of the letter, final approval. **Anindya Dasgupta:** critical review of clinical content, revision of the letter, final approval. All authors approved the final version for submission.

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Disclosure

Paperpal Prime was used solely for language editing of the final manuscript. All intellectual content, including the conception and development of the critical arguments, selection of references, and conclusions, is entirely the authors' own. No AI tool was used to generate scientific content or perform any analysis.

Ethics Statement

Ethics approval was not required for this Letter to the Editor. No original research, patient data, animal experiments, or primary data collection was conducted by the authors. All arguments are based on critical analysis of previously published, peer-reviewed literature.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This letter does not contain any original data generated or analyzed by the authors. All data referenced in the text are derived from previously published, publicly available studies cited in the reference list.

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LETTER TO THE EDITOR

Case Report: Systemic Lupus Erythematosus Complicated by Chronic Nonbacterial Osteitis: A Rare Case Report and Mechanistic Insights

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Dear Editor,

A 40-year-old woman was admitted in July 2025 with a 3-month history of progressive neck and left hip pain. The pain was persistent, nocturnally aggravated, and unrelated to physical activity or positional changes. She denied fever, weight loss, recent trauma, livestock exposure, unpasteurized dairy intake, palmoplantar pustulosis, acne vulgaris, or psoriasis.

The patient had been diagnosed with systemic lupus erythematosus (SLE) 17 years earlier, with previous manifestations including cutaneous lupus, lupus nephritis, and Guillain–Barré syndrome. Both renal and neurological involvement responded well to initial glucocorticoids and hydroxychloroquine and remained in sustained remission; renal biopsy was never performed. Prior to maintenance therapy with low-dose prednisone (5 mg/day) and hydroxychloroquine (0.2 g/day), the patient experienced SLE flares limited to cutaneous involvement and received azathioprine and thalidomide accordingly. Importantly, the patient had no prior symptoms involving bones, tendons, or joints. On admission, her SLE Disease Activity Index 2000 (SLEDAI-2K) score was 0, indicating quiescent disease.

Laboratory investigations revealed markedly elevated inflammatory markers, including an erythrocyte sedimentation rate (ESR) of 120 mm/h and a C-reactive protein (CRP) concentration of 34.2 mg/L. Peripheral blood counts were largely normal. Autoimmune serology revealed a speckled antinuclear antibody pattern (1:100) and mildly elevated anti-β_2-glycoprotein I antibodies (29.97 RU/mL; normal range: <20 RU/mL), while anticardiolipin antibodies and lupus anticoagulant were negative; anti-double-stranded DNA antibodies and complement levels remained within normal ranges. To rigorously exclude antiphospholipid syndrome (APS), a repeat serological assay was performed 12 weeks later (October 2025), at which time the anti-β_2-glycoprotein I antibodies titer had returned to the normal range (15.1 RU/mL), thus failing to fulfill the 2023 ACR/EULAR APS classification criteria.

Magnetic resonance imaging demonstrated multifocal abnormal marrow signals involving the bilateral proximal femora, sacrum, cervical spine, and thoracic vertebrae (Figure 1A). ^{18}F-FDG PET/CT demonstrated extensive hypermetabolic bone lesions in the sternum, clavicle, sacrum, spine, and proximal femora (Figure 1B), raising concern for hematologic malignancy or metastatic disease.

A comprehensive infectious work-up, including T-SPOT.TB, Brucella serology, fungal biomarkers (galactomannan, 1,3-β-D-glucan, cryptococcal antigen), and nucleic acid testing for Epstein–Barr virus and cytomegalovirus, was negative. Bone marrow aspiration, lymphocyte immunophenotyping, and repeated histopathological examinations excluded lymphoma, leukemia, and metastatic malignancy. Sternal biopsy demonstrated sterile chronic inflammatory infiltrate, fibrous hyperplasia, and necrotic bone, without evidence of malignancy or infection (Figure 1C).

Chenglong Fang and Dongming Xu contributed equally to this work as co-corresponding authors.

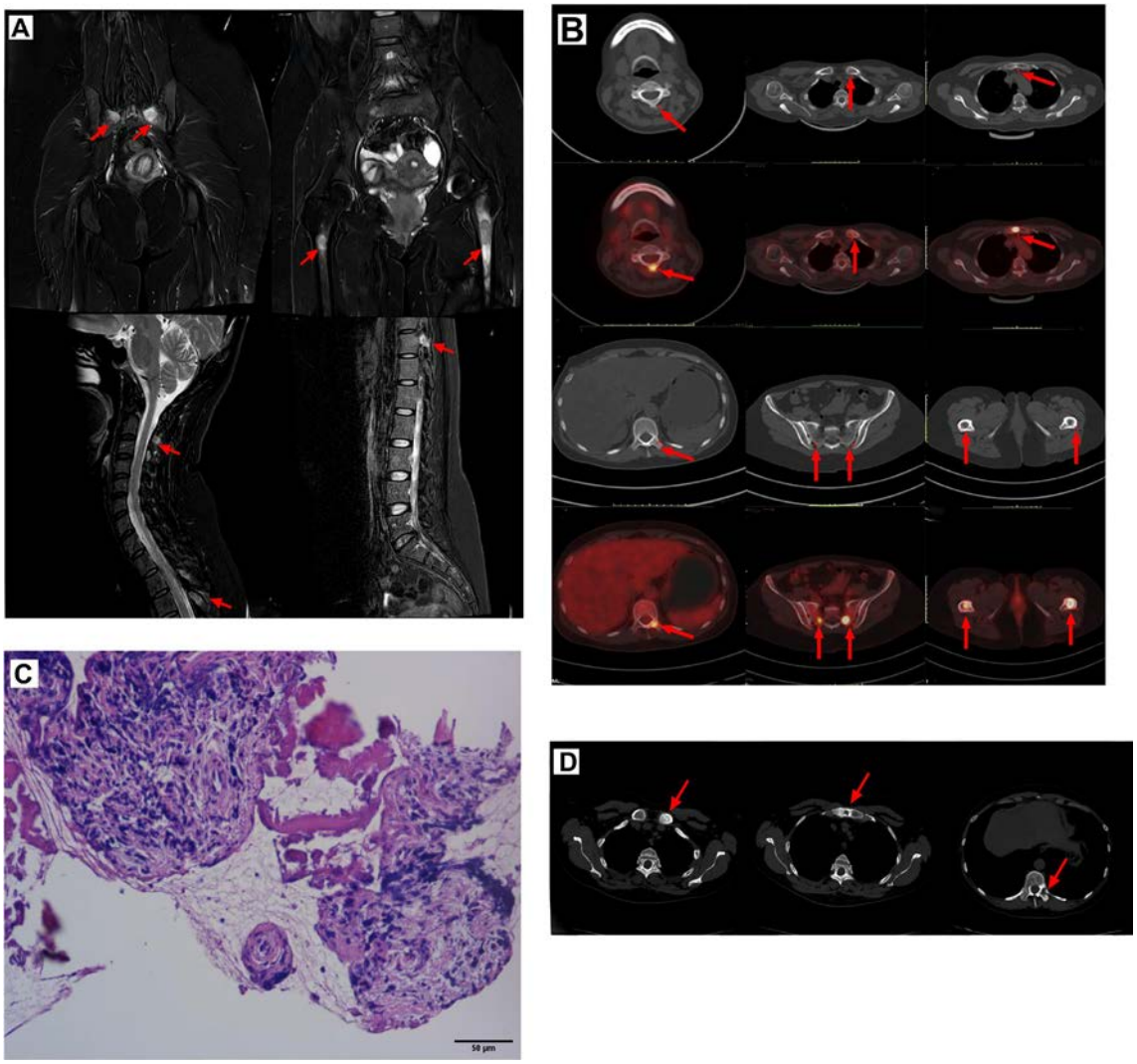

FIGURE 1 | (A) July 2025 T2-weighted fat-saturated (STIR) MRI shows bone marrow edema and osteolysis involving the bilateral proximal femora, sacrum, cervical spine, and thoracic vertebrae (arrows). (B) July 2025 PET-CT shows multifocal radiotracer uptake within the cervical spine, left proximal clavicle, manubrium sterni, thoracic vertebrae, sacrum, and bilateral proximal femora (arrows). (C) August 2025 sternal biopsy histopathology: Necrotic bone with fibrous hyperplasia and lymphocytic infiltration (H&E staining, ×200, scale bar = 50 μm). (D) January 2026 bone-window CT shows osteosclerosis accompanied by bone destruction in the left proximal clavicle, manubrium sterni, and T11 pedicle (arrows).

No anterior chest wall hyperostosis, a classic SAPHO-spectrum imaging feature, was observed on serial multimodal imaging. Serial multimodal imaging captured the characteristic evolution of lesions from bone marrow edema and osteolysis to osteosclerosis and structural destruction (Figure 1D), ultimately supporting the diagnosis of chronic nonbacterial osteitis (CNO). The diagnosis of CNO was formally established in accordance with the 2025 expert consensus recommendations [1], based on: (i) histopathologically confirmed sterile bone inflammation; (ii) multifocal skeletal involvement (anterior chest wall, spine, sacrum, proximal femurs); (iii) imaging evolution from marrow edema/osteolysis to osteosclerosis/destruction; and (iv) thorough exclusion of infection and malignancy.

The patient received sequential lines of treatment, accompanied by dynamic changes in inflammatory biomarkers and subjective pain intensity. The trends of ESR, CRP, and visual analogue scale (VAS) pain score across different therapeutic phases are summarized in Figure 2. She initially responded poorly to antibiotics (Moxifloxacin, Clindamycin), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and iguratimod. Subsequently, tofacitinib (5 mg twice daily) was added to low-dose prednisone (10 mg/day) and NSAIDs for 3 months, but failed to alleviate bone pain, and inflammatory markers rose further. Whole-exome sequencing identified three heterozygous variants in the proband: *MEFV* E148Q, *CFHR5*, and *CFTR*. Sanger segregation analysis revealed that the mother carried heterozygous variants in all three genes, whereas the father carried a homozygous *MEFV* E148Q variant and tested negative for *CFHR5* and *CFTR* variants. Because of progressive vertebral destruction and persistent inflammatory activity, therapy was escalated to high-dose prednisone (1.5 mg/kg/day) combined with adalimumab (40 mg once weekly) and methotrexate (10 mg once weekly), resulting in partial improvement. However, upon tapering prednisone to 15 mg/day, bone pain recurred and inflammatory markers increased; adalimumab 40 mg weekly was unable to maintain pain relief beyond 1 week. Consequently, zoledronic acid was added per the 2025 adult CNO consensus for its systemic dual anti-resorptive and

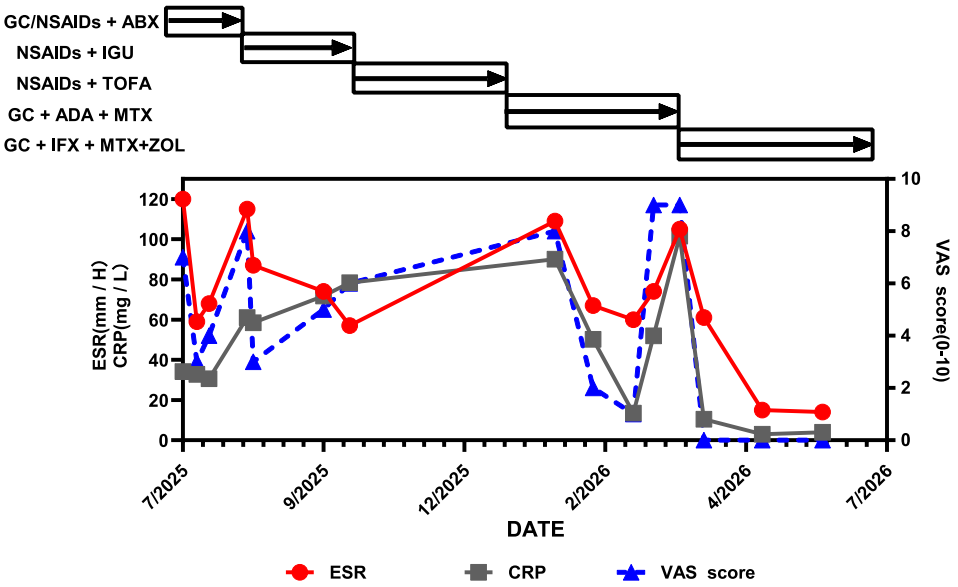

FIGURE 2 | Serial inflammatory biomarkers (ESR, CRP) and VAS pain scores across five sequential therapeutic stages: (1) Glucocorticoids (GC) + NSAIDs + antibiotics (ABX); (2) NSAIDs + iguratimod (IGU); (3) NSAIDs + tofacitinib (TOFA); (4) GC + adalimumab (ADA) + methotrexate (MTX); (5) GC + infliximab (IFX) + MTX + zoledronic acid (ZOL). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAS, visual analogue scale.

anti-inflammatory effects on multifocal skeletal lesions; prednisone was increased to 0.5 mg/kg/day, and adalimumab was switched to infliximab. Following therapy optimization, the patient achieved 3 months of sustained remission with complete pain control, with final inflammatory markers (ESR 13 mm/h, CRP 3.4 mg/L) returning to normal on maintenance prednisone 5 mg/day. No follow-up imaging was performed during this period, as clinical and laboratory remission was achieved.

CNO, a rare autoinflammatory bone disorder marked by sterile osteomyelitis, recurrent bone pain and radiologically evident inflammatory bone destruction [1, 2], arises mainly from innate immune activation via inflammasome signaling and proinflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α [3]. Although SLE is classically regarded as an adaptive immune-mediated disorder, emerging studies reveal extensive crosstalk between adaptive and innate immune cascades in lupus pathogenesis. Type I interferon (IFN) signaling and inflammasome activity are particularly involved in this interplay [4, 5]. This case illustrates that concomitant SLE and CNO supports the concept of an overlapping autoimmune-autoinflammatory disease spectrum.

Of particular interest was the heterozygous *MEFV* E148Q variant. E148Q is a low-penetrance, gain-of-function polymorphism rather than a monogenic mutation. Its carrier rate reaches up to 45.61% in the Chinese Han population, whereas classical high-penetrance *MEFV* mutations are extremely rare [6]. Functional studies show that E148Q potentiates pyrin inflammasome formation and in vitro IL-1β and IL-18 secretion [7]. This may partially explain why our patient did not present typical familial Mediterranean fever (FMF) manifestations while still possessing a lowered inflammasome activation threshold. Notably, *MEFV* mutations have been associated with earlier onset, more extensive bone lesions, and higher inflammatory burden in CNO cohorts [8]. In lupus models, E148Q may downregulate anti-double-stranded DNA antibody production, reduce memory B cells, and attenuate renal pathology [9]. We speculate that this immunological skewing toward innate immunity may simultaneously attenuate adaptive autoimmune features of SLE while increasing susceptibility to localized, innate-mediated bone tissue destruction, such as CNO.

To explain this phenotype, we hypothesize a two-hit pathogenic model. In our patient, chronic low-grade innate immune priming inherent to SLE served as the indispensable "Hit one" (even with a SLEDAI-2K score of 0). Prolonged Type I IFN exposure primes monocytes for enhanced inflammasome activation by upregulating the baseline expression of pyrin and its molecular adaptors [10], creating a permissive inflammatory background even during clinical remission. Superimposed on this was "Hit two", the E148Q gain-of-function variant that further lowers the pyrin inflammasome threshold, yielding a hyper-responsive state. In this context, subclinical stimuli, such as mechanical stress at skeletal entheses, may trigger overproduction of IL-1β and IL-18, which could ultimately induce sterile osteitis in this patient.

Differentiating CNO from osteonecrosis is critical in SLE. Long-term glucocorticoid therapy and antiphospholipid antibody raise the risk of osteonecrosis [11, 12], which typically appears as well-demarcated epiphyseal/diaphyseal lesions with serpiginous T1-hypointense rims and a T2 double-line sign [13, 14]. Extensive sternal, clavicular, and axial involvement is highly atypical for osteonecrosis [15, 16]. In our case, multifocal ill-defined bone lesions were distributed across the axial skeleton and bilateral proximal femora, with none of the typical osteonecrosis imaging signs identified on MRI (Figure 1A). The proximal femora showed mixed iso- to slightly hyperintense T1WI signals and heterogeneous T2WI signals, whereas vertebral appendages and sacrum presented diffuse patchy hyperintensity on fat-saturated T2WI. The patient only had transient low-titer anti-β_2-glycoprotein I antibodies without persistent seropositivity to predispose osteonecrosis, and serial imaging demonstrated the characteristic inflammatory-to-sclerotic transition of CNO. Sternal histology confirmed sterile

inflammation. Exhaustive work-up excluded infection and malignancy, confirming the diagnosis of CNO.

SAPHO syndrome lies within the CNO disease spectrum. The patient had no cutaneous SAPHO manifestations (palmoplantar pustulosis, acne, psoriasis), and serial imaging excluded anterior chest wall hyperostosis, consistent with isolated CNO.

The therapeutic course is further consistent with a paradigm of innate-immune dominance. The JAK inhibitor tofacitinib, a Type I IFN signaling blocker, showed limited efficacy over 3 months of treatment, suggesting that established bone lesions may become less reliant on IFN-mediated inflammation in this patient. Established sterile osteitis appears autonomously driven by a local IL-6 and TNF-α feed-forward loop [3]. Accordingly, TNF-α blockade with infliximab induced substantial and sustained improvement, consistent with current evidence for anti-TNF therapies in refractory CNO [1, 2]. By interrupting the terminal TNF-α/RANKL osteoclastogenic axis, infliximab provided a mechanistic resolution of osteolytic destruction [17, 18].

Single-case design, lack of functional validation for the *MEFV* E148Q variant, and limited 3-month follow-up without serial imaging restrict causal inference between SLE and CNO and long-term skeletal outcome prediction; the two-hit mechanistic hypothesis requires further validation.

This case offers a key clinical lesson: in patients with longstanding, quiescent SLE and persistent bone pain and elevated inflammatory markers, bone symptoms should not be readily attributed to lupus flares or glucocorticoid-induced osteonecrosis. After excluding infection and malignancy, CNO merits high differential priority. Early whole-body MRI or PET/CT enables timely diagnosis and avoids therapeutic delays. Multimodal imaging reliably distinguishes CNO from SLE-related bone infarction. Clinicians must recognize autoinflammatory-autoimmune overlap in SLE to deliver prompt, targeted therapy.

Author Contributions

Longchuan Xu drafted the initial version of this case report. Chenglong Fang and Zhen Chen participated in the design of this study and revised the manuscript. Dongming Xu guided the article and provided ideas. All authors contributed to the preparation of the manuscript. All authors read and approved the final manuscript.

Ethics Statement

This work complies with the ethical standards of the institutional research committee.

Consent

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

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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EDITORIAL

Beyond Vasodilation: Sotatercept and the Dawn of Disease Modification in Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

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1 | Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive, life-threatening condition marked by elevated pulmonary artery (PA) pressure, right ventricle (RV) failure, and eventual death if untreated [1, 2]. The pathogenesis of Connective Tissue Diseases (CTD)-PAH is complex and multifactorial. Inflammatory mediators and oxidative stress drive proliferation of endothelial and smooth muscle cells, leading to fibrosis and vascular occlusion. Systemic sclerosis (SSc) may cause PAH as well as other pulmonary hypertension forms, including those secondary to left heart dysfunction, interstitial lung disease (ILD), or pulmonary veno-occlusive disease. In SSc-PAH, vascular lesions are predominantly fibrotic with intimal thickening and venular involvement, while plexiform lesions are rare. In contrast, systemic lupus erythematosus (SLE)-PAH shows more inflammatory and immune-complex mediated vasculitis resembling idiopathic PAH. Autoantibodies targeting endothelial, smooth muscle, and fibroblast antigens contribute to endothelial injury and vascular remodeling. A persistent challenge in CTD-PAH management is addressing cases where multiple PAH groups coexist, complicating diagnosis, treatment selection, and prognosis [3].

2 | Overview of Existing Pulmonary Arterial Hypertension Therapies: Conventional Therapies

Endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, and prostacyclin analogues had each formed the cornerstone of PAH management by targeting distinct yet complementary aspects of its pathophysiology: vasoconstriction, impaired nitric oxide signaling, and deficient prostacyclin activity, respectively. ERAs act by antagonizing endothelin receptors to relieve vasoconstriction and protect the endothelium from further injury. Meanwhile, PDE5 inhibitors restore the nitric oxide–cyclic guanosine monophosphate (GMP) axis, which was dysfunctional in PAH, thereby promoting pulmonary vasodilation. Prostacyclin analogues (epoprostenol) and prostacyclin receptor agonist (selexipag) act as potent vasodilators and antiplatelet agents, compensating for the reduced endogenous prostacyclin in PAH. Besides, the phase 2 INSIGNIA-PAH trial evaluated the inhaled soluble guanylate cyclase (sGC) stimulator MK-5475. Participants received placebo or MK-5475 (32 μg, 100 μg, or 380 μg) once daily for 12 weeks. MK-5475 at 100 μg and 380 μg significantly reduced pulmonary vascular resistance (PVR) (−22.0% and −19.9% vs. placebo) without meaningful systemic effects such

Chi-Yen Wang and Po-Cheng Shih have equal contributions to this article.

as hypotension, suggesting pulmonary-selective vasodilation [4].

3 | Sotatercept: A New Treatment Strategy for Pulmonary Arterial Hypertension in Patients With Connective Tissue Diseases

Sotatercept, a novel Fc-fusion protein, presents a promising treatment option by targeting the transforming growth factor beta (TGF-β) superfamily, which plays a key role in pulmonary vascular remodeling [5]. Multiple phase III trials may have established the effect and safety of sotatercept as an add-on therapy for PAH, including among patients with CTD-PAH. In the ZENITH [1] trial, Humbert et al. randomized high-risk PAH patients already on optimal background therapy to receive sotatercept or placebo. Sotatercept significantly reduced the composite endpoint of death, lung transplantation, or hospitalization by 76%, while also improving overall survival, transplant-free survival, and WHO functional class. In this trial, 22 patients (25.6%) in the sotatercept group and 26 (30.2%) in the placebo group had CTD-PAH, and sotatercept was associated with a lower risk of adverse outcomes. The STELLAR [6] trial further confirmed sotatercept's benefits in patients with WHO functional class II and III PAH; among 163 patients treated with sotatercept and 160 receiving placebo, those in the sotatercept group showed improved exercise capacity. Of these, 29 (17.8%) in the sotatercept group and 19 (11.9%) in the placebo group had CTD-PAH, with sotatercept significantly enhancing 6-min walk distance (6MWD). A detailed haemodynamic analysis by Souza et al. revealed improvements in PA pressure, PA compliance, and RV-PA coupling, alongside reductions in tricuspid regurgitation and cardiac workload [7]. In the open-label SOTERIA study [8], which included 426 patients treated for up to 64 weeks (mean 448.6 days), sotatercept led to sustained gains in 6MWD and reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP), with 51 patients (19.7%) in the sotatercept group and 16 (11.2%) in the prior-placebo group had CTD-PAH. Although CTD-PAH subgroup analyses suggested potential clinical benefits of sotatercept, these studies were primarily powered for the overall PAH population rather than CTD-PAH-specific analyses. Subgroup findings should be interpreted cautiously and require confirmation in dedicated CTD-PAH studies. As shown in Table 1, the phase III clinical trials for PAH highlighted the therapeutic benefits of sotatercept. However, its safety profile required close monitoring. Humbert et al. reported that the most common side effects were epistaxis and telangiectasia [1]. Similarly, Hoeper et al. noted additional adverse events, such as dizziness, increased hemoglobin, thrombocytopenia, and elevated blood pressure [6]. Additionally, Preston et al. found that epistaxis (22.1%) and telangiectasia (16.9%) were the most commonly observed adverse events [8]. Case series of PAH patients receiving sotatercept reported new or enlarging pericardial effusions [9, 10]. Pericardial effusions warrant monitoring in CTD-PAH patients; however, causality remains unproven, and the overall benefit–risk profile of sotatercept appears favorable. CTD-PAH patients may require closer monitoring of hematologic parameters, blood pressure, bleeding events, and pericardial complications during sotatercept therapy.

4 | Comparing the Effectiveness of Sotatercept and Conventional Therapies in Patients With Connective Tissue Disease-Associated Pulmonary Arterial Hypertension

Previous studies aimed to determine whether combination therapy may lead to better overall outcomes in PAH patients with cardiac comorbidities. McLaughlin et al. demonstrated favorable effects of initial macitentan–tadalafil therapy on hemodynamic and functional outcomes in PAH patients with one to two cardiac comorbidities. Nevertheless, given the post hoc nature of the analysis and the absence of statistical power for mortality assessment, survival implications remain uncertain [13]. Likewise, White et al., in the TRIUMPH and FREEDOM-EV trials, reported that combination therapy with inhaled or oral treprostinil offered potential benefits for patients with PAH and cardiovascular comorbidities. Yet, these treatments also failed to demonstrate a meaningful improvement in overall survival [14]. Moutchia et al. found combination therapy targeting endothelin and nitric oxide pathways reduced mortality, but short 12–16-week follow-up limited certainty [15].

Sotatercept represents a novel approach to treating PAH by targeting the activin signaling pathway, a key driver of vascular remodeling in the disease. This mechanism may be especially relevant in CTD-PAH, where inflammation and fibrosis are more pronounced than in idiopathic forms. Unlike conventional therapies that primarily offer symptom relief, sotatercept has the potential to alter disease progression and improve long-term prognosis. While existing combination therapies, such as macitentan and tadalafil, had shown benefits in improving hemodynamic measures, their impact on overall survival remains unclear. Furthermore, some conventional combination treatments had been associated with adverse events, underscoring the need for safer and more effective alternatives. Sotatercept is currently best viewed as an add-on to optimized PAH therapy. In CTD-PAH, immunosuppression should be optimized when indicated, while sotatercept targets vascular remodeling beyond conventional vasodilatory pathways.

5 | Current Limitations

The limitations of current trials on sotatercept include a relatively small sample size and a short follow-up duration [1, 6, 7]. Most studies include fewer than 500 participants, which potentially limits generalizability to the broader PAH population. Additionally, the median follow-up period in these trials ranges from 12 to 24 weeks, which is not long enough to evaluate the long-term effects of sotatercept.

Current trials target a broad Group 1 PAH population, limiting applicability to SSc-PAH with ILD. Because real-world CTD patients frequently display overlapping ILD physiology often excluded from randomized controlled trials, evidence for sotatercept across ILD severity remains insufficient [1, 7]. Most pivotal sotatercept trials have predominantly enrolled patients with WHO functional class II/III or higher-risk profiles without evaluating its efficacy and safety in early-stage CTD-PAH.

TABLE 1 | Summary of Phase III clinical trial for pulmonary arterial hypertension.

Author	Participants	Drug (dose)	Period	Duration (weeks)	Age (mean ± SD) years	Female (%)	Study name	Location/centers	Key result summary	Design	Phase	Level of evidence
Humbert M. et al. 2025 [1]	172	Sotatercept 0.3–0.7 mg/kg	Dec 1, 2021–Jul 26, 2024	24	54.4 ± 14.3	132 (76.7%)	ZENITH	Multicenter	Lower risk of death, lung transplant, hospitalization	RCT	III	Level I
Hoeper M.M. et al. 2023 [6]	323	Sotatercept 0.3–0.7 mg/kg	Feb 16, 2021–Aug 26, 2022	24	47.9 ± 14.8	256 (79.3%)	STELLAR	Multicenter	Improved 6MWD	RCT	III	Level I
Souza R. et al. 2023 [7]	323	Sotatercept 0.3–0.7 mg/kg	Feb 16, 2021–Aug 26, 2022	24	47.9 ± 14.8	256 (79.3%)	STELLAR	Multicenter	↓ PA pressures, ↑ PA compliance, PA–RV coupling, right heart function	RCT	III	Level I
Preston I.R. et al. 2025 [8]	426	Sotatercept ≤0.7 mg/kg Q3W	Until Nov 8, 2023	64	49.4 ± 14.7	348 (81.7%)	SOTERIA	—	↑ 6MWD, ↓ NT-proBNP	Open-label	III	Level II
Galiè N. et al. 2015 [11]	500	Ambrisentan 10 mg + Tadalafil 40 mg	Oct 18, 2010–Jul 31, 2014	24	54.35 ± 14.62	388 (77.6%)	AMBITION	120 centers, 14 countries	↑ 6MWD	RCT	III–IV	Level I
Grünig E. et al. 2024 [12]	187	Macitentan 10 mg + Tadalafil 40 mg	Oct 15, 2019–Aug 23, 2022	16	≥ 18 years	—	DUE	Multicenter	↓ PVR with combination therapy	RCT	III	Level I

Abbreviations: "↑", increase; "↓", decrease; 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; PVR, pulmonary vascular resistance; RCT, randomized controlled study; RV, right ventricular.

6 | Future Research Directions

We suggest primarily enrolling patients with SSc-PAH, while allowing secondary subgroups such as SLE-, Mixed connective tissue disease-, and Rheumatoid arthritis-associated PAH. ILD stratification should be predefined using High-resolution computed tomography (HRCT)-based quantification combined with pulmonary function thresholds (forced vital capacity, FVC%) and Diffusing capacity of the lung for carbon monoxide (DLCO), such as $<45\%$, 45%–60%, $\geq 60\%$ to classify mild, moderate, and extensive disease. A multinational, multicenter, double-blind, placebo-controlled trial comparing sotatercept added to standard of care (SOC) versus continued SOC should stratify patients by CTD subtype (SSc vs. non-SSc), ILD severity, REVEAL Lite 2 risk category, and background therapy intensity (dual vs. triple therapy) [1, 8].

A dedicated CTD-PAH subgroup will likely be required to achieve adequate event rates and statistical power, rather than extrapolating from overall PAH cohorts [16]. Alternatively, a CTD-enriched enrollment strategy ($\geq 40\%$–50%) should be adopted. A real-world prospective registry should include patients with SSc-PAH and ILD overlap, those receiving intensive immunosuppression [17], or individuals at elevated bleeding risk. DLCO, FVC, and quantitative HRCT-based ILD assessments are essential to differentiate pure Group 1 physiology from Group 1/3 overlap. Musculoskeletal and skin involvement scores should also be monitored for their impact on 6MWD. In addition, autoantibody profiles (e.g., anti-centromere, anti-Scl-70, U1-RNP) and inflammatory or fibrotic biomarkers should also be incorporated for improving phenotypic characterization.

7 | Conclusion

Sotatercept shows great promise in personalized PAH treatment by targeting pulmonary vascular remodeling, especially in high-risk patients. Its ability to tailor therapy based on individual responses, along with the identification of relevant biomarkers, could improve patient outcomes and boost long-term survival. Many groups will need to work together to ensure Sotatercept is widely available. Collaboration among patients, clinicians, insurers, and policymakers will be key to fully realizing its clinical benefits and enhancing healthcare outcomes for PAH patients.

Author Contributions

Conceptualization: S.-T.S., C.-Y.W., and P.-C.S. Methodology: S.-T.S. Software: S.-T.S. Validation: C.-Y.W. and P.-C.S. Formal analysis: P.-C.S. Investigation: P.-C.S. Resources: P.-C.S. Data curation: P.-C.S. Writing – original draft: S.-T.S. Writing – review and editing: S.-T.S. Visualization: S.-T.S. Supervision: C.-Y.W. Project administration. C.-Y.W. Funding acquisition: None. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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EDITORIAL

Beyond the Genetic "Silver Bullet": The Complex Reality of Precision Rheumatology

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The allure of precision medicine in rheumatology has long been centered on the "genetic switch"—the hope that a simple germline marker could direct clinicians to the perfect biologic, sparing patients months of trial-and-error. However, the recent study by Yap et al. [1] in *Arthritis & Rheumatology* serves as a necessary reality check. Investigating the well-known HLA-DRB1 Shared Epitope (SE) and Valine at position 11, the authors found no significant evidence that these systemic markers could differentiate response between abatacept and adalimumab.

Does this negative result signal the failure of precision rheumatology? Far from it. A survey of recent literature in the *International Journal of Rheumatic Diseases* (2025–2026) reveals that the field is simply maturing. Unlike existing reviews that broadly catalog genomic advancements, this commentary specifically highlights the critical transition from static germline markers to a dynamic, multimodal framework integrating tissue-specific biology, biomechanics, and imaging. Furthermore, to ensure conceptual clarity, we use the term "precision medicine" throughout this manuscript to denote the overarching paradigm of tailored care, which relies on accurate "patient stratification" based on shared pathophysiological mechanisms, rather than mere symptomatic interventions. It is important to note, however, that while these emerging multimodal approaches show great promise, many of the current studies are limited by small sample sizes, cross-sectional designs, and a lack of external validation across diverse populations. Moving forward, larger, prospective cohorts will be necessary to confirm the clinical utility of these novel markers.

1 | From Blood to Tissue: The Synovial Signature

If systemic DNA is the blueprint, the synovium is the active construction site. The failure of germline markers like the Shared Epitope to predict specific drug responses suggests we are looking in the wrong place. Recent work published in the International Journal of Rheumatic Diseases highlights the power of shifting focus to the target organ. The expression of specific gene signatures like BHLHE40 in synovial $CD4^+$ T cells has been identified as a potential marker for rheumatoid arthritis phenotypes [2]. This offers a level of granularity that systemic markers cannot match, reinforcing that the precision we seek is likely hidden in the cellular dynamics of the joint itself rather than in the patient's static genetic code. Nevertheless, the feasibility of incorporating synovial tissue analysis into routine clinical practice remains uncertain. Significant barriers, including limited tissue accessibility, the lack of standardized sampling procedures, and high procedural costs, must be addressed before synovial biopsies can be widely adopted for everyday patient stratification.

2 | The Mechanical Phenotype

Precision medicine is frequently conflated with molecular medicine. However, comprehensive patient stratification must also integrate physical and mechanical phenotypes. Guan and Mei [3] recently published a pivotal review linking biomechanics and obesity to osteoarthritis mechanisms. They advocate for

an approach that evaluates mechanical load alongside biological inflammation. This holistic view is crucial. Distinguishing a patient whose disease is primarily driven by mechanical stress from one driven by autoimmune inflammation is essential. Clinically, identifying a dominant mechanical phenotype could redirect management from escalating immunosuppressive therapies to targeted interventions such as weight reduction, gait correction, or specific joint-loading modifications.

3 | Precision Diagnostics: Imaging Meets Biology

The integration of imaging with serology represents another leap forward. Zong et al. [4] demonstrated in a cross-sectional study of 120 patients that combining musculoskeletal ultrasound (MSUS) with serum markers like HIF-1α and COX-2 significantly optimizes the diagnosis of acute gouty arthritis. This multimodal approach—using imaging to confirm the anatomical "where" and biomarkers to confirm the metabolic "what"—exemplifies the practical application of precision medicine in daily practice. Importantly, the utility of this combined approach may extend well beyond diagnostic stratification. Characterizing baseline metabolic and structural alterations can potentially inform initial treatment selection and serve as a sensitive baseline for prognostic assessment and the longitudinal monitoring of therapeutic efficacy.

4 | Real-World Evidence, Environment, and Consensus

Our understanding of patient stratification must also account for environmental exposures that reshape the immune baseline. Su et al. [5] provided compelling evidence regarding the impact of SARS-CoV-2 infection on autoimmune risk, adding another layer to our precision algorithms. Finally, while we search for novel biomarkers, we must rely on rigorous real-world data and regionally adapted standards. The publication of the Taiwan College of Rheumatology Consensus for the Management of Systemic Lupus Erythematosus by Huang et al. [6] represents a major step forward. By adapting international guidelines to local clinical realities, this document ensures that precision does not come at the cost of standardized, high-quality baseline care.

5 | Conclusion

The study by Yap et al. [1] saves us from a clinical dead end by confirming that HLA-DRB1 is likely not the deciding factor for abatacept versus adalimumab selection. However, as the pages of the International Journal of Rheumatic Diseases demonstrate, the path forward is rich with potential. Whether through synovial gene signatures, biomechanical profiling, or updated consensus frameworks, precision rheumatology is evolving from a hunt for a single genetic "silver bullet" into a disciplined, multifaceted science. Moving forward, the critical priority for the next phase of precision rheumatology must be the integration of these multimodal datasets into accessible, clinically usable decision-support tools. The incorporation of machine learning and artificial intelligence will likely play an essential role in processing this complex, multi-dimensional data, ultimately guiding tailored therapeutic decision-making in routine clinical practice.

Author Contributions

Tang-Kai Cheng and James Cheng-Chung Wei contributed to the conception and design of this work. Tang-Kai Cheng conducted the literature review and drafted the initial manuscript. James Cheng-Chung Wei provided critical revisions for important intellectual content and supervised the project. Both authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Case Report: When Lupus Is Not Primary—Paraneoplastic Systemic Lupus Erythematosus Associated With a Duodenal Neuroendocrine Tumor

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Dear Editor,

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by heterogeneity, which can present with various clinical manifestations and is associated with multiorgan involvement [1]. Although it is often described as the "great mimicker" due to this characteristic, certain diseases can rarely mimic SLE, and sometimes SLE can be a paraneoplastic manifestation of a malignancy. We present a case with atypical features that prompted further evaluation, initially considered as isolated SLE but ultimately diagnosed with malignancy, which we believe offers important clinical insights.

A male patient in his late 60s with no medical history presented with swelling of the wrists and metacarpophalangeal (MCP) joints, which had been present for approximately 5 weeks. He reported a 6-month history of weakness predominantly affecting the distal upper and lower extremities, accompanied by significant functional limitation, and complained of numbness in both hands. Additionally, he had constitutional symptoms, which included an unintentional weight loss of approximately 10 kg over the past year and low-grade fever. He did not report Raynaud's phenomenon, oral aphthae, rash, or photosensitivity.

Physical examination demonstrated bilateral second and third MCP joints and wrist arthritis and motor weakness, more pronounced in distal muscle groups. No skin rash was observed, and basal lung crackles were heard at the lung bases. On admission, laboratory investigations revealed cytopenias, including anemia (hemoglobin 11.9 g/dL), leukopenia (1800/μL), lymphopenia (380/μL), and thrombocytopenia (98 000/μL), together with a positive direct Coombs test. Serum creatinine and liver enzyme levels were within normal limits. Immunological tests showed antinuclear antibody (ANA) positivity at a titer of 1:320, anti–double-stranded DNA (anti-dsDNA) antibodies were positive at 90 IU/mL (positive cut-off: ≥ 20 IU/mL), as measured by chemiluminescent immunoassay, and the ANA immunoblot panel showed weak positivity for anti-nucleosome antibodies. Rheumatoid factor, anti–cyclic citrullinated peptide antibodies were negative, and complement levels were normal. Acute phase reactants were elevated, with a C-reactive protein (CRP) level of 24 mg/L (reference range: 0–5 mg/L) and an erythrocyte sedimentation rate (ESR) of 80 mm/h. Serological tests for parvovirus B19, hepatitis A, B, and C, EBV, and HIV were negative, making viral causes of acute arthritis unlikely. Urinalysis was unremarkable.

Thoracic computed tomography (CT) demonstrated interstitial lung disease with a nonspecific interstitial pneumonia pattern. Electrophysiological studies revealed findings consistent with a sensorimotor axonal polyneuropathy. Nerve conduction studies showed mildly reduced amplitudes and slowed conduction velocities, particularly in the tibial and median nerves, with absent bilateral sural responses. These findings were interpreted as compatible with axonal degeneration affecting both sensory and motor fibers.

Based on the combination of clinical, serological, and imaging findings, the patient was diagnosed with SLE accompanied by sensorimotor axonal polyneuropathy. The patient was started on 20 mg of prednisolone and his rheumatic joint symptoms improved within a few days. On follow-up examination, a firm, mobile, non-tender nodular lesion measuring approximately

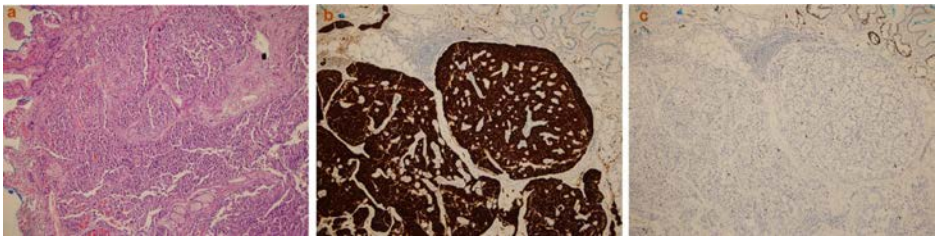

FIGURE 1 | Histopathological and immunohistochemical findings of the duodenal neuroendocrine tumor. (a) Tumoral lesion located in the subepithelial area interspersed among duodenal glandular structures (×100 H&E). (b) Immunohistochemical analysis demonstrates diffuse and strong Synaptophysin expression in tumoral cells (×100). (c) Immunohistochemical staining with Ki-67 demonstrates sparse positivity in tumor cells as well as in some intermixed inflammatory cells. The proliferative index in tumor cells is calculated as 1% in the area of highest labeling (×100).

1.5 cm in diameter was detected in the left supraclavicular region. Superficial ultrasonography suggested a lipomatous lesion; however, given the patient's history of weight loss, endoscopic evaluation was planned to investigate possible gastrointestinal malignancy. Endoscopic examination identified a duodenal lesion described as a "bulbus polyp," and a biopsy was performed. Histopathological analysis revealed a well-differentiated neuroendocrine tumor (NET), Grade 1, measuring approximately 0.7 cm in diameter. The tumor exhibited submucosal infiltration, with a low mitotic index (1 mitosis per 10 high-power fields) and a Ki-67 proliferation index below 1%. Immunohistochemical staining demonstrated positivity for pancytokeratin, chromogranin A, synaptophysin, and INSM1, confirming the diagnosis (Figure 1).

Given the low-grade nature of the neuroendocrine tumor and its small size, surgical management was considered. The patient was referred for multidisciplinary evaluation involving gastroenterology, oncology, and surgery. The patient subsequently underwent a Whipple procedure. Corticosteroid therapy was gradually tapered and discontinued within 3 months after surgery. At the 6-month follow-up, there was no recurrence of arthritis, cytopenias had resolved, and anti-dsDNA antibody titers had become negative. Close follow-up was planned to monitor both the clinical course of SLE and the behavior of the tumor.

Paraneoplastic SLE is a rare condition. In the literature, cases have been reported in association with colorectal carcinoma, dysgerminoma, cholangiocarcinoma, papillary thyroid carcinoma, oat cell lung cancer, and thymoma [2–7]. However, paraneoplastic SLE secondary to a neuroendocrine tumor has not been reported so far. Our case appears to be the first in this regard. In addition, the localization of the neuroendocrine tumor to the duodenum, which is itself uncommon [8], further adds to the rarity and distinctiveness of this case.

This case highlights several important clinical points. First, although SLE is known for its wide range of clinical presentations, it should also be kept in mind that it may rarely present as a paraneoplastic syndrome. Second, the presence of significant weight loss and atypical neurological findings should prompt a thorough evaluation for underlying malignancy. Third, given that the coexistence of SLE and malignancy is uncommon, further case series and studies are needed to better understand the pathogenesis of paraneoplastic SLE.

In conclusion, this case underscores the importance of a careful and systematic approach to systemic autoimmune diseases presenting with atypical features. Early recognition of concurrent malignancy may have been crucial for survival.

Author Contributions

Y.E.D. contributed to data collection, editing, and writing of the original draft. E.K. contributed to the provision and evaluation of the pathological images and reviewed the manuscript. M.Ç. reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Funding

The authors have nothing to report.

Consent

The study was carried out in line with the Declaration of Helsinki. Written informed consent was obtained from the patient and any accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Available upon reasonable request.

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LETTER TO THE EDITOR

Case Report: Fulminant Pediatric Vascular Behçet Disease Presenting With Budd–Chiari Syndrome and Extensive Multivessel Venous Thrombosis

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Dear Editor,

Behçet disease (BD) is a chronic, relapsing, variable-vessel vasculitis in which vascular involvement, predominantly venous thrombosis, is among the most severe manifestations and occurs mainly in young males [1]. Juvenile-onset disease is rarer, is frequently incomplete at presentation, and has a broad differential diagnosis, so classification criteria are often satisfied only late in the course [2]. Thrombosis in children is correspondingly uncommon, documented in 37 of 254 children in the EUROFEVER registry [3] and in 15 of 85 in a single-center cohort [4]. Budd–Chiari syndrome (BCS), defined by hepatic venous outflow obstruction, is a rare but particularly severe vascular phenotype of BD, for which the literature remains limited; pediatric evidence is particularly sparse, with a 2025 review retrieving only 17 sufficiently detailed pediatric thrombotic cases [5–8]. We report a fatal, treatment-refractory case addressing three questions that current guidance leaves unanswered: how extensive an inaugural thrombus burden can be in pediatric BD; how tuberculosis-oriented diagnostic anchoring in an endemic region delays both recognition and biologic escalation; and how the absence of a BD-specific protocol for BCS translates into bedside decisions.

A previously healthy 16-year-old male presented with a 3-month history of intermittent fever, night sweats, anorexia, weight loss, abdominal distension, and progressive ascites. On examination he appeared ill, with marked ascites, hepatomegaly, and peripheral edema. Initial investigations showed prominent systemic inflammation, anemia, thrombocytosis, and hypoalbuminemia, with later progressive liver dysfunction and coagulopathy. Because the tuberculin skin test measured 20 mm and constitutional symptoms predominated, extrapulmonary tuberculosis was the initial working diagnosis at the referring center, and empirical anti-tuberculous therapy was begun. However, the infectious work-up was consistently negative: thoracic computed tomography (CT) showed only nonspecific ground-glass opacity and, on repeat imaging, bilateral pleural effusion without active infiltrative or nodal disease; serial sputum, peritoneal fluid, pleural, and tissue mycobacterial smears and polymerase chain reaction assays, together with repeated blood, urine, and fluid cultures, were negative; an interferon-gamma release assay was negative; paracentesis and diagnostic laparotomy yielded transudative fluid with normal adenosine deaminase activity and no growth, and peritoneal and omental biopsies were unsupportive of tuberculous peritonitis.

During follow-up he deteriorated abruptly, with severe abdominal pain, worsening edema, acute kidney injury, rising transaminases, hyperbilirubinemia, prolonged international normalized ratio, and oliguria. Doppler ultrasonography and contrast-enhanced CT angiography demonstrated occlusion of the hepatic veins and of the entire intrahepatic and infrahepatic inferior vena cava up to the right atrial junction, together with occlusion of the right common and external iliac and right common, deep, and superficial femoral veins, occlusion of the left common and external iliac veins, and diffuse wall thickening of the patent left common femoral and great saphenous veins, in keeping with vasculitic involvement (Figure 1). Hepatomegaly with heterogeneous parenchyma, periportal edema, and absent

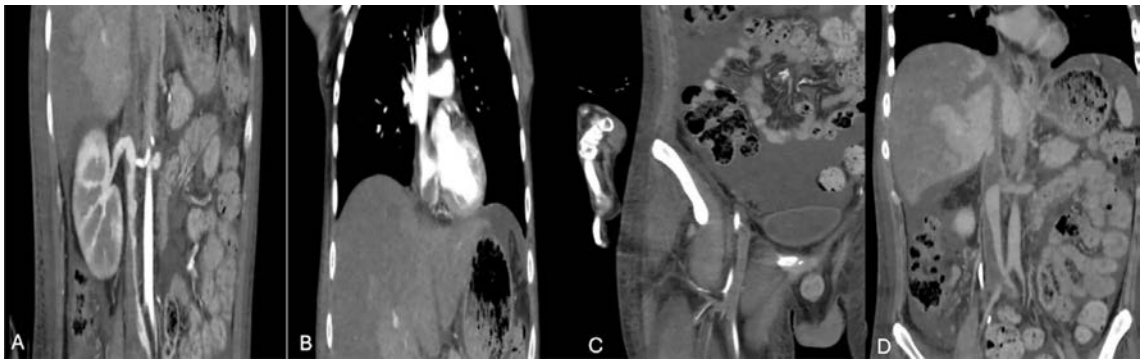

FIGURE 1 | Contrast-enhanced computed tomography angiography obtained 17 days after thrombosis was first detected on Doppler ultrasonography. (A) Extensive hypodense intraluminal filling defect occupying the infrahepatic inferior vena cava, consistent with complete occlusion. (B) Cranial extension of the thrombus through the intrahepatic inferior vena cava to the cavo-atrial junction and right atrium, with heterogeneous enhancement of the enlarged liver. (C) Bilateral common and external iliac vein occlusion with diffuse circumferential venous wall thickening of the femoral veins, in keeping with vasculitic involvement. (D) Hepatomegaly with heterogeneous, patchy hepatic parenchymal enhancement and perihepatic ascites, the parenchymal correlate of hepatic venous outflow obstruction.

hepatic venous flow confirmed BCS, whereas the portal venous system remained patent. Echocardiography showed a 12 × 7 mm thrombus at the cavo-atrial junction without valvular vegetation. Brain magnetic resonance imaging with diffusion-weighted and susceptibility-weighted sequences revealed no parenchymal, venous sinus, or hemorrhagic lesion, excluding neuro-Behçet involvement and supporting a hepatic origin for the intermittent encephalopathy.

Given the disproportionate thrombotic burden, a structured thrombophilia, autoimmune, and genetic evaluation was undertaken (Table 1). Antiphospholipid, anticardiolipin, and anti-β2-glycoprotein I antibodies, antinuclear antibody, anti-double-stranded DNA, antineutrophil cytoplasmic antibodies, and lupus anticoagulant were negative, and factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase genotyping were normal, as were hemoglobin electrophoresis, lipoprotein(a), and ADAMTS13 activity. Homocysteine was only mildly elevated. Reductions in protein C, protein S, antithrombin III, and several coagulation factors (V, VII, IX, X, XI, and XII) were observed but were interpreted with caution, as they were obtained during active thrombosis, hepatic dysfunction, and critical illness, and were therefore most consistent with impaired hepatic synthesis rather than inherited thrombophilia; factors VIII and XIII, which are less hepatocyte-dependent, were preserved. Overall, the profile did not establish a primary hypercoagulable state sufficient to explain the multivessel thrombosis.

Reassessment of the history then disclosed recurrent oral aphthae, episodic genital ulceration, pseudofolliculitis, and a positive family history of BD; pathergy testing was positive and HLA-B51 was present, whereas ophthalmologic examination showed no uveitis. Together with the extensive venous involvement, these features fulfilled the Pediatric Behçet's Disease (PEDBD) and International Criteria for Behçet's Disease (ICBD) classification frameworks and supported pediatric vascular BD [9, 10].

Therapeutic enoxaparin was administered and titrated against thrombocytopenia, fibrinogen level, and procedural bleeding risk under anti-factor Xa monitoring; no arterial aneurysm or bleeding focus was identified. He received pulse methylprednisolone followed by intravenous cyclophosphamide for severe vascular disease, with a second corticosteroid pulse and colchicine after transfer. Because thrombosis and inflammatory activity progressed, infliximab was initiated following multidisciplinary review, but only after repeated microbiologic reassessment had rendered active tuberculosis unsupported; isoniazid prophylaxis was continued with close hepatic monitoring. Only a single infliximab infusion could be delivered before the terminal deterioration. Despite anticoagulation, escalating immunosuppression, drainage, transfusion support, and broad-spectrum antimicrobial therapy for culture-signaled sepsis, he developed progressive multiorgan failure with severe metabolic acidosis, required intubation and renal replacement therapy, and died after recurrent cardiac arrest, 50 days after thrombosis was first documented. The full chronology, laboratory, and imaging data are provided in Tables S1 and S2.

This case is instructive less because BCS occurred in BD than because the inaugural manifestation was an unusually fulminant, multilevel venous phenotype extending from the hepatic veins and inferior vena cava to the right atrial junction and the iliofemoral system. Pediatric evidence is sparse: a comprehensive review of childhood BD identified hepatic vein occlusion with BCS in a single patient from an international cohort of 86 children [11], and intracardiac thrombosis is likewise exceptional in pediatric BD [4]. Diagnosis was further delayed by tuberculosis-oriented anchoring, a recognized pitfall in endemic regions, where constitutional symptoms, ascites, and a reactive tuberculin test understandably suggest extrapulmonary tuberculosis. Progressively negative microbiology, non-elevated adenosine deaminase, transudative ascites, and ultimately the extensive thrombotic pattern redirected the diagnosis, which the mucocutaneous, pathergy, HLA-B51, and family findings then confirmed [9, 10].

Management of BCS in BD is not standardized, no specific protocol exists, and morbidity and mortality remain high [6, 7, 12]. Because thrombosis in BD reflects vessel-wall inflammation rather than a conventional hypercoagulable state,

TABLE 1 | Structured thrombophilia, autoimmune, and genetic work-up and interpretive limitations.

Test category	Specific test	Result (reference range)	Interpretation/limitation
Antiphospholipid screen	Antiphospholipid (IgM and IgG), anticardiolipin, and anti-β2-glycoprotein I antibodies	Negative	Antiphospholipid syndrome not supported
Autoimmune screen	ANA; anti-dsDNA; ANCA	Negative	Alternative systemic autoimmune etiology not supported
Lupus anticoagulant	Lupus anticoagulant screening assay	39.8 s (normal)	Lupus anticoagulant not detected
Genetic thrombophilia	Factor V Leiden; prothrombin G20210A; MTHFR genotyping	Normal	Inherited thrombophilia not supported
Other inherited risk factors	Lipoprotein(a); hemoglobin electrophoresis; ADAMTS13 activity	< 10 mg/dL; HbA 97.8%, HbA2 2.2C; normal	Lipoprotein(a) excess, hemoglobinopathy, and thrombotic microangiopathy excluded
Homocysteine	Serum homocysteine	17.3 μmol/L (reference < 12)	Mildly elevated; insufficient alone to explain the thrombotic burden
Natural anticoagulants	Protein C; protein S; antithrombin III activity	Protein C 27.3% (70–140); protein S 43.4%; AT-III 50.3% (79–112)	Confounded by acute extensive thrombosis, hepatic dysfunction, and critical illness
Coagulation factors	Factors V, VII, IX, X, XI, XII; factors VIII and XIII	V, VII, IX, X, XI, XII reduced; VIII and XIII preserved	Pattern compatible with impaired hepatic synthesis and acute illness rather than inherited thrombophilia
HLA typing	HLA-B51	Positive	Supports Behçet disease susceptibility; not diagnostic in isolation

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; anti-dsDNA, anti-double-stranded DNA; AT-III, antithrombin III; HbA, hemoglobin A; HLA, human leukocyte antigen; MTHFR, methylenetetrahydrofolate reductase.

immunosuppression is the therapeutic cornerstone; cohort data indicate that immunosuppressants reduce venous thrombosis recurrence, an effect not demonstrated for anticoagulation [13, 14]. The 2018 EULAR recommendations advise glucocorticoids combined with an immunosuppressant such as azathioprine, cyclophosphamide, or cyclosporine A for acute deep vein thrombosis, monoclonal anti-tumor necrosis factor (TNF) antibodies for refractory venous disease, and anticoagulation only when bleeding risk is low and pulmonary artery aneurysms have been excluded [15]. Accordingly, our patient was escalated from corticosteroids and cyclophosphamide to infliximab; the biologic was introduced only after tuberculosis had been deemed unsupported and under continued isoniazid prophylaxis, addressing the safety tension that can otherwise delay life-saving therapy. The role of anticoagulation remains uncertain and is generally considered adjunctive; a recent systematic review found heterogeneous evidence, with potential benefit in selected clinical settings but no consistently demonstrated advantage across all patients [1, 16]. Interventional and surgical options, including percutaneous angioplasty with or without stenting, transjugular intrahepatic portosystemic shunt, surgical portal decompression, and, in end-stage disease, liver transplantation, may be considered for refractory hepatic venous outflow obstruction [6, 12], but their utility in BD is constrained by the diffuse, multilevel, inflammatory nature of the occlusion and the risk of re-thrombosis without adequate immunosuppression. In our patient, continuous thrombus from the hepatic veins to the right atrium and iliofemoral system, with rapidly progressive multiorgan failure and coagulopathy, precluded any safe procedural window; shunting and liver transplantation were formally assessed and judged unfeasible, so management remained medical.

Several diagnostic limitations should be acknowledged. Vasculitis was never confirmed histopathologically because vessel-wall sampling was unsafe and the peritoneal and omental biopsies had been obtained before the thrombosis was recognized. Tuberculosis could be rendered highly unlikely but never formally excluded since culture confirmation is inherently insensitive in paucibacillary extrapulmonary disease; this residual uncertainty, rather than doubt about the diagnosis of BD, is what deferred anti-TNF therapy. The thrombophilia panel was necessarily obtained during acute thrombosis, hepatic failure, and critical illness, so the reduced natural anticoagulant and factor

levels cannot be interpreted as inherited defects, and confirmatory retesting after recovery was impossible. Part of the early data was retrieved retrospectively from the referring center. Finally, a definite infectious source for the terminal deterioration could not be confirmed, although critical illness, invasive procedures, hepatic failure, and escalating immunosuppression plausibly amplified infection vulnerability, and no autopsy was performed.

In conclusion, BD should enter the differential diagnosis early in adolescents with BCS and disproportionate multivessel venous thrombosis, even before classical criteria are fully expressed, and particularly where an infectious explanation is plausible but unconfirmed. Once recognized, prompt guideline-based immunosuppression, escalated to anti-TNF therapy in refractory disease rather than anticoagulation alone, offers the best opportunity to alter an otherwise frequently fatal course, with interventional options reserved for patients in whom a safe procedural window exists [12, 15]. Our experience suggests that in fulminant Behçet-associated BCS the decisive variable is time: the interval between presentation and effective immunosuppression, and specifically the delay imposed by unresolved tuberculosis, may matter more than the choice of agent.

Author Contributions

Study conception and design: F.Ç., M.T.K.; data collection: F.Ç., M.T.K., N.G.A., S.A.K., E.Ş.; analysis and interpretation of results: F.Ç., M.T.K.; draft manuscript preparation: F.Ç., M.T.K. All authors reviewed the results and approved the final version of the manuscript.

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The authors have nothing to report. Declaration of Generative AI Use: During the preparation of this manuscript, the authors used a large language model (Claude; Anthropic) to assist with language editing and formatting. The authors reviewed and edited all content and take full responsibility for the final manuscript.

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The authors have nothing to report.

Ethics Statement

Formal ethics committee approval was not required for this single-patient case report in accordance with national regulations and institutional policy. All procedures were conducted in accordance with the ethical standards of Başakşehir Çam ve Sakura City Hospital, Istanbul, Türkiye, and the Declaration of Helsinki (1964, revised 2013). Written informed consent for publication of the clinical details and accompanying images was obtained from the patient's parents. The patient's perspective could not be obtained because he died during the index hospitalization before manuscript preparation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Chronological summary of the clinical course, major diagnostic steps, and therapeutic interventions. **Table S2:** Detailed laboratory, genetic, microbiologic, and radiologic findings.

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CLINICAL IMAGE

Liquefied Calcinosis Cutis Mimicking an Abscess in a Clinically Inactive Anti-MDA5 Antibody Positive Juvenile Dermatomyositis

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1 | Riddle

A 13-year-old boy, diagnosed with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis 2 years back, currently presented with a shiny, painless swelling over the back of his left knee, measuring around 4 cm × 4 cm (Figure 1A).

2 | Answer

This boy, with anti-MDA5 antibody-positive dermatomyositis, initially presented with severe muscle weakness, alongside multiple non-healing ulcers over the dorsum of his feet. His initial Childhood myositis assessment scale (CMAS) score was 21/52. Baseline muscle enzymes were elevated with serum creatine

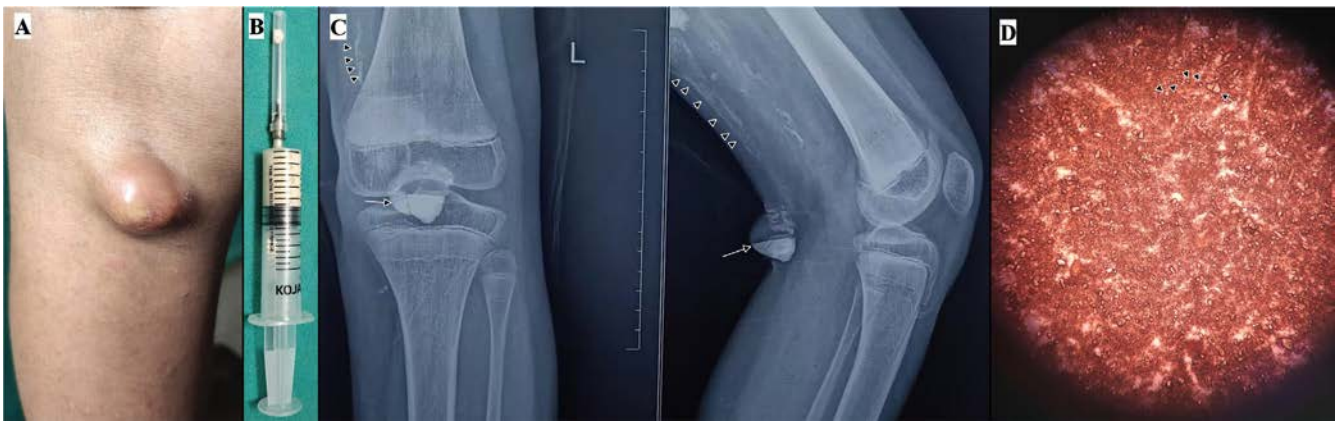

FIGURE 1 | Shiny, nodular 4 cm × 4 cm swelling at the back of the left knee (A). Milky-white calcinotic fluid aspirated in a syringe (B). X-ray left knee anteroposterior and lateral view showing sheet-like calcifications in the subcutaneous plane of left thigh (arrow-heads) with a superficial round swelling at the back of the left-knee containing an air-calcinotic fluid level (arrow), attributable to recent iatrogenic needle insertion. Light microscopic examination of the calcinotic fluid under 100× magnification showing discrete (arrow-heads) and clumps (arrow) of amorphous crystalline deposits, consistent with calcific material (D).

phosphokinase (CPK) value being 384 U/L. He was initiated on high-dose oral glucocorticoids and monthly cycles of intravenous cyclophosphamide (CYC) 500 mg each for the next 6 months. Oral glucocorticoids were slowly tapered off by 1 year, when the CMAS score stood at 45, and serum CPK value at 40 U/L. He did well on mycophenolate mofetil (MMF) 1 g/d as maintenance therapy for the last 18 months, until he developed the above-described swelling (Figure 1A). A milky-white fluid was aspirated from the swelling (Figure 1B). X-ray of the left knee revealed sheets of calcification in the subcutaneous plane of the thigh, alongside a relatively superficial rounded half-calcified swelling at the back of the knee with an air-calcinotic fluid level (Figure 1C), attributable to recent iatrogenic needle insertion. Gram stain, Ziehl-Neelsen stain, and bacterial and fungal cultures of the aspirated material were negative, thereby excluding an infected collection. Serum calcium and phosphate values came normal, suggestive of dystrophic calcification. Light microscopic examination of the calcinotic fluid under 100× magnification showed discrete and clumps of amorphous crystalline deposits, consistent with calcific material (Figure 1D). Considering such calcinotic lesions as a harbinger of a new disease activity in anti-MDA5 positive dermatomyositis, mycophenolate mofetil was switched to tofacitinib 5 mg twice daily. Two months after the change in treatment, the calcinotic lesion had stabilized. The CMAS score and the serum CPK values also remained stable with tofacitinib.

Liquefied calcinosis mimicking an abscess has rarely been reported in juvenile dermatomyositis (JDM) [1–3]. An association between anti-MDA5 antibody positivity and calcinosis has been reported in some studies [4], while anti-Nuclear Matrix Protein 2 antibody remains the more consistently recognized autoantibody association. Development of calcinosis in our JDM case suggests ongoing inflammation leading to reactive oxygen species-driven mitochondrial calcinosis [5], a possible harbinger of new disease activity in JDM. There are multiple approaches to deal with calcinosis associated with JDM, though no uniform international guidelines exist for the management of the same. Tofacitinib, being a Janus-Kinase inhibitor, targets the type I interferon pathway in the pathogenesis of anti-MDA5 antibody-positive dermatomyositis and prevents calcinosis. The underlying mechanism lies in the inhibition of the signal transducer and activator of transcription 3 (STAT3), which is involved in the regulation of calcium store release from the mitochondria [6]. Moreover, the favorable results of tofacitinib in dermatomyositis-associated calcinosis in case-reports made tofacitinib the likely choice in this case [7].

Author Contributions

K.B. conceptualized the work and drafted the manuscript, S.K.A.A. and A.C. acquired and interpretated the data, and revised for intellectual content, P.L.S. and S.B. analyzed the data, and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published and declared accountability for all aspects of the work, ensuring accuracy and integrity.

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The authors have nothing to report.

Consent

Informed consent was obtained from the patient for publication of this article.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used or analyzed in the current study are available from the corresponding authors upon reasonable request.

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CLINICAL IMAGE

Liquefied Calcinosis Cutis Mimicking an Abscess in a Clinically Inactive Anti-MDA5 Antibody Positive Juvenile Dermatomyositis

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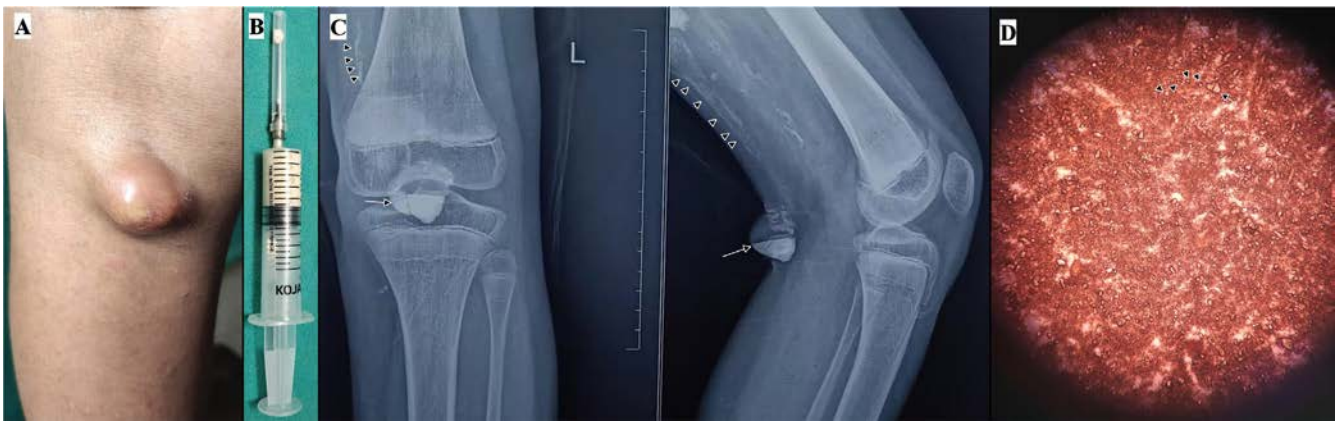
1 | Riddle

A 13-year-old boy, diagnosed with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis 2 years back, currently presented with a shiny, painless swelling over the back of his left knee, measuring around 4 cm × 4 cm (Figure 1A).

2 | Answer

This boy, with anti-MDA5 antibody-positive dermatomyositis, initially presented with severe muscle weakness, alongside multiple non-healing ulcers over the dorsum of his feet. His initial Childhood myositis assessment scale (CMAS) score was 21/52. Baseline muscle enzymes were elevated with serum creatine



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Author Contributions

K.B. conceptualized the work and drafted the manuscript, S.K.A.A. and A.C. acquired and interpretated the data, and revised for intellectual content, P.L.S. and S.B. analyzed the data, and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published and declared accountability for all aspects of the work, ensuring accuracy and integrity.

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The authors have nothing to report.

Consent

Informed consent was obtained from the patient for publication of this article.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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EDITORIAL

Dose–Response Meta-Analysis: A Quantitative Perspective on Rheumatic Diseases

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Rheumatic and immune-mediated diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), gout, and ankylosing spondylitis (AS), arise from the interplay of multiple factors in their development, including genetic susceptibility, metabolic disorders, immune imbalances, and environmental exposures. These diseases exhibit significant heterogeneity in their phenotypes and disease progression [1]. Our long-term research examines the relationship between various exposure factors—including metabolic indicators, nutritional components, and drug dosages—and disease risk or therapeutic efficacy. Traditional meta-analyses typically compare "exposed" versus "unexposed" groups or high versus low exposure levels, often overlooking the gradient information of exposure intensity. This binary research approach limits our capacity to identify the actual trend in disease risk as exposure doses change [2]. Dose–response meta-analysis (DRMA) is a specialized technique that builds on the traditional meta-analysis/meta-regression framework. It reconstructs and combines study-specific dose–response functions by integrating stratified exposure data across studies and accounting for intra-study correlations, such as through the Greenland-Longnecker method [3, 4]. Models can explore quadratic or fractional polynomial regression, though they more commonly use restricted cubic splines (RCS) for flexible nonlinear fitting [5, 6]. Given the complex, multifactorial etiology of these conditions, DRMA provides a quantitative framework to move beyond simple binary associations and uncover critical thresholds, thereby refining our understanding of how environmental, nutritional, and therapeutic factors shape disease trajectories across the rheumatology spectrum.

Numerous studies have used DRMA to investigate the dose–response relationship between nutritional intake and the risk of rheumatic and immune diseases. For example, the consumption of fruits, vegetables, and oily fish exhibits a nonlinear dose–response relationship with RA risk, where the risk decreases once intake exceeds a specific threshold [7]. Notably, DRMA allows researchers to more precisely assess specific levels of alcohol consumption or tobacco exposure that significantly increase disease risk. In terms of alcohol consumption, Jin et al.'s 2014 study revealed a J-shaped nonlinear relationship. Compared to abstinence, daily intake of about 3 g of alcohol resulted in an RR = 0.93 (95% CI 0.88–0.98), and 9 g/day resulted in an RR = 0.86 (95% CI 0.76–0.97), suggesting that low-to-moderate drinking may be linked to a reduced RA risk. However, when alcohol intake reached approximately 30 g/day, the risk increased (RR = 1.28, 95% CI 0.94–1.73), indicating that beyond a certain threshold, the protective effect disappears and may even become harmful [8]. Furthermore, studies show that compared to lifelong non-smokers, lower cumulative exposure (e.g., < 10 pack-years) significantly increases RA risk (RR = 1.26, 95% CI 1.14–1.39), with higher exposure levels conferring an even greater relative risk [9].

These examples illustrate how DRMA can transform qualitative risk factors into quantifiable risk curves. Beyond RA, analogous dose–response approaches have been applied to explore the relationships between serum uric acid (SUA) levels and metabolic syndrome risk [10], as well as between vitamin D status and disease activity in SLE [11], suggesting that the methodology is broadly applicable across the rheumatology spectrum.

Metabolic abnormalities—including hyperuricemia, insulin resistance, and obesity—are common in rheumatic and immune diseases and can also trigger or worsen immune dysregulation. Studies show that the risk of RA increases progressively with each unit increase in body mass index (BMI), although saturation or inflection points may occur at very high or low BMI extremes [12]. Moreover, cohort studies demonstrate a dose–response relationship between each 1 mg/dL increase in SUA and the risk of hypertension [13]. In clinical practice, patients frequently inquire about exercise ("Can I exercise?") and dietary restrictions ("What dietary restrictions should I follow?"). However, vague recommendations like "moderate exercise" or a "healthy iet" are no longer sufficient for modern patient care. Evidence-based medicine can guide the development of non-pharmacological treatment guidelines, providing clinicians with authoritative recommendations to improve patients' quality of life. Crucially, by utilizing DRMA, we can translate these broad lifestyle habits into precise, quantifiable guidance based on definitive evidence. This ability to define exact thresholds for benefit and harm represents a critical step in transitioning rheumatology from experiential medicine to true precision medicine.

Analyzing therapeutic dose—including initial dose, maintenance dose, cumulative dose, and dosing frequency—as a continuous variable to investigate its dose–response relationship with efficacy and safety is essential for integrating DRMA methodology into clinical decision-making and dose optimization. In early trials of new drugs for conditions such as SLE, dose–response relationships often serve as a critical indicator. For example, the Enpatoran Phase II trial reported dose-dependent differences in skin and systemic scores (e.g., cutaneous lupus erythematosus disease area and severity index (CLASI)) across dose groups. This suggests that DRMA could be used in subsequent studies to combine dose group data from different trials and reconstruct continuous curves [14]. Methotrexate (MTX) remains a first-line conventional synthetic DMARD for RA, but its starting dose and administration strategy remain controversial. Initial doses vary widely across studies (7.5–25 mg/week), and during short-term follow-up (12–24 weeks), higher starting doses do not consistently improve clinical remission rates such as those measured by the Disease Activity Score 28 (DAS28) or American College of Rheumatology 20% improvement criteria (ACR20). However, gastrointestinal reactions and elevated liver enzymes become more frequent with increasing doses [15]. Subcutaneous administration also demonstrates higher bioavailability and efficacy than oral administration at equivalent nominal doses [16]. This evidence suggests that MTX efficacy may plateau within the moderate dose range, while toxicity risks continue to increase. We must emphasize that this concurrent occurrence of a therapeutic efficacy plateau and an increased toxicity profile directly challenges the conventional clinical approach of simply escalating doses in response to perceived treatment inadequacy.

In interpreting these findings, it is important to recognize that DRMA typically synthesizes grouped data from published observational studies or trial reports, whereas dose optimization in clinical practice ultimately relies on a broader evidence base, including randomized dose-ranging trials, pharmacokinetic/pharmacodynamic (PK/PD) modeling, and continuous safety monitoring. DRMA is well-suited for detecting patterns and generating hypotheses across aggregated data, but its results should be viewed as complementary to—not a replacement for—the confirmatory evidence derived from these other approaches. Consequently, research and clinical communities must shift their priorities toward continuous dose modeling and parallel efficacy-safety assessments to identify the individualized minimum effective dose and toxicity inflection point, providing more precise evidence for personalized treatment.

Although dose–response analysis is a powerful tool for uncovering continuous and nonlinear relationships between exposure intensity and rheumatic immune outcomes, several interrelated challenges remain in its practical application, requiring methodological improvements and changes in research practices. During study design and data collection, it is essential to prioritize collecting continuous exposure data alongside median/mean dose information to support subsequent spline or first-order trend fitting [17]. Additionally, raw dose tables should be publicly shared to facilitate evidence synthesis, aligning with preferred reporting items for systematic reviews and meta-analyses (PRISMA) transparency requirements [18]. Second, established dose–response modeling tools—such as the R package dosresmeta and multivariate spline methods—should be widely adopted and promoted. Publications should include full model code and sensitivity analyses to enhance reproducibility. Third, we must issue a clear methodological cautionary statement: DRMA primarily reveals statistical associations between dosage and outcomes; it does not, in itself, establish causality. To strengthen causal inference, dose–response analysis should be combined with independent causal evidence, such as Mendelian randomization, stratified time series analysis, or natural experiments, to bolster confidence in the causality of dose-outcome relationships [19].

Just as the ancient adage "the dose determines the toxicity" has renewed relevance in modern medicine, identifying dosage variations may be crucial for discovering disease turning points in rheumatology and immunology research. To fully realize the potential of DRMA and shift the paradigm of our field, we call upon the academic community to undertake specific, actionable initiatives: (1) mandate the public sharing of continuous dose data alongside traditional median/mean reporting in clinical trials; (2) integrate advanced dose–response modeling training into epidemiological and rheumatology fellowship programs; and (3) prioritize funding and editorial support for studies that aim to define precise, individualized therapeutic windows rather than those relying on traditional, binary outcomes.

Author Contributions

Yu Lei drafted the manuscript. William Tao-Hsin Tung provided suggestions, reviewed, and edited the manuscript. All authors approved the final version of the manuscript.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Cross-Sectional and Longitudinal Association Between Biological Aging Acceleration and the Risk of Osteoarthritis: A Cohort Study From UK Biobank

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ABSTRACT

Objective: To evaluate the relationship between biological ages and the prevalence and incidence of osteoarthritis (OA).

Methods: 332 261 participants from UK Biobank were analyzed. Biological aging was measured using phenotypic age (PhenoAge) and Klemera–Doubal (KDMAge). KDMAge was derived from nine clinical biomarkers to gauge system integrity decline, while PhenoAge was computed from chronological age and nine clinical biomarkers to gauge mortality risk. Biological aging accelerations were computed as residuals from regressing KDMAge and PhenoAge against chronological age. The associations between biological aging and prevalence and incidence of OA were analyzed using logistic and Cox regression models.

Results: At baseline, 55.4% of included individuals had younger PhenoAge aging acceleration. In cross-sectional analyses, individuals with accelerated aging had higher odds of OA compared to those with non-accelerated aging (odds ratios [OR]: 1.12 [95% CI: 1.09–1.14] for PhenoAge acceleration and 1.05 [1.03–1.08] for KDMAge acceleration). In the longitudinal analyses, increased

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PhenoAge acceleration was associated with a higher risk of incident OA (hazard ratios [HR]: 1.12 [1.10–1.15]). However, the association between KDMAge acceleration and the incidence of OA was not statistically significant (HR: 0.99 [0.97–1.01]). Accelerated biological aging showed a more pronounced association with OA among individuals > 60 years. No additive or multiplicative interactions were found between OA polygenic risk score (PRS) and biological aging.

Conclusion: Advanced biological aging may increase the risk of OA, independent of OA genetic risk, particularly in individuals aged over 60 years. The two biological aging indicators hold potential as novel composite clinical biomarkers, directing prevention and intervention strategies for high-risk populations for OA.

1 | Introduction

Osteoarthritis (OA) is the most common joint disease, typically affecting weight-bearing joints such as knees and hips [1]. Affecting approximately 500 million individuals worldwide, the prevalence of OA is anticipated to rise mainly due to population aging [2]. The pathogenesis of OA involves a complex interplay of multiple risk factors, resulting in a lack of effective therapeutic approaches [3]. Thus, identifying and quantifying modifiable risk factors and enhancing OA surveillance represent crucial directions in current OA research.

OA is a recognized degenerative condition, and its relationship with chronological age has been well-established [4]. Since chronological age is an unmodifiable risk factor, identifying additional modifiable predictive indicators is crucial for effective OA prevention. Accelerated biological aging, or premature aging, along with early declines in homeostasis, have been linked to certain musculoskeletal diseases and increased mortality rates [5–7]. Previous studies have suggested a connection between OA and accelerated aging, but there is inconsistent evidence linking OA to physiological age predicted by biomarkers of accelerated aging, such as telomere length and DNA methylation [8–12]. Furthermore, the high cost and time-intensive nature of molecular biomarker testing make it impractical for routine use in large-scale populations or clinical practice. To identify more clinically practical predictive indicators, we focus on two validated algorithms that reliably predict mortality and physical health [13, 14]: Phenotype age (PhenoAge), which is derived from both age and nine plasma proteomic biomarkers [15], and Klemera–Doubal's biological age (KDMAge), a model primarily based on fundamental physiological parameters and cardiovascular function using nine clinical biomarkers [16], have both shown promise in this regard.

Recent studies have revealed that central obesity contributes to an increased risk of OA, with accelerated biological aging serving as a mediating factor in this association [17]. Cross-sectional data from the National Health and Nutrition Examination Survey demonstrated that accelerated biological aging was associated with an increased prevalence of OA, particularly among females and older adults [18]. Prospective studies are needed to elucidate the relationship between biological age and OA incidence.

Therefore, we aimed to conduct a prospective cohort study based on the UK Biobank database to explore the relationship between PhenoAge and KDMAge, two common biological ages, and the prevalence and incidence of OA. Additionally, we further examine the interaction between the polygenic risk score (PRS) of OA and biological age as determined by these algorithms.

2 | Methods

2.1 | Study Design and Population

The UK Biobank is a large prospective study that recruited over 500 000 participants aged 37 to 73 years from 2006 to 2010 across 22 assessment centers throughout the UK, with a mean follow-up of 9.0 years. The information of each participant was collected from self-completed questionnaires, physical measures and computer-assisted interviews at baseline and follow-up, including demographic characteristics, lifestyles and biological samples [19]. Written consent was obtained from all participants, and the North West Multi-Centre Research Ethics Committee granted ethical approval. In our study (Figure S1), we first included 332 261 participants from the UK Biobank who had accessible data on clinical biomarkers and their OA status for cross-sectional analysis. We then excluded 36 463 participants with OA at baseline to analyze the association between biological aging and the incidence of OA. Finally, 2097 participants lacking genetic data were excluded, and the association between the PRS and OA was calculated.

2.2 | Biological Age and Age Acceleration

We calculated two biological ages, PhenoAge and KDMAge. PhenoAge relied on chronological age and nine multi-system clinical chemistry biomarkers (mean cell volume, albumin, alkaline phosphatase, creatinine, glucose, red cell distribution width, C-reactive protein, lymphocyte percent, and white blood cell count) [15]. KDMAge was based on nine clinical biomarkers (FEV1, systolic blood pressure, concentrations of albumin, alkaline phosphatase, blood urea nitrogen, glycosylated hemoglobin, creatinine, C-reactive protein, and total cholesterol) [16]. The two biological ages both used the National Health and Nutrition Examination Survey III (NHANES III) as the training sample, but they had different meanings. KDMAge was calculated to measure the deterioration of system integrity, while PhenoAge was computed from the Gompertz proportional hazard model to assess the risk of mortality [16–20]. The difference between biological age and chronological age may vary. Thus, we regressed the biological age value with the chronological age at which biomarkers were measured and calculated the residual value (named biological aging acceleration). The values > 0 were classified as biologically older than chronological age, while values ≤ 0 were considered biologically younger. Then, we standardized the biological aging acceleration, which is the original value minus the mean and then divided by the standard deviation (named PhenoAge AAsd and KDMAge AAsd), setting their mean to 0 and standard deviation (SD) to 1, and divided them into quartiles [21].

2.3 | Ascertainment of OA

OA was determined through diagnoses derived from self-reports, primary care records, hospital inpatient records, or death data, utilizing International Classification of Diseases 9th edition and 10th edition in UK Biobank (Table S1).

2.4 | Polygenic Risk Score of OA

The GO-Consortium conducted a meta-analysis for total OA while excluding participants from UK Biobank cohorts due to the potential impact of UK Biobank on effect estimates in the original genome-wide association studies (GWAS). A set of 161 independent SNPs, identified through GWAS and characterized by low linkage disequilibrium (LD) with $r^2 < 0.05$, was chosen to construct a PRS (Table S2). The weighted polygenic risk score (wPRS) was computed using the formula: $\text{wPRS} = \sum_i^k \left(\beta_j \times \text{dosage}_{ij}\right)$, where β_j represents the per allele effect size obtained from the GWAS. They were then divided into two categories (low and high) and five categories (low [lowest quintile], intermediate [quintile 2–4] and high [highest quintile] risk).

2.5 | Covariates

We included age (continuous), sex (female or male), body mass index (BMI) (underweight, normal, overweight, and obesity), race (mixed, African/Black, East Asian, European/White, South Asian, and unknown), Townsend deprivation index (continuous), education levels (higher or lower) [22], healthy diet (yes or no) [23], smoking status (never, former, or current), drinking status (never, former, or current), history of joint injury (yes or no) [24], regular physical activity (yes or no), and glucosamine use (yes or no). BMI was calculated by a well-trained nurse at baseline by measuring height and weight, dividing weight (in kilograms) by the square of height (in meters). The participants were then classified into underweight (BMI < 18), normal (BMI 18–25), overweight (BMI 25–30), and obese (BMI ≥ 30). Education level was obtained through the questionnaire, and higher education level was defined as college or university degree; lower was defined as A levels, O levels, Certificates of Secondary Education, National Vocational Qualifications, or others [22]. History of joint injury was determined by the presence of a diagnosis in electronic health records from hospital admissions (ICD-10 codes: S700, S710, S73, S760, S800, S810, S820, S83, S870). Regular physical activity status was characterized as follows: engaging in moderate activity for ≥ 150 min per week, vigorous activity for ≥ 75 min per week, or a combination of moderate and vigorous activities totaling 150 min per week [24]. The assessment of physical activity utilized Metabolic Equivalent Task (MET) minutes, based on selected items from the short International Physical Activity Questionnaire (Table S3).

2.6 | Statistical Analyses

The baseline characteristics of the samples were overviewed considering the entire population between PhenoAge acceleration ≤ 0 and PhenoAge acceleration > 0. Categorical variables were presented as percentages, while continuous variables were expressed as means and standard deviations (SDs). The missing values of the independent covariates were imputed using multiple imputations via chained equations [25]. First, we employed logistic regression to estimate the odds ratio (OR) and 95% confidence interval (CI) between two biological aging accelerations (including continuous, quartiles, and age acceleration after standardization) and the prevalence of OA. The analysis also considered increments of 5- and 10-year increases for continuous variables. Model 1 was adjusted for age, sex, and BMI. Model 2 was additionally adjusted for race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, history of joint injury, and glucosamine use. Second, the Cox proportional hazards model was used to estimate the HR and 95% CI between biological aging accelerations and the incidence of OA after excluding participants who had OA at baseline.

To identify subgroups of OA patients in whom the impacts of biological aging accelerations were particularly significant, we conducted stratified analyses based on age (≤ 60 vs. > 60 years), gender (female vs. male), BMI (< 30 vs. ≥ 30 kg/m^2), and wPRS reflecting OA genetic predisposition (low vs. intermediate vs. high). The multiplicative and additive interactions between wPRS and two biological aging accelerations were examined using Cox proportional hazards regression. Relative excess risk (RERI) and attributable proportion (AP) were performed with the aim of gauging additive interactions [26]. In the absence of additive interaction, the 95% CI for both the RERI and AP would include 0. The dose–response relationships between biological aging and the risk of OA were assessed by fitting a flexible restricted cubic spline (RCS) regression.

We also performed several sensitivity analyses: First, participants who experienced the outcome within 2 years of follow-up were excluded from the prospective analysis to address the potential for reverse causality. Second, our analysis was further restricted to participants with complete covariate information for comparison with estimation-based results. Finally, we used mortality as a competing risk event and employed a competing risk model to calculate the relationship between two biological ages and the incidence of OA. All analyses were performed with R software (version 4.2.2).

3 | Results

3.1 | Characteristics and Biological Ages of Participants

The baseline characteristics of participants and the flowchart for selecting study participants are shown in Table 1 and Figure 1. In a cohort of 502 411 participants from the UK Biobank, we included 332 261 individuals with available clinical biomarker information on biological aging for cross-sectional analysis. Participants were stratified based on whether PhenoAge indicated a biologically younger status compared to their chronological age, resulting in biologically younger (n = 183 912) and biologically older (n = 148 349) groups. Despite both groups having similar mean chronological ages (56.4 years), there was a notable difference of 6.61 years in PhenoAge and 1.52 years

TABLE 1 | Baseline characteristics of study participants.

Characteristics	Total, $n = 332\,261$	Biologically younger[b], $n = 183\,912$	Biologically older[b], $n = 148\,349$	p[a]
Age (years), mean (SD)	56.41 (8.10)	56.41 (7.94)	56.41 (8.28)	0.890
Biological ages (years), mean (SD)				
PhenoAge	50.47 (9.34)	47.52 (8.25)	54.13 (9.32)	< 0.001
PhenoAge acceleration	0.00 (4.47)	−2.95 (2.06)	3.66 (3.92)	< 0.001
KDMAge	55.16 (8.89)	54.48 (8.64)	56.00 (9.12)	< 0.001
KDMAge acceleration	0.00 (3.84)	−0.68 (3.54)	0.84 (4.03)	< 0.001
Sex (male)	179 494 (54.0%)	109 051 (59.3%)	70 443 (47.5%)	< 0.001
Race (White)	31 379 (94.5%)	175 296 (95.3%)	138 683 (93.5%)	< 0.001
BMI (kg/cm^2), mean (SD)	27.35 (4.71)	26.62 (4.14)	28.25 (5.19)	< 0.001
Education (height qualification), mean (SD)	108 567 (32.7%)	64 295 (35.0%)	44 272 (29.8%)	< 0.001
Townsend deprivation index	−0.95 (3.34)	−1.22 (3.25)	−0.63 (3.42)	< 0.001
Healthy diet	81 929 (24.7%)	48 510 (26.4%)	33 419 (22.5%)	< 0.001
Regular physical activity	194 104 (58.4%)	110 067 (59.8%)	84 037 (56.6%)	< 0.001
Glucosamine use (yes)	64 165 (19.3%)	39 412 (21.4%)	24 753 (16.7%)	< 0.001
Smoking status				
Never	183 342 (55.2%)	107 921 (58.7%)	75 421 (50.8%)	< 0.001
Previous	114 927 (34.6%)	64 291 (35.0%)	50 636 (34.1%)	
Current	33 992 (10.2%)	11 700 (6.4%)	22 292 (15.0%)	
Drinking status				
Never	14 298 (4.3%)	7211 (3.9%)	7087 (4.8%)	< 0.001
Previous	11 371 (3.4%)	5442 (3.0%)	5929 (4.0%)	
Current	306 592 (92.3%)	171 259 (93.1%)	135 333 (91.2%)	
History of joint injury	2018 (0.6%)	993 (0.5%)	1025 (0.7%)	< 0.001
Components of biological ages				
FEV1 (mL)[c]	2821.82 (803.06)	2838.00 (796.76)	2801.76 (810.36)	< 0.001
SBP (mm Hg)[c]	139.63 (19.56)	138.91 (19.47)	140.52 (19.63)	< 0.001
Total cholesterol (mg/dL)[c]	220.56 (43.97)	224.48 (43.14)	215.70 (44.49)	< 0.001
Glycated hemoglobin (%)[c]	5.44 (0.60)	5.34 (0.40)	5.58 (0.75)	< 0.001
Blood urea nitrogen (mg/dL)[c]	15.11 (3.83)	14.84 (3.35)	15.45 (4.32)	< 0.001
Lymphocyte (%)[d]	28.99 (7.43)	30.96 (6.99)	26.54 (7.23)	< 0.001
Mean cell volume (fL)[d]	82.80 (5.30)	81.58 (4.59)	84.32 (5.71)	< 0.001
Serum glucose (mmol/L)[d]	5.11 (1.20)	4.90 (0.61)	5.38 (1.62)	< 0.001
Red cell distribution width (%)[d]	13.47 (0.96)	13.08 (0.55)	13.96 (1.13)	< 0.001
White blood cell count (1000 cells/μL)[d]	6.86 (1.91)	6.26 (1.38)	7.60 (2.20)	< 0.001
Albumin (g/L)[c,d]	45.27 (2.60)	45.79 (2.48)	44.63 (2.61)	< 0.001
Creatinine (mg/dL)[c,d]	0.82 (0.19)	0.78 (0.14)	0.86 (0.22)	< 0.001

(Continues)

TABLE 1 | (Continued)

Characteristics	Total, $n = 332\,261$	Biologically younger[b], $n = 183\,912$	Biologically older[b], $n = 148\,349$	p[a]
C-reactive protein (mg/dL)[c,d]	0.19 (0.22)	0.14 (0.14)	0.26 (0.27)	< 0.001
Alkaline phosphatase (U/L)[c,d]	83.22 (25.84)	79.44 (21.00)	87.90 (30.16)	< 0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; KMDAge, Klemera–Doubal method biological age; OA, osteoarthritis; PhenoAge, phenotypic age; SD, standard deviation.
[a]Participants were divided by whether PhenoAge indicated a biologically younger status compared to their chronological age, using analysis of the *t*-test for continuous variables and using the Pearson Chi-squared test for categorical variables.
[b]Biologically younger was defined as PhenoAge acceleration ≤ 0; Biologically older was defined as PhenoAge acceleration > 0.
[c]Employed to construct KDMAge.
[d]Employed to construct PhenoAge.

in KDMAge between the two groups. Compared to biologically older individuals, participants categorized as biologically younger tended to be male, White, had lower Townsend Deprivation Index scores and lower BMI, were more likely to be non-current smokers, maintaining a healthy diet, engaged in regular physical activity, were current alcohol consumers, used joint supplements, and were less likely to have a history of joint injuries. For prospective analysis, we included 295 798 UK Biobank participants who did not have OA at baseline. Over a median follow-up period of 12.5 years, from 2006 to 2021, 42 534 cases of OA were documented (data not shown).

3.2 | Biological Aging and Prevalence of OA at Baseline

Cross-sectional analyses suggested that participants with PhenoAge acceleration valued 1-SD older than the expectation for their chronological age had 8% higher odds of OA at baseline (OR, 1.08; 95% CI, 1.07–1.10; $p < 0.0001$; Table 2). Compared to the biologically younger group, the biologically older group was significantly associated with OA prevalence (OR, 1.12; 95% CI, 1.09–1.14; $p < 0.0001$; Table 2). Furthermore, each 5- or 10-year increase in PhenoAge acceleration was significantly associated with a 9% or 20% increase in odds of OA at baseline (Table 2). A significant gradient increase in OA prevalence was observed across quartiles 1–4 of PhenoAge acceleration, with a p for trend < 0.0001 (Figure 1). Besides, compared with participants of low accelerated aging (the bottom quintile of PhenoAge acceleration), those in the high accelerated aging group (top quintile) had a higher odd of OA (OR, 1.21; 95% CI, 1.17–1.25; $p < 0.0001$; Figure 1). Similarly, KDMAge acceleration was significantly associated with a higher prevalence of OA, with participants having a 4% higher odd of OA when exceeding 1-SD above the expected chronological age (OR, 1.04; 95% CI, 1.03–1.05; $p < 0.0001$). In dose–response analysis, we found that the prevalence of OA increased monotonically with the increase of KDMAge acceleration. In contrast, the pattern for PhenoAge acceleration was complex, being non-linear and non-monotonic (Figure 2).

3.3 | Biological Aging and Incident OA Over Follow-Up

For the association between biological aging and the risk of incident OA, the prospective analysis revealed that for a 1-SD increase of PhenoAge acceleration, the risks of incident OA increase by 8% (HR, 1.08; 95% CI, 1.07–1.09; $p < 0.0001$; Table 2) respectively. Besides, individuals with PhenoAge accelerated aging faced significantly increased risks of OA incidence compared to those classified into biologically younger groups (HR, 1.12; 95% CI, 1.10–1.15; $p < 0.0001$). Compared to the low acceleration group (bottom quartile of PhenoAge acceleration), participants in the moderate acceleration (50%–75%) and high acceleration (top quartile) groups had higher risks of incident OA, with HRs of 1.04 (95% CI, 1.01–1.07, $p < 0.0001$) and 1.19 (95% CI, 1.16–1.22, $p < 0.0001$), respectively (Figure 1). Additionally, each 5- or 10-year increase in PhenoAge acceleration was associated with a 9% or 19% rise in incident OA risk (Table 2). Meanwhile, a significant gradient increase in incident OA risk with PhenoAge acceleration was observed from the lowest to the highest quartiles, with a p for trend < 0.0001 (Figure 1). As shown in Figure 2, in dose–response analysis, we found a complex relationship between PhenoAge acceleration and the risk of incident OA, where PhenoAge acceleration standardized to below −2.05 or above −0.08 both increases the risk of incident OA. Unlike PhenoAge acceleration, KDMAge acceleration was not associated with the risk of incident OA in fully adjusted models.

3.4 | Subgroup Analysis and Sensitivity Analysis

In the subgroup analysis, we observed stronger associations between PhenoAge acceleration and the risk of incident OA in participants aged over 60 compared to younger participants (Table 3). The interactions between PhenoAge acceleration and KDMAge acceleration in other cross-sectional and longitudinal subgroup analyses based on age, gender, and BMI were not statistically significant. In the three-category analysis of wPRS, individuals with PhenoAge accelerated aging showed increased risks in both the prevalence and incidence of OA compared to those without PhenoAge accelerated aging. These associations were consistent across low, intermediate, and high levels of wPRS (Table 4), and similar results were observed in the two-category analysis of wPRS (Tables S4 and S5).

In the interaction analysis, we did not observe multiplicative interactions between wPRS and two biological ages on the incidence of OA. We also did not observe any additive interaction effects. Specifically, for people with accelerated aging in PhenoAge who have a high genetic risk, the RERI is 0.06 (95% CI, −0.004, 0.13). The same applies to people with accelerated

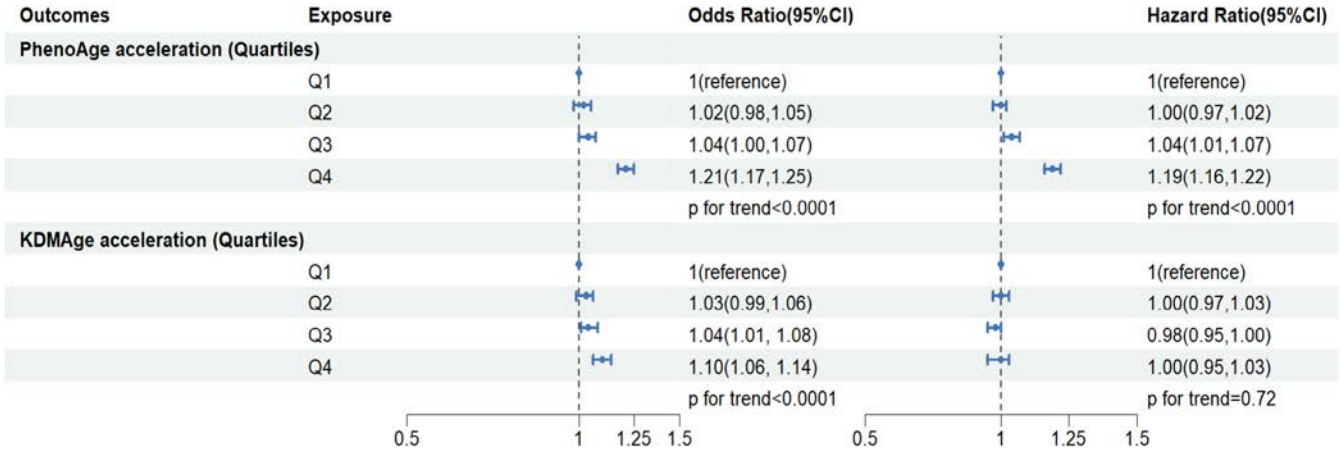

FIGURE 1 | Association between PhenoAge/KDMAge acceleration and OA. KMDAge, Klemera–Doubal method Biological Age; OA, osteoarthritis; PhenoAge, phenotypic age.

TABLE 2 | Association between biological age acceleration and risk of prevalent (odds ratio) and incident (hazard ratio) OA.

	Odds ratio (95% CI)		Hazard ratio (95% CI)	
	Model 1	**Model 2**	**Model 1**	**Model 2**
PhenoAge acceleration				
Continuous	**1.02 (1.01, 1.02)**	**1.02 (1.02, 1.02)**	**1.02 (1.02, 1.02)**	**1.02 (1.02, 1.02)**
Phenoge AAsd	**1.08 (1.07, 1.09)**	**1.08 (1.07, 1.10)**	**1.08 (1.07, 1.09)**	**1.08 (1.07, 1.09)**
Accelerated aging				
≤0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
>0	**1.11 (1.09, 1.14)**	**1.12 (1.09, 1.14)**	**1.14 (1.11, 1.16)**	**1.12 (1.10, 1.15)**
Per 5-year	**1.09 (1.07, 1.10)**	**1.09 (1.08, 1.11)**	**1.09 (1.08, 1.11)**	**1.09 (1.08, 1.10)**
Per 10-year	**1.18 (1.15, 1.21)**	**1.20 (1.17, 1.23)**	**1.20 (1.17, 1.22)**	**1.19 (1.16, 1.21)**
KDMAge acceleration				
Continuous	**1.01 (1.01, 1.01)**	**1.01 (1.00, 1.01)**	**1.00 (1.00, 1.01)**	1.00 (1.00, 1.01)
KDM AAsd	**1.04 (1.02, 1.05)**	**1.04 (1.03, 1.05)**	**1.02 (1.01, 1.03)**	1.01 (1.00, 1.02)
Accelerated aging				
≤0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
>0	**1.05 (1.02, 1.07)**	**1.05 (1.03, 1.08)**	1.01 (0.99, 1.03)	0.99 (0.97, 1.01)
Per 5-year	**1.05 (1.03, 1.06)**	**1.05 (1.04, 1.07)**	**1.02 (1.01, 1.04)**	1.01 (1.00, 1.02)
Per 10-year	**1.10 (1.06, 1.13)**	**1.11 (1.07, 1.14)**	**1.05 (1.02, 1.07)**	1.02 (0.99, 1.05)

Note: Model 1 was adjusted for age, sex, and body mass index. Model 2 was adjusted for age, sex, body mass index, race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, joint injury, and glucosamine use. Model 2 was adjusted for age, sex, body mass index, race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, joint injury, and glucosamine use. Phenoge AAsd: Phenoage acceleration after standardizing; KDM AAsd: KDMAge acceleration after standardizing. PhenoAge/KDMAge acceleration aging >0 were classified as biologically older than chronological age; PhenoAge/KDMAge acceleration aging ≤0 were considered biologically younger. Bold denotes statistically significant.

Abbreviations: KMDAge, Klemera–Doubal method biological age; OA, osteoarthritis; PhenoAge, phenotypic age.

aging in KDMage, with an RERI of 0.02 (95% CI, −0.04, 0.08) (Table S6).

Furthermore, we conducted three additional sensitivity analyses. First, we repeated the incidence analysis by restricting the sample to participants excluding patients who had incident OA within the first 2 years, and the effect size remained consistent with the main analyses (Table S7). Second, we excluded participants with missing covariates at baseline. In the cross-sectional analysis, the effect sizes of PhenoAge acceleration and KDMAge acceleration increased, corresponding to a 23% and 13% increase, respectively, in the odds of OA at baseline for each 10-year increment (PhenoAge: OR, 1.23; 95% CI, 1.18–1.27; KDMAge: OR, 1.13; 95% CI, 1.08–1.19, respectively; Table S8).

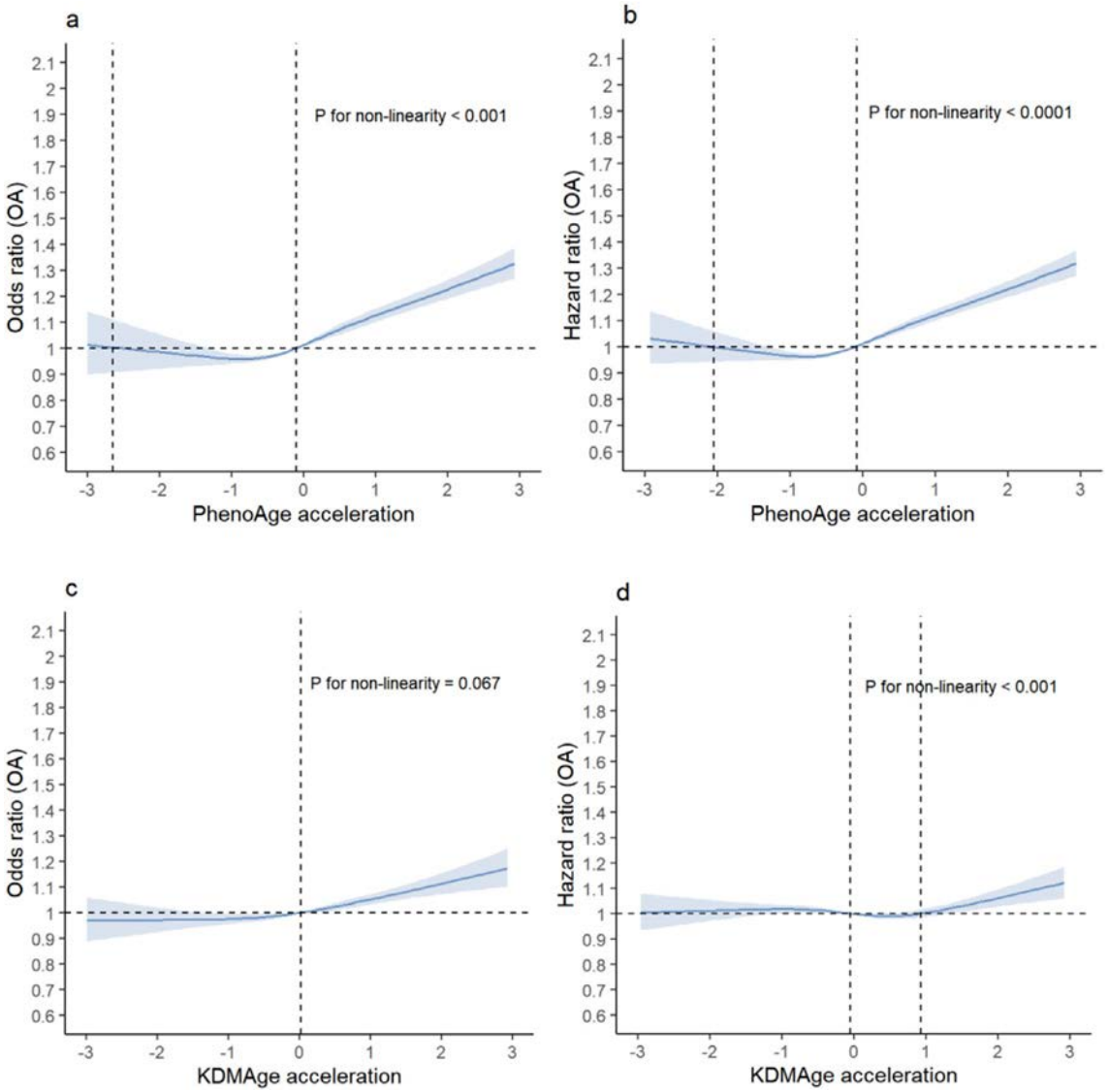

FIGURE 2 | Graphs of the best fitting models for relationships of PhenoAge acceleration and KDMAge acceleration with risk of OA prevalence (odds ratio) and incidence (hazard ratio) Panels: odds ratio (a–c) and hazard ratio (b–d); PhenoAge acceleration (a, b) and KDMAge acceleration (c, d). Solid line: point estimation; ribbons: the 95% confidence limits; restricted cubic spline regression model adjusted for age, sex, body mass index, race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, joint injury, and glucosamine use. KMDAge, Klemera–Doubal method biological age; OA, osteoarthritis; PhenoAge, phenotypic age.

Third, we repeated the longitudinal analysis using a competing risk model. Although the effect size of PhenoAge acceleration on the risk of incident OA was slightly attenuated, it remained statistically significant (Table S9).

4 | Discussion

In this study, we conducted cross-sectional and prospective analyses to explore the relationship between accelerated biological aging measured by PhenoAge and KDMAge, and the risk of OA. We found that accelerated PhenoAge aging was significantly associated with both the prevalence and incidence of OA, while accelerated KDMAge aging was only associated with the prevalence of OA. Importantly, the wPRS for OA did not exhibit multiplicative or additive interactions with either biological aging accelerations. We also found that the relationship between biological age and OA was more pronounced in individuals aged over 60 years. The findings suggest that early identification of individuals exhibiting accelerated biological aging may facilitate early detection, prevention, and management of OA.

Studies examining the association between PhenoAge or KDMAge accelerations and various diseases, including depression, anxiety [21], cancer [27], rheumatoid arthritis [7], childhood adversity [28], and chronic respiratory diseases [29], have been conducted in the UK Biobank. Those with biological accelerated age tend to have higher incidence rates of the above diseases. The latest research indicates that accelerated biological aging is significantly associated with the incidence of musculoskeletal disorders [6]. A research from He and colleagues [18] has shown that adults with accelerated biological aging have an increased risk of the OA prevalence. To our knowledge, this is

TABLE 3 | Risk of OA prevalence (odds ratio) and incidence (hazard ratio) according to PhenoAge and KDMAge accelerated aging stratified by gender, age, and BMI.

	Odds ratio (95% CI)		*p* for multiple interaction	Hazard ratio (95% CI)		*p* for multiple interaction
	Non-accelerated aging	Accelerated aging		Non-accelerated aging	Accelerated aging	
PhenoAge						
Stratified by gender			0.49			0.30
Males	1 (reference)	**1.13 (1.09, 1.16)**		1 (reference)	**1.13 (1.10, 1.16)**	
Females	1 (reference)	**1.12 (1.08, 1.16)**		1 (reference)	**1.12 (1.09, 1.15)**	
Stratified by age			0.55			**0.02**
≤ 60	1 (reference)	**1.07 (1.04, 1.11)**		1 (reference)	**1.07 (1.04, 1.10)**	
> 60	1 (reference)	**1.14 (1.10, 1.17)**		1 (reference)	**1.15 (1.12, 1.18)**	
Stratified by BMI			0.47			0.56
< 30	1 (reference)	**1.11 (1.08, 1.14)**		1 (reference)	**1.14 (1.10, 1.18)**	
≥ 30	1 (reference)	**1.13 (1.09, 1.18)**		1 (reference)	**1.12 (1.09, 1.15)**	
KDMAge						
Stratified by gender			0.76			**0.08**
Males	1 (reference)	**1.05 (1.01, 1.09)**		1 (reference)	1.02 (0.99, 1.05)	
Females	1 (reference)	**1.06 (1.02, 1.09)**		1 (reference)	0.98 (0.95, 1.00)	
Stratified by age			0.57			**0.004**
≤ 60	1 (reference)	**1.07 (1.03, 1.11)**		1 (reference)	1.01 (0.98, 1.04)	
> 60	1 (reference)	**1.05 (1.01, 1.08)**		1 (reference)	0.98 (0.96, 1.01)	
Stratified by BMI			0.18			0.18
< 30	1 (reference)	**1.14 (1.06, 1.23)**		1 (reference)	**1.03 (1.01, 1.06)**	
≥ 30	1 (reference)	1.09 (1.00, 1.19)		1 (reference)	0.98 (0.94, 1.02)	

Note: Results were adjusted for age, sex, body mass index, race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, joint injury, and glucosamine use. Non-accelerated aging: PhenoAge/KDMAge acceleration ≤ 0. Accelerated aging: PhenoAge/KDMAge acceleration > 0. Bold denotes statistically significant.
Abbreviations: BMI, body mass index; KMDAge, Klemera–Doubal method biological age; OA, osteoarthritis; PhenoAge, phenotypic age.

TABLE 4 | Cross-sectional and longitudinal association between biological age acceleration and prevalence of OA in UK Biobank, stratified by polygenic risk status.

Biological age	wPRS	Biological age acceleration	OR (95% CI)	*p*	*p* for multiple interaction	HR (95% CI)	*p*	*p* for multiple interaction
PhenoAge	Low	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	**1.10 (1.05, 1.15)**	**< 0.0001**		**1.10 (1.05, 1.15)**	**< 0.0001**	
	Intermediate	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	**1.12 (1.09, 1.15)**	**< 0.0001**	0.63	**1.12 (1.09, 1.15)**	**< 0.0001**	0.63
	High	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	**1.15 (1.10, 1.20)**	**< 0.0001**	0.14	**1.15 (1.10, 1.20)**	**< 0.0001**	0.14
KDMAge	Low	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	**1.11 (1.05, 1.17)**	**< 0.001**		0.97 (0.93, 1.02)	0.426	
	Intermediate	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	**1.04 (1.01, 1.07)**	**0.014**	0.17	1.01 (0.97, 1.04)	0.766	0.34
	High	Non-accelerated aging	1 (reference)			1 (reference)		
		Accelerated aging	1.05 (1.00, 1.11)	0.64	0.33	1.02 (0.95, 1.08)	0.634	0.44

Note: Results were adjusted for age, sex, body mass index, race, Townsend deprivation index, education level, healthy diet, smoking status, alcohol drinker status, regular physical activity, joint injury and glucosamine use. Bold denotes statistically significant.

Abbreviations: HR, hazard ratio; KMDAge, Klemera–Doubal method biological age; OA, osteoarthritis; OR, odds ratio; PhenoAge, phenotypic age; wPRS, weighted polygenic risk score.

the first study to investigate the role of PhenoAge and KDMAge accelerations in the development of OA.

Increasing evidence suggests that OA is not simply a "wear and tear" disease caused solely by chronic loading and biomechanical joint damage, but rather a more complex process involving metabolic and inflammatory factors [30, 31]. Studies have demonstrated the associations between OA and several components of metabolic syndrome, such as hypertension, type 2 diabetes, and serum cholesterol elevation, independent of obesity or any other known risk factors for OA. Additionally, both in vitro and in vitro findings indicate a deleterious effect of lipid and glucose abnormalities on cartilage homeostasis [32]. As some biomarkers used to construct biological age (e.g., SBP, cholesterol, glycated hemoglobin) are highly correlated with metabolic health and inflammation, it is reasonable that biological aging acceleration can predict the incidence and prevalence of OA [33]. Additionally, the components of biological age include inflammation markers that have been confirmed to be associated with OA and pain, including C-reactive protein and white blood cell count [34]. Therefore, PhenoAge and KDMAge are calculated based on blood-based indicators, providing two minimally invasive methods to determine biological age, making them promising candidate predictive biomarkers for OA. The findings also offer potential avenues for OA prevention and intervention. Monitoring these blood-based biological age indicators may allow for earlier identification of high-risk individuals, enabling the implementation of targeted interventions to delay or prevent the onset and progression of OA. Furthermore, studies have found that adopting a healthy diet, increasing physical activity, quitting smoking, maintaining appropriate sleep duration, and managing body weight can effectively mitigate biological aging, which offers potential for OA prevention [35–37].

In the subgroup analyses, we observed a more prominent association between biological aging acceleration and a higher incidence of OA in individuals aged over 60, indicating a need for increased attention to aging acceleration in the older population. Our study is the first to evaluate the potential interaction between biological aging and genetic susceptibility to OA. We did not observe additive or multiplicative interactions between biological aging acceleration and genetic risk of OA, suggesting changes in biological aging status may serve as an independent risk factor for OA, regardless of genetic susceptibility. The strengths of the present study include a large-scale prospective study with a substantial sample size. Clinical biomarkers, as easily accessible and objectively measurable indicators, could offer more precise predictions.

Our study also has limitations. First, the biological markers were only available at baseline, which limited our ability to observe the relationship between changes in biological aging indicators and OA. Second, most of the population in the UK Biobank database was of White ethnicity, necessitating further research to ascertain if our results can be generalized to other populations. Third, our study was observational, and causality between biological aging and OA cannot be established. However, the results remained consistent even after excluding participants who developed OA within 2 years, which further helps mitigate the potential for reverse causality. Fourth, the diagnosis of OA in the UK Biobank relied on physician diagnosis. This could underestimate OA's prevalence and incidence, potentially introducing bias. Last, the associations between biological aging and OA at different sites could vary; however, this study is unable to identify different OA phenotypes.

5 | Conclusions

In summary, our study revealed significant associations between accelerated biological aging and OA prevalence, particularly among individuals over 60 years old, independent of OA genetic susceptibility. The two biological aging indicators hold potential as novel composite clinical biomarkers, directing prevention and intervention strategies for high-risk populations for OA.

Author Contributions

Z.Z., M.Z., S.L., and W.W. designed the study. S.L., W.W., M.Z., and Y.L. managed and analyzed the data. S.L., W.W., and C.L. wrote the first draft of the article. S.L., W.W., C.L., Y.L., Z.Z., M.H., Y.Z., Y.Z., K.T., H.S., Q.Y., M.Z., T.F., Z.A.L., C.D., D.J.H., and Z.Z. contributed to data interpretation and preparation of the report. All authors provided intellectual content to the manuscript and approved the submission.

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Ethics Statement

UK Biobank has received ethical approval from the UK National Health Service's National Research Ethics Service (16/NW/0274).

Conflicts of Interest

The lead authors (the manuscript's guarantor) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. David J. Hunter provides consulting advice on scientific advisory boards for Pfizer, Lilly, TLCBio, Novartis, Tissuegene, and Biobone. The other authors declare no conflicts of interest.

Data Availability Statement

The UK Biobank data are available from the UK Biobank on request (https://www.ukbiobank.ac.uk/).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flowchart of participant selection from UK Biobank. **Table S1:** Disease definitions used in the UK Biobank Study. **Table S2:** Single-Nucleotide Polymorphisms used to build the polygenic risk score of OA. **Table S3:** Covariates definitions used in the UK Biobank Study. **Table S4:** Cross-sectional association between biological age acceleration and risk of OA in UK Biobank, stratified by polygenic risk status. **Table S5:** Longitudinal association between biological age acceleration and risk of OA in UK Biobank, stratified by polygenic risk status. **Table S6:** Relative excess risk and attributable proportion for additive interaction between biological aging acceleration and genetic risk categories on incident OA. **Table S7:** Association between biological aging and risk of incident OA after excluding participants occurring osteoarthritis within 2 years of follow-up. **Table S8:** Association between biological aging and risk of OA prevalence (odds ratio) and incidence (hazard ratio) after excluding participants with missing covariates at baseline. **Table S9:** The longitudinal association between two biological ages and the incident OA using a competing risk model.

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CORRECTION

Correction to the "Poster Presentation Abstracts" for "The 27th Asia-Pacific League of Associations for Rheumatology Congress (APLAR) 2025, 3–7 September 2025, Fukuoka, Japan"

"Poster Presentation Abstracts," *Int J Rheum Dis* 29, no. S1 (2026): e70440. https://doi.org/10.1111/1756-185x.70440

The following abstract should be added.

A Case of Lower Limb Vasculitis Associated with Temporal Arteritis

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Background
Muscle involvement is not a typical manifestation of systemic vasculitis; however, it has been occasionally reported. In most cases, muscle inflammation is secondary to medium- or small-vessel vasculitis, whereas the involvement of large vessels in muscles remains extremely rare. We report a rare case of lower limb vasculitis associated with giant cell arteritis (GCA), where histopathological findings from a temporal artery biopsy were consistent with GCA, and inflammatory changes around the muscles of the lower limbs were detected by magnetic resonance imaging (MRI).

Case
A 77-year-old woman with a history of systemic sclerosis, diabetes mellitus, and right superficial femoral artery occlusion was admitted to our hospital with a persistent headache and fever of unknown origin. Although no tenderness or diminished pulsation of the temporal arteries was observed, thickening of the left superficial temporal artery was observed. Laboratory tests revealed leukocytosis (21,300/μL) and a markedly elevated C-reactive protein (CRP) level of 15.19 mg/dL, with no elevation of creatine kinase (CK) or serological evidence suggestive of myositis. MRI of the lower limbs demonstrated T2-weighted hyperintensity around the muscles of both lower limbs, predominantly on the left side. Temporal artery biopsy showed lymphocyte-dominant infiltration of the arterial wall with intimal thickening, consistent with GCA. Following admission, the inflammatory response spontaneously improved. However, owing to poor glycemic control, non-steroidal anti-inflammatory drugs (NSAIDs) were initiated, and methotrexate (MTX) was introduced as an immunosuppressive agent.

Discussion
This case highlights a rare instance of GCA with associated lower limb vasculitis diagnosed during evaluation of fever of unknown origin (FUO). The patient met four of the five diagnostic criteria established by the American College of Rheumatology (ACR) in 1990: age ≥50 years at disease onset, new-onset headache, erythrocyte sedimentation rate (ESR) ≥50 mm/h, and abnormal findings on temporal artery biopsy. Myositis associated with GCA is a rare clinical entity, and cases with MRI-confirmed findings are rare. This case underscores the importance of considering muscle involvement in GCA, and highlights the potential role of imaging in detecting this rare complication.

We apologize for this error.

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LETTER TO THE EDITOR

Enhancing Interpretability of AI Performance Metrics in Rheumatology Systematic Reviews

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To the Editor,

We read with great interest the systematic review by Barile and colleagues [1] on artificial intelligence (AI) applications in rheumatology. The review provides a valuable synthesis of a rapidly expanding field, and we commend the authors for their comprehensive coverage. We wish to offer two observations that may further strengthen the clinical interpretability of their findings.

First, the review appropriately notes that "most studies exhibit a moderate-to-high risk of bias," yet the performance estimates in the summary table are reported without corresponding risk-of-bias (RoB) ratings. The authors cite evidence showing formal RoB assessment may meaningfully shift how AI performance data are interpreted. A referenced systematic review of machine learning in rheumatoid arthritis revealed moderate-to-high bias risk in most formally assessed models [2]. The authors also recommend that frameworks such as PROBAST can "temper the optimistic performance estimates that characterize much of the current literature" [3, 4]. Adding a RoB rating column to the existing summary table would allow readers to weigh the reported AUCs against study quality, directly aligning the review's presentation with the methodological standards it advocates.

Second, the aggregated performance metrics in the summary table combine technical endpoints (e.g., radiographic scoring accuracy) and clinical outcomes (e.g., flare prediction, treatment response), with no clear separation between the two [1]. Notably, the authors astutely observe in their Practitioner Points that evidence linking AI deployment to better patient outcomes remains scarce, and prospective studies verifying measurable gains in clinical endpoints are lacking. This observation is valuable, and its impact could be further enhanced by operationalizing it in the results table. Adding a column classifying each study's endpoint as "technical" or "clinical" would give readers a clearer picture of where AI has demonstrated robust technical performance versus where prospective validation against patient-centered outcomes is still needed.

Each of these suggestions can be implemented using data already extracted by the authors and would require only minimal additions to the existing summary table. We thank the authors for their important contribution and hope these observations are received in the constructive spirit in which they are offered.

Author Contributions

Songxiahe Zhao: writing-original draft, writing-review and editing. **Yibin Du:** writing-review and editing.

Funding

The authors have nothing to report.

Disclosure

The authors have nothing to report.

Ethics Statement

Ethical approval was not required for this letter as it does not involve new research on human or animal subjects.

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.

Linked Articles

This article is linked to Barile et al. papers. To view these articles, visit https://doi.org/10.1111/1756-185x.70816.

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EDITORIAL

Editorial: The Path in Psoriatic Disease—From Conceptual Clarity to Clinical Translation

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1 | Introduction

The management of psoriatic disease is at a transformative crossroads, shifting from reactive symptom control to proactive "disease interception" [1]. Psoriatic arthritis (PsA) develops in up to one-third of people with psoriasis, often following a prolonged subclinical phase that offers a unique window of opportunity for intervention. Despite this, diagnostic delays exceeding 2 years remain common, leading to irreversible joint damage and long-term disability. As we move toward a secondary prevention paradigm, we must address the fundamental challenges of defining the target, stratifying risk, and establishing robust trial endpoints.

2 | Defining the Moving Target: Subclinical vs. Very Early PsA

A major challenge in interception is the lack of consensus on how to define the transition from psoriasis to PsA. For clinical practice and trial design, clear operational definitions are vital. "Subclinical PsA" typically denotes the presence of immunological or imaging-confirmed inflammation in individuals without clinical musculoskeletal symptoms. In contrast, aligning with the recent conceptual framework proposed by Ciccia and colleagues [2], "very early PsA" should be defined by the crucial threshold where subtle clinical musculoskeletal symptoms (such as mild arthralgia or early tenderness) co-occur with inflammation confirmed on imaging, prior to meeting the full Classification Criteria for Psoriatic Arthritis (CASPAR) [2, 3]. Current frameworks, such as those proposed by the European Alliance of Associations for Rheumatology (EULAR) and the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN), have historically differed in how they classify these stages [3]. Recent epidemiological insights suggest that harmonizing these definitions by focusing on this intrinsic biological transition is essential to ensure that interception trials are biologically grounded and ethically robust [4].

3 | Risk Stratification: Identifying the "Who"

Effective interception requires identifying people at the highest risk of imminent transition. Clinical risk models utilize factors like psoriasis severity, nail involvement, and obesity to estimate risk. However, even at maximum risk, the 1-year absolute predicted probability remains modest. To improve precision, we must integrate these clinical markers with dynamic biological signals. Retrospective cohort studies utilizing the TriNetX network—employing rigorous propensity score matching to adjust for baseline demographics and medication use—have highlighted that comorbidities such as Type 2 diabetes and fatty liver significantly elevate transition risk, reinforcing the need for a multimodal approach [5]. Furthermore, the role of HLA-B27 as a marker for specific endotypes suggests that genetic susceptibility provides a fixed background risk that interacts with time-varying exposures [5].

4 | Measuring Progression: Imaging and Digital Biomarkers

The choice of trial endpoints remains a significant challenge. While PsA incidence (CASPAR-defined) is the most reliable outcome, its low conversion rate requires large sample sizes. As a result, there is strong interest in surrogate endpoints like musculoskeletal ultrasound. Recent real-world data suggest that IL-23 inhibitors might be associated with a lower risk of incidental PsA compared to IL-17 inhibitors [6]. However, it is crucial to acknowledge that these findings stem from observational retrospective cohorts; their inherent nature introduces potential confounding by indication, necessitating robust prospective validation [6].

Beyond imaging, "digital phenotyping" via actigraphy-derived physical activity levels and circadian rhythm parameters is a sensitive indicator of disease activity and patient-reported impact [7]. By capturing real-world movement patterns, wearable sensors can detect subtle functional declines long before overt synovitis appears. Rather than relying on theoretical digital algorithms, the current priority in rheumatology must remain strictly on clinical precision, aggressive early intervention, and acute pain management to prevent functional decline [7].

5 | Ethical Considerations and the Patient Perspective

The decision to intercept must be patient-centered. Surprisingly, the majority of individuals with psoriasis are willing to consider preventive pharmacological therapy, provided the risk reduction justifies the potential side effects [1]. However, this willingness is sensitive to perceived risk. As we approach 2028, when results from trials evaluating early interventions are expected, we must develop ethical guidance for preventive therapy [4]. We must ensure that we are not over-treating stable subclinical states but rather intercepting those on a definitive path to joint destruction.

6 | Conclusion: A Roadmap for IJRD

The path toward intercepting PsA is shifting from conceptual models to evidence-based practice. For readers of IJRD, the message is clear: the "window of opportunity" is no longer just about early treatment of established disease, but about preventing the disease from taking hold and becoming entrenched. By unifying our definitions, integrating multimodal risk models, and prioritizing clinical precision, we can finally change the natural history of psoriatic disease.

Author Contributions

Tang-Kai Cheng: conceptualization; writing – original draft; writing – review and editing. The author has read and approved the final manuscript and agrees to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

From Concurrent Response Tracking to Clinically Actionable Biomarkers in Rheumatoid Arthritis: Comment on Jhou et al.

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Dear Editor,

We read with interest the study by Jhou and colleagues, who evaluated four complete blood count (CBC)-derived indices—the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and neutrophil-to-hemoglobin and lymphocyte score (NHL)—as markers of treatment response in 308 patients with active rheumatoid arthritis receiving biological or targeted synthetic disease-modifying antirheumatic drugs [1]. NLR, SII, and NHL decreased alongside improvements in DAS28-ESR and appeared particularly informative among patients with a normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Although inexpensive and accessible, these indices warrant further scrutiny before incorporation into treat-to-target algorithms.

First, the temporal interpretation of these findings warrants clarification. Jhou et al. appropriately noted that baseline values of these hematological indices were not reliable predictors of subsequent response. Our concern therefore relates not to the interpretation of baseline measurements, but to predictive terminology applied to receiver operating characteristic analyses based on changes measured over the same 6-month interval. Changes in the hematological indices and a reduction of more than 1.2 points in DAS28-ESR were assessed concurrently. Such analyses evaluate treatment-response-monitoring performance rather than prospective predictive performance [2] and do not establish an earlier signal that could guide treatment continuation, escalation, or switching. Prospective landmark analyses should examine whether changes at 2–8 weeks predict European Alliance of Associations for Rheumatology response, sustained remission, treatment persistence, or flare at 3–6 months.

Second, the apparently greater discriminatory performance of several CBC-derived indices within the normal-ESR/CRP subgroup should not be generalized to the full cohort. In the full cohort, ΔESR achieved an AUC of 0.737, comparable to or slightly higher than those of the hematological indices (0.707–0.732) [1]. Within the normal-ESR/CRP subgroup, however, interpretation is complicated by baseline range restriction and potential regression to the mean [3]. Because subgroup entry required already-low ESR and CRP, the observable range and potential magnitude of subsequent changes in these acute-phase reactants were constrained. Analyses across the continuous distributions of ESR and CRP, with comparison groups balanced for baseline disease activity, would help determine whether the subgroup-specific incremental value persists. A further issue is structural dependency of the reference outcome: because ESR is incorporated into DAS28-ESR, comparisons involving ΔESR and ΔDAS28-ESR are partly mathematically coupled. Validation against ESR/CRP-independent outcomes such as the Clinical Disease Activity Index (CDAI) or power Doppler-detected synovitis, as well as flare, treatment escalation, or structural progression, would be more clinically informative.

Third, the biological specificity of these composite indices remains uncertain, particularly for NHL. Jhou et al. appropriately discussed the direct hematological effects of IL-6 and JAK inhibition and the possible influence of glucocorticoid tapering. Building on this limitation, specific analyses could

help distinguish inflammatory response from pharmacological effects. These should include adjustment for changes in glucocorticoid dose, treatment-class interaction analyses, and component-level decomposition of the composite CBC metrics. This is especially relevant to NHL. Anemia in rheumatoid arthritis is common and heterogeneous, arising from inflammation-related iron restriction, iron deficiency, and other clinical or treatment-related factors [4]. Because hemoglobin forms part of the NHL denominator, changes might reflect altered erythropoiesis as well as inflammatory control. Stratification by anemia status, iron indices, and renal function could complement component-level analyses. Separately, complete-case exclusion of patients without 6-month data could bias estimates if missingness was associated with inefficacy, infection, adverse events, or treatment discontinuation [5]. Sensitivity analyses under alternative missing-data assumptions are therefore warranted.

CBC-derived indices are promising low-cost treatment-response-monitoring markers, but current evidence does not establish them as predictive biomarkers capable of prospectively guiding treatment decisions. Temporal validation, assessment of baseline range restriction and regression-to-the-mean effects, and treatment-specific mechanistic decomposition are needed to strengthen their interpretation. Separately, external validation in an independent rheumatoid arthritis cohort is necessary to establish transportability across populations, treatment strategies, and clinical settings.

Author Contributions

Yiling Ying conceived the letter, conducted the literature review, and drafted the manuscript. Xiaoxiao Wang supervised the work and critically revised the manuscript for important intellectual content. Both authors contributed to the interpretation of the evidence, reviewed the manuscript, and approved the final version.

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Consent

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Data Availability Statement

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

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EDITORIAL

Atlantoaxial Dislocation: Myths, Evidence, and a Practical Clinical Framework

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1 | Introduction

Atlantoaxial dislocation (AAD) is a potentially life-threatening condition characterized by instability between the atlas (C1) and axis (C2), posing a significant risk to the upper cervical spinal cord and brainstem. Neurological complications range from cervical myelopathy to acute quadriparesis and sudden death if left undiagnosed or untreated. Despite advances in imaging and treatment, AAD remains underrecognized in clinical practice [1].

Rheumatoid arthritis (RA) is the most common non-traumatic cause due to chronic synovitis, pannus formation, and ligamentous destruction [2]. However, AAD also occurs in spondyloarthritis, psoriatic arthritis, trauma, congenital anomalies, infections, and neoplastic conditions [3]. Persistent misconceptions—such as AAD being always symptomatic, exclusive to RA, or requiring mandatory surgery or chronic steroids—largely arise from historical data reflecting late-stage disease [4]. High-risk patients are those with long-standing inflammatory arthritis (particularly RA), persistent moderate-to-high disease activity, erosive disease, RF/anti-CCP positivity, previous cervical involvement, neurological symptoms, or planned surgery requiring airway manipulation [5–8]. In the current era of early diagnosis and treat-to-target strategies, these assumptions are no longer valid, underscoring the need for a myth-based, evidence-driven review to guide appropriate management.

2 | Discussion

2.1 | Myth 1: AAD Is Always Symptomatic

2.1.1 | Reality

AAD can remain clinically silent for years and is often detected incidentally on imaging, with symptoms typically appearing late after significant instability or cord compression. Studies show that nearly 40% of RA patients with cervical subluxation are asymptomatic [5], and imaging frequently identifies subclinical disease [9]. Reliance on symptoms alone may delay diagnosis and increase the risk of neurological deterioration; therefore, routine cervical spine evaluation is recommended in high-risk patients even in the absence of symptoms [2].

2.2 | Myth 2: AAD Only Occurs in Rheumatoid Arthritis

2.2.1 | Reality

While RA remains the leading cause, AAD also occurs in spondyloarthritis, psoriatic arthritis, and congenital or post-traumatic conditions. Reported prevalence of AAD is about 2%–8% in ankylosing spondylitis [3], 12% in psoriatic arthritis [10], and below 1%–3% in inflammatory bowel disease (IBD)-associated arthritis [11], while it remains extremely rare (< 1%)

in reactive arthritis, mostly described in isolated case reports [12]. Restricting the evaluation of AAD to RA alone may therefore delay diagnosis and appropriate management in affected non-RA populations.

2.3 | Myth 3: All Patients With AAD Require Chronic Steroid Therapy

2.3.1 | Reality

No randomized controlled trials have specifically evaluated long-term corticosteroids for preventing atlantoaxial instability or ligament destruction. They may be used short-term for acute inflammation, rapidly progressive synovitis, or suspected spinal cord edema. Chronic steroid use carries significant risks, including infection and osteoporosis. Moderate to high quality longitudinal studies (Table S1) attribute the decline in cervical spine involvement primarily to early, intensive conventional synthetic disease modifying antirheumatic drugs (csDMARD)-based treatment rather than prolonged corticosteroid exposure [5, 6, 13]. Steroids should be tapered early, ideally within 3 months, in line with overall RA management strategies [1–3].

2.4 | Myth 4: Biologic Agents Are Always Superior to csDMARDs for Preventing AAD

2.4.1 | Reality

Prevention of AAD depends on early disease control using treat-to-target strategies. While biologics provide rapid disease control and reduce erosions, optimized csDMARD therapy remains equally effective, especially in combination regimens. Evidence suggests that the decline in AAD incidence is driven by overall disease control rather than biologics alone, indicating that biologics are complementary rather than universally superior [2, 6].

2.5 | Myth 5: Surgery Is the Only Treatment Option

2.5.1 | Reality

Early diagnosis and immunosuppressive therapy can stabilize AAD and may delay or avoid surgery in selected patients. While surgery is indicated for significant instability, progressive neurological deficits, or cord compression, it is not the only option. csDMARDs and biologics can control synovitis and pannus, and conservative management with monitoring or immobilization may be appropriate in mild cases with no or minimal neurological symptoms, stable or reducible dislocation, no spinal cord edema and no radiographic progression on serial imaging [5, 13]. Management should be individualized based on clinical and radiological assessment [1, 2].

2.6 | Myth 6: Neurological Outcomes Are Universally Poor

2.6.1 | Reality

Bhatia et al. studied 224 surgically treated RA cervical spine patients, showing improved 10-year survival (35%–55%; $p = 0.001$) from 2000 to 2010. Patients undergoing C1–C2 fixation had less severe preoperative myelopathy and favorable outcomes over 39.6 months. 11% undergoing C1–C2 fixation later required occipitocervical fusion, mainly due to instrumentation failure [7].

2.7 | Myth 7: Routine Imaging Is Unnecessary in Stable Disease

2.7.1 | Reality

Periodic cervical spine evaluation is essential in high-risk patients to detect silent progression and prevent complications. AAD may progress insidiously, even in clinically stable disease, with instability present despite remission and symptoms appearing late [2, 5]. Reliance on symptoms alone may delay diagnosis; therefore, regular imaging is crucial to identify subclinical disease and prevent neurological complications [2, 5].

2.8 | Myth 8: AAD Is Inevitable in Patients With Long-Standing Rheumatoid Arthritis and Cannot Be Prevented Once the Disease Is Established

2.8.1 | Reality

Current evidence demonstrates that rheumatoid atlantoaxial subluxation can be significantly reduced and potentially prevented with early diagnosis, aggressive disease control, and treat-to-target strategies with csDMARDs (especially methotrexate) and biologic agents [2, 5, 6]. In the FIN-RACo trial, intensive combination DMARD therapy in the first 2 years of treatment significantly reduced the development of AAD in early RA after 5 years of follow-up, and monotherapy was significantly associated with anterior AAD ($p = 0.019$) [13].

2.9 | Myth 9: Surgical Fixation of AAD Completely Resolves Cervical Spine Disease and Eliminates Future Instability

2.9.1 | Reality

Sub axial subluxation (SAS) can occur in 10%–25% of cases following surgical stabilization of AAD due to altered biomechanics and persistent disease activity [1, 2, 4]. Surgical failure may result from patient factors like persistent active inflammatory disease, osteoporosis, malnutrition, smoking, poor bone quality, infection, poor wound healing, and significant medical comorbidities.

Technical issues include inadequate reduction, suboptimal screw placement, inappropriate implant selection, insufficient fixation, pseudarthrosis, and failure to recognize adjacent-level instability [14], and revision surgery is often challenging due to adhesions, distorted anatomy, and altered biomechanics [15].

2.10 | Myth 10: Neck Pain in Rheumatoid Arthritis Is Always due to AAD

2.10.1 | Reality

Neck pain in RA has a broad differential, and attributing all cases to AAD may lead to misdiagnosis. Sub axial subluxation (SAS) is a common cause, often progressing silently as radiculopathy and myelopathy [5]. Basilar invagination presents with occipital pain, myelopathy, lower cranial neuropathy or long tract signs with diagnostic criteria showing high sensitivity (94%) and NPV (91%) [16] and is confirmed by dynamic cervical x-ray and MRI. Fibromyalgia causes widespread pain with normal inflammatory markers and imaging [17], while osteoporosis may present with acute localized pain following trivial trauma due to compression fractures [18], and osteoarthritis results in mechanical neck pain that worsens with activity and shows degenerative changes on imaging [19].

2.11 | Myth 11: AAD Is an Imaging Diagnosis

2.11.1 | Reality

Atlantoaxial subluxation typically presents with occipital pain radiating to the posterior head and neck, with neurological features ranging from paresthesias to quadriparesis, sphincter dysfunction, and signs of cord compression, often poorly correlating with radiographic severity [1, 2]. The Sharp–Purser test assesses transverse ligament instability and has high specificity (≈96%–99%) but moderate sensitivity; a positive test warrants further imaging [20].

2.12 | Myth 12: Baseline Quality of Life Doesn't Predict the Risk of AAD

2.12.1 | Reality

In the FIN-RACo trial, poor baseline physical function, as measured by the Health Assessment Questionnaire (HAQ), was significantly linked to the development of AAD ($p = 0.024$). Patients who developed AAD during the 5-year follow-up also demonstrated higher HAQ scores and increased Disease Activity Score 28 values [13]. These findings underscore the importance of early treat-to-target therapy and regular cervical spine surveillance in patients with persistent disease activity.

2.13 | Myth 13: MRI Doesn't Usually Add Anything in the Diagnosis or Management of AAD

2.13.1 | Reality

Evaluation of AAD requires a multimodal imaging approach. Plain radiographs (including flexion–extension views) are used for initial screening, CT provides detailed assessment of bony anatomy, and MRI is essential for evaluating pannus, ligament damage, and spinal cord compression. Screening imaging is recommended in high-risk patients, even without clinical instability [2, 5, 7].

2.14 | Myth 14: Prevalence of AAD Has Remained Similar Despite Advancing Imaging Modalities and Widespread Use of csDMARDs and Biologic Drugs

2.14.1 | Reality

In the pre-DMARD era, cervical spine involvement, including AAD, was reported in 30%–50% of patients with long-standing rheumatoid arthritis. With the advent of early diagnosis, treat-to-target strategies, csDMARDs, and biologic therapies, recent studies report a reduced prevalence of 5%–15%, with clinically significant AAD being even less frequent [2, 5]. All the included studies are summarized in the Table 1.

3 | Management

Effective management relies on a multidisciplinary team, including rheumatologists, spine surgeons, radiologists, and neurologists to facilitate timely diagnosis and appropriate treatment [1–3]. Treatment algorithm is shown in the Figure 1.

4 | Conclusion

AAD is often misunderstood as always symptomatic, RA-specific, and requiring steroids or surgery. Evidence shows outcomes improve with early diagnosis, appropriate imaging, and individualized care. Combined medical and selective surgical management with routine screening in high-risk patients helps prevent neurological complications and improves prognosis.

TABLE 1 | Summary of included studies.

Section A. Advances in imaging and diagnosis of atlantoaxial dislocation					
Authors (Year)	**Patient characteristics, sample size, mean age**	**Study design**	**Imaging modality**	**Key findings**	**Clinical implication**
Sharp J & Purser DW (1961) [20]	26 RA: 54 (47–59.25) years, 18F, 8M 22 AS: 37.5 (31–54) years, 2F, 20M	Observational	Xray cervical spine lateral view	ADI > 3 mm is suggestive of AAD both from general population (age > 45 years) and clinical studies. Almost all patients were symptomatic rather than RA patients where AAD was diagnosed by routine Xray.	Typical clinical features and long-term RA patients should undergo routine Xray cervical spine lateral, flexion and extension view to detect AAD precisely.
Moilanen A et al. (1984) [12]	Reiter's syndrome patients; $n = 38/145$ patients had cervical spine Xray, median age: 39.5 (20–56) years. 22F, 16M	Cross-sectional	X-ray Cervical spine	5/145 (3.4%): AAD	AAD is rare in reactive arthritis and is indistinguishable from other chronic rheumatic disease.
Jordan JM et al. (1986) [11]	21-year female	Case report	Xray cervical spine	Erosive cervical spine with C1-C2 subluxation with Crohn's disease	AAD can be an extra intestinal manifestation of IBD.
Salvarani C et al. (1992) [10]	Psoriatic arthritis (PsA) patients; $n = 57$	Cross-sectional	Xray cervical spine	40% had radiological cervical spine involvement, 26% erosive, 44% AS like changes. 53% had subaxial subluxation.	Presence of HLA-B39 and HLA-DR4 antigens, radiocarpal erosions, and the absence of the HLA-DR5 antigen are the predictors of inflammatory cervical spine disease in PsA.

(Continues)

TABLE 1 | (Continued)

Section A. Advances in imaging and diagnosis of atlantoaxial dislocation

Authors (Year)	Patient characteristics, sample size, mean age	Study design	Imaging modality	Key findings	Clinical implication
Riew KD et al. (2001) [16]	RA patients, $n = 131$, median age: 62.5 (39–86 years)	Cross-sectional	131: X-ray, 67/131 (29 had basilar invagination): CT and MRI of cervical spine	Combination of the Clark station, the Redlund-Johnell criterion, and the Ranawat criterion had a sensitivity of 94% and NPV of 91%	No single radiographic criteria have sensitivity > 90%. 6% basilar invagination can be missed by X-tay, so MRI and CT are important for diagnosis.
Neva MH et al. (2006) [5]	RA patients, $n = 154$; mean age: 55 years	Cross-sectional	Cervical spine X-ray	Asymptomatic cervical subluxation present in ~33% patients	Cervical instability frequently occurs without symptoms in RA
Teuber H et al. (2023) [9]	Ankylosing spondylitis patients vs. control; $n = 39/78$, mean age: 66.2 years	Case control retrospective study	CT scan of cervical spine	No difference in the radiographic parameters for other cervical pathologies between the 2 arms.	Specific parameters defined for traumatic AAD should be used for AS related AAD.
Uchino et al. (2021) [18]	RA, $n = 185$, 12M and 173F, median age: 68 (62–74 years) under csDMARD (70%), biological therapy (30%), glucocorticoid (49%) < 20 mg	Cross sectional observational study	X-ray cervical spine and BMD	57% cervical lesion, 79 AAS, 31 VS, 41 SAS.	Younger age of RA onset, longer RA disease duration, higher RA stage, and lower femoral neck BMD are the predictors of cervical lesion.
Zhu S et al. (2017) [8]	RA: 2750 patients, CSI: 733 (26.65%)	Meta-analysis	Risk factor analysis	Female (1.37), RF (1.3), long term CS (2.2), hand and feet erosions (2.5), mean age difference −2.464 years, high ESR, CRP and DAS 28.	Female gender, positive RF, long-term corticosteroids treatment, peripheral joints erosions, younger age, long RA duration, and high disease activity are the significant predictors of cervical spine involvement.

TABLE 1 | (Continued)

Section B. Advances in pharmacological and surgical management of atlantoaxial dislocation					
Authors (Year)	**Patient characteristics, sample size, mean age**	**Study design**	**Intervention**	**Key findings**	**Clinical implication**
Bhatia et al. [7]	RA cervical spine patients; $n \approx 224$, mean age: 61 (±11) years, 41M, 224F	Retrospective study (1981–2010)	C1-C2 fixation vs. Occipitocervical fixation (OCF). Patients undergoing C1-C2 fixation had less Ranawat index.	55% 10-year survival rate with C1-C2 fixation (2001–2010) compared to OCF. Statistically significant improvement in MDI and mode Ranawat index (IIIA to II) 1-year post surgery.	Early recognition and improved surgical techniques like C1-C2 fixation can improve structural, functional as well as survival rate.
Kauppi MJ et al. (2009) [13]	RA cohort; $n = 149/199$ Patients, mean age: 48 ± 10 years (FIN-RACo-trial)	Randomized controlled trial with 5 years long-term follow-up	Combination (Triple csDMARD therapy) vs. Single therapy	aAAS (9%), AAI (4%), SAS (6%). aAAS + AAI in 2 and AAI + SAS in one patient. Single group (14%) vs. Combination (3%)	Combination therapy effectively reduces the prevalence of AAD than single therapy.
Smolen JS et al. (2010) [6]	International recommendations on treat to target RA	Task force Recommendations	Treat-to-target therapy	Tight disease control improves outcomes.	Early aggressive therapy prevents structural damage. Target: remission, if not then LDA.
Sindgikar P et al. (2016) [14]	414 operated cases of CVJ anomalies	Retrospective study	Risk factors of resurgery in already operated CVJ anomalies	137 procedures (resurgery) in 13% cases. Implant failure was more after 1 year of primary surgery.	Subaxial spine scoliosis, torticollis, and asymmetric joints and OCF increased the incidence of reexploration.
Devani KK et al. (2025) [15]	20 Recurrent AAD patients after index surgery failure, 12M, 8F, median age: 30.47 (8–62) years	Retrospective observational	19/20: Traction, median duration of traction: 982.33 days (1.2–305.3 months)	Only CI (36.84%), (21.05%) only RI, both (36.84%). 17/19 patients: improved clinically after resurgery.	Patients improved with traction should undergo resurgery. Timely intervention has a similar success rate to the index surgery.

Abbreviations: aAAS, anterior atlanto axial subluxation; AAD, Atlanto-axial dislocation; AAI, atlantoaxial impaction; AS, Ankylosing spondylitis; CI, Clinical improvement; CSI, Cervical spine involvement; CVJ, Craniovertebral junction; FMS, Fibromyalgia syndrome; IBD, Inflammatory bowel disease; LDA, Low disease activity; PsA, Psoriatic arthritis; RA, Rheumatoid arthritis; RI, Radiological Improvement; SAS, subaxial subluxation.

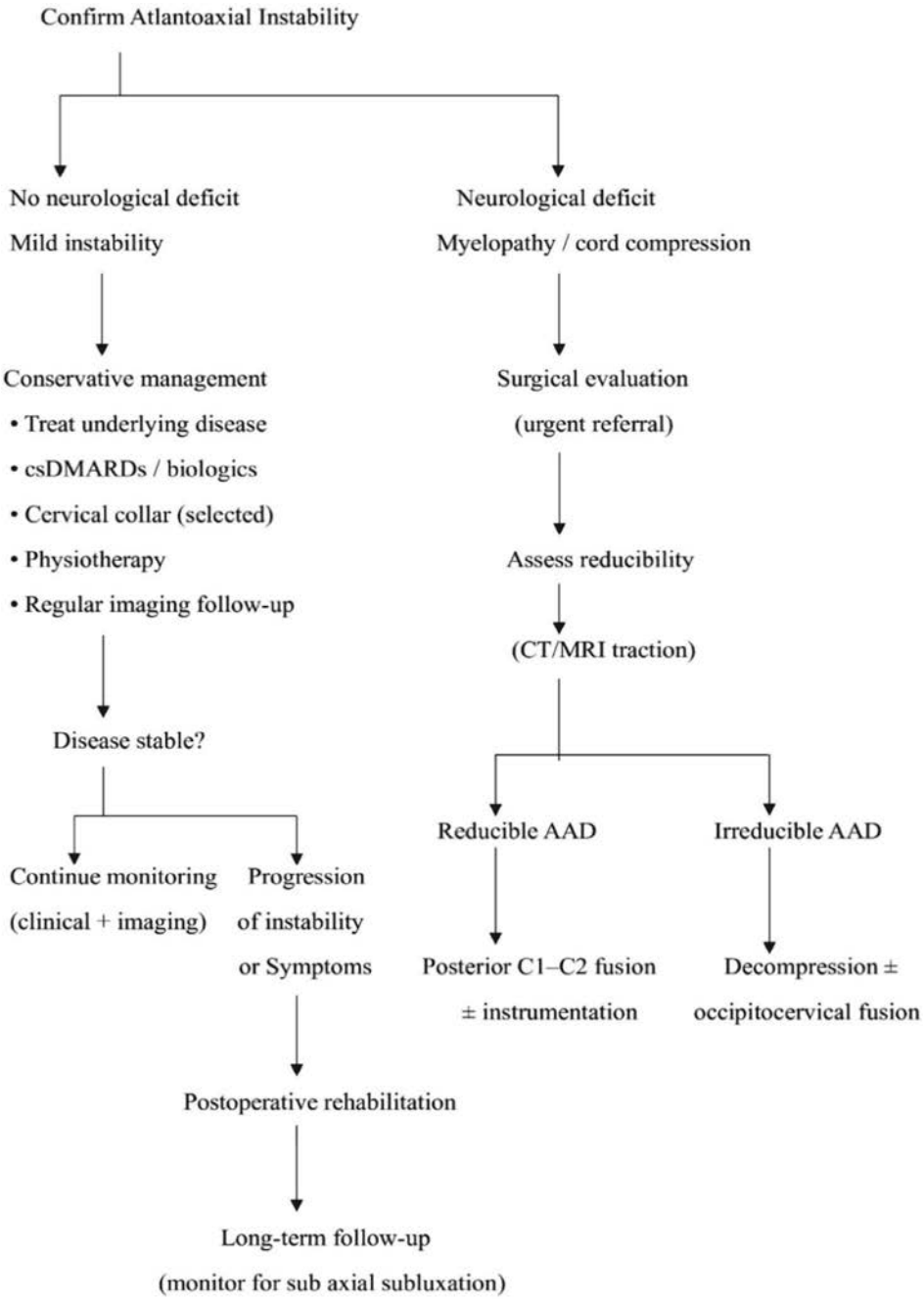

FIGURE 1 | Treatment algorithm of AAD.

Author Contributions

The conception and design of the review: R.K.S., A.G.P., M.S., U.D., P.K.; Drafting the article: R.K.S., A.G.P., M.S., U.D., P.K.; Revising it critically for important intellectual content: R.K.S., A.G.P., M.S., U.D. Final approval of the version to be submitted: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Evidence-based Summary for steroid use in Atlantoaxial dislocation.

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EDITORIAL

From Risk to Treatment: Clinical Updates in Osteoporosis Management

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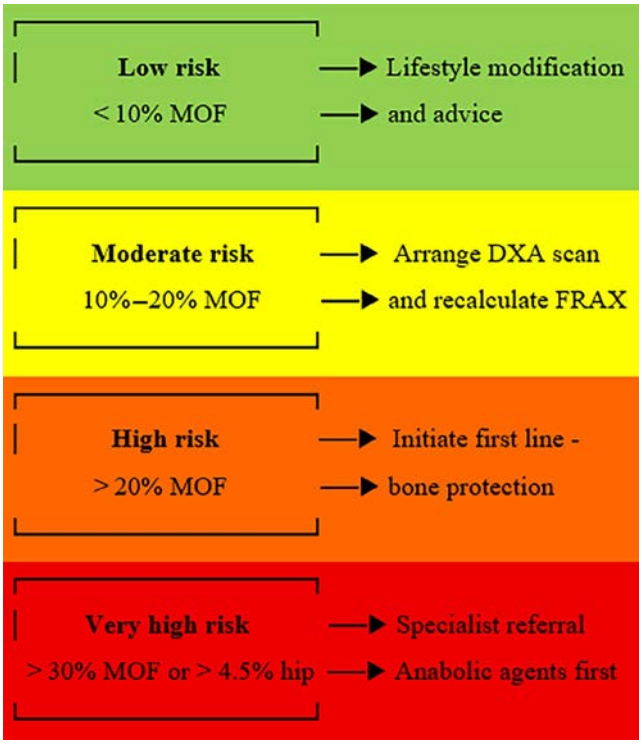
Osteoporosis is a chronic skeletal condition characterized by reduced bone mass and structural deterioration, resulting in elevated fragility fracture risk. It affects an estimated 200 million people worldwide, with approximately one in two postmenopausal women and one in four men over 50 expected to sustain an osteoporotic fracture in their lifetime; yet fewer than 30% of eligible patients receive appropriate therapy following a fracture event [1]. Hip fracture alone carries a one-year mortality of approximately 20% [2]. Two landmark guidelines published in 2024 from the National Osteoporosis Guideline Group (NOGG, UK) and the Royal Australian College of General Practitioners (RACGP, Australia) provide a contemporaneous synthesis of evidence-based recommendations for fracture prevention and osteoporosis management [3, 4].

This editorial synthesizes clinically actionable updates from these guidelines and recent trial evidence, focusing on fracture risk stratification and its international application. This includes the expanding role of osteoanabolic therapies, safe pharmacological sequencing including denosumab cessation. This was developed from an invited presentation at the 2nd Royal College of Physicians Global Medicine Conference, June 2026. A structured narrative review was conducted drawing on NOGG 2024 [3], RACGP 2024 [4], the International Osteoporosis Foundation/European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (IOF/ESCEO) European guidance [5], the American College of Rheumatology (ACR) Guideline for Glucocorticoid-Induced Osteoporosis [6], and Asia Pacific Consortium on Osteoporosis (APCO) framework statements [7], supplemented by a targeted MEDLINE and Embase search (2019–2025).

The NOGG 2024 guideline recommends a risk-stratified approach using Fracture Risk Assessment Tool (FRAX) to calculate the 10-year probability of major osteoporotic fracture (MOF: spine, hip, forearm, humerus) and/or hip fracture, stratifying individuals into low, moderate, high, or very high-risk groups (Table 1). Very high risk is now formally defined as MOF > 30% or hip fracture probability > 4.5%, the threshold triggering consideration of anabolic-first therapy. IOF/ESCEO and APCO similarly endorse FRAX-based stratification, with country-calibrated models available across the Asia-Pacific region. Patients with rheumatoid arthritis carry approximately double the population fracture risk through systemic inflammation, glucocorticoid exposure, and Receptor Activator of Nuclear factor Kappa-B Ligand (RANK-RANKL)-mediated bone loss [8]. Patients with systemic lupus erythematosus face similarly elevated fracture risk, with meta-analytic data reporting a near-doubling of osteoporosis prevalence (OR 2.03) and all-site fracture risk (RR 1.97) compared to age- and sex-matched controls [9]. For glucocorticoid-induced osteoporosis (GIOP), any patient receiving prednisolone ≥ 7.5 mg/day for ≥ 3 months should receive bone-protective therapy regardless of T-score, with FRAX corrected by multiplying hip risk by 1.20 and MOF by 1.15 [3] consistent with NOGG 2024 and the 2022 ACR GIOP guidelines.

Treatment selection should be guided by fracture risk, comorbidities, renal function, and patient preference (Table 2). Oral bisphosphonates or annual intravenous zoledronate are first line for high-risk patients (MOF > 20%), consistent across

TABLE 1 | FRAX calculator and risk stratification.

FRAX input variables	Risk stratification (NOGG 2024)
• Age (40–90 years) • Sex • Weight and height (BMI calculated) • Previous fragility fracture • Parent hip fracture (family history) • Current smoking • Corticosteroids use ≥ 3 months • Rheumatoid arthritis • Secondary osteoporosis • Alcohol (3 or more units/day) • Femoral neck BMD (T-score)—Optional	

Note: FRAX risk stratification thresholds and clinical decision pathways for osteoporosis management: Input variables, 10-year fracture probability categories (NOGG 2024), and corresponding treatment actions. FRAX calculator accessible at fraxplus.org (free, country-specific models available).

NOGG 2024, RACGP 2024, and IOF/ESCEO guidance. For very high-risk patients, all three bodies advocate anabolic-first therapy such as romosozumab or teriparatide before antiresorptive consolidation. NOGG 2024 additionally repositions hormone replacement therapy (HRT) as a first-line option for younger postmenopausal women (≤ 60 years) at high fracture risk with low cardiovascular risk, supported by updated Women's Health Initiative (WHI) analyses demonstrating a more favorable benefit–risk profile in women commencing HRT before the age of 60 [10]. Denosumab is second-line, or first-line in chronic kidney disease (CKD) stages G4–G5D. It must never be stopped without a bridging antiresorptive as rebound vertebral fractures occur in up to 7%–20% of patients and IV zoledronate 5 mg given 6 months after the last injection is preferred. Fracture Liaison Service (FLS) referral following any fragility fracture reduces subsequent fracture risk by up to 40% [11].

Patients with CKD stages G4–G5D carry substantially elevated fracture risk through CKD-related mineral and bone disorder yet remain largely excluded from osteoporosis trials [12]. Dual-energy X-ray absorptiometry (DXA) is supported by Kidney Disease: Improving Global Outcomes (KDIGO) 2017 as part of integrated CKD fracture risk assessment. Bisphosphonates carry theoretical risks including renal accumulation and potential adynamic bone disease. Denosumab is generally preferred but requires monitoring for hypocalcemia and rebound secondary hyperparathyroidism on cessation. The 2021 European consensus on osteoporosis in CKD stages G4–G5D provides current guidance for this population.

Osteoanabolic agents are now recommended as initial therapy for very high-risk patients across NOGG 2024, RACGP 2024, and IOF/ESCEO guidance. Teriparatide (20 μg SC daily for 24 months) and abaloparatide (80 μg SC daily for 18 months) are PTH receptor agonists that preferentially stimulate bone formation [13, 14]. Both agents reduce vertebral and non-vertebral fracture, and abaloparatide's sequential alendronate strategy demonstrated sustained efficacy in the ACTIVExtend trial [15]. Romosozumab (210 mg SC monthly for 12 months) inhibits sclerostin with dual anabolic and antiresorptive effects, reducing vertebral fractures by 73% at 12 months in FRAME [16, 17] and outperforming alendronate alone in ARCH. It should be avoided in patients with recent myocardial infarction or stroke. All osteoanabolics must be followed by antiresorptive consolidation (zoledronate or denosumab 2–3 years, or oral bisphosphonates 3–5 years) and a single lifetime course applies. A bisphosphonate drug pause may be considered in stable, low-risk patients. Denosumab should not be discontinued without bridging antiresorptive therapy [7]. Bone turnover markers (BTMs) should be monitored at 3–6 months with rising procollagen type 1 N-terminal propeptide (P1NP) confirming anabolic activity and falling C-terminal telopeptide (CTX) confirms antiresorptive response [18].

The importance of the recent guidelines is that it provides a clear stratified framework enabling clinicians to match treatment intensity to fracture risk systematically. There are differences from previous guidelines that impact clinical practice. The formal definition of very high risk directly triggering anabolic-first prescribing is a landmark shift for the patients

TABLE 2 | Pharmacological treatment of osteoporosis using a risk-stratified approach.

Antiresorptives	Osteoanabolics	When to use which agent
Bisphosphonates (1st line high risk) • Alendronate 70 mg weekly PO • Risedronate 35 mg weekly PO • Zoledronate 5 mg IV annual → Use IV if poor oral tolerance • AEs: esophageal irritation (oral), acute-phase reaction/flu-like symptoms (IV zoledronate), osteonecrosis of the jaw (ONJ, rare), atypical femoral fracture (prolonged use > 5 years). Denosumab (2nd line/renal impairment) • 60 mg SC every 6 months • CKD G4–G5D: preferred over bisphosphonates • ⚠ NEVER stop without bridging treatment • AEs: hypocalcaemia, rebound vertebral fractures on cessation without bridging HRT (NOGG 2024) • Younger < 60 years of age • Postmenopausal women, high risk, low CV risk—Dual benefit: symptoms + bone • AEs: thromboembolic and breast cancer risk (long-term).	Teriparatide (PTH 1–34) • 20 μg SC daily × 24 months • ↑ BMD rapidly; vertebral/non-vertebral fracture ↓ • Always follow with antiresorptive • AEs: nausea, dizziness, transient hypercalcaemia, contraindicated in prior skeletal radiation, Paget's disease, hypercalcaemia Abaloparatide (PTHrP analogue) • 80 μg SC daily × 18 months • Similar efficacy to teriparatide • Now included in NOGG 2024 • AEs: nausea, dizziness, transient hypercalcaemia, contraindicated in prior skeletal radiation, Paget's disease, hypercalcaemia Romosozumab (sclerostin inhibitor) • 210 mg SC monthly × 12 months • Dual: ↑ formation + ↓ resorption • ↓ Vertebral fracture 73% at 12 m (FRAME) • ⚠ Avoid if recent MI or stroke • AEs: cardiovascular events (contraindicated if recent MI/stroke within 1 year), ONJ (rare).	High risk (FRAX > 20% MOF): • → Start bisphosphonate (oral or IV) Very high risk (FRAX > 30% MOF or recent fragility fracture): • → Anabolic-first strategy • Romosozumab or Teriparatide • Then transition to antiresorptive Renal impairment (CKD stages G4–G5D): • → Denosumab preferred • → Cautiously consider bisphosphonates for high-risk patients (KDIGO 2017) Younger postmenopausal women (< 60 years, symptomatic): • → Consider HRT first-line (NOGG 2024)

Note: Risk-stratified pharmacological treatment of osteoporosis: antiresorptive and osteoanabolic agents, indications, doses, duration, and major adverse effects. Includes guidance for special populations (very high risk, renal impairment, younger postmenopausal women) aligned with KDIGO 2027, NOGG 2024, and RACGP 2024 recommendations. The background color scheme is to highlight three different sections, the first two being modes of actions with antiresorptive in grey and osteoanabolics in pink. The third in blue is for practical use of agents in osteoporosis.

most likely to sustain a second, potentially disabling fracture within 12 months. The persistent treatment gap with fewer than 30% treated after fracture [1], represents the central challenge these guidelines must help address. Three changes represent meaningful changes. First, anabolic-first therapy for very high-risk patients reverses the bisphosphonate-first convention dominant since the 1990s, now supported by ARCH trial head-to-head data [16]. Second, HRT's repositioning reflects a reassessment of benefit–risk balance following updated Women's Health Initiative (WHI) analyses [10]. Third, the denosumab cessation warning addresses a pharmacovigilance signal that emerged largely after the previous NOGG iteration and is now formalized as a contraindication to abrupt discontinuation.

Current controversies include romosozumab's non-significant major adverse cardiovascular event (MACE) imbalance in ARCH (2.5% vs. 1.9% with alendronate; $p = 0.07$) [16]. This is substantially contextualized by the absence of any cardiovascular signal in the larger FRAME trial [17] and post hoc analyses suggesting the difference reflects an unusually low alendronate MACE rate rather than a romosozumab harm [19]. Current guidance appropriately excludes patients with recent MI or stroke, but individual shared decision-making is essential where fracture prevention benefit is substantial. The single lifetime osteoanabolic course restriction derives from regulatory precedent rather than re-treatment trial data. The optimal vitamin D supplementation threshold, particularly in the Middle East and Asia-Pacific where deficiency rates of 70%–90% are documented, is an area that requires harmonization with guideline recommendations for supplementation to deficient individuals.

While these newer recommendations are welcome, there remain existing gaps in evidence. The near-complete exclusion of patients with advanced CKD from major trials leaves clinicians without adequate evidence for this high-risk population. Fracture risk in inflammatory rheumatic diseases where FRAX may substantially underestimate burden due to active disease and biological therapies is under-studied. Primary osteoporosis in children and young adults represents a further under-recognized population, with emerging data highlighting the diagnostic challenges and treatment outcomes in this group [20]. Long-term sequential osteoanabolic strategies and the concept of imminent fracture risk (disproportionately elevated for 12–24 months after an index fracture) both lack dedicated trial data. Opportunistic CT-based screening with automated identification of low BMD and vertebral fractures from scans performed for other indications could substantially expand fracture prevention reach. Future directions include AI tools to perform this analysis at scale as these are in development. Scaling FLS programmes across the Asia-Pacific region, where the fracture burden is growing rapidly with demographic aging, is an urgent implementation priority. Novel therapeutic targets under investigation include anti-activin receptor type IIA/IIB agents such as bimagrumab, which have shown dual musculoskeletal benefits in early studies through inhibition of activin-mediated signaling, with potential applications in osteosarcopenia. Cathepsin K inhibitors demonstrated substantial fracture reduction efficacy in Phase III trials but have not progressed to regulatory approval due to an increased risk of cerebrovascular events and remain a mechanistic proof-of-concept rather than an active clinical pipeline.

The 2024 osteoporosis guideline updates represent a substantive reconfiguration of clinical practice in a decade. Their core messages which are: stratify risk with FRAX, deploy anabolic therapy first in very high-risk patients, and never discontinue denosumab without a bridging antiresorptive are actionable in clinical settings. Closing the persistent gap between guideline recommendations and practice remains the greatest opportunity to reduce the global burden of preventable fragility fractures.

Author Contributions

Karam Alchi: writing – original draft, review and editing. Antoni Chan: conceptualization, writing – original draft, review and editing, critical revision.

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Data sharing is not applicable to this article as no new data were generated.

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LETTER TO THE EDITOR

Translation, Cross-Cultural Adaptation, and Initial Psychometric Evaluation of the Urdu COPCORD Questionnaire

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Dear Editor,

Rheumatic and musculoskeletal diseases (RMDs) are one of the leading causes of disability globally [1]. In low- and middle-income countries (LMICs), patients with musculoskeletal disease face additional barriers in the form of limited disease awareness, diagnostic delays, and lack of access to treatment [2]. Additionally, in LMICs, rates of rheumatic disease appear to be rising [3], though epidemiologic data in these regions remain limited [4].

Rheumatology in Pakistan is an evolving specialty faced with multiple challenges, including limited workforce capacity, uneven service distribution, and high professional burnout among clinicians [5, 6]. Despite advances in epidemiologic understanding of musculoskeletal disease in other regions, studies on disease burden in Pakistan remain limited.

The WHO–ILAR Community Oriented Program for Control of Rheumatic Diseases (COPCORD) Core Questionnaire is a standardized community-based screening instrument used to identify musculoskeletal pain, related functional limitations, and healthcare use. It is usually administered by trained interviewers, with screen-positive individuals referred for clinical assessment. A few Community Oriented Program for Control of Rheumatic Diseases (COPCORD) studies have been conducted in Pakistan, which used translated versions of the questionnaire but did not undertake a formal psychometric evaluation [7, 8].

The original COPCORD Core Questionnaire was developed as a community-based case-detection instrument for rheumatic and musculoskeletal complaints, and subsequent research has supported the screening validity of several of its core items. Internationally, the measurement properties of the COPCORD Core Questionnaire have been evaluated in different settings. A large multicenter study from Mexico assessed its validity as a community case-detection tool [9], while an Arabic version was validated for screening rheumatic diseases in Kuwait [10]. Regionally, the culturally adapted Bangla version demonstrated excellent content validity and test–retest reliability [11].

In the absence of a formally translated and culturally adapted Urdu version, differences in wording, cultural interpretation, and locally understood descriptions of pain and disability may lead to inconsistent responses, which may affect the accuracy of estimates of the burden of rheumatic and musculoskeletal diseases. Establishing content validity is necessary to ensure that the translated items are relevant and culturally appropriate, while test–retest reliability determines whether the questionnaire produces stable responses over time. Evaluation of these properties is therefore important before the Urdu COPCORD questionnaire is used in large-scale epidemiological surveys.

The objective of this study was to translate and culturally adapt the World Health Organization—International League of Associations for Rheumatology (WHO-ILAR) COPCORD Core Questionnaire into Urdu and to evaluate its content validity and test–retest reliability in an Urdu-speaking Pakistani population.

This was a cross-sectional validation study conducted in two phases. In the first phase, the English COPCORD questionnaire was translated and culturally adapted into Urdu through a multistep process. In the second phase, content validity and test–retest reliability were evaluated. The study followed established guidelines for cross-cultural adaptation of self-report instruments, relevant COSMIN recommendations, and ISPOR Task Force recommendations [12–14].

The translation and cultural adaptation process followed six sequential steps (Table S1). Two independent forward translations were produced and synthesized, followed by blinded back-translation. An expert panel reviewed all versions for semantic, idiomatic, and conceptual equivalence. The pre-final Urdu version was pilot-tested with 40 participants. Participant feedback focused on wording that was unclear or difficult to interpret, and minor modifications were made based on participant feedback before finalization.

The study was conducted at the Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad. For Phase I cognitive pretesting, a total of 40 participants (20 patients with RMDs and 20 non-patients) were recruited from outpatient clinics and community settings. The Phase I pretesting sample size ($n = 40$) was based on cross-cultural adaptation guidance recommending cognitive debriefing with 30–40 individuals [12]. The Phase II validation sample comprised 120 participants, including 60 rheumatology patients and 60 community participants. This is consistent with COSMIN guidance that considers a sample of at least 100 participants to be excellent for reliability assessment [15]. Participants were recruited using consecutive sampling from rheumatology outpatient clinics and surrounding community settings in Islamabad. Eligible participants were adults aged 18 years or older who could communicate in Urdu and provided informed consent. Individuals were excluded if they had an acute medical condition requiring immediate medical assessment or hospital admission, or if their physical condition prevented them from completing the interview. Individuals with cognitive or intellectual impairment that precluded informed consent or reliable questionnaire completion were also excluded.

Because the adaptation required both clinical and linguistic review, experts were purposively selected for relevant professional expertise, comprising two practicing rheumatologists from the Pakistan Institute of Medical Sciences, Islamabad, and two faculty members from the National University of Medical Sciences with academic expertise in Urdu language and literature. Inclusion criteria for experts were current clinical practice in rheumatology or academic expertise in Urdu language and literature.

Content validity was assessed in terms of item relevance and comprehensiveness. The Content Validity Index (CVI) was used to quantify agreement among experts. Experts rated each item for relevance on a 4-point scale (1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant). For the calculation of Item-level Content Validity Index (I-CVI), ratings of 3 or 4 were considered "relevant," and I-CVI was defined as the proportion of experts rating the item as relevant. The Scale-level Content Validity Index (S-CVI/Ave) was calculated as the mean of the I-CVI values across items [11, 16].

Comprehensiveness was assessed qualitatively by confirming that all items and core domains of the original COPCORD questionnaire were retained in the Urdu version. Face validity was assessed separately through qualitative review of the translated questionnaire for clarity of wording, naturalness of the Urdu phrasing, cultural appropriateness, and overall suitability for use in an Urdu-speaking population.

Test–retest reliability was assessed using linearly weighted Cohen's kappa, guided by COSMIN [17]. The same participants completed the questionnaire twice, with a 7-day interval between administrations. A 7-day interval was chosen to minimize recall bias and reduce the likelihood of true clinical change between assessments, consistent with previously reported test–retest intervals and prior ILAR–COPCORD questionnaire research [18, 19]. Participants were informed at baseline that a repeat assessment would be conducted after 7 days; however, at retest, they were not shown their baseline responses. All analyses were performed using IBM SPSS Statistics version 27.0. The study was approved by the institutional ethics committee of the Pakistan Institute of Medical Sciences, Islamabad. Written informed consent was obtained from all participants before data collection.

The Phase II validation sample comprised 120 participants, including 60 rheumatology patients and 60 community participants. The mean age of participants was 43.9 ± 13.4 years (median 41 years, range 18–75). Of 120 participants, 78 (65.0%) were female. Baseline characteristics of the study participants are presented in Table S4.

During cognitive pretesting, participants considered most items clear and easy to interpret, and minor linguistic modifications were made where required, including use of locally relevant demographic, education, occupation, and treatment-source options. Additionally, in the habits section locally prevalent tobacco forms (huqqa and naswar) were included. All items and core domains of the original WHO–ILAR COPCORD Core Questionnaire were retained in the Urdu version. A brief description of the items evaluated during Phases I and II is presented in Table S2. All items achieved acceptable content validity (I-CVI = 1.0). The Scale-level Content Validity Index (S-CVI/Ave) was 1.0 (Tables 1 and 2). Linearly weighted kappa values ranged from 0.833 to 0.983 (Table S3).

The Urdu translation of a culturally adapted COPCORD questionnaire presented here demonstrated both excellent content validity and test–retest reliability. Similar to COPCORD translations conducted in other languages [11], we sequentially performed initial forward translation with cross-cultural adaptation, modification based on participant pre-testing, expert committee validity review, and finally test–retest reliability

TABLE 1 | Expert ratings and item-level content validity indices (I-CVI) for Phase I items of the Urdu WHO–ILAR COPCORD Core Questionnaire using a 4-point relevance scale.

Item	Rating by Expert 1	Rating by Expert 2	Rating by Expert 3	Rating by Expert 4	I-CVI
Item 1.1	4	4	4	4	1.0
Item 1.2	4	3	4	4	1.0
Item 1.3	3	4	4	4	1.0
Item 1.4	4	4	4	4	1.0
Item 1.5	4	4	3	4	1.0
Item 1.6	3	3	3	4	1.0
Item 1.7	3	4	3	3	1.0
Item 1.8	4	4	4	4	1.0
Item 1.9	4	4	4	3	1.0
Item 1.10	3	4	3	4	1.0
Item 1.11	4	3	3	4	1.0
					S-CVI/Ave = 1.0

Abbreviations: COPCORD, Community Oriented Program for Control of Rheumatic Diseases; I-CVI, item-level content validity index; S-CVI/Ave, scale-level content validity index (average method); WHO–ILAR, World Health Organization–International League of Associations for Rheumatology.

TABLE 2 | Expert ratings and item-level content validity indices (I-CVI) for Phase II items of the Urdu WHO–ILAR COPCORD Core Questionnaire using a 4-point relevance scale.

Item	Rating by Expert 1	Rating by Expert 2	Rating by Expert 3	Rating by Expert 4	I-CVI
Item 2.1	4	3	4	3	1.0
Item 2.2	4	3	3	4	1.0
Item 2.3	4	4	4	3	1.0
Item 2.4	4	3	4	3	1.0
					S-CVI/Ave = 1.0

Abbreviations: COPCORD, Community Oriented Program for Control of Rheumatic Diseases; I-CVI, item-level content validity index; S-CVI/Ave, scale-level content validity index (average method); WHO–ILAR, World Health Organization–International League of Associations for Rheumatology.

testing. The excellent I-CVI and S-CVI/Ave values should be interpreted critically in the context of the adaptation process, the small number of expert raters, and the fact that the Urdu version retained the established COPCORD core domains after clinical and linguistic review. Similar findings were reported in the Bangla COPCORD adaptation [11]. In the Pakistani context, we modified the questionnaire to be more culturally relevant, for example, by expanding the habits section to include locally prevalent forms of tobacco.

Strengths of this study include robust testing of the Urdu translation, encompassing expert-developed translation, followed by adjustment for patient feedback, content validation, and finally, test–retest reliability testing. Our study also had some limitations. Unlike prior studies [10], we did not compare the results of our COPCORD translation to clinical diagnosis. We assessed content validity and test–retest reliability of the Urdu COPCORD. Other COSMIN measurement properties, including construct validity, criterion validity, and responsiveness, were not evaluated in the present study. Future studies comparing questionnaire responses with clinical diagnoses and external measures are needed to comprehensively assess these additional psychometric domains. Additionally, this was a single-center study conducted in Islamabad using consecutive sampling from a tertiary-care rheumatology clinic and surrounding community settings, which may limit the generalizability of the findings. Given Pakistan's linguistic diversity, additional cross-cultural adaptations of the COPCORD in other major languages are also needed to ensure equitable national application.

Overall, the Urdu COPCORD questionnaire demonstrated high content validity and test–retest reliability and is intended to facilitate future national COPCORD surveys and inform rheumatology policy planning in Pakistan.

Author Contributions

Writing original draft: H.S. and T.K.; Methods: M.S. and T.K.; Formal analysis: H.S. and T.K.; Data curation: M.S.; Project administration: M.S. and T.K.; Conceptualization: T.K.; Supervision: U.R. and M.A.S.; Writing review and editing: All authors.

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Ethics Statement

This study received ethical approval from Federal Medical Teaching Institute Research Review board with reference# FMTI ERRB/08/13.

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:** A summary of stages in validation and cross cultural adaptation of the COPCORD Questionnaire. **Table S2:** Item numbers and description of each item from the two phases. **Table S3:** Test–retest reliability of participant-rated item clarity using linearly weighted Cohen's kappa. **Table S4:** Sociodemographic characteristics of Phase II participants ($n = 120$).

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LETTER TO THE EDITOR

Radiological Change in Interstitial Lung Abnormalities and Interstitial Lung Disease in Patients With Rheumatoid Arthritis at 1 Year

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Dear Editor,

Interstitial lung disease (ILD) is a common comorbidity among patients with rheumatoid arthritis (RA). Estimates using radiological evaluation have indicated that the prevalence of ILD associated with RA (RA-ILD) varies from 19% to 33% [1]. In Japanese patients with RA treated with biological and targeted synthetic disease-modifying antirheumatic drugs (btsDMARDs), the mean age increased from 51.9 years in 2003 to 64.3 years in 2023, while the prevalence of lung disease rose markedly from 11.1% to 36.2% [2]. Interstitial lung abnormalities (ILAs) refer to early or mild interstitial changes identifiable on chest computed tomography (CT). A considerable proportion of patients with RA exhibit deterioration of ILAs, underscoring the importance of timely detection and appropriate management. One study found that patients with RA with ILA had more respiratory symptoms and poorer pulmonary function than those without ILA [3]. In one prior study investigating patients with RA without established ILD, ILAs were identified in 15% of individuals on screening CT [4, 5]. Further, patients with RA have a higher prevalence of both ILD and ILA compared with the general population. Understanding of the changes in ILAs may help to prevent deterioration to ILD and improve survival outcomes in patients with RA. However, information regarding changes in ILA in patients with RA remains insufficient. Clarifying the natural course and radiological evolution of ILA in patients with RA may help to facilitate the early identification of individuals at risk of disease progression and provide evidence to support appropriate monitoring and timely clinical intervention. This study therefore aimed to evaluate the radiological change of lung images in patients with RA treated at 1 year.

This study evaluated the changes in imaging findings of ILA and ILD over a 1-year period in 542 patients with RA who underwent a baseline chest CT between April 2023 and March 2024, followed by a repeat chest CT 1 year later (Figure 1). Patients who did not undergo the baseline chest CT during this period ($n = 15$) were excluded from the study. Chest CT findings at baseline and 1-year follow-up were compared to assess the radiological deterioration of ILA and ILD. These chest CT examinations were conducted as part of our institutional screening protocol for the early detection and monitoring of ILA and ILD in patients with rheumatoid arthritis. Under this protocol, all eligible patients routinely underwent a baseline chest CT, followed by a scheduled follow-up examination approximately 1 year later, irrespective of their respiratory symptoms or any clinical suspicion of lung disease. A standard chest CT was conducted because the examinations were performed for screening purposes, rather than as a definitive diagnostic assessment. To evaluate the interval radiological changes, follow-up CT was performed under the same imaging conditions as the baseline examination, thereby ensuring consistency between the baseline and follow-up assessments.

Abbreviations: anti-CCP, anti-cyclic citrullinated peptide; btsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; CT, computed tomography; DAS28-ESR, 28-joint Disease Activity Score based on erythrocyte sedimentation rate; IL, interleukin; ILA, interstitial lung abnormality; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MTX, methotrexate; NSIP, nonspecific interstitial pneumonia; RA, rheumatoid arthritis; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis; UIP, usual interstitial pneumonia.

The following clinical variables were evaluated: age, sex, body mass index, RA duration, anti-cyclic citrullinated peptide (anti-CCP) antibody level, btsDMARDs use, methotrexate (MTX) use, glucocorticoid use, C-reactive protein level, rheumatoid factor (RF) level, Krebs von den Lungen-6 (KL-6) level, 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR), and Health Assessment Questionnaire Disability Index. According to a position paper published by the Fleischner Society, ILAs were characterized by ground-glass or reticular abnormalities, accompanied by traction bronchiectasis, honeycombing, and nonemphysematous cyst formation [6]. In accordance with this position paper, ILAs in the present study were defined as subtle abnormalities observed on chest CT in individuals without a prior diagnosis of ILD that were less severe than changes observed in patients with established ILD (Figure 2a). ILD was classified as either a usual interstitial pneumonia (UIP) pattern characterized by honeycombing with or without traction bronchiectasis, irregular interlobular septal thickening typically accompanied by reticulation, mild ground-glass opacities, and occasional pulmonary ossification or a nonspecific interstitial pneumonia (NSIP) pattern with bilateral extensive ground-glass opacities (Figure 2b) [7, 8]. Radiological deterioration was defined as the presence of one or more of the following: worsening traction bronchiectasis, new or increased reticulation, new or increased honeycombing, increased traction bronchiectasis with ground-glass opacity, increased ILD extent, or progression to a UIP-like pattern. In contrast, radiological improvement was defined as one or more of the following: decreased ground-glass opacity extent, decreased reticulation, or reduced ILD extent compared with the previous chest CT. Deterioration and improvement of ILA and ILD were diagnosed based on visual evaluations and consensus discussions among a rheumatologist, respiratory physician, and radiologist. The radiologist and clinicians who assessed the chest CT images were blinded to the patients' clinical information.

A comparison of demographics and clinical characteristics of patients without both ILA and ILD (no ILA/ILD group), patients with ILA (ILA group), and patients with ILD (ILD group) was conducted using an analysis of variance and Fisher's exact test (as appropriate). To identify factors associated with ILA deterioration, the characteristics and clinical data of patients with or without ILA deterioration were compared using the Wilcoxon rank-sum test and Fisher's exact test (as appropriate). The same

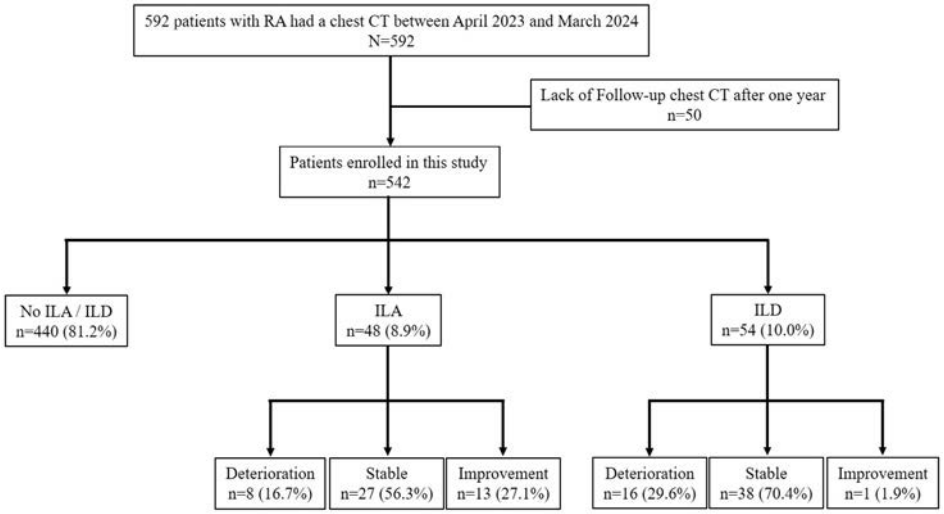

FIGURE 1 | Flow diagram of patient selection and radiological outcomes during 1-year follow-up. Flow diagram showing patient enrollment, exclusion of patients without 1-year follow-up chest CT, baseline classification into no ILA/ILD, ILA, and ILD groups, and radiological outcomes (deterioration, stable disease, or improvement) after 1 year. CT, computed tomography; ILA, interstitial lung abnormality; ILD, interstitial lung disease.

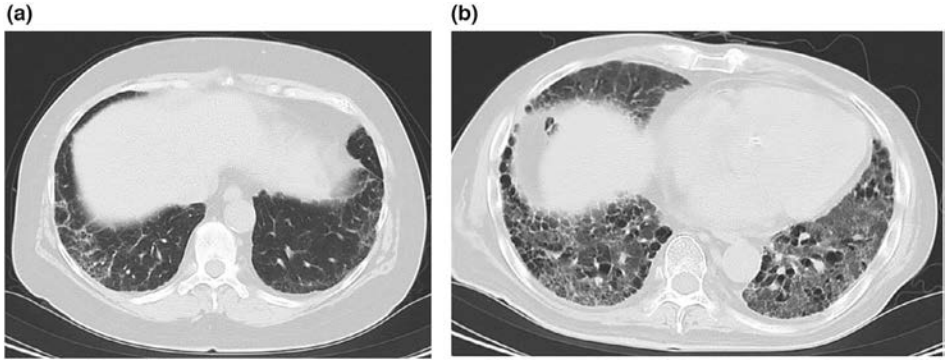

FIGURE 2 | Representative chest CT image of (a) interstitial lung abnormality and (b) interstitial lung disease in a patient with rheumatoid arthritis. (a) Chest CT demonstrates subtle peripheral and basal reticular abnormalities consistent with an interstitial lung abnormality. (b) Chest CT demonstrates advanced fibrotic interstitial lung disease with bilateral honeycombing, consistent with interstitial lung disease.

analyses were conducted for patients with ILD. Statistical significance was defined as $p < 0.05$.

A total of 542 patients with RA underwent chest CT. Table 1 summarizes the patient characteristics and clinical data of the study population at baseline, including comparisons among the no ILA/ILD, ILA, and ILD groups. Figure 1 presents the patient selection process and radiological outcomes. At baseline, 440 (81.2%) patients had no evidence of ILAs or ILD, while 48 (8.9%) and 54 (10.0%) patients had ILAs and ILD, respectively; among the latter, 26 (4.8%) and 28 (5.2%) had UIP and NSIP patterns, respectively. During the follow-up period, among patients in the ILA group, radiological deterioration was observed in 8 (16.7%) patients, stability was observed in 27 (56.3%) patients, and improvement was observed in 13 (27.1%) patients. The corresponding rates in the ILD group were 16 (29.6%), 38 (70.4%), and 1 (1.9%), respectively. In the comparison based on the presence or absence of ILA deterioration, factors associated with ILA deterioration were not identified. In the comparison conducted according to the presence or absence of ILD deterioration, only the change in RF levels was identified, with changes of 51.9 ± 99.9 IU/mL in the deterioration group and −5.1 ± 155.8 IU/mL in the non-deterioration group ($p = 0.019$). During the follow-up period, treatment modifications involving btsDMARDs, MTX, and glucocorticoids occurred in 15 (2.8%), 20 (3.7%), and 9 (1.7%) patients, respectively.

In the present study, the prevalences of ILA and ILD were 8.9% and 10.0%, respectively; these rates were comparable to or slightly lower than that reported in previous studies [9, 10]. One possible factor contributing to the relatively low prevalence may be the comparatively low disease activity of the patients included in our cohort. The prevalences of connective tissue disease-associated ILD were as follows: 0.8–42, 0.1–0.6, 0–0.1, 0.02–1.7, and 0–0.6 per 100 000 people in patients with systemic sclerosis, polymyositis/dermatomyositis, Sjögren's syndrome,

TABLE 1 | Baseline demographic and clinical characteristics of patients with rheumatoid arthritis according to the presence of interstitial lung abnormalities and interstitial lung disease, with comparisons among groups.

	All ($n = 542$)	No ILA/ILD ($n = 440$)	ILA ($n = 48$)	ILD ($n = 54$)	p (Uni)	p (OR, 95% CI)
Age, years	70.3 ± 12.0	69.2 ± 12.3	73.6 ± 8.2	73.6 ± 9.1	< 0.001	0.005 (1.06, 1.02–1.10)
Female, *n* (%)	443 (81.7)	368 (83.6)	38 (79.2)	37 (68.5)	0.028	0.032 (0.38, 0.16–0.92)
Duration of RA, years	15.5 ± 11.0	15.3 ± 10.7	17.7 ± 10.1	15.4 ± 13.9	0.354	
Body mass index	22.4 ± 3.9	22.2 ± 3.9	23.3 ± 4.6	22.4 ± 3.6	0.182	
Smoking: current/past/never, *n*	49/132/361	41/96/303	4/14/30	4/22/28	0.049	Current: 0.992 (0.99, 0.27–3.66) Past: 0.385 (1.42, 0.64–3.15)
Anti-CCP Ab positive, *n* (%)	422 (77.9)	334 (75.9)	40 (83.3)	48 (88.9)	0.057	0.064 (2.51, 0.95–6.65)
b or tsDMARDs use, *n* (%)	333 (61.4)	261 (59.3)	36 (75.0)	36 (66.7)	0.078	0.513 (0.79, 0.39–1.61)
MTX use, *n* (%)	323 (59.6)	277 (63.0)	27 (56.3)	19 (35.2)	< 0.001	0.002 (0.37, 0.17–0.66)
Glucocorticoid use, *n* (%)	89 (16.4)	70 (15.9)	7 (14.6)	12 (22.2)	0.469	
C-reactive protein level, mg/dL	0.30 ± 0.69	0.27 ± 0.59	0.36 ± 0.85	0.41 ± 0.79	0.219	
Rheumatoid factor level, IU/mL	122.6 ± 225.7	109.1 ± 224.0	142.6 ± 183.9	190.3 ± 223.5	0.031	0.554 (1.00, 1.00–1.00)
KL-6, U/mL	279.4 ± 137.9	257.1 ± 109.2	334.2 ± 154.7	413.5 ± 218.6	< 0.001	< 0.001 (1.01, 1.00–1.01)
DAS28-ESR	2.61 ± 1.17	2.57 ± 1.21	2.56 ± 0.99	3.01 ± 0.99	0.035	0.087 (1.22, 0.97–1.54)
HAQ-DI	0.41 ± 0.75	0.38 ± 0.75	0.59 ± 0.78	0.51 ± 0.65	0.109	

Abbreviations: anti-CCP Ab, anti-cyclic citrullinated peptide antibody; bDMARDs, biological disease-modifying antirheumatic drugs; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; ILA, interstitial lung abnormality; ILD, interstitial lung disease; KL, Krebs von den Lungen-6; MTX, methotrexate; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

systemic lupus erythematosus, and mixed connective tissue disease, respectively [11]. ILD has recently been recognized as a rare but serious complication of childhood chronic arthritis, particularly systemic juvenile idiopathic arthritis (sJIA). Prior studies have estimated that sJIA-associated lung disease occurs in approximately 3.6%–7% of patients and is associated with significant morbidity and mortality, highlighting the importance of early recognition [12, 13]. Recent evidence has also suggested that interleukin (IL)-1/IL-6 inhibitor-associated drug reaction with eosinophilia and systemic symptoms may contribute to the development of severe pulmonary disease in a subset of patients with sJIA [14]. Furthermore, the early diagnosis and treatment of ILD associated with childhood vasculopathy have been reported to be associated with favorable outcomes [15]. Thus, the presence of ILD is an important determinant of the clinical course in patients with RA and should be carefully considered during clinical follow-up.

The present study investigated radiological changes in ILAs and ILD in patients with RA at 1 year. The ILD group was characterized by older patients, fewer female patients, less MTX use, higher DAS28-ESR, and higher levels of RF and KL-6. Previous studies have reported that ILD development was associated with older age, longer RA duration, high anti-CCP antibody levels, and increased RF levels [16]. Although elevated RF levels have been associated with the development and progression of RA-associated ILD, the underlying mechanisms remain incompletely understood. Changes in RF may reflect alterations in systemic autoimmune and inflammatory activity, which could contribute to the progression of pulmonary disease. Other studies have found associations between ILD development and male sex, increased erythrocyte sedimentation rate, advanced joint destruction, MTX use, glucocorticoid use, and functional impairment [17]. We believe that the low rate of MTX use in this study reflected concerns regarding the potential adverse effects of MTX on ILD. KL-6 is widely used to diagnose ILD deterioration because its sensitivity (93.9%) and specificity (96.3%) are superior to those of surfactant protein-A (sensitivity, 81.8%; specificity, 86.6%) and surfactant protein-D (sensitivity, 69.7%; specificity, 95.1%) [18]. Therefore, understanding the factors associated with ILD is useful in clinical practice. In the present study, the radiological deterioration rates of ILAs and ILD were 16.7% and 29.6%, respectively. During the follow-up period of 4.4 years, 29% of patients with RA and ILAs (21 cases) exhibited radiological deterioration [9]. The discrepancy in progression rates observed during our study and those reported by previous studies may be attributable to differences in follow-up periods, patient age (75.0 ± 8.8 years vs. 65.6 ± 9.9 years), and MTX use (45% vs. 89%). In prior studies, radiological ILD deterioration occurred in 34% (follow-up period, 24 months), 44% (follow-up period, 4.4 years), and 51% (follow-up period, 19.1 months) of patients [9, 19, 20]. We believe that regular chest CT is also necessary for patients with ILAs. The present study did not identify any significant factors associated with ILA deterioration; additionally, previous studies did not identify any factors associated with ILA deterioration based on patient characteristics [5, 9, 21]. Previous studies have further reported that older age, male sex, smoking, high RA disease activity, high RF levels, anti-CCP antibody titers, and increased KL-6 levels are associated with ILD deterioration [22–26]. In this study, changes in RF levels were associated with ILD deterioration; therefore, increased RF levels in patients with ILD may be associated with the risk of ILD deterioration and may require careful monitoring.

This study had several limitations. First, chest CT was not conducted using quantitative measures. In the present study, imaging findings were evaluated by multiple observers to ensure careful assessments of ILA deterioration and ILD deterioration. Second, the clinical symptoms and pulmonary function tests, including forced vital capacity and diffusing capacity of the lung for carbon monoxide, were not routinely performed as part of the study protocol and were therefore unavailable for the analysis. Consequently, disease progression was evaluated solely based on radiological findings. Third, treatment modifications during the follow-up period may have influenced the radiological outcomes. However, changes in btsDMARDs, MTX, and glucocorticoid use occurred in only 2.8%, 3.7%, and 1.7% of patients, respectively. Therefore, although the potential impact of treatment modifications cannot be completely excluded, their overall influence on the radiological findings was likely to have been limited. Finally, the one-year follow-up period may have been insufficient to fully capture the natural progression of ILAs and ILD, which commonly evolve over longer periods. Consequently, the radiological progression rates observed in the present study may have been underestimated. In addition, the relatively small sample size may have limited the generalizability of our findings. Future studies should include larger sample sizes and longer follow-up periods, and should incorporate both pulmonary function tests and additional imaging assessments to provide a more comprehensive evaluation of disease progression. Nevertheless, we believe that the results of the present study provide important insights for future research and the management of ILAs and ILD in patients with RA in clinical practice.

In conclusion, this study demonstrated radiological changes in ILAs and ILD in patients with RA. Some patients with RA with ILAs or ILD may experience radiological deterioration. Therefore, regular imaging assessment may be considered in selected patients.

Author Contributions

T. Mochizuki and S. Katayanagi conceived and designed the study. T. Mochizuki collected the data. K. Yano performed the statistical analysis. T. Mochizuki, S. Katayanagi, and M. Sato interpreted the results. T. Mochizuki drafted the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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 Asahi Kasei, Bristol-Myers, Eisai, Eli Lilly, Mochida and Pfizer. K. Yano received honoraria

for lectures from AbbVie, Chugai, Eisai, Gilead Sciences, Janssen, Kaken, Pfizer, and UCB. The other authors declare that they have no conflicts of interest.

Data Availability Statement

Research data are not shared.

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LETTER TO THE EDITOR

Letter to Editor Regarding "Association Between Chikungunya Infection and Rheumatoid Arthritis in Taiwan—A Cross-Sectional Study"

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Dear Editor,

The authors are to be congratulated for studying the possible linkage between the chikungunya virus (CHIKV) infection and rheumatoid arthritis (RA) in a non-endemic area and for comparing various serological assays [1]. We would like to make several methodological points, however, that could affect their conclusions.

First, there is an inherent limitation that it is not possible to establish a temporal association between the CHIKV infection and the onset of RA from cross-sectional data, but the authors persevered in discussing CHIKV as a potential environmental trigger for RA. STROBE recommends that observational studies should refrain from making causal conclusions when there is no temporality provided.

Secondly, the study is very under-powered. Of the 98 patients with RA, only 2 were positive for CHIKV neutralizing antibodies compared to no healthy controls (200). The resulting odds ratio (OR = 10.4) thus had very wide 95% confidence intervals (CI = 0.5–217) that showed quite a bit of statistical imprecision and uncertainty. These estimates are unreliable and should be read with some caution and not as an indication of a biological relationship.

Thirdly, the statistical analysis is worthy of further examination. The authors appropriately reported Fisher's exact test ($p = 0.107$) because of the sparse contingency table. They also gave a chi square p value of 0.043, which means it is statistically significant. Fisher's exact test should be used as the preferred inferential test where the assumptions of the chi-square test are not met; reporting the chi-square result with Fisher's exact test could mask the strength of the evidence for the association.

Fourth, exposure assessment was different among the three study groups. Since Taiwan is non-endemic for CHIKV, the IgM testing was only done on patients with RA, not healthy controls. Different diagnostic techniques for cases and controls are likely to lead to differential misclassification bias and diminish comparability between the groups [2].

Lastly, some key confounding factors were not considered in the analyses. Only univariate comparisons were done and not multivariable analyses. Notably, residents or travelers to the CHIKV-endemic regions were identified in both antibody-positive patients, implying a travel history might be the most likely factor explaining antibody positivity. Other possible confounding factors such as smoking, work exposure, and immunosuppressive therapy were also not accounted for. When possible, the STROBE statement suggests that clinical factors associated with the study should be identified and controlled for [3].

The study offers some preliminary data on the serology of CHIKV infection among Taiwanese patients with RA. However, the findings should be interpreted with care because of the limited sample, the nature of the exposure assessment, the lack of control for other risk factors, the lack of power in the analysis for such a small sample size, and the inherent limitations of a cross-sectional study. A better understanding of the relationship between CHIKV infection and RA is warranted by future prospective, adequately-powered cohort studies that would use consistent exposure assessment and multivariable analyses.

Author Contributions

Deep Shikha: conceptualization, data curation, writing – original draft, writing – review and editing; Sunita Sharma: writing – review and editing.

Funding

The authors have nothing to report.

Ethics Statement

It is not applicable as this is a Letter to the Editor commentary on previously research which has already been published and there in no involvement of any human, animals, identifiable personal data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing does not apply to this article as no new data were created or analyzed in this study.

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LETTER TO THE EDITOR

Bilateral Plantar Fibromatosis in a Female Patient: A Rare Presentation After a 15-Year Symptom History

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Keywords: foot | inflammation | plantar fascia | ultrasound

To the Editor,

A 53-year-old female cleaning worker (weight, 90 kg; height, 155 cm; body mass index, 37.5 kg/m [1]) presented with chronic bilateral plantar pain and difficulty with weight-bearing activities that had persisted for approximately 15 years. During this period, she had not sought medical evaluation or had received any treatment, including medications, injections, or physical therapy. Her medical history was otherwise unremarkable.

Physical examination revealed firm, nodular thickenings along the medial aspects of both plantar surfaces, accompanied by localized tenderness. No plantar contracture or skin scarring was observed. A prompt bedside ultrasound (US) examination revealed diffuse, well-defined, hypo- to isoechoic lesions within the plantar fascia bilaterally, without power Doppler signal (Figure 1A,B, Video S1). These findings were consistent with plantar fibromatosis. The patient was advised to perform plantar fascia stretching exercises, apply ice massage to both heels, and use heel pads. At the 1-month follow-up, the patient reported full adherence to the exercise program, and her pain score had decreased from 8 to 3 on the visual analog scale. After 3 weeks of medical leave, she returned to work. No adverse events were reported. Plantar fibromatosis (Ledderhose disease, PF) is a rare, benign fibroproliferative disorder of the plantar fascia, characterized by nodular or diffuse fascial thickening [2]. Although its exact etiology remains unclear, several factors, including genetic predisposition, repetitive trauma, previous fascia injuries, anti-tumor necrosis factor-α therapy, and associated fibroproliferative conditions such as Dupuytren contracture, have been implicated in the literature [2]. The condition typically affects middle-aged men and is most often unilateral; however, bilateral involvement has been reported in approximately 25% of the male patients.

Despite its benign nature, PF may lead to persistent pain, gait impairment, and reduced quality of life due to its chronic course and potential for local recurrence [1, 3]. Misdiagnosis as chronic plantar fasciitis or other soft-tissue pathologies is common, frequently leading to delayed diagnosis and suboptimal management [4]. US and magnetic resonance imaging (MRI) are valuable tools for differentiating plantar fibromatosis from inflammatory or neoplastic conditions [5]. On ultrasonography, plantar fibromatosis typically presents as one or more well-defined, fusiform, hypoechoic nodules arising within the mid-portion of the plantar fascia, usually without power Doppler signal. In contrast, plantar fasciitis manifests as fusiform hypoechoic thickening of the proximal fascia at its calcaneal enthesis (commonly > 4 mm) with loss of the normal fibrillar pattern, rather than a discrete nodule, and clinically presents with focal heel pain that is worst with the first steps after rest. Other soft-tissue lesions, such as ganglion cysts (anechoic and compressible) or neurogenic and neoplastic masses (which may show internal vascularity), can usually be excluded on the basis of their distinct sonographic features and anatomic location [6, 7]. Moreover, US has several advantages over MRI in the assessment of PF. Plantar fibromas may appear as small hypointense lesions on MRI, making them difficult to distinguish from the normally low signal intensity of the plantar fascia [8, 9]. In contrast, small plantar fibromas can be readily detected on US because their hypoechoic echotexture contrasts with the fibrillar appearance of the normal plantar fascia [8, 9]. Accordingly, given the diagnostic accuracy of US for PF, we did not perform further MRI or histopathological examination. Beyond its diagnostic utility, US enables real-time, target-specific interventions such as corticosteroid or collagenase injections. Although no standardized injection technique has been clearly described in the literature, delivering corticosteroids directly into the fibromatosis nodule—thereby suppressing

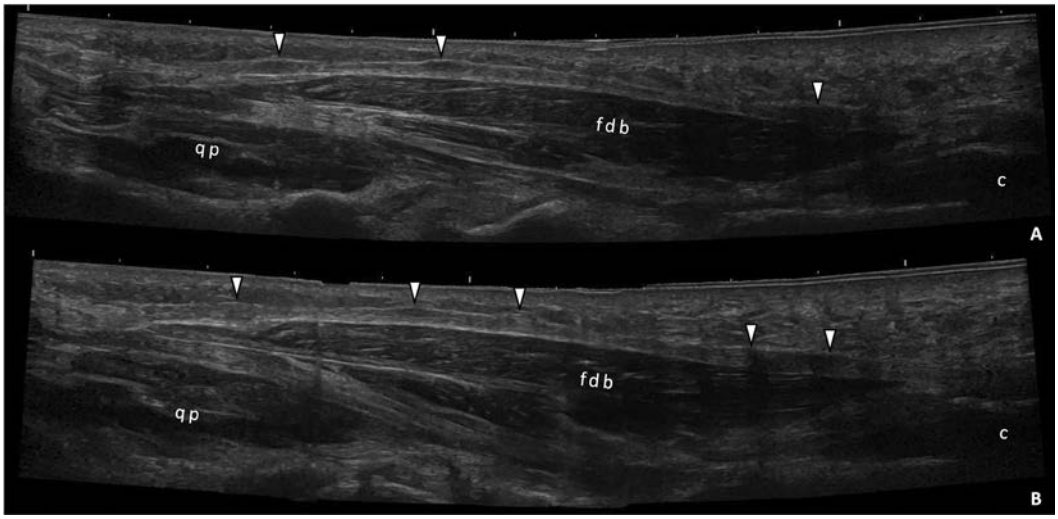

FIGURE 1 | Panoramic ultrasonographic images of the plantar fasciae of the left (A) and right (B) feet showing diffuse hypoechoic nodules (arrowheads) consistent with bilateral plantar fibromatosis. c: Calcaneus, fdb: Flexor digitorum brevis muscle, qp: Quadratus plantae muscle.

myofibroblast activity—and into the adjacent deep fascial layers to inhibit inflammation offers therapeutic benefit [2, 6, 7].

This case is noteworthy for several reasons: bilateral involvement in a female patient, absence of associated secondary systemic conditions, a prolonged 15-year delay in seeking medical care, and the possible contribution of repetitive occupational trauma and obesity. Musculoskeletal US identified the underlying cause and revealed an atypical presentation of plantar fibromatosis. Given its accessibility, noninvasive nature, and dynamic capabilities, US represents a valuable tool for early diagnosis and appropriate management. Furthermore, advanced US techniques such as panoramic imaging and power Doppler may further enhance diagnostic accuracy and therapeutic guidance, as shown in our case.

Author Contributions

H.S., B.Ç., and H.B.A. wrote the main text and investigated the literature. M.K. supervised and revised the text.

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Funding

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient for the publication of her clinical details, accompanying images, and the supplementary video.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Video S1**. Real time sonographic tracking of the plantar fascia in longitudinal axis demonstrating diffuse hypoechoic nodules (arrowheads) consistent with plantar fibromatosis.

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LETTER TO THE EDITOR

Case Report: Anifrolumab for Refractory Cutaneous Lupus Erythematosus: Relapse After Treatment Interruption and Response to Rechallenge

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Dear Editor,

Anifrolumab, a monoclonal antibody approved by the FDA that targets the type I interferon receptor subunit 1, demonstrated cutaneous response in systemic lupus erythematosus (SLE) during the phase 3 TULIP-2 trial. Numerous studies have since documented its efficacy in cutaneous lupus erythematosus of various subtypes [1, 2]. However, optimal treatment duration remains undefined.

Here, we report a case of refractory cutaneous lupus erythematosus that rapidly responded to Anifrolumab, flared shortly after discontinuation, and regained control upon rechallenge with ongoing therapy. Our case reinforces Anifrolumab's efficacy in refractory cutaneous SLE while highlighting the potential need for long-term therapy in selected patients.

A 47 year old woman with a history of SLE was referred to our rheumatology clinic for her SLE management. SLE phenotype was characterized by severe subacute cutaneous lupus erythematosus, Raynaud phenomenon, and intermittent fevers. Autoantibody profile revealed ANA titer of 1:1280, high titer double stranded DNA, anti-SS-A, anti-Smith, and anti-chromatin antibodies, as well as low C3 and C4 levels. The physical exam was significant for widespread cutaneous rashes encompassing the hands, face, bilateral upper arms, chest, and back with a CLASI-A score of 26 consistent with severe cutaneous disease (Figure 1). Skin biopsy of the upper arm revealed vacuolar interface dermatitis. Direct Immunofluorescence showed positivity for IgG, C3, IgA, and IgM confirming cutaneous lupus erythematosus diagnosis (Figure S1). Past medication history over the course of nearly 20 years included cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, and prolonged glucocorticoid use without adequate control of her cutaneous symptoms. At the time of presentation to our clinic, she was on hydroxychloroquine 400 mg daily, belimumab 200 mg subcutaneously once a week and intravenous immunoglobulins (IVIG) 2 g/kg every 4 weeks. Belimumab and IVIG were discontinued, and the patient was started on Anifrolumab 300 mg IV every 4 weeks. On follow-up visit, 7 weeks after her first dose, the patient demonstrated significant improvement and near complete resolution of active cutaneous disease with CLASI-A score of 1 (Figure 2). After 12 weeks of treatment, therapy was held for a scheduled cervical spine fusion surgery for radiculopathy symptoms, and 6 weeks later severe cutaneous flare occurred with suspected superimposed infection similar to her previous flares. Evidence for concurrent infection was limited. The patient resumed 300 mg IV Anifrolumab after a course of doxycycline with remission of her cutaneous disease to date. Patient has continued hydroxychloroquine 400 mg daily throughout her treatment and flare periods.

Studies have shown that cutaneous manifestations of SLE are associated with cytotoxic lesional inflammation driven by increased expression of type 1 interferons [3]. Anifrolumab, a monoclonal anti-type 1 interferon receptor subunit 1 antibody showed significant cutaneous response in secondary endpoint analyses of the TULIP-2 trial and since then several case reports have demonstrated this efficacy [1–3]. Our case further adds

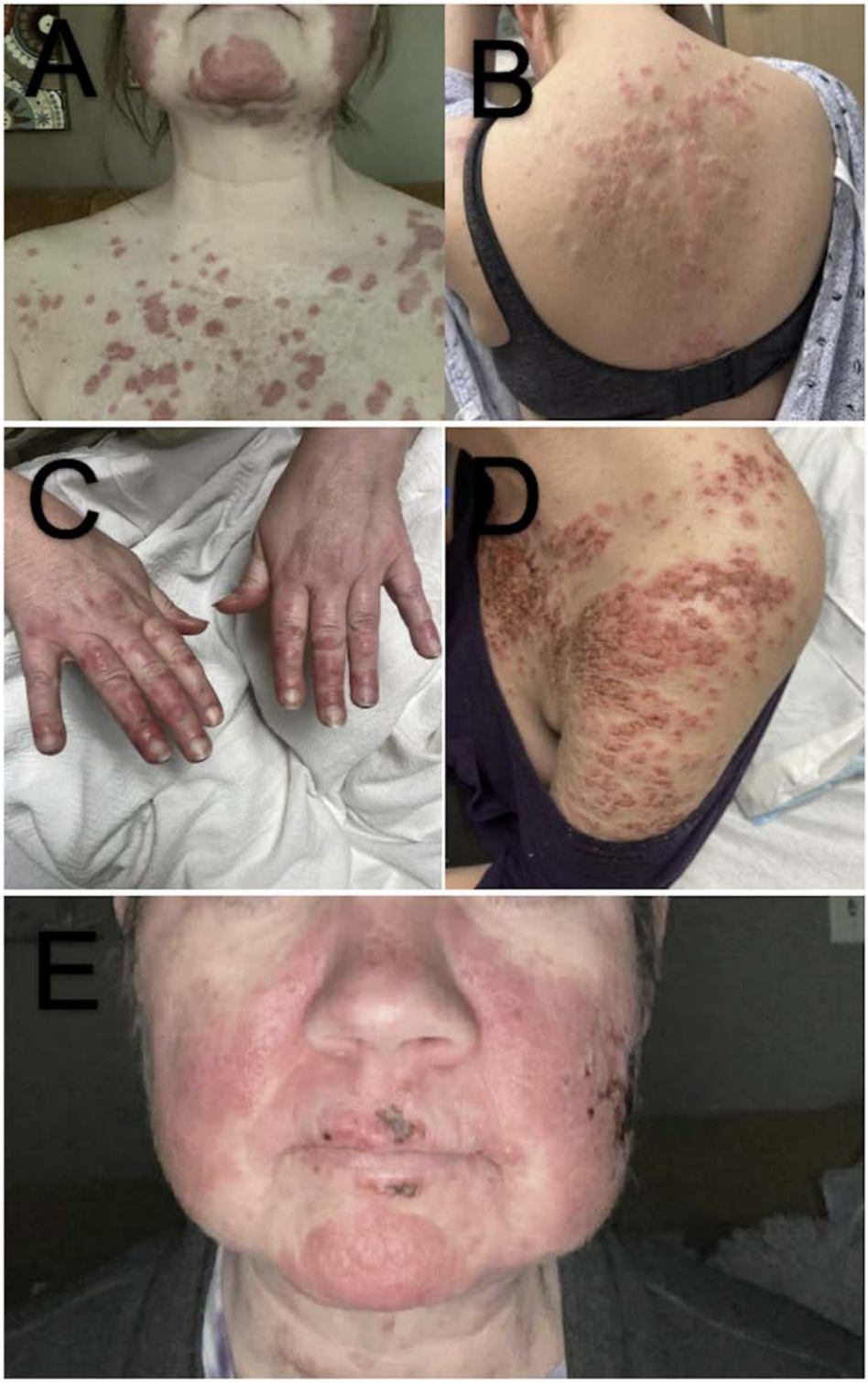

FIGURE 1 | Widespread cutaneous rashes encompassing the face, chest, hand, and back.

to this body of literature, with significant improvement in the CLASI-A score for our patient especially after failing multiple other immunosuppressive medications.

Uniquely, in our case, Anifrolumab was temporarily held for cervical spine fusion surgery for cervical myelopathy. The patient's cutaneous lupus relapsed within weeks after Anifrolumab discontinuation even though she was taking hydroxychloroquine. The temporal relationship between Anifrolumab initiation leading to cutaneous lupus resolution, Anifrolumab discontinuation, and subsequent cutaneous lupus exacerbation suggests its strong therapeutic role in cutaneous manifestations of SLE. However, given the nature of the case report, limited conclusions can be drawn regarding causal relationships.

The exacerbation of our patient's cutaneous disease after discontinuation of Anifrolumab also highlights the limitation of current literature on the optimal duration of Anifrolumab for

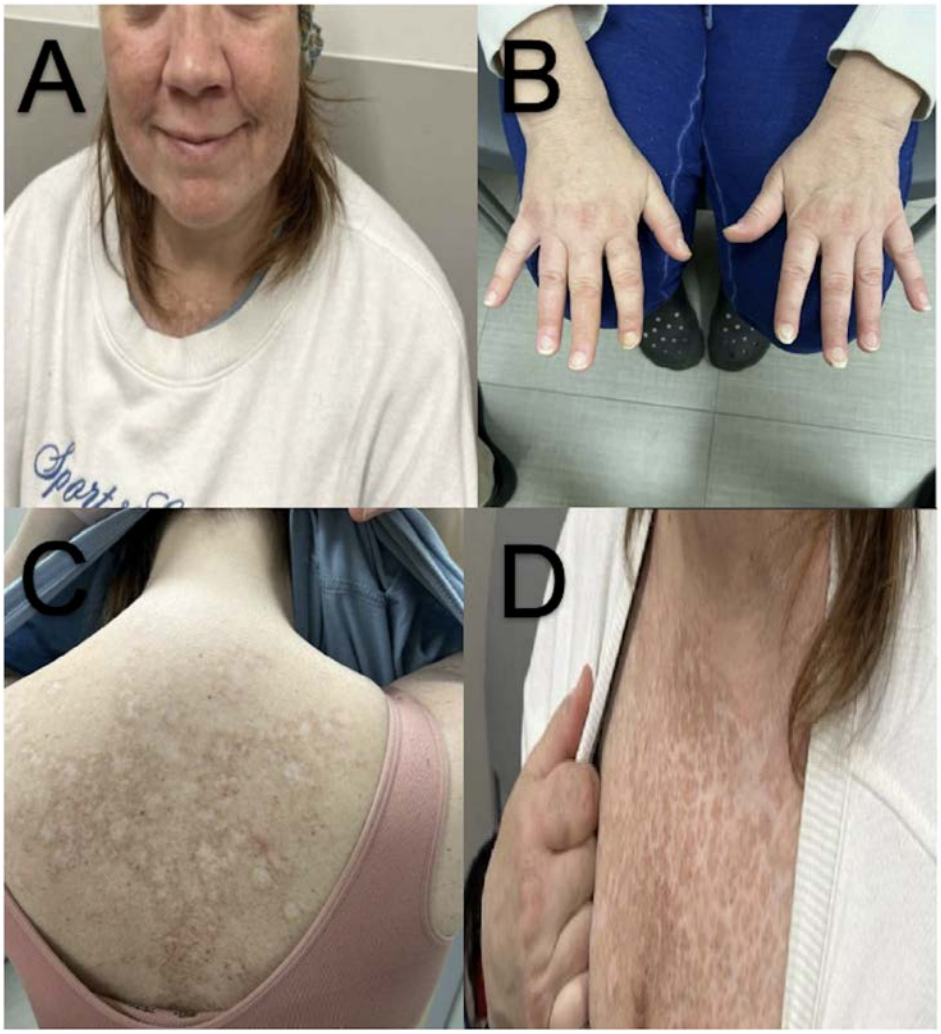

FIGURE 2 | Near complete resolution of active cutaneous disease after initiation of Anifrolumab.

cutaneous SLE. TULIP-LTE extension study demonstrated efficacy of continued Anifrolumab therapy in reducing cutaneous lupus burden up to 39 months with a favorable benefit–risk profile, but it did not provide data on optimal duration [4]. The MUSE trial showed worsening of SLE symptoms including cutaneous disease within 8 weeks of discontinuation [2]. On the other hand, some case reports have described continued remission at 6 months to 1 year of follow-up in patients who discontinued Anifrolumab [5]. A potential explanation for these divergent observations is differences in severity of disease manifestation. Case reports showing patients with sustained remission after Anifrolumab discontinuation also have limited cutaneous SLE involvement with only facial rashes [5]. Our case further highlights the need for research on this topic and guidance on maintenance of Anifrolumab, especially in patients with refractory cutaneous disease.

Author Contributions

Yuanzun Peng: conceptualization (lead), writing – original draft. **Seth Stidham:** writing – original draft. **Farina Tariq:** writing – review and editing. **Muhammad Zaheer:** supervision, validation.

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Consent

The authors confirm that written informed consent has been obtained from the patient to publish this case report and any clinical and histopathological images associated with this report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Vacuolar interface dermatitis from hematoxylin and eosin stain of patient's skin biopsy.

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ORIGINAL ARTICLE

High Immunological Activity and the Re-Evaluation of Anti-SSA/SSB Antibodies as Prognostic Markers for Major Organ Damage in Systemic Lupus Erythematosus

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ABSTRACT

Objective: Anti-SSA antibodies are among the most prevalent autoantibodies in systemic lupus erythematosus. While their association with cutaneous manifestations and neonatal lupus is established, their prognostic utility regarding long-term survival and major organ damage in adult SLE remains controversial, particularly in Asian populations. Furthermore, the added prognostic value of anti-SSB antibodies in anti-SSA-positive patients is debated. This study aimed to evaluate the impact of anti-SSA status on clinical phenotypes and long-term outcomes and to assess whether double positivity (anti-SSA+/SSB+) confers additional risk compared to single positivity (anti-SSA+/SSB-).

Methods: We conducted a retrospective cohort study of 511 SLE patients at a medical center in Taiwan. Patients were stratified into anti-SSA positive ($n = 331$) and anti-SSA negative ($n = 180$) groups. We compared clinical characteristics, serological profiles, disease activity (SLEDAI), and long-term outcomes, including mortality, end-stage renal disease (ESRD), and interstitial lung disease (ILD). A subgroup analysis was performed to compare single positive versus double positive patients.

Results: Anti-SSA positive patients were predominantly female (92.7% vs. 81.7%, $p < 0.001$) and exhibited significantly higher disease activity (SLEDAI: 13.8 ± 6.5 vs. 12.1 ± 6.0, $p = 0.003$). Immunologically, the anti-SSA positive group displayed a distinct "multiple autoantibody positivity" profile, characterized by a higher prevalence of anti-dsDNA (74.6% vs. 65.0%, $p = 0.028$), anti-Sm (44.1% vs. 22.8%, $p < 0.001$), and anti-RNP (48.3% vs. 31.7%, $p < 0.001$), along with lower C3 and C4 levels. However, despite this active serological profile, there were no significant differences between anti-SSA positive and negative groups regarding all-cause mortality (16.3% vs. 20.6%, $p = 0.282$), ESRD (10.0% vs. 8.3%, $p = 0.655$), or ILD (5.4% vs. 4.4%, $p = 0.781$). Multivariable regression models confirmed that anti-SSA status was not an independent predictor for mortality (adjusted Hazard Ratio [aHR] 0.82, $p = 0.376$), ESRD (adjusted Odds Ratio [aOR] 1.17, $p = 0.654$), or ILD (aOR 1.52, $p = 0.369$).

Conclusion: In this Asian SLE cohort, anti-SSA positivity served as a marker for a phenotype characterized by high immunological activity and multiple autoantibody positivity but was not significantly associated with poor long-term survival or irreversible organ damage in this cohort. However, larger studies are required to definitively exclude modest prognostic effects. The presence of anti-SSB antibodies provided limited additional prognostic value for adult outcomes, suggesting that risk stratification should focus on the primary driver, anti-SSA.

Key Points

- Anti-SSA positivity marks a phenotype of high immunological activity, although a significant independent association with mortality or irreversible organ damage was not observed in this cohort.
- Concomitant anti-SSB positivity confers limited additional prognostic risk for adult outcomes compared to isolated anti-SSA positivity.
- Anti-SSA status is not associated with interstitial lung disease in this Asian SLE cohort, diverging from reports in Western populations.

1 | Introduction

Beyond its serological complexity, SLE is defined by its capacity to affect virtually any organ system. However, the burden of disease is not distributed equally among patients; a significant subset suffers from major organ damage, while others experience a more benign course predominantly limited to the skin and joints [1]. Discerning the prognostic significance of specific autoantibodies is therefore essential [2]. Several studies have reported that different serological factors will influence the presentations and outcomes in SLE patients [3, 4]. Among these, antibodies against the Ro/SSA and La/SSB ribonucleoprotein complexes are some of the most frequently detected, with a prevalence ranging from 30% to 70% depending on the population studied [5, 6].

Historically, the clinical significance of anti-SSA antibodies has been linked to specific phenotypes, such as subacute cutaneous lupus, photosensitivity, and the risk of neonatal lupus syndrome (congenital heart block) in offspring [7, 8]. However, the prognostic value of anti-SSA antibodies regarding major organ involvement and long-term survival in adult SLE patients remains a subject of debate. While some studies suggest an association with interstitial lung disease (ILD) and renal involvement [9, 10], others report no significant impact on mortality or severe organ damage [11]. This discrepancy is particularly notable in Asian populations, where genetic backgrounds and disease phenotypes differ from Western cohorts [12].

Furthermore, anti-SSA and anti-SSB antibodies often coexist as a "linked set." The clinical utility of testing for anti-SSB in the presence of anti-SSA has recently been questioned. It remains unclear whether "double positive" patients (anti-SSA+/SSB+) face a worse prognosis than "single positive" patients (anti-SSA+/SSB-), or if anti-SSB is merely an epiphenomenon with limited independent prognostic significance for adult outcomes [3].

In this study, we utilized a large cohort of Taiwanese SLE patients to: (1) characterize the clinical and immunological profile of anti-SSA positive patients; (2) determine whether anti-SSA status predicts long-term outcomes such as mortality, end-stage renal disease (ESRD), and ILD; and (3) investigate whether the presence of anti-SSB antibodies results in additional risk in the anti-SSA positive subpopulation.

2 | Patients and Methods

2.1 | Study Design and Population

This retrospective cohort study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This study included 511 patients diagnosed with SLE according to the 1997 American College of Rheumatology revised criteria [13] or the 2012 SLICC criteria [14]. Patients were recruited from the lupus database of Chang Gung Memorial Hospital, a tertiary referral center in Taiwan. Patients admitted and treated for SLE at the Chang Gung Memorial Hospital between January 2005 and December 2012 were enrolled and followed up until March 31, 2019. The study protocol was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB No. 103-2394C; approval date: May 21, 2014).

2.2 | Data Collection

Demographic data, including age at diagnosis, gender, and disease duration, were collected. Clinical manifestations were recorded based on ACR criteria definitions, including malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis/pericarditis), renal disorder (proteinuria >0.5 g/day or cellular casts), and neuropsychiatric involvement (seizure/psychosis).

2.3 | Immunological Assessment

Autoantibody profiles were determined at the time of diagnosis. Anti-SSA and anti-SSB antibodies were detected using ZEUS AtheNA multi-lyte ANA-II Plus Test System (ZEUS Scientific, Branchburg, NJ, USA). Other serological markers included anti-double-stranded DNA (anti-dsDNA), anti-Sm, and anti-RNP using the same method. Serum complement levels (C3, C4) were measured by nephelometry. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

2.4 | Outcome Definitions

The primary outcomes were:

1. **All-cause Mortality**: Death from any cause during the follow-up period.
2. **End-Stage Renal Disease (ESRD)**: Requirement for chronic dialysis or renal transplantation.
3. **Interstitial Lung Disease (ILD)**: Diagnosed based on clinical evaluation of suggestive symptoms (e.g., progressive dyspnea, dry cough). All documented ILD cases were confirmed by high-resolution computed tomography (HRCT) interpreted by radiologists. Cases of suspected drug-induced ILD or active pulmonary infections were excluded through comprehensive clinical and microbiological assessments.

2.5 | Statistical Analysis

Patients were stratified into two groups: Anti-SSA positive and anti-SSA negative. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were analyzed using the Student's *t*-test, while non-normally distributed variables were compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the Chi-square test or Fisher's exact test. Kaplan–Meier survival analysis with the Log-rank test was used to compare survival curves. To establish the independent prognostic value of anti-SSA positivity, multivariable regression models were constructed. A multivariable Cox proportional hazards regression model was used to evaluate all-cause mortality, generating adjusted hazard ratios (aHR). For major organ damage outcomes (ESRD and ILD), multivariable logistic regression models were employed to calculate adjusted odds ratios (aOR), with disease duration included as an additional covariate. All multivariable models were adjusted for potential baseline confounders, including age at diagnosis, sex, baseline SLEDAI score, and the use of immunomodulatory medications (hydroxychloroquine, azathioprine, cyclophosphamide, and mycophenolate mofetil). Systemic glucocorticoids were explicitly excluded from the multivariable analyses due to their near-universal use (>97%) in this cohort, which precluded meaningful statistical comparison and would cause quasi-complete separation. A secondary subgroup analysis compared single positive (SSA+/SSB-) and double positive (SSA+/SSB+) patients. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

3 | Results

3.1 | Demographic and Clinical Characteristics

Of the 511 patients included, 331 (64.8%) were anti-SSA positive. The demographic and clinical characteristics are summarized in Table 1. Anti-SSA positive patients were significantly more likely to be female (92.7% vs. 81.7%, $p<0.001$). There was no significant difference in age at diagnosis (39.9 vs. 41.2 years, $p=0.388$) or disease duration between the two groups. Clinically, anti-SSA positive patients showed a trend toward a higher prevalence of malar rash (49.2% vs. 40.6%, $p=0.074$) and renal involvement (proteinuria) (63.4% vs. 54.4%, $p=0.059$), although these did not reach statistical significance.

3.2 | Immunological Profile and Disease Activity

Anti-SSA positivity was strongly associated with a highly active immunological profile (Table 1). As shown in Figure 1, the anti-SSA positive group displayed a distinct pattern of 'multiple autoantibody positivity,' exhibiting a markedly higher prevalence of concurrent autoantibodies compared to the negative group. Patients in the SSA positive group had a significantly higher prevalence of anti-dsDNA (74.6% vs. 65.0%, $p=0.028$), anti-Sm (44.1% vs. 22.8%, $p<0.001$), anti-RNP (48.3% vs. 31.7%, $p<0.001$), and anti-SSB antibodies (46.5% vs. 1.7%, $p<0.001$). Consistent with this multiple autoantibody positivity, SSA-positive patients had significantly lower mean C3 (64.6 vs. 74.6 mg/dL, $p=0.002$) and C4 levels (12.6 vs. 14.7 mg/dL, $p=0.017$). Consequently, the mean SLEDAI score was significantly higher in the SSA-positive group (13.8 ± 6.5) compared to the negative group (12.1 ± 6.0) ($p=0.003$).

3.3 | Long-Term Outcomes

Despite the higher disease activity and immunological burden, anti-SSA status did not translate into worse long-term outcomes (Table 2). The all-cause mortality rate was not significantly different between SSA-positive (16.3%) and negative (20.6%) groups ($p=0.282$). Regarding cause-specific mortality, infection (including pneumonia and sepsis) was the leading cause of death in both groups, accounting for 31 deaths (17.2%) in the anti-SSA negative group and 36 deaths (10.9%) in the anti-SSA positive group, followed by cardiovascular events (4 vs. 9 deaths, respectively). The total observation period comprised 6 109 person-years. The overall incidence rate of mortality was 14.9 per 1 000 person-years (17.5 in the SSA-negative group vs. 13.5 in the SSA-positive group). The incidence rates for ESRD and ILD were 7.9 and 4.3 per 1 000 person-years, respectively, with no statistically significant differences between the two groups. To account for baseline demographic differences and medication use, multivariable regression analyses were performed (Table 3). After adjusting for confounding factors—including age, sex, baseline SLEDAI, and immunomodulatory therapies—anti-SSA positivity was not independently associated with a higher risk of adverse long-term outcomes. In the multivariable Cox regression model, anti-SSA status did not significantly predict all-cause mortality (adjusted Hazard Ratio [aHR] 0.82, 95% CI 0.53–1.27, $p=0.376$). Similarly, multivariable logistic regression analyses revealed that anti-SSA positivity was not a significant independent risk factor for the development of ESRD (adjusted Odds Ratio [aOR] 1.17, 95% CI 0.59–2.34, $p=0.654$) or ILD (aOR 1.52, 95% CI 0.61–3.77, $p=0.369$). Instead, traditional risk factors such as older age at diagnosis, male sex, and higher baseline SLEDAI scores remained the primary independent predictors for mortality in this cohort. The Kaplan–Meier survival analysis, presented in Figure 2, confirmed that the survival curves for both groups overlap significantly throughout the follow-up period, indicating that anti-SSA status is not a differential predictor of long-term survival. Although median survival times were not reached due to the overall high survival rates, landmark analysis revealed 1-year and 5-year survival rates of 92.6% and 90.8% for the anti-SSA negative group, compared to 97.6% and 91.1% for the anti-SSA positive group, respectively. Similarly, there were no significant differences in the incidence of ESRD (10.0% vs. 8.3%, $p=0.655$) or ILD (5.4% vs. 4.4%, $p=0.781$). These findings were further confirmed in our multivariable analyses (Table 3).

3.4 | Subgroup Analysis: The Role of Anti-SSB

To determine if double positivity confers additional risk, we compared single positive (SSA+/SSB-, $n=177$) and double positive (SSA+/SSB+, $n=154$) patients (Supplementary Table 1). Interestingly, double positive patients were significantly younger at diagnosis compared to single positive

TABLE 1 | Demographic and clinical characteristics of SLE patients stratified by anti-SSA status.

Characteristic	SSA Negative ($n = 180$)	SSA Positive ($n = 331$)	p
Demographics			
Age at Diagnosis (years), mean ± SD	41.2 ± 17.2	39.9 ± 15.5	0.388
Female, *n* (%)	147 (81.7%)	307 (92.7%)	< 0.001*
Disease Duration (years), mean ± SD	11.8 ± 8.1	12.1 ± 8.0	0.687
Mucocutaneous Manifestations			
Malar Rash	73 (40.6%)	163 (49.2%)	0.074
Discoid Rash	15 (8.3%)	31 (9.4%)	0.820
Photosensitivity	20 (11.1%)	53 (16.0%)	0.168
Oral Ulcers	52 (28.9%)	80 (24.2%)	0.290
Other Clinical Features			
Arthritis	90 (50.0%)	194 (58.6%)	0.075
Serositis (Pleuritis or Pericarditis)	68 (37.8%)	134 (40.5%)	0.542
Pleuritis	57 (31.7%)	106 (32.0%)	1.000
Pericarditis	21 (11.7%)	56 (16.9%)	0.145
Neuropsychiatric SLE (Seizure/Psychosis)	26 (14.4%)	57 (17.2%)	0.412
Renal Involvement (Proteinuria)	98 (54.4%)	210 (63.4%)	0.059
Autoantibody Profile			
Anti-dsDNA Positive	117 (65.0%)	247 (74.6%)	0.028*
Anti-Sm Positive	41 (22.8%)	146 (44.1%)	< 0.001*
Anti-RNP Positive	57 (31.7%)	160 (48.3%)	< 0.001*
Anti-SSB (La) Positive	3 (1.7%)	154 (46.5%)	< 0.001*
Complement Levels			
C3 (mg/dL), mean ± SD	74.6 ± 35.8	64.6 ± 30.2	0.002*
C4 (mg/dL), mean ± SD	14.7 ± 9.4	12.6 ± 8.9	0.017*
Disease Activity			
SLEDAI Score, mean ± SD	12.1 ± 6.0	13.8 ± 6.5	0.003*
Medications			
Hydroxychloroquine	127 (70.6%)	262 (79.2%)	0.039*
Glucocorticoids	176 (97.8%)	324 (97.9%)	1.000
Azathioprine	62 (34.4%)	135 (40.8%)	0.190
Cyclophosphamide	25 (13.9%)	47 (14.2%)	1.000
Mycophenolate Mofetil	25 (13.9%)	38 (11.5%)	0.516

Abbreviations: SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; Anti-dsDNA, anti-double-stranded DNA; C3, complement 3; C4, complement 4; SD, standard deviation; *$p < 0.05$.

patients (38.1 ± 12.8 vs. 41.5 ± 14.2 years, $p = 0.024$). Clinically, the double positive group exhibited a higher prevalence of renal involvement, specifically proteinuria (69.5% vs. 58.2%, $p = 0.038$). This group also displayed a more intense immunological profile, characterized by significantly higher rates of anti-dsDNA (83.1% vs. 67.2%, $p < 0.001$), anti-Sm (59.1% vs. 31.1%, $p < 0.001$), and anti-RNP antibodies (67.5% vs. 31.6%, $p < 0.001$), alongside lower C3/C4 levels and higher SLEDAI scores (15.3 ± 6.6 vs. 12.5 ± 6.2, $p < 0.001$). However, despite this heightened serological activity and renal inflammation, there were no statistically significant differences in long-term hard outcomes, including all-cause mortality (16.9% vs. 15.8%, $p = 0.793$), ESRD (10.4% vs. 9.6%, $p = 0.812$), or ILD (4.5% vs. 6.2%, $p = 0.499$).

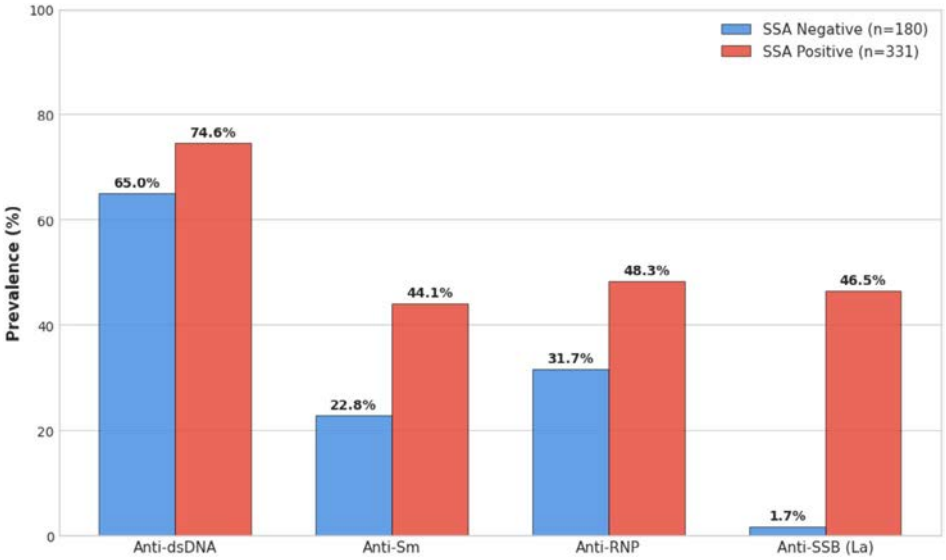

FIGURE 1 | Comparison of autoantibody profiles between anti-SSA positive and negative SLE patients.

TABLE 2 | Long-term outcomes and major organ damage in patients with SLE.

Outcome	SSA Negative ($n=180$)	SSA Positive ($n=331$)	p
Mortality			
All-cause Mortality	37 (20.6%)	54 (16.3%)	0.282
Incidence Rate (per 1 000 PY)	17.5	13.5	
Cause-Specific Mortality			
Infection/Sepsis	31 (17.2%)	36 (10.9%)	0.054
Cardiovascular Events	4 (2.2%)	9 (2.7%)	0.730
Major Organ Damage			
End-Stage Renal Disease (ESRD)	15 (8.3%)	33 (10.0%)	0.655
Incidence Rate (per 1 000 PY)	7.1	8.3	
Interstitial Lung Disease (ILD)	8 (4.4%)	18 (5.4%)	0.781
Incidence Rate (per 1 000 PY)	3.8	4.5	

Abbreviation: PY: person-years.

4 | Discussion

In our large cohort of SLE patients in Taiwan, we re-evaluated the clinical significance of anti-SSA antibodies. Our findings delineate a clear distinction between the "serological phenotype" and the "prognostic outcome" of these patients. While anti-SSA positivity was a strong marker for high immunological activity—characterized by multiple autoantibody positivity, hypocomplementemia, and higher SLEDAI scores—it was not significantly associated with an increased risk of mortality or major organ damage (ESRD, ILD) in our adjusted analyses. Furthermore, our data suggest that the concomitant presence of anti-SSB antibodies adds limited prognostic value regarding adult organ outcomes.

The association between anti-SSA and a distinct serological profile is well-documented. Our study confirmed that SSA-positive patients are more likely to harbor multiple other autoantibodies, including anti-dsDNA, Sm, and RNP. This suggests a state of polyclonal B-cell activation. The significantly higher SLEDAI scores in our SSA-positive group are likely driven by these serological abnormalities (low complement, high dsDNA) rather than severe organ manifestations, as the rates of CNS lupus, severe nephritis (ESRD), and carditis were not significantly different. Furthermore, while the mean SLEDAI score was statistically higher in the anti-SSA positive group (13.8 vs. 12.1, $p=0.003$), this absolute difference of 1.7 points is relatively modest. Its clinical significance must be interpreted cautiously, as a shift of less than 3–4 points on the SLEDAI scale often does not trigger an immediate escalation in clinical management.

Regarding survival outcomes, the dissociation between high disease activity and mortality rates in our Anti-SSA positive cohort is noteworthy. Although these patients exhibited significantly higher SLEDAI scores and lower complement levels, this 'serological storm' did not translate into a survival disadvantage. This finding suggests that the elevated disease activity scores in this subgroup are largely driven by the heavy weight of immunological variables (e.g., anti-dsDNA, low complement) in the SLEDAI scoring system rather than by life-threatening organ failure. Consequently, in the absence of severe organ damage, Anti-SSA positivity alone should not be interpreted as a harbinger of early mortality [15]. Furthermore, a closer examination of the Kaplan–Meier survival curves reveals an interesting dynamic of early separation that converges over time. Although median survival times were not reached due to the overall high

TABLE 3 | Multivariable regression analysis for predictors of long-term outcomes in SLE patients.

	All-Cause Mortality		End-Stage Renal Disease		Interstitial Lung Disease	
	aHR (95% CI)	*p*	aOR (95% CI)	*p*	aOR (95% CI)	*p*
Age at Diagnosis	1.06 (1.04–1.07)	< 0.001*	1.00 (0.98–1.02)	0.916	1.01 (0.99–1.04)	0.280
Female Sex	0.50 (0.28–0.89)	0.019*	0.35 (0.14–0.83)	0.017*	0.24 (0.09–0.64)	0.005*
Disease Duration	N/A	N/A	1.02 (0.98–1.06)	0.359	0.99 (0.93–1.05)	0.736
Baseline SLEDAI	1.09 (1.06–1.12)	< 0.001*	1.10 (1.05–1.14)	< 0.001*	1.05 (0.99–1.12)	0.089
Hydroxychloroquine	0.69 (0.44–1.09)	0.113	0.90 (0.43–1.89)	0.782	1.54 (0.55–4.28)	0.410
Azathioprine	0.88 (0.55–1.42)	0.607	1.10 (0.57–2.12)	0.785	0.44 (0.16–1.22)	0.115
Cyclophosphamide	2.04 (1.18–3.54)	0.011*	1.99 (0.92–4.28)	0.080	0.80 (0.21–3.15)	0.755
Mycophenolate	1.39 (0.72–2.69)	0.322	1.09 (0.46–2.60)	0.849	1.86 (0.54–6.43)	0.326
Anti-SSA Positivity	0.82 (0.53–1.27)	0.376	1.17 (0.59–2.34)	0.654	1.52 (0.61–3.77)	0.369

*aHR = adjusted Hazard Ratio; aOR = adjusted Odds Ratio; CI = Confidence Interval. All regression models were adjusted for baseline confounding factors including age at diagnosis, sex, baseline SLEDAI score, and the use of immunomodulatory medications (Hydroxychloroquine, Azathioprine, Cyclophosphamide, Mycophenolate Mofetil). Disease duration was additionally adjusted for in the End-Stage Renal Disease and Interstitial Lung Disease models. Systemic glucocorticoids were excluded from the multivariable models due to extremely high prevalence (> 97% in both groups), causing complete statistical separation.

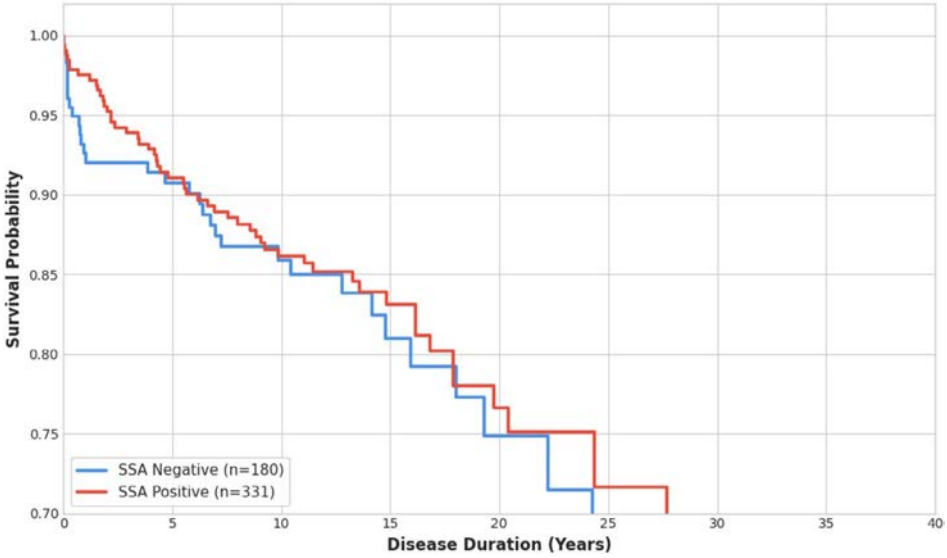

FIGURE 2 | Kaplan–Meier survival analysis of SLE patients stratified by anti-SSA status.

survival rates, landmark analysis revealed 1-year and 5-year survival rates of 92.6% and 90.8% for the anti-SSA negative group, compared to 97.6% and 91.1% for the anti-SSA positive group, respectively. This initial slight separation likely reflects early mortality events in the anti-SSA negative group, whereas the subsequent convergence suggests that long-term survival is primarily driven by chronic damage accrual (such as cardiovascular events or end-stage renal complications) rather than baseline anti-SSA status. This underscores that while acute flares may influence early survival trajectories, anti-SSA positivity does not independently worsen late mortality.

Similarly, the relationship between Anti-SSA positivity and renal prognosis appears nuanced in our study. While we observed a trend toward a higher prevalence of proteinuria in Anti-SSA positive patients and significantly higher rates in the double-positive subgroup, this did not accelerate the progression to ESRD. This implies that while Anti-SSA (and its associated multiple autoantibody positivity) may contribute to renal immune complex deposition or specific histological patterns, we did not observe a statistically significant increase in the risk for irreversible renal scarring as other risk factors [16]. Our findings do not demonstrate an independent association between anti-SSA status and ESRD in this cohort. The implications of anti-SSA positivity for therapeutic decision-making in lupus nephritis require further prospective investigation, particularly incorporating biopsy-proven histological classifications and longitudinal renal activity.

A crucial finding of our study is the lack of association between anti-SSA and ILD. Previous studies, particularly in Western cohorts, have identified anti-SSA as a risk factor for ILD [17]. However, our data showed a low prevalence of ILD (~5%) with no significant difference between groups. This discrepancy

may be attributed to ethnic differences or the specific detection methods used. Recent literature suggests that antibodies against the Ro52 subunit (often measured separately) are more strongly linked to ILD than the Ro60 subunit in several autoimmune diseases [18, 19]. Since standard clinical assays often detect a mix of Ro60/Ro52, the specific risk of Ro52 might be diluted. The discussion regarding the distinct pathogenic roles of Ro52 versus Ro60 is interesting; however, it remains purely speculative in the context of our study, as these autoantibodies were not measured separately by our composite clinical assay. Future prospective studies utilizing differentiated assays are required to confirm these specific associations in Asian populations. Our findings align with other Asian studies suggesting that age and disease duration may be more potent predictors of ILD in this population than anti-SSA status alone [20]. Furthermore, the management of SLE must increasingly focus on the heavy burden of comorbidities. In our cohort, infection and cardiovascular events were the leading causes of mortality across both groups, independent of anti-SSA status. Given that anti-SSA positivity did not independently predict early mortality, clinical attention should remain heavily directed toward screening and managing traditional SLE comorbidities, such as mitigating cardiovascular risk factors and preventing severe opportunistic infections, particularly in patients receiving potent immunosuppressive regimens.

Our subgroup analysis sheds new light on the 'double positive' (Anti-SSA+/SSB+) phenotype. We found that the presence of Anti-SSB distinguishes a subset of patients with earlier disease onset and a more intense 'multiple autoantibody positivity' profile—marked by significantly higher prevalence of anti-dsDNA, anti-Sm, and anti-RNP antibodies [7, 20]. While this heightened immunological activity correlated with a higher rate of proteinuria, it remarkably did not translate into a higher risk of irreversible renal damage (ESRD) or mortality. This dissociation reinforces the concept that while Anti-SSB serves as a marker for global B-cell hyperactivity and perhaps acute renal inflammation (proteinuria), it does not significantly predict the progression to end-stage organ failure in treated adults [21]. Thus, for long-term prognosis, the distinction between single and double positivity appears less critical than clinical parameters [22], although the association with younger onset age warrants attention in transition care and reproductive counseling.

Importantly, to address potential confounding effects by aggressive immunosuppressive therapies, our multivariable models further incorporated the use of key immunomodulatory and cytotoxic agents (including azathioprine, cyclophosphamide, and mycophenolate mofetil). Even after rigorous adjustment for these therapeutic interventions alongside baseline disease activity and demographics, anti-SSA positivity remained non-significant regarding long-term mortality, ESRD, and ILD. This confirms that the lack of prognostic divergence is not attributable to unmeasured treatment biases between the two groups, further reinforcing our conclusion that anti-SSA status should not dictate aggressive escalation of therapy in the absence of other active organ-threatening manifestations.

This study has several limitations that warrant consideration. First, the retrospective design inherently limits the assessment of causal relationships and precludes the analysis of longitudinal serological fluctuations. We utilized baseline autoantibody profiles and could not account for potential seroconversion or variations in antibody titers over the disease course. Second, our detection method did not distinguish between anti-Ro60 and anti-Ro52 antibodies. Since recent evidence suggests that anti-Ro52 is more specifically pathogenic regarding pulmonary fibrosis and interstitial lung disease, the use of a composite assay might have diluted the specific signal of Ro52, potentially obscuring a significant association with ILD in our cohort. Third, although the total sample size was substantial, the absolute number of severe outcome events—specifically ILD ($n = 26$) and ESRD ($n = 48$)—was relatively low. This may limit the statistical power (Type II error) to detect modest differences between subgroups. Consequently, the lack of statistically significant associations regarding ESRD and ILD should be interpreted cautiously and does not definitively rule out the potential prognostic value of these autoantibodies. Finally, while our multivariable models carefully adjusted for the use of major immunosuppressive agents, the possibility of residual confounding—particularly regarding longitudinal cumulative dose exposure and medication adherence—cannot be completely excluded.

5 | Conclusion

In conclusion, anti-SSA antibodies in SLE identify a subset of patients with high immunological activity and a female predominance but do not independently predict a worse prognosis regarding survival, end-stage renal disease, or interstitial lung disease in this Asian cohort. The addition of anti-SSB provides minimal additional prognostic information for adult outcomes. These findings argue against using anti-SSA/SSB status as a primary stratifier for major organ damage risk, suggesting a need to focus on other clinical and serological markers for prognosis.

Author Contributions

Yao-Fan Fang and Ping-Han Tsai contributed to the study conception and design. Material preparation and data collection were performed by Yen-Fu Chen and Che-Tzu Chang. Data analysis and interpretation were performed by Yao-Fan Fang. The first draft of the manuscript was written by Yao-Fan Fang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Funding

The authors have nothing to report.

Ethics Statement

The study protocol was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB No. 103-2394C; approval date: May 21, 2014). The requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study and the encryption of personal information.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy regulations but 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 1:** Comparison of clinical characteristics and long-term outcomes between Single Positive (Anti-SSA+/SSB-) and Double Positive (Anti-SSA+/SSB+) SLE patients.

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LETTER TO THE EDITOR

Case Report: Serum Protein Electrophoresis Incidentally Reveals Alpha-1 Antitrypsin Deficiency in p-ANCA-Positive Crescentic Glomerulonephritis

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Dear Editor,

Alpha-1 antitrypsin (AAT) deficiency is an inherited disorder caused by pathogenic variants in the SERPINA1 gene and is characterized by reduced serum levels or dysfunctional AAT protein. It predominantly affects the lungs and liver, leading to early-onset emphysema, chronic obstructive pulmonary disease, bronchiectasis, and chronic liver disease, while less common manifestations include panniculitis [1]. Although renal involvement has occasionally been reported, it is rare and is largely limited to isolated case reports of immune-mediated glomerular diseases [2].

Beyond its role in protecting tissues from neutrophil elastase, AAT is the principal endogenous inhibitor of proteinase 3 (PR3), the major autoantigen in granulomatosis with polyangiitis (GPA). Consequently, accumulating evidence suggests that AAT deficiency is a genetic susceptibility factor for ANCA-associated vasculitis (AAV) [3]. Although most published studies have focused on the association between AAT deficiency and PR3-ANCA-positive disease, p-ANCA-positive AAV has also been reported, albeit less frequently [3]. Here, we report a patient with homozygous Pi*ZZ AAT deficiency who presented with crescentic glomerulonephritis, p-ANCA positivity by indirect immunofluorescence, and negative PR3-ANCA and MPO-ANCA immunoassays.

A 50-year-old man with a 15-year history of chronic obstructive pulmonary disease (COPD) was referred to the rheumatology outpatient clinic with a one-year history of pain and swelling involving the knees, wrists, and ankles. Physical examination revealed bilateral wrist tenderness and swelling. Blood pressure at presentation was 110/70 mm Hg, and the remainder of the systemic examination was unremarkable. He had a 10 pack-year smoking history but had quit smoking 15 years earlier. Laboratory investigations demonstrated a rheumatoid factor level of 296 IU/mL, whereas anti-cyclic citrullinated peptide (anti-CCP) antibodies, antinuclear antibodies (ANA), and extractable nuclear antigen (ENA) antibodies were negative. The erythrocyte sedimentation rate (ESR) was 40 mm/h, and C-reactive protein (CRP) was 15 mg/L. During follow-up, urinalysis revealed 3+ blood and 2+ protein, with 78 red blood cells and 10 white blood cells per high-power field. Twenty-four-hour urinary protein excretion was 1137 mg/day, and serum creatinine increased to 2.21 mg/dL. The patient subsequently developed ankle arthritis accompanied by markedly elevated inflammatory markers (CRP 156.7 mg/L and ESR 50 mm/h) and was admitted to the rheumatology ward for further evaluation.

Indirect immunofluorescence demonstrated p-ANCA positivity at a titer of 1:320, whereas PR3-ANCA and MPO-ANCA by ELISA and anti-double-stranded DNA antibodies were negative. Complement C3 and C4 levels were within the normal range, and hepatitis B and C serologies were negative. There were no clinical findings suggestive of active infection, and no purpura or other vasculitic skin lesions were present. Anti-GBM antibodies were not measured because this assay was not available at our institution.

A kidney biopsy containing 30 glomeruli revealed cellular crescents in eight glomeruli (26.7%). The interstitium showed dense lymphoplasmacytic inflammatory infiltrates with scattered neutrophils, and focal tubular atrophy was present. Direct immunofluorescence was negative for immune deposits. The histopathological findings were considered consistent with Type III (pauci-immune) crescentic glomerulonephritis in the context of

ANCA positivity. As the patient did not have rapidly progressive glomerulonephritis or pulmonary or other life-threatening organ involvement, and serum creatinine improved promptly after initiation of glucocorticoid therapy, azathioprine was selected as the immunosuppressive agent rather than cyclophosphamide or rituximab. Treatment with methylprednisolone (48 mg/day) and azathioprine (100 mg/day) was continued.

Serum protein electrophoresis unexpectedly demonstrated absence of the alpha-1 globulin fraction, raising suspicion of alpha-1 antitrypsin deficiency. Chest computed tomography revealed diffuse bilateral emphysematous changes and bronchial abnormalities, together with fibrotic parenchymal bands and tubular bronchiectasis in the medial segment of the right lower lobe (Figure 1). There were no clinical or radiological findings suggestive of pulmonary hemorrhage. Pulmonary function testing demonstrated mild airflow obstruction, with an FEV_1 of 62% predicted, an FVC of 110% predicted, and an FEV_1/FVC ratio of 45%. AAT genotyping identified a homozygous SERPINA1 c.1096G>A (p.Glu366Lys; Pi*ZZ) mutation, confirming severe alpha-1 antitrypsin deficiency. Serum alpha-1 antitrypsin concentration was markedly reduced at 0.33 g/L (reference range, 0.8–2.0 g/L). Abdominal ultrasonography demonstrated heterogeneous coarse hepatic parenchymal echogenicity and left lobe hypertrophy, consistent with chronic liver disease, although liver function tests remained within the normal range.

Alpha-1 proteinase inhibitor augmentation therapy was subsequently initiated. During follow-up, glucocorticoids were gradually tapered to a maintenance dose of 4 mg/day. After 1 year of azathioprine and glucocorticoid therapy, including 8 months of augmentation therapy, serum creatinine improved to 1.03 mg/dL, with an estimated glomerular filtration rate (eGFR) of 83 mL/min/1.73 m^2. Twenty-four-hour urinary protein excretion decreased to approximately 400 mg/day. ANCA testing was repeated during follow-up. PR3-ANCA and MPO-ANCA remained negative by ELISA, while ANCA by indirect immunofluorescence showed variable and decreasing titers. No clinical relapse occurred during follow-up. Follow-up thoracic CT findings were similar to baseline, with no new pulmonary involvement. Repeat serum protein electrophoresis performed after initiation of augmentation therapy demonstrated normalization of the alpha-1 globulin fraction (2%; reference range, 1%–3%), consistent with restoration of circulating AAT levels (Figure 2).

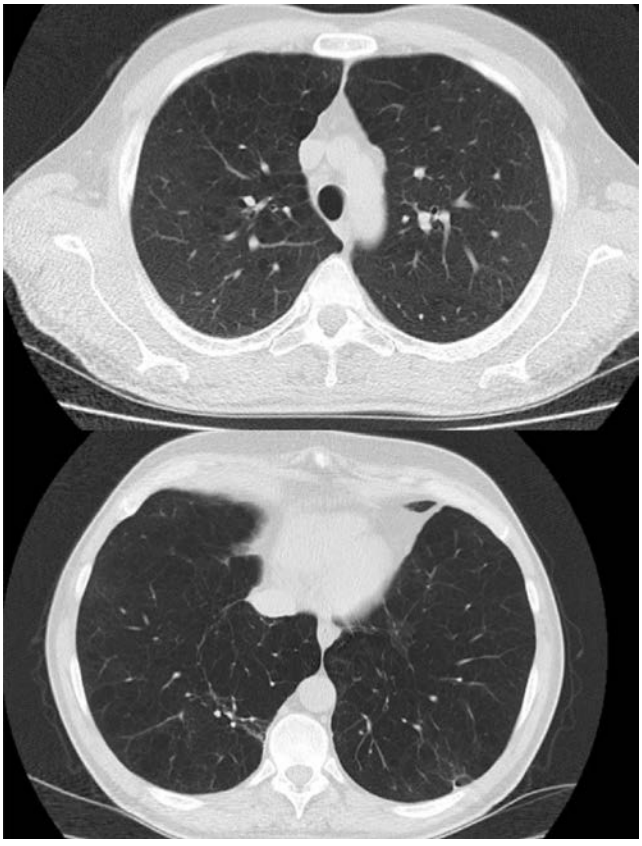

FIGURE 1 | Chest computed tomography demonstrating diffuse emphysematous changes in both lungs.

A recent systematic review and meta-analysis demonstrated that carriers of the SERPINA1 Z allele have approximately a threefold increased risk of developing GPA [3]. This association is biologically plausible because AAT is the principal endogenous inhibitor of PR3, and impaired inhibition of extracellular PR3 may promote persistent antigen exposure and autoimmunity.

Our patient represents an unusual presentation of AAT deficiency-associated AAV, with p-ANCA positivity by indirect immunofluorescence despite persistently negative PR3-ANCA and MPO-ANCA immunoassays. Audrain et al. evaluated 191 homozygous Pi*ZZ individuals and found increased antibodies against non-classical neutrophil antigens, including alpha-granule components and human leukocyte elastase, whereas PR3- and MPO-directed antibodies were not increased; importantly, none developed systemic vasculitis [4]. Similarly, Lhotta et al. reported no c-ANCA or p-ANCA positivity or clinical vasculitis among 47 patients with severe Pi*ZZ AAT deficiency [5]. In contrast, our patient developed clinically overt crescentic glomerulonephritis in association with p-ANCA positivity despite repeatedly negative PR3-ANCA and MPO-ANCA assays. This finding suggests that clinically significant vasculitic renal disease may rarely occur in severe AAT deficiency even in the absence of conventional PR3 or MPO reactivity.

Another distinctive feature of this case was that AAT deficiency was suspected after the incidental finding of an absent alpha-1 globulin fraction on serum protein electrophoresis. Together with longstanding COPD, relatively early-onset emphysema, and bronchiectasis, this finding prompted genetic testing and confirmed homozygous Pi*ZZ AAT deficiency. Previous reports of MPO-ANCA-associated vasculitis in Pi*ZZ patients further suggest that AAT deficiency may be associated with a broader range of AAV phenotypes than the classical PR3-ANCA-positive presentation [6].

Given the atypical serological profile and the relatively indolent course of renal involvement, glucocorticoids and azathioprine were selected as the initial treatment. Alpha-1 proteinase inhibitor augmentation therapy was subsequently initiated specifically for severe AAT deficiency. Although a potential role of augmentation therapy in AAV has been proposed, current evidence is limited to isolated case reports and its efficacy in vasculitis has not been established [7]. Therefore, the renal improvement observed in our patient cannot be attributed to augmentation therapy.

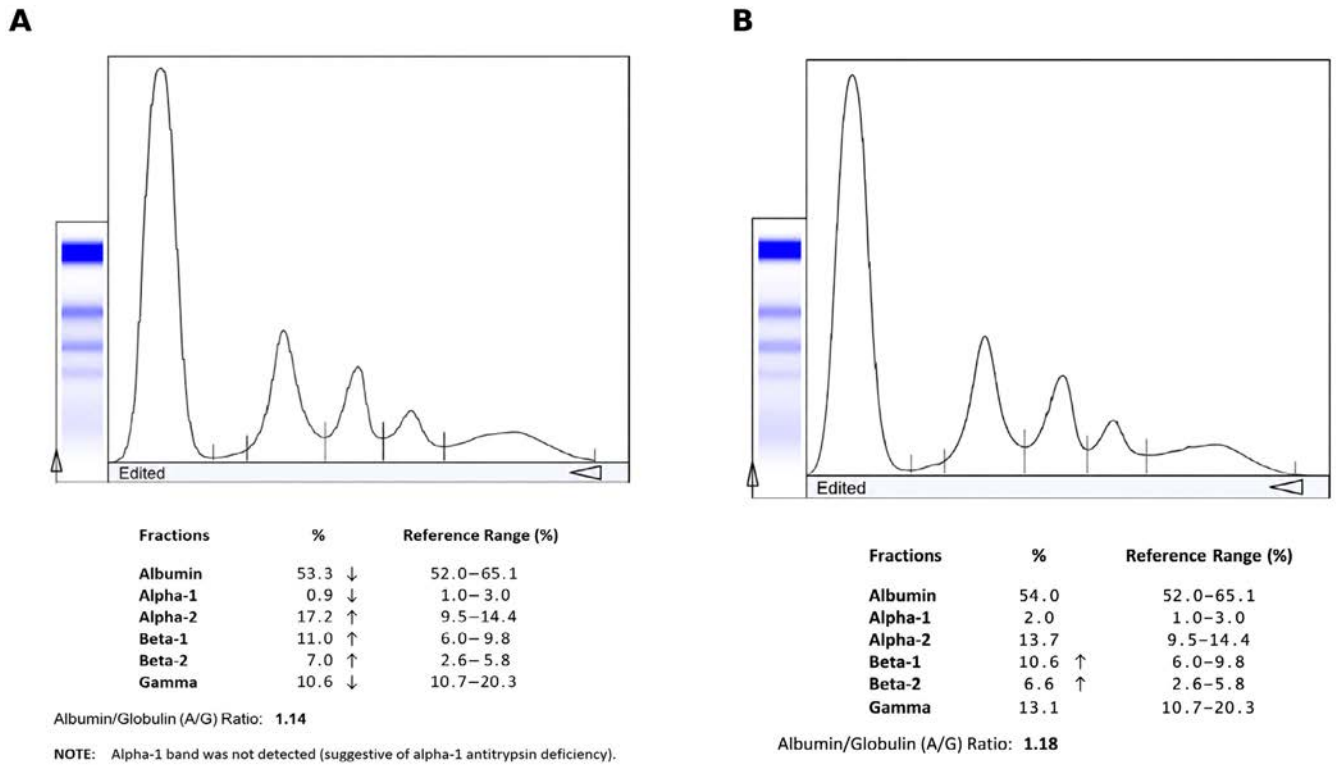

FIGURE 2 | Serum protein electrophoresis before and after alpha-1 proteinase inhibitor augmentation therapy. (A) (left) shows the pretreatment electrophoresis, in which the alpha-1 band was not detected (reported alpha-1 fraction, 0.9%; reference range, 1.0%–3.0%). (B) (right) shows the post-treatment electrophoresis, with normalization of the alpha-1 globulin fraction to 2.0%.

This case highlights the importance of considering AAT deficiency in patients with AAV, particularly those with long-standing COPD, early-onset or disproportionate emphysema, bronchiectasis, or otherwise unexplained chronic liver disease. Recognition of AAT deficiency may facilitate disease-specific management, pulmonary follow-up, genetic counseling, and family screening.

In conclusion, this case broadens the recognized clinical and serological spectrum of AAT deficiency-associated AAV and highlights serum protein electrophoresis as a useful diagnostic clue to previously unrecognized AAT deficiency.

Author Contributions

Andac Komac and Nergis Serin collected and organized the clinical data and drafted the manuscript. Nergis Serin, Duygu Temiz Karadag, and Ayse Cefle were involved in the clinical evaluation and follow-up of the patient. Serap Argun Baris contributed to the pulmonary evaluation and management of alpha-1 antitrypsin augmentation therapy. Serap Argun Baris and Ayse Cefle critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of ınterest.

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

Allopurinol Desensitization: Is There Still a Place in Clinical Practice?

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Allopurinol was the first xanthine oxidase inhibitor (XOI) approved by the US Food and Drug Administration in 1966, and has since become a cornerstone of urate-lowering therapy (ULT) for primary and secondary hyperuricemia worldwide. Allopurinol inhibits xanthine oxidase, thus reducing the conversion of hypoxanthine and xanthine to uric acid, which thereby lowers serum uric acid (SUA) and reduces urinary uric acid excretion. Its active metabolite, oxypurinol, also inhibits xanthine oxidase and has similar effects. Allopurinol is also used to prevent or treat hyperuricemia associated with tumor lysis syndrome in patients receiving cytotoxic therapy, and in those with nephrolithiasis and hyperuricosuria [1]. Beyond urate lowering, allopurinol has been reported to reduce oxidative stress and improve endothelial dysfunction, suggesting possible roles in slowing chronic kidney disease progression and reducing cardiovascular events. Recent meta-analyses have shown mixed results, suggesting potential reductions in cardiovascular morbidity but no consistent benefit for renal outcomes [2, 3]. However, these findings should be interpreted with caution, due to variability in study quality and substantial heterogeneity among the included studies.

Although allopurinol is often recommended as first-line ULT for gout by several rheumatology organizations, including the American College of Rheumatology (ACR) [4], European Alliance of Associations for Rheumatology (EULAR) [5], and Asia Pacific League of Associations for Rheumatology (APLAR) [6]; others also recommended a uricosuric agent as first-line ULT treatment, including the Japanese Society of Gout and Nucleic Acid Metabolism [7], and Chinese Society of Endocrinology [8], which alone, suggested guiding its use by renal urate excretion. These guidelines adopt a treat-to-target approach, which aims to maintain SUA below its saturation point (< 6.0 mg/dL) in order to prevent flares and promote dissolution of monosodium urate (MSU) crystal deposits.

In clinical practice, selection of ULT for the treatment of gout should be individualized and guided by current clinical guidelines. Assessment of urinary uric acid excretion and identification of underexcretion or overexcretion phenotypes may be an additional consideration in selected patients, particularly when uricosuric therapy is being considered. Allopurinol has several practical advantages, as it can be used in patients with either under- or over-excretion of uric acid, and those with renal impairment and a history of renal calculi. Its use is limited by the development of allopurinol hypersensitivity reactions, ranging from mild gastrointestinal symptoms and mild-to-moderate cutaneous eruptions (e.g., maculopapular rash, angioedema or urticaria, and fixed drug eruption) to rare but potentially severe and life-threatening reactions; namely allopurinol hypersensitivity syndrome (AHS) or severe cutaneous adverse reactions (SCARs) that include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). AHS and SCARs are strongly associated with HLA-B*58:01, which is more prevalent in East and Southeast Asian populations than in people of European ancestry [9]. Despite several guidelines recommending allopurinol as the first-line ULT, only a few of them recommend HLA-B*58:01 screening before allopurinol initiation. The ACR conditionally recommends testing for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients, and those who test positive are advised to use alternative XOIs (e.g., febuxostat or topiroxostat) or consider uricosuric therapy [4]. The APLAR weakly recommends HLA-B*58:01 screening, even in populations with ≥ 5% of this gene frequency, and genetic testing should be performed only when

Practical Points

- Gout prevalence is rising in many low- and middle-income countries (LMICs).
- In many LMICs, allopurinol is often the mainstay urate-lowering therapy (ULT) because alternative ULTs and HLA-B*58:01 testing are limited or unavailable.
- Increased allopurinol use may lead to more hypersensitivity reactions; when alternative ULTs are unavailable, allopurinol desensitization may be the only option for selected patients.

it is cost-effective in that population, and when inexpensive alternative medications are available for patients who tested positive [6]. The Hong Kong Society of Rheumatology recommends that HLA-B*58:01 screening should be considered for patients of Asian descent (e.g., Han, Chinese, Korean, Thai), African American patients, and patients with risk factors for AHS, including those ≥ 60 years or with renal insufficiency (CKD stage ≥ 3), and allopurinol should be avoided in patients who tested positive [10].

The rationale for HLA-B*58:01 screening before allopurinol initiation should probably be determined through cost-effectiveness analysis. Interestingly, cost-effectiveness analyses have shown conflicting results of HLA-B*58:01 screening before allopurinol initiation to prevent severe AHS in East and Southeast Asia, a region with a relatively high prevalence of this allele (Table S1). Such differences might have been related to several factors including the socioeconomic status and prevalence of HLA-B*58:01 in its populations, as well as the costs of genotyping and medical care, availability and cost of alternative ULTs, analytic model used and chosen time horizon. However, the decision to perform routine HLA-B*58:01 testing should depend not only on cost-effectiveness analysis, but also ethical issues because this adverse event is a serious medical condition, and a balance between payers, patients, and physicians should also be considered.

Recent reports indicate that the global prevalence of gout is increasing, particularly in Asia, Latin America and Africa, which are regions that include many low- and middle-income countries (LMICs) and other resource-limited settings (RLS) [11]. Implementing a screening-first approach in these settings is challenging because HLA-B*58:01 testing may be unavailable or costly, particularly outside tertiary centers. In these LMICs and RLS, allopurinol may be the only available XOI, while other XOIs (e.g., febuxostat or topiroxostat) and uricase-based therapy (pegloticase) may be unavailable, inaccessible or unaffordable. Uricosuric agents such as probenecid, sulfinpyrazone, and benzbromarone may be available, but their use is often constrained because they generally require adequate renal function, are most appropriate for patients with uric acid under-excretion, and are typically avoided in patients with a history of renal calculi. Consequently, as gout prevalence rises and access to HLA-B*58:01 testing remains limited, allopurinol use is expected to increase, and cases of allopurinol hypersensitivity may be encountered more frequently. A common clinical scenario is a patient with gout who has moderate renal impairment and/or history of renal calculi, who develops a cutaneous reaction soon after starting allopurinol in a setting where HLA-B*58:01 testing is unavailable or unaffordable, yet they still require long-term XOI therapy. This raises a practical clinical question: should the patient be referred to a higher-level facility for alternative therapies, or, when referral is not feasible, does allopurinol desensitization still have a role to play?

A report from the APLAR Gout Special Interest Group registry indicated that allopurinol, febuxostat, and uricosurics were used in 63%, 42%, and 3% of patients, respectively [12]. This was observed even though several participating countries are located in East and Southeast Asia, in which HLA-B*58:01 prevalence is relatively high [9]. The very low use of uricosurics in the Asia-Pacific region raises questions about how treatment aligns with gout pathophysiology, given that many gout patients have renal under-excretion of uric acid. This pattern probably reflects physician familiarity, prescribing habits, and the positioning of XOIs as first-line therapy in major guidelines [4–6].

The rationale for desensitization is gradual re-exposure to allopurinol to promote immunological tolerance while minimizing the risk of recurrent hypersensitivity. The first allopurinol desensitization regimen was developed by Meyrier in 1976 [13], and was subsequently modified by several groups, using both oral and intravenous desensitization regimens. These modified regimens vary in starting dose, dose increments, and the interval between dose increases. Oral desensitization can be categorized as slow (~1.5–3 months), standard (~4 weeks), rapid (~2 weeks), and rush (~1 week) desensitization, based on the time required to reach the target dose, while intravenous desensitization can be accomplished within 1 day (Tables S2 and S3).

Among the reported regimens, Fam's regimen is one of the most widely used [14]. However, evidence supporting efficacy remains limited, because most reports are single cases or small case series, and most patients had mild-to-moderate allopurinol hypersensitivity reactions (e.g., maculopapular rash, angioedema or urticaria, and fixed drug eruption). Allopurinol desensitization was successfully performed in 78% of a series of 32 patients with mild-to-moderate allopurinol hypersensitivity reactions [15]. On this basis, desensitization should generally be considered for patients with mild-to-moderate allopurinol hypersensitivity reactions [10], after careful risk–benefit assessment and a thorough discussion with the patient. If a patient develops a minor reaction (e.g., limited cutaneous symptoms) during desensitization, allopurinol should be stopped and the reaction managed appropriately; once symptoms have been resolved, desensitization can be restarted at the next lower dose level [14, 16]. Intravenous desensitization should be undertaken with extreme caution and performed only in hospital settings with immediate access to resuscitation equipment and appropriately trained staff.

Severe AHS is generally considered a contraindication for allopurinol desensitization. However, successful allopurinol desensitization has been reported in cases with severe AHS [17]. There has also been a report of successful desensitization at the second attempt, performed approximately 4 years after an initial failure due to severe AHS during the first desensitization [18]. These cases are extraordinarily exceptional and should

not be considered as routine efficacy; thus, allopurinol desensitization should be performed in a situation when allopurinol use is inevitable. The author experienced success in performing allopurinol desensitization in three patients with severe AHS, in circumstances when allopurinol was the only available option at the author's institution. Such cases highlight both the clinical pressure that can exist in RLS and the need for extreme caution when considering desensitization outside the usual indications.

Prevention is, of course, preferable to treatment. In addition to HLA-B*58:01, older age, concomitant diuretic use, renal impairment and a high starting dose of allopurinol are associated with increased risk of AHS [19]. A starting dose of ≥ 1.5 mg/eGFR (mL/min/1.73 m^2) has been associated with AHS; therefore, allopurinol should be initiated at <1.5 mg/eGFR [20]. The dose should then be gradually increased (e.g., monthly) until the target SUA is attained, or the maximum tolerated dose is reached ("start-low, go-slow"). Monthly increments of 50 mg and 100 mg in patients with eGFR <60 and ≥ 60 mL/min/1.73 m^2, respectively, have been reported to be safe without AHS [21].

Another emerging preventive approach is the use of non-genetic clinical prediction models that combine patient characteristics with routine laboratory data to estimate the probability of severe AHS. The first model was developed in Thailand, potentially representing East and Southeast Asian populations, and it categorizes the risk of severe AHS as low ($<1\%$), moderate (1%–2%) and high ($\geq 2\%$) [22]. The second model was developed using UK National Health Service data, in which most patients were White (with low HLA-B*58:01 prevalence) and the numbers of Chinese and other Asian ethnicities were smaller [23]. External validation is needed to confirm model performance in regions with a high prevalence of HLA-B*58:01.

In conclusion, allopurinol desensitization plays a limited role, but it remains clinically useful, particularly in LMICs and RLS where allopurinol may be the only available ULT. Desensitization should be considered only for patients with mild-to-moderate hypersensitivity reactions and it is contraindicated for patients with severe AHS. Allopurinol desensitization in severe AHS patients should be reserved for only exceptional circumstances and performed in hospital with close monitoring and immediate access to resuscitation equipment. Where desensitization is pursued, standard oral protocols are usually preferred, whereas rapid, rush, or intravenous approaches should be avoided unless there is an urgent clinical need and adequate facilities are available. Finally, the key question is not whether desensitization works, but when it is appropriate. It can be a pragmatic option when treatment choices are limited, but it should not replace prevention (risk stratification, an appropriate starting dose, and a "start-low, go-slow" strategy).

Author Contributions

Worawit Louthrenoo: conceptualization, writing – original draft, writing – review and editing.

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The author has nothing to report.

Conflicts of Interest

Dr. Louthrenoo is an Editorial Board member of the *International Journal of Rheumatic Diseases*, and the corresponding author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

Data Availability Statement

Data sharing is not applicable as this study did not generate or analyze any datasets.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Cost effective analysis of HLA-B*58:01 testing among Asian countries (selected series). **Table S2:** Allopurinol desensitization regimens (based on type and duration of desensitization). **Table S3:** Allopurinol desensitization regimens, allopurinol solution preparation, and dose-escalation schedule.

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CORRECTION

Correction to "Paradigm Guiding to Tapering or Discontinuation of Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs in the Treatment of Patients With Rheumatoid Arthritis: Results From a Local Retrospective Cohort Study"

N. Kaban and H. Harman. "Paradigm Guiding to Tapering or Discontinuation of Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs in the Treatment of Patients With Rheumatoid Arthritis: Results From a Local Retrospective Cohort Study," *International Journal of Rheumatic Diseases* 26 (2023): 689–698, https://doi.org/10.1111/1756-185X.14616.

The title of the above article was published as "Paradigm guiding to tapering or discontinuation of biologic and targeted synthetic disease-modifying antirheumatic drugs in the treatment of patients with rheumatoid arthritis: Results from a local prospective study." It should be "Paradigm guiding to tapering or discontinuation of biologic and targeted synthetic disease-modifying antirheumatic drugs in the treatment of patients with rheumatoid arthritis: Results from a local retrospective cohort study." This has been corrected in the online article.

The objective in the abstract of the above article was "We prospectively conduct the current study to figure out predicting factors whether biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) can be discontinued or tapered in patients with rheumatoid arthritis (RA)." It should be "We retrospectively conducted the current study to figure out predicting factors whether biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) can be discontinued or tapered in patients with rheumatoid arthritis (RA)."

There was no ethics statement in the above article. An Ethics Statement should be added as follows:

Ethics Statement

The protocol for the retrospective review and analysis of existing routine-care medical records was approved by the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee, Istanbul, Türkiye (Decision No. 276, 27 October 2021). The study was conducted in accordance with the Declaration of Helsinki. The analysis was based on existing routine-care records; no treatment was assigned, modified, or withheld for research purposes.

We apologize for these errors.

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LETTER TO THE EDITOR

Case Report: Sacroiliitis and Long-Term Effects on Bones and Joints Following Isotretinoin Use

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Keywords: acne vulgaris | bone | isotretinoin | magnetic resonance imaging | sacroiliitis

Dear Editor,

Isotretinoin is commonly used to treat acne and may cause sacroiliitis. Sacroiliitis is usually reversible, but in severe cases, systemic corticosteroids and biologics may be required. We report a case of a young adolescent with acute-onset, severe, disabling pain and magnetic resonance imaging (MRI) evidence of extensive sacroiliac bone marrow edema (BME), emphasizing the need for immediate biological treatment. Fortunately, clinical recovery occurred within 4 months after stopping isotretinoin without additional therapy. MRI is extremely useful for early diagnosis, monitoring, and confirming full recovery. Surprisingly, BME may persist for about 2 years despite early discontinuation of isotretinoin. Awareness of this finding is also clinically practical when accidental MRI findings of sacroiliac BME are identified in asymptomatic young people who have previously been exposed to isotretinoin.

Isotretinoin-induced acute sacroiliitis is a rare but well-recognized adverse effect of a widely used medication for common acne [1, 2]. It typically begins within 8–10 weeks of therapy, often bilaterally, regardless of the drug dose and duration of use [1]. The exact mechanism of action on bone and joints remains unknown, and why some patients develop sudden, often debilitating sacroiliac joint (SIJ) inflammation is unclear [3, 4]. It is usually reversible after discontinuing isotretinoin, with a remitting course. If diagnosis is delayed, multiple treatments—including NSAIDs, corticosteroids, and biological therapies such as tumor necrosis factor (TNF) blockers—may be necessary [3–5]. Discontinuing isotretinoin can lead to full clinical and radiologic resolution within 3–6 and 6–9 months, respectively [2, 6]. Although it is considered an uncommon condition, the incidence of isotretinoin-associated inflammatory back pain or sacroiliitis with BME is approximately 10% among isotretinoin users, as reported in some studies [7–9].

A 14-year-old boy with moderate acne vulgaris was treated with 20 mg of oral isotretinoin daily. Six weeks later, he sustained minor blunt trauma to his left thigh during a school game, resulting in limping, morning stiffness, Trendelenburg posture, and a severe waddling gait with limited mobility that required a walker. Isotretinoin was discontinued. Extensive orthopedic, neurological, and hematological evaluations were performed and were unremarkable. Although his ESR and CRP were slightly elevated, tests including muscle enzymes, electromyogram, nerve conduction studies, and MRI of the lower spine were negative. His family history revealed that his grandmother had Crohn's disease (CD) and a cousin had hidradenitis suppurativa (HS), prompting additional testing (HLA-B27, HLA-B5, gastroenterology assessment), all of which were negative, with no infectious disease identified. Due to acute inflammatory back pain, an MRI scan was performed four weeks after presentation, showing extensive bone edema and bilateral sacroiliitis (Figure 1A–C).

Isotretinoin-induced sacroiliitis was diagnosed after excluding other differential diagnoses, including SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis or osteomyelitis) and acne fulminans, which is characterized by sudden-onset

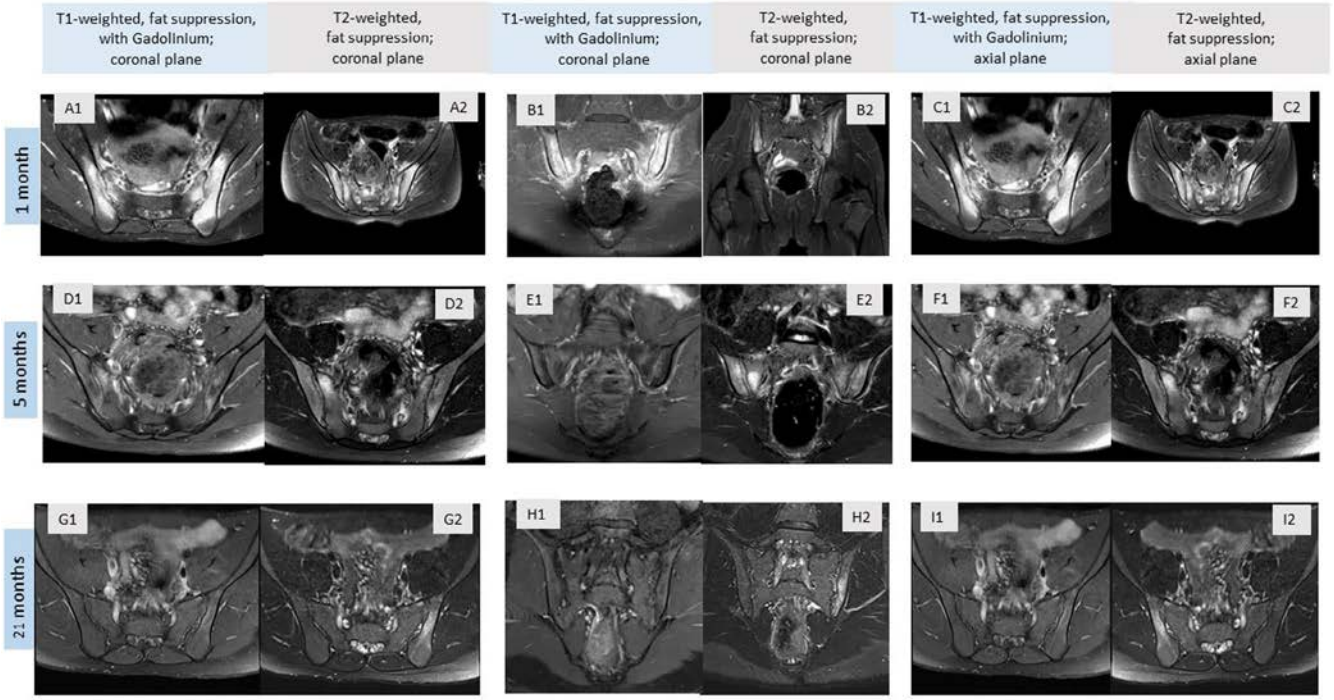

FIGURE 1 | Isotretinoin-induced sacroiliitis over time. Coronal and axial T1-weighted MRI images (T1; labeled as 1), fat-suppressed (FS) post-contrast images, and T2-weighted FS scans (T2; labeled as 2) obtained 1 month after clinical presentation (Panels A, B, C) showed bilateral subchondral bone marrow edema at the sacroiliac joints, along with soft tissue edema (post-traumatic) anterior and posterior to the joints, involving the gluteus minimus abductor muscles. Two follow-up studies demonstrated gradual resolution of these findings at 5 months (Panels D, E, F) and 21 months, with minimal bone marrow edema still visible in the iliac bone after a prolonged period following isotretinoin cessation (Panels G, H, I).

nodulocystic and ulcerative acne with systemic symptoms such as fever, malaise, and elevated inflammatory markers [1, 2].

For bilateral acute sacroiliitis unresponsive to analgesics, adalimumab, a TNF inhibitor, was recommended. However, the patient and his parents declined, and he gradually improved without treatment. Follow-up MRI scans 5 months after presentation, after discontinuation of isotretinoin, confirmed a reduction in inflammation (Figure 1D–F). Within 4 months, without treatment, he regained a normal gait and achieved complete clinical remission, which he has maintained to date at age 19. Surprisingly, MRI scans at 21 months showed improvement but not complete radiological resolution, despite the rapid clinical recovery, suggesting a prolonged effect of isotretinoin on bone tissue (Figure 1G–I).

Consent for publication of the case report was obtained directly from the patient, now 19 years old. Despite clinical quiescence, a recent follow-up MRI at 62 months showed completely normal SIJs, with no residual BME or structural changes.

Although isotretinoin is widely used to treat common acne, it may induce sacroiliitis that can be sudden and lead to severe disability. Full clinical recovery may result from immediate cessation of isotretinoin, underscoring the value of early suspicion and avoiding extensive investigation and expensive biological therapies.

Isotretinoin-reactive sacroiliitis may be linked to retinoic acid and isotretinoin's anti-osteoblast effects on bone, which increase matrix metalloproteinase activity and, through their detergent-like properties, alter lysosomal membranes in synovial cells [1, 2]. Our patient had experienced minor blunt trauma before presentation. Trauma is an important biomechanical factor in the development of sacroiliitis, even in healthy individuals such as postpartum women, military soldiers, runners, and athletes [10–13]. Moreover, genetic predisposition might increase risk, as our patient had a family history of other inflammatory conditions (CD and HS) that can manifest as sacroiliitis. The literature on whether genetically predisposed individuals face an increased risk of spondyloarthritis remains inconclusive and conflicting. Most reported cases of isotretinoin-induced sacroiliitis are HLA-B27 negative, arguing against a strong causal association [1]. Nevertheless, our patient was tested for HLA-B27, which was negative. Moreover, he underwent a complete gastroenterological evaluation that showed no evidence of Crohn's disease.

Therefore, we propose a “multiple-hit” model that leads to acute sacroiliitis in at-risk isotretinoin users, specifically young acne patients who have experienced minor trauma or have a family history suggesting a genetic predisposition to sacroiliitis.

Isotretinoin-associated sacroiliitis reported in the literature is typically limited to BME, as in our case (Figure 1). Well-established pathological sacroiliitis, as in axial spondyloarthritis (axSpA), requires both inflammatory and structural findings (e.g., erosion and fat metaplasia), whereas isotretinoin-induced sacroiliitis on MRI shows sacroiliac BME without structural damage [14, 15].

Most cases improve clinically and radiologically within 3–9 months after discontinuation [1–6]. MRI is an effective diagnostic tool that

can reveal extensive BME and active SIJ synovitis (Figure 1A–C). Longer follow-up and MRI, which have not previously been reported, may uncover the true extent of isotretinoin's impact (Figure 1G–I). Notably, despite being completely asymptomatic, the patient showed persistent bone effects of isotretinoin for about 2 years during long-term follow-up.

Therefore, our case underscores several clinical points. First, MRI is crucial for early detection of sacroiliac BME and may also be important for monitoring. Second, although isotretinoin-induced sacroiliitis is well described in the literature and is reversible after isotretinoin cessation, early diagnosis is crucial to stop the inciting drug and prevent further deterioration and the need for systemic anti-inflammatory therapy. Third, our case underscores a previously unreported finding: the effect of isotretinoin on bone and joints may persist for almost 2 years after its cessation. Moreover, as shown by MRI, this effect persists despite early clinical remission. This discrepancy between symptom recovery and radiological resolution is a unique clinical finding. Consequently, incidental MRI findings of BME may be observed in asymptomatic young individuals who previously received isotretinoin. Therefore, there may be an additional group in the general population with prevalent sacroiliac BME, beyond biomechanical conditions following obesity, pregnancy, running, and sports injuries [13]. A history of isotretinoin use should be sought in the symptomatic patient with back pain and in the asymptomatic young with MRI findings of sacroiliac BME. Finally, this case highlights a proposed hypothesis of combined risk factors for sacroiliitis during acne retinoic acid treatment: genetic predisposition, traumatic trigger, and isotretinoin use.

In conclusion, our case report emphasizes the importance of early clinical diagnosis of isotretinoin-induced sacroiliitis, supported by MRI findings that enable accurate assessment, prolonged monitoring, and appropriate treatment planning while avoiding unnecessary investigations and immunosuppressive therapies.

Author Contributions

Conceptualization: S.A. Data curation: S.A., E.A., N.S. Investigation: S.A., E.A. Methodology: N.S. Supervision: S.A., E.A., N.S. Validation: S.A. Visualization: S.A. Writing – original draft: S.A. Writing – review and editing: S.A., E.A., N.S. S.A. was involved in patient management, conducted the literature search, and drafted the manuscript. E.A. compiled patient information and organized the data. N.S. performed the radiological evaluation and reviewed, edited, and finalized the radiological description. All authors approved the final manuscript.

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Ethics Statement

Ethical approval was waived by the local Institutional Review Board (IRB) of Hadassah Medical Organization (HMO) and Assuta-Ashdod Medical Center for case reports.

Consent

Consent was obtained directly 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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