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ORIGINAL ARTICLE

Oxidative Phosphorylation Pathway in Ankylosing Spondylitis: Multi-Omics Analysis and Machine Learning

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the axial skeleton, characterized by immune microenvironment dysregulation and elevated cytokines like TNF-α and IL-17. Mitochondrial oxidative phosphorylation (OXPHOS), crucial for immune cell function and survival, is implicated in AS pathogenesis. This study explores OXPHOS-related mechanisms in AS, identifies key genes using machine learning, and highlights potential therapeutic targets for precision medicine.

Materials and Methods: Peripheral blood mononuclear cells (PBMCs) bulk transcriptomic and single-cell RNA sequencing (scRNA-seq) data from AS patients were analyzed to investigate the role of the OXPHOS pathway in AS. Weighted gene co-expression network analysis (WGCNA) was performed to identify key gene modules associated with OXPHOS. Machine learning techniques, including support vector machine with recursive feature elimination (SVM-RFE), random forest, and least absolute shrinkage and selection operator (LASSO), were applied to identify significant AS-related genes. Real-time PCR (RT-PCR) was used to quantify gene expression, examine their patterns in specific cell subtypes, and explore their functional implications.

Results: Pathway enrichment analysis identified OXPHOS as a significantly enriched pathway distinguishing AS patients from healthy controls, with high normalized enrichment scores and significant group separation in principal component analysis. ScRNA-seq revealed significantly higher OXPHOS scores in AS patients, especially in dendritic cells (DCs) and monocytes, highlighting cell type-specific dysregulation. WGCNA identified two key gene modules (MEyellow and MEtan) that are closely associated with OXPHOS. Three hub genes—*LAMTOR2*, *APBB1IP*, and *DGKQ*—were screened using machine learning methods and validated by RT-PCR and scRNA-seq. Among them, *LAMTOR2* was significantly more highly expressed in patients with AS, and functional analyses showed that it plays a role in promoting TH17 cell differentiation, which highlights its potential as a therapeutic target for ankylosing spondylitis.

Abbreviations: AS, ankylosing spondylitis; CCR, chemokine receptor; cDCs, conventional dendritic cells; DCs, dendritic cells; DEGs, differentially expressed genes; EDTA, ethylenediaminetetraacetic acid; GEO, Gene Expression Omnibus; GO, gene ontology; GSEA, gene set enrichment analysis; GSVA, gene set variation analysis; HLA-B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; IFN-γ, interferon-gamma; IL-17, interleukin-17; KEGG, Kyoto Encyclopedia of Genes and Genomes; LASSO, least absolute shrinkage and selection operator; logFC, log fold change; NES, normalized enrichment score; OOB, out-of-bag; OXPHOS, oxidative phosphorylation; PBMCs, peripheral blood mononuclear cells; PCA, principal component analysis; pDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; RT-PCR, real-time PCR; scRNA-seq, single-cell RNA sequencing; SVM-RFE, support vector machine with recursive feature elimination; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha; UPR, unfolded protein response; WGCNA, weighted gene co-expression network analysis.

Yuling Chen and Yuan Xu contributed equally to this work.

Conclusion: This multi-omics study provides valuable insights into the complex interplay between OXPHOS and AS. The identified genes, particularly *LAMTOR2*, serve as potential therapeutic targets, contributing to our understanding of AS mechanisms and paving the way for precision medicine in AS treatment.

1 | Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects young individuals, characterized by inflammation in the axial joints, including the sacroiliac joints and the spine [1]. In China, the prevalence of AS is approximately 0.2%–0.4%, with 0.42% in males and 0.15% in females [2]. The precise molecular etiology of AS remains unclear. Most studies suggest that the etiology of AS is linked to a combination of genetic, infectious, immune, and environmental factors, with human leukocyte antigen B27 (HLA-B27) being the most significant [3, 4]. The hypotheses regarding the pathogenesis of AS induced by HLA-B27 include its recognition of pathogenic peptides [5–7], or its structural abnormalities such as misfolding and heavy chain homodimer formation, which can trigger the immune system to attack self-tissues [8, 9]. This leads to dysregulation of the immune microenvironment, characterized by alterations in immune cell populations [10–12] and elevated levels of cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-17 (IL-17) [13–17]. Functional genetic studies have revealed the relationship between genetic polymorphisms and the risk of AS. For example, polymorphisms in the calcium release-activated calcium modulator 1 (CRACM1, also called ORAI1) gene are associated with the risk of HLA-B27-positive AS, and polymorphisms in the programmed cell death 1 (PD-1) and its ligands (PD-L) pathway are associated with AS development in the Taiwanese population [18, 19]. Small RNAs, such as miR-21, also play a role in AS pathogenesis, with microRNA-21 potentially promoting bone erosion by inhibiting programmed cell death 4 (PDCD4) expression in patients with short disease duration [20].

Metabolism influences the expression of cytokines and chemokines, the production of reactive oxygen species (ROS), and the functional characteristics of both innate and adaptive immune cells. OXPHOS, which takes place in the inner mitochondrial membrane, utilizes enzymes and energy released from the oxidation of various nutrients to synthesize ATP, serving as the primary mechanism by which cells generate ATP, the primary energy source for cells. Alterations in mitochondrial OXPHOS levels in immune cells are particularly critical, as they impact cell function and survival [21]. Inhibition of succinate, a key component of OXPHOS, has been shown to effectively reduce TNF-α secretion [22], a cytokine that plays a major role in the pathogenesis of AS. Therefore, OXPHOS may contribute to the development of AS by regulating immune cell function. However, metabolic changes in immune cells, particularly those involving OXPHOS, remain poorly understood in AS.

This study aims to investigate the role of OXPHOS in the pathogenesis of AS by analyzing transcriptomic and single-cell RNA sequencing (scRNA-seq) data from AS patients. The study seeks to identify key genes associated with OXPHOS using machine learning techniques and explore their expression patterns in specific immune cell subtypes. Additionally, the research aims to uncover potential therapeutic targets within the OXPHOS pathway that could inform precision medicine approaches in treating AS.

2 | Methods

2.1 | Datasets Source

This study searched the GEO database (https://www.ncbi.nlm.nih.gov/geo) using the keyword "ankylosing spondylitis" Datasets that utilized peripheral blood mononuclear cells (PBMCs) and included at least 10 samples per group were selected. Bulk RNA-seq data (GSE25101 [23]) from 16 AS patients and 16 normal control PBMCs and scRNA-seq data (GSE194315 [24]) from 10 AS patients and 29 normal control PBMCs were selected, and their expression and clinical data were downloaded for further analysis.

2.2 | Workflow for Bulk RNA-Seq Data Analysis

First, the GSE25101 dataset and associated phenotype information were loaded using the GEOquery package [25]. Expression data were filtered and pre-processed, including normalization with the normalizeBetweenArrays function to correct for technical variations. Probe-to-gene mapping was performed using annotation data from illuminaHumanv3.db [26], consolidating probe-level data into a gene-level expression matrix.

Differentially expressed genes (DEGs) between AS patients and the normal controls in GSE25101 were analyzed using the limma package in R [27]. Absolute log fold change (logFC) was set ≥ 0.3 and adjusted p value < 0.05. Functional enrichment analyses were conducted by the clusterProfiler package [28], involving gene ontology (GO) enrichment analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG), gene set enrichment analysis (GSEA) [29], and gene set variation analysis (GSVA) [30].

Pathway activity scores derived from GSVA were utilized to classify sample groups. These scores represent the relative activity levels of specific biological pathways in each sample. To reduce dimensionality while retaining significant variation, principal component analysis (PCA) was performed on the pathway scores. The first two principal components (PC1 and PC2) were used to visualize sample distribution in a two-dimensional space. Samples were colored based on their group labels, and a separation line was introduced to evaluate the effectiveness of pathway scores in distinguishing between groups.

2.3 | Comprehensive Analysis of scRNA-Seq Data Using the Seurat Pipeline

Single-cell RNA sequencing (scRNA-seq) data were analyzed using the standard Seurat pipeline [31, 32], which includes: first, pre-processing the data, encompassing quality control to filter out low-quality cells and genes, normalization to adjust for differences in sequencing depth, and identification of highly variable features. The low-quality cells were identified based on two criteria: [1] total genes expressed < 200 or > 2500; and [2] mitochondrial-associated genes expressed $> 20\%$. The top 3000 variable genes were detected using the "vst" selection method. Then, similar cells were grouped by applying dimensionality reduction techniques, including PCA, *t*-distributed stochastic neighbor embedding (t-SNE), and uniform manifold approximation and projection (UMAP), for clustering. The first 30 PCs were used for dimensionality reduction and clustering. Finally, the clusters were visualized using PCA, UMAP, and t-SNE, and differential expression analysis was conducted to identify marker genes that characterize each cluster. Cell types were annotated using a reference-mapping approach, with the PBMCs reference dataset obtained from Seuratdisk. The pathways enrichment score was calculated based on gene sets downloaded from the MsigDB database and using the AUCell package [33].

2.4 | Weighted Gene Co-Expression Network Analysis (WGCNA) Analysis

WGCNA was a systems biology method used to identify clusters (modules) of highly correlated genes and to relate these modules to external traits or phenotypes. In this study, WGCNA was performed to identify key modules of co-expressed genes associated with OXPHOS. The analysis was conducted using the WGCNA package [34] in R on the dataset GSE25101. First, the gene set variation analysis (GSVA) method was applied to calculate OXPHOS pathway scores for each sample. The conservation of network modules across the cohort was then assessed using the module preservation function. Key gene modules that were highly correlated with the oxidative phosphorylation scores were identified as significant.

2.5 | Machine Learning Analysis

In subsequent analyses within the gene modules identified by WGCNA, genes related to OXPHOS were further refined using three machine learning methods, including random forest, least absolute shrinkage and selection operator (LASSO), and support vector machine with recursive feature elimination (SVM-RFE).

The SVM-RFE model, implemented using the "e1071" package [35], served as a supervised machine learning algorithm for feature selection in predicting AS. To assess its performance, a 10-fold cross-validation was conducted on the dataset. The error estimation was then generalized for the entire dataset, and variables were screened to identify the one with the lowest common diagnosis error rate. The random forest model, using the "randomForestd" package [36] in R software, selects important variables (genes) and calculates and visualizes their relative importance. A comprehensive analysis included model evaluation metrics such as out-of-bag (OOB) error rates and confusion matrices. Additionally, the study utilized a 10-fold cross-validation procedure to generalize error estimation for the entire dataset. The importance of variables was assessed through mean decrease in accuracy, and the top 30 genes were extracted based on this criterion.

The Lasso analysis utilized the "glmnet" package [37] in R, starting with the preparation of the dataset containing gene expression information (predictors) and a binary target variable indicating survival status. The Lasso model was constructed using logistic regression with the "binomial" family parameter, introducing regularization to prevent overfitting. Cross-validation was performed to assess model performance and select the optimal regularization parameter (lambda) by evaluating classification metrics.

2.6 | Sample Collection

Blood samples used for validation were collected from the Seventh Affiliated Hospital of Sun Yat-sen University outpatient clinic, with clinical information detailed in Data S1. All patients with a diagnosis of AS met the modified New York criteria. Each participant signed an informed consent form under a protocol approved by the Ethics Committee of the Seventh Affiliated Hospital of Sun Yat-sen University (KY-2023-017-01).

2.7 | RT-PCR Analysis

Blood samples were collected from AS patients and healthy individuals using ethylenediaminetetraacetic acid (EDTA)-coated vacutainers. PBMCs were isolated from whole blood using Ficoll-Paque density gradient centrifugation. Total RNA was extracted from isolated PBMCs using AG RNAex Pro reagent (Accurate Biology, China) according to the manufacturer's instructions. The RNA concentration and purity were determined using a NanoDrop spectrophotometer. Subsequently, RNA was reverse transcribed into complementary DNA (cDNA) by HiScript III All-in-one RT SuperMix Perfect for qPCR Kit (Vazyme, China). The expression levels of target genes were analyzed by RT-PCR using ChamQ Universal SYBR qPCR Master Mix (Vazyme, China) on the Thermo CFX96 Real-Time PCR System (Thermo Fisher Scientific). Gene-specific primers were designed and synthesized commercially (Data S2). The cycling conditions were as follows: initial denaturation at 95°C for 30 s, followed by 40 cycles of denaturation at 95°C for 5 s, and annealing/extension at 60°C for 30 s. The relative gene expression levels were determined using the $2^{-\Delta\Delta Ct}$ method, normalized to the expression of the housekeeping gene GAPDH. Results and graphing were conducted using GraphPad Prism software (version 9.0.2).

2.8 | Statistical Analysis

All statistical analyses and visualization were performed using R software v4.0.4 (https://www.r-project.org/). Comparisons

between the two groups were made using the Wilcoxon test, and Pearson's correlation analysis was conducted for correlation assessments. A p value less than 0.05 was regarded as statistical significance.

3 | Results

3.1 | Function Enrichment Analysis

Pathway enrichment analysis of RNA-seq data from the GSE25101 dataset, based on DEGs, identified OXPHOS as one of the most significantly enriched pathways distinguishing AS patients from normal controls. In GO enrichment analysis, OXPHOS ranked fifth (Figure 1A), while in KEGG pathway analysis, it ranked first (Figure 1B). Furthermore, in GSEA analysis, the normalized enrichment scores (NES) for OXPHOS were consistently greater than two (Figure 1C), underscoring its potential importance. The PCA plot based on pathway activity scores derived from GSVA demonstrated a clear separation between sample groups. AS samples formed tight clusters, while normal control samples were distinctly separated along the principal component axes (Figure 1D). These findings indicate that OXPHOS pathway scores effectively capture biological variation associated with sample grouping, providing a robust framework for classification based on pathway activity.

3.2 | ScRNA-Seq Analysis

To further explore the value of OXPHOS scores in single-cell data, 15 926 AS cells and 66 433 control cells were included in the scRNA-seq analysis after stringent quality control. Using PCA, tSNE, and UMAP, all cells were classified into eight distinct

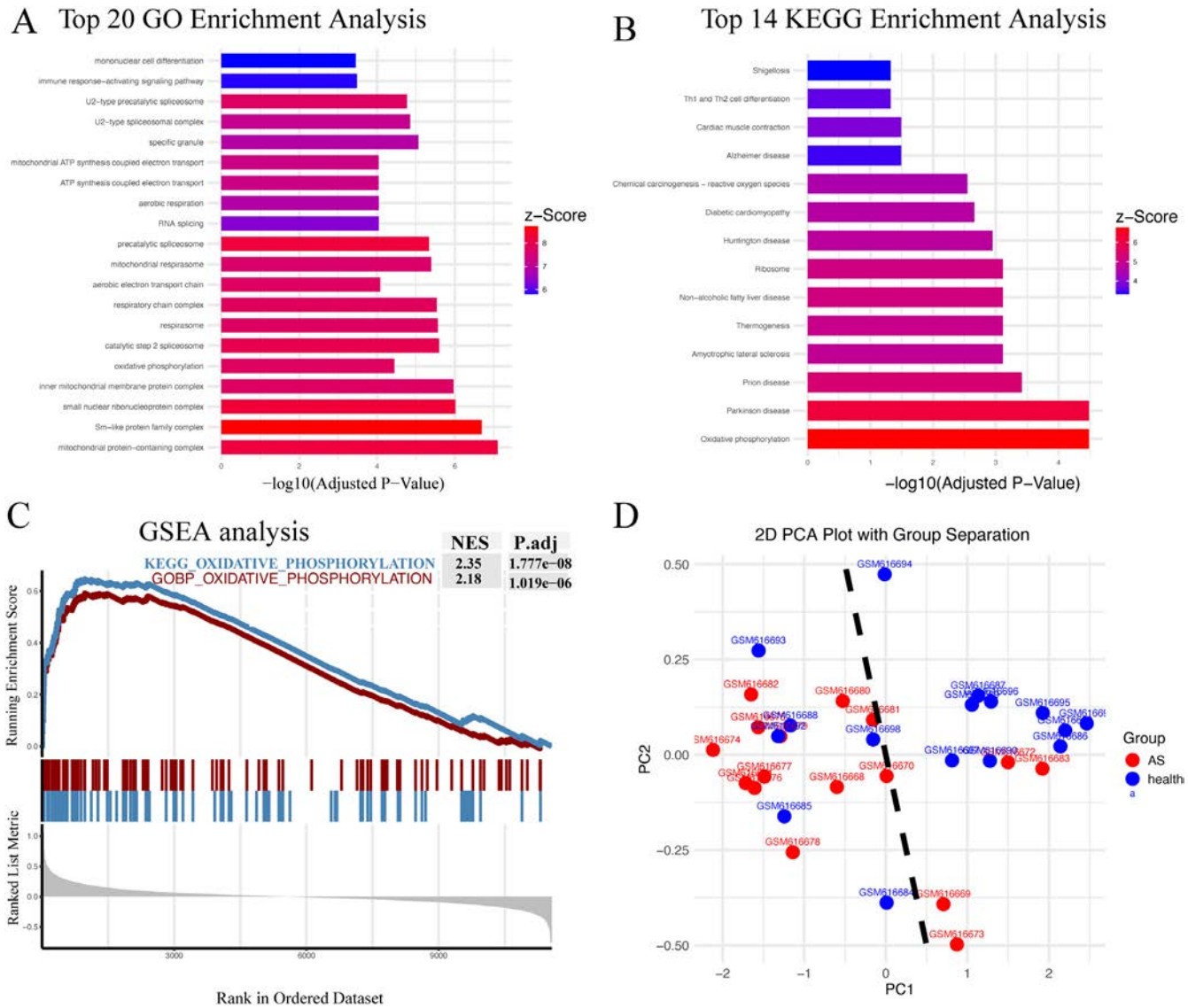

FIGURE 1 | (A) Illustrates the top 20 enriched pathways within the GO analysis. (B) The top 14 enriched pathways according to the KEGG. (C) The GSEA plot specifically focuses on the enrichment pattern of the oxidative phosphorylation pathway. (D) The 2D PCA plot illustrates the distribution of AS and control group samples in a two-dimensional space based on OXPHOS scores. AS, ankylosing spondylitis; GO, gene ontology; GSEA: gene set enrichment analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; NES, normalized enrichment score; OXPHOS, oxidative phosphorylation; PCA, principal component analysis; scRNA-seq, single-cell RNA sequencing.

clusters (Figure S1 and Figure 2A) and further characterized based on OXPHOS scores (Figure 2B) and mitochondrial content (Figure 2C). Overall, AS patients showed significantly higher OXPHOS scores compared to the normal group (Figure 2D). However, the distribution of OXPHOS scores was not uniform across different cell types, and the changes in OXPHOS scores were disproportionate to mitochondrial content (Figure 2E,F).

A detailed analysis of OXPHOS scores across individual cell subtypes revealed significant differences between AS patients and normal individuals, with AS patients showing markedly higher OXPHOS scores (Figure 2G). These findings suggest that the dysregulation of OXPHOS in AS is associated with specific cell subtypes, providing important insights into the molecular mechanisms underlying the disease.

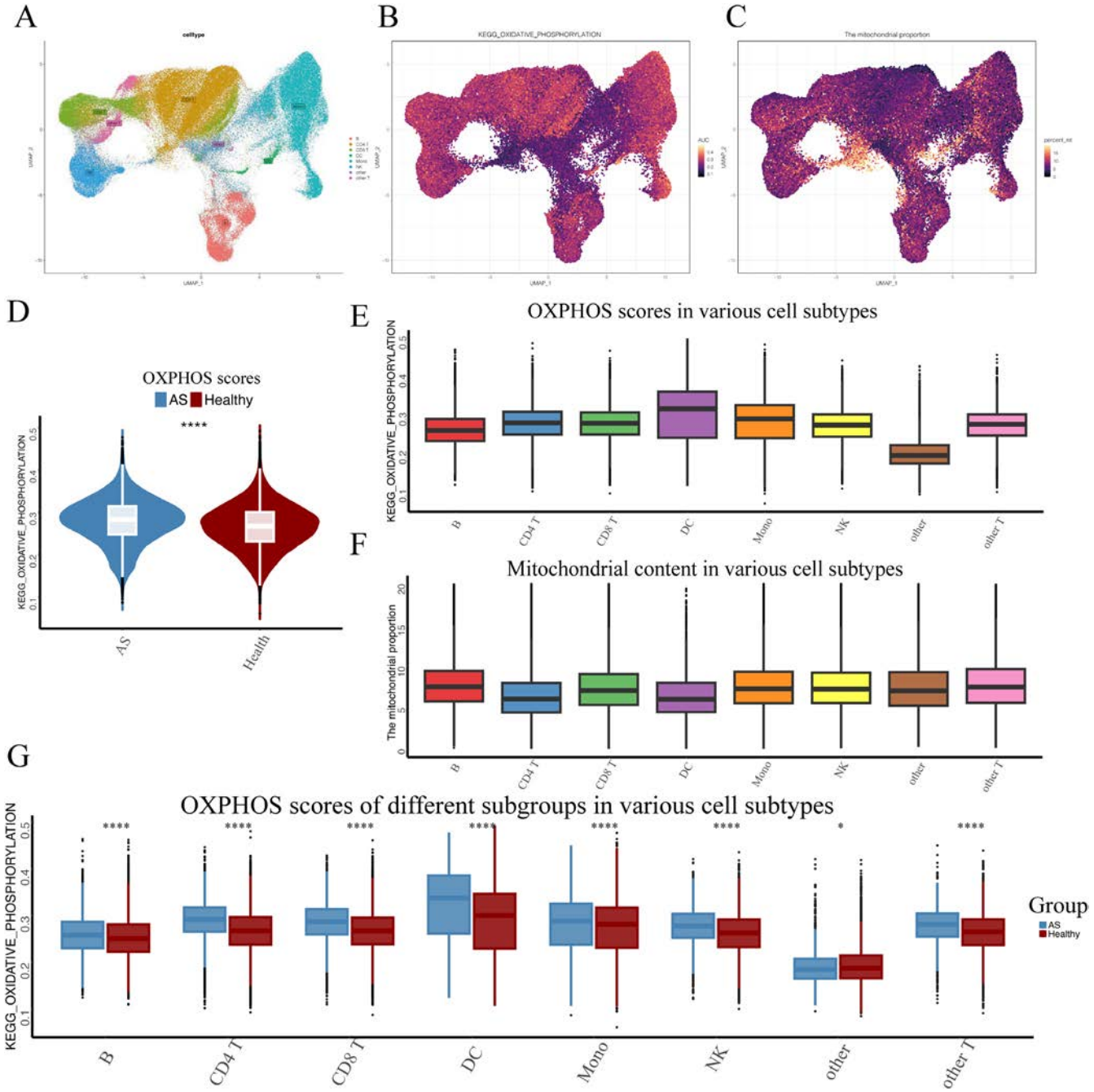

FIGURE 2 | OXPHOS score in scRNA data. (A) UMAP plot showing the clustering of immune cell populations. Different colors represent distinct cell types. (B) UMAP plot displaying OXPHOS scores across immune cell populations, with color intensity indicating expression levels. (C) UMAP plot displaying the mitochondrial content across immune cell clusters, with darker colors indicating higher mitochondrial levels. The X and Y axes represent UMAP1 and UMAP2, the two primary components derived from UMAP, which capture the major variations in the high-dimensional data structure. (D) Overall comparison of OXPHOS scores between AS patients and healthy individuals. Distribution of OXPHOS scores (E) and mitochondrial content (F) across different cell populations. (G) Comparison of OXPHOS scores between AS patients and normal individuals in various cell populations. AS, ankylosing spondylitis; cDCs, conventional dendritic cells; OXPHOS, oxidative phosphorylation; pDCs, plasmacytoid dendritic cells. ns, $p > 0.05$, *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$.

3.3 | Construction of Co-Expression Network

To identify gene modules associated with OXPHOS scores, we performed WGCNA analysis. A total of 28 co-expression gene modules were identified, of which 24 robust modules were retained after excluding four poorly preserved modules. Correlation analysis identified the modules most closely related to OXPHOS scores, namely the MEyellow and MEtan modules, as shown in the heatmap (see Figure 3). The MEyellow module showed strong correlations with GO_OXPHOS scores (r = 0.92) and KEGG_OXPHOS scores (r = 0.89), while the MEtan module showed correlations with GO_OXPHOS scores (r = 0.75) and KEGG_OXPHOS scores (r = 0.74). Additionally, these modules were also significantly associated with the sample groups, with MEyellow showing a correlation of r = 0.43 and MEtan showing r = 0.6. These results suggest that the genes within the MEyellow and MEtan modules are not only highly associated with OXPHOS but also capable of distinguishing AS samples from normal controls.

3.4 | OXPHOS-Related Genes Filtered by Machine Learning

To further identify key genes within the MEyellow and MEtan modules from the WGCNA analysis, three complementary machine learning methods were systematically applied to characterize the most relevant OXPHOS-related genes in AS. The SVM-RFE method selected the top 13 genes as optimal features, as shown in the error rate plot (Figure 4A), with details provided in Data S3. The random forest approach further refined the gene list, identifying 30 critical genes ranked by their importance, measured by the Mean Decrease Gini (Figure 4B). The complete rankings are presented in Data S4.

Additionally, the LASSO method pinpointed seven specific genes critical for distinguishing AS samples (Figure 4C,D), with details available in Data S5. By intersecting the results from all three methods, three key genes—*LAMTOR2*, *APBB1IP*, and *DGKQ*—were identified as the most relevant OXPHOS-related genes in AS.

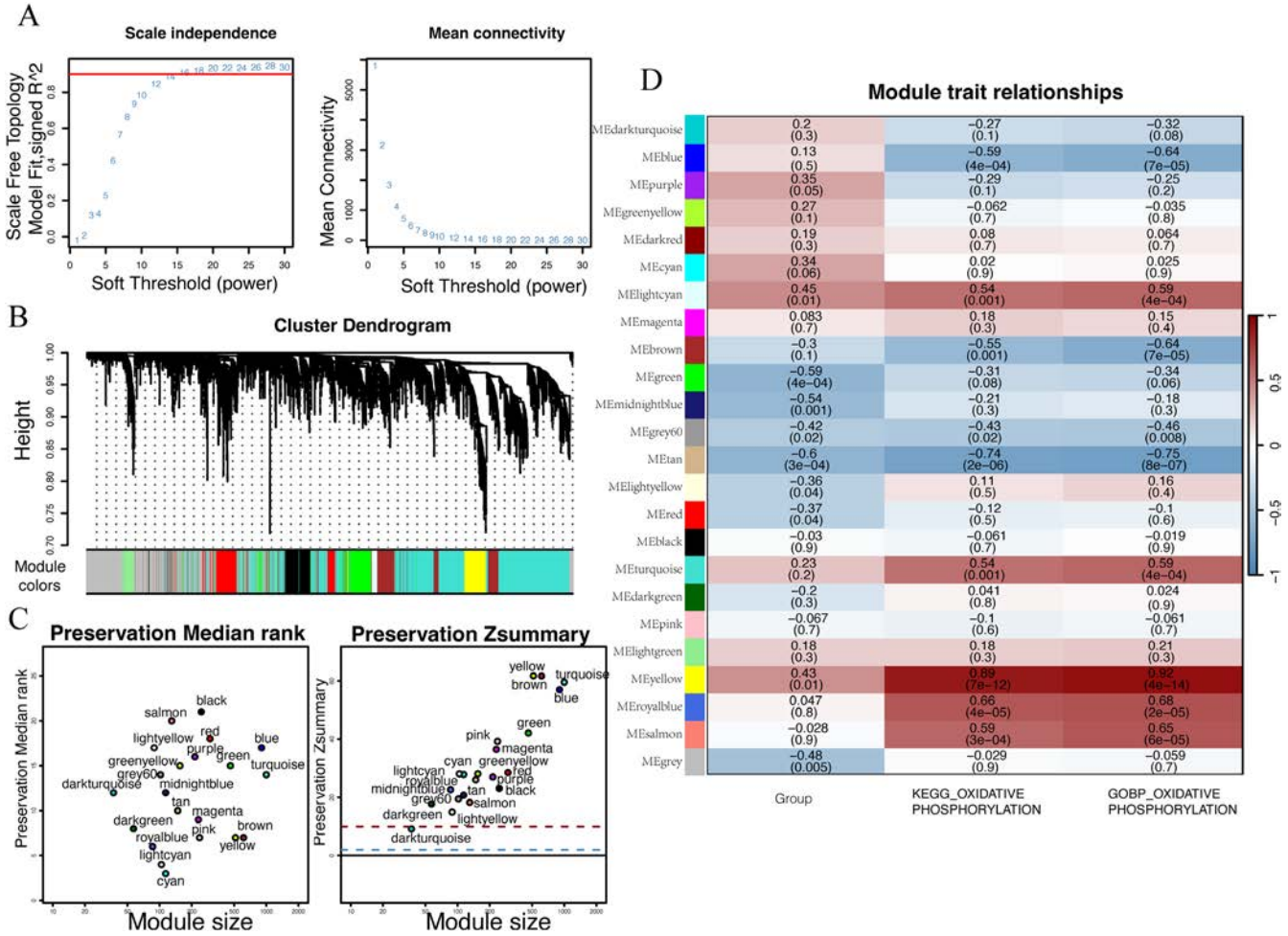

FIGURE 3 | Weighted gene co-expression network analysis (WGCNA) from GSE25101. (A) Assessment of the scale-free topology model fit index and mean connectivity for various soft-thresholding powers (β). A power value of 3 was determined to be the most suitable. (B) Creation of a dendrogram illustrating gene modules based on dissimilarity measures. Each leaf on the dendrogram represents a gene, and branches correspond to different gene modules. (C) Evaluation of module preservation using median rank and *Z* summary statistics. A median rank close to zero indicates high module preservation (left). The steel blue and dark red lines represent *Z* thresholds of 2 and 10, respectively (right). $Z > 10$ suggests strong evidence of conservation, while $2 < Z < 10$ indicates low to moderate evidence. (D) Heatmap displaying the correlation between modules and clinical features. Rows represent module eigengene (ME), and columns represent clinical features. Each cell includes a correlation number in the first row and a *p* value in the second row, with color variations indicating the degree of correlation.

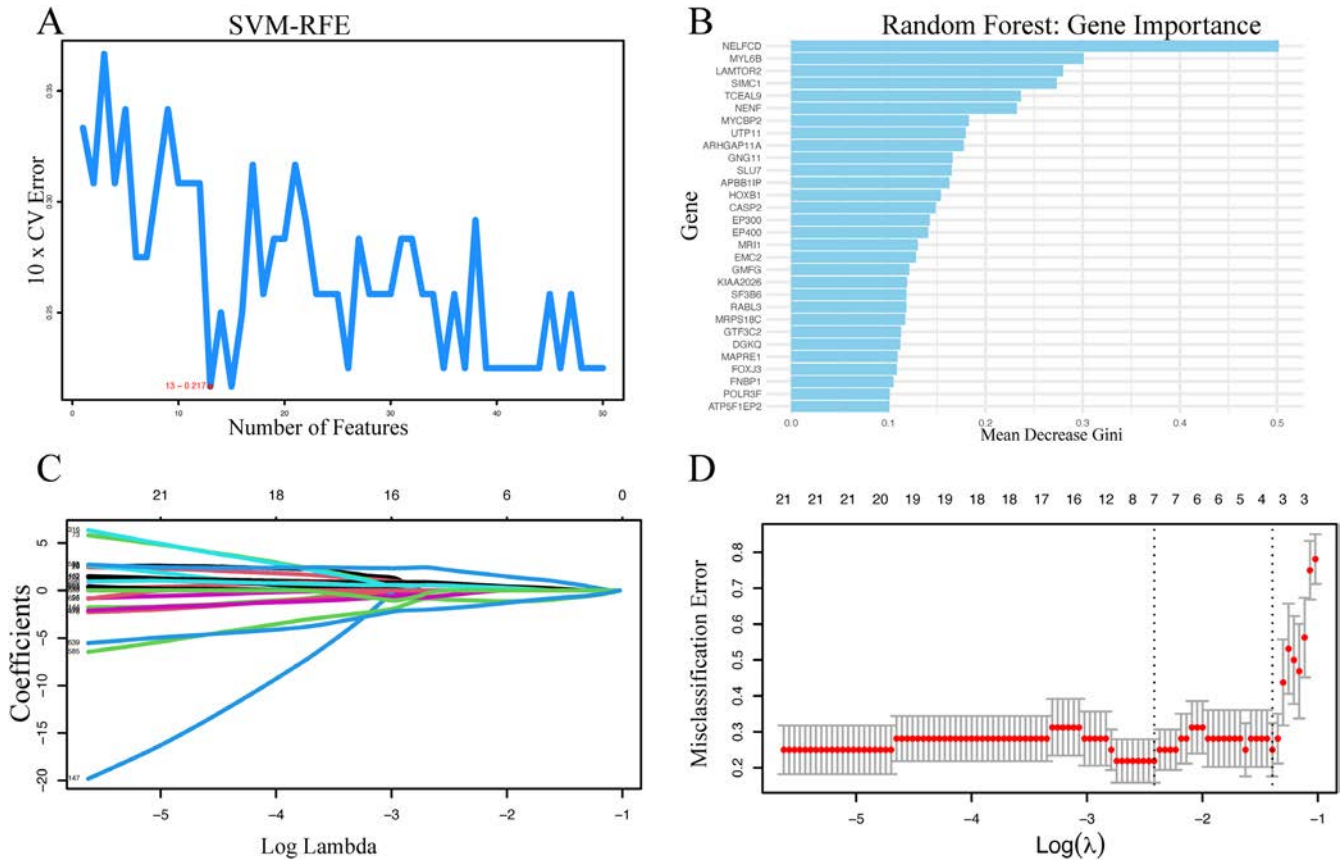

FIGURE 4 | Machine learning screening of OXPHOS-related genes. (A) SVM-RFE error plot. The x-axis represents the number of features, and the y-axis represents the corresponding error rate. Each point in the graph represents the error rate associated with a particular number of features. The curve on the graph illustrates how the error rate varies with the number of features included in the model. The points on the curve with the lowest error rates 13 represent the most efficient subset of features for the SVM model. (B) Random forest variable importance plot. The x-axis indicates the level of importance, and the y-axis indicates the variable under consideration. Each point in the graph corresponds to a specific variable, and the length of the bar or point reflects the contribution of that variable to the overall predictive accuracy of the random forest model. (C) Lasso path plot. The x-axis represents the logarithm of the tuning parameter (lambda), controlling the strength of the penalty on the coefficients. The y-axis shows the values of the coefficients for each variable in the model. Each curve in the plot corresponds to a different variable, illustrating how its coefficient changes as the regularization strength varies. (D) Cross-validated Lasso path plot. The x-axis represents the logarithm of the tuning parameter (lambda), and the y-axis displays the cross-validated error or classification error for each lambda value. SVM-RFE, support vector machine with recursive feature elimination.

These genes may play pivotal roles in the disease's pathogenesis and serve as potential targets for further investigation.

3.5 | RT-PCR and scRNA Data Validate Hub Gene Expression

Blood samples were collected from 10 AS patients (AS group) and 10 healthy controls (control group), and PBMCs were extracted. The expression levels of these three genes were quantitatively analyzed using RT-PCR. The results showed a significant increase in *LAMTOR2* expression, while no significant differences were observed in the expression of the other two genes between normal individuals and AS patients (Figure 5A). However, pathway association analysis suggested a strong correlation among the three genes (Figure 5B). Therefore, the expression of these genes was further explored in different cell subtypes.

As shown in Figure 6A, *LAMTOR2* was highly expressed in dendritic cells (DCs) and monocytes. *APBB1IP* was expressed in most cell subtypes, with the highest expression in DCs, while *DGKQ* exhibited relatively low expression levels across these cells. *LAMTOR2* showed significantly higher expression in AS patients compared to healthy controls, not only in DCs and monocytes but also in CD4+ T cells, CD8+ T cells, and NK cells (Figure 6B). Although *APBB1IP* was broadly expressed across most cell subtypes, significant differences were observed only in B cells, certain T cells, and monocytes (Figure 6C). *DGKQ* demonstrated low expression levels and no notable differences between groups (Figure 6D).

3.6 | Functional Exploration of *LAMTOR2* in AS

We further explored the function of *LAMTOR2* by dividing AS patients into two groups based on high and low expression of the *LAMTOR2* gene in the GSE25101 dataset. Differential analysis and functional enrichment analysis were performed between the two groups, and the results are shown in Figure 6E. The analysis revealed a significant correlation between *LAMTOR2* expression

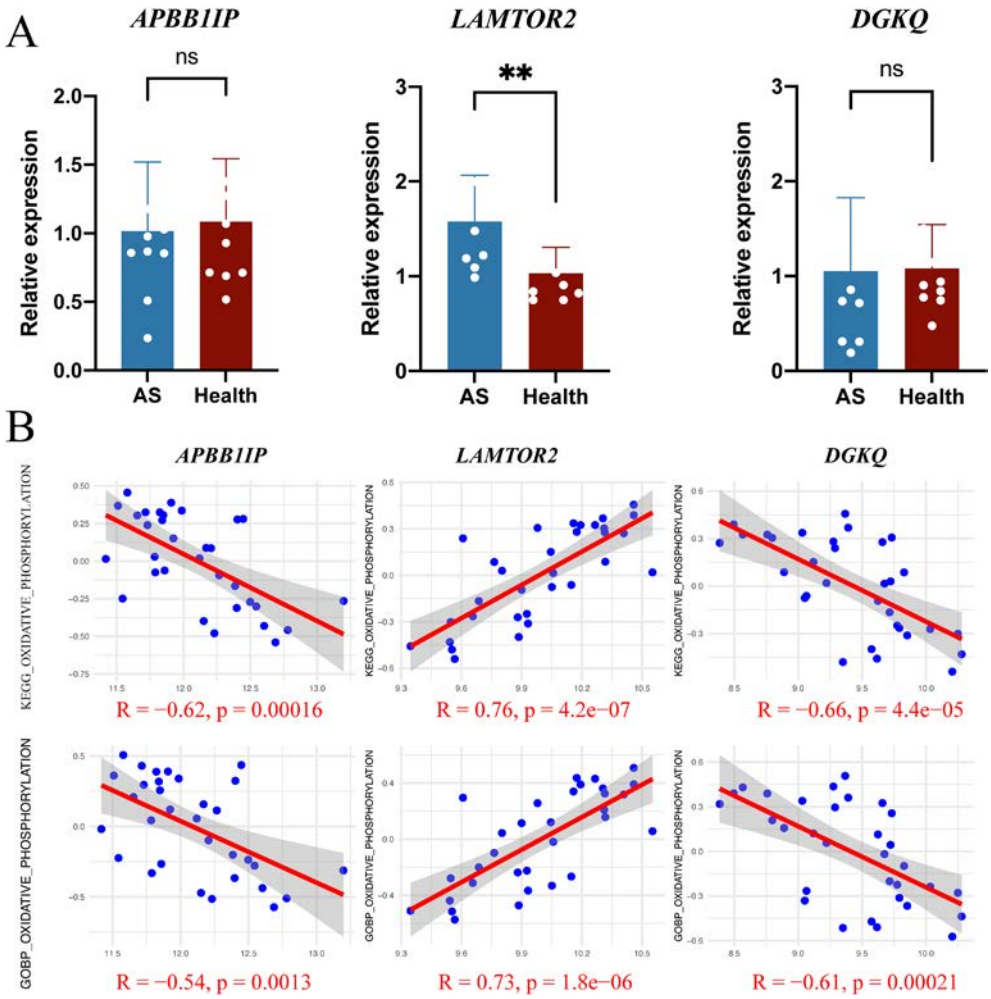

FIGURE 5 | (A) RT-PCR validation of the expression levels of three key genes (*LAMTOR2*, *APBB1IP*, and *DGKQ*) in AS and healthy control groups. The expression of the three genes in the peripheral blood of AS patients ($n = 10$, male/female = 7/3, mean age 33.1 ± 8.2 years) and healthy donors ($n = 10$, male/female = 7/3, mean age 33.4 ± 8.5 years). ns, $p > 0.05$, $^{**}p < 0.01$. (B) Correlation analysis between the expression of these three genes and OXPHOS pathway scores, highlighting their potential functional relevance.

and T cell function, particularly the differentiation of TH17 cells. High expression of *LAMTOR2* was associated with enhanced differentiation of TH17 cells, which are known to play a crucial role in the inflammatory processes of AS. The functional enrichment analysis indicated that *LAMTOR2* may be involved in the regulation of immune pathways related to T cell activation and TH17 cell differentiation, further suggesting its potential role in the pathogenesis of AS.

4 | Discussion

AS is associated with a range of autoimmune diseases, including inflammatory bowel disease (IBD), anterior uveitis, and psoriasis, exhibiting similar disruptions in the immune microenvironment [3].

Metabolic adaptation is essential for meeting the bioenergetic and biosynthetic needs linked to dendritic cell activation, migration, and the ability to initiate effective T-cell responses [38]. OXPHOS, occurring in the inner mitochondrial membrane, uses enzymes and energy released from the oxidation of various nutrients to synthesize ATP, serving as the primary mechanism by which cells generate ATP. This study explores the role of OXPHOS in the immune cells of AS using PBMCs bulk transcriptomic and scRNA-seq data. The results indicate that OXPHOS is a significant mechanism in the pathogenesis of AS, with elevated levels observed in peripheral blood DCs and monocytes. DCs, acting as guardians of the immune system, play a key role in AS [10]. The reduced circulating CD1c+ DCs in AS patients, accompanied by an increased quantity of CD14-CD16+ mononuclear cells capable of inducing CC chemokine receptor (CCR)-expressing T cells, leads to the production of interleukin (IL)-1b and IL-6, contributing to Th17 immune responses and AS-related manifestations [12]. DCs also regulate the formation and function of osteoclasts, developing functional osteoclasts during the immune interaction process with CD4+ T cells, inducing bone resorption [13].

A study on plasmacytoid dendritic cells (pDCs) demonstrated that inhibiting glutaminolysis and OXPHOS impedes plasmacytoid DCs (pDCs) activation [39]. OXPHOS is also vital in shaping the immunogenic functions of DCs. For example, type I interferons (IFNs) reprogrammed the metabolism of plasmacytoid dendritic cells (pDCs) by promoting OXPHOS through an autocrine

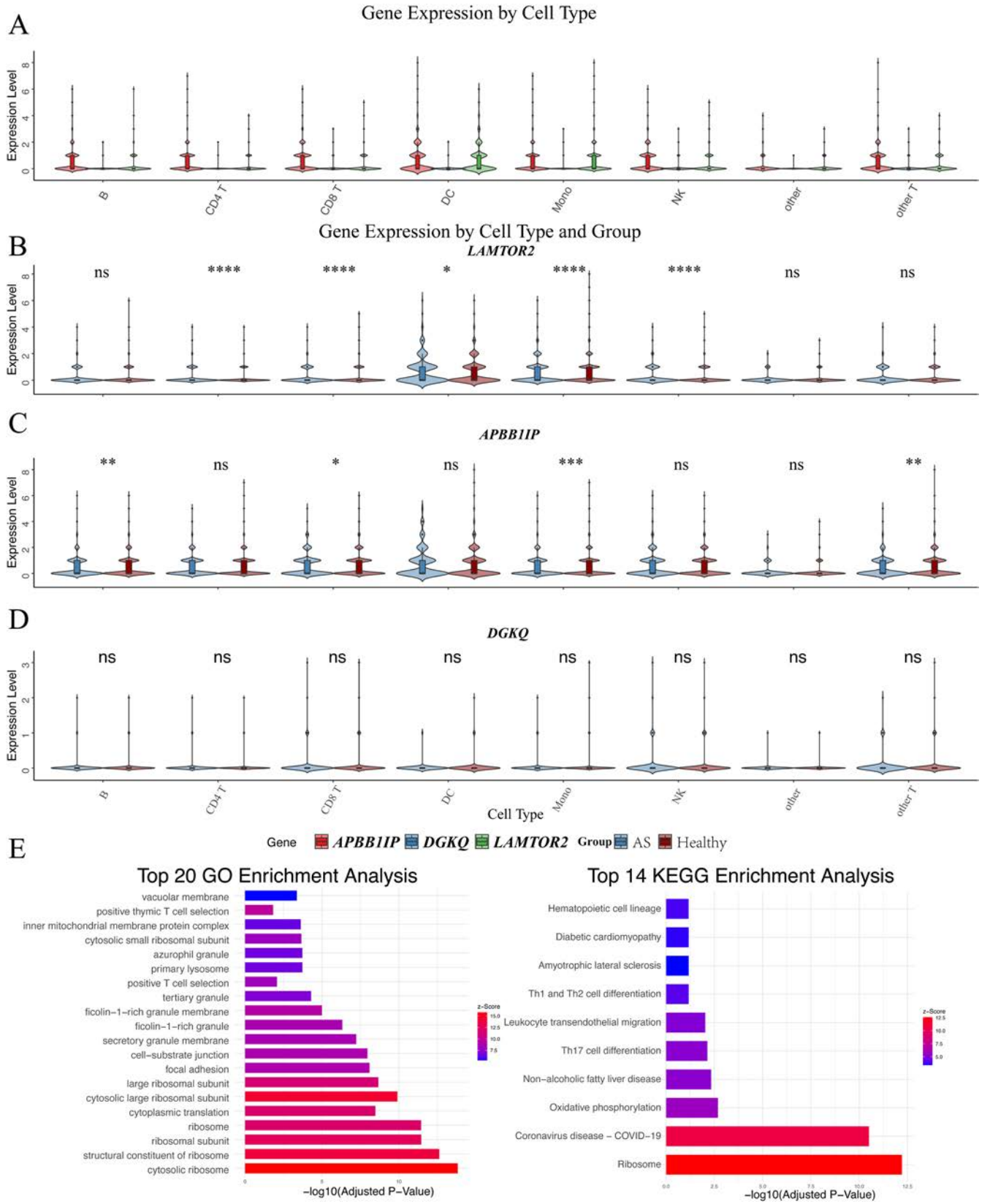

FIGURE 6 | Expression of OXPHOS-related genes in different cell subsets. Analysis of overall gene expression of three genes (*APBB1IP*, *LAMTOR2*, and *DGKQ*) across different cell subtypes (A) in scRNA-seq data and comparison between AS patients and healthy controls (B–D). ns, $p > 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$. Functional enrichment analysis of pathways based on *LAMTOR2* high and low expression groups in GSE25101 (E), including top 20 GO analysis and top 14 KEGG analysis.

mechanism, which increases intracellular ATP availability and subsequently enhances type-I IFN responses [40].

The increase in OXPHOS may lead to an increase in ROS, thereby affecting the antigen presentation of DCs [41]. Therefore, OXPHOS may lead to the activation of DCs and immune dysfunction by affecting their metabolism, which could contribute to the development of AS.

Under inflammatory conditions, circulating monocytes are recruited to the site of inflammation, where they encounter various inflammatory mediators and signals. These signals can induce monocyte activation and promote their differentiation into specific effector cells [42]. Peripheral blood monocytes entering tissues differentiate into macrophages, acting on the body's innate immune system [43]. The monocytes of AS patients exhibit a heightened pro-inflammatory phenotype, secreting increased levels of pro-inflammatory cytokines. Proteomic analysis indicates elevated activation of leukocyte extravasation, endothelial growth factors, Janus kinase/signal transduction proteins, and Toll-like receptor (TLR) pathways [44]. OXPHOS determines the differentiation of macrophages into anti-inflammatory/pro-inflammatory cells [45].

APBB1IP is a Rap1-binding protein that primarily functions as a regulatory factor in leukocyte recruitment and complement-mediated pathogen clearance [46]. It plays a crucial role in various diseases, including the clearance of cancer cells, immune responses, neural development, and the polarization of M2-type macrophages [47]. The speculated reason may be related to the secretion of cytokines by M1 macrophages derived from monocytes in AS [48], which requires further confirmation through cellular experiments.

LAMTOR2 is a gene that encodes a protein and is associated with immunodeficiency and other diseases. It belongs to the Regulator/LAMTOR complex, participating in the regulation of mTOR and ERK activation in late endosomes [49]. Research suggests that *LAMTOR2* plays a role in lipid metabolism, affecting the function of foam cells and macrophages [50]. Additionally, it influences cell quantity by regulating the homeostasis of dendritic cells (DCs) [49]. The activation of T cells depends on antigen-presenting cells (APCs), such as DCs and monocyte-macrophages, which present antigen peptides to T cell receptors (TCRs) via major histocompatibility complex (MHC) molecules and provide co-stimulatory signals to fully activate T cells. Our study showed that *LAMTOR2* was highly expressed in dendritic cells (DCs) and monocytes, and *LAMTOR2* showed significantly higher expression in AS patients compared to healthy controls in DCs and monocytes. High expression of *LAMTOR2* was associated with enhanced differentiation of TH17 cells. Therefore, *LAMTOR2* might influence the differentiation of TH17 cells by affecting the auxiliary role of DCs and monocytes in T cell activation, thereby contributing to the development of AS. However, the precise mechanisms require further investigation.

5 | Limitations of the Study

While this study provides valuable insights into the role of OXPHOS in the pathogenesis of AS, some limitations should be acknowledged. Firstly, the study relies heavily on transcriptomic and single-cell RNA sequencing (scRNA-seq) data, which may not fully capture the functional dynamics or post-transcriptional modifications of OXPHOS at the protein level. The limited sample size, particularly for scRNA-seq, may affect the generalizability of the findings, and further experiments are needed to confirm the role of oxidative phosphorylation-related genes in immune cell functions and the pathogenesis of AS. Additionally, due to the lack of clinical information in the data, we are unable to assess the correlation between gene expression and clinical disease severity. In future studies, we plan to further explore the relationship between gene expression and clinical disease activity, which will provide more comprehensive insights into the functional relevance of identified genes in the pathogenesis and progression of AS. Finally, although multiple machine learning methods were used to identify key genes, the possibility of overfitting and the need for further experimental validation should be considered when interpreting the results.

6 | Conclusion

In conclusion, the study integrates multi-omics data and employs advanced analytical approaches to elucidate the intricate relationship between OXPHOS of immune cells and AS pathogenesis. The identified genes, particularly *LAMTOR2*, may serve as potential therapeutic targets, contributing to our understanding of the disease mechanisms and paving the way for precision medicine in AS treatment.

Author Contributions

Jieruo Gu and Yuanchun Ye conceived and supervised the research; Yuanchun Ye and Yuling Chen, Yuan Xu designed the research, performed the analysis, and prepared the figures and tables. Yuling Chen wrote the manuscript. Qing Lv, Yuan Xu, and Shuangyan Cao collected the samples and performed RT-PCR. All authors contributed to interpreting the experimental data, reviewing the manuscript, and final approval.

Acknowledgments

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Ethics Statement

The blood used for RT-PCR was obtained from outpatient clinics of The Seventh Affiliated Hospital Sun Yat-sen University. All patients with AS fulfilled the modified New York criteria. All participants signed the informed consent forms according to the approved protocol by the Ethics Committees of The Seventh Affiliated Hospital Sun Yat-sen University (KY-2023-017-01).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used in the current study are publicly available data from GEO (https://www.ncbi.nlm.nih.gov/geo) databases. Further inquiries can be obtained directly 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.

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LETTER TO THE EDITOR

Patient-Reported Burden of Indolent Systemic Mastocytosis in a Managed Care Organization-Correspondence

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Dear Editors,

We read with interest the article by Robert S. Zeiger et al., titled "Patient-Reported Burden of Indolent Systemic Mastocytosis in a Managed Care Organization [1]." We appreciate the authors' contributions and would like to offer several suggestions.

First, the study employs two self-report instruments: the ISM-SAF, which uses a 2-week recall period, and the SF-12v1 questionnaire, which covers the past 4 weeks. The inconsistency in recall periods may inadvertently introduce inaccuracies if participants do not precisely recall their symptoms or experiences. Given that systemic mastocytosis is characterized by fluctuating symptoms, patients' recall can vary and is often influenced by the severity of recent episodes. This could lead to either under- or overestimation of the true impact of ISM on daily life [2]. Prior research has shown that symptom severity tends to be reported as higher with longer recall periods compared to shorter ones [3]. Future studies may benefit from aligning recall windows across tools or implementing more granular tracking methods—such as daily electronic diaries—to reduce recall bias. In addition, incorporating objective indicators, such as biomarkers or clinician-reported outcomes, could further contextualize and enhance the accuracy of patient-reported data.

Second, although the authors employed multiple outreach methods, non-responders may systematically differ from responders in ways that influence study outcomes—such as symptom burden, healthcare engagement, or treatment response. This introduces the risk of nonresponse bias, especially when these differences are not fully captured by observed variables. In longitudinal research, this bias may compound over time due to monotone patterns of missing data [4]. As a result, even well-conducted recruitment efforts may not fully mitigate concerns about sample representativeness or the generalizability of findings.

Third, while systemic mastocytosis is a rare condition—with an incidence of 0.9 per 100 000 per year and over 80% of cases classified as indolent [5]—the relatively small sample size ($n = 40$) in this study limits statistical power and reduces the likelihood of detecting significant associations [6]. Furthermore, participants were recruited solely from Kaiser Permanente Southern California, which may constrain the diversity of patient experiences captured. Given the heterogeneous symptomatology of ISM—including fatigue, dermatologic symptoms, gastrointestinal disturbances, and neuropsychiatric complaints—greater sample diversity and a larger cohort would be beneficial to better estimate population-level trends and variability.

In conclusion, the study by Zeiger et al. offers valuable insights into the burden of indolent systemic mastocytosis. However, refining the methodology—by standardizing recall periods, mitigating potential nonresponse bias, and broadening the sample size and study setting—could strengthen the validity and generalizability of future research. These improvements may provide a more comprehensive representation of the diverse experiences of ISM patients and enhance the reliability of patient-reported outcomes.

Author Contributions

Ming-Hsiang Chu and Hui-Yi Hsu contributed to the conceptualization of the correspondence, wrote the original draft, and revised the manuscript. Su-Boon Yong contributed to manuscript revision and supervision. Chin-Yuan Yii and Xiao-Ling Liu supervised the work. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Case Report: Do We Underestimate the E148Q Mutation? Uncharacterized Variant

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Dear Editor,
This report details five patients presenting with nephrotic syndrome attributed to renal amyloidosis secondary to the E148Q mutation.

Familial Mediterranean Fever (FMF) is the most common autosomal recessive autoinflammatory disease among hereditary periodic fever syndromes. It often leads to secondary AA amyloidosis (AAA) as a major long-term complication. FMF is more prevalent in Mediterranean populations like Turkish, Armenian, Jewish, and Arab individuals [1, 2].

The MEFV gene on chromosome 16 (16p13.3) causes FMF, with about 70%–80% of cases linked to V726A, M680I, E148Q, M694V, and M694I mutations [3]. In Turkey, the most frequent are M694V, E148Q, M680I, and V726A [1]. The E148Q mutation is found in about 12% of healthy individuals [4]. It typically shows low penetrance and a milder clinical phenotype. In contrast, M694V is linked to a severe course and higher amyloidosis risk. It often appears in heterozygous or compound heterozygous forms with exon 10 variants in populations with high AAA prevalence [5].

FMF's pathogenesis involves dysregulated inflammatory pathways due to abnormal pyrin production. Diagnosis often uses the Tel Hashomer criteria [1]. Secondary amyloidosis is a frequent result of chronic inflammation. Renal complications like chronic kidney disease from AAA are significant in FMF [3]. Nephrotic syndrome, with edema, proteinuria, and hypoalbuminemia, is a common sign of renal amyloidosis. Renal biopsy is considered the gold standard for the differential diagnosis of specific glomerulopathies and the quantification of renal amyloid burden [6]. If amyloid subtyping is unclear via immunodetection, genetic testing is recommended, especially when hereditary amyloidosis is suspected [7].

A 47-year-old male presented with unilateral lower extremity joint swelling. Systemic examination revealed pain, restricted joint mobility, and bilateral pretibial edema. The remaining examination findings were unremarkable. Laboratory investigations demonstrated an elevated C-reactive protein level of 30 mg/dL, an erythrocyte sedimentation rate (ESR) of 60 mm/h, a serum creatinine level of 1.68 mg/dL, and spot urine proteinuria of 10 g/day. Liver function tests and electrolyte levels were within normal limits. The patient was referred to the nephrology department due to nephrotic-range proteinuria. A renal biopsy confirmed AA-type amyloidosis. Given a familial history of Familial Mediterranean Fever (FMF), genetic testing was performed, identifying the E148Q mutation. Colchicine therapy (2 mg/day) was initiated. At baseline, urine proteinuria was 10.2 g/day, and serum creatinine was 1.68 mg/dL. However, after 3 months, serum creatinine increased to 2.34 mg/dL, and urine proteinuria rose to 15 g/day. Despite combination therapy with colchicine, azathioprine, and canakinumab, the patient's renal function continued to deteriorate, culminating in end-stage renal disease requiring hemodialysis. Subsequent clinical follow-up revealed pancytopenia, leading to the discontinuation of azathioprine. A bone marrow biopsy also confirmed AA-type amyloidosis. The patient remains on hemodialysis.

A 50-year-old male with a history of diabetes mellitus (8 years) and ischemic heart disease (11 years) presented with bilateral pretibial edema. Physical examination revealed bilateral rales and S3–S4 heart sounds. His serum creatinine

level was 1.2 mg/dL, and spot urine proteinuria was 8 g/day, with electrolyte levels and liver function within normal limits. Echocardiography and chest radiography indicated heart failure, and treatment was initiated in conjunction with cardiology. Further investigations for malignancy and diabetic retinopathy were unremarkable, and evaluations for autoinflammatory diseases and multiple myeloma yielded no significant findings. A renal biopsy confirmed AA-type amyloidosis, and genetic testing for Familial Mediterranean Fever (FMF) identified a heterozygous E148Q mutation. Colchicine therapy (2 mg/day) was commenced. Baseline urine proteinuria was 9.8 g/day, which increased to 11 g/day by the second month and 13 g/day by the third month. Despite this progression in proteinuria, renal function remained stable. The patient was referred to the rheumatology department for further management, including consideration of azathioprine and canakinumab.

A 32-year-old female, 28 weeks pregnant at the time, was referred to the nephrology department following the detection of proteinuria (1.2 g/day). She had no prior history of chronic diseases and exhibited no clinical signs of preeclampsia. Immunological investigations were unremarkable, and the pregnancy progressed without complications. Postpartum, on the 50th day, urine proteinuria increased to 2.5 g/day. Given a familial history of Familial Mediterranean Fever (FMF), a renal biopsy was performed, confirming AA-type amyloidosis. The patient was identified with the E148Q heterozygous mutation. Treatment was initiated with colchicine (2 mg/day), azathioprine (25 mg/day), and ramipril (5 mg/day). By the fourth month of treatment, urine proteinuria had decreased to 1.5 g/day, and serum creatinine remained stable. The patient continues to be monitored with ongoing treatment.

A 48-year-old male with a 15-year history of hypertension presented with a month-long episode of abdominal pain and recurrent fever. He reported a family history of FMF. The abdominal discomfort persisted for 72 h, accompanied by febrile episodes. He was referred to the nephrology department due to proteinuria (6 g/day). Renal biopsy revealed AA-type amyloidosis, and the E148Q heterozygous mutation was identified. Treatment with colchicine (0.5 mg three times daily) was initiated. After 3 months, serum creatinine decreased from 1.12 mg/dL to 0.8 mg/dL, and proteinuria was reduced to 200 mg/day. The patient continues to be monitored with this treatment regimen.

A 23-year-old female with an 11-year history of FMF presented to the rheumatology clinic with unilateral lower extremity joint swelling. Systemic examination revealed bilateral pretibial edema, but no other pathological findings. She was referred to the nephrology department for evaluation of proteinuria, which was found to be 5.3 g/day. Her creatinine level was 0.46 mg/dL. One year prior, her proteinuria had been 454 mg/day, with a creatinine level of 0.48 mg/dL. Renal biopsy confirmed AA-type amyloidosis and genetic testing identified the E148Q heterozygous mutation. The patient was started on colchicine and subsequently transitioned to canakinumab. After 3 months of treatment, urine proteinuria decreased to 3.4 g/day, and serum creatinine remained stable at 0.4 mg/dL. The patient is currently under monitoring and is receiving ongoing treatment.

Detailed laboratory and treatment data for our cases are presented in Table 1.

The current study presents a rare case series of patients presenting with nephrotic syndrome, an atypical manifestation of FMF, and subsequently diagnosed with amyloidosis via renal biopsy. Genetic analysis revealed the heterozygous E148Q mutation. A literature review indicates a lack of studies addressing amyloidosis cases associated with the heterozygous E148Q mutation in the adult age group. Available evidence suggests that in the pediatric age group, the E148Q variant is associated with amyloidosis in a homozygous state [6]. This case series underscores the necessity for further research to elucidate the less understood aspects of FMF mutations.

FMF is an autoinflammatory disorder necessitating comprehensive, multidisciplinary follow-up and treatment. Proteinuria is a significant clinical finding and a key indicator of renal amyloidosis. The presence of amyloid deposits increases the risk of adverse renal outcomes [6]. Early recognition and management of amyloidosis are crucial for preserving renal function. Untreated AA amyloidosis can progress to chronic kidney disease. In FMF-associated amyloidosis, colchicine remains the mainstay of treatment [7].

Genetic evaluation is pivotal in the diagnosis of FMF. The M694V and E148Q mutations are the most frequently observed. While amyloidosis is more commonly associated with the M694V mutation, Arici et al. demonstrated that the E148Q mutation is also capable of promoting the development of renal amyloidosis [6]. Consistent with the study, arthritis was infrequent in our patient cohort, whereas the presence of amyloidosis at diagnosis in their homozygous E148Q mutation group correlated with a severe clinical course in our patients with heterozygous variants.

Ardalan et al. similarly reported a patient with FMF and the E148Q mutation who presented with massive proteinuria, elevated serum creatinine, and acute glomerulonephritis [7]. In contrast, Aydın et al. observed that patients homozygous for the E148Q mutation presented with a later onset of clinical symptoms and a milder disease course, although their clinical findings were similar to those with other variants [8].

Our findings corroborate that the E148Q mutation is associated with atypical presentations of FMF, as previously documented by Tatar et al. They identified a case of post-transplantation nephrotic syndrome occurring in a renal transplant recipient without a prior childhood diagnosis of FMF, which was associated with amyloidosis. Clinical correlation with genetic evaluation revealed a heterozygous E148Q mutation in this patient [9]. Contrary to the typical mild renal impairment seen in type AA amyloidosis, we observed instances of rapidly progressive renal disease. Etta et al. reported a similar case of nephrotic syndrome culminating in dialysis due to type AA amyloidosis [10]. The case presentation highlights a 62-year-old female patient initially investigated for nephrotic syndrome, without a prior history of either rheumatoid arthritis or FMF, who was subsequently diagnosed with AA amyloidosis. Similarly, the severe nephrotic syndrome observed in our follow-up cases also occurred in patients lacking a known FMF history, and the age of clinical presentation was comparable to the case above.

TABLE 1 | Demographic and clinical features of our five case.

Patient			Period of FMF (year)	Symptoms of FMF			MEFV mutation heterozygosis	Renal Bx	Treatment			Pretreatment		Posttreatment	
Sex	Age	Comorbidity		Pain	Arthritis	Serositis			C	A	Cn	Cre mg/dL	Pro g/day	Cre mg/dL	Pro g/day
M	47	–	–	+	+	–	E148Q	AA amyloidosis	+	+	+	1.68	10.2	2.34	15
M	50	DM, CVD	–	–	–	–	E148Q	AA amyloidosis	+	+	+	0.6	9.8	0.8	13
F	32	–	–	+	–	–	E148Q	AA amyloidosis	+	+	–	0.7	2.5	0.6	1.5
M	48	HT	–	+	–	–	E148Q	AA amyloidosis	+	–	–	1.12	6	0.8	0.2
F	23	–	11	–	+	–	E148Q	AA amyloidosis	+	–	+	0.46	5.3	0.4	3.4

Abbreviations: A, azotiopurin; Age, age at diagnosis; C, colchium dispert; Cn, canacinumab; Cre, creatinine; CVD, cardiovascular disease; DM, diabetes mellitus; HT, hypertension; Pro, proteinuria.

Notably, our cohort with heterozygous E148Q variants exhibited a later disease onset and a more severe disease trajectory than previously reported. In a follow-up study of 30 patients with AA amyloidosis homozygous for the E148Q variant, Topaloğlu R. et al. reported a median age of disease onset of 60 years and a median age at diagnosis of 94 years. Furthermore, they noted that one patient experienced a severe disease course, and seven patients demonstrated colchicine resistance. Based on these observations, they posited that the E148Q homozygous variant may predispose individuals to a moderate or severe disease phenotype [11]. In our follow-up patients, the late-onset nephrotic syndrome in those with the heterozygous E148Q variant was observed to be unresponsive to colchicine therapy.

Amyloidosis in FMF patients typically exhibits a favorable response to colchicine. The study by Elham Orouk Awaad et al. observed that the group with moderate disease severity had a mean disease onset age of 9 years and required increased colchicine dosages. Notably, the heterozygous E148Q group within the genetic variants presented with a moderate disease phenotype [12]. However, as demonstrated in our case series, the E148Q mutation should no longer be categorized as a variant of uncertain clinical significance. Our findings, coupled with existing literature, suggest that this mutation may be associated with colchicine-resistant amyloidosis. A study by H Van Gorp et al. observed low response rates to ex vivo colchicine testing in patients with the E148Q variant, similar to the group synthesizing wild-type pyrin. Consequently, they suggested that the identified variant might be classified as pyrin-associated periodic fever, distinct from FMF [13].

Studies conducted in pediatric populations have indicated that individuals with homozygous or heterozygous E148Q mutations tend to manifest an FMF phenotype and generally experience a mild disease course, contrasting with those harboring other MEFV gene variants such as M694V, M680I, or V726A. Tanatar et al.'s study associated the E148Q mutation in the pediatric group with a mild clinical and laboratory follow-up [14]. Conversely, our current case series involving adult patients revealed that those with the heterozygous E148Q variant did not present with the characteristic clinical features of FMF, but rather exhibited a severe disease trajectory. We observed that patients with late-onset disease exhibited increased resistance to colchicine treatment.

In a comparative study of disease severity in pediatric patients diagnosed with FMF, Tirosh et al. stratified patients into groups based on the presence of the heterozygous E148Q variant, the heterozygous M694V variant, and the homozygous M694V variant. The researchers noted that patients with the heterozygous E148Q variant commonly presented with clinical symptoms of abdominal pain and fever. Their findings further indicated that this specific variant has a low predisposition for the development of AA amyloidosis and is generally not associated with significant clinical sequelae [15]. In our case series, the presence of the identified mutation in the adult population was observed to result in severe clinical presentations. Further research in the adult age group is warranted to investigate this association.

In conclusion, the E148Q mutation in FMF has historically been classified as a variant of uncertain clinical significance.

However, contemporary research has demonstrated its potential to induce AA-type amyloidosis, thereby contributing to substantial renal damage, akin to the well-established M694V mutation. This underscores the necessity of considering the E148Q heterozygous mutation in the clinical evaluation and management of FMF, particularly in patients presenting with amyloidosis-related renal involvement.

Author Contributions

Beyza Doğan: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review and editing. **Fatih Ergül:** conceptualization, data curation, writing – review and editing. **Süleyman Karaköse:** conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review and editing. **İbrahim Güney:** conceptualization, data curation, writing – review and editing. **Edip Erkuş:** conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review and editing. **Serpil Ergülü Eşmen:** conceptualization, data curation, writing – review and editing.

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

Prevalence and Predictive Factors of Difficult-To-Manage Axial Spondyloarthritis: Results From the KOBIO Registry

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Dear Editor,

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the spine and sacroiliac joints, often leading to disability [1]. Despite therapeutic advances, some patients experience persistent disease activity and multiple treatment failures.

In 2024, the Assessment of SpondyloArthritis International Society (ASAS) introduced the concept of difficult-to-manage axSpA (D2M axSpA). This definition, established through a structured consensus, aims to identify patients with suboptimal disease control. However, real-world data on D2M axSpA remain limited. Previous studies have explored the occurrence of D2M axSpA, which is primarily defined by multiple treatment switches and associated factors [2–4]. However, other criteria, such as disease activity, have not been integrated into the definition of D2M axSpA. The profiles of D2M axSpA patients are complex and not yet fully understood [5]. Identifying these patients early may help prevent disease progression and multidrug failure [6]. This study aimed to investigate the prevalence and characteristics of D2M axSpA using data from a nationwide prospective cohort.

We obtained data from the Korean College of Rheumatology Biologics (KOBIO) Registry, an ongoing, nationwide, multicenter, prospective cohort established in December 2012. The dataset included patients enrolled between December 2012 and February 2024. The registry monitors real-world data on disease activity, treatment patterns, efficacy, and safety in adult patients with RA, axSpA, and PsA initiating, restarting, or switching b/tsDMARDs [7]. Patients undergo follow-up assessments at 12-month intervals. The study followed the Declaration of Helsinki, with ethical approval from each participating center and the researchers' affiliated hospital (SCH 2013-03-003). Written informed consent was obtained from all patients. Patients aged >19 years with axSpA starting with the first b/tsDMARD and with at least one follow-up were included in the study. AxSpA was classified into non-radiographic (nr-axSpA) or radiographic (r-axSpA) per ASAS and modified New York criteria [8]. Those with prior biologic use were excluded due to the inability to determine previous treatment duration or reasons for switching. Baseline demographic and clinical data, including disease duration, extra-musculoskeletal manifestations (EMMs), comorbidities, and ASDAS-CRP, were collected. Disease activity indices, peripheral manifestations, EMMs, and treatment status were monitored annually.

According to ASAS definition, D2M axSpA is characterized by the presence of all three of the following criteria: (1) Treatment failure: Inadequate response to at least two b/tsDMARDs with different mechanisms of action, (2) Insufficient control of signs/symptoms of axSpA: presence of at least one of the following: (a) high or very high disease activity (ASDAS ≥ 2.1), (b) signs or symptoms suggestive of active disease (musculoskeletal or extra-musculoskeletal manifestations, elevated CRP, or active inflammation on MRI), (3) The present signs/symptoms are perceived as problematic by either the treating rheumatologist or the patient.

The second criterion of the ASAS definition included rapid radiographic spinal progression and persistent axSpA-related symptoms affecting quality of life despite well-controlled disease based on objective measures. However, due to the limitations of

the KOBIO data, this criterion could not be fully analyzed, and only the first two components were included in the analysis.

Clinical characteristics were compared between D2M and non-D2M axSpA groups using chi-square (or Fisher's exact) tests for categorical variables and Student's *t*-test (or Mann–Whitney *U* test) for continuous variables. Logistic regression identified factors associated with D2M axSpA, with variables ($p < 0.10$) from univariable analysis included in the multivariable model. Odds ratios (ORs) with 95% confidence intervals were reported, with statistical significance set at $p < 0.05$. Analyses were performed using R version 4.3.

Of 2,541 KOBIO registry patients, 1,784 were b/tsDMARD-naïve with follow-up data (Figure S1). Among them, 31 (1.7%) had D2M axSpA, while 1,753 (98.3%) had non-D2M axSpA. Most patients (90.6%) had radiographic axSpA. Table S1 compares the demographic and clinical characteristics of D2M axSpA and non-D2M axSpA patients at the time of enrollment.

Mean age was similar between groups (38.6 vs. 38.9 years, $p = 0.884$), and female patients were more common in D2M axSpA (32.2% vs. 24.5%, $p = 0.436$). D2M axSpA patients had fewer years of education (14.8 vs. 20.8, $p < 0.001$), higher baseline BASDAI (7 vs. 6.2, $p = 0.042$), and lower HLA-B27 positivity (74.1% vs. 89.3%, $p = 0.016$). Comorbidities, extramusculoskeletal and peripheral manifestations, ASDAS-CRP, baseline syndesmophytes, and combined medication usage were comparable between the two groups.

During follow-up, 77.7% remained on first-line b/tsDMARDs, while 16.7% switched to second-line therapy. Few progressed beyond third-line treatment (5.5%) (Figure 1A). All D2M axSpA patients initially received TNF inhibitors, with 61.2% switching to IL-17 inhibitors (Figure 1B). While many patients remained on TNF inhibitors across various lines, a few progressed beyond 4th-line therapy.

Median follow-up was longer in D2M axSpA than that in the non-D2M group (6.2 vs. 4.5 years, $p = 0.014$) (Table S2). During follow-up, psoriasis was more frequent in D2M axSpA (24.3% vs. 3.6%, $p < 0.001$), and they were more likely to receive csDMARDs (32.5% vs. 10.3%, $p = 0.038$). Among D2M patients ($n = 31$), psoriasis was present at baseline in 6.4% of HLA-B27–negative patients and 3.2% of HLA-B27–positive patients, and developed during follow-up in 9.6% and 16.1%, respectively. In contrast, among non-D2M patients ($n = 1753$), psoriasis was present at baseline in 0.5% (HLA-B27 negative) and 1.3% (HLA-B27 positive), and developed during follow-up in 0.6% and 2.8%, respectively. At the last follow-up, D2M axSpA patients had higher BASDAI and ASDAS-CRP. Switching to or discontinuing the first b/tsDMARDs within the first year was more common in the D2M axSpA group than in the non-D2M axSpA group (53.1% vs. 19.1%, $p < 0.001$).

Univariate analysis linked D2M axSpA with psoriasis at baseline and during follow-up, baseline BASDAI, and negative HLA-B27 status (Table 1). Multivariate analysis confirmed negative HLA-B27 (OR 3.92, 95% CI 1.57–9.81) and psoriasis during follow-up (OR 12.09, 95% CI 3.80–38.49) as independent factors. In an additional univariate analysis combining HLA-B27 status and psoriasis, the risk of D2M axSpA was highest in patients with both psoriasis developed during follow-up and HLA-B27 negativity (OR 21.42, 95% CI 5.48–83.72, $p < 0.001$), compared to those with either factor alone. A similar trend was observed for psoriasis present at baseline combined with HLA-B27 negativity (OR 13.42, 95% CI 2.77–65.03, $p = 0.001$). Adverse events did not differ significantly between groups.

In this study, 1.7% of axSpA patients met the ASAS definition of D2M axSpA. Psoriasis during follow-up and HLA-B27 negativity were independently associated with D2M axSpA. The lower prevalence compared to previous reports (8%–28.3%) may be due to differences in definitions, patient characteristics, and treatment access [2–4]. Prior studies primarily defined D2M axSpA by multiple b/tsDMARD failures, whereas our study also considered disease activity. Interestingly, patients who were HLA-B27 negative and had psoriasis at baseline exhibited a markedly higher risk of developing D2M axSpA, potentially reflecting a more treatment-refractory disease phenotype. This observation

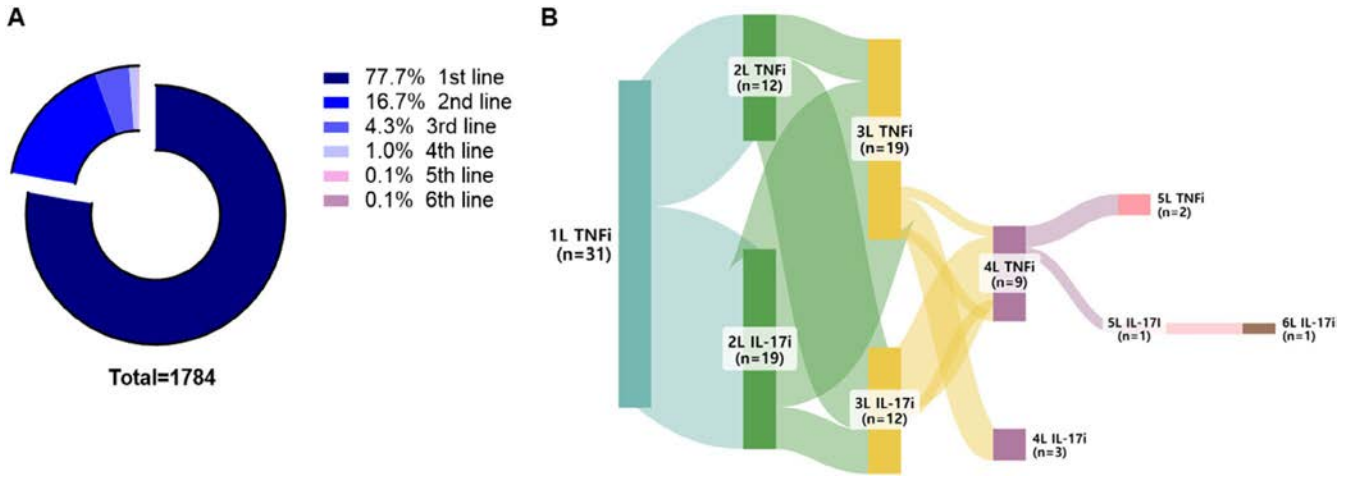

FIGURE 1 | Patient Distribution by b/tsDMARD prescription and treatment trajectory for difficult-to-manage (D2M) Patients. (A) Patient distribution based on the total number of prescribed b/tsDMARDs in axSpA patients, (B) Treatment pathway for D2M patients from first to sixth line. *L* line, *TNFi* TNF alpha inhibitors, *IL-17i* IL 17 inhibitors.

TABLE 1 | Univariable and multivariable analysis of factors associated with D2M axSpA.

	Univariable regression		Multivariable regression	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age	1.00 (0.95–1.06)	0.991		
Female sex	1.90 (0.78–4.64)	0.158		
Years of Education	0.98 (0.94–1.02)	0.370		
Current smoker	1.71 (0.68–4.25)	0.252		
BMI	1.04 (0.93–1.16)	0.504		
Disease duration, year	1.03 (0.97–1.10)	0.322		
Follow-up duration, year	1.13 (0.97–1.31)	0.104		
Comorbidities				
Hypertension	2.09 (0.80–5.47)	0.133		
Diabetes	1.99 (0.76–5.19)	0.162		
Manifestations, disease activity, and medication at baseline				
Peripheral arthritis	1.54 (0.63–3.76)	0.341		
Enthesitis	2.89 (0.82–10.25)	0.100		
Uveitis	0.48 (0.06–3.62)	0.475		
Psoriasis	5.65 (1.22–26.08)	0.027	0.22 (0.03–1.63)	0.139
SJC out of 44	0.93 (0.66–1.31)	0.664		
TJC out of 44	1.02 (0.91–1.14)	0.725		
BASDAI	1.30 (1.01–1.67)	0.045	1.22 (0.95–1.56)	0.115
Baseline CRP	1.01 (0.88–1.16)	0.872		
Baseline ASDAS-CRP	1.29 (0.84–1.98)	0.251		
Baseline syndesmophyte	0.83 (0.32–2.17)	0.709		
Negative HLA B27 status	4.55 (1.79–11.55)	0.001	3.92 (1.57–9.81)	0.004
First bDMARDs				
Adalimumab	Reference			
Infliximab	1.01 (0.32–3.25)	0.982		
Etanercept	0.67 (0.24–1.88)	0.449		
Golimumab	0.15 (0.02–1.22)	0.077	0.30 (0.06–1.50)	0.143
Manifestations occurring during follow-up				
Peripheral arthritis	2.28 (0.95–5.48)	0.065	1.28 (0.53–3.08)	0.582
Enthesitis	0.79 (0.10–5.98)	0.819		
Uveitis	1.50 (0.50–4.53)	0.470		
Psoriasis	7.83 (2.73–22.49)	< 0.001	12.09 (3.80–38.49)	< 0.001
Combination of NSAIDs	2.21 (0.89–5.53)	0.089	0.98 (0.41–2.33)	0.960
Combination of csDMARDs	2.55 (0.92–7.10)	0.073	1.48 (0.54–4.10)	0.447

Abbreviations: *ASDAS-CRP*, Activity Score with CRP; *axSpA*, axial spondyloarthritis; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Index; *bDMARDs*, biological disease-modifying anti-rheumatic drugs; *CRP*, C-reactive protein; *csDMARDs*, conventional synthetic disease-modifying anti-rheumatic drugs; *D2M*, difficult-to-manage.

raises an important clinical question regarding whether the use of non-TNF biologics, such as IL-17 inhibitors or JAK inhibitors, as a first-line therapy might help mitigate the risk of developing D2M axSpA in this high-risk subgroup. Further prospective studies are needed to determine the most appropriate initial therapeutic strategy for these patients.

Our cohort was younger, had a shorter disease duration, lower BMI, and fewer cases of nr-axSpA and depression than previous studies. These factors may have contributed to the lower prevalence of D2M axSpA. Observational data suggest that younger age, shorter disease duration, and male sex are associated with higher response rates to TNF inhibitors, whereas obesity is linked to lower response rates to axSpA [9]. Whether the same predictors apply to drugs that target IL-17 or JAK remains unclear. However, given that a significant proportion of our cohort responded well to TNF inhibitors, which were the only bDMARDs available as first-line treatment during most of the study period, it is plausible that this contributed to the low prevalence of D2M axSpA observed in our study. In the context of South Korea, TNF inhibitors were available as first-line bDMARDs, with IL-17 inhibitors limited to second-line options. Since December 2023, IL-17 inhibitors are also available as first-line options, and JAK inhibitors as second-line options. Therefore, in real-world practice, prescriptions are made according to health insurance guidelines. In this study, most first-line treatments were TNF inhibitors. This highlights the need for further studies to investigate the prevalence and related factors of D2M SpA once JAK inhibitors, a newly available class, become an option for first-line treatment to avoid selection bias.

Psoriasis is linked to greater disease burden, peripheral involvement, and csDMARD use, influencing treatment choices and increasing the likelihood of multiple b/tsDMARD failures [4]. HLA-B27 negativity is associated with lower response rates to TNF inhibitors and a higher frequency of peripheral arthritis and EMMs, potentially contributing to treatment resistance [10]. In this context, it is noteworthy that all patients included in this study were diagnosed with radiographic or non-radiographic axSpA by rheumatologists, based on clinical judgment and relevant imaging and laboratory findings. However, in a subset of patients who were HLA-B27 negative and had psoriasis at baseline, the possibility of axial PsA cannot be entirely excluded due to overlapping clinical features. The KOBIO registry does not contain detailed dermatologic assessments and radiographic evaluations of peripheral joints for formal classification using the CASPAR criteria, limiting our ability to distinguish axial PsA from axSpA in such cases.

This study has limitations, including its retrospective design, small sample size of D2M axSpA cases, and the lack of systematic fibromyalgia evaluation. Additionally, treatment guidelines in South Korea during the study period restricted IL-17 inhibitors to second-line therapy, which may have influenced outcomes. Due to limitations in the KOBIO registry, we were unable to investigate rapid radiographic spinal progression and persistent axSpA-related symptoms affecting quality of life—components included in the second criterion of the ASAS definition. Therefore, the full ASAS definition of D2M axSpA could not be completely applied, which may limit the generalizability of our findings. Given the exploratory nature of this study, we included a broad range of clinical variables potentially associated with D2M axSpA, as its contributing factors are likely multifactorial. However, we acknowledge that the limited sample size may have reduced the statistical power of our analyses and restricted the depth of interpretation. Nevertheless, this is the first study to investigate the prevalence and associated factors of D2M axSpA in a real-world setting using the ASAS criteria. Further large-scale prospective studies are needed to refine the understanding of D2M axSpA and its management.

In conclusion, applying the ASAS definition, D2M axSpA represented a very low proportion of patients. Psoriasis during follow-up and HLA-B27 negativity were key factors associated with D2M axSpA.

Author Contributions

Kyung-Ann Lee: conceptualization, methodology, and writing – original draft preparation. **Heeyeon Lee:** analysis, data curation, software. **Hyun-Sook Kim:** supervision, writing – reviewing and editing.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

International Journal of Rheumatic Diseases

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LETTER TO THE EDITOR

Letter to Editor: Efficacy of Telitacicept in the Treatment of Sjögren's Syndrome-Associated Interstitial Lung Disease: A Case Report

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Dear Editor,

Sjögren's syndrome is an autoimmune disease that is commonly characterized by dryness of the eyes and mouth. However, it can also affect multiple organs and tissues in some patients, including the skin, joints, lung, and the hematological system, among others [1–3]. Our case report presents the medical history of a 70-year-old female patient who presented with recurrent skin rashes a year ago, followed by symptoms such as hair loss and fatigue. The patient initially sought treatment at a local clinic, where the administration of prednisone therapy failed to yield significant improvement in the skin rashes. Subsequently, she sought care at a dermatology hospital, where she received a diagnosis of "sunburn." Topical medication was applied along with an increased dosage of prednisone, resulting in partial relief; however, the rashes persisted and recurred. the patient developed symptoms such as respiratory difficulties, which rapidly worsened and significantly affected her daily life. After considering the patient's symptoms and examination results, the final diagnosis was determined to be Sjögren's syndrome accompanied by pulmonary fibrosis and osteoporosis, along with a tendency towards systemic lupus erythematosus (SLE) that does not meet the diagnostic criteria for SLE. The primary treatment approach focused on anti-inflammatory and immunomodulatory therapies specifically tailored for managing Sjögren's syndrome, and considering that the patient's symptom progressed despite long-term prednisone treatment, we introduced a biologic agent called Telitacicept which inhibits the abnormal proliferation and differentiation of B lymphocytes. The following report provides a comprehensive account of the patient's medical history, diagnosis, and treatment plan.

A 70-year-old Asian female presented to our hospital with a history of skin rashes, hair loss, and fatigue for over a year, accompanied by abdominal distension, fatigue, and shortness of breath upon exertion for the past 3 months. In 2022, the patient did not have any respiratory symptoms such as difficulty breathing or coughing but experienced recurrent red rashes on the face, anterior chest, abdomen, and thighs, followed by symptoms such as hair loss and fatigue. The patient initially received topical treatment at a local clinic, which showed limited effectiveness. Subsequently, prednisone at a dosage of 10 mg/day was initiated, but her rash continued to recur. Consequently, the prednisone dosage was gradually increased to 25 mg/day. In June 2023, she experienced abdominal distension, fatigue, and shortness of breath without identifiable triggers. These symptoms rapidly deteriorated over approximately 2 months, substantially impairing her daily functioning. The local hospital added cyclophosphamide treatment, but the patient experienced severe systemic pain and hematuria. Hemorrhagic cystitis was considered, and her symptoms did not improve, leading her to seek care at our hospital.

Upon admission, her vital signs were as follows: respiratory rate of 20 breaths per minute, heart rate of 83 beats per minute, blood pressure of 138/69 mmHg, and body temperature of 36.6°C. After an inquiry with the patient, it was revealed that she has not had any exposure to allergens. Her medical history indicates a state of overall good health, without any pre-existing illnesses or specific prior to the onset of these symptoms. She tested positive for SSA antibodies, exhibited positive corneal staining in both eyes, and had a positive Schirmer's test for tear secretion. Based on the 2016 ACR/EULAR criteria, she was diagnosed with Sjögren's syndrome. HRCT scan showed extensive pulmonary fibrosis and confirmed its pattern as non-specific interstitial pneumonia (NSIP). The radiological findings at the

time of diagnosis are outlined in Figure 1. Auscultation revealed fine crackles in both lung fields and normal heart sounds. Hematological and laboratory investigations showed elevated levels of C-reactive protein (CRP, 6.83 mg/L) and erythrocyte sedimentation rate (ES, 95 Mm/h). Pulmonary function testing demonstrated decreased diffusion capacity of carbon monoxide/alveolar volume DLCO, 47 without restrictive or characteristic obstructive ventilatory impairment (forced vital capacity [FVC] 88.4% and forced expiratory volume in 1 s [FEV1] 82.7%). To ensure the absence of an infectious component, the patient underwent a comprehensive diagnostic workup. This included a thorough examination of vital signs, clinical symptoms, and laboratory tests such as cultures and serological assays, all of which returned negative results. According to global guidelines, the patient was diagnosed with Sjögren's syndrome-associated interstitial lung disease. A detailed description of the patient's clinical course is provided in Figure 2.

Considering the patient's severe interstitial lung disease, as well as the severe side effects she experienced from previous cyclophosphamide use, we recommended the patient to use a CD20 monoclonal antibody. However, the patient refused due to financial reasons. Therefore, we opted for the treatment of the patient's Sjögren's Syndrome-Associated Interstitial Lung Disease with telitacicept. the patient was started on telitacicept (160 mg/week for 12 weeks) in September 2023. The patient's dyspnea symptoms rapidly improved, and she was discharged on September 17, 2023. After 8 weeks of telitacicept treatment, the patient showed improvement in the mMRC grade (from 3 to 1), ground-glass opacities on high-resolution computed tomography (Figure 1), (FVC increased to 98.8%, DLCO increased to 56.5%), and the European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) (21 to 10). The dose of prednisolone was gradually reduced to 5 mg/day. At the time of publication, the patient showed no signs of ILD worsening and demonstrated significant improvement in the 6-min walk distance (168 m to 393 m). In addition, symptoms such as rash, hair loss, fatigue, and dyspnea have also improved significantly compared with before treatment.

This is the first report of the use of telitacicept for the treatment of Sjögren's syndrome with Pulmonary Interstitial Fibrosis. Additionally, the patient exhibited symptoms of rash, hair loss, and fatigue. According to clinical empirical research on adult primary Sjogren's syndrome, telitacicept has good clinical efficacy, tolerance, and safety in the treatment of primary Sjögren's syndrome [4–6]. Therefore, we prescribed a new drug, telitacicept, to control the progression of the disease. Eventually, the

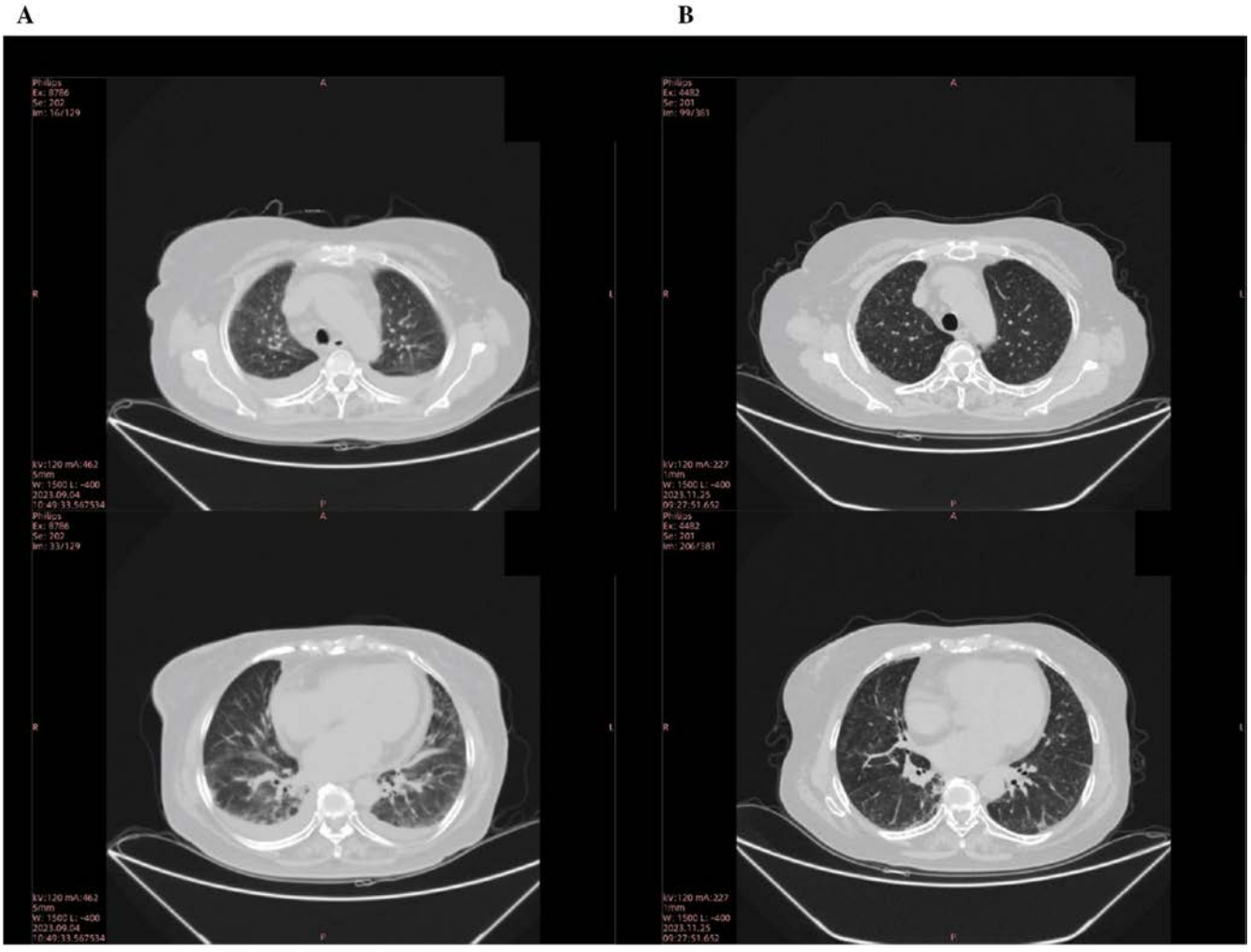

FIGURE 1 | Images from chest radiography and high-resolution computed tomography. (A) Chest CT at the time of administration with Telitacicept. (B) Chest CT after 2 months of Telitacicept use.

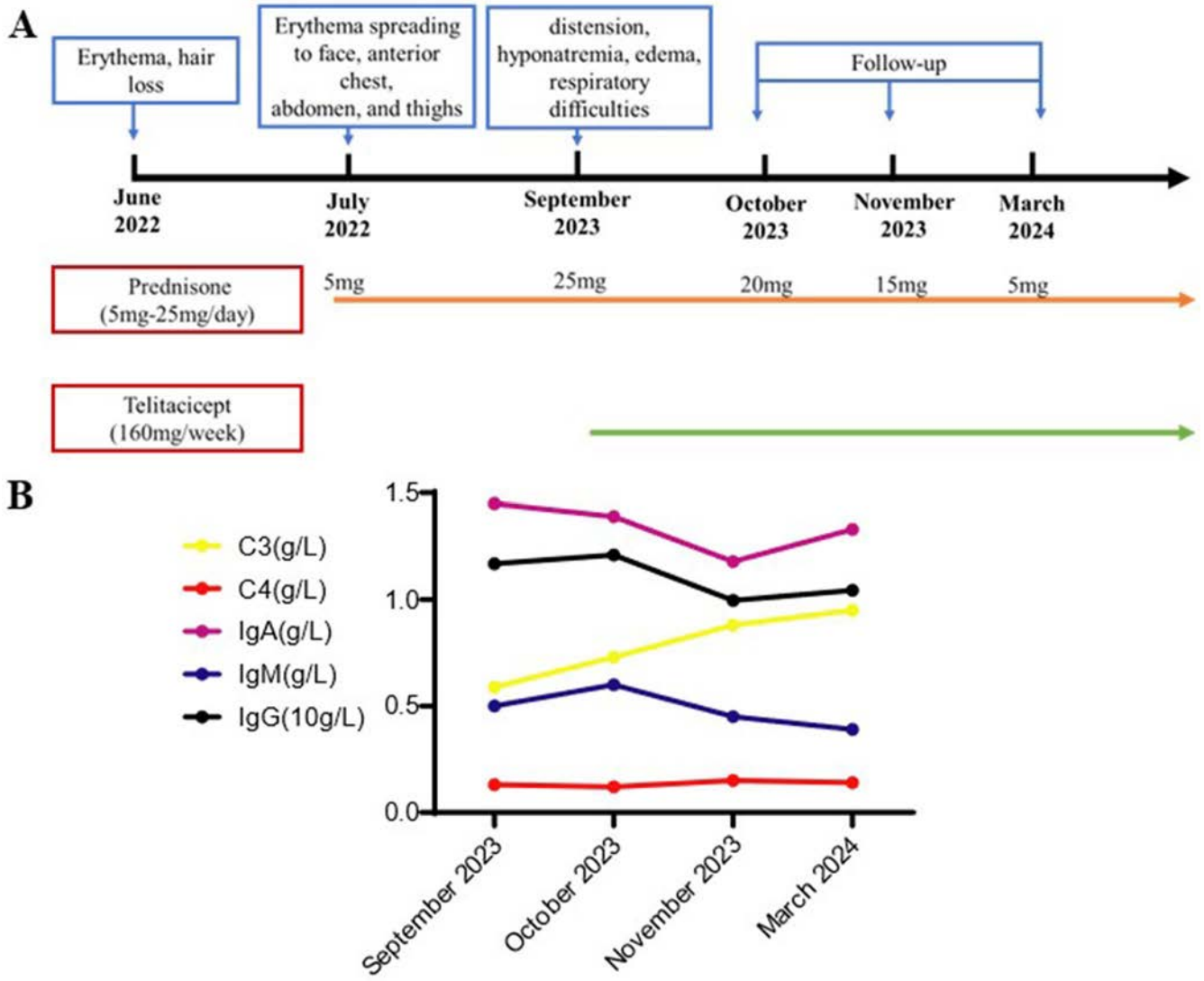

FIGURE 2 | (A) Map of the patient's course. (B) Changes in immunoglobulins and complement during the treatment.

patient benefited significantly, and the symptoms such as rash, hair loss, fatigue, hyponatremia, and shortness of breath improved after medication; ESSDAI also decreased significantly, and the degree of pulmonary fibrosis has also significantly improved.

B cells are a major type of antibody-producing lymphocytes in the immune system [7]. In autoimmune diseases, dysregulation of the immune system leads to abnormal generation and differentiation of B cells, resulting in the production of autoreactive antibodies [8–10]. The excessive production of autoantibodies by these cells is a key factor in tissue damage associated with autoimmune diseases.

Aberrant B cell activation and subsequent accumulation of plasma cells in the lung contribute to the pathogenesis of pulmonary fibrosis. These plasma cells produce autoantibodies, exacerbating the inflammatory response and tissue damage [9, 11]. Elevated levels of B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are observed in patients with pulmonary fibrosis and animal models. Several studies have demonstrated that B cells are necessary for bleomycin-induced pulmonary fibrosis, and depletion of plasma cells can reduce bleomycin-induced fibrosis [12]. During plasma cell differentiation and survival, APRIL plays a significant role. In patients with Sjögren's syndrome-associated interstitial lung disease, there have been reports of abnormal activation and clonal expansion of B cells [13]. Animal experiments have also confirmed excessive activation of B lymphocytes in interstitial lung disease. Furthermore, clinical trials have demonstrated the effectiveness of B cell depletion therapy in treating ILD [14, 15].

The traditional treatment of Sjögren's syndrome with pulmonary interstitial fibrosis mainly includes corticosteroids, cyclophosphamide and other immunosuppressive agents, which can non-specifically inhibit B cells and short-lived plasma cells [2, 16]. However, the efficacy has significant limitations, such as a low complete response rate, a long treatment cycle, and a significantly increased risk of infection and osteoporosis [17]. Therefore, there is an urgent need to develop targeted drugs with better efficacy and safety. Telitacicept inhibits the B-cell survival factors BAFF and APRIL, preserving autoimmunity while exerting therapeutic effects. BAFF/APRIL overexpression

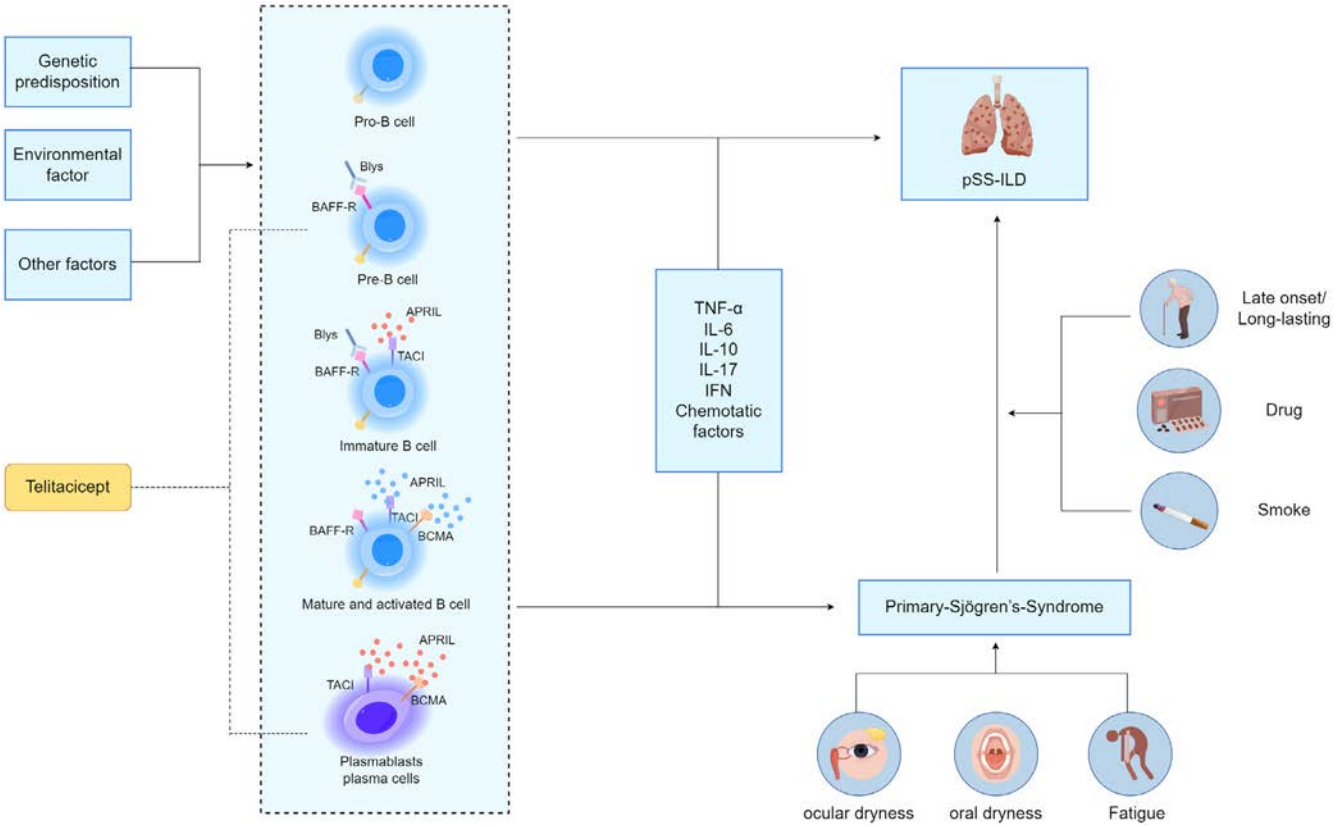

FIGURE 3 | Telitacicept inhibits APRIL and BLyS to alleviate the autoimmune response.

is a common characteristic of autoimmune diseases. So far, telitacicept is effective in clinical trials of SLE, rheumatoid arthritis, primary Sjogren's syndrome, relapsing–remitting multiple sclerosis, and systemic myasthenia gravis. Therefore, it is theoretically possible that Telitacicept may also prove effective in treating pulmonary interstitial fibrosis associated with abnormal BAFF/APRIL expression [4, 16, 18–20]. Schematic diagram of the effect of B cells on pSS-ILD and the mechanism of Telitacicept has shown in Figure 3. However, this case report has certain limitations. Due to the lack of evidence for the treatment of pulmonary interstitial fibrosis with telitacicept, the treatment regimen that we adopted needs further research and observation. It is not yet clear whether the patient's condition will recur in the future and whether there will be adverse reactions. Further evaluation is needed to determine whether a multitarget inhibitor for B cells would be superior to single-target drugs.

Author Contributions

The author takes full responsibility for this article.

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

Neutrophil Z Is a Novel Marker to Differentiate Disease Flares From Bacterial Infections in Febrile SLE Patients

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Keywords: anti-dsDNA autoantibody | bacterial infections | biomarkers | interleukin-6 | neutrophil Z | procalcitonin | systemic lupus erythematosus

ABSTRACT

Aim and Objectives: To assess the role of newer biomarkers like neutrophil Z, myeloid-related protein 8/14 (MRP 8/14), IL-6, sCD14, and neutrophil CD64 (nCD64) to distinguish flare from infection in febrile lupus patients.

Methods: In this prospective multicentric observational study to determine the etiology of fever in febrile lupus patients, in addition to routine tests, serum procalcitonin, neutrophil X, neutrophil Y, and neutrophil Z were done. sCD14, MRP8/14, and IL-6 were done by ELISA. nCD64 expression was measured by flow cytometry. All these biomarkers were assessed individually and in combination to see their ability to distinguish between infection and lupus flare.

Results: Among 159 febrile SLE patients, there were 55 infections, 65 disease flares, 38 flares and infections combined, and 1 malignancy. Patients with bacterial infections had a higher CRP, procalcitonin, neutrophil-to-lymphocyte ratio, Neutrophil Z, sCD14 levels, and neutrophil CD64 expression. While patients with flares had lower C3, C4, and higher anti-DsDNA antibody levels. IL-6 and MRP8/14 levels were similar in both groups. Combination of neut-Z with C3 or anti-dsDNA antibody could discriminate between flare and infection with AUC 0.88 (0.80–0.96) and 0.86 (0.78–0.95). Addition of TLC or procalcitonin or nCD64 MFI to these scores improved them marginally. Though composite scores with CRP and anti-dsDNA/procalcitonin also performed well but these were inferior to neutrophil Z-based composite models. These results were consistent in sensitivity analysis.

Conclusion: Neutrophil Z, complement C3, anti-dsDNA antibody levels, and TLC or procalcitonin-based composite score are good tools to differentiate between infection and flare in a febrile lupus patient. Serum MRP 8/14, IL-6, sCD14, and nCD64 did not perform well. Simple biomarkers such as neut-Z should be investigated further in SLE.

Abbreviations: AUC, area under the curve; AUC, area under the ROC Curve; CBC, complete blood count; CIs, confidence intervals; CRP, C-reactive protein; DLC, differential leukocyte count; DsDNA, double stranded DNA; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; MFI, mean fluorescence intensity; MRP 8/14, myeloid-related protein 8/14; nCD64, neutrophil CD64; neut-X, neutrophil X; neut-Y, neutrophil Y; neut-Z, neutrophil Z; NLR, neutrophil–lymphocyte ratio; ORs, odds ratios; PCT, procalcitonin; ROC, receiver operating characteristic; sCD14, soluble CD14; SLE, systemic lupus erythematosus; SLEDAI 2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC criteria, Systemic Lupus International Collaborating Clinics criteria; TLR, Toll-like receptor.

Summary

- Neutrophil Z and CRP individually are better than expensive markers like sCD14, MRP8/14, or IL-6 in differentiating bacterial infections from SLE flares.
- The composite score of the neut-Z, C3, anti-dsDNA antibody, procalcitonin performed best in distinguishing bacterial infection from lupus flare.
- The composite score of neut-Z, C3, anti-dsDNA is cost-effective model with good discrimination between infection and disease flare.

1 | Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disease that affects young women and adolescents [1]. Fever is one of the most prevalent clinical manifestations of active SLE, along with other organ involvement. In the early 1950s, fever was reported in 86% of SLE patients in one of the studies, but later studies reported its frequency to be around 40% in active SLE patients [2–4]. In addition to disease activity, infection, macrophage activation syndrome, malignancy, and other unrelated causes can also cause fever in SLE patients. Disease activity and infection constituted 42% and 54%, respectively, as the cause of fever in patients with SLE [5]. Patients with SLE have Infection-related hospitalization rates ranging from 10% to 35%, while mortality rates range from 29% to 53% [6–9]. Half of all SLE patients experience at least one episode of a serious infection during their lifetime [10]. It is crucial to distinguish between flares and infections because treatment of disease activity with immunosuppressive therapy may worsen the infection, resulting in significant morbidity and mortality. Similarly, delaying immunosuppression in patients with active disease leads to an increase in disease-related complications.

Conventionally used individual biomarkers as indicators of infection include blood counts, the neutrophil-to-lymphocyte ratio, high C-reactive protein (CRP), and elevated procalcitonin (PCT). Moreover, leukopenia and low complement (C), C3, and C4 levels, as well as raised antibodies (Abs) to double-stranded DNA (dsDNA), are indicative of a disease flare [11–15]. When these biomarkers are used individually, they are suboptimal for use in clinical practice.

Recently, neutrophil expression of the CD64-Fc receptor for IgG and the delta neutrophil index have shown promise [16, 17]. Neutrophil X (neut-X) is the numerical representation of neutrophil granules measured as sideward scattering light (SSC) when neutrophils pass through the Sysmex XE-5000 hematological analyzer. Neutrophil Y (neut-Y) is the numerical measurement of neutrophil nucleic acid (DNA and RNA) content measured as sideward fluorescence light. Neutrophil Z (neut-Z) is a combined vector of both. Neutrophil Z has shown promise in assessing infection in patients with malignancy [18].

Markers such as myeloid-related protein (MRP) 8/14, interleukin 6 (IL-6), and soluble CD14 (sCD14) are being investigated as markers of sepsis in the intensive care unit setting [19]. MRP8/14 is produced by myeloid cells in response to Toll-like receptor (TLR) and cytokine-induced activation; IL-6 is produced by monocyte/macrophage lineage cells, and sCD14 is shed in the circulation when monocytes get activated. There is limited evidence that these new biomarkers can distinguish SLE flares from infections [20–22]. Furthermore, owing to the limitations of single biomarkers, composite scores using multiple parameters were developed to differentiate flares from infections in febrile SLE patients [23, 24].

In this study, we evaluated the role of conventional biomarkers and non-conventional biomarkers like neut-X, neut-Y, and neut-Z, IL-6, sCD14, MRP 8/14, and nCD64, in isolation and combination, in distinguishing flare from infection in febrile SLE patients.

2 | Material and Methods

2.1 | Study Design and Setting

This was a multicentric, prospective observational study. The patients were recruited from the rheumatology inpatient and outpatient clinics at tertiary care institutions: Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow, Jawaharlal Institute of Postgraduate Medical Education and Research Puducherry, and All India Institute of Medical Sciences New Delhi, India, between 2018 and 2023. The Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences approved the study on March 19, 2018, with approval number PGI/BE/89/2018. The study was also approved by the Institutional Ethics Committee at other centers. All subjects gave informed consent.

2.2 | Participants Recruitment

2.2.1 | Inclusion Criteria

The study included adult and juvenile patients who met the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE classification and had a fever > 38.3°C or 101°F for more than 48 h and ≤ 15 days in an outpatient rheumatology clinic or inpatient rheumatology ward [25].

2.2.2 | Exclusion Criteria

We excluded patients with fever lasting less than 48 h or more than 15 days, patients with chronic renal disease with an eGFR ≤ 60, patients with chronic liver failure, and patients with congestive heart failure. Female patients who were pregnant or breastfeeding were also excluded from the study. We excluded patients with proven viral infections, including herpes zoster reactivation, and those with mycobacterial, fungal, or protozoal infections and malignancies from the analysis.

2.3 | Methodology

Part of the data on conventional biomarkers was reported earlier by Mehta et al. [24]. This prospective observational multicentric

study reported the utility of conventional biomarkers in differentiating flares and infections. This study was continued by recruiting new patients across multiple centers, testing them for conventional biomarkers like CBC, ESR, CRP, anti-dsDNA antibodies, and complement levels C3 and C4, neut-X, neut-Y, and neut-Z; serum procalcitonin; and other biomarkers such as serum IL-6, sCD14, MRP-8/14, and nCD64 in newly recruited patients. Additionally, in the present study, we used patient data from 66 patients and stored serum samples (stored at −80°C) of those patients from a prior study [24] to measure MRP 8/14, sCD14, and IL-6 levels.

Clinical details retrieved included organ domains ever involved due to SLE based on history and previous hospital records, the patient's current active clinical manifestations, fever pattern, clinical signs, comorbidities, and immunosuppressives used in the last 6 months: current dose of corticosteroids (prednisolone equivalent), pulse dose of methylprednisolone in the last 3 weeks, and the use of a steroid-sparing agent. We measured SLE disease activity via the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2K) [26].

Based on the treating physician's discretion, all patients were evaluated for the cause of fever using microbiological investigations such as cultures, and radiological imaging was performed. Blood cultures were performed on all patients, and the remaining microbiological investigations and imaging were performed based on the patient's symptoms and signs, clinical examination, and the treating physician's decision. All patients were evaluated with the following investigations: complete hemogram (CBC), differential leucocyte count (DLC), neutrophil-lymphocyte ratio (NLR), and erythrocyte sedimentation rate (ESR) by the Westergren method (normal value 0–20 mm). Serum C-reactive protein (CRP) (0–6 mg/L) and complement levels C4 and C3 were measured by nephelometry. Anti-DsDNA was measured by ELISA. Electrochemiluminescence was used to measure serum procalcitonin (PCT) (normal: <0.05 ng/mL). Neutrophil X and neutrophil Y indices obtained by objective evaluation of neutrophil granularity and nucleic acid by the Sysmex counter (XT 2000I, Japan) were noted, and neutrophil Z was calculated by the vector sum of neutrophil X and neutrophil Y [computational formula $(\text{neut-X})^2 + (\text{neut-Y})^2 = (\text{neut-Z})^2$] [18]. MRP 8/14 (Legend Max, USA), IL-6 (R&D, USA), and sCD14 (R&D, USA) levels in stored sera were measured by sandwich ELISA in stored sera. Neutrophil CD64 (nCD64) was measured by flow cytometry in a freshly collected blood sample after 100 μL of whole blood was stained with anti-CD64 antibodies (BD Biosciences, USA). nCD64 is expressed both as a percentage of neutrophils expressing CD64 and as the mean fluorescence intensity (MFI) of CD64 on neutrophils. Blood samples for all these investigations were taken within 24 h of a hospital visit.

2.4 | Patient Stratification

The diagnosis of infection was based on the presence of clinical signs and symptoms, microbiological confirmation, radiological imaging, and laboratory parameters. Both serious and nonserious infections were included. The SLE flare was diagnosed based on the SELENA SLEDAI flare index [27].

Based on the cause of fever, we stratified the patients into the following groups: SLE flare, infection, combination of disease flare and infection, or other causes. We have not stratified these patients into severe or nonsevere infections. Stratification was confirmed at the time of discharge and after 2 weeks of follow-up based on the response to treatment.

2.5 | Statistical Methods

Continuous variables were expressed as the mean with standard deviation (mean ± SD) or median with interquartile range, and the two groups were bacterial infection and SLE flare. Both were compared using the *t*-test or Mann–Whitney *U* test based on normality assessments done by the Shapiro–Wilk test. Categorical variables are presented as proportions, and intergroup comparisons were done using the chi-squared or Fisher's exact test. We assessed the performance of conventional biomarkers-TLC, ESR, CRP, neutrophil-lymphocyte ratio, serum procalcitonin- and nonconventional biomarkers-neut-X, neut-Y, neut-Z, nCD64, sCD14, MRP 8/14, and IL-6-in differentiating flares from infections. Using ROC curve analysis, the performance of all biomarkers was assessed individually to differentiate bacterial infection from lupus flare. Composite scores were made using the two best individually performing biomarkers for infection combined with disease flare biomarkers. Later, other conventional and nonconventional biomarkers that were significantly different in univariate analysis (nCD64 MFI, sCD14) were added to see if they would be able to improve the performance of the composite models.

The results are presented as *p* values (two-tailed), odds ratios (ORs), and 95% confidence intervals (CIs). GraphPad Prism v9.4.1 was used for statistical analysis, with two-tailed *p* values <0.05 considered to indicate statistical significance.

3 | Results

A total of 159 febrile patients were studied, of whom 55 had infections, 65 had disease flares, 38 had both infections and flares, and 1 had a malignancy (carcinoma of the cervix). In the infection group, nine out of 55 patients had mycobacterial, viral, fungal, or protozoal infections. Those with both infection and flare ($n=38$), nonbacterial infections ($n=9$), and malignancies ($n=1$) were removed from further analysis.

The respiratory system ($n=17$, 37%) was the most common site in patients with bacterial infection, followed by the urinary tract ($n=14$, 30%) and skin and soft tissue. 50% of the bacterial infections were microbiologically confirmed (Table S1).

Among the 65 patients with disease flares, the most common flares were hematological (anemia, leukopenia, and thrombocytopenia) flares ($n=27$, 41%), followed by skin and mucocutaneous flares ($n=22$, 34%) and renal flares ($n=22$, 34%). Other disease flares included musculoskeletal flares such as arthritis and myositis, which were observed in 18 (28%) patients; serositis was observed in eight (12%) patients; neuropsychiatric lupus

flares, which were observed in seven (11%) patients; and gastrointestinal flares, which were observed in two (3%) patients.

Data regarding organ involvement and levels of various biomarkers in patients with both infection and disease flare are provided in supplement (Table S2).

3.1 | Flare Versus Infection Group: Univariate Analysis

The median age of patients with infection was significantly higher, while the duration of fever was significantly longer in the flare group (Table 1). There was no significant difference between the two groups in terms of disease duration, distribution of organ involvement, or use of corticosteroids or steroid-sparing drugs (Table 1). Among conventional biomarkers, TLC ($p = 0.011$), the NLR ($p = 0.014$), the CRP level ($p = 0.0002$), the ESR/CRP ratio ($p = 0.005$), and the PCT level ($p < 0.0001$) were significantly higher in the infection group. Higher neutrophil X ($p < 0.0001$), neutrophil Y ($p = 0.0056$), and neutrophil Z ($p < 0.0001$) levels were seen in patients with infection than in patients with flares (Table 1). sCD14 ($p = 0.04$) and nCD64 MFI ($p < 0.0001$) were higher in patients with infections (Table 1). MRP 8/14 ($p = 0.15$) and IL-6 ($p = 0.87$) levels were similar between the infection and lupus flare groups (Table 1).

Anti-dsDNA antibodies were found to be elevated in 63 (98%) patients with a disease flare (Table 1). Among the patients with disease flare, 52 (80%) had lower levels of complements. Among the patients with infection, 18 (38% of patients) had lower complement levels, 11 (24% of patients) had high complement levels, and 18 (38% of patients) had normal complement levels. The elevation of anti-dsDNA and low complement levels was significantly higher in the flare group.

3.1.1 | Infection Biomarkers

To differentiate infections from lupus flares, the ROC curve revealed a good AUC for neutrophil Z 0.79 (0.68–0.90) and CRP 0.70 (0.60–0.80). However, other biomarkers had modest AUC: 0.62 (0.52–0.73) for TLC, 0.62 (0.51–0.72) for NLR, 0.66 (0.54–0.77) for serum procalcitonin, 0.55 (0.43–0.67) for sCD14, 0.58 (0.47–0.69) for interleukin-6, 0.60 (0.47–0.73) for MRP 8/14, and 0.62 (0.49–0.74) for nCD64 mean fluorescent intensity (MFI) (Figure 1a,b).

3.1.2 | Complement C3, C4, and Anti DsDNA Antibody Levels

We also assessed the performance of biomarkers for disease activity, that is, anti dsDNA, complement C3, and C4 alone or in combination. The ROC curve revealed AUC of 0.69 (0.58–0.80) for C4, 0.73 (0.62–0.82) for C3, 0.74 (0.65–0.83) for anti dsDNA antibody level, and 0.77 (0.67–0.85) for the combination of C3 and Anti dsDNA. When all 3 were combined (Anti dsDNA, C3, C4) the ROC curve revealed AUC 0.77 (0.68–0.86) to differentiate lupus flare from infections. (Figure 1c).

3.2 | Selection of Biomarkers for Combination to Generate Composite Models

During the analysis of individual biomarkers, two biomarkers for infection performed best: neut-Z with AUC 0.79 (0.68–0.90) and CRP with AUC 0.7 (0.6–0.8). The other good individual biomarkers were markers of disease activity: C3 and anti-dsDNA, with AUCs of 0.73 (0.62–0.82) and 0.74 (0.65–0.83). As we had planned to make composite models using good biomarkers of infection with markers of disease flare, we made two models, one with neut-Z and another with CRP along with disease activity markers (anti dsDNA, C3). As these two models performed well, we added a conventional biomarker like PCT, TLC, and a non-conventional biomarker like sCD14 and nCD64, which were significant in the univariate analysis to see if the performance of the composite score improves or not.

3.2.1 | Composite Models Including Neutrophil Z

The addition of an anti-dsDNA antibody to neut-Z improved AUC to 0.86 (0.78–0.95) with a positive predictive value of 80% and a negative predictive value of 75%. The addition of C3 to neut-Z also enhanced AUC to 0.88 (0.80–0.96) with an 82% positive predictive value and an 80% negative predictive value. When neut-Z was combined with anti-dsDNA and TLC, it showed AUC 0.88 (0.80–0.96), but this model has predominantly neutrophil-based biomarkers.

Further, the addition of three routinely done tests (anti-dsDNA antibody, C3, and procalcitonin) along with neut-Z provided excellent discrimination between flare and infection [AUC of 0.92 (0.86–0.99)]. (Figure 2a). The addition of the expression of nCD64 [MFI] to neut-Z and C3 resulted in good discrimination, with an AUC of 0.93 (0.86–0.99) and positive predictive value of 86% and negative predictive value of 83%. (Figure 2b).

3.2.2 | Composite Models Using CRP

The addition of anti-dsDNA to CRP improved AUC to 0.77 (0.68–0.86), while the addition of complement C3 to CRP improved AUC to 0.78 (0.69–0.97). Further addition of TLC to CRP improved AUC to 0.81 (0.72–0.89) (Figure 3a). The addition of procalcitonin to these 3 markers (CRP, anti dsDNA, TLC) showed only a minor improvement to 0.83 (0.75–0.91) (Figure 3b).

3.3 | Sensitivity Analysis

We also performed sensitivity analysis for various biomarkers as individual and in combination in patients with microbiology confirmed bacterial infections. Except for Procalcitonin, which has improved the AUC in ROC analysis 0.84 (0.72–95) other biomarkers individually showed similar results. The ROC curve revealed improved AUC 0.93 (0.85–1) for the combination of Neutrophil Z with C3, and 0.94 (0.86–1) for the combination of Neutrophil Z, C3, Anti DsDNA and 0.91 (0.84–0.97) for the combination of Neutrophil Z, anti DsDNA, TLC, C3 in patients with microbiologically confirmed bacterial infections.

TABLE 1 | Comparison between bacterial infection and disease flare group.

	Infection ($n=47$)[a]	Disease flare ($n=65$)[a]	p
Age, median (range) (years)	28 (19.7–35.5)	24 (18.5–30)	**0.02**
Juvenile (< 18 years), *n* (%)	5 (10%)	6 (9%)	
Female, *n* (%)	39 (85%)	61 (94%)	0.11
Duration of disease (months), median (range)	24 (11–72)	24 (6.5–47)	0.17
Clinical manifestation at baseline, *n* (%)			
Musculoskeletal	40 (87%)	50 (83.3%)	0.18
Renal	16 (35%)	28 (43%)	0.37
Serositis	9 (19.5%)	12 (18.5%)	0.79
CNS	19 (41%)	19 (29.2%)	0.13
Mucocutaneous	29 (63%)	43 (65.1%)	0.97
APS	3 (6.5%)	0	0.07
Hematological	19 (41%)	28 (43%)	0.85
Current HCQ usage	47 (100%)	65 (100%)	1.00
Prednisolone > 7.5 mg, *n* (%)	28 (61%)	39 (60%)	0.93
Current prednisolone dose (mg)			
< 7.5	18 (38%)	26 (40%)	
7.5–15	17 (36%)	11 (17%)	
16–30	7 (15%)	20 (30.8%)	0.06
> 30	4 (8.5%)	8 (12.2%)	
MPS pulse in last 3 weeks	4 (8.5%)	10 (15.4%)	
Steroid sparing agent use, *n* (%)	31 (65%)	35 (54%)	0.056
Methotrexate	4 (13%)	2 (5%)	
Cyclophosphamide	4 (13%)	7 (20%)	
Azathioprine	6 (20%)	10 (35%)	
Mycophenolate mofetil	16 (50%)	12 (33%)	
Tacrolimus	3 (10%)	1 (3%)	
Rituximab	5 (16%)	3 (8%)	
Fever duration (days)	7 (5–8.2)	10 (5.5–15)	**0.001**
TLC (per mm^3) (median with IQR)	7110 (4298–12 275)	6336 (3220–8415)	**0.011**
Neutrophil lymphocyte ratio	4.7 (3.49–10.55)	4.1 (2.8–5.9)	**0.014**
Neutrophil X	135.5 (127–146.5)	123.2 (116–127.3)	**< 0.0001**
Neutrophil Y	48.2 (43.2–54.2)	43.05 (35.7–47.8)	**0.0056**
Neutrophil Z	142.8 (136.4–154.4)	132.2 (125–137.2)	**< 0.0001**
Erythrocyte sedimentation rate (mm in 1st hour)	104 (57–128)	85 (55–117)	0.08
C reactive protein (mg/L)	47.3 (11.33–105.3)	13.4 (5.5–39)	**0.0002**
ESR/CRP ratio (median)	1.67 (0.2–14.2)	6.37 (1.3–25.8)	**0.005**
Anti DsDNA (IU/mL) (median)	172.16 (18.6–212.7)	285 (105–419)	**< 0.0001**
Distribution of Anti DsDNA titer levels, *n* (%)			

(Continues)

TABLE 1 | (Continued)

	Infection ($n=47$)[a]	Disease flare ($n=65$)[a]	p
<20	12 (25.5%)	1 (1.5%)	
21–50	10 (21.27%)	6 (9.23%)	
51–100	5 (10.6%)	7 (10.76%)	
>100	19 (40.42%)	51 (78.46%)	
Procalcitonin (ng/mL)	1.08 (0.22–4.09)	0.14 (0.06–0.52)	**<0.0001**
C3 (mg/dL)	91.5 (62.2–128.8)	55 (40–83.5)	**<0.0001**
C4 (mg/dL)	21.45 (13.2–33)	11.3 (7.07–17.5)	**0.0004**
Number with low C3 or C4	22 (46.8%)	52 (80%)	**0.0009**
SLEDAI 2 K	4 (1–9)	12.5 (7–19)	**<0.0001**
MRP8/14 (μg/mL)	9.36 (2.6–26.2)	15.78 (7.0–41.77)	0.15
Soluble CD14 (μg/mL)	5.43 (3.99–8.98)	4.63 (3.50–6.0)	**0.04**
IL-6 (pg/mL)	26 (5–54)	11.43 (0.85–40.76)	0.3
Neutrophil CD64 (MFI)	4144 (2299–10941)	1422 (886–2689)	**<0.0001**

Note: Bold values indicate that it is less than $p < 0.05$.
Abbreviations: CRP, C reactive protein; dsDNA, double stranded deoxy ribonucleic acid; ESR, erythrocyte sedimentation rate; IL, interleukin; MFI, mean fluorescent intensity; MRP, myeloid related protein; N/L, neutrophil to lymphocyte; sCD14, soluble CD 14; SLEDAI 2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
[a]Continuous data expressed as, and median with IQR and categorical as *n* (%).

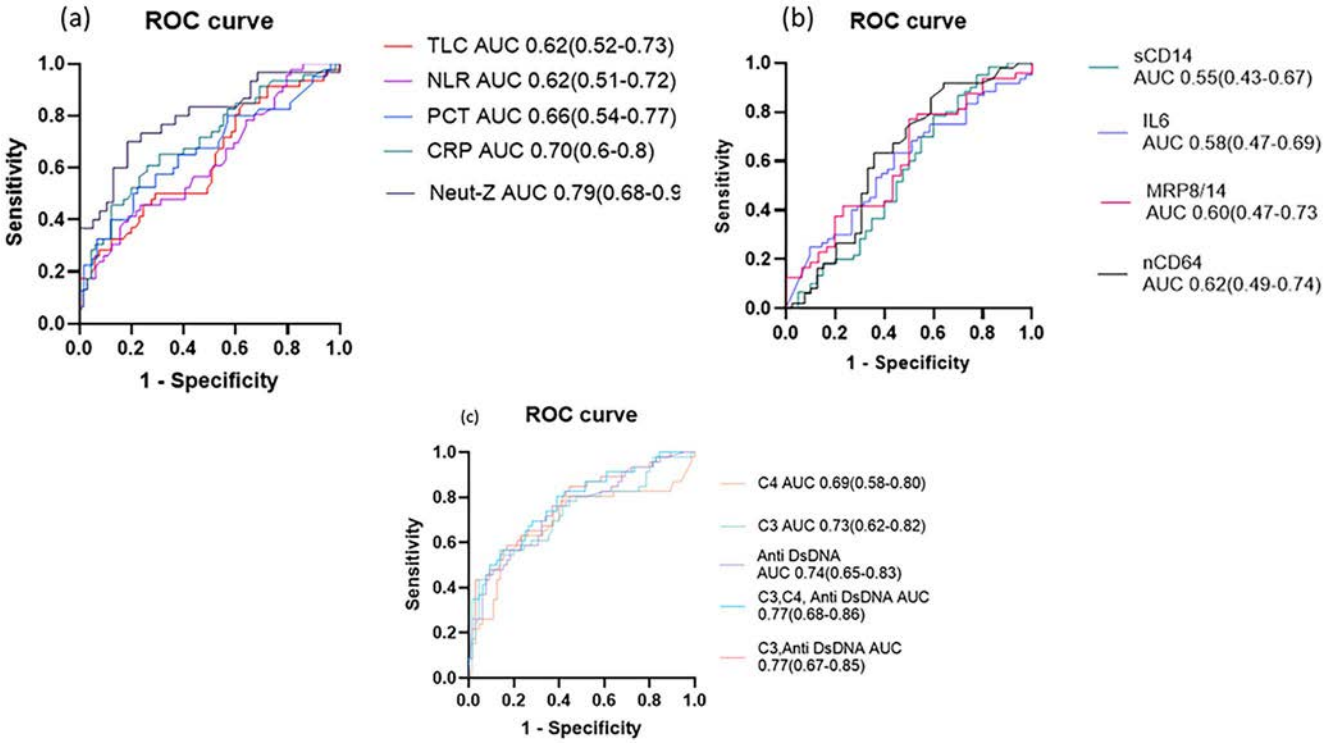

FIGURE 1 | ROC curve demonstrating the AUC different biomarkers individually. (a) Conventional biomarkers and Neutrophil Z. (b) non-conventional biomarkers and (c) Biomarkers of disease activity-C3, C4, and Anti-dsDNA antibody levels as individual and in combination.

Among CRP based models during the ROC analysis, the combination of CRP and C3, the combination of CRP and Anti DsDNA showed AUC of 0.77 (0.65–0.91), the combination of CRP, Anti DsDNA, TLC showed AUC 0.8 (0.69–0.92), and when all 4 combined (CRP, anti dsDNA, TLC, procalcitonin) the AUC improved to 0.9 (0.81–0.98).

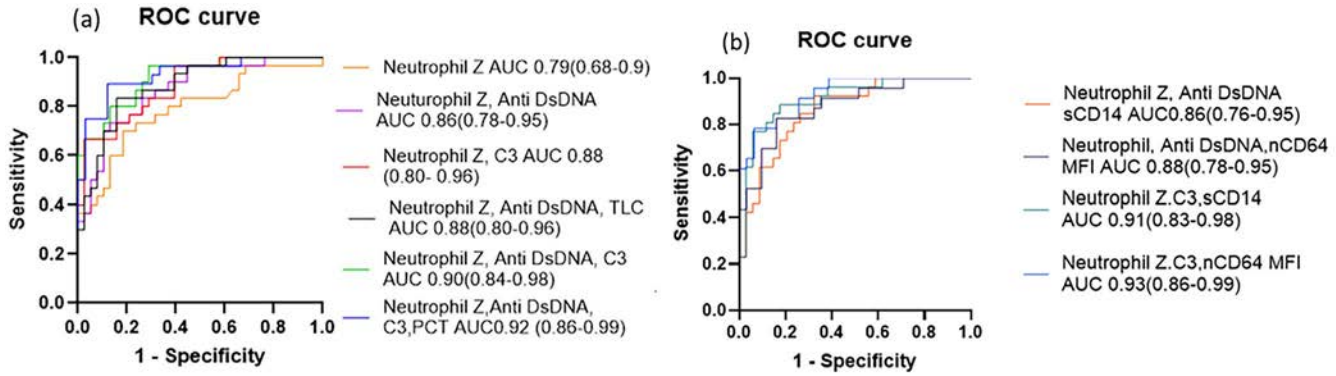

FIGURE 2 | ROC curve demonstrating the AUC using a combination of Neutrophil Z with different biomarkers. (a) Conventional biomarkers (b) non-conventional biomarkers.

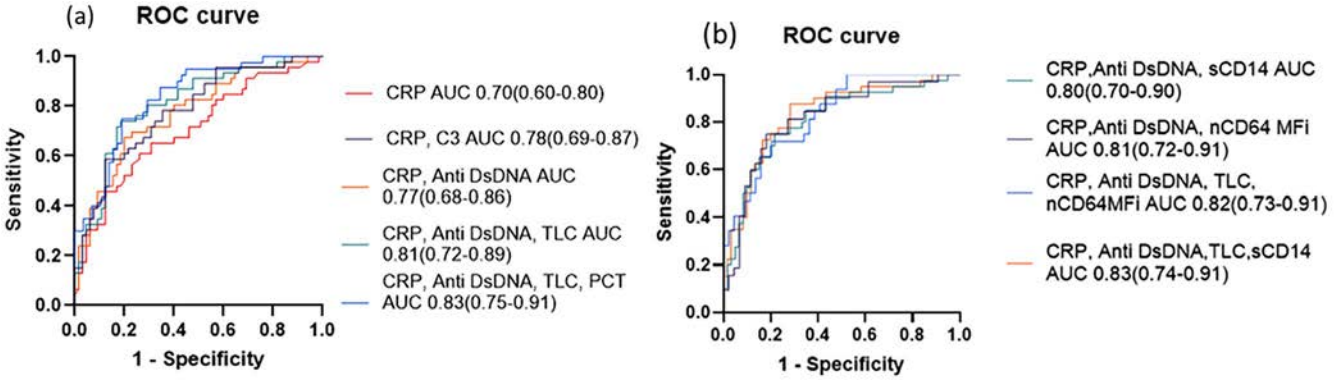

FIGURE 3 | ROC curve demonstrating the AUC using a combination of CRP with different biomarkers. (a) Conventional biomarkers and (b) non-conventional biomarkers.

4 | Discussion

In the present study, we evaluated the role of various conventional and newer biomarkers, such as neutrophil Z, sCD14, nCD64, and MRP 8/14, in distinguishing lupus flares from infection, individually and in combination. We found that neut-Z and CRP were the best individually performing biomarkers for infection among all, with neut-Z performing better than CRP, while among disease activity markers, complement C3 and anti dsDNA antibody levels performed well. Among composite scores, neut-Z and C3 had high AUCs in distinguishing between flare and infection, besides being cheap. Another combination of neut-Z with anti dsDNA antibody level and TLC also showed good results in discriminating against lupus flare from infections, and it is also cost effective. The addition of anti-dsDNA and serum procalcitonin to C3 and neut-Z improved the AUC at an added cost. However, combining novel biomarkers with CRP did not increase AUC for distinguishing infection from flare. The composite model with the combination of complement C3, C4, and anti dsDNA showed moderate discrimination between lupus flare and infection but was inferior to neut-Z based composite models.

In this study, the spectrum of infections was dominated by respiratory and urinary tract infections. This observation is consistent with that reported in the Spanish RELESSER registry, where respiratory tract infections occurred in one-third of patients and urinary tract infections in 15% of patients [28]. Bacteriological confirmation was present in 50% of patients with infections, compared to 70% in the RELESSER registry. This difference could be attributed to the widespread use of empiric antibiotics by primary care physicians in India, which resulted in a negative culture in the biological sample [28].

Patients with infections were older and had lower disease activity. However, no difference in the mean prednisolone dose or use of steroid-sparing agents was seen compared with those with flares. In a study by Beca et al., higher age was reported in patients with infection, but in contrast to our data, they found more patients on corticosteroids and steroid-sparing agents in the infection group [25].

Patients with infection had higher CRP and lower ESR/CRP ratios than did those with disease flare, and there was no significant difference noted in ESR between the two groups. While individuals with disease flares had higher levels of anti-dsDNA and lower levels of C3 and C4, there was no significant difference in ESR between the two groups. In a previous study, Littlejohn et al. found no significant difference in the ESR between the two groups; however, patients with infections had higher CRP levels and a considerably lower ESR/CRP ratio than those with disease flares [29, 30]. In our study, PCT was significantly different in patients with infections compared to flares. A systematic review revealed elevated serum procalcitonin levels in infection but not during disease flare in Asian patients [31].

TLC was significantly higher in patients with infection compared to disease flare. Among neutrophil-based biomarkers, NLR, neut-X, neut-Y, neut-Z, and nCD64 MFI were significantly elevated in patients with infection, even though the percentage of neutrophils expressing CD64 was similar in both groups. Like earlier studies, our study also found an elevated NLR and TLC in patients with infection compared to individuals with disease flare [28]. However, even in lupus patients who do not have active infections, NLR and TLC levels can be changed since glucocorticoids cause neutrophilic leukocytosis, and steroid-sparing immunosuppressive drugs can cause neutropenia. For these reasons, they are unreliable markers for distinguishing lupus flares and infections.

Previously, toxic granules in peripheral smears were used as markers of neutrophil activation in patients with cytopenia and infections. Neut-Z is a combined vector of both neut-X and neut-Y, and higher values show more neutrophil activation. In our study, neut-X, neut-Y, and neut-Z values were significantly higher in infected patients compared to those with flares. In our study, neut-Z was the best individual biomarker with an AUC of 0.79 (0.68–0.90), like data in sepsis [18].

Expression of CD64, as measured by the MFI, was higher in patients with infection than in those without infection, but the percentage of neutrophils expressing CD64 was not different from that in patients with infection. When exposed to bacterial lipopolysaccharides and various cytokines, neutrophils increase the expression of CD64 (nCD64), a high-affinity IgG-Fc receptor. Earlier studies, albeit with fewer patients, have shown either an increased percentage of neutrophils expressing CD64 or an increased MFI of CD64 on neutrophils as a differentiating factor between infection and flare [32–35]. The lack of difference in the percentage of neutrophils expressing CD64 could be related to a minor increase in CD64 expression on neutrophils owing to cytokine increases related to flare-up.

Monocytes secrete soluble CD14 (sCD14), also known as presepsin, when activated. Patients with an infection had higher levels of serum sCD14 than did those with a lupus flare. Our findings confirm observations from an earlier study of 27 patients with SLE (12 with infection) that revealed that sCD14 was higher in patients with infection than in those with lupus flare [18]. Another study with 94 patients reported that sCD14 had better specificity but similar sensitivity to that of hs-CRP [36].

Other soluble products produced by neutrophils and monocyte–macrophage lineage cells in response to LPS-mediated TLR signaling include myeloid-related protein 8/14 (S100A8/S100A9) and IL-6, as well as proinflammatory cytokines. In sepsis, IL-6 levels have been used to determine the presence of infection and the severity of infection [37–39]. In patients with lupus, the data are limited, and one study found that the IL-6 levels were twofold higher during infection [22]. In contrast to the present study, MRP8/14 levels were found to be higher in infections than in controls, but they did not outperform CRP in discriminating against infections from flares [21, 40]. One possible explanation for the lack of difference in our study could be the high disease activity in our patients who had disease flares compared to the previous study [22]. High mRNA expression of MRP 8/14 has been seen in lupus nephritis, and high salivary and urinary MRP 8/14 levels have been found in lupus patients with high disease activity [41, 42].

Compared to other biomarkers, neutrophil Z and CRP complement C3 and anti DsDNA antibody levels were better at distinguishing infections from disease flares. Because studies using single markers yielded variable results, the tendency is toward a strong, robust composite score. The composite scores using neutrophil Z with C3/anti-dsDNA antibody levels or a combination of 4 (neutrophil Z, C3, Anti-dsDNA, TLC) will be feasible and cost-effective in resource-limited settings. In another setting where procalcitonin is routinely done, the combination of four biomarkers (neutrophil Z, anti-DsDNA, C3, and serum procalcitonin) would be ideal. Though the addition of nCD64 to neut-Z and C3 had an excellent AUC of 0.93 (0.88–0.99) to distinguish between infection and disease flare, the availability of flow cytometry is an issue in most institutions.

The strengths of the present study are that it was conducted in a real-world setting with high infection rates. The multicenter setting across India increases the generalizability of the study. The sensitivity analysis in microbiologically confirmed bacterial infection also showed better results in neutrophil Z-based composite models, which showed similar results in all patients. The limitations of the current study include the modest number of infection episodes and bacteriological confirmation of infection in only half of the patients.

The current study concludes that neutrophil Z, complement C3, anti-DsDNA antibody levels, and TLC or procalcitonin-based composite score are excellent tools to differentiate infection from flare in a febrile lupus patients.

In the future, further validation of these biomarkers and the proposed combination of markers in composite scores may help clinicians better differentiate infection from flares in SLE patients.

Author Contributions

K.M.: first draft manuscript, statistical analysis, revising the manuscript. P.M.: statistical analysis, revising manuscript. C.K.: revising manuscript. A.A.: study conception, study design, study framework, revising manuscript, study monitoring. All other authors contributed to study conception, data collection, critically reviewing the manuscript, and final approval of the manuscript.

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Ethics Statement

This study was approved by the institutional ethics committee (IEC) of Sanjay Gandhi Postgraduate Institute of Medical Sciences on March 19, 2018, with approval number PGI/BE/89/2018.

Consent

Informed written consent was obtained from all the participants. Patient confidentiality is maintained.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The raw data underlying this article cannot be shared publicly to protect the privacy of the participants. The data will be shared on reasonable request to the corresponding author.

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Supporting Information

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ORIGINAL ARTICLE

Increased Periprosthetic Joint Infection Rate Following Total Knee Arthroplasty in Rheumatoid Arthritis Patients: Insights From a Japanese Nationwide Medical Claims Database Study

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ABSTRACT

Introduction: Advances in pharmacological treatments have reduced joint deformities in rheumatoid arthritis (RA), leading to a decline in total knee arthroplasty (TKA) among RA patients. However, RA remains associated with higher risks of postoperative complications. This study compares postoperative complications during hospitalization in patients with RA and osteoarthritis (OA) undergoing TKA in Japan.

Methods: This retrospective cohort study utilized data from the Japanese Diagnosis Procedure Combination database from April 2016 to March 2023. Patients who underwent TKA were identified, and propensity score (PS) matching was performed to balance age, sex, body mass index, simultaneous surgeries, and comorbidities, resulting in 9048 matched pairs. Outcomes included periprosthetic joint infections (PJI), cognitive dysfunction, deep vein thrombosis (DVT), pulmonary embolism (PE), and periprosthetic fractures. Statistical analyses were conducted using multivariate logistic regression with a significance threshold of $p < 0.01$.

Results: RA patients had higher risks of PJI (odds ratio [OR]: 1.473, 95% CI: 1.134–1.912, $p = 0.004$) and postoperative cognitive dysfunction (OR: 1.721, 95% CI: 1.190–2.488, $p = 0.004$) compared to OA patients. In contrast, no significant differences were observed in the incidence of DVT, PE, or periprosthetic fractures.

Conclusion: RA patients undergoing TKA are at increased risk of PJI and cognitive dysfunction, highlighting the need for tailored perioperative management. These findings provide important insights into optimizing outcomes for RA patients.

Abbreviations: BMI, body mass index; CI, confidence interval; DPC, diagnosis procedure combination; DVT, deep vein thrombosis; OA, osteoarthritis; PE, pulmonary embolism; PJI, periprosthetic joint infection; PS, propensity score; RA, rheumatoid arthritis; TKA, total knee arthroplasty.

1 | Introduction

Treatment for rheumatoid arthritis (RA) includes biological and targeted synthetic agents that reduce synovitis and prevent the progression of joint destruction [1, 2]. Advances in pharmacological therapies and imaging diagnostics for RA have led to improved suppression of joint deformity progression [3–5], contributing to a declining trend in the number of surgical procedures [6, 7]. The number of total knee arthroplasty (TKA) procedures in the general population has increased over the past two decades, suggesting a growing demand driven by population aging and the associated rise in the incidence of knee osteoarthritis (OA) [8]; the proportion of TKA procedures among patients with RA has been reported to be declining [9]. Additionally, the percentage of TKA performed for RA patients decreased from 2.4% of all TKA procedures in 2003 to 0.9% in 2016 [10]. Conversely, studies have reported that in patients who initiated RA treatment after the widespread adoption of biological disease-modifying anti-rheumatic drugs (bDMARDs), the 8-year incidence of TKA was 12.6% lower than the rate predicted based on pre-bDMARDs trends [9].

The multifaceted etiology of RA, the use of immunomodulatory treatments, and the higher prevalence of joint deformities are believed to contribute to an increased risk of complications in RA patients compared to the general population [11]. Studies based on databases and systematic reviews have examined the outcomes of TKA in RA patients compared to those with OA [12–15]. Patients with RA have been reported to exhibit a higher risk of periprosthetic joint infection (PJI) following TKA compared to those with OA [12–15]. Conversely, other studies have found no significant difference in infection risk between RA and OA patients [16]. There are discrepancies between meta-analyses and large database studies, suggesting the need for further detailed investigation. The incidence of deep vein thrombosis (DVT) after TKA was comparable between RA and OA patients [16]. Furthermore, the risk of pulmonary embolism (PE) is reported to be either equivalent or lower in RA patients relative to OA patients [16]. Current evidence suggests that there is no significant difference in the incidence of PE and DVT after TKA between patients with RA and those with OA, although the risk of PE may be slightly lower in RA patients. However, the number of large-scale studies remains insufficient, and factors such as the use of anticoagulant therapy may have a substantial impact. Therefore, further comprehensive investigations are warranted.

A study using the Diagnosis Procedure Combination (DPC) database in Japan found that elderly patients with RA who suffered hip fractures had a higher risk of developing pneumonia and PE compared to their non-RA counterparts [17]. On the other hand, studies on total hip arthroplasty using the DPC database have revealed that the RA group has a higher risk of postoperative dislocation and reoperation [18]. The Japanese DPC database serves as a valuable resource for large-scale cohort studies in orthopedics, particularly for research on hip fractures [19–23]. However, the risk of complications associated with TKA in Japanese RA patients has not been thoroughly investigated. This study aims to utilize a nationwide database of Japanese patients who have undergone TKA to compare the incidence of in-hospital complications between RA and OA patients. We conducted a large-scale nationwide case-cohort study utilizing a Japanese insurance database to assess the risk of complications in RA patients who underwent TKA, comparing them with an age-, sex-, body mass index (BMI)-, and comorbidity-matched cohort of OA patients.

2 | Methods

2.1 | Study Design

This retrospective study adhered to the ethical principles stated in the Declaration of Helsinki and was approved by the ethical review boards of Tokyo Medical and Dental University (approval number: M2000-788) and Tohoku University (approval number: 2021-1-1082). Data were retrospectively obtained from the Japanese National Administrative DPC reimbursement system database [24]. Comprehensive informed consent was obtained from all patients upon admission, covering both their approval of the proposed treatment methods and the academic use of data collected during their care. Furthermore, this manuscript does not include any identifiable information about the participants. The study period spanned from April 2016 to March 2023 and constituted a nationwide survey of hospitals participating in the DPC system in Japan. During this time, approximately 1100 DPC-participating hospitals consistently submitted medical records and provided consent for their use in research. Patients who underwent TKA at these hospitals across Japan were included in the analysis, providing a comprehensive overview of the current landscape of TKA in the country. This clinical study analyzed a cohort of primary TKA patients, with a specific focus on comparing RA patients to those with OA, particularly regarding postoperative complications in RA patients. Patients who had undergone revision TKA or unicompartmental knee arthroplasty were excluded from this study. Patients who underwent primary TKA for bone tumors or trauma were also excluded from the analysis. Cases with missing data were excluded from the analysis, and no imputation was performed. Postoperative complications evaluated in this study included PE, DVT, cerebrovascular disease, postoperative cognitive dysfunction, pneumonia, PJI, and periprosthetic fracture. PJI following TKA were identified using the ICD-10 code T84.5, which indicates infection and inflammatory reaction due to internal joint prosthesis. Postoperative cognitive dysfunction was identified using ICD-10 codes F010, F011, F012, F019, F03, F107, G238, G300, G301, G308, G309, G310, and G318, which encompass cognitive dysfunction and delirium occurring during the postoperative period, as previously described [21]. The primary diagnoses for TKA were categorized using ICD-10 codes, with RA coded as M0586, M0606, M0686, and M0696, and OA coded as M170–M175, M179. Patients in the TKA cohort were identified based on three key criteria: (1) primary diagnosis, (2) the main reason for hospitalization, and (3) the condition necessitating the highest utilization of medical resources.

2.2 | Propensity Score Matching

A one-to-one propensity score (PS) matching was performed to compare RA and OA patients who received TKA. The analysis adjusted for confounding factors, including age, sex, BMI, and

comorbidities such as hypertension, ischemic heart disease, cerebrovascular disease, chronic renal dysfunction, chronic lung disease, diabetes, cognitive impairment, and hyperlipidemia. The model's discriminative ability was evaluated using C-statistics. PS estimates were utilized to perform nearest-neighbor matching without replacement, with calipers set at 0.2 times the standard deviation of the PS estimates [25]. This approach generated matched pairs that formed RA and OA groups based on PS matching.

2.3 | Statistical Analyses

Data are expressed as mean ± standard deviation. Group differences between RA and OA patients who underwent TKA were assessed using the χ^2 test and Student's *t*-test for each clinical parameter. Multivariate logistic regression analysis was performed to identify independent risk factors and evaluate variables associated with severe complications, such as PJI and DVT during hospitalization, in relation to RA, age, sex, BMI, and comorbidities in the PS-matched cohort. For the multivariate logistic regression analysis, we included the same confounding factors used for propensity score matching, excluding body mass index (BMI). These variables were selected based on their clinical relevance and previously reported associations with the outcomes [18, 21]. All statistical tests were two-sided, and statistical significance was defined as $p < 0.01$. Statistical analyses were conducted using JMP version 17 (SAS, Cary, NC, USA).

3 | Results

Figure 1 illustrates the schematic model of the patient selection process. From the dataset spanning April 2016 to March 2023, a total of 228 595 patients who met the inclusion and exclusion criteria were identified. Of these, 9105 patients underwent TKA for RA, while 219 490 underwent the procedure for OA. After PS matching based on age, sex, BMI, simultaneous bilateral surgery, and comorbidities, both the RA and OA groups consisted of 9048 cases each.

Table 1 summarizes the characteristics of patients who underwent TKA for RA and OA. Before performing PS matching, significant differences were observed between the two groups in terms of sex, age, BMI, comorbidities, and the performance of simultaneous bilateral surgery. The RA group had a higher prevalence of comorbidities, such as chronic pulmonary disease, while the OA group showed a higher prevalence of hypertension, cerebrovascular disease, ischemic heart disease, and hyperlipidemia. Simultaneous bilateral surgery was performed in 4.6% of patients with RA. Following one-to-one PS matching, the standardized mean differences (SMD) were reduced to ≤ 0.1, indicating that differences in age, sex, BMI, comorbidities, and simultaneous bilateral surgery between the RA and OA groups were adequately balanced. The Charlson comorbidity index was higher in the RA group, and the length of hospital stay was longer in the RA group. Additionally, the use of blood transfusions on the day of surgery and the following day was higher in the RA group. The use of bone cement during surgery was more frequent in the RA group, whereas navigation systems were more commonly used in the OA group. The C-statistic was calculated as 0.867.

Table 2 presents the usage of anticoagulants and antiplatelet drugs for thromboprophylaxis. Edoxaban was the most frequently used medication in both groups. Before PS matching, significant differences were observed in the usage of aspirin and clopidogrel between the two groups. However, after PS matching, no significant differences were detected. Prophylactic administration for the prevention of DVT and PE was appropriately implemented in both groups.

Table 3 shows the results of the analysis comparing the incidence of complications between the RA and OA groups. The risk

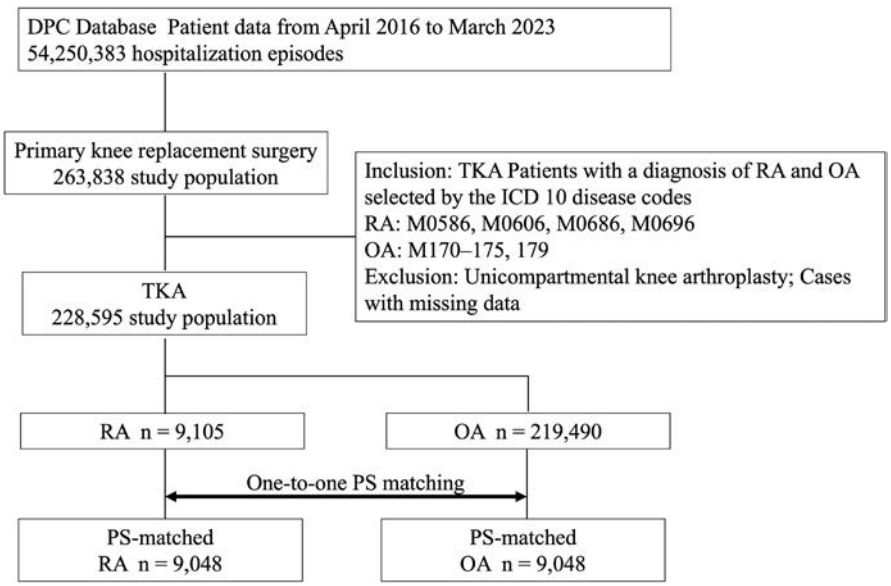

FIGURE 1 | The flow diagram illustrates the patient selection process for rheumatoid arthritis (RA) and osteoarthritis (OA) patients who underwent total knee arthroplasty (TKA) and propensity score (PS) matching. It details the methodology used to extract target patients from the Diagnosis Procedure Combination (DPC) database and the subsequent PS matching process for RA and OA patients who underwent TKA.

TABLE 1 | Characteristics of patients before and after propensity score matching.

	Before PS matching			After PS matching			
	OA	RA	*p*	OA	RA	SMD	*p*
n	219 490	9105		9048	9048		
Sex							
Men	46 379 (21.1%)	1460 (16.0%)	< 0.0001	1380 (15.2%)	1451 (16.0%)	0.022	0.15
Women	173 111 (78.9%)	7645 (84.0%)		7668 (84.8%)	7597 (84.0%)		
Age	74.9 ± 7.7	72.1 ± 9.5	< 0.0001	72.1 ± 9.1	72.1 ± 9.5	0.003	0.84
Body mass index	26.2 ± 4.7	24.7 ± 7.5	< 0.0001	24.7 ± 4.5	24.7 ± 4.4	0.006	0.69
Comorbidities							
Hypertension	78 613 (35.8%)	2946 (32.4%)	< 0.0001	2891 (32.0%)	2924 (32.3%)	0.008	0.61
Diabetes	47 503 (21.6%)	1870 (20.5%)	0.012	1776 (19.6%)	1860 (20.6%)	0.023	0.12
Cerebrovascular disease	7221 (3.3%)	198 (2.2%)	< 0.0001	194 (2.1%)	197 (2.2%)	0.002	0.88
Ischemic heart disease	13 156 (6.0%)	459 (5.0%)	0.0002	438 (4.8%)	457 (5.1%)	0.01	0.51
Chronic renal dysfunction	6155 (2.8%)	283 (3.1%)	0.086	262 (2.9%)	282 (3.1%)	0.013	0.38
Chronic lung disease	1159 (0.5%)	191 (2.1%)	< 0.0001	175 (1.9%)	188 (2.1%)	0.01	0.49
Cognitive impairment	3476 (1.6%)	118 (1.3%)	0.031	115 (1.3%)	115 (1.3%)	0	1
Hyperlipidemia	43 804 (20.0%)	1446 (15.9%)	< 0.0001	1379 (15.2%)	1436 (15.9%)	0.017	0.24
Bilateral surgery	14 956 (6.8%)	419 (4.6%)	< 0.0001	421 (4.6%)	416 (4.6%)	0.003	0.86
	OA	RA	*p*	OA	RA	*F* value or χ^2 statics	*p*
Charlson comorbidity index	0.66 ± 0.93	1.62 ± 0.94	< 0.0001	0.66 ± 0.93	1.62 ± 0.94	4719	< 0.0001
Glucocorticoid use	4113 (1.9%)	2023 (22.2%)	< 0.0001	261 (2.9%)	2011 (22.2%)	1541	< 0.0001
Length of hospitalization (days)	28.6 ± 15.7	29.5 ± 20.5	< 0.0001	27.9 ± 14.0	29.3 ± 16.7	38.3	< 0.0001
Blood transfusion Day 0 (unit)	0.06 ± 0.41	0.12 ± 0.60	< 0.0001	0.06 ± 0.39	0.12 ± 0.60	74.0	< 0.0001
Blood transfusion Day 1 (unit)	0.03 ± 0.29	0.07 ± 0.43	< 0.0001	0.03 ± 0.27	0.07 ± 0.43	58.3	< 0.0001
Bone cement use	198 134 (90.3%)	8398 (92.2%)	< 0.0001	8199 (90.6%)	8349 (92.3%)	15.9	< 0.0001
Navigation use	63 464 (28.9%)	2424 (26.6%)	< 0.0001	2662 (29.4%)	2406 (26.6%)	17.9	< 0.0001

Note: One-to-one PS matching was performed. Data is shown as mean ± standard deviation; *p* values of < 0.01 are considered significant by the Student's *t*-test and χ^2 test.
Abbreviations: OA, osteoarthritis; RA, rheumatoid arthritis; SMD, standard mean difference.

of PJI and postoperative cognitive dysfunction was significantly higher in the RA group, with *p* values of 0.003 and 0.002, respectively. In contrast, the incidence of DVT was significantly higher in the OA group ($p = 0.003$).

Table 4 shows the results of a multivariate logistic regression analysis aimed at identifying factors contributing to PJI in patients with TKA during hospitalization. Among the various factors examined, the presence of RA emerged as the apparent risk factor, with an odds ratio of 1.473 (95% CI: 1.134–1.912, $p = 0.004$). Hypertension was also identified as a risk factor, with an odds ratio of 1.732 (95% CI: 1.322–2.268, $p < 0.0001$). Age, sex, simultaneous bilateral surgery, and other comorbidities were not identified as significant risk factors.

Table 5 shows the results of a multivariate logistic regression analysis examining factors associated with postoperative cognitive dysfunction in patients who underwent TKA. The presence of RA was identified as a significant risk factor, with an odds ratio of 1.721 (95% CI: 1.190–2.488, $p = 0.004$). Age

TABLE 2 | Comparison of antithrombotic therapies before and after propensity score matching.

	Before PS matching				After PS matching			
	OA	RA	χ^2 statics	*p*	OA	RA	χ^2 statics	*p*
Edoxaban	135 825 (61.9%)	5611 (61.6%)	0.2	0.62	5623 (62.2%)	5582 (61.7%)	0.4	0.53
Fondaparinux	4371 (2.0%)	155 (1.7%)	3.8	0.052	188 (2.1%)	154 (1.7%)	3.4	0.06
Enoxaparin	21 638 (9.9%)	960 (10.5%)	4.6	0.03	941 (10.4%)	950 (10.5%)	0.05	0.83
Aspirin	18 324 (8.4%)	635 (7.0%)	21.7	< 0.0001	618 (6.8%)	628 (6.9%)	0.09	0.77
Warfarin	4900 (2.2%)	221 (2.4%)	1.5	0.22	202 (2.2%)	221 (2.4%)	0.9	0.35
Clopidogrel	6120 (2.8%)	193 (2.1%)	14.6	< 0.0001	188 (2.1%)	193 (2.1%)	0.07	0.79
Apixaban	5687 (2.6%)	226 (2.5%)	0.4	0.52	203 (2.2%)	225 (2.5%)	1.2	0.28

Note: One-to-one PS matching was performed. *p* values of < 0.01 are considered significant by the χ^2 test.
Abbreviations: OA, osteoarthritis; PS, propensity score; RA, rheumatoid arthritis.

TABLE 3 | Comparison of sequelae before and after propensity score matching.

	Before PS matching				After PS matching			
	OA	RA	χ^2 statics	*p*	OA	RA	χ^2 statics	*p*
Deep vein thrombosis	20 533 (9.4%)	729 (8.0%)	18.8	< 0.0001	838 (9.3%)	726 (8.0%)	8.8	0.003
Pulmonary embolism	655 (0.3%)	31 (0.3%)	0.5	0.47	34 (0.4%)	31 (0.3%)	0.1	0.71
Cerebrovascular disorder	782 (0.4%)	30 (0.3%)	0.2	0.67	22 (0.2%)	30 (0.3%)	1.2	0.27
Cognitive dysfunction	1634 (0.7%)	79 (0.9%)	1.8	0.18	45 (0.5%)	79 (0.9%)	9.4	0.002
Pneumonia	420 (0.2%)	24 (0.3%)	2.4	0.13	21 (0.2%)	23 (0.3%)	0.1	0.76
Periprosthetic joint infection	2595 (1.2%)	144 (1.6%)	11.7	0.0006	96 (1.1%)	141 (1.6%)	8.7	0.003
Periprosthetic fracture	129 (0.06%)	10 (0.1%)	3.7	0.053	7 (0.1%)	10 (0.1%)	0.5	0.47

Note: One-to-one PS matching was performed. *p* values of < 0.01 are considered significant by the χ^2 test.
Abbreviations: OA, osteoarthritis; PS, propensity score; RA, rheumatoid arthritis.

and the presence of cognitive impairment were also identified as significant risk factors, with odds ratios of 1.102 (95% CI: 1.074–1.132, $p < 0.0001$) and 2.857 (95% CI: 1.312–6.219, $p = 0.008$), respectively. In contrast, sex, simultaneous bilateral surgery, and other comorbidities were not found to be significant risk factors.

4 | Discussion

This study is the largest investigation to date on TKA in RA patients, leveraging a comprehensive database of individuals who underwent TKA in Japan. It evaluates the association between RA and the occurrence of complications, including PJI, periprosthetic fracture, DVT, PE, pneumonia, and cognitive dysfunction after TKA. The results of this study showed that compared to TKA for patients with OA, TKA for patients with RA was associated with an increased risk of PJI and postoperative cognitive dysfunction. Furthermore, RA was identified as an independent risk factor for PJI and cognitive dysfunction following TKA, with odds ratios of 1.473 (95% CI: 1.134–1.912, $p = 0.004$) and 1.712 (95% CI: 1.190–2.488, $p = 0.004$), respectively. On the other hand, the presence of RA as a comorbidity was not linked to an increased risk of pneumonia, DVT, PE, or periprosthetic fractures.

Several studies have reported that patients with RA have higher rates of PJI, DVT, PE, and periprosthetic fractures following TKA compared to those with OA [12, 13, 26]. On the other hand, there are reports indicating no difference in the incidence of DVT and PE between the two groups following TKA [16]. Although the findings of this study reflect short-term outcomes after TKA, it was evident that patients with RA had an increased risk of PJI. On the other hand, no significant short-term increase in the risk of periprosthetic fractures was observed. Consistent with previous studies, the incidence of DVT and PE after TKA did not differ between the RA and OA groups. This study also thoroughly examined the use of antithrombotic therapy, confirming that both groups received equivalent antithrombotic treatment after PS matching. The finding that RA is not a high-risk factor for DVT and PE in a study like this, where patient backgrounds were carefully matched, represents an important contribution to the understanding of these complications.

Patients with RA undergoing joint replacement surgery may face an increased risk of both delirium and cognitive dysfunction.

TABLE 4 | Multivariate logistic analysis for risk factors for periprosthetic joint infection after TKA during hospitalization.

Variable	Odds ratio (95% CI)	χ^2 statics	*p*
Age	0.995 (0.981–1.009)	0.44	0.51
Sex (Male)	1.021 (0.719–1.448)	0.01	0.91
Rheumatoid arthritis	1.473 (1.134–1.912)	8.6	0.004
Simultaneous bilateral surgery	1.101 (0.613–1.980)	0.1	0.74
Hypertension	1.732 (1.322–2.268)	15.6	<0.0001
Diabetes	0.915 (0.661–1.267)	0.3	0.59
Cerebrovascular disease	0.872 (0.356–2.132)	0.1	0.76
Chronic renal dysfunction	1.318 (0.694–2.506)	0.7	0.39
Ischemic heart disease	1.310 (0.791–2.170)	1.0	0.29
Cognitive impairment	0.654 (0.161–2.654)	0.4	0.55
Chronic lung disease	1.925 (0.976–3.795)	3.0	0.06
Hyperlipidemia	1.395 (1.017–1.913)	4.1	0.04

Note: p values of <0.01 are considered significant by the χ^2 test.
Abbreviations: CI, confidence interval; TKA, total knee arthroplasty.

TABLE 5 | Multivariate logistic analysis for risk factors for postoperative cognitive dysfunction after TKA during hospitalization.

Variable	Odds ratio (95% CI)	χ^2 statics	*p*
Age	1.102 (1.074–1.132)	64.6	<0.0001
Sex (Male)	1.669 (1.093–2.541)	5.1	0.02
Rheumatoid arthritis	1.721 (1.190–2.488)	8.6	0.004
Simultaneous bilateral surgery	2.782 (0.685–11.31)	2.9	0.15
Hypertension	0.791 (0.533–1.174)	1.4	0.25
Diabetes	1.123 (0.734–1.718)	0.3	0.59
Cerebrovascular disease	1.239 (0.452–3.399)	0.2	0.67
Chronic renal dysfunction	0.997 (0.365–2.723)	0.1	0.99
Ischemic heart disease	1.009 (0.487–2.090)	0.1	0.98
Cognitive impairment	2.857 (1.312–6.219)	5.3	0.008
Chronic lung disease	2.356 (0.942–5.888)	2.7	0.07
Hyperlipidemia	1.160 (0.712–1.888)	0.3	0.55

Note: p values of <0.01 are considered significant by the χ^2 test.
Abbreviations: CI, confidence interval; TKA, total knee arthroplasty.

Risk factors for postoperative delirium include advanced age, preexisting cognitive impairment, and comorbidities commonly observed in RA patients [27, 28]. Chronic inflammation associated with RA may contribute to cognitive decline independent of surgical interventions [29]. In this study, the mean age after PS matching was 72.1 years, yet postoperative cognitive dysfunction was significantly more prevalent in the RA group. These findings suggest that elderly RA patients and those with preoperative cognitive impairment require particular attention regarding the potential for postoperative cognitive dysfunction and delirium.

There are several limitations to this large study, as outlined below. First, the study population was limited to patients who underwent TKA in acute care hospitals included in the DPC data system. This excludes patients admitted to non-DPC-reported beds, which account for approximately 30% of all general hospital beds, as well as patients who were never treated in an acute care hospital [19]. Secondly, this study is limited by the inability to verify the accuracy of DPC disease classifications and the inability to assess the severity of symptoms associated with comorbidities in the actual patients. Thirdly, this study is limited by the inability to confirm the severity of knee joint deformities, the details of RA disease activity, or the specifics of the surgical approach or equipment used. Lastly, long-term outcomes such as infection, periprosthetic fracture, reoperation, and mortality after discharge were not evaluated. RA is a well-recognized risk factor for osteoporosis [30, 31]. Accordingly, the long-term incidence of periprosthetic fractures warrants evaluation through rigorous observational studies in clinical patient populations. Further large-scale studies utilizing detailed patient data are necessary to address these limitations.

5 | Conclusion

This study represents the largest investigation to date on TKA in patients with RA, utilizing data from Japan to examine the risk of complications and sequelae following TKA in RA patients. Compared to the OA group, the RA group demonstrated a higher risk of PJI and cognitive dysfunction during the postoperative hospitalization period. Conversely, no significant differences were observed between the RA and OA groups in terms of periprosthetic fracture, DVT, or PE. These findings highlight the increased risk of PJI and postoperative cognitive dysfunction in RA patients undergoing TKA, emphasizing the importance of

careful surgical planning to optimize outcomes in this patient population.

Author Contributions

All authors are responsible for the work described in this paper. Y.M., K.T., H.T., R.K., H.H., N.M., K.F., T.A., and K.F. were involved in the study's conception, design, or planning. Y.M. and H.T. were involved in the data analysis. Y.M., K.T., H.T., R.K., H.H., N.M., K.F., T.A., and K.F. interpreted the study results. All authors contributed to the critical review and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available 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

GPA and EGPA: Comparison of the 1990 ACR Criteria With the 2022 ACR/EULAR Criteria in a Monocentric Cohort of Patients

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Dear Editor,
The diagnosis of systemic small vessel vasculitides is often challenging because of the proteiform manifestations of the disease and the severity of organ involvement.

The discovery of ANCA, autoantibodies targeting proteins contained in neutrophil granules, shed light on the immunopathogenesis of a subset of small vessel vasculitides and offered new diagnostic tools [1].

Classification criteria have been developed to help clinicians in the diagnosis of vasculitides, to allow the collection of homogeneous cohorts of patients for clinical and pharmacological studies. In 1990, a panel of experts first proposed diagnostic criteria [2, 3], that have been subsequently modified and recently extensively revised [4, 5].

We compared the performance of the two criteria sets on patients followed in the Rheumatology and Clinical Immunology Units of the University Hospital in Pisa, with the diagnosis of granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis with polyangiitis (EGPA).

The study was approved by the local Ethics Committee CEAVNO (prot n 29 108).

Among 82 patients with the diagnosis of GPA, retrospectively evaluated at disease onset, 65 matched both criteria; 5 fulfilled only the 1990 criteria and 12 only the 2022 criteria. The concordance rate is 79%.

The analysis of discordant cases directly addresses the differences between the 2 sets of criteria (Table 1). Out of the 12 patients positive for the 2022 criteria only, 92% are anti PR3 positive; 33% have renal involvement, 33% have nasal involvement, 25% have cartilage involvement, and 25% have lung infiltrates. Out of the 5 patients positive only for the 1990 criteria, 4 are anti-MPO positive, 3 have lung involvement, and 3 have renal involvement. Two patients also fulfilled the 2022 criteria for the diagnosis of microscopic polyangiitis (MPA) [6] and were re-classified as MPA; one patient was considered undifferentiated vasculitis, and two patients were confirmed GPA, displaying the clinical features of the MPO-positive subset of GPA, previously described in Caucasian and Chinese GPA patients [7, 8].

Conversely, anti-PR3 antibody positivity is the hallmark of patients classified as GPA only for the 2022 criteria. Besides ANCA PR3 positivity, however, these patients have manifestations of systemic disease, with upper airways, lower airways, and renal involvement.

Chiara Baldini and Paola Migliorini contributed equally to the work.

TABLE 1 | Itemized analysis of previously diagnosed GPA patients fulfilling only one set of criteria.

DETAILS OF THE PATIENTS FULFILLING ACR/EULAR 2022 ONLY											
Patient number	Clinical criteria			Laboratory, imaging and biopsy criteria							Total score
	Nasal involvement	Cartilagineous involvement	Hearing loss	Anti-PR3	Lung nodules, mass or cavitation	granuloma	Sinusitis/mastoiditis	Pauciimmune glomerulonephritis	Anti MPO	Eosinophilia	
1	3	0	0	5	0	0	1	0	0	0	9
2	0	0	1	5	2	0	0	0	0	0	8
3	0	2	0	5	0	0	0	0	0	0	7
4	3	2	0	0	0	0	1	0	-1	0	5
5	0	0	0	5	0	0	0	0	0	0	5
6	0	0	0	5	0	0	0	0	0	0	5
7	3	2	1	5	0	0	0	0	0	0	11
8	0	0	0	5	0	0	0	1	0	0	6
9	0	0	0	5	0	0	0	0	0	0	5
10	0	0	0	5	2	0	0	1	0	0	8
11	0	0	0	5	2	0	0	0	0	0	7
12	3	0	0	5	0	0	1	0	0	0	9

Patients with GPA diagnosis: 82	ACR 1990 FULFILLED	ACR 1990 NOT FULFILLED
ACR/EULAR 2022 FULFILLED	65	12
ACR/EULAR 2022 NOT FULFILLED	5	

DETAILS OF THE PATIENTS FULFILLING ACR 1990 ONLY									
Patient number	Nasal or oral inflammation	Hemoptysis*	Abnormal chest radiograph	Urinary sediment	Granulomatous inflammation on biopsy	Score 1990	Score 2022	Notes	FINAL CLASSIFICATION
A	1	0	0	1	0	2	4	MPO-ANCA POS FULFILLS MPA ACR/EULAR CRITERIA 2022	MPA
B	1	0	0	0	1	2	4	MPO-ANCA POS FULFILLS MPA ACR/EULAR CRITERIA 2022	MPA
C	1	0	1	0	0	2	4	MPO-ANCA POS	GPA MPO POS
D	0	0	1	1	0	2	1	MPO-ANCA POS	GPA MPO POS
E	0	1	1	0	1	4	4		Undifferentiated Vasculitis

TABLE 2 | Prevalence of each criterion among EGPA patients fulfilling ACR/EULAR 2022 criteria but not ACR 1990 criteria.

ACR 1990 criteria for EGPA			ACR/EULAR 2022 for EGPA
Eosinophilia > 10% on white blood cell differential count.	100%	100%	Blood eosinophil count $\geq 1\ 1 \times 10^9$cells/L
History of wheezing or diffuse high-pitched rales on expiration	80%	90%	Obstructive airways disease
History of acute or chronic paranasal sinus pain or tenderness or radiographical opacification of the paranasal sinuses.	40%	70%	Nasal polyps
Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to a systemic vasculitis.	50%		
Development of mononeuropathy, multiple mononeuropathies, or poly neuropathy attributable to a systemic vasculitis.	30%	30%	Mononeuritis multiplex
Biopsy including artery, artriole, or venule, showing accumulatons of eosinophils in extravsculaer areas.	10%	10%	Extravascular eosinophilic-predominat inflammation on bipsy
		0%	cANCA or ANCA-PR3 positivity
		0%	Hematuria

Out of 69 patients with the diagnosis of EGPA, 59 were positive with both sets of criteria and 10 were positive only with the 2022 criteria. The percent of agreement is 86%.

Among the 10 patients positive for the 2022 criteria only (Table 2), all have eosinophilia, 80% have asthma, 70% have nasal polyps/sinus involvement, and 30% have peripheral neuropathy; lung infiltrates are also observed in 50% of these patients.

The ACR 2022 criteria allow diagnosing EGPA in a higher number of patients, mostly characterized by asthma and eosinophilia. Such a high prevalence of clinical manifestations, typical of type 2 airway inflammation, stresses the need to apply these criteria only when vasculitis has been demonstrated and other hypereosinophilic syndromes have been excluded.

On the whole, evaluating the performance of the criteria developed in 1990 and 2022 in a monocentric cohort of Caucasian patients, we found a good agreement of the 2 sets of criteria.

Previous comparisons have been conducted on monocentric cohorts of different ethnicity, selected according to previous criteria (1990 and 2007) and reclassified according to the ACR 2022 criteria [9, 10].Despite a different study design and the different ethnicity (Asians vs. Caucasians) the concordance rate is similar for GPA (79% in Caucasians and 73.8% in Asians) and identical in EGPA (86%).

In conclusion, the results of the present study show a good performance of the ACR 2022 criteria in classifying real-life vasculitis patients. Moreover, taken together with previous studies, these results suggest that ACR 2022 criteria can be applied with a similar outcome to patients of different ethnic groups.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Lorenzo Puccetti, Francesco Ferro, Michele Moretti, and Ilaria Puxeddu. The first draft of the manuscript was written by Paola Migliorini and Chiara Baldini, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Letter to the Editor for "Which Is the Best Option for AxSpA Patients After First TNFi Failure: Switch to Secukinumab or Cycling With Other TNFi?"

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Dear Editor,

We read with great interest the study by Kaya et al. which explored real-world treatment trajectories for axial spondyloarthritis (axSpA) patients experiencing failure with their first tumor necrosis factor inhibitor (TNFi) [1]. A comparative analysis of switching to secukinumab (SEC) versus cycling within TNFi agents addresses a vital clinical conundrum. However, several methodological and interpretative aspects merit further discussion to optimize future treatment decisions.

A key limitation lies in the omission of a comprehensive disease burden assessment, particularly functional and structural parameters such as the Bath Ankylosing Spondylitis Functional Index (BASFI) or radiographic progression. These measures can critically influence drug discontinuation independent of inflammatory biomarkers or disease activity indices [2]. Furthermore, no data were presented on quality-of-life metrics, fatigue, or sleep disturbances, despite their established relevance in axSpA outcomes and biologic adherence. The over-reliance on C-reactive protein (CRP) and Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS-CRP) as treatment response predictors neglects the subset of patients with clinically active disease but normal CRP levels, a phenomenon frequently observed in non-radiographic axSpA and female patients [3].

Additionally, while the exclusion of patients with extra-articular manifestations such as uveitis or psoriasis aims to homogenize the cohort, this narrows the generalizability of the study. These manifestations often dictate biologic disease-modifying anti-rheumatic drugs (bDMARD) and are integral to axSpA management [4]. Moreover, the absence of imaging-based evaluation for enthesitis despite its statistical relevance in the SEC subgroup raises concerns about the accuracy of Achilles enthesitis diagnosis, which is known to be misclassified without ultrasonographic validation.

The study also did not delineate whether patients received loading doses for SEC or if any variations in dose frequency occurred. SEC's pharmacodynamic profile differs from that of TNFi agents, and dosing inconsistencies may confound the drug survival outcomes. Furthermore, medication adherence, which is an important determinant of drug discontinuation, was not assessed, especially in real-world settings with self-injected therapies.

One of the most striking findings was that higher CRP levels at the second TNFi initiation predicted better survival, yet the study did not explore the additive impact of concurrent conventional synthetic disease-modifying anti-rheumatic drug

(csDMARD) use, which could modulate immunogenicity and alter drug retention [5]. Also unexamined was whether anti-drug antibody testing was performed, which might clarify the mechanistic differences between primary and secondary TNFi failures.

In summary, while the authors offer meaningful data on second-line bDMARD decisions in axSpA, future studies should integrate comprehensive functional, imaging, and adherence data. A prospective design with stratified patient selection and standardized imaging-based enthesitis assessment could better delineate the optimal treatment strategies in post-TNFi axSpA care.

Author Contributions

Renu Sah: validation, supervision, project administration, writing – original draft, writing – review and editing. **Ankita Mathur:** writing – original draft, writing – review and editing. **Venkata Dileep Kumar Veldi:** conceptualization, methodology, writing – original draft, writing – review and editing.

Disclosure

Generative AI Use Statement: Generative AI tools, including Paperpal and ChatGPT-4o, were utilized solely for language, grammar, and stylistic refinement. These tools had no role in the conceptualization, data analysis, interpretation of results, or substantive content development of this manuscript. All intellectual contributions, data analysis, and scientific interpretations remain the sole work of the authors. The final content was critically reviewed and edited to ensure accuracy and originality. The authors take full responsibility for the accuracy, originality, and integrity of the work presented.

Ethics Statement

The authors have nothing to report.

Consent

No patient data were collected or analyzed in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Ankita Mathur
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LETTER TO THE EDITOR

Case Report: Surgery for the Patient With Systemic Lupus Erythematosus Complicated by Type A Aortic Dissection

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Dear Editor,

We report a case of a 55-year-old female admitted with sudden, severe retrosternal chest pain lasting 6 h. Initial tests at a local hospital, including electrocardiograph (ECG) and myocardial enzyme analysis, ruled out acute myocardial infarction. Aortic Computed Tomography Angiography (CTA) (Figure 1A,B) revealed a true and false lumen extending from the ascending aortic root to the proximal left common iliac artery, with a tear in the ascending aorta. The patient was transferred to our cardiovascular surgery department for further treatment.

The patient had an 18-year history of systemic lupus erythematosus (SLE), treated with 20 mg prednisone daily, and a 20-year history of hypertension, managed with nifedipine. She also had a 2-year history of type 2 diabetes mellitus and hyperlipidemia, both untreated, and a history of depression (details unknown). She was 157 cm tall, weighed 66 kg, with a BMI of 26.8. Upon admission, her vitals were stable: temperature 36.7°C, pulse 112 bpm, respiratory rate 22 breaths per min, and blood pressure readings of 173/95 mmHg (right arm), 161/88 mmHg (left arm), and 155/79 mmHg (lower limbs). She was conscious but in low spirits, with weak bilateral dorsal foot artery pulses. She received low-flow oxygen, sedation, analgesia, and continuous monitoring, along with urapidil to control her blood pressure within 130–110/90–70 mmHg.

Laboratory results included: WBC 12.8×10^9/L (↑), N 82.2% (↑), RBC 3.1×10^{12}/L (↓), Hb 102 g/L (↓), PLT 147×10^9/L, TC 7.15 mmol/L (↑), TG 3.54 mmol/L (↑), LDL-C 4.63 mmol/L (↑), ALT 52 U/L (↑), AST 86 U/L (↑), BUN 8.4 mmol/L (↑), Cr 122 μmol/L (↑), CRP 54 mg/L (↑), anti-nuclear antibody < 1:80, anti-dsDNA antibody 5.87 IU/mL (↑), anti-ENA profiles negativity, C3 0.92 g/L, C4 0.22 g/L, anti-cardiolipin IgG 0.95 U/mL. ECG showed sinus tachycardia with ST-T changes in the inferior and lateral walls. Ultrasonic cardiogram (UCG) revealed intimal tear echoes in the aortic sinus, ascending aorta, and left common carotid artery, along with partial prolapse of the right coronary cusp into the left ventricular outflow tract, causing inadequate valve closure.

This was our center's second case of SLE complicated with type A aortic dissection (TAAD), similar to the first [1]: both middle-aged women with over 10 years of SLE and long-term steroid use, along with multiple comorbidities. Based on prior experience, we promptly initiated supportive care and prepared for surgery in collaboration with a multidisciplinary team, including cardiovascular surgeons, rheumatologists, perfusionists, anesthesiologists, and intensivists.

6 h after admission, the patient underwent the Sun's procedure with total arch replacement and a 26 mm elephant trunk stent implantation with general anesthesia and cardiopulmonary bypass (CPB) under moderate hypothermic circulatory arrest combined with bilateral cerebral perfusion. Intraoperative exploration revealed an ascending aortic dissection (AD) with extensive intimal detachment, tears near the coronary artery openings, and poor aortic valve leaflet coaptation with right coronary cusp prolapse. Thus, the Bentall procedure was performed to replace the involved aortic root and valve.

Intraoperative transfusions included 4 units of red blood cells, 400 mL of plasma, and 16 units of cryoprecipitate. The

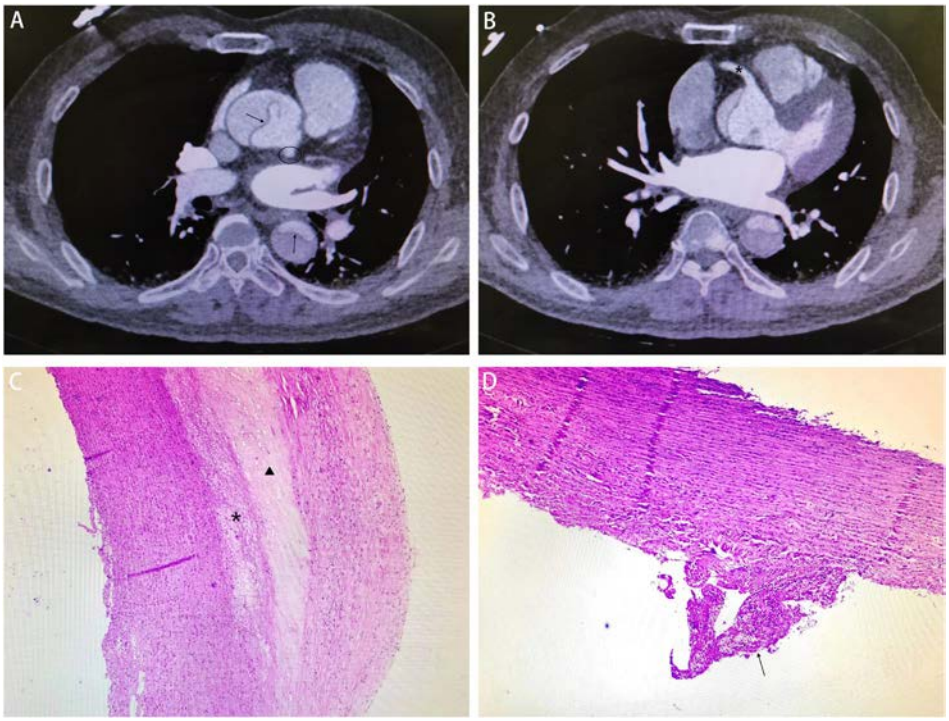

FIGURE 1 | (A) The Aortic CTA. The black arrow shows the intima flap of the ascending and descending aorta and the black circle shows the left main coronary artery supplied by the true lumen. (B) The Aortic CTA. The black asterisk shows the right coronary artery supplied by the true lumen. (C) Aortic pathological examination. The black asterisk shows the foam cells and the black triangle shows the dissection. (D) Aortic pathological examination. The black arrow shows the thrombus.

operation lasted 6 h 45 min, with CPB for 3 h 54 min, aortic cross-clamping for 2 h 19 min, and circulation arrest for 20 m. The CPB time was approximately 1 h longer than in the previous case, while the circulation arrest time was more than halved.

Based on the previous case's treatment experience, we administered 20 mg of hydrocortisone intraoperatively, followed by 40 mg of methylprednisolone daily for 5 days, then resumed the routine dose of 20 mg of prednisone. We minimized synthetic colloids and used human albumin when possible. In the cardiac intensive care unit (ICU), we conducted daily blood sampling to monitor various indicators. The peak postoperative liver and kidney function values were ALT 348 IU/L, AST 462 IU/L, BUN 41.7 mmol/L, and Cr 235 μmol/L. Peak inflammatory markers included hs-CRP 182.42 mg/L, PCT 35.9 ng/mL, and IL-6 > 1000 pg/mL. Most indicators peaked between the 2nd and 4th postoperative days before gradually returning to baseline. We actively administered hepatoprotective and nephroprotective drugs, such as glutathione, ulinastatin, magnesium isoglycyrrhizinate, and niaoduqing granules. Along with antibiotics for infection prophylaxis, we added 20 g of immunoglobulin for three consecutive days to enhance immunity.

Pathology (Figure 1C,D) of the aortic wall revealed fibrous tissue proliferation with myxoid degeneration, accompanied by thrombus formation. Atherosclerotic changes were present in the local arterial wall. The patient was offered 2 days of mechanical ventilation, 4 days of drainage, 5 days in ICU, and a total hospital stay of 12 days. The patient was stable at discharge, ambulated early, and was similar to the previous case.

We recommend the patient control her blood pressure actively after discharge and follow up at the cardiac surgery clinic with a frequency of 3, 6, and 12 months after surgery, then annually. She should also visit the rheumatology clinic every 3 months for monitoring and timely adjustment of treatment plans. The specific outcome measures include the patient's quality of life, medication adherence, and risk of recurrence, among others. The first patient with SLE and TAAD, who has been followed for 2 years, is now stable, with no restrictions on daily activities and no new aortic disease progression. We will continue long-term follow up for these two patients.

1 | Discussion

Existing studies suggest that SLE complicated by AD arises from multiple factors, including atherosclerosis, hypertension, and corticosteroid use. Atherosclerosis, linked to AD, causes arterial degeneration and increases tear risk under blood flow. SLE raises early atherosclerosis risk independently [2]. Hypertension, a key risk factor for AD, causes pressure-related aortic damage and reduction in vascular wall compliance, leading to intimal tears and dissection [3, 4]. Corticosteroids, widely used in SLE, may indirectly promote aortic lesions by accelerating atherosclerosis and hypertension [5, 6]. Additionally, vasculitis and immune complex-mediated endothelial injury may also be one of the pathogenic mechanisms [7].

Literature review showed that most SLE-related aortic disease patients undergo surgery (Table 1), including a previous case at our center [1], with surgery generally having lower mortality

TABLE 1 | 31 cases of SLE-related aortic diseases in PubMed from 2004 to 2023.

Age/sex	Duration of SLE (year)	Steroid (year)	Hypertension	Aortic diseases	Treatment methods	Pathology	Outcomes
47/F [1]	12	Yes (Duration unspecified)	Yes	TAAD	Surgery	Aortitis	Alive
49/F [8]	7	Yes (Duration unspecified)	No	Ascending AA	Medication	—	Died
55/F [9]	34	34	Yes	TAAD	Surgery	Cystic degeneration, atherosclerosis	Alive
69/F [10]	34	1	Yes	TAAD	Surgery	—	Alive
39/M [11]	2	Yes (Duration unspecified)	No	TAAD	Surgery	—	Died
46/F [12]	16	5	Yes	TBAD	Medication	—	Alive
47/F [13]	17	Yes (Duration unspecified)	Yes	Abdominal AA	Surgery	Atherosclerosis	Alive
41/F [14]	Not mentioned	Not mentioned	No	Abdominal AA	Surgery	—	Died
47/F [14]	Not mentioned	Not mentioned	Yes	Abdominal AA	Medication	—	Died
40/F [15]	16	Yes (Duration unspecified)	Yes	Abdominal AA	Surgery	—	Alive
49/F [16]	22	22	Not mentioned	Abdominal AA	Surgery	—	Died
63/M [17]	2	No	No	Ascending AA	Surgery	Cystic degeneration	Alive
62/F [18]	23	23	Not mentioned	TAAD	Surgery	—	Alive
50/M [19]	Not mentioned	Yes (Duration unspecified)	Not mentioned	TAAD	Surgery	—	Alive
59/M [20]	9	8	No	Thoracoabdominal AA	Surgery	Aortitis	Alive
47/F [21]	Not mentioned	Not mentioned	Not mentioned	Ascending AA	Surgery	—	Alive
40/F [22]	5	Yes (Duration unspecified)	No	Thoracic AA	Surgery	—	Alive
9/M [23]	2	2	Yes	Ascending AA	Surgery	Cystic degeneration	Alive
49/F [24]	27	10	Yes	Thoracoabdominal AA	Surgery	—	Alive
17/F [25]	8	8	Yes	TBAD	Surgery	—	Alive

(Continues)

TABLE 1 | (Continued)

Age/sex	Duration of SLE (year)	Steroid (year)	Hypertension	Aortic diseases	Treatment methods	Pathology	Outcomes
17/M [3]	7	7	Yes	TBAD	Medication	—	Died
25/F [26]	19	19	Not mentioned	Thoracic AA	Surgery	—	Died
35/F [27]	23	23	Not mentioned	Descending AA	Surgery	—	Alive
37/M [28]	13	13	No	Ascending AA	Surgery	Cystic medial necrosis	Alive
31/M [29]	Not mentioned	Yes (Duration unspecified)	Not mentioned	TAAD	Surgery	Myxoid degeneration	Alive
23/F [30]	Not mentioned	No	Not mentioned	Ascending AA	Surgery	Aortitis	Alive
29/F [31]	Not mentioned	Not mentioned	Yes	Thoracoabdominal AA	Surgery	—	Died
61/F [32]	22	22	No	Thoracoabdominal AA	Medication	Atherosclerosis, cystic medial necrosis	Died
42/F [33]	Not mentioned	Yes (Duration unspecified)	No	TAAD	Medication	—	Died
43/M [34]	2	No	Not mentioned	TAAD	Surgery	—	Alive
28/F [35]	14	Not mentioned	Yes	Thoracoabdominal AA	Not mentioned	—	Not mentioned

Abbreviations: AA, aortic aneurysm; F, female; M, male; TAAD, type A aortic dissection; TBAD, type B aortic dissection.

than conservative treatment. However, some patients may not qualify for surgery and must rely on conservative treatment, limiting the clinical insights provided by existing case reports.

Close collaboration and accurate judgment among the medical team are essential for such patients. For example, ensuring brain protection during deep hypothermic circulatory arrest was critical. Despite the lack of a cerebral Magnetic Resonance Angiography (MRA) report, perfusionists quickly identified poor patency of the Circle of Willis during unilateral cerebral perfusion, leading to an immediate switch to bilateral perfusion. Recently, near-infrared spectroscopy (NIRS) has been widely used to monitor regional cerebral oxygen saturation (rSO_2), reflecting the local oxygen supply–demand balance [36, 37]. The lack of this device in these cases highlights a potential area for improvement.

The surgical approaches for the two cases differed slightly. In the previous case, the dissection tear was about 2 cm above the sinotubular junction, extending to the area above the right coronary sinus, with well-closing aortic valve leaflets and a non-enlarged annulus. Thus, we transected the ascending aorta at the sinotubular junction and reconstructed the proximal aorta using the "sandwich technique", preserving the native valve. In the present case, the dissection involved the aortic root and valve, requiring a Bentall procedure.

In usual TAAD cases, continuous suture for the distal end of the main lumen of the artificial vessel was used [38]. However, for these two cases of SLE-TAAD in our center, we opted for the interrupted suture with pledgets technique due to their unhealthy aortic wall tissue. This approach minimized the cutting effect on the vessel wall and reduced the risk of postoperative re-tearing.

Postoperatively, we closely monitored the patient's vital signs, provided sedation and analgesia, and actively managed blood pressure to prevent recurrence of aortic events. We opted for human albumin over synthetic colloids to increase colloid osmotic pressure, ensuring adequate cardiac output and tissue perfusion with minimal impact on renal and coagulation function. SLE history and prolonged CPB can both impair kidney function, making it crucial to dynamically monitor renal function indicators and use renal protective medications.

The patient had suffered from SLE since a young age, severely impacting her physical and mental health, along with a diagnosis of depression. This recent admission due to TAAD significantly affected her again. The success of the surgery does not mark the end of treatment; in chronic disease management, we must focus on humanistic care and provide psychological and spiritual support to the patient.

Author Contributions

Kaiyue Sun and Ruyuan Wei conceptualized and drafted the manuscript. Fushun Lin and Dexin Zhang contributed to data collection and image description. Kai Liu reviewed and edited the manuscript. All authors contributed to the text and content of the manuscript and approve of the content of the manuscript.

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Ethics Statement

This case report abided by the Declaration of Helsinki and was exempted by our local institutional ethics committee. Written consent was obtained from the patient for publication of this case report and accompanying image.

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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Ruyuan Wei
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Kai Liu

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LETTER TO THE EDITOR

VEXAS Syndrome: Phenotype Alteration in the Long-Term Disease Duration

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Dear editor,
Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a genetic disorder caused by somatic mutations of ubiquitin-activating enzyme 1 (UBA1). Most cases occur in men in their later life. VEXAS syndrome presents with both autoinflammatory features and hematologic abnormalities [1].

We describe a case of VEXAS syndrome with progression from Sweet's syndrome to a cytopenic phenotype. A 71-year-old man first presented in 2015 with recurrent fever and red maculopapular eruptions on his limbs, trunk and head (Figure 1A). A skin biopsy revealed neutrophilic infiltration around dermal blood vessels (Figure 1B), consistent with Sweet's syndrome. Skin lesions were characterized by alternating periods of flares and remissions. Glucocorticoids (GCs) were effective for rash and fever control, but responses were dose-dependent (requiring methylprednisolone > 8 mg/day).

During the progression of the disease, anemia, thrombocytopenia, and pneumonia developed in August 2022. Complete blood count showed severe anemia (hemoglobin, 27 g/L), normal white blood cell count, and thrombocytopenia (platelets, 25×10^9/L). Laboratory results showed a normal mean corpuscular volume (MCV) and an unremarkable peripheral blood smear without evidence of dyspoiesis or abnormal cellular morphology. Serological tests were negative for anti-nuclear antibodies (ANA), antibodies to extractable nuclear antigens (anti-ENA), anti-neutrophil cytoplasmic antibodies (ANCA), and anti-phospholipid antibodies. Bone marrow biopsy demonstrated active hematopoietic hyperplasia. He was initially diagnosed as Sweet's syndrome and immune-mediated cytopenias and treated with GCs, tacrolimus (TAC), andriol, cyclophosphamide (CTX), and blood transfusions. Due to repeated pulmonary bacterial infection, he was also treated with multiple antibiotics. However, anemia and thrombocytopenia did not improve.

Given the treatment refractoriness, we reviewed the medical history and found a possibility of VEXAS syndrome in this case. Bone marrow aspirates were examined for the presence of vacuoles. Bone marrow biopsy showed vacuoles in myeloid precursors (Figure 1C). Genetic testing identified a UBA1 mutation (c.122T>C, p.Met41Thr; Figure 1D), confirming the diagnosis of VEXAS syndrome. Following diagnosis, a janus kinase (JAK)1/2 inhibitor was initiated in September 2023, but due to the high cost of ruxolitinib, baricitinib (2 mg/day)—a JAK1/2 inhibitor with a similar mechanism—was substituted. After 2 weeks of administration, the frequency of blood transfusions decreased from weekly to biweekly. Figure 2 summarizes laboratory results and treatment response. Despite improvements in hematological parameters, the patient had recurrent fever and cough and tested positive for H1N1 influenza by polymerase chain reaction (PCR) from a nasopharyngeal swab. On October 31, 2023, he developed viral pneumonia and septic shock and died in hospital.

This case highlights the importance of the early detection of VEXAS syndrome. Our patient initially presented with recurrent fevers and cutaneous inflammation. As the disease progressed, pulmonary infiltrates, and treatment-refractory hematologic abnormalities appeared, prompting consideration of VEXAS syndrome. Our report demonstrates that autoinflammatory symptoms appeared much earlier than hematologic abnormalities. Therefore, in elderly males with adult-onset autoinflammation, VEXAS syndrome should be considered to shorten the time of diagnosis.

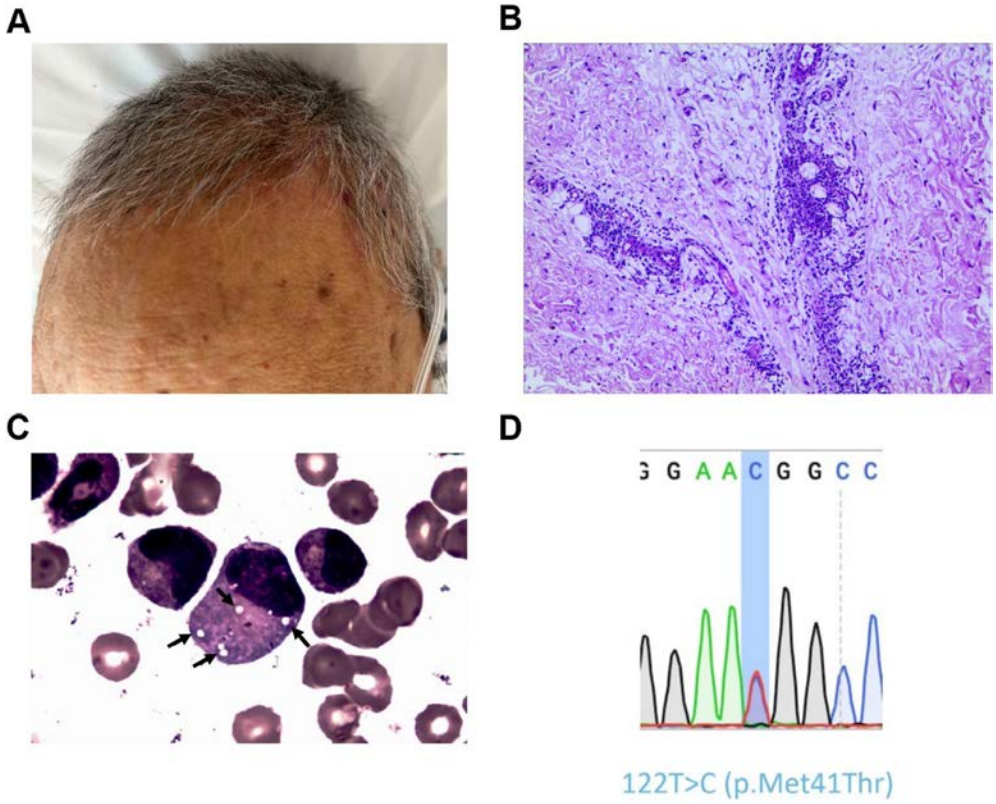

FIGURE 1 | (A) Erythematous maculopapular rash on the patient's forehead. (B) Skin biopsy demonstrated neutrophilic infiltrates (hematoxylin–eosin stain; original magnification ×100). (C) Bone marrow aspirate showed characteristic vacuolization (black arrows) in myeloid precursor cells (Wright-Giemsa stain). (D) Sequencing of peripheral blood leukocytes showed a somatic UBA1 variant (c.122T>C, p.Met41Thr; blue box highlights the variant locus).

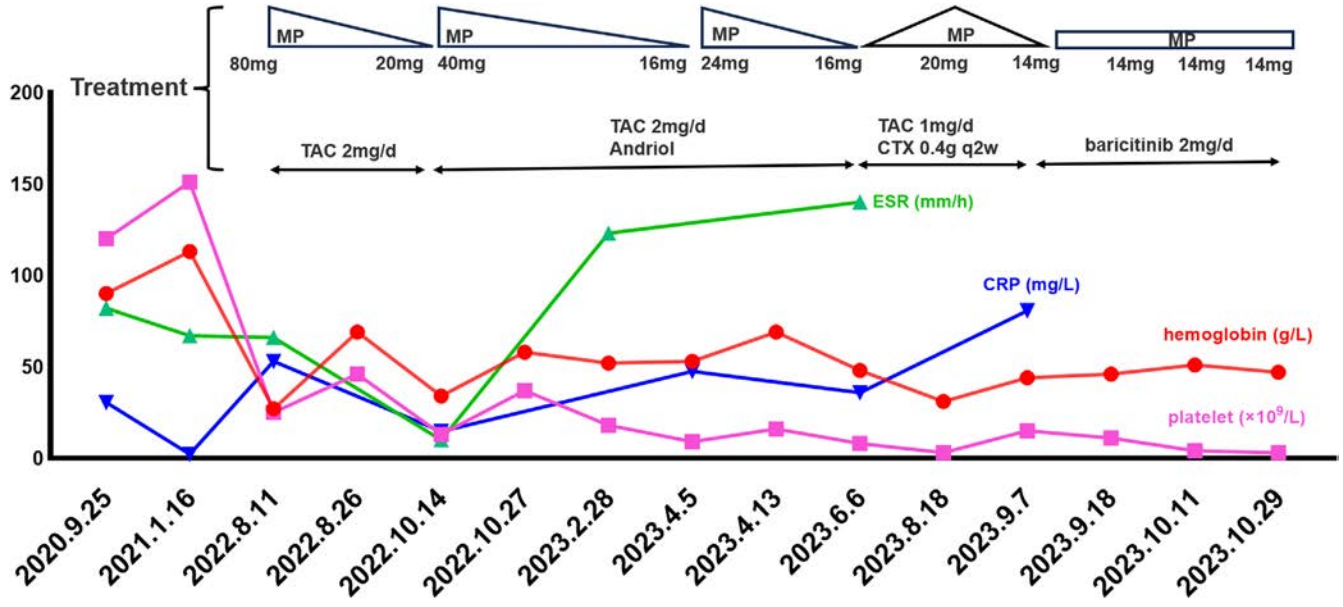

FIGURE 2 | Laboratory results and treatment response from 2020 to 2023. Hematologic trends: Hemoglobin (g/L, red line), platelets ($\times 10^9$/L, pink line). Inflammatory markers: CRP (mg/L, blue line), ESR (mm/h, green line). Treatment timeline: Glucocorticoid (MP, mg/day), TAC, CTX, and JAK1/2 inhibitor periods. CRP, C-reactive protein; CTX, cyclophosphamide; ESR, erythrocyte sedimentation rate; MP, methylprednisolone; TAC, tacrolimus.

The treatment of VEXAS syndrome can also be challenging. Currently, the only potentially curative option is hematopoietic stem cell transplantation (HSCT) [2]. GCs and synthetic immunosuppressants may help control clinical manifestations. Given the inflammatory pathogenesis, JAK inhibitors, IL-6 inhibitors, and anti-IL1R antagonists are the promising therapeutic

candidates for VEXAS syndrome [3]. In this case, a JAK1/2 inhibitor appeared to slow the rate of hemoglobin decline. However, after prolonged disease progression, the patient ultimately succumbed to a viral infection. For patients with a protracted disease course and a compromised immune system, determining the optimal timing for JAK inhibitor use is difficult, and breaking the vicious cycle without immunosuppressive therapy is even more challenging. The paradoxical role of immunosuppression in VEXAS syndrome (controlling inflammation vs. exacerbating infections) provides a real-world example of risk–benefit balancing in immune-dysregulated syndromes. This case also demonstrates that UBA1 testing should be considered even before cytopenias develop in elderly males with refractory inflammation, as early molecular diagnosis may enable timely intervention. In addition, the patient's trajectory—from dermatology (skin lesions) to rheumatology (autoinflammation) to hematology (cytopenias)—models the necessity of cross-specialty collaboration for rare diseases.

Author Contributions

Yue Sun: drafted the original manuscript; **Zhuoya Zhang:** performed visualization; **Hong Wang:** collected clinical data; **Yun Zhu:** supervised the whole research process; **Lingyun Sun:** critically revised the manuscript for intellectual content.

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.

Yue Sun
Zhuoya Zhang
Hong Wang
Yun Zhu
Lingyun Sun

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EDITORIAL

WTAP's Dual Role in Disease: Orchestrating Inflammation in Rheumatoid Arthritis and Challenging Renal Clear Cell Carcinoma Outcomes

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The study by Wang et al. titled "WTAP-Mediated m6A Modification of TRAIL-DR4 Suppresses MH7A Cell Apoptosis" highlights the critical role of Wilms tumor 1-associating protein (WTAP), a regulatory component of the N6-methyladenosine (m6A) methyltransferase complex, forms a functional unit with METTL3 and METTL14 to mediate m6A deposition [1]. WTAP promotes mRNA destabilization of TNF-related apoptosis-inducing ligand death receptor 4 (TRAIL-DR4), thereby inhibiting apoptosis and contributing to synovial hyperplasia and persistent inflammation. These findings are consistent with earlier reports demonstrating WTAP's role in inflammatory regulation through m6A-dependent mechanisms, including modulation of cytokine expression in activated macrophages [2]. Building on these foundations, our current investigation expands the scope of WTAP's functional landscape by exploring its relationship with the tumor immune microenvironment, in parallel with its role in inflammatory signaling. This integrated approach is crucial, given the mechanistic overlaps between chronic inflammation and tumorigenesis [3].

Our study utilized a comprehensive multi-omics approach to elucidate the impact of WTAP expression on genetic landscapes, biological processes, and drug responses in Kidney Renal Clear Cell Carcinoma (KIRC), leveraging data from the TCGA database. We extracted WTAP expression profiles from KIRC patients and visualized the top 20 affected genes using a waterfall plot (Figure 1A). The genetic alterations included oncogenes, tumor suppressor genes, splice site mutations, and frameshift variants, providing a broad genomic context. Comparative analysis of mRNA (Figure 1B) and protein (Figure 1C) expression levels between normal and KIRC tissues revealed a significant reduction in WTAP expression in tumor samples, consistent across TCGA and proteomic datasets.

Further prognostic analysis using Kaplan–Meier curves demonstrated that low WTAP expression in KIRC is associated with poor overall survival and progression-free survival (Figure 1D,E). This suggests that WTAP's function may be highly tissue- and disease-specific, differing from its anti-apoptotic and anti-inflammatory role in RA. To explore the immunological underpinnings, we assessed T-cell interactions across six independent databases, consistently identifying a positive correlation between WTAP expression and T-cell activation (Figure 1F). We extended our analysis to T-cell-related biological processes, evaluating activation, homeostasis, proliferation, and chemotaxis in KIRC patients stratified by WTAP expression levels (Figure 1G). This contrasts with the MH7A cell model, where WTAP-mediated m6A modification of TRAIL-DR4

Chen-Yueh Wen and Po-Hung Chen contributed equally to this study.

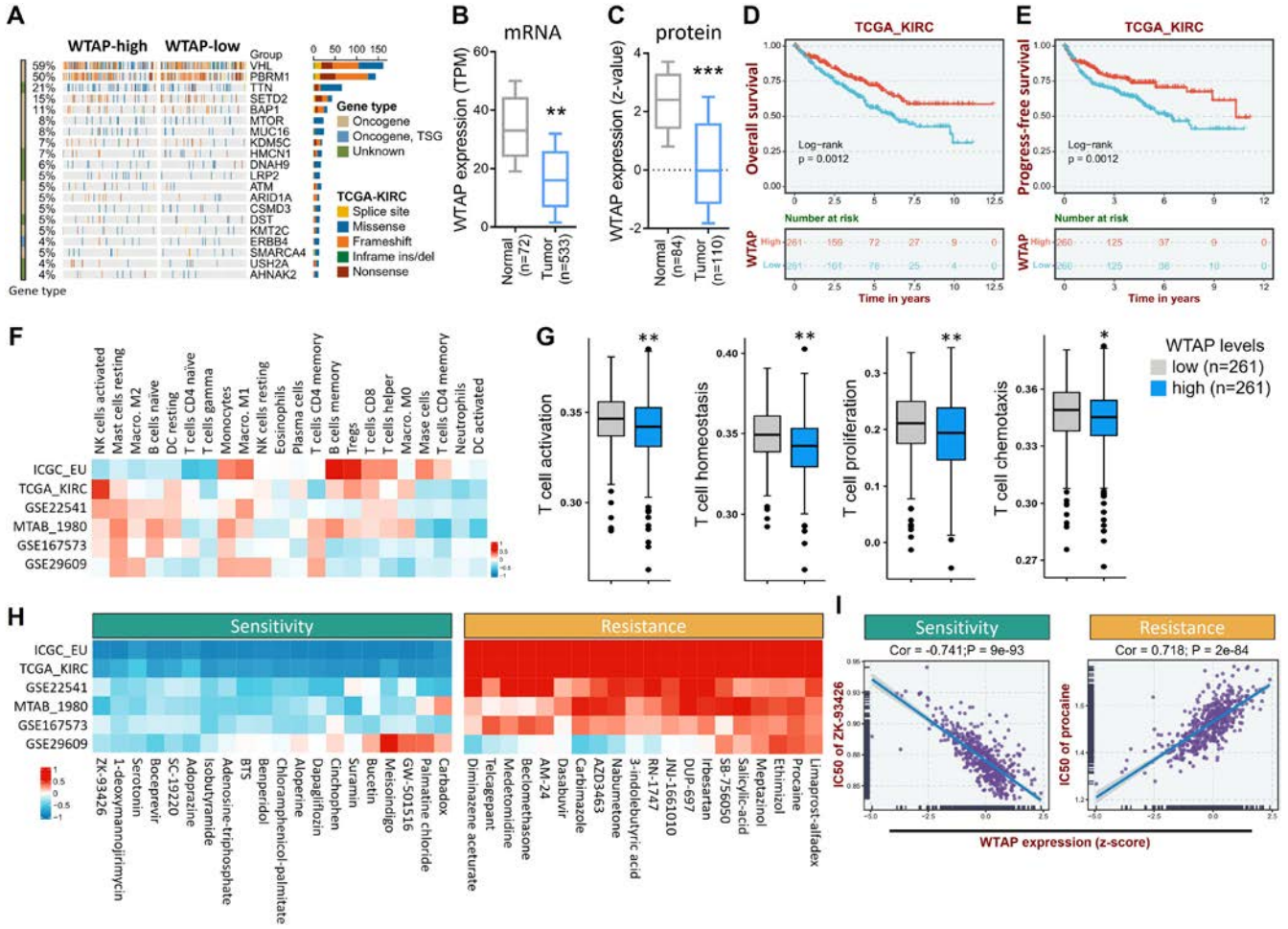

FIGURE 1 | Genetic landscape, expression analysis, prognostic significance, immune interactions, and drug response profiling of WTAP in KIRC. (A) Waterfall plot illustrating WTAP expression data in KIRC patients from TCGA, highlighting the top 20 affected genes and their respective genetic alterations, including oncogenes, tumor suppressor genes, splice sites, and frameshift mutations. (B, C) Boxplots comparing WTAP expression at mRNA and protein levels between normal and tumor tissues, based on TCGA transcriptomic data (B) and proteomic datasets (C). (D, E) Kaplan–Meier analysis of overall survival (OS) and progression-free survival (PFS) in KIRC patients stratified by WTAP expression levels. (F) Correlation analysis of WTAP expression and immune cell interactions, validated across six independent databases, with a focus on T cell association. (G) Comparative analysis of T cell activation, homeostasis, proliferation, and chemotaxis between high and low WTAP expression groups. (H) Drug sensitivity analysis using PRISM Pharmacogenomic Database, identifying 20 drugs associated with increased sensitivity and 20 drugs associated with resistance in WTAP-high KIRC tumors. (I) Correlation analysis of WTAP expression and IC50 values of resistant and sensitive drugs in TCGA_KIRC data, including ZK93426 and procaine. *$p < 0.05$; **$p < 0.01$.

inhibits apoptosis and modulates inflammation. Additionally, we interrogated the PRISM Pharmacogenomic Database to assess drug sensitivity and resistance, identifying 20 drugs where high WTAP expression predicted increased sensitivity and 20 where it predicted resistance (Figure 1H). Correlation analyses with IC50 values in the TCGA_KIRC cohort confirmed these trends, with the highly sensitive drug ZK93426 exhibiting negative regulation and procaine showing positive regulation with WTAP levels (Figure 1I). These pharmacogenomic insights suggest that WTAP expression could serve as a biomarker for tailoring therapy in KIRC, contrasting with its therapeutic targeting strategy in the MH7A cell model.

These findings challenge the uniform application of epigenetic targets like WTAP across malignancies. While the WTAP study demonstrates its role in suppressing apoptosis and inflammation in RA via TRAIL-DR4 mRNA destabilization—confirmed by MeRIP-qPCR and actinomycin D assays [1]—the low WTAP levels in KIRC may reflect a loss of regulatory control over apoptosis and inflammatory pathways, contributing to disease progression. This discrepancy may arise from differences in tumor microenvironment, genetic alterations, or the interplay between m6A modification, immune checkpoints, and inflammation beyond TRAIL-DR4, as seen in other cancers where m6A dysregulation influences tumor immunity [2].

This editorial advocates for a context-specific approach to targeting epigenetic regulators in oncology, with a particular emphasis on their inflammatory dimensions. The success of WTAP modulation in RA should not be extrapolated to KIRC without further validation. Future research should leverage multi-omics analyses to dissect the pathways linking WTAP, m6A modification, immune responses, and inflammation in KIRC, potentially identifying compensatory mechanisms or alternative targets.

Integrating these findings with clinical trials could refine therapeutic strategies, ensuring that WTAP agonists or antagonists are tailored to the specific disease context and its inflammatory profile.

In conclusion, the low WTAP expression in KIRC, as revealed by our data, contrasts with its protective role in RA and invites a nuanced exploration of its therapeutic potential, particularly in the context of inflammation and the tumor immune microenvironment. Collaborative efforts to bridge epigenetic, immunological, and inflammatory research will be essential to unlocking precision medicine's full potential across diverse cancer landscapes.

Author Contributions

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

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors do not have permission to share data.

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LETTER TO THE EDITOR

Burden of Infection-Related Hospitalization and the Impact of Multidisciplinary Care in ANCA-Associated Vasculitis: A Retrospective Cohort

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Dear Editor,

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are multisystem autoimmune disorders causing small vessel inflammation [1]. Current management strategies for AAV involve combination immunosuppressive therapies that have increased overall remission rates and survival [2]. Infectious complications contribute to early and long-term mortality due to a high immunosuppression burden [3].

Hospital readmissions are increasingly recognized as a measure to understand health care quality and improve resource allocation [4]. While infections, cardiovascular disease, and pulmonary disease have been reported as leading reasons for hospitalization for AAV patients in the United States [5] and Europe [2], trends in Australia are unknown. Multidisciplinary care in rheumatological diseases is generally recognized as beneficial [6], but with substantial variation in reported cost, health-related quality of life improvements, [7] and efficacy in reducing disease burden [8]. It is not known if this model improves outcomes in people with AAV.

1 | Methods

1.1 | Patient Selection and Study Design

This was a retrospective, single-center, cohort study. All adult (age > 18 years) patients diagnosed with AAV at Monash Health, Australia, between January 1, 2000 and February 28, 2018 were included. Monash Health is the largest public health service in the state of Victoria. An AAV diagnosis was made in the presence of ANCA positivity (on ELISA testing), and symptoms and signs compatible with small vessel vasculitis supported by histopathology or radiology fulfilling American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2022 criteria. EGPA and ANCA-negative patients were not included due to their different phenotype and potential diagnostic uncertainty, respectively.

Hospitalization data within 12 months of AAV diagnosis was extracted. Day admissions, including admissions for dialysis and infusions, were excluded. Death was assessed within the first

12 months and overall. Cause of death categories were infection (bacterial, viral, fungal, protozoal, or unknown), cardiac, vascular, malignancy, kidney failure, other, or unknown. The exposure of interest was vasculitis type (GPA or MPA) defined by the 2012 revised Chapel Hill classification of vasculitides [2].

1.2 | Outcome Measures

The primary outcome was the rate of hospitalization for infection within the first 12 months of AAV diagnosis, comparing rates before and after the establishment of a dedicated vasculitis clinic on March 1, 2014. This multidisciplinary clinic is attended by nephrologists, rheumatologists, and a specialized vasculitis nurse, with support from infectious disease, respiratory, and ear, nose, and throat (ENT) specialists in other clinics. Infection-related hospitalization before and after 2010 was also compared, given changes in immunosuppression practices at this time with the publication of clinical trials demonstrating the non-inferiority of rituximab compared to cyclophosphamide.

Secondary outcomes were survival and non-infection-related causes of hospitalization. These were divided into admissions involving the cardiovascular, renal, neurological, endocrine, respiratory, hematological, gastrointestinal, or rheumatological systems. Admissions related specifically to thrombosis or bleeding, malignancy, treatment complications, and refractory or relapsing disease were also investigated. More than one reason could be listed as a cause of admission.

1.3 | Statistical Methods

Demographic characteristics were compared using the chi-squared test for categorical variables, and Mann–Whitney *U*-test for continuous variables. Hospitalization rate was established by counting the number of hospitalizations as a proportion of the total time at risk. Survival analysis was performed with patients entering the analysis at the date of AAV diagnosis. An alpha of 0.05 was used as a threshold for statistical significance. Statistical analysis was performed using Stata/IC 15.0 and Python packages (scipy and lifelines).

2 | Results

There were 164 patients included, with 53 patients classified as GPA and 111 patients classified as MPA. The average follow-up time was 2556 days (7.0 years).

2.1 | Baseline Characteristics

The overall average age of the cohort was 67.5 years (61.9 years (GPA) vs. 70.1 years (MPA), $p < 0.001$). The mean age at diagnosis was 54.7 years (GPA) versus 63.4 years (MPA) ($p < 0.001$). There was a male predominance, accounting for 53.2% of those with MPA and 67.9% of those with GPA (Table 1).

Renal involvement at diagnosis, need for dialysis, and development of end-stage kidney disease (ESKD) were more common in

TABLE 1 | Demographics and characteristics of included patients.

	MPA $n = 111$	GPA $n = 53$	p
Serology			
MPO-ANCA positive	111 (100)	0 (0)	
PR3-ANCA positive	0 (0)	51 (96.2)	
Dual MPO/PR3-ANCA positive	0 (0)	2 (3.7)	
Age at diagnosis, years (95% CI)	63.4 (60.7–66.1)	54.7 (50.0–59.3)	**< 0.001**
Male	59 (53.1)	36 (67.9)	**< 0.001**
System involvement			
Renal	103 (92.8)	38 (71.7)	**0.001**
Dialysis	48 (43.2)	16 (30.2)	**0.001**
ESKD[a]	37 (33.0)	11 (20.8)	**0.001**
ENT	11 (9.9)	27 (50.9)	**0.001**
Lung	39 (34.8)	33 (62.3)	**0.001**
Eye	2 (1.8)	9 (17.0)	**0.001**
Musculoskeletal	13 (11.6)	13 (24.5)	**0.04**
Neurological	8 (7.1)	5 (9.4)	0.85
Gastrointestinal	6 (5.4)	4 (7.5)	0.25
Skin	11 (9.8)	8 (15.1)	0.05

Note: Values are means (95% confidence interval) or numbers (%). Bolded values indicate statistically significant comparisons.
[a]ESKD defined as requiring dialysis for ≥ 90 days.

those with MPA compared to those with GPA (92.8% vs. 71.7%, 43.2% vs. 30.2%, and 33.0% vs. 20.8% respectively, $p = 0.001$ for all comparisons). As expected, those with GPA were more likely to have ENT, lung, and eye involvement (50.9% vs. 9.9%, 62.3% vs. 34.8%, and 17.0% vs. 7.1% respectively, $p = 0.001$ for all comparisons), as well as arthritis (24.5% vs. 11.6%, $p = 0.04$) (Table 1).

2.2 | Hospitalization Rate

Overall, 64 (39%) patients were admitted to the hospital within the first 12 months of AAV diagnosis. Of these, 22 (13%) were hospitalized for infection (viral, bacterial, or other), accounting for 24 admissions totaling 405.8 hospital days (median length of stay 9.4 days), with a hospitalization rate of 15 per 100 person-years. Hospitalization rate for infection did not change before and after 2010 (9 vs. 13 per 100 person-years, $p = 0.10$). After infection, the hospitalization rate (per 100 person-years) was highest for non-dialysis-related renal (7.7), cardiovascular (7.0), endocrine (6.4), and treatment-related issues (3.8).

2.3 | Vasculitis Clinic Establishment

After establishment of the vasculitis clinic, the hospitalization rate for any cause reduced significantly from 70 to 51 per 100 person-years ($p = 0.02$). The hospitalization rate for infection trended toward but did not achieve significance, reducing from 18 to 8 per 100 person-years ($p = 0.10$).

2.4 | Survival

There were 32 deaths within the first 12 months (24 patients with MPA and 8 patients with GPA), and 46 deaths overall (34 patients with MPA and 12 patients with GPA). There was no survival difference between those with MPA and GPA within the first 12 months (HR 1.22, 95% CI 0.53–2.80, $p = 0.64$) or overall (HR 1.19, 95% CI 0.60–2.35, $p = 0.61$) (Figure 1).

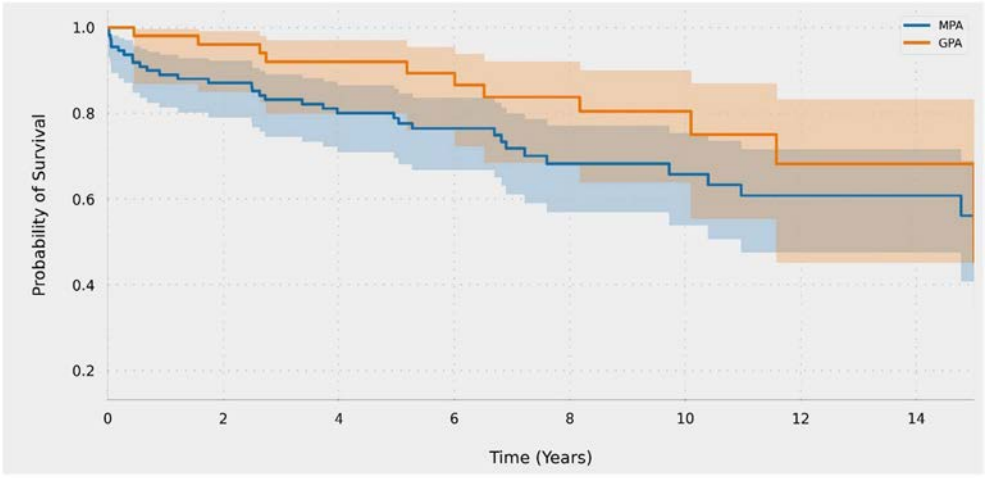
Survival at 1, 2, 5, and 10 years for the overall cohort was 92%, 90%, 83%, and 70%, respectively. Survival at the same intervals for those with MPA was 89%, 87%, 79%, and 66%, and for those with GPA was 98%, 96%, 92%, and 80%. Of those who died, 31 (97%) had renal involvement. For those with MPA, death was most commonly due to infection and malignancy, followed by cardiovascular disease and renal failure. There were fewer deaths in those with GPA in this cohort, with infection and cardiovascular disease being the leading causes.

3 | Discussion

This study found a significant burden of infection-related hospitalization and mortality in patients with AAV despite the routine use of chemoprophylaxis per local protocol, with an association between a reduction in hospitalization rate and the establishment of a specialized vasculitis clinic.

Survival data in the current report are in line with international reports of a 5-year survival of 70%–80% [1]. The worldwide age-standardized mortality rate for AAV has been reported at 0.53 deaths per million inhabitants, with similar death rates in North America and Europe, lower rates in Latin America, and higher rates in Oceania [1, 9]. In Western Australia, patients with AAV or polyarteritis nodosa had reduced survival compared to matched controls (HR 3.5, 95% CI 3.1–4.1), with the greatest excess mortality in the first year after diagnosis, and persistently increased risk of death thereafter [10].

Although cardiovascular disease remains the most common cause of death in people with AAV, the most significant cause of excess mortality is infection [11] despite the changes in treatment protocols in the last decade [12]. Infection rates are highest in the first 6–12 months post diagnosis when the immunosuppressive burden is highest [3]. Standardized mortality ratios for infection were 16.4 (95% CI 8.8–30.6) in MPA and 6.5 (95% CI 1.6–26.3) in GPA in an American cohort [11]. A Scottish cohort study of AAV patients found that at 3.5 years, 74.6% had required an antibiotic



Risk Table

MPA	111	97	89	85	76	73	67	67
GPA	53	51	49	47	44	43	36	36

FIGURE 1 | Survival curve (overall).

prescription and 35.6% had experienced severe infection [13]. This study did not analyze infections by affected system, and only a small proportion of patients required intensive care support, insufficient to gather significant insights. It is possible that the increased use of rituximab and the adoption of lower dose corticosteroid protocols have resulted in the lower rate of infectious complications observed more recently. This study was not able to analyze the mean initial corticosteroid dose or duration of corticosteroid wean and did not compare outcomes in people who received cyclophosphamide or rituximab as induction therapy. However, infection-related hospitalization rates did not change appreciably pre- and post- 2010 (approximating the time of practice change away from the use of cyclophosphamide) in this cohort, and infections have remained a significant concern in recent clinical trials [14].

The establishment of a specialized vasculitis clinic may be an effective framework to reduce the burden of infection and resultant hospitalizations in this patient population. Multidisciplinary care models reduce barriers to evidence-based care, an essential component of improving outcomes in chronic diseases [15]. These findings should be interpreted within the inherent limitations of an observational study.

Infection-related hospitalizations remain a significant burden for patients with AAV, including in an Australian population. The establishment of a multidisciplinary vasculitis clinic was associated with reduced hospitalization rates for any cause, with a trend toward reduced hospitalization rates for infection-related hospitalizations in this cohort, supporting this care model for improving outcomes for patients with this chronic, relapsing disease.

Author Contributions

J.S. was involved in the design of the study. K.P. and E.Y. were involved in the data analysis. All authors participated in drafting the paper and revising it critically. All authors have read and agreed to the published version of the manuscript.

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We thank our patients who attend the Monash Health vasculitis clinic.

Ethics Statement

This study was approved by the Monash Health Human Research Ethics Committee (RES-21-0000-679A).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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EDITORIAL

A Bite of B Cells: The Potential Role of Bispecific T Cell Engager Therapy (BiTE) in Autoimmune Diseases

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Presently, systemic autoimmune rheumatic diseases are deemed to be incurable chronic conditions. In the current era of biologics and small molecule inhibitors between 5% and 20% of rheumatoid arthritis (RA) diagnoses are categorized as "difficult-to-treat RA" [1]. Despite the long-term survival rate of patients with systemic lupus erythematosus (SLE) improving in recent decades, for those with late-onset SLE, infections remain the primary cause of reduced long-term survival. Additionally, the presence of multiple comorbidities significantly limits the choice of medication, thus underscoring an urgent need for innovative therapeutic approaches [2].

Chimeric antigen receptor (CAR) T cell therapy may represent a revolutionary breakthrough in the treatment of autoimmune rheumatic diseases, which involves using retroviruses to insert genetically engineered genes into T cells, transforming them to express receptors that bind to specific cells and target them for destruction. The most notable success of CAR T cell therapy has been observed in lymphoma treatment, where CD19-targeted CAR T cells achieved complete remission in 40%–54% of cases involving relapsed or refractory aggressive B-cell lymphomas [3]. A research team from the University of Erlangen-Nuremberg in Germany was the first to explore the potential application of CAR T cell therapy to systemic autoimmune rheumatic diseases, such as SLE, with the hope of even achieving a cure in cases where traditional treatments have failed. According to a case series published by Fabian Müller and colleagues, CD19-targeted CAR T cell therapy has the potential to maintain disease remission in SLE for more than 2 years [4]. Successful cases have also been reported in idiopathic inflammatory myopathies (IIMs) and systemic sclerosis (SSc), as well as pediatric SLE [5, 6]. Recently, Wang et al. [7] applied allogeneic CAR T cells for the treatment of three patients with severe autoimmune diseases and published the initial positive outcomes. The success of allogeneic CAR T cells may significantly reduce the cost and time required for CAR T cell therapy.

Before undergoing CAR T cell therapy, patients must receive chemotherapy to eliminate existing T cells in the body to prevent them from attacking the CAR T cells, which can affect the therapy's effectiveness. Nonetheless, this therapeutic modality may provoke cytokine-release syndrome and immune effector cell-associated neurotoxicity syndrome due to CAR T cell hyperactivation. Additionally, the depletion of most B cells targeted by CD19-directed CAR T cells may lead to insufficient antibody production and increased susceptibility to recurrent

Jie-Fu Zheng and Shih-Wen Kao have contributed equally.

infections, although this issue can be mitigated with immunoglobulin supplementation. For individuals with SLE, particularly those with severe disease unresponsive to standard therapies, the potential advantages of CD19-targeted CAR T cell therapy may outweigh the associated risks, warranting further exploration of its long-term safety and effectiveness. In certain systemic autoimmune rheumatic diseases, including RA, the potential risks inherent to CD19-directed CAR T cell therapy may be deemed excessive. Additionally, concerns regarding the potential carcinogenicity associated with CAR T cell therapy have recently emerged [8].

The remarkable efficacy of CAR T cell therapy in patients with SLE suggests that B-cell depletion therapy may hold promise for a significant breakthrough in the treatment of current autoimmune diseases. B cells play a crucial role in the pathogenesis of autoimmune rheumatic diseases, such as SLE, where autoantibodies produced by B cells, including anti-double-stranded DNA antibodies and extractable nuclear antigen antibodies, are associated with disease manifestations. In RA, rheumatoid factors and anti-citrullinated protein antibodies are not only crucial for diagnosis but also correlate with the prognosis of arthritis. Rituximab, an anti-CD20 chimeric monoclonal antibody initially used for treating B-cell lymphoma, represents a classical form of B-cell depletion therapy. By binding to the CD20 antigen on B cells, rituximab can eliminate CD20+ B cells through complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cellular cytotoxicity [9]. Currently, the role of B-cell depletion therapy has been established in the treatment of severe autoimmune rheumatic diseases or those with poor response to other treatments, including RA, anti-neutrophil cytoplasmic antibody-associated vasculitis, and SLE [10–12]. However, the emerging association between belimumab and increased risks of psychiatric adverse events in adult patients with SLE may limit the scope of clinical application of existing treatment modalities [13].

Beyond its B-cell depletion function, rituximab also affects T cells [14]. In most patients with RA treated with rituximab, a significant reduction in T cell concentrations, especially CD4+ T cells, has been observed, correlating with a better treatment response [15, 16]. However, the inability of rituximab to target B cells lacking the CD20 antigen due to late differentiation limits its efficacy. Comparatively, CD19 is more ubiquitously expressed on B cells, and CD19-targeted CAR T cell therapy has shown potential in achieving long-term remission or even cure in autoimmune rheumatic diseases like SLE, making CD19-directed B-cell depletion therapy a promising candidate for future treatments [17]. Blinatumomab, engineered through the Bispecific T-cell engager (BiTE) platform and comprising dual specificity for T cell CD3ε and B cell CD19, exemplifies an innovative approach by facilitating direct cytotoxic T cell engagement with CD19+ B cells without necessitating genetic modification of the patient's T cells or lymphodepleting chemotherapy. Its pharmacological effect duration can be controlled by its half-life, offering the possibility of repeated treatments. Notably, blinatumomab's therapeutic profile, characterized by a reduced risk of severe hematologic toxicity, cytokine-release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) compared to CD19-targeted CAR T cell therapy, underscores its therapeutic promise [18].

A recent clinical trial led by Laura Bucci and her team evaluated blinatumomab's efficacy in a cohort of six individuals with refractory RA, demonstrating significant disease activity reduction and improved clinical outcomes with minimal adverse effects. Blinatumomab was administered intravenously at a regimen of 9 μg/day continuously over a span of 5 days, succeeded by a secondary course after an intermission of 1 week. The monitoring of disease activity was meticulously conducted utilizing the Disease Activity Score in 28 joints (DAS28), in conjunction with ultrasound and fibroblast activation protein inhibitor-based positron emission tomography-computed tomography (FAPI-PET-CT) imaging to evaluate synovitis. The results indicated a noteworthy decline in DAS28 scores from a baseline average of 4.72 to 2.28 post-treatment, signifying a marked reduction in disease activity. Both ultrasound and FAPI-PET-CT imaging corroborated the observed decreases in synovitis. Furthermore, the study documented a significant reduction in the levels of autoantibodies, inclusive of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, indicative of the targeting of antibody-secreting cells, specifically CD19+ plasmablasts, by blinatumomab. Successful attenuation of B cell populations was observed within synovial tissues, which is not attainable with conventional anti-CD20 monoclonal antibody-mediated B cell ablation strategies. The administration of blinatumomab was well-tolerated among the patients, with the occurrence of only mild adverse effects such as mild elevation of body temperature and an elevation in C-reactive protein levels during the initial infusion phase [19]. This trial, along with the inaugural administration of blinatumomab in SSc, as reported by Marion Subklewe and colleagues, highlights the therapeutic potential of BiTE therapy in autoimmune diseases [20] (Table 1).

BiTE therapy offers several advantages, including specific targeting, potential for rapid therapeutic onset, and the ability to overcome mechanisms of resistance inherent to traditional treatments. Furthermore, by mitigating the potential side effects associated with high-dose steroids and chemotherapy, including those affecting growth and reproduction, blinatumomab may offer an advantage in children and young adults. Moreover, the successful treatment experiences of blinatumomab in pediatric leukemia further support the exploration of its role in the treatment of pediatric autoimmune diseases. However, challenges in determining the optimal dosage, managing potential side effects, and ensuring long-term safety remain. Furthermore, the significant cost associated with BiTE therapy presents a barrier to its widespread adoption. Future research endeavors should focus on comprehensive clinical trials to establish the efficacy and safety profile of BiTE therapies across a spectrum of autoimmune diseases. Investigations into combination therapies to enhance treatment efficacy and the identification of biomarkers for patient stratification are crucial in determining those most likely to benefit from BiTE therapy. Additionally, ongoing surveillance to monitor adverse effects and confirm sustained therapeutic benefits is essential. The ongoing quest to revolutionize the treatment paradigm for autoimmune rheumatic diseases, aiming for long-term remission with therapies like blinatumomab, continues to inspire hope and innovation in the medical community.

TABLE 1 | Representative case series of CD19-directed CAR T cell and BiTE therapies in treating systemic autoimmune diseases.

Author, year	Autoimmune disease (*n*)	Treatment	Follow-up duration	Treatment efficacy	Major adverse events (*n*)
Muller et al. (2024) [4]	SLE (8), IIMs (3), SSc (4)	Autologus CD19-directed CAR T cell therapy	Median 15 (range 4 to 29) months	All the patients with SLE had DORIS remission All the patients with IIMs had an ACR-EULAR major clinical response All the patients with SSc had a decrease in the score on the EUSTAR activity index	CRS (11), ICANS (1)
Wang et al. (2024) [7]	IMNM (1), SSc (2)	Allogenic CD19-directed CAR T cell therapy	6 months	The patient with IMNM had improvement in TIS The patient with SSc had improvement in ACR-CRISS score	None had CRS or ICANS
He et al. (2025) [6]	Pediatric SLE (2)	Autologus CD19-directed CAR T cell therapy	Patient 1: 5 months Patient 2: 4 months	Patient 1's SLEDAI-2 K score decreased from 12 at baseline to 0 at follow-up Patient 2's SLEDAI-2 K score decreased from 12 at baseline to 4 at follow-up	Patient 1 had ICANS. Patient 2 had CRS.
Bucci et al. (2024) [19]	RA (6)	Blinatumomab	3 months	DAS28-CRP dropped from a mean of 4.72 units (4.108, 5.870) at baseline to 2.28 units (2.075, 2.640) after 3 months	None had CRS or ICANS

Abbreviations: ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology; ACR-CRISS, American College of Rheumatology Composite Response Index in Systemic Sclerosis; CRS, cytokine release syndrome; DAS28-CRP, Disease Activity Score 28 using C reactive protein; DORIS, Definition of Remission in SLE; EUSTAR, European Scleroderma Trials and Research group; ICANS, immune effector cell-associated neurotoxicity syndrome; IIMs, idiopathic inflammatory myopathies; IMNM, immune-mediated necrotizing myopathy; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLEDAI-2 K, Systemic Lupus Erythematosus Disease Activity Index 2000; SSc, systemic sclerosis; TIS, Total Improvement Score.

Author Contributions

J.-F.Z., Y.-H.L., S.-W.K., and J.C.-C.W. contributed significantly to the conception, design, and execution of this article. J.-F.Z. and S.-W.K. led the conceptual framework and coordinated the overall structure of the manuscript. Y.-H.L. conducted an extensive review of the literature and provided critical insights into the roles of B cells in autoimmune diseases. J.C.-C.W. contributed to data analysis, interpretation, and the exploration of modern therapeutic strategies. All authors actively participated in drafting, revising, and approving the final manuscript, ensuring the integrity and accuracy of the content.

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The authors have nothing to report.

Conflicts of Interest

James Cheng-Chung Wei is the editor-in-chief of the International Journal of Rheumatic Diseases, so he should be excluded from the peer-review process and all editorial decisions related to the acceptance of this article. Publication of this article, and peer-review should be handled independently by other editors to minimize bias. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/, reference number 1–20.

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CORRECTION

Correction to "Poster Abstracts Part A. APLAR 26th Asia-Pacific League of Associations for Rheumatology Congress, 21–25 August 2024"

(2024), Poster Abstracts Part A. Int J Rheum Dis, 27(S3): e15345. https://doi.org/10.1111/1756-185X.15345

In the abstract "Bilateral lipoma arborescens: A rare cause of persistent bilateral painful knee swellings in a patient with Ankylosing Spondylitis", the below images should be added. Images were not included in the article, only text caption.

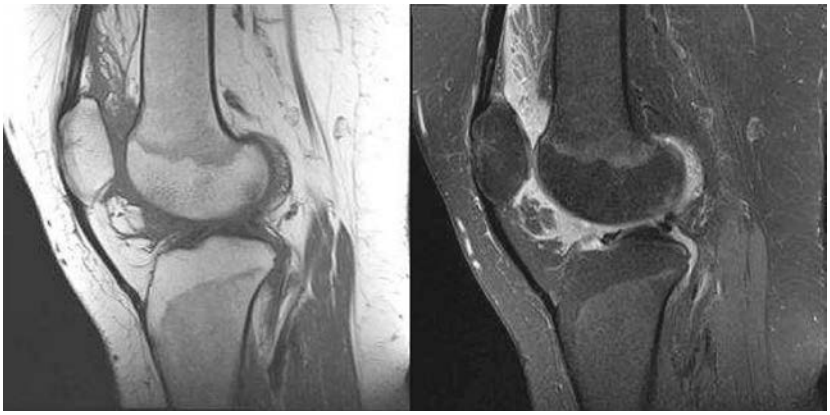

Image 1 Sagittal T1 & STIR sequence: Frond-like synovial based soft tissue at the suprapatellar bursa with high signal on T1 and suppression of signal on STIR sequence, compatible with fat.

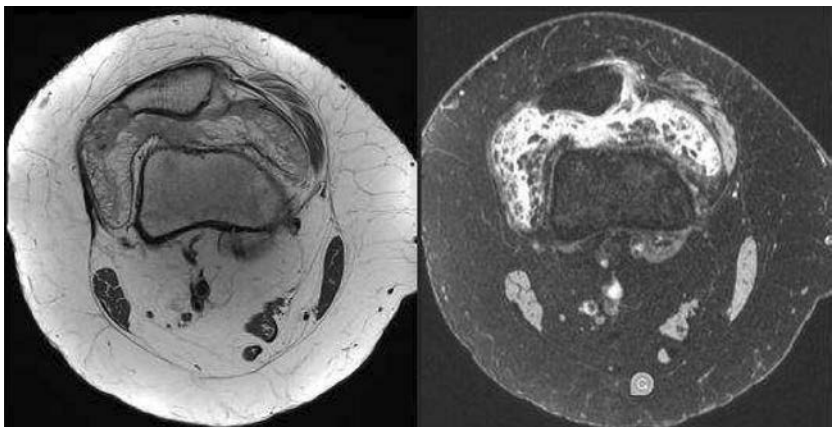

Image 2 Axial T1 & STIR sequence: Frond-like synovial based soft tissue at the suprapatellar bursa with high signal on T1 and suppression of signal on STIR sequence, compatible with fat.

In the abstract “Hyaline vascular Castleman's Disease in a patient with long-standing systemic sclerosis”, the below images should be added. Images were not included in the article, only text caption.

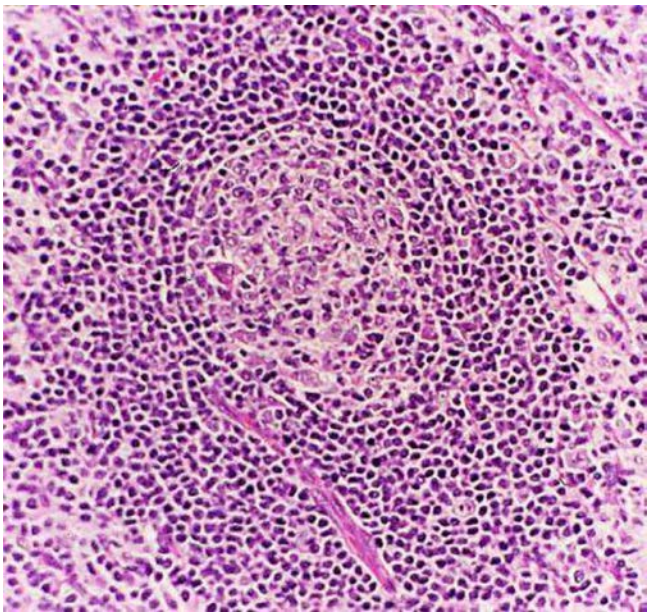

Image 1 Atretic geminal center in HVCD. There is thickened mantle zone with concentric (onion skin) pattern (H&E, 200X).

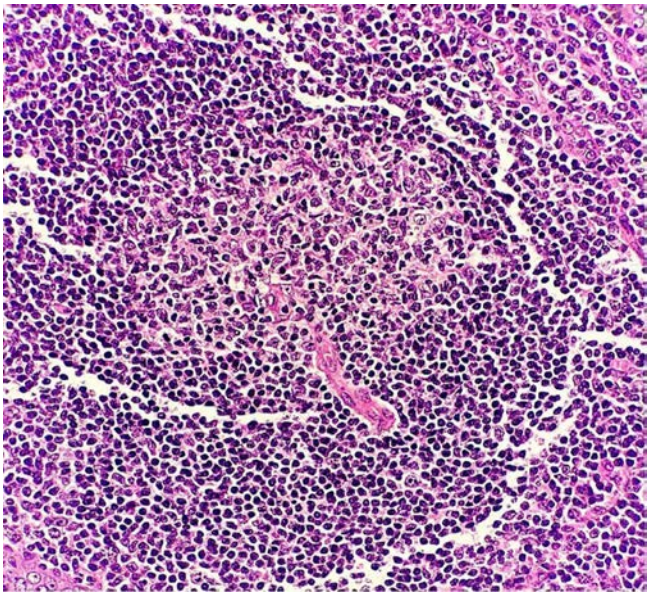

Image 2 Lollipop follicle in HVCD. An atretic germinal center transverse by a penetrating vessel (H & E, 400X).

We apologize for the errors.

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CORRECTION

Correction to "Poster Abstracts Part B. APLAR 26th Asia-Pacific League of Associations for Rheumatology Congress, 21–25 August 2024"

(2024), Poster Abstracts Part B. Int J Rheum Dis, 27(S3): e15346. https://doi.org/10.1111/1756-185X.15346

The following abstract should be added.

Real-world Insights on Tofacitinib in Ankylosing Spondylitis Amongst Indian Rheumatologists: JOINT Survey.

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1 | Background

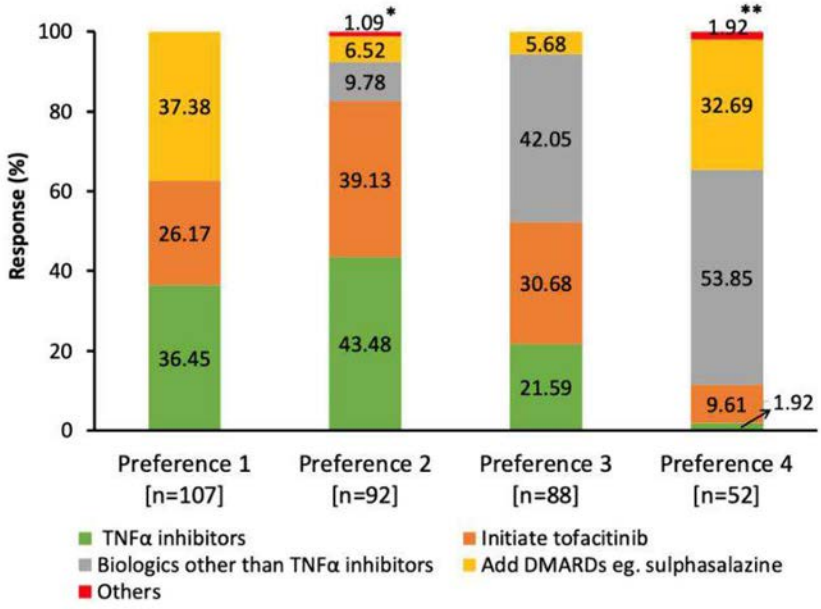
The wider availability of tofacitinib, a Janus kinase inhibitor (JAKi), has created a paradigm shift in the management of rheumatoid arthritis (RA) in resource-limited settings like India. Real-world data on effectiveness and safety of tofacitinib in ankylosing spondylitis (AS) in the Indian scenario is scarce. The present study aimed to evaluate clinical practice and treatment patterns with tofacitinib in RA and AS amongst Indian rheumatologists.

2 | Methods

An online questionnaire-based, nationwide survey was conducted amongst rheumatologists. The internally validated questionnaire included a set of 28 questions to gauge the real-world practices with tofacitinib. This sub-analysis focused on the treatment patterns with tofacitinib in AS.

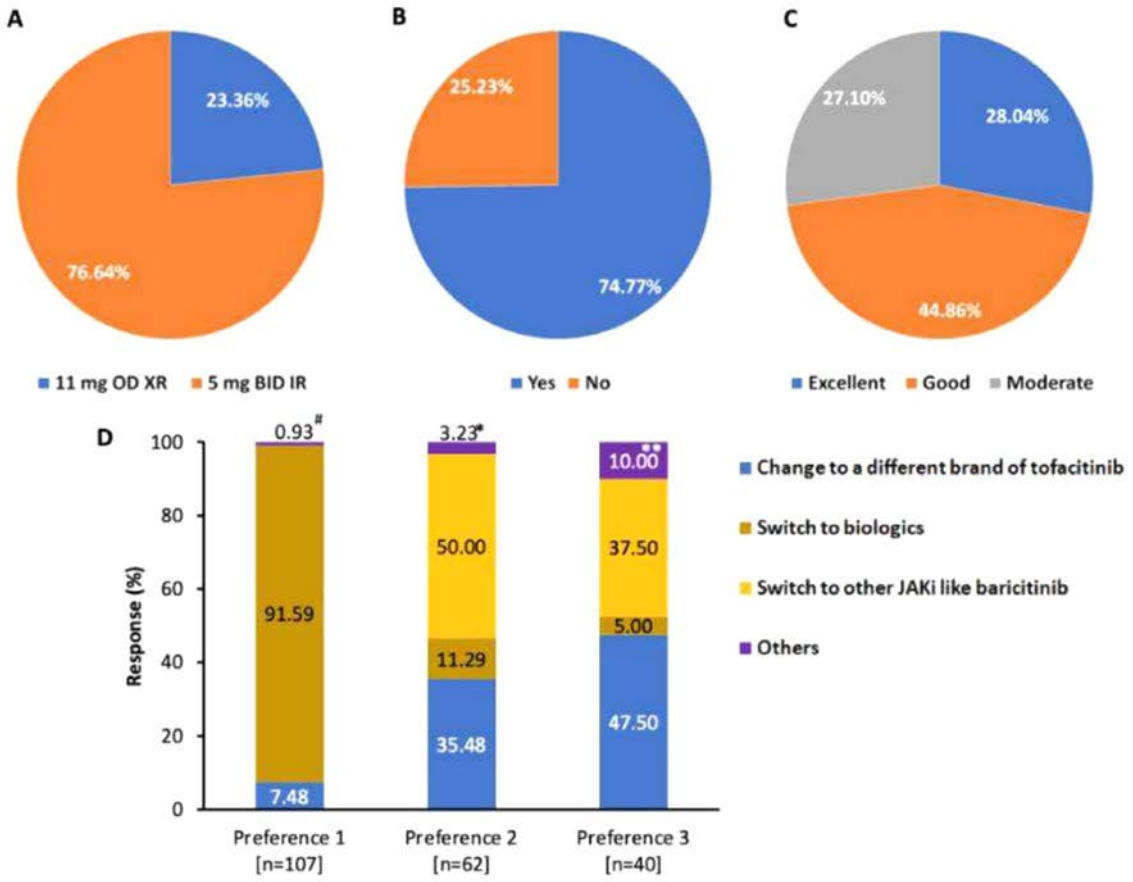
3 | Results

A total of 107 rheumatologists who dealt with~51–100 AS patients/month across academic institutions, corporate hospitals, and private clinics were included. Short courses of non-steroidal anti-inflammatory drugs (NSAIDs) are primarily used for initial treatment



Others: *methotrexate (n=1); **leflunomide (n=1).
Abbreviations: DMARDs, disease-modifying anti-rheumatic drugs; n, number of rheumatologists/HCPs; TNFα, tumor necrosis factor-alpha.

FIGURE 1 |



Others: #sulfasalazine (n=1); *IL-17 inhibitors (secukinumab) (n=2); **combining TNFα inhibitors with methotrexate (n=1); NSAIDs (n=1); combination of tofacitinib with sulfasalazine (n=1); secukunimab (n=1).
Abbreviations: OD: IR, immediate release; JAKi, Janus kinase inhibitor; n, number of rheumatologists/HCPs; TNFα, tumor necrosis factor alpha; XR, extended-release.

FIGURE 2 |

and managing acute flares in AS. Rheumatologists preferred to initiate TNFα inhibitors (36.45%) or sulfasalazine (37.38%) in AS patients post inadequate response to NSAIDs. Interestingly, 39% rheumatologists ranked JAKi viz. tofacitinib as the next preferred option (Figure 1) and 51% have used tofacitinib as monotherapy in AS. Notably, 87% rheumatologists preferred tapering tofacitinib dosage once AS patients achieve low disease activity/remission with down-titration usually to 5 mg OD. Extended-release formulation of tofacitinib (11 mg OD) was preferred by 23% rheumatologists with 75% reporting improved patient compliance (Figure 2A and 2B). More than 70% of rheumatologists rated tofacitinib as good to excellent and 27% rated it as moderate for its efficacy and safety in AS (Figure 2C). Most rheumatologists reported 11%–20% inadequate response and < 5% intolerance to tofacitinib in AS. In such AS patients, rheumatologists (92%) preferred switching to biologics or other JAKi like baricitinib as second choice (50%) or changing to a different brand of tofacitinib as third choice (48%) (Figure 2D). More than 80% rheumatologists recommended complete blood count, liver and kidney function tests, and screening for latent tuberculosis, Hepatitis B and C before initiating tofacitinib. Around 42% rheumatologists have observed major adverse effects, most commonly infections including herpes zoster. Gastrointestinal disturbances and nausea were reported as the most common side effects by 35% rheumatologists followed by upper respiratory tract infections (30%) and lipid alterations (24%).

4 | Conclusion

In AS patients with inadequate response to NSAIDs, TNFα inhibitors/sulfasalazine remained the primary choice of therapy. Insights from this study indicate that Indian rheumatologists are also considering tofacitinib as an option in AS management, favoring its efficacy and safety.

We apologize for this error.