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ORIGINAL ARTICLE

Therapeutic Targeting of Apoptosis-Driven Inflammation in Rheumatoid Arthritis: A Biochemical and Molecular Modeling Approach Using Plant-Derived Compounds

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, joint destruction, and resistance to apoptosis in fibroblast-like synoviocytes and immune cells. This apoptotic imbalance promotes unchecked cell proliferation and invasive pannus formation, contributing to disease progression. Current therapies predominantly target inflammatory pathways, often overlooking the crucial role of restoring apoptosis. Our study explores the potential of plant-derived phytochemicals to modulate both inflammation and apoptosis in RA. Using an integrated computational approach, 12 bioactive compounds were evaluated for their interactions with key apoptosis-associated proteins MMP9, SRC, and EGFR, which are known to influence cell survival, matrix degradation, and invasive behavior in RA. Molecular docking revealed that quercetin, apigenin, resveratrol, and naringenin exhibit strong binding affinities with MMP9, SRC, and EGFR. These interactions were further supported by stable molecular dynamics (MD) simulations, indicating favorable binding stability and structural compatibility. The modulation of these targets suggests a dual therapeutic effect—suppressing inflammation and restoring apoptotic signaling, thus potentially reversing pathological synovial hyperplasia. This study underscores the importance of targeting apoptosis-related proteins in RA and highlights plant-derived compounds as promising candidates for multi-target therapeutic development. By addressing both inflammatory and apoptotic dysregulation, these natural agents may offer a safer and more effective strategy for RA management.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that is marked by sustained inflammation of the synovial tissue, destruction of cartilage, and progressive deformation of the joints [1, 2]. Affecting nearly 1% of the world's population, RA represents a sizable burden not only on patient quality of life but also on public health systems in auxiliary countries [3, 4]. Although the pathogenesis of RA is multifactorial, it primarily arises from an excess of inflammatory pro-immune responses and an incomplete resolution mechanism, including failure of apoptosis in resident joint cells. This combined insufficiency perpetuates inflammation in the tissues and drives abnormal proliferation of FLS, eventually resulting in the development of the pannus, erosion of joints, and loss of function. The underlying inflammation associated with RA is caused by activated T and B lymphocytes, macrophages, and the excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [5, 6]. These cytokines are responsible for activating important downstream

signaling pathways, including but not limited to NF-κB, JAK/STAT, and MAPK. These pathways sustain synovial inflammation, the recruitment of immune cells, and bone loss mediated by osteoclasts. At the same time, RA synovial tissues demonstrate a remarkable degree of apoptotic resistance, particularly in the FLS and infiltrating immune cell population, which drives the abnormal expansion and invasive growth of synovial tissue into the adjacent cartilage and bone [7]. Dysregulated apoptosis is observed in several RA-related genes such as BCL2, CASP3, and AKT1, which highlights the importance of these findings in manipulating apoptosis alongside immunosuppression [8].

Relatively recent therapeutic milestones, including NSAIDs, DMARDs, and biologics that target cytokines or immune-immune checkpoints, still enable a substantial proportion of patients to attain long-term remission [9–11]. Additionally, these RA treatments are accompanied by potent side effects and treatment-induced immunosuppression. There is a critical need for more safe and affordable multi-targeted therapies that can effectively balance inflammatory and apoptotic pathways. Bioactive compounds with polypharmacological effects are abundant in nature, and even more so in the products of medicinal plants [12–14]. Several plant-derived phytochemicals, such as curcumin, resveratrol, quercetin, and withaferin A, exhibit anti-inflammatory and pro-apoptotic activities in numerous models of autoimmune disorders [15, 16]. These compounds possess a favorable safety profile, and their diverse actions make them attractive candidates for rheumatic diseases, such as RA, wherein many cellular and molecular pathways are simultaneously perturbed. However, the detailed knowledge concerning interactions of these phytochemicals with RA-specific molecular targets, particularly those involved in apoptosis-linked inflammatory signaling, is lacking.

With the aim of addressing this issue, network pharmacology, an intersection of systems biology, bioinformatics, and pharmacology, provides a solid foundation to explore the intricate relationships between natural compounds and disease from a holistic perspective [17–20]. Network pharmacology builds these frameworks by combining target prediction, gene-disease association, PPI network mapping, and functional enrichment analysis, thus facilitating the determination of key molecular nodes and pathways that may mediate the therapeutic actions of plant-derived compounds. These predictions, along with those made using molecular docking, can be corroborated by simulating the binding affinity and structural interactions of phytochemicals with their protein targets. Thus, the current study intends to explore the therapeutic effects of certain selected plant-derived phytochemicals with respect to inflammation-related apoptosis in RA. It specifically seeks to elucidate the fundamental molecular mechanisms and biological interactions of the compounds by integrated target prediction, disease gene intersection analysis, GO/KEGG enrichment, construction of the PPI network, and molecular docking to identify core molecular drivers. The effort aims at identifying new candidates from natural sources that may offer multifaceted pharmacological effects as adjunctive treatments for RA, wherein the treatment would eliminate inflammation while restoring balanced apoptosis in the affected tissues.

2 | Materials and Methods

2.1 | Phytochemical Screening

The bioactive compounds from nine medicinal plants, which include *Curcuma longa*, *Emblica officinalis*, *Camellia sinensis, Boswellia serrata, Polygonum cuspidatum, Tinospora cordifolia, Berberis vulgaris, Glycyrrhiza glabra, Piper nigrum, Berberis vulgaris, Scutellaria baicalensis*, and *Curcuma longa*, are collected based on scientific literature with the aid of phytochemical databases, including Indian Medicinal Plants Phytochemistry and Therapeutics (IMPPAT) [21], Traditional Chinese Medicine Systems Pharmacology (TCMSP) [22], and KNApSAcK [23]. Both the common and scientific names of each plant were used as keywords for searching on Google Scholar and PubMed for a broader search. Compounds were selected based on recurrence across phytochemical databases (IMPPAT, TCMSP, KNApSAcK), literature support for anti-inflammatory or apoptotic relevance in autoimmune diseases, and pharmacokinetic properties including compliance with Lipinski's Rule of Five and ADMET predictions.

ADMET screening for absorption, distribution, metabolism, excretion, and toxicity was performed on phytochemicals of interest using the ADMETSAR web tool (http://lmmd.ecust.edu.cn/admetsar2). In phytochemical screening, drug-likeness criteria were applied. The model predicts important pharmacokinetic parameters such as absorption, blood–brain barrier (BBB) permeability, Caco-2 permeability, AMES toxicity, carcinogenicity, and inhibition of P450 isoenzymes (CYP3A4, CYP2D6). Compounds with poor absorption and a high potential for toxicity were deprioritized along with those that had multiple P450 inhibitions. This step increased the likelihood that the selected candidates had favorable physicochemical, safety, and metabolic profiles. Any compounds that did not fulfill these criteria were eliminated to enhance the pharmacokinetic plausibility of the shortlisted candidates.

2.2 | Target Prediction and Disease Association

Predicted bioactive compound targets were obtained using SwissTargetPrediction (http://www.swisstargetprediction.ch) [24] with a specialized focus on *Homo sapiens* for clinical relevance indicating facilitators for diseases. Relatives of the targeted genes were obtained from OMIM (Online Mendelian Inheritance in Man) [25] and GeneCards [26], focusing primarily on genes that feature rheumatoid arthritis. RA-related genes were retrieved using keyword combinations ("Rheumatoid Arthritis," "Apoptosis," "Inflammation") across GeneCards and OMIM. GeneCards entries with relevance scores ≥ 10 were retained. All gene entries were deduplicated to yield a curated set of 6629 RA-associated genes for intersection analysis. These targets were deemed potential therapeutic targets as they were common between predicted compound targets and disease-associated gene targets.

2.3 | Functional Enrichment Analysis

The common targets were analyzed for gene ontology (GO) and pathway enrichment analyses in the DAVID database [27].

Within each domain, the genes were organized into GO terms: biological process (BP), molecular function (MF), and cellular component (CC). KEGG pathway analysis was also done to provide context for the molecular interactions. A focus on interpretation centered around apoptosis linked to RA for biological GO relevance was restricted to the top 10 GO terms and KEGG pathways with adjusted p values ≤ 0.05.

2.4 | Network Construction

A compound–target interaction network was created in Cytoscape 3.8.0 [28]. In the network, nodes were compounds or gene targets, while edges indicated interactions between them. Topological measures, particularly degree centrality, which identifies hub targets, were computed using Cytoscape's Network Analyzer. These hub targets, highly interconnected and therefore ideal for pharmacological intervention, were found to be the most important for the network.

In this specific network, every node corresponds to either a compound of plant origin or a target gene, with edges denoting their predicted interaction(s) based on target prediction and relevance to the disease. The network was formed by bringing in the list of 12 phytochemicals and their 316 gene targets (those common to both compound prediction and RA-related diseased genes). Compound nodes, typically colored shapes, were differentiated from target nodes through visual attributes, and node size was modified based on degree centrality, a prominent topological measure indicating the number of direct links. To detect key molecular drivers within the system, topological analysis was performed using Cytoscape's Network Analyzer plugin. Degree centrality was computed for each target gene node, and those with the highest connections were termed hub targets. It is plausible that these hub nodes significantly influence modulation of apoptosis and inflammation in RA, thereby serving as promising candidates for therapeutic intervention. With this network, it was possible to visually and quantitatively systematize the compounds and targets to prioritize them for further pathway enrichment, molecular docking, and dynamic simulation studies. This is helpful for the identification of multi-targeted therapeutic actions, which are polypharmacological in nature and typical of compounds derived from plants.

2.5 | Analysis of PPI Network and Molecular Docking

To examine the biological functions of the hub targets, a protein–protein interaction (PPI) network was created using the STRING database [29], and interactions with a score greater than 0.4 were considered. The network was visualized in Cytoscape, and key hub genes were extracted with the help of the CytoHubba plugin. Molecular docking studies were then performed to confirm interactions of selected hub proteins and the phytochemicals. The 3D structures of the protein targets were sourced from the RCSB Protein Data Bank (PDB) [30] and subsequently prepared using UCSF Chimera. The CASTp tool [31] was used to locate the binding sites, and docking was executed using PyRx [32]. The complexes with the most optimal binding affinities (kcal/mol) and reasonable RMSD values were chosen for further evaluation. The protein-ligand interactants were inspected in UCSF ChimeraX [33] and BIOVIA Discovery Studio [34] to evaluate the non-covalent interactions such as hydrogen bonding, the hydrophobic effect, and other forces that enhance the stability of the complex.

2.6 | MD Simulation

Molecular dynamics (MD) simulations were employed to assess the conformational stability, atomic fluctuations, and solvent exposure of protein–ligand complexes under near-physiological conditions. All simulations were performed using GROMACS with a suitable force field (e.g., CHARMM36 or AMBER99SB). The systems were solvated using the SPC/E water model within a defined simulation box and neutralized with counter-ions. After energy minimization via the steepest descent algorithm, equilibration was carried out in two phases: constant volume (NVT) and constant pressure (NPT), followed by a 100 ns production run at 300 K and 1 atm. The dynamics of atoms during the simulation were governed by Newton's second law of motion:

$$F = m.a = m.d^2r/dt^2$$

where F is the force on an atom, m is its mass, and d^2r/dt^2 is the acceleration, calculated as the second derivative of position with respect to time.

To evaluate simulation outcomes, three key parameters were calculated. Root mean square deviation (RMSD) was used to measure the structural deviation of the complex from its initial configuration over time, using the formula:

$$\mathrm{RMSD}(t) = \frac{1}{N}\sum_{i=1}^{N}\left(r_i(t) - r_i^0\right)^2$$

where N is the number of atoms, $r_i(t)$ is the position of atom i at time t, and r_i^0 is its reference position. Root mean square fluctuation (RMSF) was calculated to quantify the flexibility of individual residues throughout the simulation where $\langle r_i \rangle$ is the average position of atom i over the simulation time T. Solvent accessible surface area (SASA) was computed to estimate the surface area of the protein or complex that is accessible to solvent molecules. It was calculated using a rolling sphere algorithm based on the solvent probe radius and atomic van der Waals radii: where A_i is the accessible surface area of atom iii, computed by simulating the path of a probe (typically water-sized, ~1.4 Å radius) around the molecular surface. Together, these parameters provided a comprehensive understanding of the dynamic stability, flexibility, and solvent interactions of the complexes throughout the simulation.

3 | Results

3.1 | Screening of Putative Phytocompounds

A total of 12 plant-derived phytochemicals were selected for virtual screening based on their known activity against inflammation and apoptosis-related targets in RA (Table 1 and

TABLE 1 | Drug-likeness evaluation of screened phytochemicals.

Phytochemical	Plant source	Molecular weight	LogP	H_Donors	H_Acceptors	Lipinski_ violation	PubChem_CID
Curcumin	*Curcuma longa*	368.385	3.3699	2	6	0	969516
Resveratrol	*Emblica officinalis*	228.247	2.9738	3	3	0	445154
Berberine	*Camellia sinensis*	336.367	3.0963	0	4	0	2353
Quercetin	*Boswellia serrata*	302.238	1.988	5	7	0	5 280343
Withaferin A	*Polygonum cuspidatum*	470.606	3.3529	2	6	0	265237
Luteolin	*Tinospora cordifolia*	286.239	2.2824	4	6	0	5 280445
Daidzein	*Berberis vulgaris*	254.241	2.8712	2	4	0	5 281708
Naringenin	*Glycyrrhiza glabra*	272.256	2.5099	3	5	0	439246
Apigenin	*Piper nigrum*	270.24	2.5768	3	5	0	5 280443
Silibinin	*Berberis vulgaris*	482.441	2.3627	5	10	0	31553
Formononetin	*Scutellaria baicalensis*	268.268	3.1742	1	4	0	5 280378
Tinosporaside	*Tinospora cordifolia*	492.521	0.6304	4	10	0	14194109

Figure 1). These compounds were sourced from various medicinal plants including *Curcuma longa*, *Emblica officinalis*, *Camellia sinensis*, *Boswellia serrata*, *Polygonum cuspidatum*, *Tinospora cordifolia*, and others. All selected phytochemicals complied with Lipinski's Rule of Five, suggesting favorable oral bioavailability. Notably, curcumin (PubChem CID: 969516) from *Curcuma longa* displayed a molecular weight of 368.38 g/mol, LogP of 3.37, and a balanced hydrogen bonding profile (2 donors, 6 acceptors). Similarly, resveratrol from *Emblica officinalis* and berberine from *Camellia sinensis* met all drug-likeness criteria, indicating potential for further development. Other compounds such as quercetin, withaferin A, luteolin, and silibinin also showed promising physicochemical properties consistent with favorable ADME profiles. Interestingly, tinosporaside, a high-molecular-weight compound (492.52 g/mol) from *Tinospora cordifolia*, remained compliant with Lipinski's criteria, highlighting its potential despite its size. These results support the viability of these compounds as candidates for targeting apoptosis-linked inflammatory pathways in RA.

3.2 | Target Prediction and Intersection Analysis

The SwissTargetPrediction database was used for target prediction matching with the 12 shortlisted phytochemicals, which resulted in the retrieval of 513 unique potential targets. Concurrently, a total of 6629 disease-specific genes relevant to the apoptosis-linked inflammatory pathways in RA were extracted from GeneCards, OMIM, and DisGeNET. This was done through a systematic integration search using relevant keywords. The analysis revealed 316 overlapping targets, and these were found to be common molecular components between the selected plant-derived compounds and pathways associated with the disease. These genes more likely serve as important intermediaries for the biopharmaceutical action of the screened phytochemicals and were chosen to conduct further network assembly and enrichment analyses. The Venn diagram illustrating this intersection is presented in Figure 2A.

3.3 | Protein–Protein Interaction (PPI) Network and Hub Gene Analysis

Utilizing the STRING database (https://string-db.org), a PPI network was generated to explore the molecular interplay within the 316 common targets that are both phytochemical and disease related. All derived targets were submitted to STRING with the confidence interaction score criteria set at >0.7, and the species designated as *Homo sapiens*. The interaction network obtained from STRING was visualized as a Cytoscape layout, in which node degree served as a measure of the protein's topological significance or importance within the network. Within this network, data consisting of 316 nodes and their edges were captured, depicting the interaction relationships, which are more complex than in simple diagrams; therefore, they are also presented as Figure S1. Employing a simple topological analysis focusing on degree centrality, it was possible to determine the 10 central hub genes possessing the highest connectivity as AKT1, TNF, EGFR, STAT3, SRC, BCL2, CASP3, JUN, HIF1A, and MMP9.

3.4 | Functional Enrichment Analysis

In order to understand the biological functions of the 316 intersecting genes among the phytochemical targets and the RA-associated genes, a comprehensive gene ontology (GO)

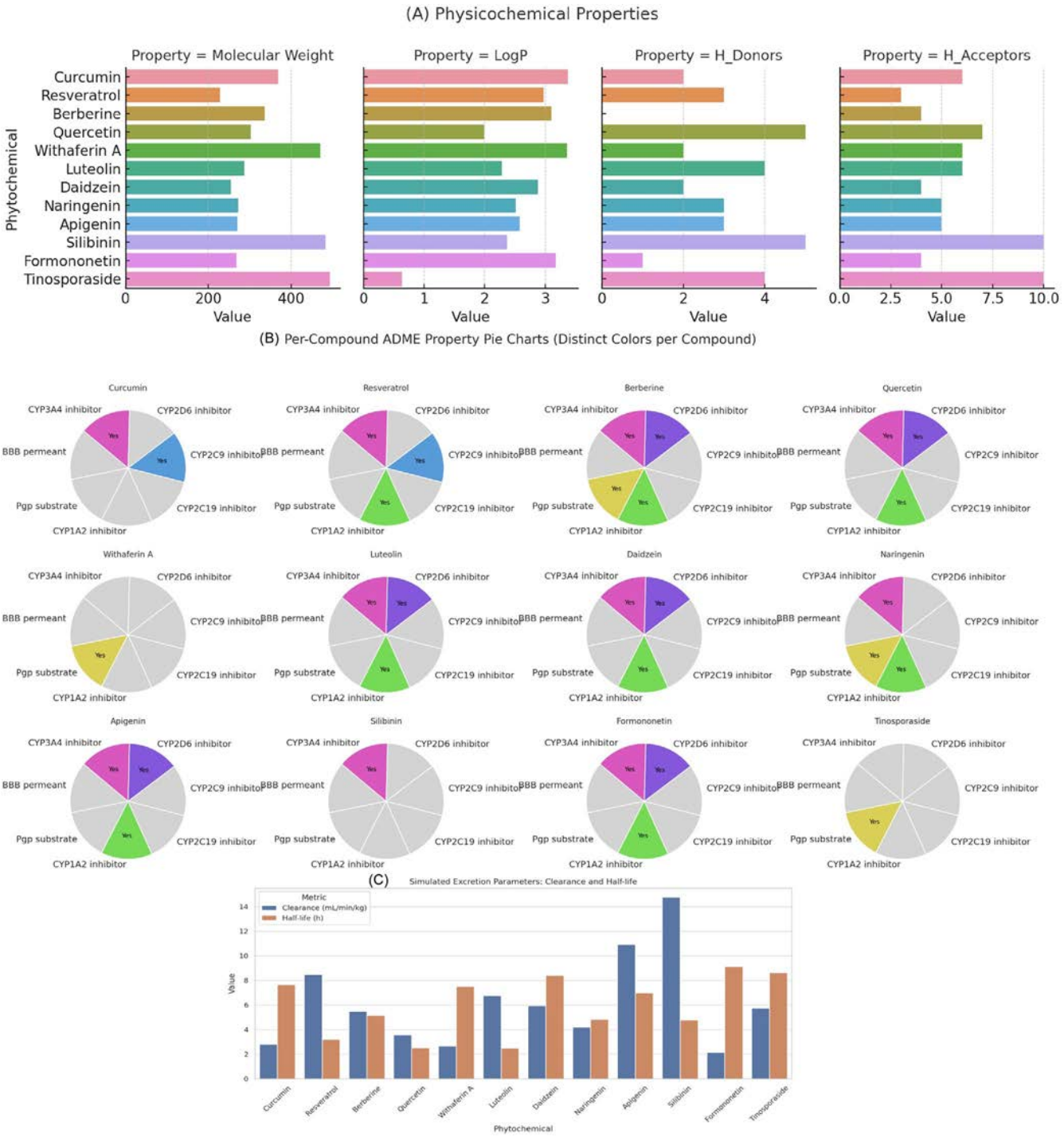

FIGURE 1 | Physicochemical, ADME, and excretion profiling of selected phytochemicals. It illustrates an integrated analysis of pharmacokinetic and physicochemical properties for multiple phytochemicals evaluated in the study. (A) Bar plots representing key physicochemical properties, including molecular weight, LogP (lipophilicity), hydrogen bond donors (H_Donors), and hydrogen bond acceptors (H_Acceptors). These properties are essential in predicting drug-likeness and oral bioavailability, with most compounds aligning well within the acceptable range defined by Lipinski's Rule of Five. (B) Pie charts summarizing individual ADME features per compound, such as interactions with major cytochrome P450 enzymes (e.g., CYP3A4, CYP2D6, CYP2C9, CYP1A2), P-glycoprotein (Pgp) substrate status, and blood–brain barrier (BBB) permeability. Each chart shows the distribution of "Yes" or "No" predictions for each property, offering insights into potential metabolic liabilities and CNS penetrance. (C) Bar chart displaying predicted excretion parameters, including simulated clearance rate (mL/min/kg) and biological half-life (h). Compounds such as tinosporaside and formononetin showed higher clearance rates, while others like curcumin and resveratrol displayed longer half-lives, suggesting extended systemic retention.

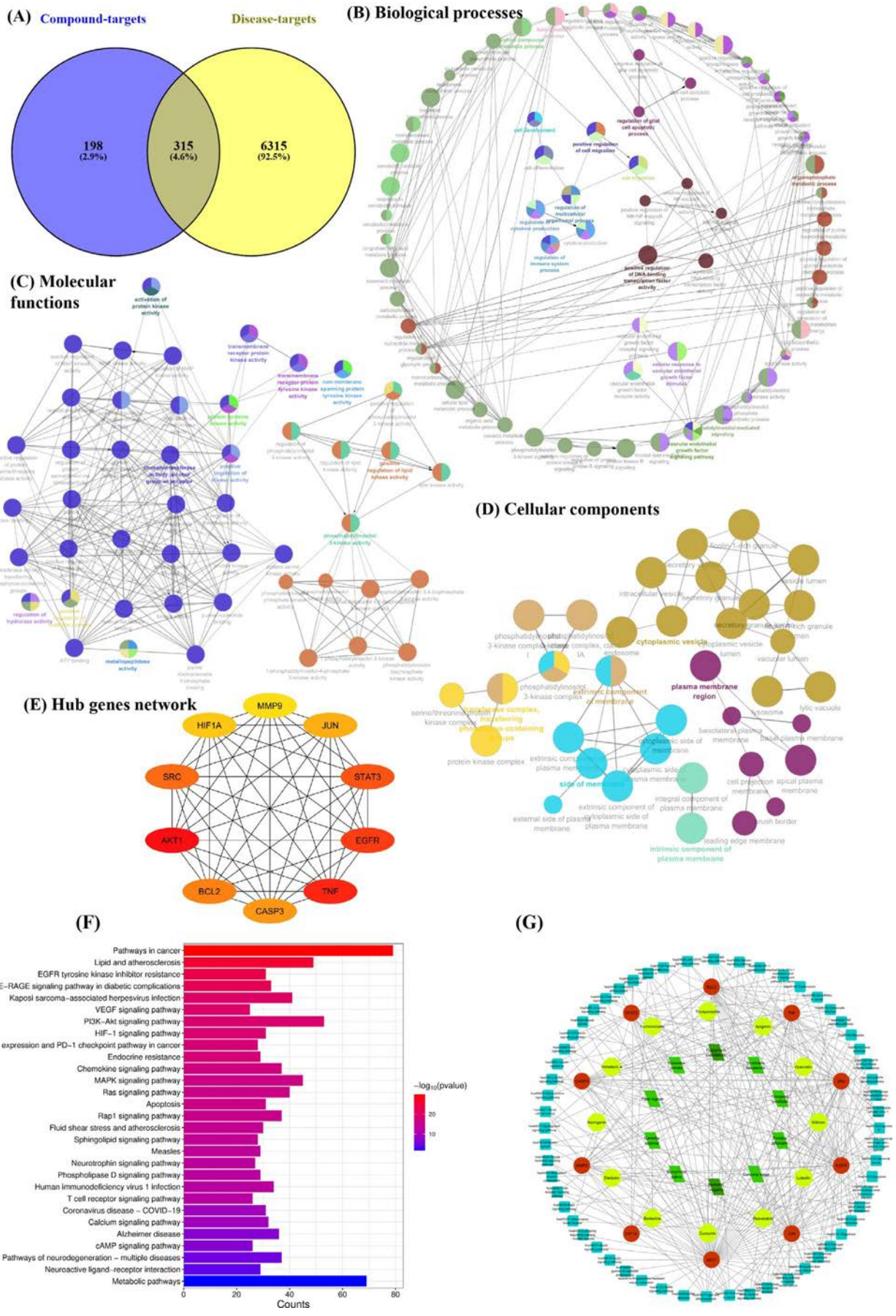

FIGURE 2 | Legend on next page.

FIGURE 2 | (A) Venn diagram illustrating the overlap between predicted compound targets (blue) and disease-associated targets (yellow), identifying 315 common genes. (B) GO enrichment analysis of common targets under BPs showing major functions like regulation of cell proliferation and inflammatory responses. (C) GO enrichment for molecular functions (MFs) including kinase activity, receptor binding, and oxidoreductase activity. (D) GO enrichment for cellular components (CCs) highlighting localization in regions such as the plasma membrane, vesicles, and extracellular space. (E) Hub gene network derived from PPI analysis identifying key genes (e.g., AKT1, EGFR, TNF, CASP3, STAT3). (F) KEGG Pathway enrichment bar plot of disease-associated targets. Bar plot illustrating the enriched KEGG pathways associated with disease-relevant target genes. The *x*-axis represents the number of genes involved in each pathway (counts), while the *y*-axis lists the significantly enriched pathways. The color gradient corresponds to the $-\log_{10}$(*p*-value), with red shades indicating higher statistical significance. (G) Plant compound–target–pathway network analysis.

enrichment analysis was performed. The results are depicted in the multi-panel network Figure 1, which integrates the information across three GO domains: BPs, MFs, and CCs. The BPs are represented (Figure 2B). For them, the inflammatory response together with the regulation of apoptotic signaling pathways, cellular response to cytokines, as well as oxidative stress were significant pathways among inflammatory processes of RA. These processes are essential for the chronic inflammation and abnormal cell survival conducted in RA synovial tissues. In the analysis of MFs (Figure 2C), significant enrichment of kinase activity, binding of some transcription factors, and some cytokine receptors were noted, suggesting the presence of a significant number of immune and non-immune factors controlling the inflammation and joint destruction in RA; therefore, signifying the majority of these targets partake in signal transduction, transcriptional control, and immune signaling, which are fundamental pathways for inflammation and degeneration of joints in RA. For CCs, Figure 2D, most gene products were located in the plasma membrane, cytosol, nucleoplasm, and protein kinase complexes, thus suggesting that these proteins actively participate in cell communication and signal relaying.

3.5 | KEGG Pathway Analysis

KEGG pathway enrichment analysis was performed to understand the biological significance and mechanistic functions of the 316 intersecting genes. The outcomes were displayed as an elaborate interaction network (Figure 2E) revealing enriched pathways and their relevant gene sets. All connected nodes represent specific signaling cascades, metabolic pathways, immune pathways, and disease processes, with pie charts depicting the proportional gene count in each pathway. Pathways with the most profound immune-inflammatory response and apoptosis impact were the TNF signaling pathway, IL-17 signaling pathway, Toll-like receptor signaling, and NF-κB signaling pathway. These pathways are also known to promote chronic inflammation, immune cells, and tissue destruction of the joints in RA (Figure 2F). In addition, apoptosis, cellular senescence, and p53 signaling pathways showed a strong emphasis on programmed cell death, highlighting the stressed cells within the tissues as a hallmark of disease advancement. Notably enriched were also some cancer-related pathways such as PI3K-Akt signaling, MAPK signaling, and pathways in cancer, reflecting the shared molecular pathways in RA and tumoral-like hyperplasia of synovial fibroblasts. Also noted were metabolic and endocrine-related pathways like insulin resistance, estrogen signaling, and AGE-RAGE signaling in diabetic complications, indicating a more systemic involvement and potential links of inflammation within metabolic conditions.

3.6 | Plant Compound–Target–Pathway Network Analysis

To further dissect the therapeutic potential of the selected phytochemicals, a comprehensive compound–target–pathway network was constructed and is presented in Figure 2G. This tripartite network integrates 12 bioactive plant-derived compounds (green squares), their top 10 hub gene targets (orange and yellow circles), and associated KEGG signaling pathways (blue nodes). The visualization provides a systemic overview of how plant metabolites may interact with molecular targets to influence biological pathways relevant to apoptosis-linked inflammation in RA. In this network, several phytochemicals such as curcumin, resveratrol, withaferin A, silibinin, and apigenin exhibited a high degree of connectivity, suggesting they potentially regulate multiple hub genes simultaneously. For example, curcumin was linked to major targets like AKT1, CASP3, TNF, and BCL2, which are central regulators of inflammation, apoptosis, and immune signaling. This multi-target interaction supports the compound's pleiotropic effects reported in both preclinical and clinical RA studies. The hub gene layer (colored orange for the highest connectivity and yellow for moderate) prominently features critical regulators such as AKT1, TNF, STAT3, EGFR, SRC, BCL2, CASP3, JUN, HIF1A, and MMP9. These genes form the molecular core of RA pathogenesis by modulating synovial inflammation, apoptosis resistance, angiogenesis, and cartilage destruction. Their central positioning in the network underlines their importance as therapeutic intervention points. Furthermore, the outer ring of blue nodes represents enriched KEGG pathways that are mechanistically relevant to RA, including the TNF signaling pathway, NF-κB signaling, IL-17 signaling, apoptosis, and Toll-like receptor signaling pathway. These pathways are tightly interconnected with the hub genes and represent the functional consequences of target modulation by plant-derived compounds. Altogether, this integrative network underscores the polypharmacological nature of phytochemicals and their ability to target multiple molecular nodes and pathways simultaneously. It validates their potential to restore immune balance and modulate apoptotic signaling, both of which are dysregulated in RA. The network also provides a strong rationale for selecting certain compounds and targets for downstream docking, MD, or experimental validation. MMP9, SRC, and EGFR were selected from the top 10 hub genes due to their well-characterized structures, availability of high-resolution crystal forms, and their documented involvement in

both apoptotic regulation and inflammatory signaling relevant to RA pathology.

3.7 | Molecular Docking Analysis

Docking analyses were performed to explore the binding interactions of the chosen phytochemicals with the three crucial hub proteins MMP9, SRC, and EGFR that are associated with the RA-linked inflammation and apoptosis pathways. The top three proteins linked with apoptosis linked RA were retrieved from rcsb pdb including EGFR (2RGP), SRC (2BDF), and MMP9 (6ESM). The interactions of different compounds with MMP9, SRC, and EGFR indicated promising inhibitory action, as depicted with the potential interactions in the docking calculations. The data for the binding energy calculations along with the visual representations can be seen in Figure 3. Resveratrol turned out to be the most potent compound with MMP9 receiving a binding energy of −9.40 kcal/mol. This translates to significant blockage potential through multiple hydrogen bonds and numerous hydrophobic bonds with critical active site residues such as GLU252, LEU212, and ARG143. Daidzein and apigenin also exhibited favorable binding energy with MMP9 at −8.29 and −7.67 kcal/mol. SRC kinase is another key part of inflammatory signaling, and it was observed that quercetin and luteolin had the highest binding energies at −8.82 kcal/mol, with those two claiming the second strongest binding energy receiving the lowest energy value for the docking. Apigenin, naringenin, and quercetin were the strongest compounds for EGFR, those values being bound at −10.37, −10.21, and −10.22 showing low energy requirement for binding. These ligands formed several intermolecular hydrogen bonds and π-interactions within the kinase domain, augmenting the strong binding capabilities. The interaction patterns described in Figures 3 and S1 corroborated these results, showing the amino acid residues and molecular interactions of interest, and the amino acid contacts. The majority of compounds calculated also demonstrated highly acceptable RMSD values, which corroborate the stability of their docked conformations. Altogether, these findings indicate that the compounds apigenin, quercetin, resveratrol, and naringenin possess significant multi-target strong binding potential and are likely to play an important role in the modulation of apoptosis and RA inflammatory signaling pathways.

3.8 | MD Simulation

To understand the structural stability and dynamic characteristics of certain protein–phytochemical complexes, MD simulations were conducted on three primary target proteins (EGFR, MMP9, and SRC) with six different ligand-bound systems. The assessed ligands were bioactive ligands with known activity for apigenin, naringenin, daidzein, resveratrol, quercetin, and luteolin. Each simulation was conducted for 100 ns. The RMSD, RMSF, and SASA outputs generated during the simulation were analyzed to determine movement, residue flexibility, and spatial area bound of the molecule (Figure 4).

The RMSD plots provided significant interpretations regarding the stability of the ligand–protein complexes over time. Notably, the lowest and most stably enduring RMSD values throughout the simulation for apigenin–EGFR and quercetin–SRC complexes were between 2.0 and 2.8 Å. This indicates a robust interaction and low conformational change from the initial docked position. Luteolin–SRC also maintained a stable trajectory but was slightly more variable at the end of the simulation, ranging from 2.5 to 3.5 Å. The daidzein–MMP9 and resveratrol–MMP9 complexes, on the other hand, showed greater variability after 40 ns, with RMSD values rising to 4.5–5.0 Å. This suggests some degree of conformational flexibility, less stable binding, or partial reorientation of the ligand within the binding pocket. Naringenin–EGFR complex demonstrated moderate structural rearrangement during the simulation with oscillating RMSD values around 3.0–4.0 Å.

In the quest to understand localized flexibility further, we performed an RMSF analysis on the backbone atoms of the EGFR, MMP9, and SRC proteins. Among the proteins analyzed, the structure of MMP9 demonstrated the highest fluctuation values, primarily in the loops and terminal residues, with some RMSF peaks greater than 12 Å. The high mobility in those regions may account for the decreased stability of binding in the complexes with resveratrol and daidzein. In contrast, EGFR and SRC showed more restrained fluctuations. The EGFR protein was observed to have an RMSF value mostly below 4 Å, suggesting little motion and only minimal dynamic motion in the apigene and naringenin complexes. SRC proved to be slightly more flexible than EGFR, particularly in the sides of the ligand-binding domain, but stayed mostly between 4 and 6 Å, which is consistent with the stable interaction profiles in the quercetin and luteolin complexes.

The rationale provided by SASA analysis further determined the folds compound binding and solvent exposure in the complexes. All complexes maintained a relative constancy in SASA over the 100 ns simulation, showing some minor fluctuations. Notably, apigenin–EGFR as well as quercetin–SRC and luteolin–SRC showed the least variation in SASA, which suggests that complexo formation is tightly packed and the ligand is stably buried within the binding cavity. This is consistent with the low RMSD and RMSF values that these complexes showed. On the contrary, resveratrol–MMP9 and daidzein–MMP9 showed bursts of high SASA values, at times peaking close to 1100 $Å^2$, which indicates that these complexes are more exposed to solvent and thus more likely to be unstable or weakly bound to the active site.

In conclusion, the results from MD simulations suggest that apigenin, quercetin, and luteolin displayed the highest level of structural stability and strongest binding as they formed more complex structures with the EGFR and SRC targets. These ligands consistently showed low RMSD, low fragment level oscillation, and compact SASA values during the simulation, indicating significant potential to act as modulators. In contrast, MMP9 in combination with daidzein and resveratrol displays greater flexibility, increased range of motion, and greater exposure to solvent, which may undermine their biological functionality and attachment strength. These insights highlight the role of dynamic stability when assessing the pharmacological potential of candidate phytochemicals.

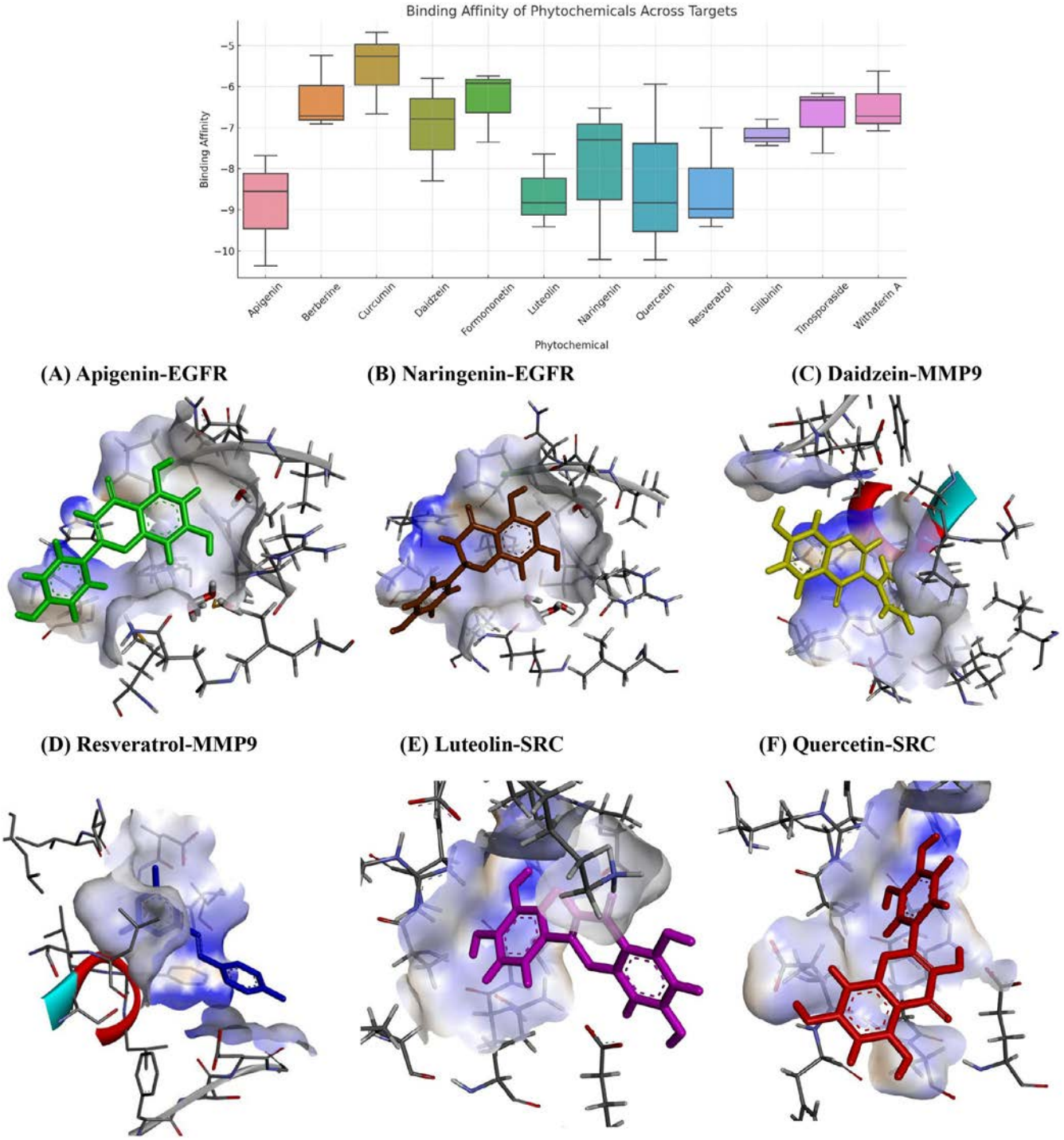

FIGURE 3 | Molecular docking of bioactive compounds with key target proteins (A) Apigenin docked with EGFR, showing hydrogen and hydrophobic interactions. (B) Naringenin binding to EGFR, engaging with residues such as ARG776 and LYS846. (C) Daidzein interacting with MMP9 via contacts with ALA140 and LEU212. (D) Resveratrol docked with MMP9, stabilized by bonds with ARG143 and ASP139. (E) Luteolin binding to SRC kinase, forming hydrogen bonds with HIS319 and GLU331. (F) Quercetin interacting with SRC, forming significant hydrogen and electrostatic contacts.

4 | Discussion

Rheumatoid arthritis is a chronic autoimmune disease associated with inflammation, joint damage, and systemic involvement [35]. One of the defining traits of RA is the chronic inflammation coupled with immune homeostasis dysregulation and apoptosis imbalance, especially in the microenvironment of the synovial joint [36]. Synovial fibroblasts (FLS) in RA patients undergo neoplastic hyperplasia and acquire resistance to apoptosis, exacerbating cartilage and bone erosion [37, 38]. At the same time, activated macrophages and T cells excessively produce pro-inflammatory

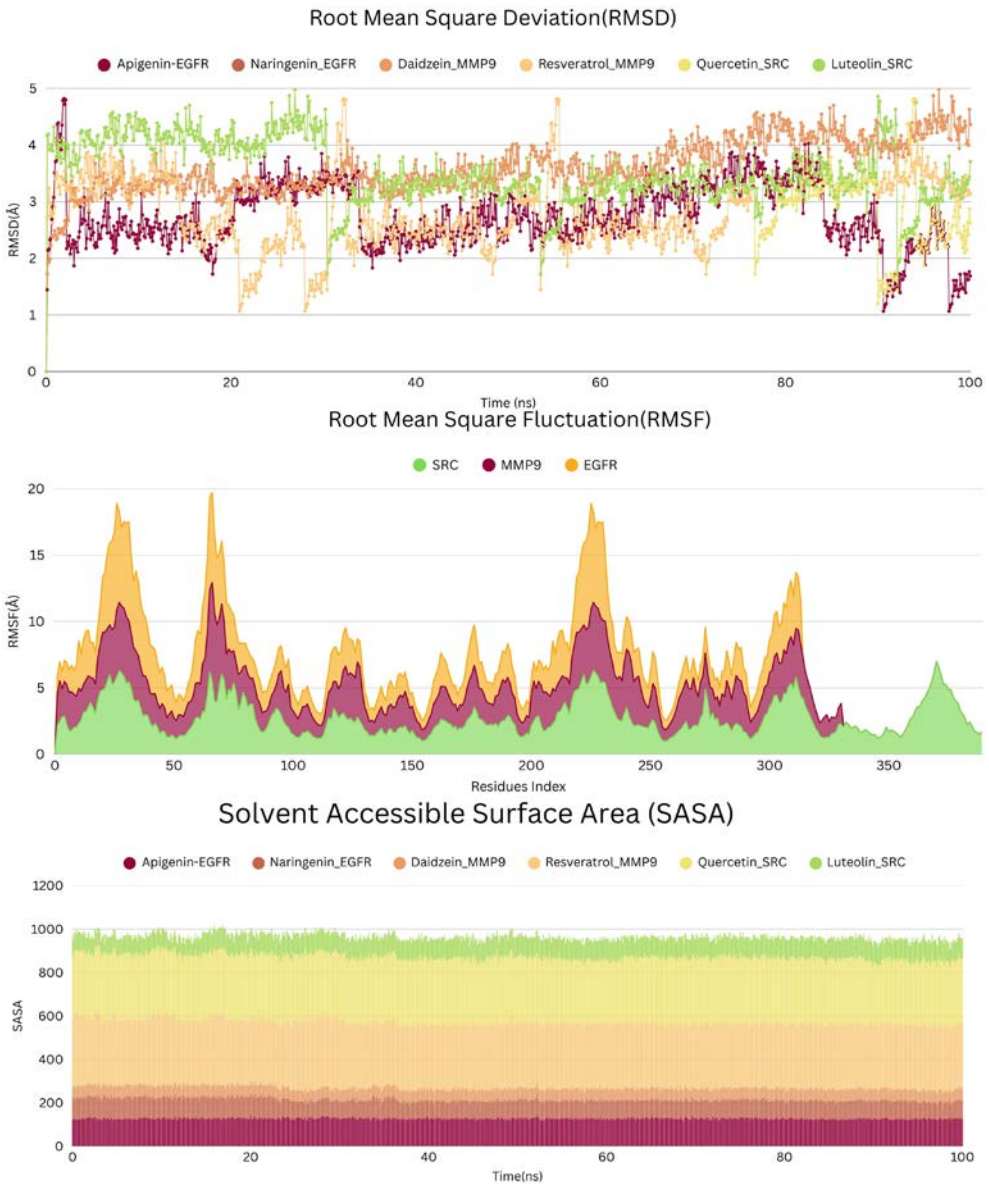

FIGURE 4 | Root mean square deviation (RMSD) plots display the overall stability of each protein–ligand complex over time. Apigenin–EGFR and quercetin–SRC showed the lowest and most stable RMSD values (2–3 Å), indicating strong and stable interactions. daidzein–MMP9 and resveratrol–MMP9 exhibited higher fluctuations (up to 5 Å), reflecting greater structural variability. Root mean square fluctuation (RMSF) plots represent the residue-level flexibility of EGFR, MMP9, and SRC. MMP9 showed the highest residue fluctuations (above 10 Å) in loop regions, whereas EGFR and SRC demonstrated more restrained fluctuations, consistent with more stable binding. Solvent accessible surface area (SASA) plots illustrate the degree of solvent exposure of the protein–ligand complexes. apigenin–EGFR, quercetin–SRC, and luteolin–SRC maintained consistent and compact SASA values (~800–1000 $Å^2$), supporting their structural integrity and stability. In contrast, daidzein–MMP9 and resveratrol–MMP9 showed increased solvent exposure, correlating with their higher RMSD values. Together, these results suggest that apigenin, quercetin, and luteolin form the most stable and compact interactions with their respective targets, highlighting their potential as strong therapeutic candidates.

cytokines, including TNF-α, IL-6, and IL-1β, sustaining the amplification loop of inflammation and triggering more inflammatory cascades involving NF-κB, STAT3, and MAPK [39, 40]. These self-sustained pathways promote the unrelenting inflammation and proliferation of immune and stromal cells while firmly anchoring the apoptotic pathways. Thus, in RA, control of inflammation and enhancement of apoptosis together provide a better long-term outcome. Unfortunately, the majority of conventional treatment options, including NSAIDs and some biologics like TNF inhibitors, focus on reducing inflammation and often neglect the underlying mechanisms of apoptotic resistance that drive the overgrowth of synovium.

Our study utilized an integrative network pharmacology and molecular modeling strategy to screen for bioactive plant compounds capable of modulating apoptotic inflammatory pathways in RA. A screened set of 12 phytochemicals with anti-inflammatory and/or pro-apoptotic activity was assessed for drug-likeness using Lipinski's Rule of Five. All compounds met the criteria for potential oral bioavailability. These phytochemicals were sourced from traditional medicinal plants including

Curcuma longa, *Boswellia serrata*, *Polygonum cuspidatum*, *Emblica officinalis*, and *Scutellaria baicalensis*. Target prediction by SwissTargetPrediction provided 513 unique targets, which were subsequently intersected with the 6629 RA-related genes identified from the GeneCards, OMIM, and DisGeNET databases using the query "Apoptosis-Linked Inflammatory Pathways In Rheumatoid Arthritis." This intersection yielded 316 common genes, indicating significant mechanistic convergence between the actions of the plant compounds and the biology of the disease.

The STRING database enabled the construction of a PPI network that was visualized through Cytoscape, revealing 10 hub genes identified from degree centrality: AKT1, TNF, EGFR, STAT3, SRC, BCL2, CASP3, JUN, HIF1A, and MMP9. Apoptosis, cytokine signaling, oxidative stress response, angiogenesis, and immune activation are critical tenets of RA pathophysiology where these genes function as pivotal regulators. Of particular importance is the fact that TNF and STAT3 are well-characterized RA biologic therapeutic targets, with TNF inhibitors being the foundational drugs of backbone RA biologic therapy. AKT1, BCL2, and CASP3 are key cell-surviving and cell-death executable factors and are frequently dysregulated in RA synovial cells. Though more conventionally regarded as falling within the domain of cancer, EGFR and SRC have recently been recognized as driving factors of RA and associated with increased proliferation and invasiveness of rheumatoid synovial fibroblasts (FLS). The centrality of these genes underscores the ability of certain phytochemicals to effect fundamental changes in the biology of the disease rather than its mere symptoms.

These findings were supplemented by functional enrichment analysis. GO annotation indicated that these common targets are enriched in BPs such as regulation of apoptotic signaling, response to cytokines, and positive regulation of inflammatory response. In terms of MF, these targets participated in kinase activity, receptor binding, and modulation of transcription factors, whereas the analysis of CCs indicated localization to the plasma membrane, nucleus, and cytosol, which are essential for signal transduction as well as gene regulation. The enriched KEGG pathways demonstrated significant association with TNF signaling, NF-κB pathway, IL-17 signaling, apoptosis, PI3K-AKT signaling, and Toll-like receptor signaling, which are known to contribute to the pathogenesis of RA.

The docking findings were pivotal in corroborating the in silico research. MMP9, a matrix metalloproteinase associated with RA cartilage degradation, had the strongest binding to resveratrol at −9.40 kcal/mol. Tian et al. [41] reported that where they showcased that resveratrol inhibits the expression of MMP in RA synovial fibroblasts. EGFR also had remarkable binding with apigenin, quercetin, and naringenin with scores of −10.36, −10.21, and −10.22 kcal/mol respectively. These binding sites included important side chains within the EGFR kinase domain and suggest that these flavonoids might have the potential to suppress fibroblast-like synovial cell proliferation, which was demonstrated by Pan et al. [42], where quercetin was shown to downregulate the EGFR/PI3K/AKT signaling axis in RA. Quercetin and luteolin also proved to have notable binding to SRC kinase at −8.82 kcal/mol. This receptor is vital in inflammation caused by cytokines and the migration of the synoviocyte. The 2D interaction diagrams validated stable hydrogen bonding together with hydrophobic interactions. In addition, RMSD values below 3.0 Å for most ligands suggested stable docking poses. It was also clear that these compounds bound strongly to several hub proteins, which reinforces the RA multi-target claim.

The systematized multi-target approach is reminiscent of the concepts underpinning polyherbal therapy, where the therapeutic effect of a given formulation is thought to occur due to the enhancement of multiple biological pathways. Li and Zhang [43] have underscored the benefits of such approaches concerning complex autoimmune disorders like RA, where the intrinsic redundancy in signaling and compensatory feedback mechanisms tends to frustrate single-target intervention strategies. Moreover, these compounds exhibit only moderate binding within the system, suggesting that other constituents of the extracts and their analogs, like curcumin and withaferin A, invoke significant immunomodulatory and antioxidant effects to augment the dosed therapeutic effects.

In essence, the findings of this study suggest strong computational evidence indicating that certain selected plant-derived compounds are capable of interacting with pivotal hub genes and signaling pathways in RA apoptosis dysregulation and inflammatory overactivation. The intersection of network pharmacology, GO enrichment, KEGG analysis, and molecular docking and dunamix simulations at 100 ns suggests that quercetin, resveratrol, apigenin, and naringenin are potent multi-target phytotherapeutic leads. These results justify further investigation through in vitro validation, followed by preclinical and clinical studies. The combination of strategies employed in this study provides an innovative approach toward natural products-based drug development, particularly for highly intricate diseases like RA, where complex diabolic immune and apoptotic pathway interplay requires dual balance for long-lasting remission.

The scope and duration of the MD simulation represent one limitation of this study. A 100 ns simulation time is often adequate for complex stabilization and significant conformational changes, but it is unlikely to capture rare binding events or slower structural transitions. Moreover, only six representative complexes with the best docking scores and biological relevance were chosen for simulation. Due to limited computational resources, longer or replicate simulations were not conducted. These additional simulations would significantly improve statistical certainty, exposing varying degrees of stable kinetic conformations. It is recommended that future work incorporate multiple extended time as well as replica simulation runs to improve the robustness and reproducibility of the results.

The multi-target approach of using phytochemicals in complex disorders like RA may be beneficial, but one must consider their off-target effects due to their multitasking properties. Numerous herbal compounds such as quercetin, apigenin, and resveratrol have metabolic, cell cycle, and even neurological interactions, which are not directly related to RA. Although these therapeutic effects may be useful, the risk of off-target therapeutic effects of non-disease-specific pathways could be harmful, posing safety and specificity concerns. Despite the fact that the compounds chosen in this study have low toxicity and high safety profiles from prior in vivo and clinical trials, these compounds

still require validation through in vitro selectivity testing and in vivo toxicity profiling. Such studies are important to establish the therapeutic windows for the drugs in order to limit harmful effects in the later stages of drug development.

5 | Conclusion

In this study, we aimed to evaluate the efficacy of certain phytochemicals in apoptosis and inflammation, which are two interconnected pathological processes in RA. Using network pharmacology and molecular docking along with gene-disease association analysis, we mapped disease-associated genes and discovered 316 genes in common among the data sets, subsequently selecting 10 hub genes as the focus of our apoptotic and inflammatory cytokine signaling pathways. Functional enrichment analysis confirmed the involvement of these targets with significant participation in the TNF, IL-17, NF-κB, and apoptosis pathways. Strong candidates included apigenin, quercetin, resveratrol, and naringenin due to their stable interaction and high affinity binding with the primary targets MMP9, SRC, and EGFR. These compounds validated the mallemstrom hypothesis by exhibiting multi-target binding and confirming cystabilization as potential RA pathogenesis modulators. Their dual action in apoptosis and inflammation has the potential to overcome the limitations of conventional treatments that fail to restore immune tolerance and resolve synovial hyperplasia. Such findings not only reinforce the growing evidence needing natural products for the treatment of autoimmune diseases but also serve as a basis for further in vitro and in vivo studies and clinical applications. Future studies should aim at the experimental validation of these interactions as well as studying the pharmacokinetics, toxicity, and synergistic effects of these phytochemicals in vivo.

Author Contributions

Z.S.A.s.: Conceptualized and designed the study, supervised the overall research process, and critically revised the manuscript. Provided critical insights and approved the final manuscript for submission.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

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

References

1. K. Sharif, A. Sharif, F. Jumah, R. Oskouian, and R. S. Tubbs, "Rheumatoid Arthritis in Review: Clinical, Anatomical, Cellular and Molecular Points of View," *Clinical Anatomy* 31, no. 2 (2018): 216–223.

2. A. A. Hasan, H. R. Khudhur, and A. K. Hameed, "Rheumatic Autoimmune Diseases (Focus on RA): Prevalence, Types, Causes and Diagnosis. Karbala," *Journal of Pharmaceutical Sciences* 1, no. 20 (2022): 243.

3. S. Safiri, A. A. Kolahi, D. Hoy, et al., "Global, Regional and National Burden of Rheumatoid Arthritis 1990–2017: A Systematic Analysis of the Global Burden of Disease Study 2017," *Annals of the Rheumatic Diseases* 78, no. 11 (2019): 1463–1471.

4. S. W. Wan, H. G. He, A. Mak, et al., "Health-Related Quality of Life and Its Predictors Among Patients With Rheumatoid Arthritis," *Applied Nursing Research* 30 (2016): 176–183.

5. A. K. Shrivastava and A. Pandey, "Inflammation and Rheumatoid Arthritis," *Journal of Physiology and Biochemistry* 69 (2013): 335–347.

6. F. Wu, J. Gao, J. Kang, et al., "B Cells in Rheumatoid Arthritis: Pathogenic Mechanisms and Treatment Prospects," *Frontiers in Immunology* 12 (2021): 750753.

7. Z. Wu, D. Ma, H. Yang, et al., "Fibroblast-Like Synoviocytes in Rheumatoid Arthritis: Surface Markers and Phenotypes," *International Immunopharmacology* 93 (2021): 107392.

8. J. Zhao, P. Jiang, S. Guo, S. J. Schrodi, and D. He, "Apoptosis, Autophagy, NETosis, Necroptosis, and Pyroptosis Mediated Programmed Cell Death as Targets for Innovative Therapy in Rheumatoid Arthritis," *Frontiers in Immunology* 12 (2021): 809806.

9. P. Brown, A. G. Pratt, and K. L. Hyrich, "Therapeutic Advances in Rheumatoid Arthritis," *BMJ* 384 (2024): e070856.

10. T. Doan and E. Massarotti, "Rheumatoid Arthritis: An Overview of New and Emerging Therapies," *Journal of Clinical Pharmacology* 45, no. 7 (2005): 751–762.

11. M. Abbasi, M. J. Mousavi, S. Jamalzehi, et al., "Strategies Toward Rheumatoid Arthritis Therapy; the Old and the New," *Journal of Cellular Physiology* 234, no. 7 (2019): 10018–10031.

12. N. Chaachouay, "Synergy, Additive Effects, and Antagonism of Drugs With Plant Bioactive Compounds," *Drugs and Drug Candidates* 4, no. 1 (2025): 4.

13. R. A. Dar, M. Shahnawaz, M. A. Ahanger, and I. Majid, "Exploring the Diverse Bioactive Compounds From Medicinal Plants: A Review," *J. Phytopharm* 12, no. 3 (2023): 189–195.

14. N. Vaou, E. Stavropoulou, C. C. Voidarou, et al., "Interactions Between Medical Plant-Derived Bioactive Compounds: Focus on Antimicrobial Combination Effects," *Antibiotics* 11, no. 8 (2022): 1014.

15. Z. Long, W. Xiang, Q. He, et al., "Efficacy and Safety of Dietary Polyphenols in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of 47 Randomized Controlled Trials," *Frontiers in Immunology* 14 (2023): 1024120.

16. N. Sharma, R. M. Kumari, N. Gupta, and S. Nimesh, "Plant Based Bioactive Compounds as an Alternative for Cancer Therapy," *Cancer Ther* 3 (2019): 215.

17. S. Batool, M. R. Javed, S. Aslam, et al., "Network Pharmacology and Bioinformatics Approach Reveals the Multi-Target Pharmacological Mechanism of Fumaria Indica in the Treatment of Liver Cancer," *Pharmaceuticals* 15, no. 6 (2022): 654.

18. F. Noor, A. Rehman, U. A. Ashfaq, et al., "Integrating Network Pharmacology and Molecular Docking Approaches to Decipher the Multi-Target Pharmacological Mechanism of *Abrus precatorius* L. Acting on Diabetes," *Pharmaceuticals* 15, no. 4 (2022): 414.

19. A. Rahman, F. Noor, U. A. Ashfaq, et al., "Multitarget Mechanisms of Monocarbonyl Curcuminoid Analogues Against HL-60 Cancer Cells: In Vitro and Network Pharmacology-Based Approach," *ACS Omega* 9, no. 10 (2024): 11836–11847.

20. F. Noor, M. Tahir ul Qamar, U. A. Ashfaq, A. Albutti, A. S. S. Alwashmi, and M. A. Aljasir, "Network Pharmacology Approach for Medicinal Plants: Review and Assessment," *Pharmaceuticals* 15, no. 5 (2022): 572.

21. R. P. Vivek-Ananth, K. Mohanraj, A. K. Sahoo, and A. Samal, "IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants," *ACS Omega* 8, no. 9 (2023): 8827–8845.

22. J. Ru, P. Li, J. Wang, et al., "TCMSP: A Database of Systems Pharmacology for Drug Discovery From Herbal Medicines," *Journal of Cheminformatics* 6 (2014): 1–6.

23. S. Martello and P. Toth, "North-Holland Mathematics Studies," in *Algorithms for Knapsack Problems*, vol. 132 (Elsevier, 1987), 213–257.

24. A. Daina, O. Michielin, and V. Zoete, "SwissTargetPrediction: Updated Data and New Features for Efficient Prediction of Protein Targets of Small Molecules," *Nucleic Acids Research* 47, no. W1 (2019): W357–W364.

25. A. F. Scott, J. Amberger, B. Brylawski, and V. A. McKusick, "OMIM: Online Mendelian Inheritance in Man," *Bioinformatics: Databases and Systems* 46903 (1999): 77–84.

26. M. Safran, I. Dalah, J. Alexander, et al., "GeneCards Version 3: The Human Gene Integrator," *Database* 2010 (2010): baq020.

27. N. Niaid and Database for Annotation, Visualization and Integrated Discovery (DAVID), *Book Database for Annotation, Visualization and Integrated Discovery (DAVID)* (Genome Biology, 2006).

28. P. Shannon, A. Markiel, O. Ozier, et al., "Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks," *Genome Research* 13, no. 11 (2003): 2498–2504.

29. C. von Mering, M. Huynen, D. Jaeggi, S. Schmidt, P. Bork, and B. Snel, "STRING: A Database of Predicted Functional Associations Between Proteins," *Nucleic Acids Research* 31, no. 1 (2003): 258–261.

30. S. Ahmad, N. Bano, and K. Raza, "RCSB Protein Data Bank: Revolutionising Drug Discovery and Design for Over Five Decades," *Medical Data Mining* 8 (2025): 7–11.

31. W. Tian, C. Chen, X. Lei, J. Zhao, and J. Liang, "CASTp 3.0: Computed Atlas of Surface Topography of Proteins," *Nucleic Acids Research* 46, no. W1 (2018): W363–W367.

32. S. Dallakyan and A. J. Olson, "Small-Molecule Library Screening by Docking With PyRx," in *Chemical Biology: Methods and Protocols* (Springer, 2014), 243–250.

33. E. F. Pettersen, T. D. Goddard, C. C. Huang, et al., "UCSF Chimera—A Visualization System for Exploratory Research and Analysis," *Journal of Computational Chemistry* 25, no. 13 (2004): 1605–1612.

34. B. L. Jejurikar and S. H. Rohane, *Drug Designing in Discovery Studio* (Asian Journal of Research in Chemistry, 2021).

35. D. Wu, Y. Luo, T. Li, et al., "Systemic Complications of Rheumatoid Arthritis: Focus on Pathogenesis and Treatment," *Frontiers in Immunology* 13 (2022): 1051082.

36. Q. Fang, C. Zhou, and K. S. Nandakumar, "Molecular and Cellular Pathways Contributing to Joint Damage in Rheumatoid Arthritis," *Mediators of Inflammation* 2020, no. 1 (2020): 3830212.

37. M. J. Mousavi, J. Karami, S. Aslani, et al., "Transformation of Fibroblast-Like Synoviocytes in Rheumatoid Arthritis; From a Friend to Foe," *Autoimmunity Highlights* 12 (2021): 1–13.

38. E. H. Noss and M. B. Brenner, "The Role and Therapeutic Implications of Fibroblast-Like Synoviocytes in Inflammation and Cartilage Erosion in Rheumatoid Arthritis," *Immunological Reviews* 223, no. 1 (2008): 252–270.

39. A. A. Al-Qahtani, F. S. Alhamlan, and A. A. Al-Qahtani, "Pro-Inflammatory and Anti-Inflammatory Interleukins in Infectious Diseases: A Comprehensive Review," *Tropical Medicine and Infectious Disease* 9, no. 1 (2024): 13.

40. H. Zhao, L. Wu, G. Yan, et al., "Inflammation and Tumor Progression: Signaling Pathways and Targeted Intervention," *Signal Transduction and Targeted Therapy* 6, no. 1 (2021): 263.

41. J. Tian, J. W. Chen, J. S. Gao, L. Li, and X. Xie, "Resveratrol Inhibits TNF-α-Induced IL-1β, MMP-3 Production in Human Rheumatoid Arthritis Fibroblast-Like Synoviocytes via Modulation of PI3kinase/Akt Pathway," *Rheumatology International* 33 (2013): 1829–1835.

42. F. Pan, L. Zhu, H. Lv, and C. Pei, "Quercetin Promotes the Apoptosis of Fibroblast-Like Synoviocytes in Rheumatoid Arthritis by Upregulating lncRNA MALAT1," *International Journal of Molecular Medicine* 38, no. 5 (2016): 1507–1514.

43. S. Li and B. Zhang, "Traditional Chinese Medicine Network Pharmacology: Theory, Methodology and Application," *Chinese Journal of Natural Medicines* 11, no. 2 (2013): 110–120.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Molecular docking of bioactive compounds with key target proteins (A) Apigenin docked with EGFR showing hydrogen and hydrophobic interactions. (B) Naringenin binding to EGFR, engaging with residues such as ARG776 and LYS846. (C) Daidzein interacting with MMP9 via contacts with ALA140 and LEU212. (D) Resveratrol docked with MMP9, stabilized by bonds with ARG143 and ASP139. (E) Luteolin binding to SRC kinase, forming hydrogen bonds with HIS319 and GLU331. (F) Quercetin interacting with SRC, forming significant hydrogen and electrostatic contacts.

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REVIEW

A Scoping Review of Respiratory Dysfunction in Inclusion Body Myositis

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ABSTRACT

Objectives: Inclusion body myositis (IBM) can result in deadly respiratory consequences. Yet, the mechanism driving this issue remains equivocal. We mapped the literature to identify physiological respiratory characteristics in IBM and the types of respiratory assessments used.

Methods: We performed a scoping review using seven databases and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

Results: Our search yielded 381 studies, of which 17 studies were reviewed. Case studies/series predominated (53%). Studies mainly used pulmonary function testing (76%), suggesting restrictive respiratory abnormalities. However, insufficient reporting of race/ethnicity (82%), disease duration (59%) and severity (77%), and assessment operations (82%) and interpretation (59%) protocols were problematic. Half of the studies relied on standalone assessments, and 75% of studies that reported interpretation protocols applied interpretation cutoff thresholds.

Conclusion: Low-level evidence guides our understanding of IBM-induced respiratory dysfunction. Future studies should ensure detailed and transparent reporting and follow current best practices for respiratory assessment to define IBM-induced respiratory dysfunction.

1 | Introduction

Inclusion body myositis (IBM) remains the most common idiopathic inflammatory myopathy (IIM) in older adults without an effective treatment [1, 2]. Pathogenetic interactions between rheumatic and degenerative pathways have been well-documented. Notably, IBM histopathology shows myofiber-invading cytotoxic T cells and multiprotein deposit formation [1, 2]. The coexistence and likely role of the aging immune system has also been proposed [3]. However, the primary driver of the disease mechanism and its progression remains ambiguous [1–3].

More defined information exists on IBM's distinct clinical features resulting from the aforementioned pathogenetic interactions. The recently updated European Neuromuscular Center

(ENMC) diagnostic criteria highlight IBM's hallmark clinical features as slowly progressive and asymmetric muscle weakness, especially affecting the deep finger flexor and/or knee extensor muscles, and are often accompanied by dysphagia [4]. Respiratory-related complications, particularly aspiration pneumonia, are also commonly reported sequelae of IBM and notoriously cited as a leading cause of death [5–8]. Moreover, subclinical or asymptomatic respiratory involvement has been linked to IBM [9], suggesting respiratory dysfunction may even be under-detected.

While respiratory involvement appears to be a pervasive symptom of IBM, the physiological characteristics underlying respiratory dysfunction and how it has been assessed are unclear. Additionally, this topic is understudied and was of interest to international IBM experts who participated in the 2023 ENMC IBM diagnostic criteria revision meeting [4]. To our knowledge, no published reviews or systematic efforts have surveyed the literature on this topic. For these reasons, we aimed to map the literature to identify the studies available describing physiological respiratory characteristics underlying respiratory dysfunction in IBM and the types of respiratory assessments used.

2 | Materials and Methods

In considering our objectives and established review guidelines by Munn et al. [10], we conducted a scoping review without critical appraisal. Our review protocol and reporting framework followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [11].

2.1 | Eligibility Criteria

We included peer-reviewed studies and gray literature that involved human adults with IBM and reported a respiratory-related outcome. Studies that were unobtainable, unavailable in English, or nonempirical were excluded. We further excluded studies in which IBM subgroup data could not be differentiated from another group (e.g., other IIMs) and when a potentially confounding comorbid respiratory condition was present (e.g., chronic pulmonary obstructive disease, pulmonary fibrosis, and obstructive sleep apnea [OSA]). Of note, we are aware of a few studies that have posited strong links between IBM and OSA due to pharyngeal and respiratory muscle weakness [9, 12]. We ultimately excluded studies involving OSA because its pathogenesis can be heterogeneous and multifactorial, including components not directly caused by muscle weakness. For example, OSA can involve upper airway volume loss due to obesity or craniofacial structural defects, nocturnal rostral fluid shift, and a reduced respiratory arousal threshold [13, 14].

2.2 | Information Sources and Search Strategy

Our search covered seven databases, including PubMed, CINAHL, Scopus, Web of Science, Google Scholar, OpenGrey, and Clinicaltrials.gov. The search timeline was set from the date of database inception through January 12, 2024, across all databases. The first author (KRA) drafted and iterated the initial search strategy based on discussions with the corresponding author (KLG). The search strategy was further refined by coauthor GK, an experienced biomedical librarian, who compiled the final search strategy with team approval. Briefly, we included variations of the following terms: *inclusion body myositis*, *lung diseases*, *respiratory insufficiency*, *respiration disorders*, *pneumonia*, and *respiratory muscles*. See Appendix S1 for the final search strategy. We imported the search results into the Rayyan review management platform, where we completed duplicate removal and screened studies for eligibility.

2.3 | Study Screening

Two raters (KRA and KLG) screened each study. An initial calibration meeting was held to increase consistency between both raters. This step was followed by two rounds of blind independent screening. The first round focused only on screening titles and abstracts, and the second round involved full-text screening of all remaining studies. We calculated the interrater percent exact agreement for each round. Discrepancies were resolved by discussion until consensus was reached in each round.

2.4 | Data Extraction and Synthesis

We developed a spreadsheet for data extraction of the eligible studies included for final review. All available study demographics were recorded, including country; study design; sample size; age; sex; race/ethnicity; disease duration; and IBM Functional Rating Scale (IBMFRS) scores, the most widely used standard metric for capturing IBM disease severity [15]. We also recorded the types of respiratory assessments used, including whether the studies provided sufficient details about their assessment operations and interpretation protocols. Finally, we recorded the physiological respiratory characteristics captured with each assessment, whether the studies explicitly reported the presence of respiratory dysfunction, and the respiratory dysfunction classification reported (i.e., obstructive versus restrictive). We documented instances when information was unspecified by the studies and handled these data as appropriate. Two reviewers (KRA and BRR) completed data extraction. Similar to the screening phase, they completed an initial calibration meeting followed by independent study reviews. Subsequently, the reviewers compared and discussed the extracted data and computed interrater percent exact agreement for the data recorded in the spreadsheet columns for a randomly selected 20% subset of the eligible studies. Any discrepancies were resolved via consensus, and if necessary, by consulting the corresponding author (KLG). The updated results were reported in a master spreadsheet for data synthesis, which involved organizing data based on our review objectives. Frequency counts and percentages were computed to provide an overview of the data.

3 | Results

Our search generated 381 studies from all the databases. After removing duplicates, we screened 192 studies. Seventeen of these studies met the eligibility criteria and were included

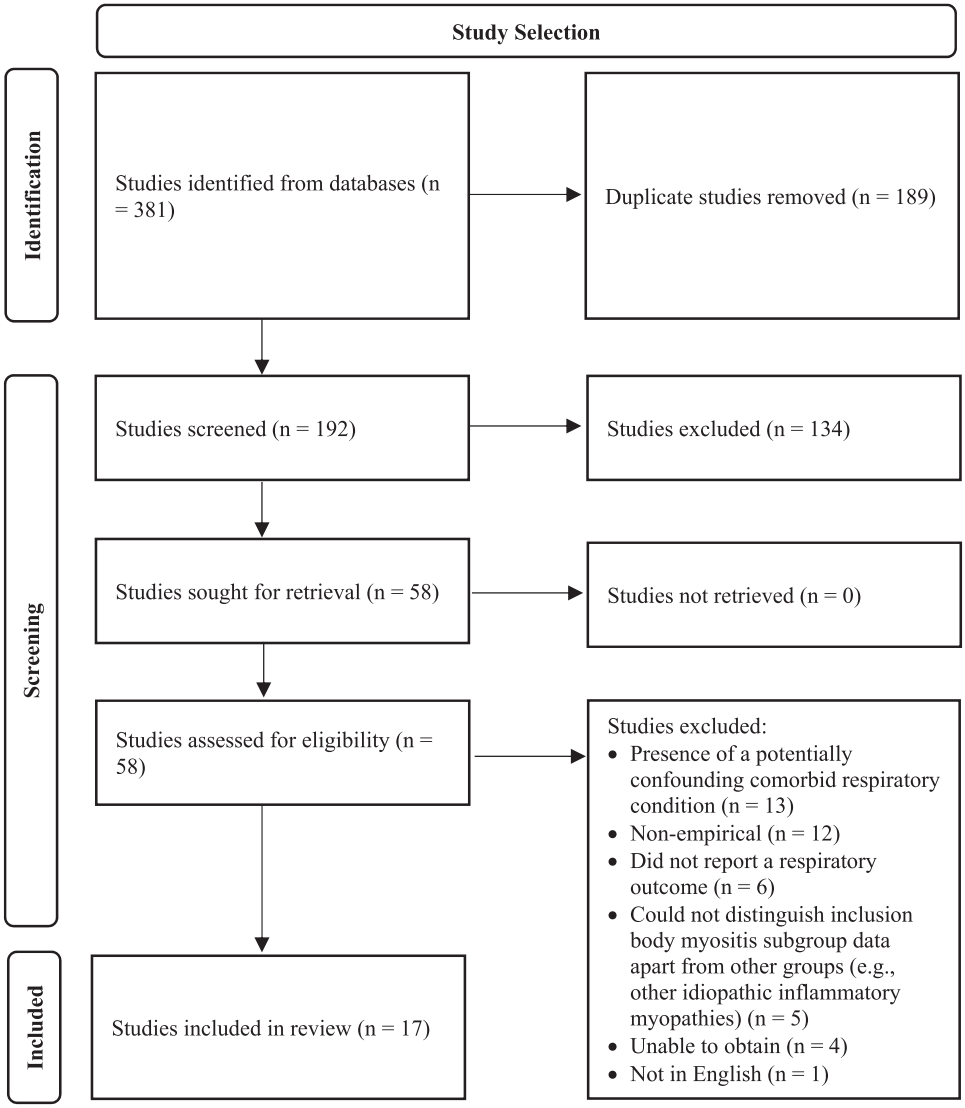

FIGURE 1 | PRISMA 2020 screening flowchart.

for final data extraction and synthesis. Figure 1 provides the PRISMA 2020 flowchart [16] displaying the screening process and results. A breakdown of the number of studies retrieved from each database can be found in Appendix S1. Interrater reliability was achieved with 82% and 84% exact agreement for screening rounds one and two, respectively. For data extraction, interrater reliability was attained with 95% exact agreement.

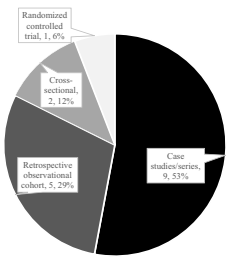

FIGURE 2 | Distribution of study designs. The values listed represent the number of studies, %.

3.1 | Sources of Evidence

Fifteen studies were published peer-reviewed journal articles (88%) [17–31]. Gray literature comprised the remaining two studies, which were published conference abstracts (12%) [32, 33]. Ten studies were from North America (59%) [17, 19, 20, 22–26, 32, 33], five from Europe (29%) [18, 27, 28, 30, 31], one from South America (6%) [21], and one from Asia (6%) [29]. The literature was most densely populated with case studies/series ($n = 9$, 53%) [20–22, 24, 26, 27, 31–33]. Other study designs identified were retrospective observational cohort ($n = 5$, 29%) [17, 19, 25, 28, 29], cross-sectional ($n = 2$, 12%) [23, 30], and a randomized controlled trial ($n = 1$, 6%) [18]. As such, there were three prospective studies (18%) [18, 23, 30]. Figure 2 displays the overall frequency distribution of study designs. One hundred percent of the studies specified details about the aggregate sample size, age, and sex of patients with IBM [17–33]. Details regarding patients' race/ethnicity ($n = 3$, 18%) [19, 22, 27], disease duration ($n = 7$, 41%) [18, 19, 23, 25, 27, 29, 30], and disease severity (in studies published after the IBMFRS was first publicized; $n = 3$, 23%) [18, 23, 29] were less frequently reported. Complete study demographics can be found in Table 1.

TABLE 1 | Study demographics.

Study	Country	Study design	Sample size (patients with IBM included in the study)	Age (years)	Sex	Race/Ethnicity	Disease duration (years)	Disease severity (IBMFRS)
Alhammad & Naddaf [17]	USA	Retrospective observational cohort	2	Mdn (range) = 76 (65–87)	1 female, 1 male	Unspecified	Unspecified	Unspecified
Benveniste et al. [18]	France	Randomized, double blind, placebo-controlled proof of concept trial	Sirolimus group: • 22 Placebo group: • 22	Sirolimus group: • Mdn (IQR) = 68 (63.5–72.3) Placebo group: • Mdn (IQR) = 66 (58.5–70.5)	Sirolimus group: • 12 male, 10 female Placebo group: • 11 male, 11 female	Unspecified	Sirolimus group: • Mdn = 8 Placebo group: • Mdn = 8	Sirolimus group: • Mdn (IQR) = 32.5 (30–34.8) Placebo group: • Mdn (IQR) = 33 (28.3–34)
Brokamp et al. [19]	USA	Retrospective observational cohort	54 (32 of the patients were classified as having ventilatory pump impairment based on demonstrating a forced vital capacity < 79% predicted and subanalyzed against the rest of the cohort without ventilatory pump impairment [$n = 22$])	Entire cohort: • M (SD) = 65.2 (9.4) Ventilatory pump impairment group: • M = 65.18 Nonventilatory pump impairment group: • M = 65.28	Entire cohort: • 35 female, 19 male Ventilatory pump impairment group: • Unspecified Nonventilatory pump impairment group: • Unspecified	Entire cohort: • 44 White, 7 African American, 1 Asian, and 2 unknown race/ethnicity Ventilatory pump impairment group: • Unspecified Nonventilatory pump impairment group: • Unspecified	Entire cohort: • M (SD) = 7.04 (7.26) Ventilatory pump impairment group: • M = 5.06 Nonventilatory pump impairment group: • M = 9.88	Unspecified
Cohen et al. [20]	USA	Case study	1	69	Female	Unspecified	Unspecified	Not applicable; IBMFRS was first published in 2008
Cordeiro de Souza et al. [21]	Brazil	Case study	1	43	Male	Unspecified	Unspecified	Unspecified

(Continues)

TABLE 1 | (Continued)

Study	Country	Study design	Sample size (patients with IBM included in the study)	Age (years)	Sex	Race/Ethnicity	Disease duration (years)	Disease severity (IBMFRS)
Dardis et al. [22]	USA	Case study	1	48	Female	African American	Unspecified	Unspecified
Goyal et al. [23]	USA	Cross-sectional	Seropositive group: • 18 Seronegative group: • 7	Seropositive group: • Mdn (min, max) = 67 (47, 77) Seronegative group: • Mdn (min, max) = 70 (60, 85)	Seropositive group: • 13 male, 5 female Seronegative group: • 6 male, 1 female	Unspecified	Seropositive group: • Mdn (min, max) = 10 (3–15) Seronegative group: • Mdn (min, max) = 11 (4–24)	Seropositive group: • Mdn (min, max) = 23 (17–36) Seronegative group: • Mdn (min, max) = 29 (22–35)
Martin et al. [24]	USA	Case study	1	42	Female	Unspecified	Unspecified	Unspecified
Oh et al. [25]	USA	Retrospective observational cohort	26	M (range) = 72.2 (54.6–84.5)	20 female, 6 male	Unspecified	M = 3.5	Not applicable; IBMFRS was first published in 2008
Ramirez Ramirez & Hillman [26]	USA	Case study	1	57	Female	Unspecified	Unspecified	Unspecified
Salam et al. [27]	UK	Case series	5	Mdn (range) = 56 (34–67)	4 female, 1 male	1 Pakistani; the race/ethnicity of the other patients were unspecified	Mdn (range) = 7 (3–16)	Unspecified
Schrey et al. [28]	Finland	Retrospective observational cohort	40	Mdn (range) age at diagnosis = 69 (43–87)	25 male, 15 female	Unspecified	Unspecified	Unspecified

(Continues)

TABLE 1 | (Continued)

Study	Country	Study design	Sample size (patients with IBM included in the study)	Age (years)	Sex	Race/Ethnicity	Disease duration (years)	Disease severity (IBMFRS)
Taira et al. [29]	Japan	Retrospective observational cohort	CPB+ group: • 15 CPB− group: • 22	CPB+ group: • Mdn (IQR) age at onset = 68 (64–70); Mdn (IQR) age at diagnosis = 76 (70–79) CPB− group: • Mdn (IQR) age at onset = 60 (51–58); Mdn (IQR) age at diagnosis = 67 (62–66)	CPB+ group: • 8 female, 7 male CPB− group: • 16 male, 6 female	Unspecified	CPB+ group: • Mdn (IQR) = 6.2 (5.2–12) CPB− group: • Mdn (IQR) = 8.1 (5–12)	CPB+ group: • Mdn (IQR) = 33 (30–37) CPB− group: • Mdn (IQR) = 31 (29–34)
Teixeira et al. [30]	France	Cross-sectional	6	M (SD) = 60.2 (9.9)	5 male, 1 female	Unspecified	M (SD) = 10.5 (7.97)	Not applicable; IBMFRS was first published in 2008
Voermans et al. [31]	The Netherlands	Case study	1	58	Female	Unspecified	Unspecified	Not applicable; IBMFRS was first published in 2008
*Aggarwal et al. [32]	USA	Case series	3	Mdn (range) = 72 (52–84)	2 female, 1 male	Unspecified	Unspecified	Unspecified
*Bautista et al. [33]	USA	Case study	1	68	Male	Unspecified	Unspecified	Unspecified

Note: An asterisk indicates that the study was obtained from gray literature.
Abbreviations: CPB, cricopharyngeal bar; IBM, inclusion body myositis; IBMFRS, Inclusion Body Myositis Functional Rating Scale; IQR, interquartile range; M, mean; Max, maximum; Mdn, median; Min, minimum; SD, standard deviation; UK, United Kingdom; USA, United States of America.

3.2 | Respiratory Assessment

Most of the studies reported the respiratory assessments used ($n = 14$, 82%) [17–24, 27, 29–33], while the remaining studies failed to specify their assessments despite reporting a respiratory outcome ($n = 3$, 18%) [25, 26, 28]. Of those that reported their assessments, seven studies used one type of assessment (50%) [17–19, 22–24, 32], with pulmonary function testing (PFT) being most common ($n = 6$, 86%) [17–19, 22, 23, 32]. The remaining seven studies reported more than one assessment (50%) [20, 21, 27, 29–31, 33]. Across all studies, PFT was most frequently implemented ($n = 13$, 76%) [17–23, 27, 29–33], followed by arterial blood gas (ABG) testing ($n = 5$, 29%) [20, 21, 30, 31, 33], imaging ($n = 4$, 24%) [20, 24, 27, 29], clinical assessments ($n = 3$, 18%) [20, 29, 30], electrophysiological testing ($n = 2$, 12%) [30, 31], and sleep studies ($n = 1$, 6%) [27]. Figure 3 displays the distribution of assessments used. One study reported sufficient details about their assessment operations protocol (6%) [30], two studies reported partially sufficient details (12%) [19, 23], and the remaining studies had insufficient details (82%) [17, 18, 20–22, 24–29, 31–33]. Three studies had sufficient details about their assessment interpretation protocol (18%) [18, 19, 23], four studies provided partial details (23%) [29–31, 33], and the remaining studies had insufficient information (59%) [17, 20–22, 24–28, 32]. Score thresholds for forced vital capacity (FVC), obtained from PFT, were most commonly reported in four studies that described aspects of their interpretation protocol (57%) [18, 19, 23, 29]. Out of these four studies, three of them employed fixed cutoff interpretation thresholds (75%) [19, 23, 29]. Table 2 further specifies the assessments deployed across studies.

3.3 | Physiological Respiratory Characteristics

Table 3 provides specific details regarding the physiological respiratory characteristics underlying respiratory dysfunction associated with IBM. Respiratory dysfunction was either explicitly reported ($n = 13$, 76%) [17, 19–24, 27, 29–33] or can be implied based on the reported outcomes ($n = 4$, 24%) [18, 25, 26, 28]. Four studies specified a respiratory dysfunction classification (24%) [19, 22, 31, 32], each indicating restrictive respiratory abnormalities. All other studies did not indicate a respiratory dysfunction classification ($n = 13$, 76%) [17, 18, 20, 21, 23–30, 33].

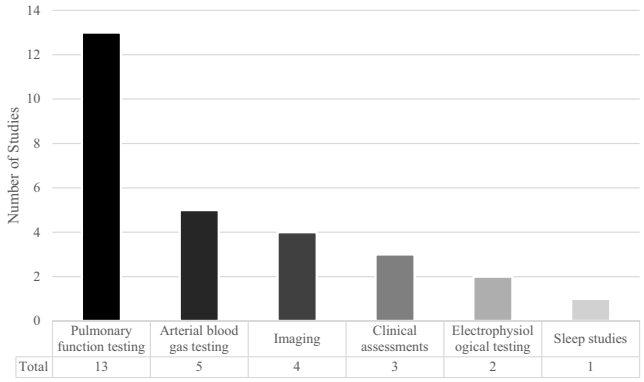

FIGURE 3 | Distribution of respiratory assessments used.

4 | Discussion

We conducted a scoping review to identify and map the available literature on respiratory dysfunction in IBM, a critical problem often associated with significant mortality [5–8]. Our findings feature a paucity in research. There were a limited number of studies that were relevant to our search and eligible for inclusion, which highlighted this evidence gap. Furthermore, the 17 studies included for final review mainly comprise lower evidence levels (OCEBM Levels of Evidence Working Group) [34], particularly case studies/series or retrospective observational cohort studies (Table 1). We also identified only three prospective studies [18, 23, 30], which are advantageous for reducing information and bias recall and intentionally controlling variables of interest [35].

Most studies reported the respiratory assessments they used, but three studies that reported aspiration pneumonia as an outcome did not specify their assessment [25, 26, 28]. A fourth study that reported aspiration pneumonia as an outcome used a combination of clinical history review (i.e., observed macroaspiration), patient interviews, and chest radiography to identify this outcome [29]. This combination of assessments is mostly sufficient for diagnosing aspiration pneumonia, but greater fidelity may have been achieved by also examining vital signs, procalcitonin serum biomarkers [36], and oral colonization risk factors [37]. According to Almirall et al. [37] and Košutova and Mikolka [36], a host typically develops aspiration pneumonia as a result of bacterial macroaspiration from oropharyngeal content, with dysphagia often being involved. Those with a strong immune system and an effective cough, a critical defense mechanism against aspiration, can aspirate content into the airway without respiratory sequelae [36, 37]. The physiological mechanism underlying dysphagia in IBM has been explored [38], with preliminary work integrating well-tested functional swallowing analyses [39]. However, it is surprising that cough function has yet to be assessed in IBM despite its role in protecting the airway from ingested or endogenous content.

Of the studies that reported their respiratory assessments, we identified a wide range of assessment types that provide insight into the mechanism underlying respiratory dysfunction in IBM (Table 2). There were assessments that either measured structural or functional status of the respiratory mechanism. The former helps detect issues related to structural abnormalities, muscle and nerve integrity, and the mechanism's morphology. The latter provides information about the mechanism's mechanical performance. Few studies applied the former (i.e., imaging and electrophysiological testing), while most studies used the latter (i.e., PFT, ABG testing, clinical assessments, and sleep studies).

Nearly half of the studies drew conclusions about respiratory involvement using only one type of assessment [17–19, 22–24, 32]. In this subset and more broadly across over three-fourths of all studies, PFT was most commonly used [17–23, 27, 29–33]. Pulmonary function testing is the criterion standard for distinguishing between obstructive and restrictive respiratory abnormalities [40] and has been widely applied to provide valuable information about the physiological properties of the respiratory mechanism [41]. Yet, clinical standards advise against using PFT thresholds as a standalone metric for

TABLE 2 | Types of respiratory assessments.

Study	Assessments	Sufficient details about assessment operations protocol?	Sufficient details about assessment interpretation protocol?
Alhammad & Naddaf [17]	PFT (FVC, $n=1$; overnight oximetry, $n=1$)	No	No
Benveniste et al. [18]	PFT (FVC)	No	Yes; the percent change in FVC from baseline to follow-up was used
Brokamp et al. [19]	PFT (FVC)	Partial; the study only reported that the same respiratory therapist performed PFT, with the patients sitting in an upright position	Yes; FVC < 79% predicted was used to identify respiratory dysfunction
Cohen et al. [20]	• Imaging (chest radiography) • Clinical assessment (physical examination) • ABG testing (pH, PCO_2, and PO_2) • PFT (NIF)	No	No
Cordeiro de Souza et al. [21]	• ABG testing (PaO_2 and $PaCO_2$) • PFT (static lung compliance, breathing frequency, VT, f/VT index, SpO_2, $P_{0.1}$, MIP, and timed inspiratory effort)	No	No
Dardis et al. [22]	PFT (FVC)	No	No
Goyal et al. [23]	PFT (FVC and NIF)	Partial; the study only reported that a trained respiratory therapist performed PFT using a Renaissance III spirometer (a facemask was only used for those with facial weakness) and MicroRPM handheld pressure meter, with the patients sitting in an upright position	Yes; FVC < 50% predicted and NIF < 60 cm were used to identify respiratory dysfunction
Martin et al. [24]	Imaging (computed tomography)	No	No
Oh et al. [25]	Unspecified	No	No
Ramirez Ramirez & Hillman [26]	Unspecified	No	No
Salam et al. [27]	• PFT (FVC, $n=4$) • Imaging (diaphragmatic ultrasound, $n=1$) • Sleep studies ($n=1$)	No	No
Schrey et al. [28]	Unspecified	No	No

(Continues)

TABLE 2 | (Continued)

Study	Assessments	Sufficient details about assessment operations protocol?	Sufficient details about assessment interpretation protocol?
Taira et al. [29]	• PFT (FVC) • A combination of clinical assessment (clinical history review [i.e., observed macroaspiration] and patient interviews) and imaging (chest radiography) to identify aspiration pneumonia	No	Partial; FVC < 80% predicted was used to identify respiratory dysfunction, but the parameters for the other assessments were not reported sufficiently
Teixeira et al. [30]	• Clinical assessment (10 cm dyspnea visual analog scale, tidal inspiratory abdominal paradox, and respiratory pulse) • PFT (VC, FEV_1, FEV_1/VC, TLC, FRC, RV, TLCO, MIP, and MEP) • ABG testing (PaO_2, $PaCO_2$, and pH) • Electrophysiological testing (phrenic nerve conduction study [i.e., static mouth pressure twitch, rib cage and abdominal displacements, and transdiaphragmatic pressure] and diaphragmatic EMG)	Yes	Partial; some parameters were reported (e.g., static mouth pressure twitch < 10 cm H_2O, MIP < 50% predicted, and MEP < 50% predicted) but other parameters were unspecified (e.g., other PFT properties, rib cage and abdominal displacements, and diaphragmatic EMG)
Voermans et al. [31]	• ABG testing (PCO_2 and HCO_3) • Electrophysiological testing (phrenic nerve conduction study and EMG of respiratory muscles) • PFT (VC, MIP, and MEP)	No	Partial; VC of 2.6 L, MIP of 6.9 kPa, and MEP of 8.9 kPa were used to identify respiratory dysfunction, but the parameters for the other assessments were not reported
*Aggarwal et al. [32]	PFT (spirometry was used, but the properties measured were unspecified)	No	No
*Bautista et al. [33]	• ABG testing (pH, PCO_2, and HCO_3) • PFT (rapid shallow breathing index and NIF)	No	Partial; the parameters for PFT were reported but not for ABG testing

Note: An asterisk indicates that the study was obtained from gray literature.
Abbreviations: ABG, arterial blood gas; EMG, electromyography; f/VT, respiratory frequency to tidal volume ratio; FEV_1, forced expiratory volume in 1 s; FEV_1/VC, forced expiratory volume in 1 s to vital capacity ratio; FRC, functional residual capacity; FVC, forced vital capacity; HCO_3, bicarbonate; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; NIF, negative inspiratory force; $P_{0.1}$, airway occlusion pressure at 100 ms; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; PFT, pulmonary function testing; pH, acidity or alkalinity level of blood; PO_2, partial pressure of oxygen; RV, residual volume; SpO_2, oxygen saturation; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; VC, vital capacity; VT, tidal volume.

determining underlying respiratory dysfunction [41, 42]. It is recommended that PFT results be correlated to or interpreted with other assessments and clinical information (e.g., symptoms and exposures) [41, 42]. We can appreciate relatively more comprehensive assessments in the other half of those studies that used a combination of assessments [20, 21, 27, 29–31, 33]. Interestingly, all of the studies that used a combination of assessments implemented PFT.

TABLE 3 | Physiological respiratory characteristics.

Study	Respiratory properties reported	Respiratory dysfunction explicitly identified?	Respiratory dysfunction classification
Alhammad & Naddaf [17]	• FVC (% predicted) = 54 • **Oximetry was "normal"	Yes	Unspecified
Benveniste et al. [18]	Sirolimus group: *Baseline* • FVC (% predicted): Mdn (IQR) = 109.5 (97.3–121.8) • FVC (L): Mdn (IQR) = 3.5 (2.5–4.5) *Follow-up (12 months)* • Percent change in FVC (% predicted): Mdn (IQR) = 2.4 (−3.6–7.65) • Percent change in FVC (L): Mdn (IQR) = 0.38 (−4.68–6.28) Placebo group: *Baseline* • FVC (% predicted): Mdn (IQR) = 109 (89.8–115) • FVC (L): Mdn (IQR) = 3.28 (2.75–4.24) *Follow-up (12 months)* • Percent change in FVC (% predicted): Mdn (IQR) = −5.26 (−8.8–(−0.45)) • Percent change in FVC (L): Mdn (IQR) = −5.95 (−9.39–(−1.47))	No; however, respiratory dysfunction can be inferred because the placebo group's FVC decreased over time	Unspecified
Brokamp et al. [19]	Entire cohort: • FVC (% predicted): M (SD) = 80.57 (20.99) • FVC (L): M (SD) = 3.08 (1.0) Ventilatory pump impairment group: • FVC (% predicted): M = 68.60 • FVC (L): M = 2.77 Nonventilatory pump impairment group: • FVC (% predicted): M = 97.97 • FVC (L): M = 3.52 Patients with available follow-up data (n = 29): *Baseline* • FVC (% predicted): M = 80.83 • FVC (L): M = 3.001 • 66% of patients had an atypical FVC *Follow-up (duration from baseline [M] = 2.6 years)* • FVC (% predicted): M = 73.64 • FVC (L): M = 2.7 • 76% of patients had an atypical FVC	Yes	Restrictive

(Continues)

TABLE 3 | (Continued)

Study	Respiratory properties reported	Respiratory dysfunction explicitly identified?	Respiratory dysfunction classification
Cohen et al. [20]	• **Chest radiograph was "normal" • **Physical examination showed poor airway entry into the lungs • pH = 7.4 • PCO_2 (mm Hg) = 49 • PO_2 (mm Hg) = 55 • NIF (cm H_2O) = −12	Yes	Unspecified
Cordeiro de Souza et al. [21]	Baseline (before azathioprine treatment and inspiratory muscle training was initiated): • PaO_2 (mm Hg) < 60 • $PaCO_2$ (mm Hg) > 45 • Static lung compliance (mL/cm H_2O) = 55 • Breathing frequency (bpm) = 21 • VT (L) = 0.39 • f/VT index (bpm/L) = 54 • SpO_2 (%) = 95; FIO_2 (%) = 35 • $P_{0.1}$ (cm H_2O) = 4.66 • MIP (cm H_2O) = 20 (about 17% of the expected value) • Timed inspiratory effort (cm H_2O/s) = 0.54 (about 50% of the expected value) Follow-up (4 weeks): • MIP (cm H_2O) = 50	Yes	Unspecified
Dardis et al. [22]	Baseline: • FVC (% predicted) = 30 Follow-up (5 years): • The patient was unable to perform PFT on recurrent admissions; later, an autopsy revealed severe diaphragmatic atrophy and fibrosis in the setting of IBM	Yes	Restrictive
Goyal et al. [23]	Seropositive group: • FVC (% predicted): Mdn (min, max) = 81.5 (32, 97) • NIF (cm H_2O): Mdn (min, max) = −66 (−112, −24) Seronegative group: • FVC (% predicted): Mdn (min, max) = 92 (84, 102) • NIF (cm H_2O): Mdn (min, max) = −102 (−150, −29)	Yes	Unspecified

(Continues)

TABLE 3 | (Continued)

Study	Respiratory properties reported	Respiratory dysfunction explicitly identified?	Respiratory dysfunction classification
Martin et al. [24]	**Computed tomography showed bilateral widespread diaphragmatic thickening	Yes	Unspecified
Oh et al. [25]	**8 patients died due to respiratory failure in the setting of aspiration pneumonia	No; however, respiratory dysfunction can be inferred because aspiration pneumonia was reported	Unspecified
Ramirez Ramirez & Hillman [26]	**The patient developed two episodes of aspiration pneumonia	No; however, respiratory dysfunction can be inferred because aspiration pneumonia was reported	Unspecified
Salam et al. [27]	• FVC (% predicted): Mdn (range) = 51 (22–68) • **Diaphragmatic ultrasound showed left diaphragmatic weakness • **Sleep study showed nocturnal hypoventilation	Yes	Unspecified
Schrey et al. [28]	**Prior to cricopharyngeal Botox injection, 3 patients had frank aspiration pneumonia; at least 6 months postinjection, no patients developed aspiration pneumonia	No; however, respiratory dysfunction can be inferred because aspiration pneumonia was reported	Unspecified
Taira et al. [29]	CPB+ group: • FVC (% predicted): Mdn (IQR) = 91 (82–101) CPB− group: • FVC (% predicted): Mdn (IQR) = 118 (101–122) Entire cohort: • FVC (% predicted): Mdn (IQR) = 107 (88–119) • FVC of 5 patients were < 80% (the threshold used as a marker for reduced FVC) **10 patients (9 patients in the CPB+ group) developed aspiration pneumonia	Yes	Unspecified

(Continues)

TABLE 3 | (Continued)

Study	Respiratory properties reported	Respiratory dysfunction explicitly identified?	Respiratory dysfunction classification
Teixeira et al. [30]	• Dyspnea rating: M (SD) = 1.1 (1.4) • **Tidal inspiratory abdominal paradox was absent for all patients • **Respiratory pulse was absent for all patients • VC (% predicted): M (SD) = 0.94 (0.22) • FEV_1 (% predicted): M (SD) = 0.86 (0.16) • FEV_1/VC: M (SD) = 1.09 (0.38) • TLC (% predicted): M (SD) = 0.93 (0.16) • FRC (% predicted): M (SD) = 0.95 (0.13) • RV (% predicted): M (SD) = 0.96 (0.12) • TLCO (% predicted): M (SD) = 0.72 (0.12) • PaO2 (mmHg): M (SD) = 86.3 (10.1) • $PaCO_2$ (mmHg): M (SD) = 36.2 (1.6) • pH (mmHg): M (SD) = 7.43 (0.03) • Static mouth pressure twitch (cm H_2O): M (SD) = 6.81 (2.99) • **MIP, MEP, rib cage and abdominal displacements, transdiaphragmatic pressure, and diaphragmatic EMG results were unspecified	Yes	Unspecified
Voermans et al. [31]	• PCO_2 (kPa) = 7.9 • HCO_3 (mmol/L) = 33.7 • **Phrenic nerve conduction study showed that the compound motor action potential of the diaphragm had low amplitudes bilaterally • **EMG of respiratory muscles showed inadequate recruitment and no spontaneous activity of the diaphragm and intercostal muscles • VC (L) = 1.87 • MIP (kPa) = 1.90 • MEP (kPa) = 3.01	Yes	Restrictive

(Continues)

TABLE 3 | (Continued)

Study	Respiratory properties reported	Respiratory dysfunction explicitly identified?	Respiratory dysfunction classification
*Aggarwal et al. [32]	• **Spirometry showed a restrictive pattern for all patients, ranging from mild to moderately severe	Yes	The study reported a restrictive abnormality, but the precise respiratory properties were unspecified
*Bautista et al. [33]	• pH = 7.39 • PCO_2 (mmHg) = 62 • HCO_3 (mmol/L) = 37 • Rapid shallow breathing index = 151 • NIF (cm H_2O) = −12	Yes	Unspecified

Note: A single asterisk (*) indicates that the study was obtained from grey literature. A double asterisk (**) indicates that there were insufficient details about the precise physiological respiratory properties measured with the assessment performed.

Abbreviations: CPB, cricopharyngeal bar; EMG, electromyography; f/VT, respiratory frequency to tidal volume ratio; FEV_1, forced expiratory volume in 1 s; FEV_1/VC, forced expiratory volume in 1 s to vital capacity ratio; FIO_2, fraction of inspired oxygen; FRC, functional residual capacity; FVC, forced vital capacity; HCO_3, bicarbonate; IBM, inclusion body myositis; IQR, interquartile range; M, mean; Max, maximum; Mdn, median; MEP, maximal expiratory pressure; Min, minimum; MIP, maximal inspiratory pressure; NIF, negative inspiratory force; $P_{0.1}$, airway occlusion pressure at 100 ms; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; PFT, pulmonary function testing; pH, acidity or alkalinity level of blood; PO_2, partial pressure of oxygen; RV, residual volume; SD, standard deviation; SpO_2, oxygen saturation; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; VC, vital capacity; VT, tidal volume.

Across all studies, some degree of respiratory involvement was observed. Several physiological respiratory characteristics that may explain respiratory dysfunction in IBM emerged from the assessments (Table 3). A major challenge to interpreting and extrapolating these data is the insufficiently detailed reporting of information. This trend mainly involved the lack of information reported about race/ethnicity, disease duration and severity, and assessment operations and interpretation protocols (Tables 1 and 2). These variables are important for better understanding IBM and its impact on the respiratory mechanism. Although IBM has historically been considered a disease affecting White individuals, recent work has shown that IBM can have a substantial impact on non-White patients [43]. The lack of race/ethnicity details ignores potentially relevant genetic, cultural, and environmental differences that may affect the progression of respiratory dysfunction and intervention responsiveness. Atypical and heterogeneous phenotypes of IBM have also been detected, particularly at early disease onset [44]. Thus, poor reporting of disease duration and severity across the reviewed studies may limit our ability to explain any variability in physiological respiratory phenotypes, classify such phenotypes, and perform predictive modeling. It can also lead to delayed diagnosis or misdiagnosis.

Insufficient reporting of assessment operations and interpretation protocols poses significant problems that undermine the reliability, reproducibility, and internal validity of the evidence. For example, differences in PFT technique and the sensitivity and specificity of equipment may impact measurements of respiratory function. As such, a nuanced comparison of data between studies is limited and not advisable, so we opted to only comment on the broader respiratory dysfunction classification reported. There were four studies that classified respiratory dysfunction [19, 22, 31, 32]. Each study indicated restrictive respiratory abnormalities based on PFT results. Two studies reported reduced FVC [19, 22]. One study reported reduced maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and vital capacity (VC) [31]. The last study did not indicate the PFT respiratory properties used to determine a restrictive respiratory abnormality [32]. Reduced FVC [41, 45], MIP, MEP, and VC scores [46–49] can be suggestive of restrictive respiratory abnormalities.

However, the findings associated with respiratory dysfunction classification in IBM should be carefully construed because assessment interpretation protocols were insufficiently or partially described across studies [17, 20–22, 24–33]. In addition, fixed cutoff thresholds for interpreting properties like FVC were mainly employed for respiratory dysfunction classification [19, 23, 29], but this approach is no longer recommended. Present-day standards state that it is more superior to interpret PFT properties comprehensively by capturing metrics of airflow, lung volume, and gas transfer to detect the type of respiratory dysfunction classification [41]. In the setting of IBM's insidious chronic skeletal muscle weakness, restrictive respiratory abnormalities seem logical, as this pattern of respiratory dysfunction involves difficulty inhaling fully because of extrapulmonary issues (e.g., weakness and decreased chest compliance). Restrictive respiratory abnormalities are also common in neuromuscular diseases like Parkinson's disease [50] that share similar molecular and clinical phenotypes to IBM [51, 52]. Nonetheless, the classification of restrictive respiratory abnormalities requires FVC, forced expiratory volume in 1 s, and total lung capacity scores to fall below the lower boundaries of normal, defined according to an individual's baseline or predisease status [41].

We acknowledge that our review had some limitations. First, we only included obtainable English records in our review. Second, we did not perform a critical appraisal of the studies, which is permissible for scoping reviews. Third, we excluded studies that involved patients with IBM and comorbid OSA, which likely contributed to the predominance of restrictive respiratory abnormalities. However, obstructive respiratory abnormalities may not always be linked to OSA (e.g., paradoxical chest wall insufficiency). Because we intended to isolate respiratory involvement directly ascribed to IBM, we removed OSA's potential confounding effect as it can have heterogeneous and multifactorial pathogenesis. Fourth, we included two conference abstracts from gray literature in our calculations. This choice was made to provide a broader representation of the evidence, but we are aware that conference abstracts are word-constrained and inherently limited in the information they can report. Finally, while we aimed to broadly capture respiratory dysfunction in IBM, our discussion largely focused on the functional aspects surrounding such issues because most studies assessed functional respiratory outcomes as opposed to measures of structural integrity.

5 | Conclusion

Despite respiratory dysfunction being extensively documented as a primary source of mortality in IBM, the mechanism underlying this issue has yet to be well defined. Our scoping review intended to clarify this issue. However, in the limited and mainly low-level evidence available, we found that accurate and nuanced interpretations of the physiological respiratory characteristics reported are primarily based on insufficiently described study demographics and assessment protocols, and outdated assessment interpretation standards. Nonetheless, reflecting on the available evidence provides valuable insight and gives us the opportunity to recalibrate future work to maximize the reliability, validity, and generalizability of conclusions drawn about respiratory dysfunction in IBM. We recommend that future work focus on systematic, rigorous, and prospective efforts in exploring respiratory biomechanics and function in IBM, including standardized cough, lung, and respiratory muscle metrics. Future work should strive to comply with the current best practices for performing, interpreting, and reporting respiratory assessments as outlined by the American Thoracic Society and the European Respiratory Society.

Author Contributions

K.R.A. led the conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, and writing (original draft, reviewing, and editing). B.R.R. assisted with the investigation and validation. R.A. contributed to the methodology, validation, and writing (reviewing and editing). D.L. contributed to the methodology, validation, and writing (reviewing and editing). G.K. contributed to the investigation, methodology, resources, and writing (reviewing and editing). K.L.G. supervised and contributed to

conceptualization, investigation, methodology, validation, and writing (reviewing and editing).

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

All data generated or analyzed during this study are included in this published article and the Supporting Information file.

References

1. N. C. Anderson and T. E. Lloyd, "Inclusion Body Myositis: An Update," *Current Opinion in Rheumatology* 37, no. 1 (2024): 80–85, https://doi.org/10.1097/bor.0000000000001060.

2. S. A. Greenberg, "Inclusion Body Myositis: Clinical Features and Pathogenesis," *Nature Reviews Rheumatology* 15, no. 5 (2019): 257–272, https://doi.org/10.1038/s41584-019-0186-x.

3. V. Guglielmi, M. Cheli, P. Tonin, and G. Vattemi, "Sporadic Inclusion Body Myositis at the Crossroads Between Muscle Degeneration, Inflammation, and Aging," *International Journal of Molecular Sciences* 25, no. 5 (2024): 2742, https://doi.org/10.3390/ijms25052742.

4. J. B. Lilleker, E. Naddaf, C. G. J. Saris, et al., "272nd ENMC International Workshop: 10 Years of Progress—Revision of the ENMC 2013 Diagnostic Criteria for Inclusion Body Myositis and Clinical Trial Readiness. 16–18 June 2023, Hoofddorp, the Netherlands," *Neuromuscular Disorders* 37 (2024): 36–51, https://doi.org/10.1016/j.nmd.2024.03.001.

5. F. M. Cox, M. J. Titulaer, J. K. Sont, A. R. Wintzen, J. J. G. M. Verschuuren, and U. A. Badrising, "A 12-Year Follow-Up in Sporadic Inclusion Body Myositis: An End Stage With Major Disabilities," *Brain* 134, no. 11 (2011): 3167–3175, https://doi.org/10.1093/brain/awr217.

6. E. Naddaf, S. Shelly, J. Mandrekar, et al., "Survival and Associated Comorbidities in Inclusion Body Myositis," *Rheumatology* 61, no. 5 (2022): 2016–2024, https://doi.org/10.1093/rheumatology/keab716.

7. M. Price, V. Barghout, O. Benveniste, et al., "Mortality and Causes of Death in Patients With Sporadic Inclusion Body Myositis: Survey Study Based on the Clinical Experience of Specialists in Australia, Europe and the USA," *Journal of Neuromuscular Diseases* 3, no. 1 (2016): 67–75, https://doi.org/10.3233/jnd-150138.

8. S. Shelly, M. M. Mielke, J. Mandrekar, et al., "Epidemiology and Natural History of Inclusion Body Myositis: A 40-Year Population-Based Study," *Neurology* 96, no. 21 (2021): e2653–e2661, https://doi.org/10.1212/WNL.0000000000012004.

9. P. M. Rodríguez Cruz, M. Needham, P. Hollingsworth, F. L. Mastaglia, and D. R. Hillman, "Sleep Disordered Breathing and Subclinical Impairment of Respiratory Function Are Common in Sporadic Inclusion Body Myositis," *Neuromuscular Disorders* 24, no. 12 (2014): 1036–1041, https://doi.org/10.1016/j.nmd.2014.08.003.

10. Z. Munn, M. Peters, C. Stern, et al., "Systematic Review or Scoping Review? Guidance for Authors When Choosing Between a Systematic or Scoping Review Approach," *BMC Medical Research Methodology* 18, no. 1 (2018): 1–7, https://doi.org/10.1186/s12874-018-0611-x.

11. A. C. Tricco, E. Lillie, W. Zarin, et al., "PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation," *Annals of Internal Medicine* 169, no. 7 (2018): 467–473, https://doi.org/10.7326/M18-0850.

12. G. Della Marca, C. Sancricca, A. Losurdo, et al., "Sleep Disordered Breathing in a Cohort of Patients With Sporadic Inclusion Body Myositis," *Clinical Neurophysiology* 124, no. 8 (2013): 1615–1621, https://doi.org/10.1016/j.clinph.2013.03.002.

13. D. J. Eckert and A. Malhotra, "Pathophysiology of Adult Obstructive Sleep Apnea," *Proceedings of the American Thoracic Society* 5, no. 2 (2008): 144–153, https://doi.org/10.1513/pats.200707-114MG.

14. R. Lv, X. Liu, Y. Zhang, et al., "Pathophysiological Mechanisms and Therapeutic Approaches in Obstructive Sleep Apnea Syndrome," *Signal Transduction and Targeted Therapy* 8, no. 1 (2023): 218, https://doi.org/10.1038/s41392-023-01496-3.

15. C. E. Jackson, R. J. Barohn, G. Gronseth, et al., "Inclusion Body Myositis Functional Rating Scale: A Reliable and Valid Measure of Disease Severity," *Muscle & Nerve* 37, no. 4 (2008): 473–476, https://doi.org/10.1002/mus.20958.

16. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

17. R. M. Alhammad and E. Naddaf, "Myopathies Presenting With Head Drop: Clinical Spectrum and Treatment Outcomes," *Neuromuscular Disorders* 30, no. 2 (2020): 128–136, https://doi.org/10.1016/j.nmd.2019.12.001.

18. O. Benveniste, J. Y. Hogrel, L. Belin, et al., "Sirolimus for Treatment of Patients With Inclusion Body Myositis: A Randomised, Double-Blind, Placebo-Controlled, Proof-Of-Concept, Phase 2b Trial," *Lancet Rheumatology* 3, no. 1 (2021): e40–e48, https://doi.org/10.1016/S2665-9913(20)30280-0.

19. G. Brokamp, L. Hurst, L. Hartog, et al., "Characterizing Ventilatory Muscle Dysfunction in Inclusion Body Myositis," *American Journal of Physical Medicine & Rehabilitation* 102, no. 5 (2023): 427–432, https://doi.org/10.1097/PHM.0000000000002114.

20. R. Cohen, S. Lipper, and D. R. Dantzker, "Inclusion Body Myositis as a Cause of Respiratory Failure," *Chest* 104, no. 3 (1993): 975–977, https://doi.org/10.1378/chest.104.3.975.

21. L. Cordeiro de Souza, J. F. Campos, L. P. Daher, et al., "Mechanical Ventilation Weaning in Inclusion Body Myositis: Feasibility of Isokinetic Inspiratory Muscle Training as an Adjunct Therapy," *Case Reports in Critical Care* 2014 (2014): 902541, https://doi.org/10.1155/2014/902541.

22. C. Dardis, A. Antezana, K. Tanji, and P. J. Maccabee, "Inclusion Body Myositis: A Case Presenting With Respiratory Failure and Autopsy Findings Leading to the Hypothesis of a Paraneoplastic Cause," *American Journal of Case Reports* 18 (2017): 700–706, https://doi.org/10.12659/ajcr.903566.

23. N. A. Goyal, T. M. Cash, U. Alam, et al., "Seropositivity for NT5c1A Antibody in Sporadic Inclusion Body Myositis Predicts More Severe Motor, Bulbar and Respiratory Involvement," *Journal of Neurology, Neurosurgery, and Psychiatry* 87, no. 4 (2016): 373–378, https://doi.org/10.1136/jnnp-2014-310008.

24. S. E. Martin, D. D. Gondim, and E. M. Hattab, "Inclusion Body Myositis Involving the Diaphragm: Report of a Pathologically Confirmed Case," *Neurology India* 62, no. 1 (2014): 66–67, https://doi.org/10.4103/0028-3886.128313.

25. T. H. Oh, K. A. Brumfield, T. L. Hoskin, J. L. Kasperbauer, and J. R. Basford, "Dysphagia in Inclusion Body Myositis: Clinical Features, Management, and Clinical Outcome," *American Journal of Physical Medicine & Rehabilitation* 87, no. 11 (2008): 883–889, https://doi.org/10.1097/PHM.0b013e31818a50e2.

26. O. A. Ramirez Ramirez and L. Hillman, "An Unusual Disease With a Common Presentation: Cricopharyngeal Dysfunction in Inclusion

Body Myositis," *ACG Case Reports Journal* 10, no. 11 (2023): e01194, https://doi.org/10.14309/crj.0000000000001194.

27. S. Salam, J. M. Morrow, R. Howard, J. A. L. Miller, R. M. Quinlivan, and P. M. Machado, "Two Emerging Phenotypes of Atypical Inclusion Body Myositis: Illustrative Cases," *Clinical and Experimental Rheumatology* 41, no. 2 (2023): 340–347, https://doi.org/10.55563/clinexprheumatol/jq7zxd.

28. A. Schrey, L. Airas, M. Jokela, and J. Pulkkinen, "Botulinum Toxin Alleviates Dysphagia of Patients With Inclusion Body Myositis," *Journal of the Neurological Sciences* 380 (2017): 142–147, https://doi.org/10.1016/j.jns.2017.07.031.

29. K. Taira, T. Yamamoto, M. Mori-Yoshimura, et al., "Obstruction-Related Dysphagia in Inclusion Body Myositis: Cricopharyngeal Bar on Videofluoroscopy Indicates Risk of Aspiration," *Journal of the Neurological Sciences* 413 (2020): 116764, https://doi.org/10.1016/j.jns.2020.116764.

30. A. Teixeira, P. Cherin, A. Demoule, et al., "Diaphragmatic Dysfunction in Patients With Idiopathic Inflammatory Myopathies," *Neuromuscular Disorders* 15, no. 1 (2005): 32–39, https://doi.org/10.1016/j.nmd.2004.09.006.

31. N. C. Voermans, M. Vaneker, G. J. Hengstman, et al., "Primary Respiratory Failure in Inclusion Body Myositis," *Neurology* 63, no. 11 (2004): 2191–2192, https://doi.org/10.1212/01.wnl.0000145834.17020.86.

32. P. Aggarwal, W. Arnold, J. Reynolds, J. Kissel, and B. Elsheikh, "Restrictive Ventilatory Defect in Patients With Inclusion Body Myositis (P07.222)," *Neurology* 78 (2012): P07.222, https://doi.org/10.1212/wnl.78.1_meetingabstracts.p07.222.

33. M. T. Bautista, R. Sharma, A. Orenstein, and M. J. Farmer, "1362: Primary Respiratory Failure in a Patient With Inclusion Body Myositis," *Critical Care Medicine* 41, no. 12 (2013): A353, https://doi.org/10.1097/01.ccm.0000440592.22156.dd.

34. OCEBM Levels of Evidence Working Group*, *The Oxford Levels of Evidence 2* (Oxford Centre for Evidence-Based Medicine, 2011), https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.

35. X. Wang and M. W. Kattan, "Cohort Studies: Design, Analysis, and Reporting," *Chest* 158, no. 1S (2020): S72–S78, https://doi.org/10.1016/j.chest.2020.03.014.

36. P. Košutova and P. Mikolka, "Aspiration Syndromes and Associated Lung Injury: Incidence, Pathophysiology and Management," *Physiological Research* 70, no. Suppl4 (2021): S567–S583, https://doi.org/10.33549/physiolres.934767.

37. J. Almirall, R. Boixeda, M. C. de la Torre, and A. Torres, "Aspiration Pneumonia: A Renewed Perspective and Practical Approach," *Respiratory Medicine* 185 (2021): 106485, https://doi.org/10.1016/j.rmed.2021.106485.

38. K. R. Ambrocio, K. L. F. Garand, B. Roy, A. M. Bhutada, and G. A. Malandraki, "Diagnosing and Managing Dysphagia in Inclusion Body Myositis: A Systematic Review," *Rheumatology (Oxford, England)* 62, no. 10 (2023): 3227–3244, https://doi.org/10.1093/rheumatology/kead194.

39. K. R. Ambrocio, R. Aggarwal, D. Lacomis, X. Zhang, and K. L. F. Garand, "Features of Swallowing Function in Sporadic Inclusion Body Myositis: Preliminary Evidence Using Well-Tested Assessment Frameworks," *American Journal of Speech-Language Pathology* 33, no. 6 (2024): 2793–2804, https://doi.org/10.1044/2024_AJSLP-24-00061.

40. E. J. Heckman and G. T. O'Connor, "Pulmonary Function Tests for Diagnosing Lung Disease," *Journal of the American Medical Association* 313, no. 22 (2015): 2278–2279, https://doi.org/10.1001/jama.2015.4466.

41. S. Stanojevic, D. A. Kaminsky, M. R. Miller, et al., "ERS/ATS Technical Standard on Interpretive Strategies for Routine Lung Function Tests," *European Respiratory Journal* 60, no. 1 (2022): 2101499, https://doi.org/10.1183/13993003.01499-2021.

42. T. J. Barreiro and I. Perillo, "An Approach to Interpreting Spirometry," *American Family Physician* 69, no. 5 (2004): 1107–1114.

43. E. H. Michelle, I. Pinal-Fernandez, M. Casal-Dominguez, et al., "Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis," *Neurology* 100, no. 13 (2023): e1406–e1417, https://doi.org/10.1212/WNL.0000000000206777.

44. M. Alamr, M. V. Pinto, and E. Naddaf, "Atypical Presentations of Inclusion Body Myositis: Clinical Characteristics and Long-Term Outcomes," *Muscle & Nerve* 66, no. 6 (2022): 686–693, https://doi.org/10.1002/mus.27716.

45. L. McMahon, D. McGrath, C. Blake, and O. Lennon, "Responsiveness of Respiratory Function in Parkinson's Disease to an Integrative Exercise Programme: A Prospective Cohort Study," *PLoS One* 19, no. 3 (2024): e0301433, https://doi.org/10.1371/journal.pone.0301433.

46. X. Dong, Y. Gao, M. Li, D. Wang, J. Li, and Y. Zhang, "Characteristics of Chest HRCT and Pulmonary Function Tests in Elderly-Onset Primary Sjögren Syndrome With Interstitial Lung Disease," *Medicine (Baltimore)* 102, no. 8 (2023): e32952, https://doi.org/10.1097/MD.0000000000032952.

47. J. H. Park, S. W. Kang, S. C. Lee, W. A. Choi, and D. H. Kim, "How Respiratory Muscle Strength Correlates With Cough Capacity in Patients With Respiratory Muscle Weakness," *Yonsei Medical Journal* 51, no. 3 (2010): 392–397, https://doi.org/10.3349/ymj.2010.51.3.392.

48. K. H. Park, R. B. Kim, J. Yang, et al., "Reference Range of Respiratory Muscle Strength and Its Clinical Application in Amyotrophic Lateral Sclerosis: A Single-Center Study," *Journal of Clinical Neurology* 12, no. 3 (2016): 361–367, https://doi.org/10.3988/jcn.2016.12.3.361.

49. R. Pellegrino, G. Viegi, V. Brusasco, et al., "Interpretative Strategies for Lung Function Tests," *European Respiratory Journal* 26, no. 5 (2005): 948–968, https://doi.org/10.1183/09031936.05.00035205.

50. Y. C. Aquino, L. M. Cabral, N. C. Miranda, et al., "Respiratory Disorders of Parkinson's Disease," *Journal of Neurophysiology* 127, no. 1 (2022): 1–15, https://doi.org/10.1152/jn.00363.2021.

51. V. Askanas, W. K. Engel, and A. Nogalska, "Sporadic Inclusion-Body Myositis: A Degenerative Muscle Disease Associated With Aging, Impaired Muscle Protein Homeostasis and Abnormal Mitophagy," *Biochimica et Biophysica Acta* 1852, no. 4 (2015): 633–643, https://doi.org/10.1016/j.bbadis.2014.09.005.

52. C. Terracciano, A. Nogalska, W. K. Engel, S. Wojcik, and V. Askanas, "In Inclusion-Body Myositis Muscle Fibers Parkinson-Associated DJ-1 Is Increased and Oxidized," *Free Radical Biology & Medicine* 45, no. 6 (2008): 773–779, https://doi.org/10.1016/j.freeradbiomed.2008.05.030.

Supporting Information

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LETTER TO THE EDITOR

Sociodemographic and Hospital-Level Disparities in Cardiovascular Hospitalizations Among Adults With Systemic Lupus Erythematosus: A Retrospective Cohort Study

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Dear Editor,

Survival in systemic lupus erythematosus (SLE) has improved, yet cardiovascular morbidity and mortality remain disproportionately high [1–3]. Chronic inflammation, endothelial dysfunction, and traditional risk factors synergistically accelerate atherosclerosis in SLE, with systemic inflammation independently predicting adverse cardiovascular events [4]. Although hospitalization rates for cardiovascular complications are rising, the drivers of these admissions and the role of social determinants of health are incompletely understood [5]. We therefore examined sociodemographic and hospital-level predictors of cardiovascular-related hospitalizations in a contemporary, national SLE cohort.

This retrospective cohort study utilized hospitalization records from the Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) from January 1, 2016, to December 31, 2021 [6]. This database is the largest publicly available all-payer inpatient database in the United States, which, when weighted, provides national estimates representing more than 35 million hospitalizations annually. As publicly available, de-identified data were used, informed consent or local institutional review board approval was waived. Hospitalizations were identified for adults aged ≥18 years with a diagnosis of SLE using the International Classification of Diseases, Tenth Revision (ICD-10) codes—M32.1x, M32.8, and M32.9. Cardiovascular hospitalization was determined by the principal diagnosis (ICD-10-CM codes I00–I99) recorded for each admission. The primary outcome of interest was cardiovascular-related hospitalization, categorized into specific events, including heart failure (HF), coronary artery disease (CAD), atrial fibrillation (AF), and stroke. National-level estimates were generated from discharge weights assigned to each hospitalization. Descriptive statistics were used to characterize the cohort, with categorical variables reported as counts and percentages. Multivariable modified Poisson regression with robust variance estimates was used to assess associations between sociodemographic and hospital-level factors and cardiovascular hospitalizations. We constructed a model that adjusted for sociodemographic factors and comorbid conditions. Generalized estimating equations (GEEs) with a compound symmetry correlation matrix were used to account for clustering at the hospital level. Effect sizes were expressed as relative risk (RRs) and their corresponding 95% confidence intervals (CIs). Statistical significance was set at a two-sided $p < 0.05$.

A total of 165 290 cardiovascular hospitalizations from 2016 to 2021 for patients with SLE were identified (Table 1). Most

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence intervals; CKD, chronic kidney disease; HF, heart failure; IHD, ischemic heart disease; NHB, non-Hispanic Black; NHW, non-Hispanic White; RR, relative risk; SLE, systemic lupus erythematosus.

TABLE 1 | Characteristics of major cardiovascular causes of admission among hospitalizations with SLE.

Variables	2016	2017	2018	2019	2020	2021	Total	*p*
N	24 910	28 235	28 675	30 230	25 675	27 565	165 290	
Age								
18–44	6405 (25.71)	6930 (24.54)	7015 (24.46)	7540 (24.94)	6240 (24.30)	6190 (22.46)	40 320 (24.39)	< 0.001
45–64	9795 (39.32)	11 405 (40.39)	11 150 (38.88)	11 330 (37.48)	9490 (36.96)	10 350 (37.55)	63 520 (38.43)	
65+	8710 (34.97)	9900 (35.06)	10 510 (36.65)	11 360 (37.58)	9945 (38.73)	11 025 (40.00)	61 450 (37.18)	
Female	21 175 (85.01)	23 955 (84.84)	24 330 (84.85)	25 470 (84.25)	21 805 (84.93)	23 355 (84.73)	140 090 (84.75)	0.9264
Race								
White	12 160 (48.82)	13 445 (47.62)	13 545 (47.24)	14 465 (47.85)	12 490 (48.65)	13 530 (49.08)	79 635 (48.18)	0.4996
Black	8770 (35.21)	9970 (35.31)	9980 (34.80)	10 735 (35.51)	8860 (34.51)	9050 (32.83)	57 365 (34.71)	
Hispanic	2755 (11.06)	3315 (11.74)	3705 (12.92)	3570 (11.81)	3005 (11.70)	3570 (12.95)	19 920 (12.05)	
Asian or Pacific Islander	430 (1.73)	645 (2.28)	590 (2.06)	670 (2.22)	440 (1.71)	610 (2.21)	3385 (2.05)	
Native American	125 (0.50)	190 (0.67)	165 (0.58)	130 (0.43)	145 (0.56)	150 (0.54)	905 (0.55)	
Other	670 (2.69)	670 (2.37)	690 (2.41)	660 (2.18)	735 (2.86)	655 (2.38)	4080 (2.47)	
Hospital bed size								
Small	3670 (14.73)	4655 (16.49)	4880 (17.02)	5485 (18.14)	5015 (19.53)	4965 (18.01)	28 670 (17.35)	0.1784
Medium	6610 (26.54)	8085 (28.63)	7925 (27.64)	8410 (27.82)	6840 (26.64)	7290 (26.45)	45 160 (27.32)	
Large	14 630 (58.73)	15 495 (54.88)	15 870 (55.34)	16 335 (54.04)	13 820 (53.83)	15 310 (55.54)	91 460 (55.33)	
Hospital teaching status								
Rural	1495 (6.00)	1470 (5.21)	1520 (5.30)	1565 (5.18)	1295 (5.04)	1605 (5.82)	8950 (5.41)	< 0.001
Urban non-teaching	5585 (22.42)	5485 (19.43)	4960 (17.30)	4595 (15.20)	3710 (14.45)	4055 (14.71)	28 390 (17.18)	
Urban teaching	17 830 (71.58)	21 280 (75.37)	22 195 (77.40)	24 070 (79.62)	20 670 (80.51)	21 905 (79.47)	127 950 (77.41)	
Admission								
Elective	2805 (11.26)	3190 (11.30)	2935 (10.24)	3415 (11.30)	2465 (9.60)	2840 (10.30)	17 650 (10.68)	0.0401

(Continues)

TABLE 1 | (Continued)

Variables	2016	2017	2018	2019	2020	2021	Total	*p*
Median household income, $								
1–28 999	9085 (36.47)	10 610 (37.58)	10 315 (35.97)	10 990 (36.35)	9555 (37.22)	9740 (35.33)	60 295 (36.48)	0.8246
29 000–35 999	6095 (24.47)	7080 (25.08)	7345 (25.61)	7675 (25.39)	6680 (26.02)	6865 (24.90)	41 740 (25.25)	
36 000–46 999	5595 (22.46)	6035 (21.37)	6320 (22.04)	6610 (21.87)	5365 (20.90)	6165 (22.37)	36 090 (21.83)	
47 000+	4135 (16.60)	4510 (15.97)	4695 (16.37)	4955 (16.39)	4075 (15.87)	4795 (17.40)	27 165 (16.43)	
Hospital region								
Northeast	4740 (19.03)	4895 (17.34)	4875 (17.00)	5165 (17.09)	4555 (17.74)	5055 (18.34)	29 285 (17.72)	0.9973
Midwest	4905 (19.69)	5735 (20.31)	6165 (21.50)	6480 (21.44)	5325 (20.74)	5845 (21.20)	34 455 (20.85)	
South	11 155 (44.78)	13 025 (46.13)	12 635 (44.06)	13 565 (44.87)	11 515 (44.85)	12 085 (43.84)	73 980 (44.76)	
West	4110 (16.50)	4580 (16.22)	5000 (17.44)	5020 (16.61)	4280 (16.67)	4580 (16.62)	27 570 (16.68)	
Primary insurance								
Medicare	14 255 (57.23)	16 225 (57.46)	16 970 (59.18)	17 805 (58.90)	14 920 (58.11)	15 945 (57.85)	96 120 (58.15)	0.4915
Medicaid	4295 (17.24)	4870 (17.25)	4610 (16.08)	4910 (16.24)	4225 (16.46)	4905 (17.79)	27 815 (16.83)	
Private insurance	5300 (21.28)	5865 (20.77)	5805 (20.24)	6205 (20.53)	5255 (20.47)	5410 (19.63)	33 840 (20.47)	
Self-pay	585 (2.35)	745 (2.64)	790 (2.76)	720 (2.38)	770 (3.00)	800 (2.90)	4410 (2.67)	
No charge	80 (0.32)	90.001 (0.32)	50 (0.17)	40 (0.13)	60 (0.23)	45 (0.16)	365 (0.22)	
Other	395 (1.59)	440 (1.56)	450 (1.57)	550 (1.82)	445 (1.73)	460 (1.67)	2740 (1.66)	
Comorbidities								
Hypertension	19 715 (79.14)	22 895 (81.09)	23 605 (82.32)	25 115 (83.08)	21 310 (83.00)	23 005 (83.46)	135 645 (82.06)	< 0.001
Diabetes	6285 (25.23)	7420 (26.28)	7370 (25.70)	7835 (25.92)	6970 (27.15)	7490 (27.17)	43 370 (26.24)	0.1724
Chronic IHD	8860 (35.57)	10 360 (36.69)	10 320 (35.99)	11 115 (36.77)	9590 (37.35)	10 275 (37.28)	60 520 (36.61)	0.4505
Peripheral vascular disease	3310 (13.29)	4005 (14.18)	3950 (13.78)	4485 (14.84)	3600 (14.02)	4235 (15.36)	23 585 (14.27)	0.0548
Atrial fibrillation	5035 (20.21)	6075 (21.52)	6320 (22.04)	6420 (21.24)	4685 (18.25)	5575 (20.22)	34 110 (20.64)	< 0.001
Congestive heart failure	10 740 (43.12)	13 310 (47.14)	14 035 (48.95)	14 875 (49.21)	13 160 (51.26)	14 305 (51.90)	80 425 (48.66)	< 0.001
Smoking	3755 (15.07)	4510 (15.97)	4550 (15.87)	4675 (15.46)	3950 (15.38)	4355 (15.80)	25 795 (15.61)	0.8399
Hyperlipidemia	9140 (36.69)	10 950 (38.78)	11 115 (38.76)	12 140 (40.16)	11 085 (43.17)	12 500 (45.35)	66 930 (40.49)	< 0.001

(Continues)

TABLE 1 | (Continued)

Variables	2016	2017	2018	2019	2020	2021	Total	*p*
Family history of CAD	2420 (9.71)	2410 (8.54)	2295 (8.00)	2395 (7.92)	1790 (6.97)	1825 (6.62)	13 135 (7.95)	< 0.001
Chronic lung disease	6775 (27.20)	8550 (30.28)	8580 (29.92)	9185 (30.38)	7855 (30.59)	8415 (30.53)	49 360 (29.86)	0.0032
CKD	10 140 (40.71)	11 995 (42.48)	12 270 (42.79)	13 530 (44.76)	11 625 (45.28)	12 080 (43.82)	71 640 (43.34)	< 0.001
Cancer	675 (2.71)	750 (2.66)	815 (2.84)	810 (2.68)	830 (3.23)	950 (3.45)	4830 (2.92)	0.0678
Liver disease	1105 (4.44)	1320 (4.68)	1400 (4.88)	1465 (4.85)	1565 (6.10)	1610 (5.84)	8465 (5.12)	< 0.001
Obesity	4410 (17.70)	5460 (19.34)	5880 (20.51)	6190 (20.48)	5845 (22.77)	6430 (23.33)	34 215 (20.70)	< 0.001
Substance abuse	1080 (4.34)	1500 (5.31)	1580 (5.51)	1670 (5.52)	1510 (5.88)	1675 (6.08)	9015 (5.45)	0.005

Note: Variables are expressed as *n* (%).
Abbreviations: CAD, coronary artery disease; CKD, chronid kidney disease; IHD, ischemic heart disease.

patients were women (84.8%) and either 45–64 years (38.4%) or ≥65 years (37.2%). Non-Hispanic White (NHW) patients accounted for 48.2% of admissions, non-Hispanic Black (NHB) 34.7%, and Hispanics 12.0%. Over one-third (36.5%) came from the lowest income quartile, and 58.2% were Medicare-insured. Admissions clustered in large (55.3%), urban teaching hospitals (77.4%), predominantly in the Southern region of the US (44.8%). Hypertension (82.1%) and chronic kidney disease (43.3%) were the leading comorbidities.

HF was the leading cause (24.8%), followed by CAD (14.2%), hypertension (10.5%), stroke (10.2%), and AF (6.7%) (Figure 1). Across strata, cardiovascular hospitalization rates rose steeply with age; hypertension-related admissions, however, remained relatively constant (≈16–18 per 1000 all-cause SLE admissions). NHB patients had more hypertension admissions than NHW peers (23.6 vs. 19.0 per 1000). Most events occurred in large, urban teaching hospitals in the South. Low-income individuals (quartile 1) experienced the greatest absolute burden of cardiovascular admissions (Figures S1–S5).

Compared with 18–44 years, patients ≥65 years faced markedly higher risks of HF (RR 2.46, 95% CI 2.32–2.60), CAD (RR 2.18, 1.99–2.39), AF (RR 3.34, 2.99–3.74), and stroke (RR 2.27, 2.01–2.56) (Table S1). Hypertension admissions were more common in younger patients (RR 0.47, 0.41–0.52 for ≥65 years vs. 18–44 years). Female sex conferred lower risks for CAD (RR 0.87, 0.81–0.93) and stroke (RR 0.88, 0.80–0.98) but did not significantly affect AF (RR 1.11, 0.94–1.32). Furthermore, NHB patients were more likely to be hospitalized for hypertension (RR 1.47, 1.34–1.61) and stroke (RR 1.17, 1.08–1.27) but less likely for CAD (RR 0.88, 0.82–0.94) than NHW patients. Hispanics had higher hypertension risk (RR 1.29, 1.16–1.45) yet lower stroke risk (RR 0.88, 0.78–0.95). Compared with the lowest income quartile, the highest quartile had lower risks of any cardiovascular admission (RR 0.95, 0.92–0.98), hypertension (RR 0.91, 0.84–0.99), and CAD (RR 0.88, 0.78–0.98). Lastly, large hospitals and urban teaching centers were independently associated with more overall cardiovascular and stroke admissions.

In a study of 165 290 cardiovascular hospitalizations among SLE patients, HF emerged as the leading cause of hospitalizations, followed by CAD and hypertension. Older age was significantly associated with increased risks of HF, CAD, AF, and stroke hospitalizations, while younger patients were more likely to be hospitalized for hypertension. Females exhibited lower risks for CAD and stroke but slightly higher AF hospitalization rates compared to males. NHB and Hispanic patients faced higher risks for hypertension hospitalizations but lower risks for CAD compared to NHW.

Sex differences were notable, with female sex being linked to a reduced risk of cardiovascular hospitalizations after multivariable adjustment. Supporting this, Mihailovic et al. and Pons-Estel et al. identified male sex as a significant predictor of CAD and myocardial infarction (MI) [7, 8]. Similarly, Urowitz et al. reported that male sex was independently associated with atherosclerotic events [9]. Racial disparities in cardiovascular outcomes were prominent. Joyce et al. found higher cardiovascular event prevalence among younger males, Hispanics, and NHB individuals [10]. Garg et al. reported a sevenfold increase

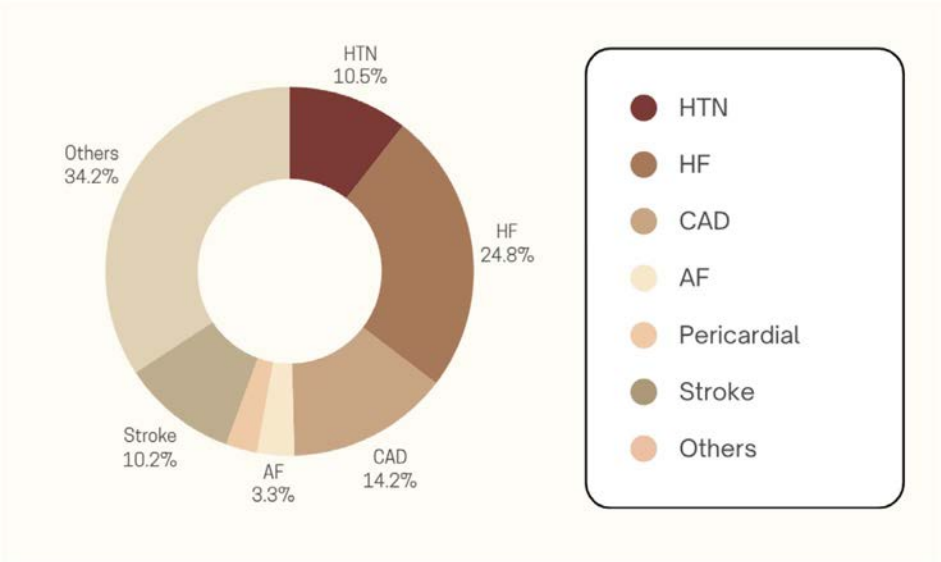

FIGURE 1 | Proportion of major cardiovascular causes of hospitalizations among SLE hospitalizations.

in incident cardiovascular diseases among Black individuals compared to non-Blacks in the Georgia Lupus Registry [11]. Barbhaiya et al. noted elevated cardiovascular disease risks among Blacks, with Hispanics and Asians showing lower MI risks but higher stroke risks, particularly hemorrhagic stroke [12, 13]. In contrast, our study found lower total stroke hospitalization risks among Hispanics, possibly due to the inclusion of varied stroke types. Socioeconomic factors also played a role. Bolla et al. observed lower cardiovascular risk factor prevalence in middle-income countries but poorer risk factor control compared to high-income countries [14]. Maynard et al. linked low income to increased MI and stroke risks in White SLE patients, though not in African Americans [15]. Our findings confirmed higher cardiovascular hospitalization rates in lower-income groups, persisting after demographic adjustments. The limitations of our study include the absence of data on SLE disease duration, disease activity indices, specific medication use (including glucocorticoids, immunosuppressants, and biologics), and relevant laboratory markers such as complement levels or inflammatory biomarkers. These factors are known to influence cardiovascular risk and hospitalization patterns in SLE, and their omission may lead to residual confounding. Consequently, our findings should be interpreted as descriptive of population-level patterns rather than definitive causal associations, emphasizing the need for future studies with clinically granular datasets to validate and extend these observations.

In summary, HF drives cardiovascular hospitalizations in SLE, with Black race, older age, and lower socioeconomic status as key risk factors. These findings highlight the need for targeted interventions to address differences and improve cardiovascular outcomes in SLE patients.

Author Contributions

Song Peng Ang: conception, methodology; **Song Peng Ang** and **Jia Ee Chia:** data acquisition, formal analysis, Investigation; **Song Peng Ang**, **Jia Ee Chia**, and **Kanan Jahangirli:** writing – original draft; **Jose Iglesias** and **Debabrata Mukherjee:** writing – review and editing; **Debabrata Mukherjee:** supervision.

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Disclosure

The authors have nothing to report.

Ethics Statement

This study involved the utilization of publicly available databases with de-identified patient data. Hence, ethical approval was not required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are obtained from the National Inpatient Sample and are available upon application at https://hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp. Restrictions are applied as these were used under license for this study.

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References

1. H. DiGregorio, E. Avenatti, R. Gullapelli, et al., "Burden of Atherosclerotic Disease Risk Factors in Patients With and Without Rheumatologic Disease: A Retrospective Cohort Study," *American Journal of Cardiology* 230 (2024): 37–40.

2. S. P. Ang, J. E. Chia, K. Misra, et al., "Autoimmune Rheumatic Diseases and Outcomes Following Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis," *Angiology* 0 (2024): 33197241255167.

3. J. E. Chia, S. P. Ang, J. Iglesias, C. Krittanawong, and D. Mukherjee, "Clinical Characteristics and Outcomes of Acute Ischemic Stroke in Patients With Systemic Lupus Erythematosus. A Nationwide Cohort Study," *International Journal of Rheumatic Diseases* 28, no. 6 (2025): e703–e707.

4. J. E. Chia and S. P. Ang, "Elevated C-Reactive Protein and Cardiovascular Risk," *Current Opinion in Cardiology* 40 (2025): 237–243.

5. J. Buie, E. McMillan, J. Kirby, et al., "Disparities in Lupus and the Role of Social Determinants of Health: Current State of Knowledge and Directions for Future Research," *ACR Open Rheumatology* 5, no. 9 (2023): 454–464.

6. Agency for Healthcare Research and Quality, *Healthcare Cost and Utilization Project (HCUP), 2016–2021* (Agency for Healthcare Research and Quality, 2016).

7. J. Mihailovic, C. Ribi, C. Chizzolini, et al., "Worse Cardiovascular and Renal Outcome in Male SLE Patients," *Scientific Reports* 13, no. 1 (2023): 18628.

8. G. J. Pons-Estel, L. A. González, J. Zhang, et al., "Predictors of Cardiovascular Damage in Patients With Systemic Lupus Erythematosus: Data From LUMINA (LXVIII), a Multiethnic US Cohort," *Rheumatology* 48, no. 7 (2009): 817–822.

9. M. B. Urowitz, D. Gladman, D. Ibañez, et al., "Atherosclerotic Vascular Events in a Multinational Inception Cohort of Systemic Lupus Erythematosus," *Arthritis Care & Research* 62, no. 6 (2010): 881–887.

10. D. P. Joyce, J. S. Berger, A. Guttmann, et al., "Prevalence of Cardiovascular Events in a Population-Based Registry of Patients With Systemic Lupus Erythematosus," *Arthritis Research & Therapy* 26, no. 1 (2024): 160.

11. S. Garg, C. M. Bartels, G. Bao, C. G. Helmick, C. Drenkard, and S. S. Lim, "Timing and Predictors of Incident Cardiovascular Disease in Systemic Lupus Erythematosus: Risk Occurs Early and Highlights Racial Disparities," *Journal of Rheumatology* 50, no. 1 (2023): 84–92.

12. M. Barbhaiya, C. H. Feldman, H. Guan, et al., "Racial/Ethnic Variation in Stroke Rates and Risks Among Patients With Systemic Lupus Erythematosus," *Seminars in Arthritis and Rheumatism* 48, no. 5 (2019): 840–846.

13. M. Barbhaiya, C. H. Feldman, H. Guan, et al., "Race/Ethnicity and Cardiovascular Events Among Patients With Systemic Lupus Erythematosus," *Arthritis & Rhematology* 69, no. 9 (2017): 1823–1831.

14. E. Bolla, A. G. Semb, A. M. Kerola, et al., "Prevalence and Target Attainment of Traditional Cardiovascular Risk Factors in Patients With Systemic Lupus Erythematosus: A Cross-Sectional Study Including 3401 Individuals From 24 Countries," *Lancet Rheumatology* 6, no. 7 (2024): e447–e459.

15. J. W. Maynard, H. Fang, and M. Petri, "Low Socioeconomic Status Is Associated With Cardiovascular Risk Factors and Outcomes in Systemic Lupus Erythematosus," *Journal of Rheumatology* 39, no. 4 (2012): 777–783.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Association of sociodemographic variables and major cardiovascular causes of admission using multivariate modified poisson regression. **Figure S1:** Proportion of cardiovascular hospitalizations among all-cause hospitalizations. **Figure S2:** Proportion of heart failure (HF) hospitalizations among all-cause hospitalizations. **Figure S3:** Proportion of coronary artery disease (CAD) hospitalizations among all-cause hospitalizations. **Figure S4:** Proportion of stroke hospitalizations among all-cause hospitalizations. **Figure S5:** Proportion of hypertension-related hospitalizations among all-cause hospitalizations.

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LETTER TO THE EDITOR

Salazosulfapyridine and Pneumocystis Jirovecii Pneumonia in Rheumatoid Arthritis: Promising Signal or Premature Conclusion?

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Dear Editor,

I read with great interest the article titled "Risk Factors for Pneumocystis jirovecii Pneumonia in Rheumatoid Arthritis: The Protective Potential of Salazosulfapyridine", which investigates the predictors of Pneumocystis jirovecii pneumonia (PCP) in rheumatoid arthritis (RA) patients and the potential prophylactic benefit of salazosulfapyridine (SASP) [1]. The study addresses the clinically important but relatively underexplored overlap between RA management and opportunistic infection risk. The observation that SASP might serve a dual role—providing disease control and potentially reducing PCP incidence—is indeed noteworthy. Nevertheless, a number of methodological, mechanistic, and safety considerations merit closer scrutiny. By grouping these points, I first address methodological concerns, followed by mechanistic and safety considerations, and finally conclude with a brief synthesis and future directions.

First, the retrospective single-center design inherently limits causal inference. While the correlation between SASP use and reduced PCP incidence is intriguing, causality cannot be conclusively inferred from this retrospective design. This is an inherent challenge of observational studies, which, despite robust statistical adjustments, cannot fully eliminate residual confounding. Observational designs are prone to unmeasured confounding and selection bias, particularly when treatment allocation—in this case, SASP prescription—is influenced by clinical judgment. It is plausible that SASP was preferentially prescribed to patients perceived to be at lower risk of infection, and residual confounding may not have been fully mitigated despite the use of propensity score matching [2]. Future studies could adjust for factors like disease severity or comorbidities that may influence both SASP prescription and PCP risk, thereby further reducing residual confounding. Second, the small number of PCP events ($n = 16$) imposes substantial constraints on statistical precision. Rare outcome events can lead to unstable effect estimates and inflated odds ratios, increasing the risk of type I error. For example, the wide 95% confidence interval for SASP's odds ratio (0.00–0.81) underscores the high degree of uncertainty around the protective effect. Third, the absence of a post hoc power analysis further limits interpretability. A post hoc power analysis—performed after data collection—estimates the probability that the study could detect a true effect of a given size, given the sample size and event rate. While such analyses have their own limitations, they can help contextualize the reliability of statistically significant findings in studies with rare events. Fourth, potential heterogeneity between SASP users and nonusers—even after matching—may still exist. Propensity score methods can only adjust for observed covariates; unmeasured factors, such as prior infection history, functional status, or clinician perception of pulmonary vulnerability, may still confound the observed association. In summary, these methodological limitations collectively suggest that the observed association between SASP and reduced PCP risk, while intriguing, should be regarded as hypothesis-generating rather than confirmatory. The authors' proposed biological rationale for SASP's protective effect is biologically plausible. SASP is metabolized into 5-aminosalicylic acid (5-ASA) and sulfapyridine, compounds with known anti-inflammatory and potential antimicrobial activity. 5-ASA may attenuate inflammatory cytokines implicated in PCP pathogenesis, while sulfapyridine could theoretically inhibit dihydropteroate synthase (DHPS), an enzyme essential for P. jirovecii growth [3, 4]. However, the present study does not provide direct mechanistic evidence to support these hypotheses. Specifically, no immunological profiling, cytokine

measurements, or microbiological assays were performed to validate these pathways in vivo. The DHPS-inhibition hypothesis, although mechanistically appealing, remains speculative in the absence of experimental confirmation in RA populations. Future work might incorporate in vitro susceptibility testing of P. jirovecii to sulfapyridine, or assess immunomodulatory markers in SASP-treated patients. Additionally, the diagnostic criteria for PCP in the present study, while consistent with real-world practice, could allow for some degree of misclassification. The reliance on β-D-glucan and PCR results, though combined with clinical and radiological findings, carries a known risk of false positives and cannot always distinguish colonization from active infection. A stricter diagnostic algorithm or reporting of diagnostic concordance rates would strengthen confidence in the outcome definition. Safety is another key consideration. While the authors correctly highlight the adverse effect profile of trimethoprim-sulfamethoxazole (TMP/SMX), SASP itself is not without potential toxicity. Hepatotoxicity, neutropenia, gastrointestinal intolerance, and rare but severe hypersensitivity reactions are all recognized adverse effects [5]. The current study does not provide comparative safety data for SASP versus TMP/SMX, nor does it report SASP-related adverse events within the cohort. Without these data, it is premature to conclude that SASP is a safer alternative for PCP prophylaxis in high-risk RA patients [6]. Given SASP's known adverse effects (e.g., hepatotoxicity, neutropenia), future studies should provide a more comprehensive safety profile, especially for RA patients.

In summary, the study contributes valuable observational evidence affirming interstitial pneumonia as a major risk factor for PCP in RA and raising the possibility that SASP use may confer a protective effect. The dual potential of SASP—as a disease-modifying antirheumatic drug and as a prophylactic agent against PCP—is conceptually attractive, particularly for patients intolerant to TMP/SMX. However, the retrospective design, small number of events, potential for unmeasured confounding, absence of mechanistic validation, and lack of safety data together warrant cautious interpretation of the findings. Future research should prioritize prospective, adequately powered, multi-center randomized controlled trials to confirm SASP's protective effect, alongside mechanistic studies elucidating its immunomodulatory and antimicrobial actions. Long-term observational studies assessing both efficacy and safety, as well as qualitative work exploring clinical decision-making around SASP initiation, could further define its place in RA management. Until such data are available, integrating SASP into routine prophylactic strategies for PCP should remain a hypothesis rather than a recommendation. While the results are intriguing, the clinical implications—especially the use of SASP as a prophylactic agent—should be considered in light of further validation through RCTs and long-term safety studies.

Author Contributions

Since there is one author, the writing, design, idea, review are all made by me.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

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

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References

1. Y. Hara, T. Nii, T. Matsuki, et al., "Risk Factors for Pneumocystis Jirovecii Pneumonia in Rheumatoid Arthritis: The Protective Potential of Salazosulfapyridine," *International Journal of Rheumatic Diseases* 28 (2025): e70318.

2. S. Mori and M. Sugimoto, "Pneumocystis Jirovecii Pneumonia in Rheumatoid Arthritis Patients: Risks and Prophylaxis Recommendations," *Clinical Medicine Insights. Circulatory, Respiratory and Pulmonary Medicine* 9 (2015): 29–40.

3. G. L. Plosker and K. F. Croom, "Sulfasalazine: A Review of Its Use in the Management of Rheumatoid Arthritis," *Drugs* 65 (2005): 1825–1849.

4. H. Tokuda, F. Sakai, H. Yamada, et al., "Clinical and Radiological Features of Pneumocystis Pneumonia in Patients With Rheumatoid Arthritis, in Comparison With Methotrexate Pneumonitis and Pneumocystis Pneumonia in Acquired Immunodeficiency Syndrome: A Multicenter Study," *Internal Medicine* 47 (2008): 915–923.

5. H. Jick, "Adverse Reactions to Trimethoprim-Sulfamethoxazole in Hospitalized Patients," *Reviews of Infectious Diseases* 4 (1982): 426–428.

6. K. Mizushina, A. Hirata, N. Hayashi, et al., "Possible Preventive Effect of Salazosulfapyridine Against Development of Pneumocystis Pneumonia in Methotrexate-Receiving Patients With Rheumatoid Arthritis," *Modern Rheumatology* 26 (2016): 976–978.

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ORIGINAL ARTICLE

Musculoskeletal Ultrasound Assessment Changes Management Decisions in Rheumatoid Arthritis Patients With Moderate Disease Activity

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Keywords: DAS-28 score | disease activity | MSUS | musculoskeletal ultrasound | power doppler | rheumatoid arthritis | synovitis | ultrasonography

ABSTRACT

Background: Musculoskeletal ultrasound (MSUS) provides valuable information about disease activity and anatomical damage in rheumatoid arthritis (RA); therefore, in combination with clinical assessment, it may be a useful tool in clinical decision-making with treatment.

Objectives: (1) To evaluate the impact of MSUS assessment on treatment decisions in patients with moderately active RA receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). (2) To determine the level of concordance between MSUS assessment and DAS28 in these patients.

Methods: RA patients with a DAS-28 ranging from 3.22–5.1, inadequate response to csDMARDs, and indication for escalating treatment were enrolled. All patients underwent an ultrasound (US) examination (B and PD modes) of the bilateral 5-joint count (5USJC), the symptomatic joints of the DAS-28 score (28USJC), and of a comprehensive 78-joint count (78USJC). A Likert scale (pre- and post-MSUS) was used to assess patients' and clinicians' desires to escalate treatment. The outcome of the treatment decision based on US assessment was reviewed at 24 months' follow-up.

Results: Among the 27 patients included, the mean (SD) DAS-28 score was 4.4 (0.7). Following US assessment, there was a change in the decision to escalate treatment in 18 patients (66.7%), and at a median follow-up of 24 months, only in 5 of the 18 patients had the treatment had been escalated. Treatment escalation was associated with a higher US score across all assessments (5USJC, 28USJC, 78USJC) ($p < 0.05$). The 78USJC was the most reliably aligned with the treatment decision ($p = 0.009$). A comparison of the US and clinical assessment revealed poor concordance between all variables of the DAS-28 and US scores, except for the swollen joint count.

Conclusion: The addition of MSUS assessment to the DAS-28 score affected management decisions in 66.7% of patients.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory immune-mediated disease that significantly impacts patients' quality of life. Compared to the general population, RA is associated with varying degrees of disability and increased mortality rates [1]. Over the past two decades, significant advances have been made in treating RA with injectable biological disease-modifying

Summary

- The addition of musculoskeletal ultrasound to the clinical assessment has impacted the clinical decision-making process in 66.7% of cases.
- This study revealed a poor correlation between the clinical assessment of disease activity via the DAS-28 score and the MSUS assessment in all domains, except for the swollen joint score.

antirheumatic drugs (bDMARDs) and oral targeted synthetic DMARDs (tsDMARDs), leading to improvements in both clinical and functional outcomes [2]. After reviewing the scientific evidence from clinical trials, national health authorities and international rheumatology societies have proposed clinical guidelines and recommendations for the use of these new therapies based on cost-effectiveness criteria [2–5]. Recently, in the United Kingdom, a series of National Institute for Health and Care Excellence (NICE) technology appraisals in 2021 approved the use of both biologic agents and JAK inhibitors for moderate RA, as defined as a DAS-28 score between 3.2 and 5.1 [6]. Previously reserved only for patients with severe disease, this has greatly improved access for RA patients. However, these therapies are not risk-free and are significantly costlier than conventional disease-modifying therapies; therefore, appropriate patient selection is necessary.

Treatment decisions for RA management rely on composite disease activity indices, such as DAS-28 [7]. However, this score is not without pitfalls, given the two subjective domains: visual analogue score (VAS) and tender joint count. Fibromyalgia, chronic pain syndrome, or established joint damage can lead to higher DAS-28 scores that are not necessarily correlated with evidence of active inflammation [8, 9]. This raises the possibility of exposing patients without active synovitis to the potential side effects of these medications, without the associated benefits provided to those with active inflammatory disease. In an economically constrained system, the pragmatic use of real-time MSUS to assess whether a moderate disease activity score is driven primarily by synovitis could be used to appropriately focus resources.

Previous publications [10, 11] have shown that the only DAS-28 components that independently predict objective measures of inflammation with either MRI or ultrasound-detected synovitis are the swollen joint count and the CRP/ESR. A modified DAS-28 formula, which excludes tender joint count and patient global VAS score, is more strongly associated with imaging-detected inflammation in RA patients [12].

In the last decade, there has been increasing interest in the application of MSUS in clinical rheumatology. MSUS enables the direct visualization of pathological features in joints affected by RA, such as synovial thickening and vascularity, with high sensitivity, specificity, and reproducibility. It also provides valuable information about disease activity, anatomical damage, and response to therapy with high sensitivity compared with clinical assessment alone; thus, it may potentially be a useful and objective tool in clinical decision-making. Some observations suggest that the presence of power Doppler (PD) ultrasound synovitis is highly predictive of an increased frequency of RA flares and damage progression, whereas patients with no signs of US synovitis in PD mode should be treated less aggressively [13, 14]. In addition, some studies have shown that the use of MSUS assessment combined with standard rheumatology assessment can optimize treatment escalation/de-escalation in patients with RA [15, 16].

In RA, shared decision-making between the patient and physician is encouraged; however, there can be discordance between the patient's and physician's assessments of disease activity. The primary objective of this study was to assess the impact of MSUS assessment on clinical decision-making from the perspective of both patients and clinicians when determining the appropriateness of escalating csDMARDs treatment to anti-TNF-α or JAK inhibitors following either clinical or ultrasound assessment. The secondary objectives were to assess the correlation between the clinical assessment of RA disease activity via a routine DAS-28 score and the US score of target joints affected in RA and to assess the concordance between the US score and the different components of the DAS-28 score.

2 | Methods

2.1 | Patients

Consecutive patients diagnosed with RA with moderate disease activity (DAS-28 ≥ 3.2) who had responded inadequately to therapy with two or more csDMARDs and, therefore, with an indication to escalate therapy to bsDMARDs or tsDMARDs were enrolled in the study. All patients were aged 18 years or older and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria. Patients diagnosed with fibromyalgia or those unable to undergo clinical evaluation were excluded from the study. The study was conducted from September 2022 to January 2023, and patients were recruited under routine daily practice conditions as a representative sample of the cohort of RA patients attending rheumatology outpatient clinics.

2.2 | Data Collection

The following variables were recorded for all patients: demographics (age and sex), RA duration from the time of diagnosis, current treatment (csDMARDs, steroids, and NSAIDs), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACPA) antibodies, C-reactive protein (CRP) levels, visual analogue scale patients' and rheumatologists' global evaluation of disease activity in the past 2 weeks, DAS 28 scores, SDAI, and CDAI scores.

The patients and their referring consultants completed a Likert scale (0–4), before and after the US examination, grading the willingness to escalate the csDMARDs to bsDMARDs or tsDMARDs. The sonographer issued a report with the results of the US assessment for the three US scores, which was sent to the referring consultant. With this information and the clinical assessment, the decision to escalate or not escalate the treatment

was made after reaching an agreement between both the referring consultants and the patients, who were classified into two groups: those with the decision to escalate treatment and those with the decision not to escalate. At an average follow-up of 24 months, the records of patients were reviewed to determine if the initial decision to escalate or not escalate treatment had been subsequently revised.

2.3 | MSUS Assessment

All patients underwent a US examination on the same day as the DAS-28 clinical assessment, which was performed by the same sonographer with more than 15 years of experience in US. The US examination was performed using a real-time scanner (LOGIQ e, GE Healthcare, Milwaukee, WI, USA) equipped with two multifrequency linear transducers (12 L-RS, 5–12 MHz and L10–12RS, 10–22 MHz). Synovitis and tenosynovitis were assessed in grayscale (B) and power Doppler (PD) modes using a semiquantitative scale from 0 to 3 according to the OMERACT proposed scoring system [17]. The presence of erosions in wrist, second and third MCP and PIP joints was recorded as 'positive' if noted during scanning. The scanning method was performed following the standardized procedures proposed by EULAR [18] and all US findings were described following the OMERACT US definitions for synovitis, tenosynovitis, and erosions [19]. All patients underwent a US examination of the 5-joint count, including the wrist (dorsal and ulnar approach), and the second and third MCP and PIP joints bilaterally. The tendons evaluated during the reduced 5-joint US exam included the second to fifth dorsal tendinous compartments (extensor radialis longus and brevis, extensor pollicis longus, common extensors and extensor digiti minimi), the extensor ulnaris tendon, and the flexor digitorum profundus and superficialis of the second and third fingers bilaterally. The US examination was extended to include the additional symptomatic joints found during the DAS 28-joint score and a comprehensive 78-joint count. The sonographer was blinded to the clinical assessment when performing the reduced 5-joint count but was directed to the patient's symptomatic joints for the 28 and 78-joint count. Two different US scores were calculated: the total score (B + PD modes) for the 5-joint count (0–60), the symptomatic joints for the 28-joint count (0–168), and the 78-joint count (0–468), and the EULAR/OMERACT US score (B + PD mode) for the 5-joint count (0–30), the symptomatic joints for the 28-joint count (0–84), and the 78-joint count (0–234). If the patients were currently being treated with oral prednisolone or NSAIDs, they were asked to miss the morning dose before the US examination.

2.4 | Ethics Statement

All participants provided written informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Gloucestershire NHS Foundation Trust Local Research Ethics Committee (Local Project Reference No: 22/042/GHT). The study was performed in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, revised in 1983.

2.5 | Data Management and Analysis

Statistical analysis was performed using the SPSS software (version 17). The results of the descriptive analyses are presented as frequencies and percentages for qualitative variables and as median or mean values for continuous variables. Between-group comparisons were made using the chi-square test or Fisher's exact test to analyze differences between proportions. Student's t-test was used for comparisons between means.

Pearson's correlation coefficient was used to assess the linear relationship between continuous variables, whereas Spearman's rank correlation was used to examine the association between variables that may not follow a linear trend. Univariate and multivariate logistic regression models were used to investigate the factors associated with changes in clinical management. All statistical tests were 2-sided; P values < 0.05 were considered to indicate a statistically significant result.

3 | Results

Twenty-nine patients with RA who met the inclusion criteria were referred from the rheumatology outpatient clinics and recruited for the study. However, two of them were unable to complete the study follow-up and were excluded. The 27 patients included in the study had a baseline DAS 28-score assessment consistent with moderate disease activity and were considering escalation of their treatment in accordance with the NICE criteria.

The demographic, clinical, and laboratory data are presented in Table 1. The baseline csDMARD treatment was as follows: 14 patients on methotrexate, 2 patients on sulfasalazine, 1 patient on hydroxychloroquine, and 3 patients on leflunomide. Seven patients were receiving combination therapy with two csDMARDs. All patients were treated with at least 2 csDMARDs prior to considering treatment escalation.

The means (SDs) of the Likert scales evaluating the willingness to escalate treatment prior to and following the US examination are shown in Table 2. There was a significant reduction in the Likert scale score before and after the US assessment for the patient, but there was no notable change in the referring consultant score.

Among the 27 patients included, following US assessment, there was a change in the decision to escalate treatment in 18 patients (66.7%), and this decision was maintained in 13 patients (72.2%) over an average of 24 months of follow-up.

Comparing the 2 groups of patients, a higher swollen joint count (SJC) and higher DAS-28 score were correlated with treatment escalation, whereas a longer disease duration was associated with a lower likelihood of treatment escalation ($p < 0.05$) (Table 1).

TABLE 1 | Demographic and clinical characteristics of rheumatoid arthritis patients.

Parameter	Total $N=27$	NO ESCALATE TREATMENT $N=18$ (66.7%)	ESCALATE TREATMENT $N=9$ (33.3%)	*P*
Age (years)	56.1 ± 12.5	56.72 ± 10.66	54.89 ± 16.23	0.727
Sex (female)	18 (66.7%)	11 (61%)	7 (77.8%)	0.386
Time since diagnosis (months)	87.8 ± 24.49	134.71 ± 145.48	42.33 ± 42.8	**0.025**
Anti CCP+	17 (63%)	8 (61.1%)	9 (66.7%)	0.778
Rheumatoid factor+	16 (59.3%)	9 (50%)	7 (77.8%)	0.166
Researcher tender joint count	8.7 ± 5.2	7.94 ± 1.2	10.11 ± 4.59	0.317
Researcher swollen joint count	3.04 ± 2.2	2.0 ± 1.74	5.11 ± 1.36	**0.001**
Patient global assessment score	6.2 ± 2.1	6.22 ± 2.36	5.89 ± 1.45	0.703
Physician global assessment score	4.9 ± 1.9	4.72 ± 1.77	5.33 ± 2.06	0.431
CRP	8.7 ± 8.3	9.67 ± 9.06	6.67 ± 6.55	0.387
HAQ score	1.1 ± 0.6	1.14 ± 0.65	1.13 ± 0.69	0.988
Researcher DAS 28 PCR	4.4 ± 0.7	4.24 ± 0.72	4.74 ± 0.48	**0.041**
SDAI	23.5 ± 7.04	22.06 ± 7.71	26.44 ± 4.5	0.130
CDAI	22.9 ± 7.6	20.89 ± 8.11	26.89 ± 4.85	0.053

Note: Bold values indicate statistically significant values $p < 0.05$.

TABLE 2 | Liker scales evaluating the desire to escalate the treatment prior to and following the US examination.

	Liker score (pre-US)	Liker score (post-US)	*P*
Referring consultant	3.62 ± 0.9	3.05 ± 1.5	0.137
Patient	3.85 ± 0.9	3.30 ± 1.1	**0.013**

Note: Bold values indicate statistically significant values $p < 0.05$.

In terms of US assessment, treatment escalation was associated with a higher US score across all assessments (5 USJC, 28 USJC, 78 USJC, and EOUS) ($p < 0.05$). There were no differences between the two groups in terms of the tenosynovitis US score or presence of erosions in the US assessment (Table 3). Across the different US assessments (univariate analysis OR > 1) (Table 4), the 78 USJC was the most reliably aligned with the escalation treatment decision (multivariate logistic regression analysis, $p = 0.009$) (Table 5).

When the clinical DAS-28 and US scores were compared, there was no concordance between the different variables, apart from the swollen joint count.

4 | Discussion

Treat-to-target strategies (T2T) have been shown to be more effective than usual care in improving outcomes in RA management at no additional cost (NICE Guideline NG 100). However, treatment decisions in RA patients still rely on composite clinical disease activity scores, which have significant limitations [20]. A potential pitfall of the widely employed used DAS-28 is that the more subjective parameter of the tender joint count has a greater weight on the overall score than the more objective swollen joint count. This is because the DAS28 formula dictates the square root of the tender joint count multiplied by 0.56, whereas the swollen joint count is multiplied by 0.28 [8]. Moreover, patients with certain comorbidities, particularly fibromyalgia or central pain sensitization syndromes, may have high scores that do not accurately reflect active synovitis [21, 22]. We decided to exclude from our research those patients with a established diagnosis of fibromyalgia to ensure the homogeneity of our study cohort and avoid potential bias.

It has been widely demonstrated that MSUS has greater sensitivity than physical examination in detecting synovitis in RA, and combining clinical examination with US assessment would improve therapeutic decisions as part of a T2T strategy [23]. Our study revealed that the addition of the MSUS assessment to the DAS-28 score influenced the shared referring consultant/patient decision regarding treatment escalation in 18 of the 27 (66.7%) patients of our RA cohort, and this outcome was maintained in 13 (72.2%) patients in a 24-month follow-up. Although we reviewed the outcomes of the treatment decisions in the 27 patients, our primary focus was to emphasize the accuracy of the decision of not escalating treatment primarily based on the US assessment. We consider that these decisions appeared to be correct as a high percentage of them maintained the decision of not escalating after a 24-month follow-up. Therefore, these results suggest that the use

TABLE 3 | US scores of patients: Differences between decision escalate-no escalate treatment.

US Scores	Total $N=27$	Decisión of NO ESCALATE Treatment $N=18$ (66.7%)	Decisión of ESCALATE Treatment $N=9$ (33.3%)	P
5-joint total US score	7.7 ± 5.3	5.94 ± 5.48	11.22 ± 2.48	**0.011**
5-joint B mode US score	5.8 ± 3.8	4.78 ± 4.14	8.0 ± 1.5	**0.007**
5-joint PD mode US score	1.8 ± 2.2	1.17 ± 1.46	3.22 ± 2.81	0.067
5-joint tenosynovitis score	0.6 ± 0.8	0.39 ± 0.6	1.0 ± 1.0	0.059
US total extended to 28-joint score	10.4 ± 7.6	8.06 ± 7.54	15.11 ± 5.27	**0.019**
US B mode extended to 28-joint score	8.1 ± 5.7	6.83 ± 6.10	10.56 ± 4.00	0.111
US PD mode extended to 28-joint score	1.9 ± 2.6	1.22 ± 1.62	3.22 ± 3.66	0.151
US total extended to 78-joint score	12.1 ± 8.9	8.44 ± 8.0	19.33 ± 5.91	**0.001**
US B mode extended to 78-joint score	9.8 ± 6.8	7.17 ± 6.54	15.11 ± 3.48	**0.002**
US PD mode extended to 78-joint score	2.3 ± 2.7	1.28 ± 1.63	4.22 ± 3.56	**0.041**
EULAR-OMERACT 5-joint US score	5.8 ± 3.5	4.67 ± 3.74	8.0 ± 1.22	**0.002**
EULAR-OMERACT extended to 28-joint score	8.2 ± 5.6	6.67 ± 5.93	11.33 ± 3.20	**0.038**
EULAR-OMERACT extended to 78-joint score	9.2 ± 6.5	7.0 ± 6.44	13.56 ± 4.39	**0.011**
Erosions	14 (52%)	8 (44.4%)	6 (66.7%)	0.276

Note: Bold values indicate statistically significant values $p < 0.05$.

of the DAS-28 score in isolation appears to overestimate the degree of active inflammation compared to objective synovitis demonstrated on MSUS.

In routine practice, an increasing number of rheumatologists are either in favor of, or already using, MSUS as part of the extended clinical evaluation in RA, although its impact on the outcome of treatment decision-making still needs to be defined. A few studies have suggested that the addition of an MSUS assessment may have a favorable impact on treatment decisions and improve clinical outcomes [23, 24]. In contrast, two relevant RCTs, TaSER [25] and ARTIC [26], suggested that a treatment strategy based on MSUS assessment did not lead to an improved clinical outcome compared with a conventional T2T approach, suggesting that the systematic use of MSUS in the follow-up of RA patients would not be justified.

Our results suggest that the information gained from MSUS assessment may affect the management of patients with RA. This is consistent with other studies, including Diaz-Torné et al., who reported that in 32% of their RA cohort of 78 patients, there was a change in the treatment decision to escalate or deescalate the treatment after the US assessment, and this change in decision was more frequent in patients with low or moderate disease activity according to the DAS-28 score than in those with high disease activity or in remission [27]. Ceponis et al. analyzed the overall likelihood of change in the management of patients with RA after an MSUS assessment using a quantitative Likert scale, like our research. This study revealed that the physicians' intended treatment plan changed in 16 of 46 patients after the ultrasound report was available, which is in accordance with the results of the present study [28]. Sifuentes-Cantu et al. also assessed the impact of adding the MSUS information to treatment decisions in their cohort of RA outpatients and reported that it resulted in a change in management in 34 of 170 clinical scenarios (20%) [29].

As some investigations have shown that MSUS scores are better predictors of joint damage than DAS-28 scores, some authors have proposed composite scores that combine clinical, biological, and MSUS parameters [30]. Damajow et al. investigated the validity and reliability of an MSUS disease activity score compared with the DAS-28 in predicting damage as determined by MRI in a subgroup of patients. They reported that the MSUS score was better able to identify patients who would experience structural damage progression than the DAS-28 score, supporting its use in clinical assessments [31].

In agreement with previous publications [32], we did not find a correlation between the DAS-28 score and the different US scores, except for the SJC, which showed a statistically significant correlation. Coras et al. [30] analyzed the correlation between the DAS-28 score and its ultrasonographic equivalent in patients with RA and, as observed in our study, reported only

TABLE 4 | Univariate analysis of the variables showing statistically significant differences between groups: Escalate-no escalate treatment.

Variable	Odds ratio	IC (95%)	*P*
Time since diagnosis (months)	0.98	0.97–1.03	0.122
Referring consultant DAS-28 PCR	3.89	0.83–18.13	0.084
Referring consultant swollen joint count	2.98	1.34–6.62	**0.007**
5-joint total US score	1.25	1.03–1.54	**0.026**
5-joint B mode US score	1.29	1.00–1.68	0.050
US total extended to 28-joint score	1.15	1.01–1.34	**0.034**
US total extended to 78-joint score	1.18	1.04–1.35	**0.009**
US B mode extended to 78-joint score	1.24	1.05–1.46	**0.012**
US PD mode extended to 78-joint score	1.59	1.05–2.43	**0.029**
EULAR-OMERACT 5-joint US score	1.40	1.03–1.91	**0.032**
EULAR-OMERACT extended to 28-joint score	1.18	0.99–1.39	0.055
EULAR-OMERACT extended to 78-joint score	1.19	1.02–1.39	**0.025**

Note: Bold values indicate statistically significant values $P < 0.05$.

TABLE 5 | Multivariate logistic regression analysis of the 3 variables with highest statistically significance from the univariate analysis.

Variables	Odds ratio	IC (95%)	*P*
5-joint total US score	0.74	0.42–1.29	0.294
US total extended to 28-joint count score	1.56	0.79–3.06	0.198
US total extended to 78-joint count score	0.84	0.74–0.95	**0.009**

Note: Bold values indicate statistically significant values $P < 0.05$.

moderate agreement between the SJC and the US score, but no agreement between the TJC joints and synovitis detected by US. Moreover, they reported no significant difference between the DAS-28 and the US score and found that the DAS-28 score was significantly higher than the US score in patients with high disease activity (DAS-28 score > 5.1). They proposed a composite score that should include US parameters combined with clinical and biological data for a better assessment of RA disease activity. However, in our study, a higher DAS-28 score was correlated with treatment escalation ($p < 0.05$), which was likely driven by the SJC, but not by the TJC, and the SJC was also correlated with the decision to escalate treatment.

Our pilot study was designed in real clinical settings to explore the potential usefulness of routine MSUS to accurately select, for our cohort of RA patients with moderate disease activity, those amenable to treatment escalation. We used the validated semiquantitative scoring methods widely published for grading synovitis, tenosynovitis, and erosions [33]. For feasibility, we decided to perform a reduced 5-joint US count, a modification of the validated German 7-joint count [34]. This simplified bilateral 5-joint US score has demonstrated usefulness in clinical practice [35]; however, when additional joints are examined, we can detect inflammation that is not captured by the simplified US scores. For this reason, we decided to extend the examination to include all symptomatic joints of the 28-joint count and of a comprehensive 78-joint count to avoid missing the evaluation of other tender or swollen joints. Moreover, this method allowed us to compare the DAS-28 clinical score with three MSUS scores. As expected, the 78sUSJC, which included the simplified bilateral 5-joint US score plus the ultrasound assessment of all symptomatic joints with a comprehensive 78-joint count, was the most reliably aligned with the escalation treatment decision ($p = 0.009$).

Our study has several limitations. First, given the small sample size, we cannot ensure that our results can be extrapolated to all RA patients. However, although we included only 27 patients in the study, we detected a statistically significant difference in the desire to escalate treatment between the 2 main groups. The duration of patient recruitment (4 months) was short, since this research was planned as a pilot study for future clinical investigations in our cohort of patients with RA. Second, we did not undertake a cost-effectiveness analysis to assess whether the time and resources spent on the MSUS assessments are worth the financial savings by not escalating the treatment to bs/tsDMARDS. In our opinion, a few questions still need to be answered before MSUS can be routinely used as the basis of decisions regarding escalating treatment in patients with RA. These include establishing the most feasible MSUS standardized protocol for examination, how to interpret the data when there is a discrepancy between the clinical and US assessments, and the cost effectiveness of the routine use of MSUS in clinical practice. We believe that our study contributes modestly to establishing the impact of MSUS in the management of RA in real clinical settings.

5 | Conclusion

The findings of this study support the use of MSUS in the assessment of patients with moderately active RA as a useful tool for determining the need to escalate or not escalate treatment to biologic or targeted synthetic therapy. Larger-scale longitudinal studies may lead to more significant results and a better understanding of long-term outcomes following treatment decisions.

Author Contributions

H.C. and C.A. contributed equally to this study; both contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. L.R.-C. performed the analytical calculations and aided in interpreting the results. All authors made

substantial contributions to the acquisition of data, the discussion of results, critical revision, and approval 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.

References

1. A. M. Kerola, A. Kazemi, S. Rollefstad, et al., "All-Cause and Cause-Specific Mortality in Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis: A Nationwide Registry Study," *Rheumatology (Oxford, England)* 28 (2022): 4656–4666.

2. J. S. Smolen, R. B. M. Landewé, S. A. Bergstra, et al., "EULAR Recommendations for the Management of Rheumatoid Arthritis With Synthetic and Biological Disease-Modifying Antirheumatic Drugs: 2022 Update," *Annals of the Rheumatic Diseases* 82 (2023): 3–18.

3. L. Fraenkel, J. M. Bathon, B. R. England, et al., "American Collegue of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis," *Arthritis Care & Research* 73 (2021): 924–939.

4. R. Sanmartí, S. García-Rodríguez, J. M. Álvaro-Gracia, et al., "2014 Update of the Consensus Statement of the Spanish Society of Rheumatology on the Use of Biological Therapies in Rheumatoid Arthritis," *Reumatologia Clinica* 11 (2015): 279–294.

5. M. Fornaro, F. Benaglio, C. Montecucco, et al., "Adherence of Italian Rheumatologists to the EULAR Recommendations and Outcomes in Early Rheumatoid Arthritis Patients After Starting Conventional DMARDs: Methotrexate in Italian Patients With Rheumatoid Arthritis (The MITRA Study). A Cohort Study of the Italian Society for Rheumatology," *Clinical and Experimental Rheumatology* 40 (2022): 1693–1700.

6. NICE National Institute for Health and Care Excellence, "Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed," (2021), https://www.nice.org.uk/guidance/ta715.

7. M. L. Prevoo, M. A. Van't Hof, H. H. Kuper, et al., "Modified Disease Activity Scores That Include Twenty-Eight-Joint Counts. Development and Validation in a Prospective Longitudinal Study of Patients With Rheumatoid Arthritis," *Arthritis & Rheumatism* 38 (1995): 44–48.

8. F. Salaffi, M. Di Carlo, M. Carotti, and P. Sarzi-Puttini, "The subjective components of the Disease Activity Score 28-joints (DAS28) in rheumatoid arthritis patients and coexisting fibromyalgia," *Rheumatology International* 38 (2018): 1911–1918.

9. S. Pezzato, C. Bonetto, C. Caimmi, et al., "Depression is associated with increased disease activity and higher disability in a large Italian cohort of patients with rheumatoid arthritis," *Adv Rheumatol* 61 (2021): 57.

10. J. F. Baker, P. G. Conaghan, J. S. Smolen, et al., "Development and Validation of Modified Disease Activity Scores in Rheumatoid Arthritis: Superior Correlation With Magnetic Resonance Imaging-Detected Synovitis and Radiographic Progression," *Arthritis & Rhematology* 66 (2014): 794–802.

11. E. M. A. Hensor, P. McKeigue, S. F. Ling, et al., "Validity of a Two-Component Imaging-Derived Disease Activity Score for Improved Assessment of Synovitis in Early Rheumatoid Arthritis," *Rheumatology (Oxford, England)* 58 (2019): 1400–1709.

12. B. Hameed, J. Pilcher, C. Heron, et al., "The Relation Between Composite Ultrasound Measures and the DAS-28 Score, Its Components in Acute Phase Markers in Adult RA," *Rheumatology (Oxford, England)* 47 (2008): 470–480.

13. C. A. Scire, C. Montecucco, V. Codullo, O. Epis, M. Todoerti, and R. Caporali, "Ultrasonographic Evaluation of Joint Involvement in Early Rheumatoid Arthritis in Clinical Remission: Power Doppler Signal Predicts Short-Term Relapse," *Rheumatology* 48 (2009): 1092–1097.

14. D. Sreerangaiah, M. Grayer, B. A. Fisher, M. Ho, S. Abraham, and P. C. Taylor, "Quantitative Power Doppler Ultrasound Measures of Peripheral Joint Synovitis in Poor Prognosis Early Rheumatoid Arthritis Predict Radiographic Progression," *Rheumatology* 55 (2016): 89–93.

15. J. Dale, D. Purves, A. McConnachie, I. McInnes, and D. Porte, "Tightening Up? Impact of Musculoskeletal Ultrasound Disease Activity Assessment on Early Rheumatoid Arthritis Patients Treated Using a Treat to Target Strategy," *Arthritis Care & Research* 66 (2014): 19–26.

16. A. N. Colebatch, C. J. Edwards, M. Østergaard, et al., "EULAR Recommendations for the Use of Imaging of the Joints in the Clinical Management of Rheumatoid Arthritis," *Annals of the Rheumatic Diseases* 72 (2013): 804–814.

17. P. Mandl, E. Naredo, R. J. Wakefield, P. G. Conaghan, M. A. D'Agostino, and OMERACT Ultrasound Task Force, "A Systematic Literature Review Analysis of Ultrasound Joint Count and Scoring Systems to Assess Synovitis in Rheumatoid Arthritis According to the OMERACT Filter," *Journal of Rheumatology* 38 (2011): 2055–2062.

18. I. Moller, I. Janta, M. Backhaus, et al., "The 2017 EULAR Standardised Procedures for Ultrasound Imaging in Rheumatology," *Annals of the Rheumatic Diseases* 76 (2017): 1974–1979.

19. G. A. Bruyn, A. M. Iagnocco, E. Naredo, et al., "OMERACT Definitions for Ultrasonographic Pathology and Elementary Lesions of Rheumatic Disorders Fifteen Years on," *Journal of Rheumatology* 46 (2019): 1388–1393.

20. H. Jensen, M. Inger, A. Amussen, et al., "The Reliability of Disease Activity Score in 28 Joints–C-Reactive Protein Might Be Overestimated in a Subgroup of Rheumatoid Arthritis Patients, When the Score Is Solely Based on Subjective Parameters: A Cross-Sectional, Exploratory Study," *Journal of Clinical Rheumatology* 23 (2017): 102–106.

21. L. C. Pollard, G. H. Kingsley, E. H. Choy, and D. L. Scott, "Fibromyalgic Rheumatoid Arthritis and Disease Assessment," *Rheumatology (Oxford)* 49 (2010): 924–928.

22. A. N. Mian, K. Chaabo, J. Wajed, et al., "Rheumatoid Arthritis Patients With Fibromyalgic Clinical Features Have Significantly Less Synovitis as Defined by Power Doppler Ultrasound," *BMC Musculoskeletal Disorders* 17 (2016): 404.

23. R. J. Wakefield, M. A. DÁgostino, E. Naredo, et al., "After Treat-To-Target: Can a Targeted Ultrasound Initiative Improve RA Outcomes?," *Annals of the Rheumatic Diseases* 71 (2012): 799–803.

24. A. Ceponis, J. J. Cush, and A. Kavanaugh, "Effect of Musculoskeletal Ultrasound Examination on Therapeutic Decision Making in Inflammatory Arthritis," *Arthritis & Rheumatism* 62 (2010): S673.

25. J. Dale, A. Stirling, R. Zhang, et al., "Targeting Ultrasound Remission in Early Rheumatoid Arthritis: The Results of the TaSER Study, a Randomised Clinical Trial," *Annals of the Rheumatic Diseases* 75 (2016): 1043–1050.

26. E. A. Haavardsholm, A. B. Aga, I. C. Olsen, et al., "Ultrasound in Management of Rheumatoid Arthritis: ARCTIC Randomised Controlled Strategy Trial," *BMJ (Clinical Research Ed.)* 354 (2016).i4205.

27. C. Díaz-Torné, C. Moragues, E. Toniolo, et al., "Impact of Ultrasonography on Treatment Decision in Rheumatoid Arthritis: The IMPULSAR Study," *Rheumatology International* 37 (2017): 891–896.

28. A. Ceponis, M. Onishi, H. G. Bluestein, K. Kalunian, J. Townsend, and A. Kavanaugh, "Utility of the Ultrasound Examination of the Hand

and Wrist Joints in the Management of Established Rheumatoid Arthritis," *Arthritis Care and Research* 66 (2014): 236–244.

29. C. Sifuentes-Cantú, I. Contreras-Yáñez, L. Saldarriaga, et al., "The Added Value of Musculoskeletal Ultrasound to Clinical Evaluation in the Treatment Decision of Rheumatoid Arthritis Outpatients: Physician Experience Matters," *BMC* 18 (2017): 390.

30. R. Coras, G. Añez, M. Barceló, et al., "Analysis of the Correlation Between Disease Activity Score 28 and Its Ultrasonographic Equivalent in Rheumatoid Arthritis Patients," *European Journal of Rheumatology* 7 (2020): 118–123.

31. N. Damjanov, G. Radunovic, S. Prodanovic, et al., "Construct Validity and Reliability of Ultrasound Disease Activity Score in Assessing Joint Inflammation in RA: Comparison With DAS-28," *Rheumatology (Oxford)* 51 (2012): 120–128.

32. H. B. Hammer, B. Michelsen, J. Sexton, et al., "Swollen, but Not Tender Joints, Are Independently Associated With Ultrasound Synovitis: Results From a Longitudinal Observational Study of Patients With Established Rheumatoid Arthritis," *Annals of the Rheumatic Diseases* 78 (2019): 1179–1185.

33. L. Terslev, E. Naredo, P. Aegerter, et al., "Scoring Ultrasound Synovitis in Rheumatoid Arthritis: A EULAR-OMERACT Ultrasound Taskforce-Part 2: Reliability and Application to Multiple Joints of a Standardised Consensus Based Scoring System," *RMD Open* 3 (2017): 427.

34. M. Backhaus, S. Ohrndorf, H. Kellner, et al., "Evaluation of a Novel 7-Joint Ultrasound Score in Daily Rheumatology Practice: A Pilot Project," *Arthritis & Rheumatism* 61 (2009): 1194–1201.

35. P. Sivakumaran, S. Hussain, L. Attipoe, et al., "Diagnostic Accuracy of Simplified Ultrasound Hand Examination of Protocols for Detection of Inflammation and Disease Burden in Patients With Rheumatoid Arthritis," *Acta Radiologica* 60 (2019): 92–99.

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LETTER TO THE EDITOR

Causal Associations Between Ankylosing Spondylitis and Chronic Kidney Disease: A Two-Sample Mendelian Randomization Analysis

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Dear Editor,

Ankylosing spondylitis (AS) is an inflammatory disorder that, in its severe form, can cause the fusion of vertebral joints [1]. Its atypical symptoms often lead to missed or misdiagnosed cases, and its poor prognosis imposes significant social and economic burdens, necessitating attention.

Chronic kidney disease (CKD) has emerged as a leading cause of death and suffering in the 21st century, affecting an estimated 843.6 million people worldwide in 2017 due to escalating risk factors such as obesity and diabetes mellitus [2]. While mortality rates have decreased in end-stage kidney disease (ESKD) patients, CKD remains a major global cause of mortality. Therefore, it is crucial to identify, monitor, and treat CKD, implementing preventative and therapeutic measures globally. Observational studies have shown a connection between AS and CKD, indicating increased rates of renal complications in AS patients [3, 4]. However, no studies have investigated the causal relationship between AS and CKD. This study is the first to explore this relationship using Mendelian randomization.

MR is a novel analytical approach that can assess causality between exposures and outcomes without interference from confounders. This study is the first to explore this relationship using MR. We extracted summary-level statistics from large-scale genome-wide association studies (GWAS) (Table 1) by utilizing single nucleotide polymorphisms (SNPs) with significance ($p < 5 \times 10^{-8}$). To ensure independence, SNPs were restricted based on limited linkage disequilibrium (LD, $r^2 < 0.001$, 1 Mb). In the end, we selected 21 SNPs as our final genetic instruments (IVs).

We used the inverse variance weighted (IVW), weighted median, weighted mode, and MR-Egger methods to investigate causal associations. Additionally, we conducted sensitivity analyses, including Cochran's Q, to estimate potential horizontal pleiotropy. These sensitivity analyses aimed to ensure the reliability of the MR results, as violations of MR assumptions are often attributed to horizontal pleiotropy. Ultimately, the MR estimates revealed higher risks of CKD in AS patients compared to the general population [odds ratio (OR_{ivw}): 1.19, 95% confidence interval (CI) 1.04–1.36], $p = 0.01$. Meanwhile, the Q statistics ($Q = 16.6$, $p = 0.68$) validated the IVW results and indicated no significant heterogeneity. Furthermore, leave-one-out sensitivity analysis for AS on CKD is respectively shown in Figure 1.

The inflammatory response is a common and important pathogenic mechanism in both AS and CKD. AS is an immunologically

Abbreviations: AS, Ankylosing spondylitis; CI, confidence interval; CKD, chronic kidney disease; GWAS, genome-wide association studies; IVs, genetic instruments; IVW, Inverse variance weighted; LD, linkage disequilibrium; MR, Mendelian randomization; OR, odds ratio; SNPs, single nucleotide polymorphisms.

Qian Fang and Weici Feng contributed equally to this work and share the first authorship.

Yanjun Wang and Zhiming Wu contributed equally to this work and share the senior authorship.

mediated chronic inflammatory disease [5], while chronic, low-grade inflammation is a critical component of CKD, contributing in part to cardiovascular and all-cause mortality [6]. CKD patients often experience systemic inflammatory responses, and the progression of CKD is closely associated with systemic inflammation and oxidative stress, responsible for numerous complications such as malnutrition, atherosclerosis, coronary artery calcification, heart failure, anemia, mineral and bone disorders, as well as increased cardiovascular mortality [7–9]. Inflammation and oxidative stress are inseparable elements that promote kidney fibrosis and loss of function, potentially leading to kidney damage and the occurrence and progression of CKD [6].

AS is considered an immune-mediated disease, and a dysregulated immune system can have direct or indirect effects on the kidneys, leading to a broad spectrum of renal diseases. The loss of immune homeostasis in renal disease results in continual recruitment of immune cells and worsening kidney damage [10, 11]. Deposition of immune complexes in the glomerulus is a pathological characteristic of CKD, and autoimmune responses can cause glomerulonephritis, tubulointerstitial inflammation, and other conditions, contributing to the development of CKD [12].

Chronic pain and stress are common pathogenic mechanisms shared by AS and CKD. AS primarily affects the spine joints, and in advanced cases, it can lead to spine fusion and severe, chronic pain. AS patients often experience long-term chronic pain and limited mobility, which can contribute to a state of chronic stress [13, 14]. Moreover, studies have shown that chronic stress is associated with the onset and progression of CKD [15]. CKD patients exhibit impaired physiological defense mechanisms, resulting in elevated levels of oxidative stress, which is a non-traditional risk factor for overall mortality. Interestingly, high levels of oxidative stress have been detected even in the early stages of CKD [16].

Above all, intensive attention should be given to protecting AS patients from CKD and promoting individual protections. Future research is needed to confirm causality and uncover potential mechanisms.

Yours sincerely,
All Authors.

TABLE 1 | Details of GWASs analyzed in the present MR analyses.

Phenotype	First author	Number of cases	Number of controls	Sample size	Number of variants	Ethnicity	Year	Pubmed ID	Trait ID in GWAS
Exposure									
AS	Cortes A	9069	1550	22 647	99 962	European	2013	23 749 187	ebi-a-GCST005529
Outcomes									
CKD	Pattaro C	12 385	104 780	117 165	2 179 497	European	2016	26 831 199	ebi-a-GCST003374

Abbreviations: AS, Ankylosing spondylitis; CKD, chronic kidney disease; MR, Mendelian Randomization; SNPs, single nucleotide polymorphisms.

Author Contributions

Q.F. and W.F. conducted the analyses and wrote the first draft of the article. J.Z. and L.H. interpreted the results. Y.W. and Z.W. designed the study and supervised the study. All authors contributed to the article and approved the submitted version.

Ethics Statement

Data sources for MR data are publicly available online. This study utilized publicly available summary statistics, and thus, did not require ethical approval.

Consent

Patient consent was not required as this study was based on publicly available data.

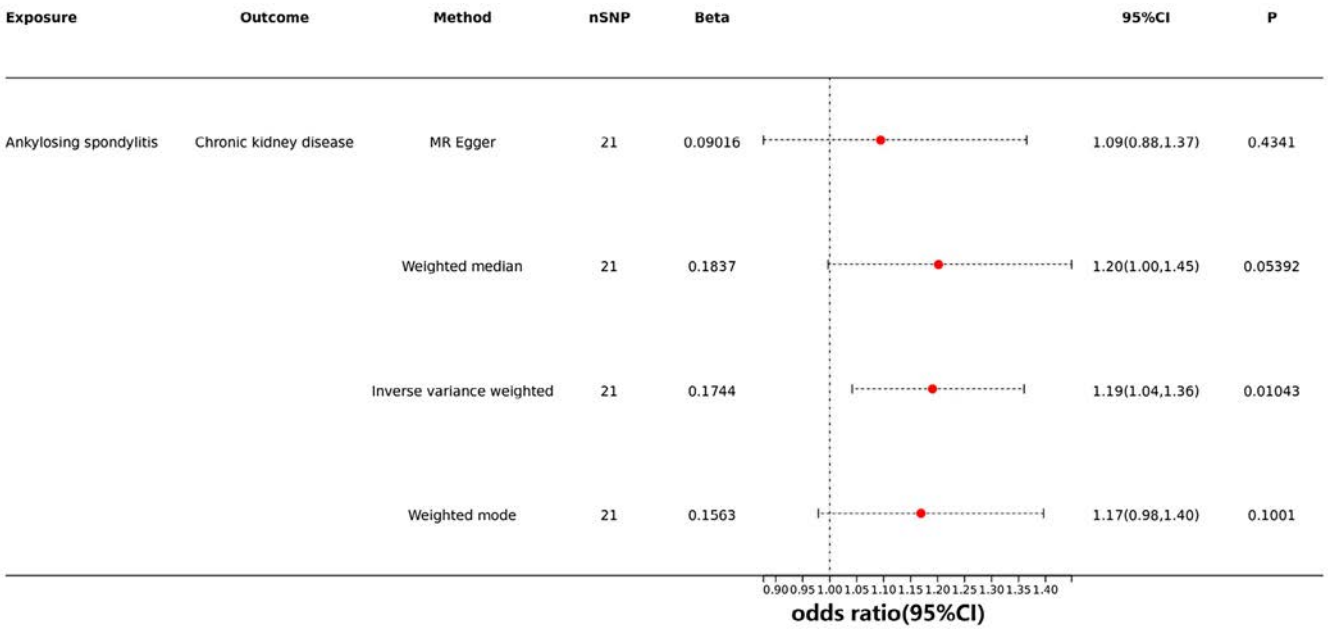

FIGURE 1 | The results of MR analyses, including inverse variance weighted (IVW), weighted-median, MR-Egger and weighted mode. CI, confidence interval; SNPs, single nucleotide polymorphisms.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The original data are available in the published GWASs. The data that support the findings of this study are available on request from the corresponding author. All GWAS data is based on the public website http://app.mrbase.org/.

Qian Fang
Weici Feng
Jiamin Zeng
Long Huang
Yanjun Wang
Zhiming Wu

References

1. J. D. Taurog, A. Chhabra, and R. A. Colbert, "Ankylosing Spondylitis and Axial Spondyloarthritis," *New England Journal of Medicine* 374, no. 26 (2016): 2563–2574, https://doi.org/10.1056/NEJMra1406182.

2. C. P. Kovesdy, "Epidemiology of Chronic Kidney Disease: An Update 2022," *Kidney International. Supplement* 12, no. 1 (2022): 7–11, https://doi.org/10.1016/j.kisu.2021.11.003.

3. A. R. Levy, S. M. Szabo, S. R. Rao, M. Cifaldi, and W. P. Maksymowych, "Estimating the Occurrence of Renal Complications Among Persons With Ankylosing Spondylitis," *Arthritis Care & Research (Hoboken)* 66, no. 3 (2014): 440–445, https://doi.org/10.1002/acr.22176.

4. W. Ye, J. Zhuang, Y. Yu, et al., "Gender and Chronic Kidney Disease in Ankylosing Spondylitis: A Single-Center Retrospectively Study," *BMC Nephrology* 20, no. 1 (2019): 457, https://doi.org/10.1186/s12882-019-1658-6.

5. K. Bidad, E. Gracey, K. S. Hemington, J. C. S. Mapplebeck, K. D. Davis, and R. D. Inman, "Pain in Ankylosing Spondylitis: A Neuro-Immune Collaboration," *Nature Reviews Rheumatology* 13, no. 7 (2017): 410–420, https://doi.org/10.1038/nrrheum.2017.92.

6. W. Frąk, J. Kućmierz, M. Szlagor, E. Młynarska, J. Rysz, and B. Franczyk, "New Insights Into Molecular Mechanisms of Chronic Kidney Disease," *Biomedicine* 10, no. 11 (2022): 2846, https://doi.org/10.3390/biomedicines10112846.

7. M. Diaz-Ricart, S. Torramade-Moix, G. Pascual, et al., "Endothelial Damage, Inflammation and Immunity in Chronic Kidney Disease," *Toxins (Basel)* 12, no. 6 (2020): 361, https://doi.org/10.3390/toxins12060361.

8. S. S. Ghosh, T. W. Gehr, and S. Ghosh, "Curcumin and Chronic Kidney Disease (CKD): Major Mode of Action Through Stimulating Endogenous Intestinal Alkaline Phosphatase," *Molecules* 19, no. 12 (2014): 20139–20156, https://doi.org/10.3390/molecules191220139.

9. S. F. Rapa, B. R. Di Iorio, P. Campiglia, A. Heidland, and S. Marzocco, "Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites," *International Journal of Molecular Sciences* 21, no. 1 (2019): 263, https://doi.org/10.3390/ijms21010263.

10. O. Foresto-Neto, L. Menezes-Silva, J. A. Leite, M. Andrade-Silva, and N. O. S. Câmara, "Immunology of Kidney Disease," *Annual Review of Immunology* 42, no. 1 (2024): 207–233, https://doi.org/10.1146/annurev-immunol-090122-045843.

11. P. Romagnani, G. Remuzzi, R. Glassock, et al., "Chronic Kidney Disease," *Nature Reviews. Disease Primers* 3 (2017): 17088, https://doi.org/10.1038/nrdp.2017.88.

12. O. M. Akchurin and F. Kaskel, "Update on Inflammation in Chronic Kidney Disease," *Blood Purification* 39, no. 1–3 (2015): 84–92, https://doi.org/10.1159/000368940.

13. J. Braun and J. Sieper, "Ankylosing Spondylitis," *Lancet* 369, no. 9570 (2007): 1379–1390, https://doi.org/10.1016/S0140-6736(07)60635-7.

14. S. Ramiro, E. Nikiphorou, A. Sepriano, et al., "Response to: Correspondence on 'ASAS-EULAR Recommendations for the Management of Axial Spondyloarthritis: 2022 Update' by Braun Et Al," *Annals of the Rheumatic Diseases* 82, no. 9 (2023): e206, https://doi.org/10.1136/ard-2023-223937.

15. J. Tecklenborg, D. Clayton, S. Siebert, and S. M. Coley, "The Role of the Immune System in Kidney Disease," *Clinical and Experimental Immunology* 192, no. 2 (2018): 142–150, https://doi.org/10.1111/cei.13119.

16. G. Ye, Z. Xie, H. Zeng, et al., "Oxidative Stress-Mediated Mitochondrial Dysfunction Facilitates Mesenchymal Stem Cell Senescence in Ankylosing Spondylitis," *Cell Death & Disease* 11, no. 9 (2020): 775, https://doi.org/10.1038/s41419-020-02993-x.

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LETTER TO THE EDITOR

Comment on: "Who Is the Convict: COVID-19 or Corticosteroid? Late-Onset Avascular Necrosis of the Hips After COVID-19. A Case Report With Literature Review"

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Dear Editor,

We read with great interest a case report and literature review titled "Who is the Convict: COVID-19 or Corticosteroid? Late-onset avascular necrosis of the hips following COVID-19" reported by Nejadhosseinian et al. [1]. This case report and review evaluate the development of late-onset avascular necrosis 20 months following COVID-19 infection in an adult patient receiving steroid treatment. In this article, the authors concluded that ischemic necrosis of the femoral head could be caused by COVID-19 infection or steroid use. In contrast to steroid-related avascular necrosis, we present an adolescent boy with bilateral avascular necrosis or osteonecrosis after recurrent COVID-19 infection, who was previously diagnosed with severe factor (F) XI deficiency and successfully treated with iloprost to postpone surgery. The 15-year-old child was referred to the orthopedic department after complaining of severe back and hip pain and limping for a year. Pelvic magnetic resonance imaging (MRI) revealed bilateral osteonecrosis in the femoral heads (Figure 1). Because of the patient's young age and the risk of bleeding, orthopedic surgery was not first considered. He has a history of two recurrent COVID-19 infections during the pandemic period, the first from a household contact 25 months before the onset of avascular necrosis and the second from a positive SARS-CoV-2 PCR in school 18 months before avascular necrosis. He was not vaccinated against COVID-19. We learned that before the pandemic period and his diagnosis of FXI deficiency, he used to play football and cycle regularly. The patient was referred to the hematology department to rule out any possible hemostatic causes of osteonecrosis. His APTT assessment was prolonged to 110 s. His factor XI level was 0.1%, indicating a severe FXI deficiency. Protein C, protein S, antithrombin III, and homocysteine levels were examined to establish the role of avascular necrosis and were found to be within normal ranges. The abdominal and pelvic ultrasound was normal. Endocrine consultation was done due to low levels of parathyroid hormone, calcitonin, and vitamin D, but no pathology was found. However, vitamin D supplementation and calcium support were administered. The patient was admitted to the Physical Medicine and Rehabilitation department and given muscle-strengthening exercises for 6 weeks, but there was no improvement. Muscle and joint motions improved slightly after 12 weeks of hyperbaric oxygen therapy, which included up to 60 sessions. The patient's requirement for analgesics has decreased. However, after discontinuing hyperbaric oxygen therapy, the patient's pain intensity and difficulty walking returned. Our patient received off-label approval for intravenous iloprost (25 μg/day for 5 days) and oral alendronate (70 mg weekly). Pain was assessed using the Visual Analog Scale (VAS) available at https://orthopowertools.com/VAS. This score, which ranged from 1 to 10, indicated the intensity of the pain. This means that pain scores of 1–4 were mild, 5–6 were moderate, and 7–10 were severe. At the start of iloprost treatment, VAS scores during exercise were 10/10 for back pain, 8/10 for hip pain, and 6/10 for knee pain. After the first month of iloprost therapy, the knee (4/10) and hip (6/10) pains gradually decreased, but the back (10/10) pain continued. After 4 months of treatment, the scores were 4/10 for hip pain, 7/10 for back pain, and 2/10 for knee pain. Only the pain in the back worsened with physical activity. After 6 months, the patient was still taking

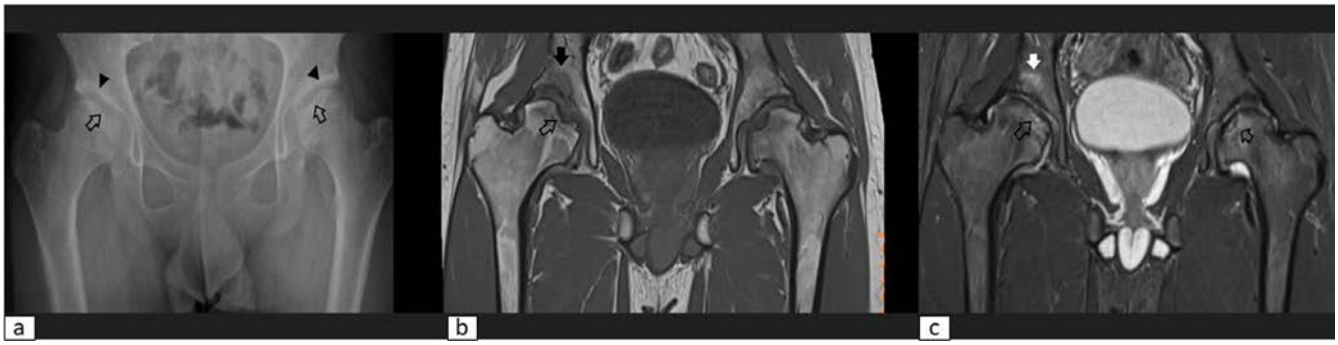

FIGURE 1 | On the PA pelvis radiograph, a disruption of the spherical contour of both femoral heads (empty black arrow) and increased sclerosis in the adjacent acetabular surfaces (black arrowhead) (a); Subsequent hip MRI revealed sclerosis and edema accompanying the cartilage erosion of the femoral heads (empty black arrow) (b); On the right acetabular bone surface, a subchondral bone defect with medullary edema on fat-suppressed sequences (white arrow) (c).

iloprost and alendronate. There were no adverse effects from iloprost. Repeated pelvic MRI scans did not reveal any changes. Genetic testing demonstrated that the boy and his sister carry a homozygous nonsense mutation in the FXI gene (c.1566G>A; p.Trp519Ter) during their family screening [2]. His parents had the heterozygous FXI mutation. The inherited thrombophilia panel revealed that both siblings were homozygous for the MTHFR A1298C mutation, whereas their parents were heterozygous carriers.

The prevalence of avascular necrosis related to COVID-19 has been reported to be around 0.07% [1]. Nonsteroid-related avascular necrosis has been reported in 33% of patients secondary to COVID-19 infection in a comprehensive review [1]. The mean time between COVID-19 and the onset of avascular necrosis was 132.8 days in a few reports [3, 4]. We detected bilateral avascular necrosis 18 months following COVID-19 infection, which is consistent with a case reported by Nejadhosseinian et al. [1]. Although there are various causes of avascular necrosis, including long-term steroid usage, sickle cell anemia, malignancy, and endocrine issues, we were unable to identify any in this case [5]. However, a systematic review demonstrated that recurrent joint bleeding caused by hemophilia decreases blood flow in the bone microcirculation, which is linked to femoral head osteonecrosis [6]. Furthermore, it has been shown that repeated microtrauma from sporting activities causes joint hemorrhage in a patient with FXI deficiency [7]. Similarly, in our case, regular football and cycling activities before the FXI deficiency diagnosis may cause joint microbleeding, which impacts bone microcirculation. In a comprehensive literature search, only one study demonstrated that heterozygous mutations in the MTHFR C677T and MTHFR A1298C genes, together with the use of steroids, could result in multifocal osteonecrosis in a young spinal cord injury patient [8]. In addition to the endothelial damage caused by repeated COVID-19 infection, prothrombotic risk factors (homozygous mutation in the MTHFR A1298C gene) and traumatic joint microbleeding due to severe FXI deficiency, both of which affect bone microcirculation, may have contributed to the development of nonsteroid-related avascular necrosis in our case.

Anticoagulant drugs can be used to treat patients who have developed avascular necrosis secondary to COVID-19 infection. According to this data, another comprehensive review proposed various treatment modalities for non-surgical intervention management options for early detected avascular necrosis, including protected weight bearing, physical therapy, vasodilators, oral anticoagulants, and bisphosphonates in 80% of COVID-19 patients [4]. These authors indicated that the anticoagulants may be used to treat microvascular thrombosis and increase bone microcirculation in COVID-19 patients with osteonecrosis [9]. However, avascular necrosis or osteonecrosis is difficult to treat in children suffering from bleeding disorders [10]. Because of the young age and risk of bleeding, prosthetic surgery and anticoagulant medications are not recommended. Thus, anticoagulant medication cannot be preferred in our case due to the high bleeding risk [11]. A few studies have shown that long-term Iloprost treatment improves patients with avascular necrosis [12, 13]. A recent study showed that early Iloprost treatment in osteonecrosis patients decreased the progression of prosthetic surgery, reduced bone pain, enhanced bone function, and improved MRI results [12]. We also chose iloprost due to its vasodilation and platelet dysfunction effects. Furthermore, a recent review showed that when Iloprost was combined with bisphosphonates in osteonecrosis patients, bone marrow edema and osteoclastic activity decreased, while microcirculation increased due to vasodilation, potentially relieving bone pain and functional loss [13]. The patient was successfully treated for 6 months with Iloprost, a prostacyclin analog, and alendronic acid, a bisphosphonate. There were no side effects recorded. Our findings in this case suggest that recurrent COVID-19 infection, a homozygous MTHFR A1298C gene defect, and traumatic joint microbleeding caused by severe FXI deficiency may have all contributed to the development of avascular necrosis. Furthermore, iloprost combined with alendronate may be beneficial in treating avascular necrosis in those with high-risk bleeding if anticoagulants are contraindicated and surgery is not an option.

Author Contributions

All authors read and approved the final manuscript.

Consent

Informed consent was obtained from parents.

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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References

1. M. Nejadhosseinian, H. Haerian, M. Tabatabaie Nejad, et al., "Who Is the Convict; COVID-19 or Corticosteroid? Late Onset Avascular Necrosis of Hips After COVID-19. A Case Report With Literature Review," *International Journal of Rheumatic Diseases* 26, no. 10 (2023): 2069–2072.

2. A. Kahraman, M. Yazol, G. Kayhan, and Z. Kaya, "Unusual Comorbid Condition in a Child With Severe Factor XI Deficiency: Spina Bifida," *Turkish Journal of Hematology* 42 (2025): 238–239, https://doi.org/10.4274/tjh.galenos.2025.2025.0043.

3. A. Uysal and M. Erdem Uysal, "Bilateral Avascular Necrosis of the Femoral Head After COVID-19 Infection: A Case Report," *Batı Karadeniz Tıp Dergisi* 6, no. 2 (2022): 235–238.

4. G. Daltro, B. Franco, D. Veiga, T. Faleiro, V. Lima, and F. Vitório, "Osteonecrosis Development Post-COVID-19 Infection," *Journal of Regenerative Biology and Medicine* 3, no. 5 (2021): 1–8.

5. W. Konarski, T. Poboży, A. Śliwczyński, et al., "Avascular Necrosis of Femoral Head-Overview and Current State of the Art," *International Journal of Environmental Research and Public Health* 19, no. 12 (2022): 7348.

6. E. Rezus, B. I. Tamba, M. C. Badescu, D. Popescu, I. Bratoiu, and C. Rezus, "Osteonecrosis of the Femoral Head in Patients With Hypercoagulability-From Pathophysiology to Therapeutic Implications," *International Journal of Molecular Sciences* 22, no. 13 (2021): 6801.

7. S. M. Douthett and L. Fallat, "Severe Ankle Arthritis After Multiple Hemarthroses Secondary to Factor XI Deficiency: A Case Report," *Journal of Foot and Ankle Surgery* 57, no. 6 (2018): 1242–1245.

8. C. Tıkız, C. Özbek İlhan, and E. Onağ, "Multifocal Osteonecrosis in Spinal Cord Injury," *European Journal of Therapeutics* 30, no. 3 (2024): 382–385.

9. A. A. A. Hassan and A. A. Khalifa, "Femoral Head Avascular Necrosis in COVID-19 Survivors: A Systematic Review," *Rheumatology International* 43, no. 9 (2023): 1583–1595.

10. E. Y. Keskin, T. Gürsel, Z. Kaya, et al., "Molecular Basis and Bleeding Manifestations of Factor XI Deficiency in 11 Turkish Families," *Blood Coagulation & Fibrinolysis* 26, no. 1 (2015): 63–68.

11. P. Guo, F. Gao, Y. Wang, et al., "The Use of Anticoagulants for Prevention and Treatment of Osteonecrosis of the Femoral Head: A Systematic Review," *Medicine (Baltimore)* 96, no. 16 (2017): e6646.

12. T. Claßen, A. Becker, S. Landgraeber, et al., "Long-Term Clinical Results After Iloprost Treatment for Bone Marrow Edema and Avascular Necrosis," *Orthopedic Reviews* 8, no. 1 (2016): 6150.

13. A. Eidmann, M. Eisert, M. Rudert, and I. Stratos, "Influence of Vitamin D and C on Bone Marrow Edema Syndrome-A Scoping Review of the Literature," *Journal of Clinical Medicine* 11, no. 22 (2022): 6820.

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EDITORIAL

Flow Cytometric Expression of Nucleotide-Binding Oligomerization Domain Containing 2 (NOD2) Protein: An Effective Screening Tool for Blau Syndrome

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Blau syndrome (BS) is a rare autosomal dominant autoinflammatory disorder presenting in early childhood and characterized by a triad of granulomatous arthritis, dermatitis, and uveitis. It is caused by variants in the nucleotide oligomerization domain 2 (*NOD2*) gene that encode for the NOD2 protein, having two caspase recruitment (CARD) domains, a centrally located NACHT domain and six leucine-rich repeats (LRRs) [1]. This cytosolic pattern recognition receptor protein is expressed in various immune cells and recognizes muramyl dipeptide (MDP) derived from intracellular bacterial lipopolysaccharides and triggers an immune response by activating the NFKB pathway. Mutations in the *NOD2* gene decrease the capability of spontaneous oligomerization of the protein. Over the years, the number of NOD2 mutations associated with BS has expanded, and most variants are found at or near the nucleotide-binding NOD/NACHT domain or extending into the C-terminal region of the LRR structure, with the R334W variant being the most common. Frequent variants of uncertain significance, incomplete penetrance, as well as recognition of asymptomatic carriers have made genotype–phenotype correlation difficult to understand. Clinically, patients with BS are often diagnosed late, and as a result, patients develop significant ocular morbidity and/or end-organ damage. So, early identification is crucial for timely intervention and management. Genetic testing is expensive and time-consuming, so a need was felt to have a flow cytometry-based rapid screening test to identify the subset of patients who would benefit from further evaluation by expensive and time-consuming genetic tests. Flow cytometry enables rapid and cost-effective assessment of NOD2 protein levels in different immune cell subsets, with same-day turnaround time, making it particularly useful in acute or resource-constrained clinical settings.

Patients with clinical suspicion of BS were screened for *NOD2* variants and enrolled in the study after informed written consent. The patients were registered at the Pediatric Immune Deficiency Clinic and Pediatric Rheumatology Clinic, Advanced Pediatric Centre, PGIMER, Chandigarh, India. The clinical profile of 11 BS patients (10 children, 1 adult) from our cohort was published (PMID: 36189202) highlighting that 54.5% of patients had a classic triad, while the frequency of arthritis, dermatitis, and uveitis was 100%, 81.8%, and 72.7%, respectively. Among these 11 patients, flow cytometry and gene expression studies could be carried out on only 9 patients, as 1 patient died and one was lost to follow up. Whole blood (5 mL) was obtained from patients with BS and healthy controls (HC). NOD2 protein expression was assessed in BS ($n=9$) and HC ($n=7$) by intracellular staining of different immune cells by flow cytometry. Isolation of peripheral blood mononuclear cells (PBMCs) was carried out from patients with BS and HC using the density gradient centrifugation method. Cells were stained with a titrated volume of mouse anti-human CD3-FITC (561802- Becton Dickinson, USA), mouse anti-human CD19-APC (555415- Becton Dickinson, USA) mouse anti-human CD16 BV421 (562878-Becton Dickinson, USA), mouse anti-human CD14 PE-Cy7 (560919-Becton Dickinson, USA), mouse anti-human CD11c PerCP-Cy5.5 (565227-Becton Dickinson, USA), mouse

Rajni Kumrah and Jyoti Sharm Share the joint first authorship.

anti-human CD4 BV510 (563094-Becton Dickinson, USA), and mouse anti-human CD8 BUV395 (563796- Becton Dickinson, USA). The cells were then washed, lysed, and fixed using lyse and fix (558049, Becton Dickinson, USA), permeabilized using Triton X-100, and incubated for 10 min. Finally, cells were stained with mouse anti-human NOD2 labeled with PE (NB100-524PE- Novus Biosciences, USA) and acquired on the BD LSRFortessa X-20 flow cytometer. The proportion of T cells and subsets, B cells, NK cells, and monocyte subsets was assessed. The gating strategy for assessing NOD2 protein expression in different immune cells is highlighted in Figure 1. Statistical comparison among patients and healthy control was performed by non-parametric *t* test (not normally distributed data) followed by Mann–Whitney U test and value of $p < 0.05$ was considered significant. Results were analyzed using GraphPad Prism 9 Software (8.3.0.538). Graphs were obtained from GraphPad. The data variability was presented using median ± interquartile range (IQR).

We corroborated flow cytometry results with *NOD2* gene expression on whole blood using real time polymerase chain reaction in patients with BS ($n = 9$) and HC ($n = 8$). For gene expression, total RNA was isolated using QIAamp RNA Blood Mini Kit (Qiagen) as per standard protocol and quantified. cDNA was synthesized from messenger RNA (mRNA) using cDNA synthesis Kit. Gene specific primers were designed, and Ct method was used to calculate quantitative gene expression (Kenneth and Thomas, 2001).

The patients with BS had lower NOD2 protein expression expressed as delta median fluorescence intensity (ΔMFI) across all immune cells: T cells, CD4 + T cells, CD8 + T cells, B cells, NK cells, classical monocytes, intermediate monocytes and non-classical monocytes as compared to healthy control. However, a significant difference in ΔMFI was obtained for B cells ($p = 0.03$) as well as for CD8 + T cells ($p = 0.05$). The ΔMFI, median ± IQR

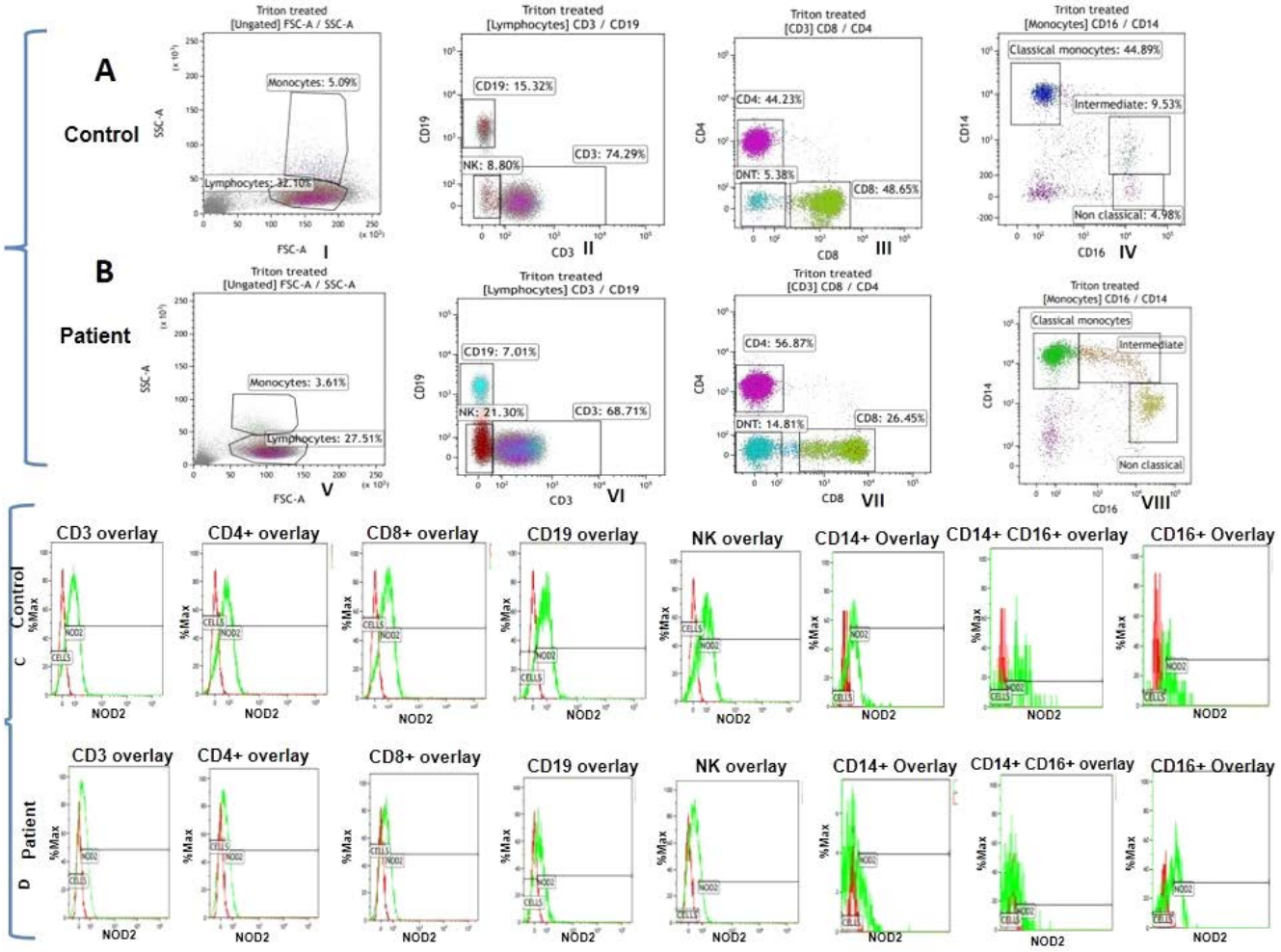

FIGURE 1 | Gating strategy for data acquisition for intracellular staining of NOD2 protein. (Panel A and panel B) shows gating strategy for NOD2 protein expression in different immune cell subsets in healthy control and patients with BS respectively. Graph I and V shows forward scatter versus side scatter in which lymphocytes and monocytes were gated in HC and BS respectively. Lymphocytes were further gated in graph II and VI for CD3 + T cells, CD19 + B cells and NK cell population in HC and BS patients. The CD3 + T cells were then gated on CD4 + Th cells and CD8 + Tc cells in graph III and VII in HC and BS patients respectively. Graph IV and VIII highlighted the gated monocytes as CD14 + classical monocytes, CD16+ non-classical monocytes and dual positive CD14 + CD16 + intermediate monocytes in HC and BS patients respectively. (Panel C and panel D) shows the overlays for NOD2 expression in different immune cell subsets in HC and BS patients respectively depicting reduced NOD2 protein expression in all immune cells in BS patients when compared to HC with statistical significant difference in CD8 + T cells ($p = 0.05$) and B cells ($p = 0.03$).

TABLE 1 | Comparison of ΔMFI of NOD2 protein on different immune cell subsets in patients with Blau syndrome and healthy controls.

Subject ID	CD3+ T cells	CD4+ T cells	CD8+ T cells	B cells	NK CELLS	Classical monocytes
BS1	26.92	57.3	46.7	48.8	57.8	10.3
BS2	43.18	47.8	66.3	32.1	34.7	6.42
BS3	49.79	211	56.8	199	140	233
BS4	190.04	129	44.2	60.4	68.1	147
BS5	49.52	62	39.1	48.8	53.9	71.9
BS6	125.36	132.2	106.3	16.7	28.2	−5.13
BS7	53.97	54	44	66.8	84.8	252
BS8	66.86	101.2	201	146	179	443
BS9	69.0	115.6	43.8	28.2	33.4	−20.5
Median ± IQR	49.79 (43.18–66.86)	101.2 (55.65–130.6)	46.70* (43.90–86.30)	48.80** (30.15–106.4)	57.80 (34.05–112.4)	71.90 (0.645–242.5)
HC1	718.54	640	1390	837	340	1206
HC2	143.5	61.3	55	78.4	107	127
HC3	58.88	55	49.1	56.5	37.2	111
HC4	32.29	48.2	52	121	125	185
HC5	78.5	58	123	56.5	62.9	44.9
HC6	57.07	1248	721	1123	1232	2292
HC7	254.3	701	621	703	835	NA
Median ± IQR	78.50 (57.07–254.3)	61.30 (55–701)	123 (52–721)	121 (56.50–837)	125 (62.90–835)	156 (94.48–1478)

Note: Results reported as median ± interquartile range (IQR). **ΔMFI of NOD2 in B cells ($p = 0.03$) and *ΔMFI of NOD2 in CD8 + T cells ($p = 0.05$) was estimated by non-parametric independent *t* test followed by Mann–Whitney *U* test. The value of $p < 0.05$ was considered significant.

Abbreviations: ΔMFI, delta median fluorescence intensity; IQR, interquartile range; NA, not available.

of NOD2 expression on different immune subsets in patients and healthy controls has been highlighted in Table 1.

Gene expression analysis revealed reduced *NOD2* gene expression in patients with BS ($p = 0.04$) as compared to healthy controls. Expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-18) was reduced in BS patients (ns) while comparable values were noted for TNF-α and transcription regulators of inflammation (NF-κB1 and NF-κB2) (Figure 2). It is difficult to correlate NOD2 protein expression with clinical outcomes in this small cohort. However, we tried to correlate NOD2 protein expression with clinical parameters like age at disease onset, presence of family history, uveitis and treatment response. Two patients with reduced NOD2 protein expression in all immune cell subsets had early onset of disease with classical Blau syndrome, positive family history and required multiple immunosuppressive therapies.

Early identification is crucial for timely intervention and management of BS. Genetic sequencing of the *NOD2* gene remains the gold standard for diagnosis. However, genetic sequencing can be expensive and time-consuming. Flow cytometric assessment of NOD2 protein expression presents a promising alternative for screening due to its cost-effectiveness and rapid turnaround. While it does not replace traditional genetic testing, which will remain the definitive diagnostic tool, flow cytometry serves as a valuable pre-screening method to identify high-risk individuals who should undergo confirmatory genetic sequencing. Flow cytometry will also enable the identification of individuals who are otherwise detected negative by most common hot spot genetic screenings but are clinically symptomatic. Flow cytometry has been successfully used in other conditions, such as Wiskott Aldrich syndrome and Bruton's Tyrosine Kinase deficiencies. In BS, reduced NOD2 protein expression has been observed in mutation-positive patients, suggesting it could be a useful marker for the disease.

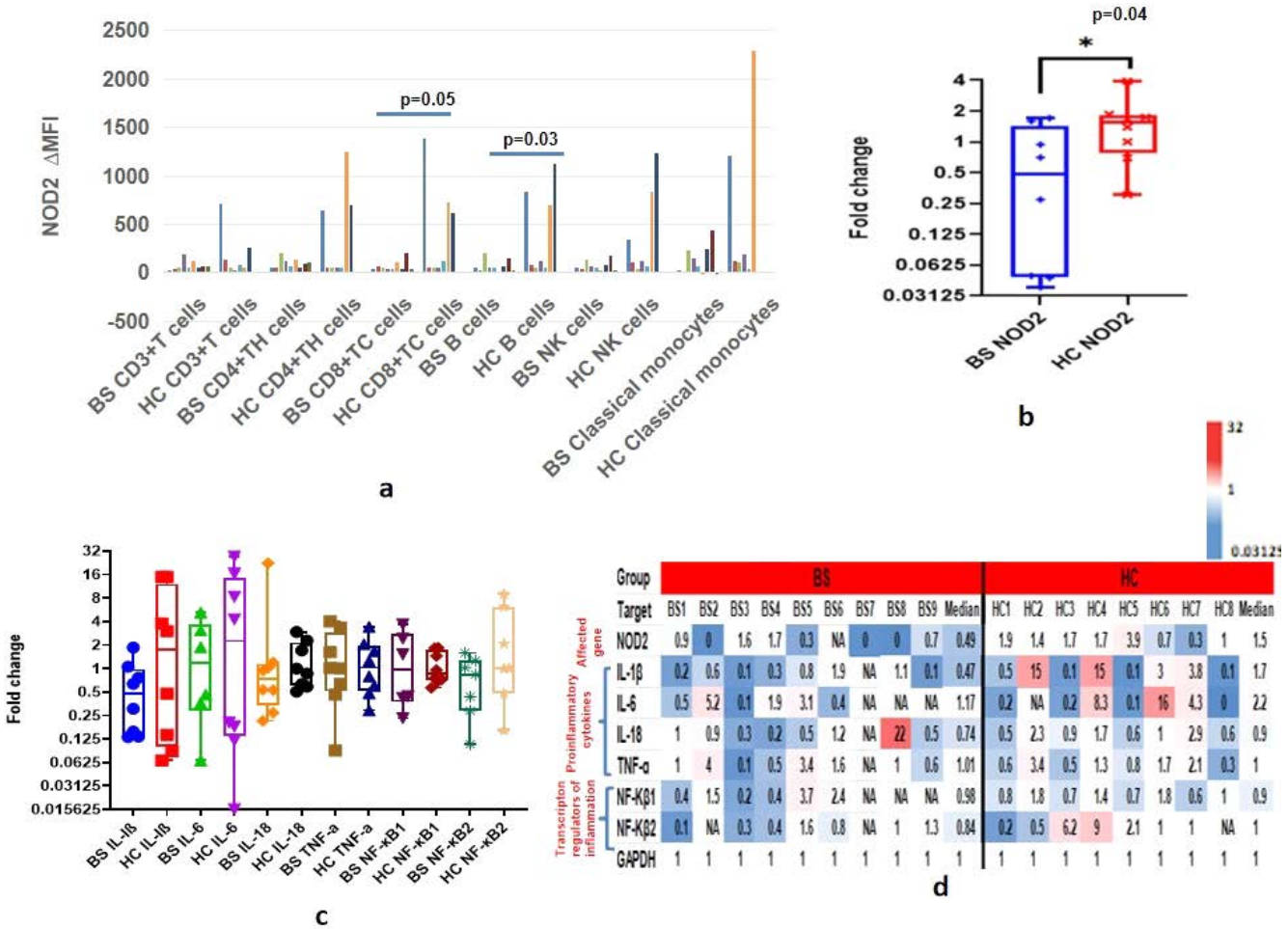

FIGURE 2 | (a) Shows significantly reduced ΔMFI of NOD2 in B cells ($p = 0.03$), CD8 + T cells ($p = 0.05$) and in NK cells with near significance ($p = 0.07$) in patients with BS ($N = 9$) when compared to HC ($N = 7$). (b) Shows reduced *NOD2* gene expression in patients with BS ($N = 9$) ($p = 0.04$) as compared to HC ($N = 8$) on whole blood by real time PCR. (c) Reduced expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-18) in BS patients (ns) while expression of TNF-α and transcription regulators of inflammation (NF-κB1 and NF-κB2) was comparable in patients with BS ($N = 9$) and HC ($N = 8$). (d) Heat map representing fold changes of *NOD2* gene and inflammatory cytokines in patient with BS and HC. Statistical comparison among patients and healthy control was performed by non-parametric independent t-test followed by Mann–Whitney *U* test (small sample size and non-normal distribution of data) and value of $p < 0.05$ was considered significant. Results were analyzed using GraphPad Prism 9 Software (8.3.0.538). Graphs were obtained from GraphPad. Results were reported as median ± interquartile range (IQR). BS, Blau syndrome; HC, Healthy control.

Despite advancements in understanding BS, the exact mechanism by which NOD2 variants cause the syndrome remains unclear. It is particularly unclear whether these variants result in gain-of-function (GOF) or loss-of-function (LOF) mutations. The hypothesis of GOF mutations has been widely accepted due to the autosomal dominant inheritance pattern of BS [2]. Supporting this hypothesis, in vitro studies using overexpression systems have shown that BS-associated *NOD2* mutations lead to hyperactivation of the NF-κB and MAPK pathways, resulting in increased inflammatory cytokine production [3]. Contrarily, clinical studies challenge the GOF hypothesis [4]. For example, peripheral blood cells from BS patients do not exhibit spontaneous cytokine release and show reduced IL-1β response compared to controls, which is not consistent with the hyperactive immune response seen in GOF conditions [4]. There are few in vivo studies in the literature so far. Moreover, these observations are more aligned with the LOF mutations seen in Crohn's disease (CD), where NOD2 mutations fail to activate the NF-κB pathway [3, 5].

The conflicting evidence from in vitro and clinical studies suggests that the pathogenesis of BS may involve a more complex mechanism than a straightforward GOF or LOF mutation. It underscores the necessity for further research to elucidate the precise role of NOD2 in BS. A comprehensive understanding of NOD2 signaling and its impact on immune regulation in BS is vital. This requires collaborative efforts across basic research, translational studies, and clinical investigations to unravel the intricacies of NOD2-related immune dysregulation and improve patient outcomes in Blau syndrome.

The present study compares NOD2 protein expression by flow cytometry. Patients with the R334W variant in the *NOD2* gene have lower expression of NOD2 protein in B cells and CD8 + T cells by flow cytometry. Real-time PCR analysis also revealed reduced expression of the *NOD2* gene and pro-inflammatory cytokines in patients with BS. Flow-based assessment may serve as a rapid screening test for patients with uveitis and a diagnostic aid for identifying patients with BS. Our results are consistent with in vivo studies and showed reduced NOD2 protein expression by flow cytometry as well as by qPCR in R334W variant-positive BS patients and reduced inflammatory cytokine production, hence supporting/suggesting loss-of-function (LOF) in Blau syndrome. There is a need to develop animal models of NOD2 mutated mice and perform functional validation of our findings.

The present study includes a small number of patients from a single center, which is a limitation that can indeed lead to sample variability and may limit the robustness of statistical power and generalizability of our findings. BS being a rare condition and recruiting a larger cohort presents significant logistical and clinical challenges. Despite the limited sample size, consistent trends were observed across multiple outcome measures and appropriate statistical analyses to account for the sample limitations. Furthermore, the study provides valuable preliminary insights that open many new avenues and provide groundwork for future multi-center studies with larger cohorts for functional validation.

Author Contributions

Conceptualization: D.S.; Writing-original draft preparation: R.K., J.S.; Writing-review & editing: D.S., A.R., V.G., S.S.; Formal analysis: R.K., J.S., K.A., A.R. Clinical care: V.G., D.S., S.S. R.K. & J.S. have equally contributed and share the first authorship. All authors have approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

References

1. R. Kumrah, R. K. Pilania, N. K. Menia, et al., "Blau Syndrome: Lessons Learned in a Tertiary Care Centre at Chandigarh, North India," *Frontiers in Immunology* 13 (2022): 932919.

2. C. Miceli-Richard, S. Lesage, M. Rybojad, et al., "CARD15 Mutations in Blau Syndrome," *Nature Genetics* 29 (2001): 19–20.

3. N. Kanazawa, I. Okafuji, N. Kambe, et al., "Early-Onset Sarcoidosis and CARD15 Mutations With Constitutive Nuclear Factor-kappaB Activation: Common Genetic Etiology With Blau Syndrome," *Blood* 105 (2005): 1195–1197.

4. J. Dugan, E. Griffiths, P. Snow, et al., "Blau Syndrome-Associated Nod2 Mutation Alters Expression of Full-Length NOD2 and Limits Responses to Muramyl Dipeptide in Knock-In Mice," *Journal of Immunology* 194, no. 1 (2015): 349–357.

5. M. Chamaillard, D. Philpott, S. E. Girardin, et al., "Gene-Environment Interaction Modulated by Allelic Heterogeneity in Inflammatory Diseases," *Proceedings of the National Academy of Sciences of the United States of America* 100 (2003): 3455–3460.

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REVIEW

Exploring the Relationship Between Alcohol Consumption and Gout: A Narrative Review

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ABSTRACT

Gout, a chronic inflammatory condition, is intricately linked to lifestyle factors such as diet and alcohol consumption. Alcohol significantly influences gout development and flares through mechanisms including hyperuricemia, oxidative stress, and purine metabolism. The impact of alcohol varies by type and quantity, with beer and spirits posing a higher risk due to their purine and ethanol content, while moderate wine consumption may confer potential anti-inflammatory benefits. Recent advances underscore the multifactorial nature of gout, revealing how host genetics and epigenetic modifications modulate alcohol's effects. Variants in genes regulating urate transport (SLC2A9, ABCG2) and alcohol metabolism (ADH1B, ALDH2) influence individual susceptibility, highlighting the need for personalized management strategies. This narrative review synthesizes evidence from genetics, lifestyle, and public health perspectives, emphasizing the importance of moderation, pharmacogenomics, and tailored interventions in improving gout outcomes.

1 | Introduction

Gout is widely recognized as an inflammatory rheumatic condition characterized by arthritis and an abnormal metabolism of uric acid [1]. The condition is triggered by the deposition of monosodium urate (MSU) crystals in the joints, resulting in episodes of severe pain, swelling, redness, and tenderness, particularly in the big toe [1]. However, other joints, such as the knees, ankles, elbows, and wrists, can also be affected. These painful episodes, known as gout flares, can last from days to weeks and may become more frequent and severe over time if left untreated. Gout is also associated with other complications, including tophi (hard lumps of urate crystals under the skin), kidney stones, and long-term joint damage, which can lead to chronic disability [1].

Across historical periods, gout has consistently been associated with lifestyle factors, primarily linked to a diet high in purines compounds found in many foods, particularly seafood, red meat, organ meats, and certain vegetables like asparagus and spinach [2]. When purines are metabolized, uric acid is produced as a byproduct. In individuals prone to gout, the body's inability to efficiently eliminate uric acid results in its accumulation in the blood, known as hyperuricemia, eventually leading to the formation of MSU crystals in the joints [2]. This connection between diet and disease has been

recognized since ancient times, when food scarcity and luxury were intertwined with social class. Gout, referred to as the "king's disease" or "rich man's disease," was particularly prevalent among the wealthy, who had access to large quantities of meat, seafood, and alcohol [3]. The indulgence in these luxury items became a symbol of prosperity, while gout was seen as a consequence of an affluent lifestyle [3].

In ancient societies, gout symbolized more than just a health condition; it reflected wealth, privilege, and status, often depicted in art, literature, and medical writings [3]. Figures like King Henry VIII and Sir Isaac Newton, who suffered from gout, reinforced its association with royalty and the elite. In classical Greek and Roman times, the disease was seen as an inevitable consequence of a privileged lifestyle, with physicians advising moderation in diet and alcohol to avoid its onset. Far from universally negative, gout was sometimes viewed as a mark of distinction, indicating a life of abundance [3]. This perception persisted through the medieval and Renaissance periods, where depictions of nobility afflicted by gout were common. Early treatments focused on lifestyle modifications, but the precise link between gout and alcohol wasn't fully understood until modern research revealed its role in uric acid metabolism and the disease's progression [1, 3].

Notably, the relationship between gout and alcohol consumption has been a subject of extensive research in the modern era. Several studies have confirmed that alcohol, particularly beer and spirits, can increase the risk of gout flares by contributing to hyperuricemia.

This narrative review aims to elucidate the intricate interplay between these factors, providing a framework for understanding individual variability in gout risk. By exploring the genetic mechanisms underlying alcohol metabolism and its role in purine metabolism, this review highlights the necessity of integrating genetics into gout management strategies. While past studies have extensively analyzed lifestyle factors and genetics separately, this review seeks to innovate by synthesizing their combined impact, offering a personalized perspective on gout pathogenesis and treatment.

2 | Methods

We conducted a narrative review using PubMed, OVID (Medline), and Web of Science to examine the relationship between gout and alcohol consumption. Search terms included "gout," "hyperuricemia," "alcohol consumption," "beer," "spirits," "genetics," "urate metabolism," and "oxidative stress." Eligible studies were clinical, epidemiological, or review articles in English that addressed alcohol's role in gout development, flares, or management. We excluded letters, conference abstracts, and unpublished works.

The review followed six structured steps: (A) defining research questions and inclusion/exclusion criteria, (B) study selection using predefined search terms and databases, (C) quality assessment with the Critical Appraisal Skill Program (CASP), (D) data extraction (study aims, context, demographics, methods, and key findings), (E) data synthesis, and (F) writing and critical reflection. The search (July 2022–February 2024) retrieved 1524 records; after removing duplicates and screening, 832 remained. Two reviewers (ALAC, MCMA) independently assessed titles and abstracts, retrieving full texts when necessary. Discrepancies were resolved through team discussion (PAMP, WBM, GQL). A second screening excluded studies with ineligible participants, methodological limitations, or insufficient relevance. CASP evaluation excluded an additional 28 studies. Ultimately, 21 studies (5.75% of initial results) were included.

Key characteristics of the selected studies—including setting, sample size, age range, and methods—are synthesized in the following sections.

3 | Results

3.1 | Host Genetics and Gout Susceptibility

Recent studies have shed light on the role of host genetics in determining susceptibility to gout, emphasizing key genetic loci, epigenetic modifications, and the interaction of these factors with alcohol consumption [4].

The study titled A Genome-Wide Association Analysis Reveals New Pathogenic Pathways in Gout explores the molecular underpinnings of gout through the largest genome-wide association study (GWAS) to date, encompassing 2.6 million participants and identifying 377 genetic loci associated with the disease [4]. Of these, 149 loci were novel discoveries, highlighting the complexity of gout pathogenesis. The research emphasizes key inflammatory processes, including the role of epigenetic modifications and NLRP3 inflammasome activation, driven by interactions between genetic predispositions and MSU crystal deposition. Additionally, sex-specific genetic differences were explored, providing insights into the male predominance of gout [4].

A major finding was the identification of genes linked to urate metabolism and immune responses, such as ABCG2, FADS2, and IL1R1, which play a significant role in modulating susceptibility to hyperuricemia and the inflammatory cascade underlying gout flares. The study highlights the critical role of epigenetic mechanisms, including DNA methylation and histone modification, in shaping the inflammatory and metabolic processes driving gout. These insights reveal potential therapeutic targets, particularly pathways involving chromatin modifiers and cytokine signaling [4].

3.2 | Alcohol and Gout Development

3.2.1 | Alcohol Consumption and Purine Metabolism

The association between alcohol consumption and the risk of developing gout centers on its impact on purine metabolism, uric acid production, and excretion. Purines, fundamental building blocks of nucleotides, are metabolized mainly in the liver, where their catabolism generates uric acid as a byproduct [2, 5]. Diets rich in purines provide abundant substrates for this process, predisposing one to hyperuricemia.

When purine-rich foods are consumed together with alcohol, hepatic metabolism is altered. Ethanol increases the hepatic NADH/NAD$^+$ ratio, which favors lactate production; lactate competes with uric acid for renal excretion, reducing urate clearance [5, 6]. Chronic alcohol intake also promotes hepatic steatosis and mitochondrial dysfunction, impairing purine recycling and uric acid elimination [7]. Additionally, alcohol can disrupt intestinal homeostasis and urate transport mechanisms, contributing to systemic urate accumulation [8].

Excess uric acid precipitates as monosodium urate (MSU) crystals once concentrations exceed the solubility threshold. This risk is magnified by acidic microenvironments induced by alcohol metabolism, fasting, or salt deposition, all of which reduce urate solubility [9, 10]. Higher calcium ion concentrations in acidic conditions further destabilize urate solubility, promoting crystal nucleation and growth [10].

MSU crystal deposition initiates a potent inflammatory cascade. Phagocytosis of MSU crystals by macrophages activates the NLRP3 inflammasome and promotes the production of interleukin-1β (IL-1β). In humans, a secondary signal—often dietary or alcohol-related—stimulates Toll-like receptor (TLR) pathways, intensifying neutrophil infiltration and joint inflammation [10]. The overall sequence of these processes is illustrated in Figure 1, which summarizes how alcohol-driven changes in purine metabolism and urate handling create a favorable environment for gout development.

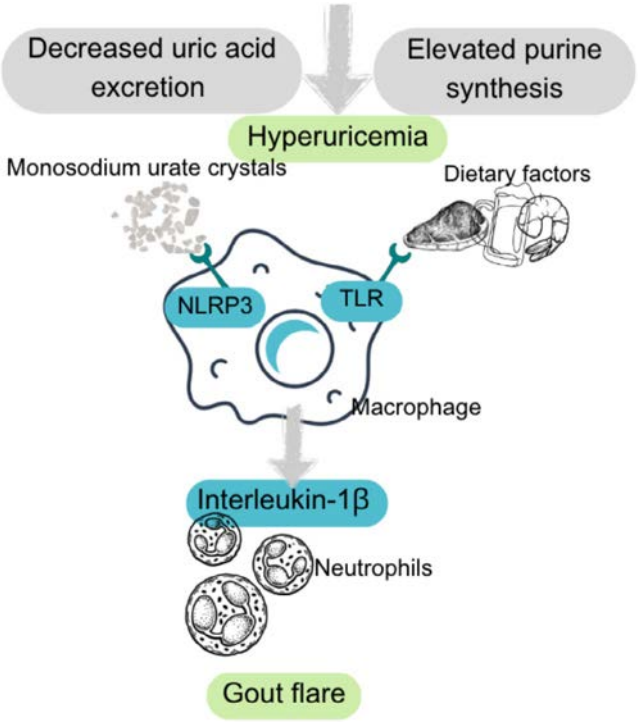

FIGURE 1 | Mechanism of hyperuricemia to gout. This figure is original and created by the author(s).

3.2.2 | Differential Impact of Alcoholic Beverages

Different types of alcoholic beverages have varying effects on gout risk, underscoring the complexity of this relationship [11]. Research has consistently shown that beer is associated with a significantly increased risk of developing gout, with a relative risk (RR) of 1.49 (95% CI 1.32–1.70). This elevated risk is likely due to the high purine content found in beer, particularly from the yeast used in its fermentation process. However, the relationship between alcohol consumption and gout is not uniformly detrimental across all types of alcoholic beverages. For instance, wine has been suggested to possess protective effects against gout, which may be attributed to its rich content of polyphenolic compounds and potential anti-inflammatory properties [5, 12]. These compounds are believed to help modulate uric acid levels and reduce inflammation, thereby potentially mitigating the risk of gout attacks.

A recent study further elucidated the differential impact of various alcohol types on serum urate levels, revealing that each type of alcoholic beverage influences urate concentrations in distinct ways [13]. For instance, the study found that for each additional 1-unit increase in beer consumption, serum urate levels increased by 0.12 mg/dL in men and 0.21 mg/dL in women. In contrast, whiskey consumption was associated with a rise of 0.19 mg/dL in men and 0.16 mg/dL in women, while wine consumption resulted in an increase of 0.10 mg/dL for both sexes [13]. These findings indicate that not only does the quantity of alcohol consumed matter, but also the type of alcohol plays a crucial role in determining the risk of developing gout.

The intricate distinctions between different alcohol types emphasize the necessity for a nuanced approach in understanding their impact on gout development (Table 1). Recognizing these differences can help inform dietary recommendations and lifestyle modifications for individuals at risk of gout, ultimately contributing to better management of this painful condition. Furthermore, continued research is essential to unravel the underlying mechanisms by which specific alcoholic beverages affect uric acid

TABLE 1 | Impact of different alcoholic beverages on serum uric acid levels.

Type of alcoholic beverage	Average alcohol content (% ABV)	Increase in serum uric acid levels (mg/dL per 1 unit increase)	References
Beer	4%–6%	Men: 0.12 mg/dL Women: 0.21 mg/dL	[6, 9]
Whiskey	40%	Men: 0.19 mg/dL Women: 0.16 mg/dL	[9]
Wine	9%–14%	Both Sexes: 0.10 mg/dL	[5, 7, 9]

metabolism, paving the way for more effective prevention strategies tailored to individual consumption patterns.

3.3 | Alcohol Influencing Gout Flares

3.3.1 | Acute Attacks and Alcohol Intake

The influence of alcohol on the frequency of acute gout attacks represents a complex interplay that extends beyond mere associations, emphasizing the need for a deeper understanding of this relationship. Numerous studies have indicated that higher alcohol intake, particularly from beer and spirits, is linked to an increased risk of gout flares [8, 14]. However, the variability among individuals highlights that this relationship is highly individualized, suggesting that personalized approaches to clinical management are essential.

A meta-analysis conducted by Wang et al. synthesized data from 12 studies and identified a significant association between alcohol consumption and the risk of developing gout [15]. The pooled Relative Risk (RR) for individuals with the highest levels of alcohol consumption compared to non-occasional drinkers was found to be 1.98, with a 95% Confidence Interval (CI) ranging from 1.52 – 2.58. Table 2

These findings suggest a clear dose-dependent relationship between alcohol consumption and the risk of gout, indicating that higher levels of alcohol intake are significantly associated with an elevated risk of developing gout [15]. The increased risk is particularly pronounced at higher levels of consumption, reinforcing the importance of moderation in alcohol intake for individuals with a predisposition to gout.

Moreover, the variability in individual responses to alcohol underscores the necessity for healthcare professionals to consider personalized strategies when advising patients on alcohol consumption [15]. Tailoring recommendations based on individual risk factors, including genetic predispositions, dietary habits, and existing health conditions, can help mitigate the risk of gout flares and improve the overall management of this painful condition.

3.3.2 | Mechanisms by Which Alcohol Contributes to Gout Flares

The mechanisms through which alcohol contributes to gout flares are multifaceted and involve several biological processes that interconnect to exacerbate the condition [1]. One significant pathway is the metabolism of ethanol, which generates lactate. This lactate competes with uric acid for renal excretion, leading to reduced uric acid clearance and contributing to hyperuricemia, a key precursor for gout attacks [6]. As uric acid levels rise in the bloodstream, the likelihood of monosodium urate crystal formation increases, particularly in cooler peripheral joints, although this remains theoretical [15].

TABLE 2 | Relative risk for different levels of alcohol consumption.

Level of alcohol consumption	Relative risk (RR)	95% Confidence interval (CI)
1 drink/day	1.16	1.07 – 1.25
> 1 to < 3 drinks per day	1.58	1.50 – 1.66
≥ 3 drinks per day	2.64	2.26 – 3.09

Moreover, the relationship between alcohol consumption and oxidative stress further complicates the clinical picture. Alcohol-induced oxidative stress results in the production of reactive oxygen species (ROS), which can damage cellular structures and promote inflammation. This oxidative damage not only affects joint tissues but can also disrupt the normal function of immune cells, leading to an exaggerated inflammatory response when gout flares occur [14]. The presence of inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-alpha, is heightened during alcohol consumption, intensifying the inflammatory response in joints already affected by urate crystal deposits [14].

3.4 | Mechanisms of Action: Pathways Affected by Alcohol Consumption

3.4.1 | Oxidative Stress and Inflammation

Alcohol's role in promoting oxidative stress and inflammation adds another layer to its complex relationship with gout, further complicating the understanding of this condition. The metabolism of ethanol leads to the generation of reactive oxygen species (ROS), highly reactive molecules that can damage lipids, proteins, and DNA [6, 16]. This oxidative damage plays a significant role in inflammatory processes, particularly in joint tissues affected by gout. Elevated ROS levels can activate key inflammatory pathways such as the NLRP3 inflammasome and NF-κB signaling, amplifying cytokine production and worsening joint inflammation [17].

The presence of ROS triggers a cascade of biological responses, including increased production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) [6]. Alcohol-induced oxidative stress can also impair endogenous antioxidant defenses, including reduced activity of superoxide dismutase and glutathione peroxidase, tipping the balance toward a pro-inflammatory state [18].

Emerging evidence also suggests that antioxidant-based dietary interventions such as polyphenol-rich foods may attenuate ROS generation, modulate NLRP3 activity, and reduce gout flare severity [19]. Although still under investigation, these approaches highlight the potential for targeting oxidative stress as part of a comprehensive strategy to manage alcohol-related gout flares. The sequence of these processes is summarized in Figure 2, which illustrates how alcohol-induced oxidative stress activates inflammatory cascades leading to gout flares.

3.4.2 | Role of Alcohol Metabolizing Enzymes: ADH and ALDH

The metabolism of alcohol, mediated primarily by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), is a

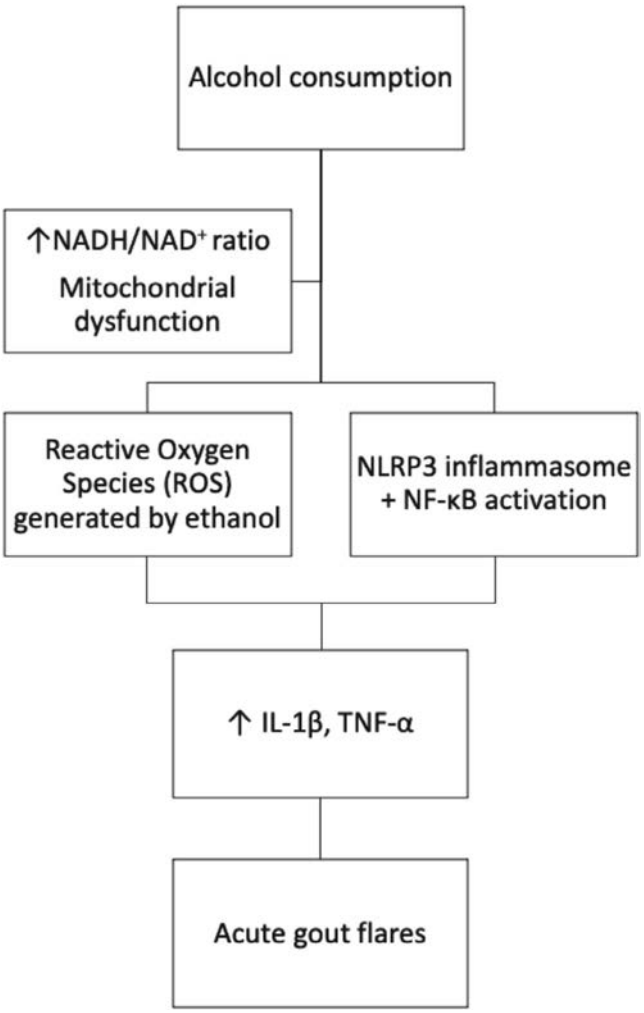

FIGURE 2 | Alcohol-induced oxidative stress and inflammation in gout. Ethanol metabolism increases the NADH/NAD⁺ ratio and promotes mitochondrial dysfunction, generating ROS that activate the NLRP3 inflammasome and NF-κB signaling. This cascade elevates pro-inflammatory cytokines (IL-1β, TNF-α), driving acute gout flares. Original figure created by the authors.

critical factor in understanding how genetics and environmental influences, such as alcohol consumption, converge to impact gout susceptibility [20, 21]. Genetic polymorphisms in these enzymes can significantly alter the processing of ethanol and its byproducts, which in turn affect the risk and severity of gout. Variations in ADH1B and ADH1C modify the rate at which ethanol is converted to acetaldehyde, an intermediate metabolite known for its association with oxidative stress and inflammation. Rapid conversion due to these variants can lead to elevated acetaldehyde levels, which amplify the inflammatory responses that drive gout flares [20, 21].

Similarly, polymorphisms in ALDH2, particularly prevalent in East Asian populations, reduce the efficiency of acetaldehyde detoxification, causing it to accumulate in the body [20, 21]. This accumulation exacerbates oxidative damage and promotes the deposition of urate crystals, a hallmark of gout pathogenesis. These genetic factors not only influence the metabolism of alcohol but also modulate the body's inflammatory and metabolic responses, creating a complex interplay between genetic predisposition and environmental triggers [20, 21].

3.4.3 | Alcohol-Induced Modulation of Genetic Risk: Ethnic Variability

Ethnicity plays a crucial role in shaping the prevalence and severity of gout, driven by a complex interplay of genetic predispositions and cultural factors. Polymorphisms in genes such as SLC2A9, ABCG2, ADH, and ALDH exhibit significant variability across populations, influencing susceptibility to hyperuricemia and gout [20, 21]. For instance, East Asian populations frequently carry ALDH2 polymorphisms that impair acetaldehyde metabolism, heightening oxidative stress and the risk of alcohol-induced gout. Similarly, Pacific Islander and Māori communities show an elevated genetic predisposition to hyperuricemia, possibly due to evolutionary adaptations favoring urate retention, which becomes problematic when combined with high alcohol consumption. Among African and African American populations, variations in ABCG2 are associated with reduced urate excretion, exacerbating gout prevalence when lifestyle factors are added to the equation [20, 21].

In Southeast Asian populations, high gout prevalence has been linked to both genetic and lifestyle factors. Genome-wide association studies reveal a higher frequency of ABCG2 and SLC2A9 risk alleles in certain Southeast Asian subgroups, leading to reduced renal urate clearance. When coupled with increasing alcohol consumption particularly beer and spirits these genetic factors markedly elevate hyperuricemia risk [22]. Epidemiological surveys from countries such as Thailand and the Philippines report rising gout incidence, which parallels economic growth, urbanization, and shifts toward Westernized diets, further compounding the impact of alcohol on disease progression [23].

Cultural attitudes toward alcohol further modulate gout risk [20, 21]. European populations, for example, experience a strong correlation between high beer consumption and gout prevalence, a relationship shaped by cultural practices and genetic susceptibility. Indigenous populations, on the other hand, face increased gout rates due to rapid lifestyle shifts and the adoption of Westernized diets, including alcohol consumption, which amplify the effects of genetic predispositions. Together, these examples highlight the intricate connections between genetics, culture, and lifestyle in determining gout risk across diverse ethnic groups [20, 21].

In Colombia, the prevalence of gout is estimated to be between 2% and 4% of the population, primarily affecting men aged 30 to 70. These figures align with those observed in other Western countries, where prevalence rates range from 3% to 6% in men and 1% to 2% in women [4]. Regarding alcohol consumption in Latin America, there is significant variability between countries. For example, Argentina has a per capita alcohol consumption of 8 L of pure alcohol annually, exceeding the global average of 5.5 L and the regional average of 7.5 L [4]. Although specific data for Colombia are not available, alcohol consumption is a recognized risk factor for exacerbating gout. The intake of alcoholic beverages, particularly beer, can elevate uric acid levels in the blood, triggering acute episodes of the disease [4].

Additionally, cultural and lifestyle factors in Colombia and other Latin American countries may influence gout prevalence. The adoption of Westernized diets rich in purines, combined with an increase in alcohol consumption, likely contributes to rising rates of hyperuricemia and gout in the region. Promoting healthier dietary habits and moderating alcohol intake are essential preventive measures to mitigate the incidence of this condition [4].

3.5 | Striking the Balance: Personalized Management and Moderation

3.5.1 | Importance of Moderation

Moderation is a critical factor in mitigating the risks associated with alcohol consumption in gout management. Guidelines define moderation as no more than one drink per day for women and no more than two drinks per day for men [24]. This recommendation aligns with those of the World Health Organization (WHO) and various national health authorities, which standardize one drink as containing approximately 10 g of ethanol. However, the definition of a "standard drink" varies globally due to cultural and regulatory differences [11]. These discrepancies highlight the necessity of tailoring moderation guidelines to individual and regional contexts.

Research suggests that moderate wine consumption may provide potential anti-inflammatory benefits due to its polyphenolic compounds [5, 12]. However, this effect is not universal, as genetic factors play a pivotal role in modulating the relationship between alcohol and gout. For instance, variants in SLC2A9 and ABCG2 influence urate metabolism, while polymorphisms in ADH1B, ADH1C, and ALDH2 affect alcohol metabolism, exacerbating oxidative stress and urate crystal formation in genetically predisposed individuals [1, 5, 11]. Additionally, alcohol-induced epigenetic changes, such as DNA methylation and histone modifications, can alter the expression of genes regulating inflammation and urate transport, further complicating this dynamic [12].

Educating patients about moderation should be a cornerstone of gout management. Healthcare providers must emphasize that while some alcohol may be permissible, excessive consumption significantly increases the risk of gout flares. Integrating knowledge of genetic and epigenetic factors into patient guidance is essential, enabling individuals to make informed decisions tailored to their unique risk profiles. Promoting moderation not only helps reduce gout flares but also empowers patients to adopt lifestyle choices that enhance their overall health and well-being.

3.5.2 | Individualized Approaches

Recognizing the multifactorial and individualized nature of gout, healthcare providers must adopt personalized management strategies. This entails comprehensive assessments that consider factors such as the type and quantity of alcohol consumed, genetic predisposition, lifestyle habits, and overall health status. For example, individuals with genetic variants in ALDH2 common in East Asian populations may experience heightened sensitivity to alcohol's effects due to impaired acetaldehyde detoxification [11, 20]. Additionally, patients with a family history of gout or pre-existing conditions may exhibit an increased susceptibility to the effects of alcohol on uric acid levels [11, 20].

A Mendelian randomization (MR) analysis investigating alcohol's causal role in gout revealed that genetically predicted weekly alcohol intake does not directly increase gout risk ($p = 0.35$) or serum uric acid levels ($p = 0.73$) [15]. Conversely, genetic predisposition to gout was significantly associated with increased alcohol consumption ($p = 0.03$), suggesting a behavioral correlation rather than a direct causal relationship. This was corroborated by a cohort study involving alcohol-consuming and alcohol-abstaining subgroups, which found no significant differences in serum uric acid levels within the gout ($p = 0.92$) and hyperuricemia ($p = 0.23$) groups [20]. These findings underscore the importance of a multifaceted approach that incorporates genetic, lifestyle, and dietary factors into gout management.

Recent guidelines reinforce the importance of moderation. The European League Against Rheumatism (EULAR) recommends reducing alcohol consumption, particularly beer, due to its high purine content and strong association with gout risk [25]. Similarly, the American College of Rheumatology advises limiting alcohol intake regardless of gout activity level [21]. Both emphasize lifestyle modifications such as maintaining a balanced diet, staying hydrated, and managing body weight as essential components of effective gout care. By integrating these strategies with personalized approaches that consider genetic and environmental factors, healthcare providers can foster holistic and patient-centered management.

4 | Discussion

Alcohol consumption plays a significant role in the pathogenesis of gout, disrupting the body's biochemical and inflammatory balance. Its impact extends beyond dietary contributions, with research highlighting complex interactions between alcohol, genetic predispositions, and epigenetic modifications. For example, polymorphisms in SLC2A9, ABCG2, and alcohol-metabolizing genes such as ADH1B, ADH1C, and ALDH2 significantly influence individual responses to alcohol. These genetic variations modulate urate metabolism, oxidative stress, and inflammatory responses, underscoring the necessity for personalized prevention and management strategies.

The interplay between purine metabolism, oxidative stress, and inflammatory responses forms the foundation of gout development and exacerbation. Elevated purine levels from both dietary sources and alcohol intake can lead to increased uric acid production, while alcohol-induced oxidative stress further triggers inflammatory pathways that worsen joint symptoms (Figure 3). Our synthesis also highlights a clear dose–response relationship: individuals consuming ≥ 3 drinks per day had a relative risk of 2.64 (95% CI 2.26–3.09) of developing gout compared with occasional drinkers, while even moderate intake of 1 drink/day was associated with increased risk (RR 1.16, 95% CI 1.07–1.25) (Tables 1 and 2). Likewise, the type of alcohol

matters—beer consumption contributed the largest increase in serum urate levels, particularly among women (0.21 mg/dL per unit), whereas wine showed a smaller effect (0.10 mg/dL for both sexes). These quantitative findings reinforce the mechanistic pathways outlined in Figure 2. In genetically predisposed individuals, these effects are magnified, emphasizing the importance of tailoring prevention and treatment strategies to individual risk profiles.

While studies have consistently shown that abstaining from alcohol can reduce the frequency and severity of gout flares, the relationship between alcohol and gout is not uniform. Alcohol-induced epigenetic modifications, such as DNA methylation and histone changes, can alter the expression of genes regulating urate metabolism and inflammation, reinforcing the need for multifaceted management approaches.

Pharmacogenomics offers an additional layer of personalization in gout management. Understanding genetic variations may guide the selection of pharmacological treatments, such as urate-lowering therapies, optimizing their efficacy in genetically susceptible individuals [21]. For example, individuals with specific variants in ABCG2 may benefit from targeted therapies that improve urate excretion while minimizing side effects. Incorporating pharmacogenomic insights into routine care could allow clinicians to stratify patients not only by urate levels but also by their genetic ability to metabolize alcohol, enabling more precise urate-lowering therapy selection. This highlights the importance of integrating genetic insights into clinical decision-making to enhance therapeutic outcomes.

Ethnicity also plays a crucial role in shaping gout risk, as shown in our analysis. For example, populations with ALDH2

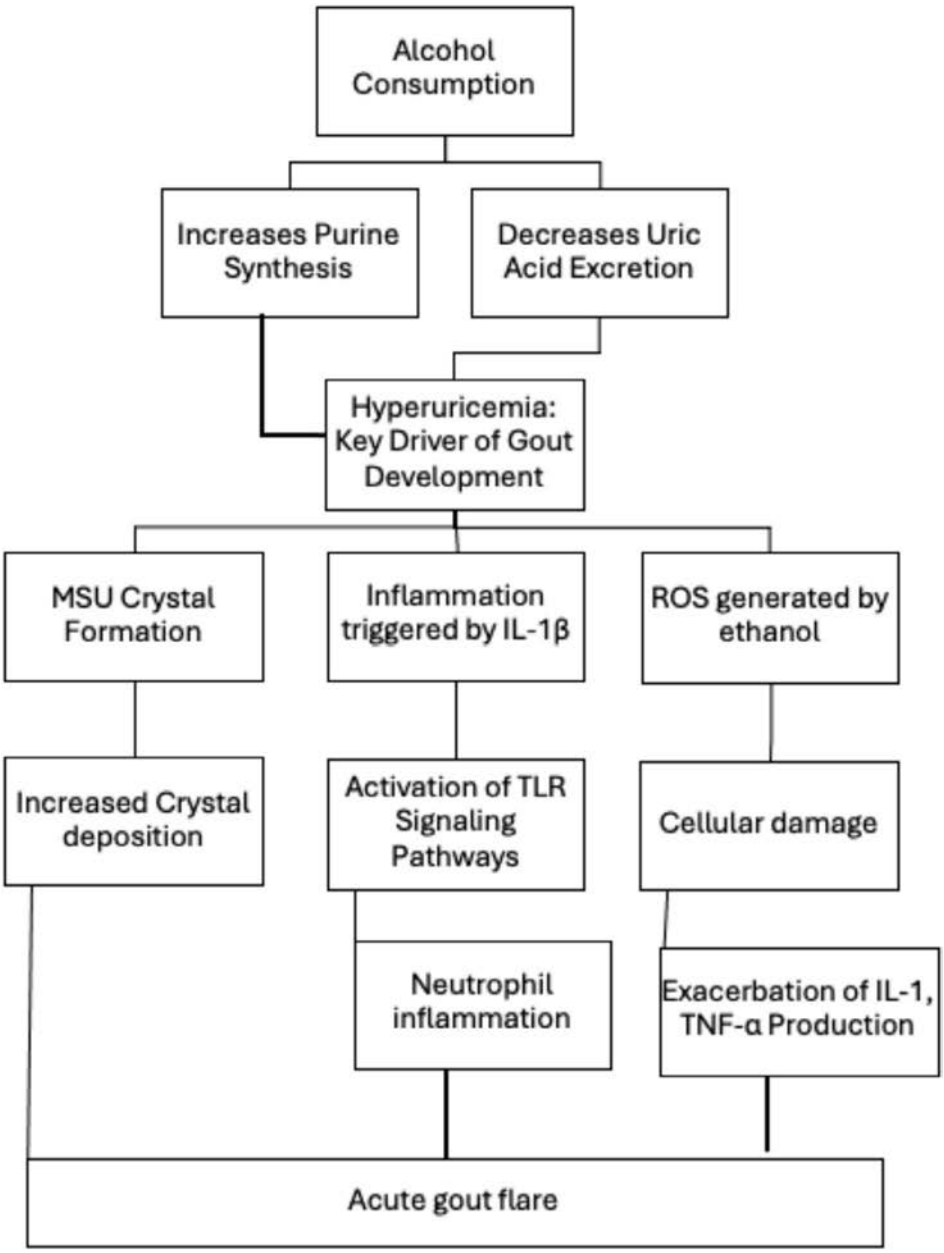

FIGURE 3 | Pathways affected by alcohol consumption, illustrating how elevated purine synthesis, decreased uric acid excretion, and oxidative stress contribute to hyperuricemia and subsequent gout flares. This figure is original and created by the author(s).

polymorphisms (common in East Asians) have reduced acetaldehyde metabolism, heightening oxidative stress and alcohol-induced gout risk, while Pacific Islander and Māori communities carry urate-retaining alleles that exacerbate hyperuricemia when combined with alcohol intake. In Southeast Asia, epidemiological studies report some of the world's highest gout prevalence rates, particularly in urban male populations, with alcohol consumption especially beer emerging as a major modifiable risk factor. Cultural norms around drinking, combined with dietary purine intake, appear to potentiate the effects of genetic predisposition in these populations [26].

Public health initiatives focusing on education about moderation are critical, but these messages must be refined to consider genetic, epigenetic, and ethnic factors. For instance, individuals of East Asian descent, who commonly exhibit ALDH2 polymorphisms, may have a heightened sensitivity to alcohol's effects. Moderation guidelines, such as limiting alcohol intake to one drink per day for women and two for men, remain valuable but should be adapted based on individual genetic risk profiles and cultural contexts. Moreover, different alcoholic beverages pose varying risks; beer and spirits are associated with higher gout risk due to their purine and ethanol content, while moderate wine consumption may confer anti-inflammatory benefits through polyphenolic compounds.

Future research should prioritize large-scale studies integrating genetic and environmental data to elucidate gene–environment interactions in gout [5]. Investigating the development of epigenetic therapies targeting alcohol-induced modifications could provide innovative solutions for mitigating gout risk [6]. Evaluating the efficacy of personalized interventions that combine pharmacological and lifestyle modifications in reducing gout incidence and severity is also essential for advancing clinical practice [25].

Healthcare providers should prioritize individualized patient assessments, considering not only the type and quantity of alcohol consumed but also genetic predispositions, pharmacogenomic profiles, and overall health status. Educational efforts should emphasize these complexities, equipping patients with the knowledge to make informed decisions. By fostering a deeper understanding of gout's multifactorial etiology, including the role of genetic, epigenetic, and environmental influences, healthcare professionals can enhance patient outcomes and improve quality of life.

5 | Conclusion

The relationship between alcohol consumption and gout underscores the importance of a multifaceted approach to prevention and management. Alcohol exacerbates gout pathogenesis through purine metabolism, oxidative stress, and inflammation, with these effects further amplified by genetic predispositions and epigenetic changes. Personalized management strategies that integrate pharmacogenomics with tailored lifestyle recommendations offer promising avenues for improving patient outcomes.

Public health campaigns should emphasize moderation while accounting for genetic and cultural contexts, while future research should prioritize gene–environment interactions and therapies targeting alcohol-induced epigenetic modifications. Ultimately, translating these insights into clinical guidelines that combine education, personalized care, and evidence-based interventions will be key to reducing the global burden of alcohol-related gout and improving patients' quality of life.

Author Contributions

A.L.A.C. and MCMA conducted the initial screening of titles and abstracts; when the abstract lacked sufficient clarity regarding the study's rationale, they reviewed the full text. P.A.M.-P., W.B.-M., and G.Q.-L. helped determine the search terms, databases employed, and the inclusion and exclusion criteria alongside the analytical framework adopted. G.Q.-L. and W.B.-M. reviewed the full texts and made further decisions regarding their inclusion. P.A.M.-P., A.L.A.C., and MCMA wrote the initial manuscript. All authors read and approved the final manuscript.

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Consent

Written informed consent was not needed due to the nature 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.

References

1. T. Bardin and P. Richette, "Definition of Hyperuricemia and Gouty Conditions," *Current Opinion in Rheumatology* 26, no. 2 (2014): 186–191.

2. Y. Zhang, S. Chen, M. Yuan, Y. Xu, and H. Xu, "Gout and Diet: A Comprehensive Review of Mechanisms and Management," *Nutrients* 14, no. 17 (2022): 3525.

3. G. Nuki and P. A. Simkin, "A Concise History of Gout and Hyperuricemia and Their Treatment," *Arthritis Research & Therapy* 8, no. 1 (2006): 1–5.

4. T. J. Major, R. Takei, H. Matsuo, et al., "A Genome-Wide Association Analysis Reveals New Pathogenic Pathways in Gout," *Nature Genetics* 56, no. 11 (2024): 2392–2406, https://doi.org/10.1038/s41588-024-01921-5.

5. H. K. Choi, K. Atkinson, E. W. Karlson, W. Willett, and G. Curhan, "Alcohol Intake and Risk of Incident Gout in Men: A Prospective Study," *Lancet* 363, no. 9417 (2004): 1277–1281.

6. M. G. Battelli, L. Polito, M. Bortolotti, and A. Bolognesi, "Xanthine Oxidoreductase-Derived Reactive Species: Physiological and Pathological Effects," *Oxidative Medicine and Cellular Longevity* 2016 (2016): 3527579, https://doi.org/10.1155/2016/3527579.

7. S. Zakhari, "Alcohol Metabolism and Epigenetics Changes," *Alcohol Research: Current Reviews* 35, no. 1 (2013): 6–16.

8. C. F. Kuo, K. H. Yu, L. C. See, et al., "Risk of Myocardial Infarction Among Patients With Gout: A Nationwide Population-Based Study," *Rheumatology* 52, no. 1 (2013): 111–117.

9. M. Kuwabara, T. Fukuuchi, Y. Aoki, et al., "Exploring the Multifaceted Nexus of Uric Acid and Health: A Review of Recent Studies on Diverse Diseases," *Biomolecules* 13, no. 10 (2023): 1519, https://doi.org/10.3390/biom13101519.

10. N. Dalbeth, H. K. Choi, L. A. B. Joosten, et al., "Gout," *Nature Reviews Disease Primers* 5, no. 1 (2019): 1–17.

11. B. Nieradko-Iwanicka, "The Role of Alcohol Consumption in Pathogenesis of Gout," *Critical Reviews in Food Science and Nutrition* 62, no. 25 (2022): 7129–7137.

12. Y. Zhang, C. Chen, H. Choi, et al., "Purine-Rich Foods Intake and Recurrent Gout Attacks," *Annals of the Rheumatic Diseases* 71, no. 9 (2012): 1448–1453.

13. S. Fukui, M. Okada, M. Rahman, et al., "Differences in the Association Between Alcoholic Beverage Type and Serum Urate Levels Using Standardized Ethanol Content," *JAMA Network Open* 6, no. 3 (2023): e233398.

14. L. K. Stamp, P. T. Chapman, M. Barclay, et al., "Allopurinol Dose Escalation to Achieve Serum Urate Below 6 Mg/dL: An Open-Label Extension Study," *Annals of the Rheumatic Diseases* 76, no. 12 (2017): 2065–2070.

15. M. Wang, X. Jiang, W. Wu, and D. Zhang, "A Meta-Analysis of Alcohol Consumption and the Risk of Gout," *Clinical Rheumatology* 32, no. 11 (2013): 1641–1648.

16. L. He, "Ethanol-Induced Oxidative Stress and Mitochondrial Dysfunction," *Redox Biology* 36 (2020): 101607.

17. J. Zhao, "ROS-Induced NLRP3 Inflammasome Activation: Mechanisms and Therapeutic Potential," *Frontiers in Immunology* 9 (2018): 2028.

18. P. E. Molina, "Alcohol, Oxidative Stress, and Inflammation: Focus on the Gut–Liver–Brain Axis," *Alcohol Research: Current Reviews* 38, no. 2 (2018): 243–259.

19. J. J. Jhang, "Polyphenols and Gout: A Review of Potential Therapeutic Mechanisms," *Nutrients* 13, no. 4 (2021): 1341.

20. A. A. S. Syed, A. Fahira, Q. Yang, et al., "The Relationship Between Alcohol Consumption and Gout: A Mendelian Randomization Study," *Genes* 13, no. 4 (2022): 557, https://doi.org/10.3390/genes13040557.

21. J. D. FitzGerald, N. Dalbeth, T. Mikuls, et al., "2020 American College of Rheumatology Guideline for the Management of Gout," *Arthritis Care & Research (Hoboken)* 72, no. 6 (2020): 744–760.

22. T. F. Chan, "The Genetics of Hyperuricemia and Gout in Asians: An Update," *Current Rheumatology Reports* 23, no. 4 (2021): 26.

23. R. Yin, "Urate Genetics and Epidemiology in Asia," *Rheumatology* 57, no. 1 (2018): i36–i44.

24. G. M. Oppenheimer and R. Bayer, "Is Moderate Drinking Protective Against Heart Disease? The Science, Politics and History of a Public Health Conundrum," *Milbank Quarterly* 98, no. 1 (2020): 39–56.

25. P. Richette, M. Doherty, E. Pascual, et al., "2016 Updated EULAR Evidence-Based Recommendations for the Management of Gout," *Annals of the Rheumatic Diseases* 76, no. 1 (2017): 29–42.

26. G. G. Teng, "Gout in Asia – Epidemiology, Diagnosis and Management," *Annals of the Academy of Medicine, Singapore* 47, no. 12 (2018): 501–510.

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ORIGINAL ARTICLE

Vitamin D Status in Paraguayan Children With Autoimmune Diseases

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ABSTRACT

Introduction: Vitamin D plays a crucial role in modulating the immune system. Numerous studies have elucidated the association between low serum levels of vitamin D and autoimmune diseases. Vitamin D deficiency has been implicated in systemic lupus erythematosus, rheumatoid arthritis (RA), Hashimoto's thyroiditis, juvenile dermatomyositis, inflammatory bowel disease, among others.

Objective: This study aims to assess the vitamin D levels in a cohort of pediatric patients diagnosed with autoimmune diseases.

Methodology: This descriptive study, complemented with an analytical cross-sectional component, enrolled individuals under the age of 18 diagnosed with autoimmune disorders who underwent vitamin D assessment. The study spanned from January 2016 to December 2020 and was conducted across three specialized clinics.

Results: Among the 81 pediatric patients with autoimmune pathologies enrolled during the study period, 60 (74.04%) were female. The mean age of the participants at the time of the study was 9 years, ranging from 2 to 17 years old. Of the total cohort, 78 individuals (96.3%) were Latin-American. The most prevalent diagnosis was Juvenile Idiopathic Arthritis (JIA) in 53 patients (65.43%), followed by autoimmune thyroiditis in 9 patients (11.11%), systemic lupus erythematosus (SLE) in 8 patients (9.88%), and other conditions in 11 patients (11.11%), including dermatomyositis and celiac disease. Regarding vitamin D levels, the mean concentration was 24.69 ng/mL. Specifically, 19 patients (23.46%) had sufficient levels (≥ 30 ng/mL), 41 patients (50.62%) had insufficiency, 20 patients (24.69%) had deficiency, and 1 patient (1.23%) had severe deficiency. No statistically significant differences were observed between vitamin D levels and sex ($p = 0.82$), age ($p = 0.88$), disease remission ($p = 0.97$), antinuclear antibody (ANA) value ($p = 0.78$), or season of the year.

Conclusion: Our findings suggest that the currently referenced levels of vitamin D do not exhibit a significant correlation with disease activity in pediatric patients with autoimmune diseases.

1 | Introduction

Vitamin D, a steroid hormone renowned for its potent immunomodulatory properties [1], plays a fundamental role in maintaining calcium-phosphate homeostasis and regulating bone metabolism. In contemporary understanding, beyond its primary functions, it has been increasingly recognized for its multifaceted roles, including immune system modulation and

beneficial anti-inflammatory effects in the management of chronic diseases such as diabetes [2], asthma [3], and rheumatoid arthritis [4].

The synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D), from circulating 25-hydroxyvitamin D necessitates the enzyme cytochrome P450 27B1 (CYP27B1). Upon binding to the vitamin D receptor (VDR), a nuclear transcription factor, 1,25(OH)2D exerts its actions by interacting with a specific genetic sequence known as the vitamin D response element (VDRE), located in the promoter region of genes regulated by vitamin D [5].

Vitamin D exerts pivotal regulatory roles in the immune system, influencing both innate and adaptive immunity [6]. It enhances innate immune responses, including antimicrobial activity and antigen presentation by monocytes/macrophages, while concurrently suppressing adaptive immune functions mediated by T and B lymphocytes [7]. Notably, various immune cells express VDR and CYP27B1, suggesting the capacity of active vitamin D to modulate immune function at multiple levels [1].

Numerous investigations have underscored the association between low serum levels of vitamin D and autoimmune diseases [8], with deficiencies implicated in systemic lupus erythematosus (SLE) [9], rheumatoid arthritis (RA) [10], Hashimoto's thyroiditis [11], juvenile dermatomyositis [12], inflammatory bowel disease [13], among others.

Studies conducted over time have consistently highlighted the significance of vitamin D in SLE, often identifying a deficiency in this disease [14–17]. The serum levels of 25-hydroxyvitamin D (25(OH)D) are influenced by various factors, including ethnic background, ultraviolet B radiation exposure, seasonal variations, and dietary supplementation [14, 18]. SLE patients, advised to minimize sun exposure due to photosensitivity and frequently subjected to prolonged corticosteroid treatment, are particularly susceptible to 25(OH)D deficiency, compounded by the risk of renal impairment [19]. Emerging evidence suggests that vitamin D deficiency may correlate with disease activity, renal involvement, and clinical manifestations in SLE patients, given its immunosuppressive effects [20]. Notably, reduced vitamin D levels have been associated with elevated proinflammatory mediators and heightened disease activity, substantiating its role as a predisposing factor for rheumatoid arthritis development and exacerbation [21].

Numerous global studies have documented high prevalence rates of vitamin D deficiency and insufficiency among pediatric populations [22]. Currently, serum concentrations of 25(OH)D are deemed the most reliable indicator of vitamin D status, reflecting both dietary intake and cutaneous synthesis [23]. According to various authorities and scholarly sources, vitamin D status can be categorized based on 25(OH)D levels as follows: sufficiency (≥ 30 ng/mL), insufficiency (20–29 ng/mL), deficiency (< 20 ng/mL), and severe deficiency (< 10 ng/mL) [24].

In a study conducted in Paraguay by Acosta et al. (2022), an association was made between vitamin D concentrations and the activity of systemic lupus erythematosus in adult patients. They found that serum levels of vitamin D equal to or < 30 ng/mL are associated with increased SLE activity [25].

In this study, we assessed the status of 25-OH-vitamin D in children with autoimmune pathologies and determined its association with clinical variables, laboratory parameters, and disease activity.

2 | Materials and Methods

2.1 | Patients and Methods

We conducted a descriptive study with an analytical component, utilizing a cross-sectional design. This study involved patients under 18 years old diagnosed with autoimmune conditions, who underwent vitamin D testing and received care at three reference clinics (Hospital de Clínicas, Hospital Central de IPS and a Private Office), from January 2016 to December 2020.

The following variables were recorded: age, sex, race, place of origin, and baseline diagnoses. We evaluated the serum concentration of 25-OH-VD in the same laboratory, measured at 7:00 a.m., alongside the disease activity at the time of consultation. Plasma levels of 25-OH-VD were quantified using chemiluminescent microparticle immunoassay (CMIA). The status of vitamin D was defined as follows, in accordance with values established by Holick: sufficiency (≥ 30 ng/mL), insufficiency (20–29 ng/mL), deficiency (< 20 ng/mL), and severe deficiency (< 10 ng/mL) [15, 24]. All patients had not received vitamin D supplementation, and we do not have baseline levels of vitamin D before the onset of the disease.

The datasets generated during and/or analyzed during the current study are not publicly available because they contain personal data of the patients, but are available from the corresponding author on reasonable request.

2.2 | Ethical Considerations

The three principles of bioethics established for research involving human subjects were respected. Privacy was upheld, and personal data were not disclosed. Ethical approval was not obtained because it is not necessary in our country for descriptive studies.

2.3 | Statistical Analysis

Statistical analyses were conducted using Stata version 15.1 software, employing descriptive statistics. Comparison of quantitative variables was performed using Student *T*-Test or ANOVA, while chi-squared tests were employed for qualitative variables. A significance level of $p < 0.05$ was considered.

3 | Results

A total of 81 patients under 18 years of age diagnosed with autoimmune disorders were included in the study. Among them,

60 (74.04%) were female. The average age of the patients at the time of the study was 9 years, ranging from 2 to 17 years old. Notably, 78 out of 81 patients (96.3%) were of Latin-American descent, with 60 out of 81 (74.07%) originating from the Asuncion and Central regions. Juvenile Idiopathic Arthritis (JIA) emerged as the most common diagnosis, affecting 53 out of 81 patients (65.43%). Autoimmune thyroiditis followed with 9 patients (11.11%), then SLE with 8 patients (9.88%). Other conditions, including dermatomyositis and celiac disease, were diagnosed in the remaining 11 patients (11.11%) (Table 1). The evolution time between the onset of the disease and the dosage of vitamin D in this study varies between 0 and 7 years (mean: 4 years), because some patients were included in the first visit and others had a longer history of the underlying pathology.

Regarding treatment, 17 out of 81 (20.99%) patients were receiving methotrexate, 13 out of 81 (16%) patients were taking NSAIDs (naproxen or ibuprofen), 10 out of 81 (12.3%) patients were on biologics (adalimumab or etanercept), 8 out of 81 (9.9%) patients were prescribed prednisone (6 of them at a dose of 5 mg/day and 2 of them at a dose of 10 mg/day, at the time of the vitamin D dosage), 7 out of 81 (8.6%) patients were taking hydroxychloroquine, and 39 out of 81 (48.1%) patients were not receiving any medication. As for vitamin D levels, the mean concentration found in these patients was 24.69. Nighteen out of 81 (23.46%) had sufficient levels equal to or greater than 30 ng/mL, 41 out of 81 (50.62%) had insufficiency, 20 out of 81 (24.69%) had deficiency, and 1 out of 81 (1.23%) had severe deficiency of vitamin D, as shown in Table 2.

In terms of laboratory analysis, among the cohort of 81 patients, 34 individuals (41.98%) tested positive for antinuclear antibodies (ANA), with levels exceeding 1:160 in 20 of these cases (58.8%), with no statistical difference between the diseases. Disease activity was observed in 51 patients (62.96%) (using activity scales for each type of pathology, e.g., SLEDAI-2 k for SLE, JADAS-10 for JIA, active hypothyroidism or hyperthyroidism in thyroiditis), whereas 30 patients (37.04%) were in a state of disease remission.

Vitamin D levels showed an inverse correlation with disease activity parameters, but without statistical significance ($p = 0.84$); for example, 34 JIA patients with active disease, of whom 6 patients had more than 30 ng/mL of vitamin D, and 19 JIA patients without active disease, of whom 4 patients had more than 30 ng/mL of vitamin D. Additionally, there was no statistically significant difference found between vitamin D levels and sex ($p = 0.82$), age ($p = 0.88$), disease remission ($p = 0.97$), ANA positivity ($p = 0.78$), or season ($p = 0.84$) (Tables 3 and 4).

TABLE 1 | Characteristics of study population ($n = 81$).

Variable	*n*	%
Sex		
Male	21	25.93
Female	60	74.07
Ethnicity		
Latin-American	78	96.30
German	2	2.47
Arab	1	1.23
Origin		
Asuncion and Central	60	74.07
Interior	19	23.46
Abroad	2	2.47
Diagnosis		
JIA	53	65.43
Lupus	8	9.88
Thyroiditis	9	11.11
Others	11	13.58

TABLE 2 | Vitamin *D* values ($n = 81$).

Vitamin D (ng/mL)	*n*	%
30 or more	19	23.46
20 to 29	41	50.62
10 to 19	20	24.69
< 10	1	1.23

TABLE 3 | Vitamin D levels in rheumatology patients ($n = 81$).

Variable	*n*	Vitamin D level (ng/mL) (median)	*p*
Sex			
Male	60	24.55	0.82
Female	21	25.1	
Age			
0 to 5	21		0.883
6 to 12	30		
More than 12	30		
Disease activity			
Yes	51	24.53	0.84
No	30	24.97	
Remission			
Yes	30	24.73	0.97
No	51	24.67	
Treatment			
None	39	24.36	0.75
Yes	42	25	

TABLE 4 | Vitamin D levels in different seasons ($n = 81$).

	Autumn	Winter	Spring	Summer	*p* (0.84)
0–9.99 ng/mL				1	
10–19.99 ng/mL	2	7	5	6	
20–29.99 ng/mL	7	10	9	15	
≥ 30 ng/mL	4	4	4	7	

4 | Discussion

Levels of vitamin D can be influenced by various factors, including ethnic origin, genetic predispositions, skin types, medication usage (such as antiepileptics and glucocorticoids), and the presence of chronic diseases that hinder intestinal absorption or disrupt the physiological metabolism of vitamin D [24]. In addition, inadequate exposure to sunlight, which is crucial for vitamin D synthesis, is another significant risk factor for vitamin D deficiency; hence, seasonal variations also play a role in determining vitamin D levels [23, 26]. Age is another recognized risk factor, with infants being particularly vulnerable to developing hypovitaminosis [27]. Furthermore, insufficient dietary intake of vitamin D remains a common cause of deficiency, even among older children and adolescents, particularly in those who are overweight or obese [28]. Additionally, as previously mentioned, low serum levels of vitamin D have been associated with autoimmune diseases.

In the southern cone region of South America, de Melo Bacha et al. [29] found in a retrospective study in Brazil that individuals aged 0 to 17 years had 32.2% of vitamin D deficiency, while in the Pathogonia region (Argentina) they describe a prevalence of vitamin D deficiency of 2.8% in children aged 6 to 23 months [30].

According to the findings of our study, the majority of patients with autoimmune pathology exhibited insufficient levels of vitamin D, based on the thresholds established by Holick (normal > 30 ng/mL, insufficiency 20-29 ng/mL, and deficiency < 20 ng/mL); specifically, 41 out of 81 patients demonstrated average vitamin D concentrations between 20 and 29 ng/mL. These findings are consistent with a study conducted in Mexico in 2015, which found that patients with JIA had average vitamin D concentrations of 21.97 ng/mL (indicative of insufficiency), whereas those with SLE exhibited deficient values [15]. Similarly, in a cohort of Italian patients with JIA, the majority also presented with insufficient levels of vitamin D (80.6%) [31].

The available evidence suggests an association between the level of vitamin D and RA activity [32]. According to our study, vitamin D levels exhibited an inverse correlation with disease activity parameters; however, this association did not reach statistical significance. This finding aligns with a study conducted by AlSaleem et al. [14], which demonstrated an inverse relationship between vitamin D levels and SLE activity. In accordance with international recommendations, it is advised to assess vitamin D levels during the winter, spring, and summer seasons [18].

A study conducted in a pediatric population in Argentina revealed adequate vitamin D levels during fall and inadequate levels during other seasons of the year [18]. In our study, inadequate levels of vitamin D were observed throughout all seasons; however, this correlation was not statistically significant. Measurements were conducted during all seasons and at consistent times of the day.

There is increasing evidence that vitamin D supplementation could enhance the treatment of autoimmune disorders. Undoubtedly, steroid usage serves as a pivotal factor prompting the necessity for adequate vitamin D supplementation, given that steroid administration poses the highest risk of vitamin D insufficiency [8, 9, 12, 19, 20, 28].

The principal limitations of the present study are the small number of patients, the absence of a control group, potential confounding factors such as differences in disease characteristics, treatment, dietary habits, sunlight exposure, genetic factors, and others. However, it is important to note that the reference values for vitamin D are originating from studies conducted in adult populations and then extrapolated to pediatric populations; these values are influenced by age, ethnic origin, gender, season of the year, and vitamin D supplementation. Therefore, further global studies should be conducted to obtain more appropriate values for the pediatric age group and to conduct comprehensive research on vitamin D levels in children with autoimmune diseases, taking into account the following factors for future studies:

- To perform a more extensive statistical analysis, incorporating multivariate analysis to control for confounding variables influencing Vitamin D levels and disease activity. To incorporate a healthy control group from the identical geographic region. Focus on a particular autoimmune disease, ensuring an adequate sample size. Longitudinal follow-up to assess the relationship between Vitamin D levels and the progression of the disease.

5 | Conclusion

We did not find a significant relationship between the vitamin D levels currently used as reference and disease activity in pediatric patients with autoimmune pathologies.

In the studied population, 76.5% exhibited vitamin D levels below the normal range.

Multicenter studies should be conducted in pediatric patients worldwide, at different ages and genders, times of day, and seasons, in order to evaluate more appropriate values for vitamin D levels in children.

Author Contributions

Z.M.: conceptualization, data interpretation, drafting of the manuscript, critical review of content, and final approval for publication. I.B.: conceptualization, data interpretation, critical review of content, and final approval for publication. M.L.R.P.: data analysis, data interpretation, critical review of content, and final approval for publication. L.P. and H.J.J.: manuscript drafting, critical review of content, and final approval for publication.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

References

1. F. Sassi, C. Tamone, and P. D'Amelio, "Vitamin D: Nutrient, Hormone, and Immunomodulator," *Nutrients* 10, no. 11 (2018): 1656, https://doi.org/10.3390/nu10111656.

2. J. Y. Dong, W. G. Zhang, J. J. Chen, Z. L. Zhang, S. F. Han, and L. Q. Qin, "Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies," *Nutrients* 5, no. 9 (2013): 3551–3562, https://doi.org/10.3390/nu5093551.

3. E. Ramos-Martínez, M. R. López-Vancell, J. C. Fernández de Córdova-Aguirre, et al., "Reduction of Respiratory Infections in Asthma Patients Supplemented With Vitamin D Is Related to Increased Serum IL-10 and IFNγ Levels and Cathelicidin Expression," *Cytokine* 108 (2018): 239–246, https://doi.org/10.1016/j.cyto.2018.01.001.

4. E. M. Colin, P. S. Asmawidjaja, J. P. van Hamburg, et al., "1,25-Dihydroxyvitamin D3 Modulates Th17 Polarization and Interleukin-22 Expression by Memory T Cells From Patients With Early Rheumatoid Arthritis," *Arthritis and Rheumatism* 62, no. 1 (2010): 132–142, https://doi.org/10.1002/art.25043.

5. M. Hewison, "Vitamin D and the Immune System: New Perspectives on an Old Theme," *Rheumatic Diseases Clinics of North America* 38, no. 1 (2012): 125–139, https://doi.org/10.1016/j.rdc.2012.03.012.

6. I. Szymczak and R. Pawliczak, "The Active Metabolite of Vitamin D3 as a Potential Immunomodulator," *Scandinavian Journal of Immunology* 83, no. 2 (2016): 83–91, https://doi.org/10.1111/sji.12403.

7. M. Cutolo, C. Pizzorni, and A. Sulli, "Vitamin D Endocrine System Involvement in Autoimmune Rheumatic Diseases," *Autoimmunity Reviews* 11, no. 2 (2011): 84–87, https://doi.org/10.1016/j.autrev.2011.08.003.

8. N. Charoenngam and M. F. Holick, "Immunologic Effects of Vitamin D on Human Health and Disease," *Nutrients* 12, no. 7 (2020): 2097, https://doi.org/10.3390/nu12072097.

9. W. L. Lee, F. K. Lee, and P. H. Wang, "Vitamin D and Systemic Lupus Erythematous," *Journal of the Chinese Medical Association* 85, no. 8 (2022): 811–812, https://doi.org/10.1097/JCMA.0000000000000746.

10. J. Vojinovic and R. Cimaz, "Vitamin D—Update for the Pediatric Rheumatologists," *Pediatric Rheumatology Online Journal* 13 (2015): 18, https://doi.org/10.1186/s12969-015-0017-9.

11. M. Cvek, D. Kaličanin, A. Barić, et al., "Vitamin D and Hashimoto's Thyroiditis: Observations From CROHT Biobank," *Nutrients* 13, no. 8 (2021): 2793, https://doi.org/10.3390/nu13082793.

12. A. B. Robinson, E. Y. Wu, and E. C. Rabinovich, "Change in Disease Activity After Vitamin D Supplementation in Children With Systemic Lupus Erythematosus and Juvenile Dermatomyositis," *Pediatric Rheumatology Online Journal* 10, no. Suppl 1 (2012): A13, https://doi.org/10.1186/1546-0096-10-S1-A13.

13. J. Fletcher, S. C. Cooper, S. Ghosh, and M. Hewison, "The Role of Vitamin D in Inflammatory Bowel Disease: Mechanism to Management," *Nutrients* 11, no. 5 (2019): 1019, https://doi.org/10.3390/nu11051019.

14. A. AlSaleem, A. AlE'ed, A. AlSaghier, and S. M. Al-Mayouf, "Vitamin D Status in Children With Systemic Lupus Erythematosus and Its Association With Clinical and Laboratory Parameters," *Clinical Rheumatology* 34, no. 1 (2015): 81–84, https://doi.org/10.1007/s10067-014-2811-z.

15. V. H. Rosiles, C. D. Salazar, R. M. Velazquez, R. R. Ruiz, and P. Clark, "Determinación de Concentraciones Séricas de 25(OH) D en Niños Con Lupus Eritematoso Sistémico y Artritis Idiopática Juvenil [Determination of 25(OH)D Serum Levels in Children With Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis]," *Boletín Médico del Hospital Infantil de México* 72, no. 2 (2015): 99–105, https://doi.org/10.1016/j.bmhimx.2015.05.002.

16. S. Stagi and D. Rigante, "Vitamin D and Juvenile Systemic Lupus Erythematosus: Lights, Shadows and Still Unresolved Issues," *Autoimmunity Reviews* 17, no. 3 (2018): 290–300, https://doi.org/10.1016/j.autrev.2018.01.004.

17. S. Y. Guan, H. Y. Cai, P. Wang, et al., "Association Between Circulating 25-Hydroxyvitamin D and Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis," *International Journal of Rheumatic Diseases* 22, no. 10 (2019): 1803–1813, https://doi.org/10.1111/1756-185X.13676.

18. J. Chiarpenello, F. Corbacho, A. L. Baella, et al., "Influencia de la Estación del Año en los Niveles de Vitamina D de Una Población Pediátrica," *Revista Médica de Rosario* 84, no. 3 (2018): 121–124.

19. S. Chaiamnuay, L. O. Chailurkit, P. Narongroeknawin, P. Asavatanabodee, S. Laohajaroensombat, and P. Chaiamnuay, "Current Daily Glucocorticoid Use and Serum Creatinine Levels Are Associated With Lower 25(OH) Vitamin D Levels in Thai Patients With Systemic Lupus Erythematosus," *Journal of Clinical Rheumatology* 19, no. 3 (2013): 121–125, https://doi.org/10.1097/RHU.0b013e318289bd16.

20. L. Athanassiou, I. Kostoglou-Athanassiou, M. Koutsilieris, and Y. Shoenfeld, "Vitamin D and Autoimmune Rheumatic Diseases," *Biomolecules* 13, no. 4 (2023): 709, https://doi.org/10.3390/biom13040709.

21. S. A. Sakyi, M. Owusu-Yeboah, C. Obirikorang, et al., "Profiling Vitamin D, Its Mediators and Proinflammatory Cytokines in Rheumatoid Arthritis: A Case–Control Study," *Immunity, Inflammation and Disease* 10, no. 8 (2022): e676, https://doi.org/10.1002/iid3.676.

22. C. M. Gordon, H. A. Feldman, L. Sinclair, et al., "Prevalence of Vitamin D Deficiency Among Healthy Infants and Toddlers," *Archives of Pediatrics & Adolescent Medicine* 162, no. 6 (2008): 505–512, https://doi.org/10.1001/archpedi.162.6.505.

23. C. Braegger, C. Campoy, V. Colomb, et al., "Vitamin D in the Healthy European Paediatric Population," *Journal of Pediatric Gastroenterology and Nutrition* 56, no. 6 (2013): 692–701, https://doi.org/10.1097/MPG.0b013e31828f3c05.

24. G. Saggese, F. Vierucci, F. Prodam, et al., "Vitamin D in Pediatric Age: Consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, Jointly With the Italian Federation of Pediatricians," *Italian Journal of Pediatrics* 44, no. 1 (2018): 51, https://doi.org/10.1186/s13052-018-0488-7.

25. I. Acosta-Colman, Z. Morel, A. Paats, et al., "Association Between Vitamin D Deficiency and Disease Activity in Paraguayan Patients With Systemic Lupus Erythematosus," *Revista Colombiana de Reumatologia* 29, no. 1 (2022): 19–25, https://doi.org/10.1016/j.rcreu.2020.12.010.

26. D. Lapatsanis, A. Moulas, V. Cholevas, P. Soukakos, Z. L. Papadopoulou, and A. Challa, "Vitamin D: A Necessity for Children and Adolescents in Greece," *Calcified Tissue International* 77, no. 6 (2005): 348–355, https://doi.org/10.1007/s00223-004-0096-y.

27. C. L. Wagner, F. R. Greer, A. Academy, and of Pediatrics Committee on Nutrition, "Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents," *Pediatrics* 122, no. 5 (2008): 1142–1152, https://doi.org/10.1542/peds.2008-1862.

28. W. G. Tsiaras and M. A. Weinstock, "Factors Influencing Vitamin D Status," *Acta Dermato-Venereologica* 91, no. 2 (2011): 115–124, https://doi.org/10.2340/00015555-0980.

29. F. V. de Melo Bacha, F. L. C. Gomez, A. L. G. Silva, M. D. Reis, E. D. L. Cabral, and L. D. de Carvalho, "Vitamin D: A 14-Year Retrospective Study at a Clinical Laboratory in Brazil," *Archives of Endocrinology and Metabolism* 66, no. 1 (2022): 19–31, https://doi.org/10.20945/2359-3997000000427.

30. P. Duran, G. Mangialavori, A. Biglieri, L. Kogan, and E. Abeya, "Nutrition Status in Argentinean Children 6 to 72 Months Old. Results From the National Nutrition and Health Survey (ENNyS)," *Archivos Argentinos de Pediatría* 107 (2009): 397–404.

31. F. Marini, F. Falcini, S. Stagi, et al., "Study of Vitamin D Status and Vitamin D Receptor Polymorphisms in a Cohort of Italian Patients With Juvenile Idiopathic Arthritis," *Scientific Reports* 10, no. 1 (2020): 17550, https://doi.org/10.1038/s41598-020-74861-9.

32. G. G. Song, S. C. Bae, and Y. H. Lee, "Association Between Vitamin D Intake and the Risk of Rheumatoid Arthritis: A Meta-Analysis," *Clinical Rheumatology* 31, no. 12 (2012): 1733–1739, https://doi.org/10.1007/s10067-012-2080-7.

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LETTER TO THE EDITOR

Moyamoya Syndrome or Moyamoya Disease? Primary CNS Vasculitis in a Child? The Importance of Nomenclature

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Dear Editor,

The term Moyamoya (a Japanese word for "puff of smoke" or hazy) has been used to describe the cerebral angiographic findings tangled appearance of tiny vessels compensating for the vascular obstruction [1]. Moyamoya disease (MMD) is considered a primary disorder of unknown etiology, characterized by stenotic-occlusive lesions at the bifurcation of the terminal internal carotid arteries with the presence of a neovascular network nearby creating a "puff of smoke". In contrast, Moyamoya syndrome (MMS) refers to MMD associated with other underlying disease. Some of these diseases are autoimmune in nature requiring immunomodulatory medications [2]. A pediatric case was diagnosed with primary vasculitis of the CNS associated with Moyamoya syndrome (MMS) and responded to treatment, so we reflect on the topic. *Case report*: A previously healthy 7-year-old boy presented with a 6-month history of retro-ocular and frontal headache, upper limb and face paresthesia, and episodes of expressive aphasia. He was diagnosed with migraine headache by his primary care provider and received analgesics with partial improvement. A month later, he experienced a generalized tonic–clonic seizure followed by right face and body hemiplegia. He was hospitalized and started on antiepileptics; computed tomography of the brain revealed a left frontal ischemic infarction vs. central nervous system vasculitis, and he received systemic corticosteroids. Three weeks later, he presented with another seizure; MRI of the brain showed subacute ischemic lesions in the right frontal area and a new left lesion in the premotor cortico-subcortical area. He was eventually referred to our hospital to continue evaluation and management.

Physical examination showed expressive aphasia, right gaze deviation, right and left-sided hemiparesis (rated 3/5 and 4/5, respectively); blood pressure was within normal limits in all extremities. Routine laboratory work-up showed complete blood count, electrolytes, and renal function tests within normal range. Cytochemical, cytological, and microscopical analysis of the cerebrospinal fluid was unremarkable. MRI reported ischemic infarctions in bifrontal cortico-subcortical areas and narrowing of the middle and anterior cerebral arteries (Figure 1). With a presumptive clinical and imaging diagnosis of central nervous system vasculitis vs. primary antiphospholipid syndrome, the patient was started on intravenous immunoglobulin (IVIG) 2 g/kg and hydroxychloroquine and methylprednisolone 1 mg/kg/day. Autoimmune screen (ANA, ANCA and antiphospholipid antibodies) was negative. Electroencephalography demonstrated slowing of baseline cerebral activity. Cardiac pathology was ruled out. A cerebral angiography reported left supraclinoid carotid occlusion, partial segmental occlusion of the right supraclinoid carotid, and posterior–anterior-lateral collateral circulation through communicating and leptomeningeal vessel findings compatible with Moyamoya vasculopathy.

Micophenolic acid and anticoagulation were initiated, and five pulses of methylprednisolone were administered. Improvement

and further remission of symptoms were achieved after several years of treatment with immunosuppressants, anticoagulation, and corticosteroids. Nowadays, the patient goes to school and lives a normal life.

Primary CNS vasculitis is a non-infectious, inflammatory disease that involves the small and medium vessels of the brain [3]. Our case fulfilled diagnostic criteria with evidence of an acquired neurological deficit, angiographic features of vasculitis and no evidence of a systemic disease [3]. Importantly, in our case, Moyamoya angiographic features were found. MMD is a cerebrovascular arteriopathy characterized by progressive stenosis and occlusion of the distal intracranial internal carotid arteries and proximal branches of the anterior and middle cerebral arteries. In the past has also known as "Nishimoto-Takeuchi-Kudo" disease, "spontaneous occlusion of the circle of Willis" has been suggested as an alternative name [4, 5]. In MMD pathological analysis has revealed that affected vessels do not show arteriosclerotic or inflammatory changes leading to vessel occlusion secondary to hyperplasia of smooth muscle cells and luminal thrombosis. Interestingly, Lin et al. studied the histopathological findings of 3 autopsy cases in MMD, reporting an aberrant expression of IgG and S100A4 protein in intracranial vascular walls suggesting that an immune-related factor may be involved in the pathogenesis of the disease [6]. Also, in an autopsy study, scattered macrophages and T-cells were found in the thickened intima [7]. The long-term outcome of MMD is poor as inevitable progression occurs in most patients.

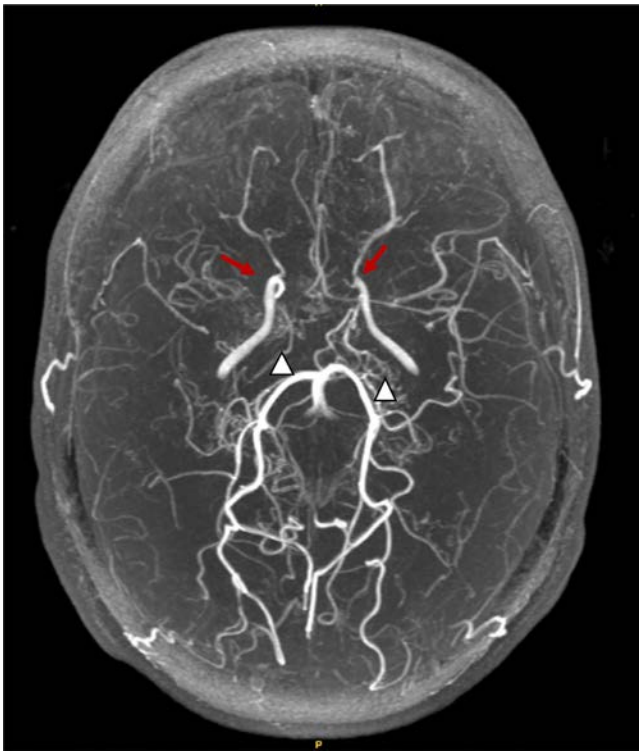

FIGURE 1 | Cerebral magnetic resonance imaging (MRI) showing bilateral narrowing of the internal carotid arteries (arrows) and abnormal vascular networks (arrowheads) confirming a definitive diagnosis of MMD.

MMD is considered a primary disorder of unknown etiology; in contrast, MMS refers to MMD associated with underlying diseases (1). MMS describes the same vascular changes as MMD but is associated with acquired or inherited conditions, including Marfan syndrome, Down syndrome (DS) and sickle cell anemia, or autoimmune diseases such as systemic lupus erythematosus (SLE) (Table 1). Several cases of MMS have been associated with SLE [8]. In SLE, evidence suggests that dysregulation of type I interferon and aberrant neutrophils have key roles in the pathogenesis of vascular damage [9] with IFN-1 promoting endothelial dysfunction. Recently, CNS involvement in some monogenic disorders has been emphasized, in which tissue damage is attributable to inappropriately enhanced type I interferon signaling (interferonopahies) [10]. In these diseases, CNS vasculitis and MMS have been described [11]. Also, there is a well-established association between DS and the development

TABLE 1 | Comparison of MMD and MMS: clinical features, etiology, and treatment.

	MMD	Inherited MMS	Acquired MMS
Incidence	Korea 9.1/100000 in 2008	NR	NR
Ethnicity	Predominantly Asian (Japan and Korea)	No predominance	No predominance
Age	Peak 5–14 years-old, 45–54 years-old	NR	NR
Pathology	Fibrocellular thickening of the intima, smooth muscle proliferation	Unknown	Unknown
Etiology	Unknown, mutation RNF213	MELAS, sickle cell anemia, Turner syndrome, Marfan syndrome, neurofibromatosis, Williams syndrome, Down syndrome	Lupus, Sjögren, APS, Down syndrome (?), Takayasu arteritis, PACNS, anti-MOG encephalitis, post-infectious?
Treatment	Surgical neurovascularization	Surgical neurovascularization	Steroids, anticoagulation, immunosuppressants, JAK-inhibitors

Abbreviations: APS, antiphospholipid syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MMD, Moyamoya disease; MMS, Moyamoya syndrome; PACNS, primary angiitis of the Central Nervous System.

of MMS. In DS, the extra copy of chromosome 21 carries four of the six interferon receptor genes on its long arm, resulting in an interferonopathy [12]. Santoro et al. report elevated levels of autoimmune disease in DS with MMS, suggesting a role of autoimmunity in the angiopathy in this population [13]. JAK-inhibitors have been used in interferonopathies and DS associated with immune dysregulation, with promising results [14]. It is vital to differentiate between MMD and MMS, since MMD treatment involves neurosurgical revascularization and MMS could involve enhanced type I interferon signaling, thus requiring immunomodulatory treatment (Table 1). In fact, in MMD, no medication can inhibit or reverse its progression.

Graf et al. have reported missed or delayed diagnosis of MMD patients [15]. Our concern is the opposite, patients with MMS secondary to an inflammatory condition misdiagnosed as MMD. Our patient was diagnosed with CNS vasculitis associated with MMS, and the response to immunomodulatory treatment highlights the need to differentiate MMD from MMS, particularly when it is associated with an autoimmune background.

Moyamoya patients should be comprehensively evaluated, and autoimmune and autoinflammatory etiology should be considered.

Author Contributions

H.O.Z. and M.Y.N. conceived the idea, H.O.Z. wrote the manuscript in support from E.O.T. and M.Y.N., H.O.Z., E.O.T. and M.Y.N. reviewed and analyzed the literature, P.H.M. and M.Y.N. diagnosed and treated the patient, all authors provided critical feedback.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on request from the authors.

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References

1. J. Suzuki and A. Takaku, "Cerebrovascular "Moyamoya" Disease. Disease Showing Abnormal Net-Like Vessels in Base of Brain," *Archives of Neurology* 20, no. 3 (1969): 288–299, https://doi.org/10.1001/archneur.1969.00480090076012.

2. R. M. Scott and E. R. Smith, "Moyamoya Disease and Moyamoya Syndrome," *New England Journal of Medicine* 360, no. 12 (2009): 1226–1237, https://doi.org/10.1056/NEJMra0804622.

3. C. Salvarani, G. G. Hunder, and R. D. Brown, Jr., "Primary Central Nervous System Vasculitis," *New England Journal of Medicine* 391, no. 11 (2024): 1028–1037, https://doi.org/10.1056/NEJMra2314942.

4. H. Oshima and Y. Katayama, "Discovery of Cerebrovascular Moyamoya Disease: Research During the Late 1950s and Early 1960s," *Child's Nervous System* 28, no. 4 (2012): 497–500, https://doi.org/10.1007/s00381-012-1708-x.

5. E. R. Smith and R. M. Scott, "Spontaneous Occlusion of the Circle of Willis in Children: Pediatric Moyamoya Summary With Proposed Evidence-Based Practice Guidelines. A Review," *Journal of Neurosurgery. Pediatrics* 9, no. 4 (2012): 353–360, https://doi.org/10.3171/2011.12.PEDS1172.

6. R. Lin, Z. Xie, J. Zhang, et al., "Clinical and Immunopathological Features of Moyamoya Disease," *PLoS One* 7, no. 4 (2012): e36386, https://doi.org/10.1371/journal.pone.0036386.

7. J. Masuda, J. Ogata, and C. Yutani, "Smooth Muscle Cell Proliferation and Localization of Macrophages and T Cells in the Occlusive Intracranial Major Arteries in Moyamoya Disease," *Stroke* 24, no. 12 (1993): 1960–1967, https://doi.org/10.1161/01.str.24.12.1960.

8. R. Wang, Y. Xu, R. Lv, and J. Chen, "Systemic Lupus Erythematosus Associated With Moyamoya Syndrome: A Case Report and Literature Review," *Lupus* 22, no. 6 (2013): 629–633, https://doi.org/10.1177/0961203313485828.

9. Y. Zhou and H. M. Song, "Type I Interferon Pathway in Pediatric Systemic Lupus Erythematosus," *World Journal of Pediatrics* 20, no. 7 (2024): 653–668, https://doi.org/10.1007/s12519-024-00811-4.

10. Y. J. Crow, "CNS Disease Associated With Enhanced Type I Interferon Signalling," *Lancet Neurology* 23, no. 11 (2024): 1158–1168, https://doi.org/10.1016/S1474-4422(24)00263-1.

11. C. Troedson, M. Wong, J. Dalby-Payne, et al., "Systemic Lupus Erythematosus due to C1q Deficiency With Progressive Encephalopathy, Intracranial Calcification and Acquired Moyamoya Cerebral Vasculopathy," *Lupus* 22, no. 6 (2013): 639–643, https://doi.org/10.1177/0961203313486950.

12. H. Chung, P. H. R. Green, T. C. Wang, and X. F. Kong, "Interferon-Driven Immune Dysregulation in Down Syndrome: A Review of the Evidence," *Journal of Inflammation Research* 14 (2012): 5187–5200, https://doi.org/10.2147/JIR.S280953.

13. J. D. Santoro, S. Lee, A. C. Wang, et al., "Increased Autoimmunity in Individuals With Down Syndrome and Moyamoya Disease," *Frontiers in Neurology* 12 (2021): 724969, https://doi.org/10.3389/fneur.2021.724969.

14. A. L. Rachubinski, E. Wallace, E. Gurnee, et al., "JAK Inhibition Decreases the Autoimmune Burden in Down Syndrome," *eLife* 13 (2024): RP99323, https://doi.org/10.7554/eLife.99323.

15. J. Graf, J. C. Schwitalla, P. Albrecht, et al., "Misdiagnoses and Delay of Diagnoses in Moyamoya Angiopathy—A Large Caucasian Case Series," *Journal of Neurology* 266, no. 5 (2019): 1153–1159, https://doi.org/10.1007/s00415-019-09245-9.

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LETTER TO THE EDITOR

The Role of Smoking as a Potential Contributor to Digital Ulcer Development in Patients With Systemic Sclerosis: A Cross-Sectional Study

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Dear Editor,

Systemic sclerosis (SSc) is a devastating disease characterized by impaired immunity, vascular disease, and diffuse fibrosis. One of the hallmark clinical manifestations of SSc is the emergence of digital ulcers (DUs), which ensue from progressive vascular compromise [1]. A substantial proportion ranging from 40% to 50% of SSc patients experience DUs, with recurrence rates fluctuating between 31% and 71% [2]. Recognized risk factors for DUs development encompass former ulcer history, high skin scores, earlier age at diagnosis, interstitial lung disease (ILD), gastrointestinal involvement, and smoking [3].

While empirical evidence does indicate a noticeable influence of smoking on disease severity, it reveals no significant association between smoking and the onset of SSc [4]. Conflicting data exist regarding the precise influence of smoking on digital vascular pathology [5–8]. In this study, our intention was to analyze the factors influencing the development of DUs, with particular emphasis on its correlation with smoking.

For this study, a cross-sectional evaluation of patients receiving care from an outpatient rheumatology clinic was carried out. The study population comprised individuals diagnosed with SSc who were being monitored at the Division of Rheumatology, Izmir Katip Celebi University Ataturk Education and Research Hospital. In total, 86 individuals (18 years of age and older) who satisfied the 2013 criteria for SSc set by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) were enrolled in the study between 2020 and 2021 after giving written informed consent. Clinical and demographic data collected included information on pulmonary hypertension (PH), interstitial lung disease (ILD), gastroesophageal reflux disease (GERD), dysphagia, past and current medical treatments, and smoking status.

DUs were defined as disruptions of the skin epithelium, characterized by discernible depth [9], with particular attention given to their location distal to the proximal interphalangeal joint. The occurrence of DUs at the time of enrollment was assessed by examining physicians (EO), with historical data on previous ulcer episodes also reviewed.

Smoking history, categorized as nonsmoker, ex-smoker, or current smoker, was obtained from the patient at the time of recruitment. Ever smokers and never smokers were delineated for further analyses. Patients were queried about their daily cigarette consumption, and the number of packs smoked per year was documented. Heavy smokers were accepted as those who had smoked for more than 20 pack-years [10].

A right cardiac catheterization-derived mean pulmonary artery pressure of more than 20 mmHg was considered to be PH [11]. ILD was diagnosed by radiologists based on findings from high-resolution chest computed tomography and/or thoracic computed tomography scans.

The modified Rodnan skin score (mRSS) of patients at the time of enrollment was evaluated by examining physician (EO). Patients had been categorized into diffuse or limited SSc subgroups according to the Leroy criteria at the time of diagnosis [12].

The presence of autoantibodies, including antinuclear antibodies, anticentromere antibodies, antitopoisomerase I

TABLE 1 | The association between demographic characteristics and the development of digital ulcers.

	DUs, yes $n=32$	DUs, no $n=54$	OR (%95 C.I for ExB)	p	All patients $n=86$
Demographics					
Follow-up duration from diagnosis, yrs.[a]	8.8 (8.0)	7.7 (5.2)	1.028 (0.960–1.100)	0.426	8.1 (6.4)
Female	28 (87.5)	52 (96.3)	0.269 (0.046–1.562)	0.144	80 (93.0)
Age at diagnosis[a]	42.4 (14.9)	45.3 (12.6)	0.984 (0.952–1.017)	0.333	44.2 (13.5)
Age, current[a]	51.2 (14.7)	53.0 (12.3)	0.990 (0.957–1.023)	0.546	52.4 (13.2)
BMI[a] kg/m^2, $n=74$	26.3 (5.5)	27.7 (5)	0.946 (0.862–1.039)	0.245	27.2 (5.2)
Smokers, ever	15 (46.9)	11 (20.4)	3.449 (1.321–9.004)[a]	0.011	26 (30.2)
current smokers	5 (15.6)	5 (9.3)	1.815 (0.482–6.832)	0.378	10 (11.1)
ex-smoker	10 (31.3)	6 (11.1)	3.636 (1.174–11.268)[a]	0.025	16 (18.6)
Disease subtype					
dcSSc	13 (40.6)	17 (31.5)	1.489 (0.600–3.698)	0.391	30 (34.9)
lcSSc	19 (59.4)	37 (68.5)	0.672 (0.270–1.668)	0.391	56 (65.1)

Note: All other paramaters are *n* (%).
Abbreviations: BMI, body mass index; dcSSc, diffuse cutaneous systemic sclerosis; DUs, digital ulcers; lcSSc, limited cutaneous systemic sclerosis.
[a]mean (SD).

antibodies, and anti-U1 RNP antibodies, was documented. Among the study cohort, eight patients tested positive for anti-U1 RNP antibodies and were further classified into limited or diffuse SSc categories based on the extent of their skin involvement.

Statistical analysis was conducted using the SPSS software (version 26.0, IBM Corp., NY, USA). The Shapiro–Wilk test and histogram tests were employed to assess data distribution. Quantitative data were presented as both mean and median, while categorical data were expressed as percentages. Chi-square analysis and logistic regression was conducted to examine differences and relationships among DU groups. Statistical significance was defined as a p value of <0.05.

Among the cohort of 86 SSc patients, comprising predominantly females (80, 93%) with a mean age of 52.4 years (±13.2) and a mean disease duration of 8.1 years (±6.4), 32 patients (37%) had experienced DUs at some point. Twenty-six (30.2%) patients were smoked at any time. At the time of enrollment, 14 patients (43%) presented with DUs, out of 32 patients who experienced digital ulcers at any point during the study period. Interestingly, no discernible differences were seen in terms of body mass index (BMI), disease subtype, current age, or age at diagnosis when groups were compared based on the existence of DUs at any time (Table 1).

However, individuals with a history of smoking exhibited a markedly higher prevalence of DUs (OR 3.449, 95% CI 1.321–9.004, $p<0.05$). Digital ulcers were found more frequently among ex-smokers (OR 3.636, 95% CI 1.174–11.268, $p<0.05$) (Table 1). Specifically, among ex-smokers, 50% (7 out of 14) of patients were heavy smokers, whereas only 11.1% (1 out of 10) of current smokers had a similar smoking history (Table 2).

TABLE 2 | Distribution of smoking intensity among ex-smokers and current smokers.

Smoking status	Ex-smokers $n=14$	Current smokers $n=9$
>20 pack/years patients, *n* (%)	7 (50)	1 (11.1)
<20 pack/years patients, *n* (%)	7 (50)	8 (88.9)

There were no notable disparities among the DU subgroups concerning the cumulative clinical manifestations, except for GERD. Notably, individuals with a history of DUs exhibited a heightened likelihood of GERD (OR 2.552, 95% CI 1.018–6.398, $p<0.05$) (Table 3).

In this single-center study involving 86 patients, we conducted an analysis to delineate the disparities between the SSc patients with and without digital ulcers. Our findings revealed that smoking plays a role in DUs development.

The literature presents conflicting data regarding the association between smoking and vascular complications in SSc, largely attributed to methodological variations and study heterogeneity [13]. For instance, in a study of 101 SSc patients, current smokers were found to be 3–4 times more susceptible to digital vascular complications than nonsmokers [14]. Similarly, Bertolino et al. reported smoking as an independent risk factor for amputation [15]. Furthermore, Hudson et al. showed that there were more digital ulcers in smokers and a decrease in Raynaud's phenomenon severity with cessation of smoking [5]. Conversely, Khimdas et al. found no relationship between smoking and the presence of DUs [8]. Furthermore, smoking was not associated with an

TABLE 3 | The association between clinical and radiological features and digital ulcer development.

	DUs, yes $n=32$	DUs, no $n=54$	OR (%95 C.I for ExB)	p	All patients $n=86$
Cumulative clinical manifestations					
Raynoud's phenomenon	31 (96.9)	51 (94.4)	1.824 (0.182–18.312)	0.610	82 (95.3)
Artralji or arthritis	25 (78.1)	48 (88.9)	0.446 (0.135–1.472)	0.185	73 (84.9)
Telangiectasia	15 (46.9)	22 (40.7)	1.283 (0.532–3.098)	0.579	37 (43)
GERD	22 (68.8)	25 (46.3)	2.552 (1.018–6.398)[a]	0.046	47 (54.7)
Dysphagia	8 (25)	16 (29.6)	0.792 (0.294–2.132)	0.644	24 (27.9)
Pulmonary hypertension ($n=84$)	2 (6.3)	5/52 (9.6)	0.627 (0.114–3.439)	0.591	7 (8.3)
mRSS[a]	16 (14.2)	11.4 (10.7)	1.030 (0.994–1.068)	0.106	13.1 (12.2)
Cumulative radiological manifestations					
ILD	15 (46.9)	18 (33.3)	1.765 (0.721–4.322)	0.214	33 (38.4)
Esophageal dilatation ($n=84$)	11 (34.4)	13/52 (25)	1.571 (0.600–4.114)	0.357	24 (28.6)
Pericardial effusion ($n=85$)	8 (25)	7/53 (13.2)	2.190 (0.709–6.768)	0.173	15 (17.6)
Antibody status					
ANA	28 (84.8)	44 (83)	1.591 (0.455–5.567)	0.468	72 (83.7)
Anti-scl70	13 (40.6)	16 (29.6)	1.625 (0.650–4.061)	0.299	29 (33.7)
Anti-centromer	11 (34.4)	24 (44.4)	0.655 (0.265–1.620)	0.359	35 (40.7)

Note: All other paramaters are *n* (%).
Abbreviations: ANA, antinuclear antibodies; BMI, body mass index; DUs, digital ulcers; GERD, gastroesophageal reflux disease; ILD, interstitial lung disease.
[a]mean (±SD).

increased incidence of gangrene in individuals with SSc in a significant population from the EUSTAR database [7].

When examining smoking intensity in this study, the proportion of heavy smokers was significantly greater among ex-smokers compared to current smokers (50% vs. 11%). This led us to hypothesize that the higher frequency of DUs among ex-smokers may be attributed to smoking intensity. Indeed, the Longitudinal European Scleroderma Trials and Research Group Study involving 3,319 patients corroborated this, revealing a nearly 50% increase in the odds of DUs among heavy smokers (more than 25 pack-years) [10].

The presence of nicotine and other harmful components found in cigarettes has been observed to elevate plasma levels of endothelin-1, a potent vasoconstrictor primarily produced by compromised endothelial cells. This versatile molecule not only induces significant vasoconstriction but also stimulates endothelial cell proliferation and fibrotic processes. Recognized as a pivotal factor in the pathogenesis of Raynaud's phenomenon, endothelin underscores the utilization of anti-endothelin therapies for its management [16, 17]. Although the hypothesis regarding the impact of smoking on the development of DUs is consistent with the underlying pathophysiology, current literature lacks clarity in delineating the precise correlation between smoking duration, intensity, and DU incidence.

The study was limited by the small sample size and inconsistent assessment of prior digital ulcer condition by the same clinician; however, the confirmation of previous digital ulcer development during patient interviews mitigated this limitation. On the other hand, direct acquisition of smoking history through face-to-face interviews with patients was one of the strengths.

Our findings point to a potential connection between smoking and the development of DUs in SSc patients. Furthermore, the degree of smoking exposure might also play a role in the occurrence of DUs. Further research is warranted to clarify the fundamental processes and therapeutic ramifications of this association.

Author Contributions

E.O. and M.O. designed the study protocol. All authors studied data collection and interpretation. E.O., D.S. analyzed the data. E.O., S.G. performed literature review. E.O. and M.O. drafted the manuscript. S.A. and D.S. contributed revising the manuscript. All authors 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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References

1. V. Steen, C. Denton, J. Pope, C. P. Denton, J. E. Pope, and M. Matucci-Cerinic, "Digital Ulcers: Overt Vascular Disease in Systemic Sclerosis," *Rheumatology* 48, no. suppl_3 (2006): iii19–iii24.

2. I. Silva, J. Almeida, and C. Vasconcelos, "A PRISMA-Driven Systematic Review for Predictive Risk Factors of Digital Ulcers in Systemic Sclerosis Patients," *Autoimmunity Reviews* 14, no. 2 (2015): 140–152.

3. M. Hughes and A. L. Herrick, "Digital Ulcers in Systemic Sclerosis," *Rheumatology* 56, no. 1 (2017): 14–25.

4. P. Chaudhary, X. Chen, S. Assassi, et al., "Cigarette Smoking Is Not a Risk Factor for Systemic Sclerosis," *Arthritis and Rheumatism* 63, no. 10 (2011): 3098–3102.

5. M. Hudson, E. Lo, Y. Lu, et al., "Cigarette Smoking in Patients With Systemic Sclerosis," *Arthritis and Rheumatism* 63, no. 1 (2011): 230–238.

6. P. Hissaria, P. J. Roberts-Thomson, S. Lester, M. J. Ahern, M. D. Smith, and J. G. Walker, "Cigarette Smoking in Patients With Systemic Sclerosis Reduces Overall Survival: Comment on the Article by Hudson Et al," *Arthritis and Rheumatism* 63, no. 6 (2011): 1758–1759.

7. C. Mihai, O. Distler, A. M. Gheorghiu, et al., "Incidence and Risk Factors for Gangrene in Patients With Systemic Sclerosis From the EUSTAR Cohort," *Rheumatology (Oxford, England)* 59, no. 8 (2020): 2016–2023.

8. S. Khimdas, S. Harding, A. Bonner, B. Zummer, M. Baron, and J. Pope, "Associations With Digital Ulcers in a Large Cohort of Systemic Sclerosis: Results From the Canadian Scleroderma Research Group Registry," *Arthritis Care & Research (Hoboken)* 63, no. 1 (2011): 142–149.

9. K. Morrisroe, W. Stevens, J. Sahhar, et al., "Digital Ulcers in Systemic Sclerosis: Their Epidemiology, Clinical Characteristics, and Associated Clinical and Economic Burden," *Arthritis Research & Therapy* 21 (2019): 1–12.

10. V. K. Jaeger, G. Valentini, E. Hachulla, et al., "Brief Report: Smoking in Systemic Sclerosis: A Longitudinal European Scleroderma Trials and Research Group Study," *Arthritis & Rhematology* 70, no. 11 (2018): 1829–1834.

11. G. Simonneau, D. Montani, D. S. Celermajer, et al., "Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension," *European Respiratory Journal* 53, no. 1 (2019): 1801913.

12. E. C. LeRoy, C. Black, R. Fleischmajer, et al., "Scleroderma (Systemic Sclerosis): Classification, Subsets and Pathogenesis," *Journal of Rheumatology* 15, no. 2 (1988): 202–205.

13. Y. J. Zhang, L. Zhang, X. L. Huang, Y. Duan, L. J. Yang, and J. Wang, "Association Between Cigarette Smoking and Impaired Clinical Symptoms in Systemic Sclerosis: A Review," *Cellular Immunology* 318 (2017): 1–7.

14. B. J. Harrison, A. J. Silman, S. L. Hider, and A. L. Herrick, "Cigarette Smoking as a Significant Risk Factor for Digital Vascular Disease in Patients With Systemic Sclerosis," *Arthritis and Rheumatism* 46, no. 12 (2002): 3312–3316.

15. J. Bertolino, E. Jouve, S. Skopinski, et al., "Characteristics of Patients With Systemic Sclerosis Suffering From a Lower Limb Amputation: Results of a French Collaborative Study," *J Scleroderma Relat Disord* 5, no. 3 (2020): 224–230.

16. M. M. Rahman, S. Elmi, T. K. Chang, et al., "Increased Vascular Contractility in Isolated Vessels From Cigarette Smoking Rats Is Mediated by Basal Endothelin Release," *Vascular Pharmacology* 46, no. 1 (2007): 35–42.

17. A. Sulli, S. Soldano, C. Pizzorni, et al., "Raynaud's Phenomenon and Plasma Endothelin: Correlations With Capillaroscopic Patterns in Systemic Sclerosis," *Journal of Rheumatology* 36, no. 6 (2009): 1235–1239.

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LETTER TO THE EDITOR

Case Report: Atlantoaxial Rotatory Subluxation as a Rare Manifestation of Juvenile Enthesitis Related Arthritis

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Dear Editor,

Atlantoaxial rotatory subluxation (AARS) is an uncommon yet serious complication in juvenile enthesitis-related arthritis (ERA), a subset of juvenile idiopathic arthritis (JIA). While axial involvement in ERA is well recognized, upper cervical spine manifestations such as AARS remain sparsely reported. We present a compelling case of an adolescent male with ERA who developed symptomatic AARS, emphasizing the need for heightened clinical vigilance and timely imaging in patients presenting with a persistent neck pain or torticollis.

A 14-year-old boy presented with a six-month history of intermittent neck pain and stiffness. He has now noticed sudden worsening of symptoms and significant restriction of neck movements for the last 3 days. He also reports experiencing inflammatory back pain with morning stiffness lasting 30 min and left ankle pain and swelling for the last 2 months. There was no history of trauma or prior infection. Past history is significant for severe right ankle pain and swelling, with an inability to walk 3 years ago, which was relieved by over-the-counter pain killers, followed by frequent recurrences (2–3 episodes per week) occurring till 1.5 years thereafter. The patient also had a history of non-pruritic skin rash over the neck region and bilateral lateral ankles spreading to the shin region 1 year ago, which was treated with an unknown injectable at a local clinic; however, there was no personal or family history of psoriasis. There were no complaints of trauma, fever, redness or dryness of eyes or mucosa, dactylitis, nail changes, cough, Raynaud's phenomenon, blood in stools, and other peripheral joint involvement. Family history is not significant for any inflammatory back pain, uveitis, psoriasis, inflammatory bowel disease, or autoimmune disorders.

Clinical examination revealed significant torticollis with restricted and painful neck movement in all directions (< 20 degrees mobility by goniometer) with multiple cervical spinal tender points; bilateral FABER's test was positive, and tenderness in the left ankle joint was noted. Due to significant torticollis, assessment of Schober's and lateral lumbar flexion tests was not possible. A healed hypopigmented rash over bilateral ankles and shins was observed. Systemic examination was unremarkable.

Laboratory results revealed a macrocytic anemia with an Hb of 8.4 g/dL, WBC of 6000 cells/mm^3 with polymorphs at 47.2%, lymphocytes at 34%, eosinophils at 3.7%, basophils at 0.6%, monocytes at 14.5%, platelets at 468 000 cells/mm^3, ESR at 78 mm/h, and CRP level at 26.5 mg/L, serum creatinine at 0.60 mg/dL, SGPT at 10.1 IU/L, and a positive HLA B27 (by PCR). Rheumatoid factor and Anti-CCP antibodies were negative. Urinalysis did not reveal proteinuria or hematuria. HIV, HBsAg, HCV, and Mantoux test (2 × 2 mm) were all negative.

Plain radiographs revealed anterior C1/C2 subluxation and bilateral sacroiliitis (Figure 1). MRI of the cervical spine showed anterior atlantoaxial subluxation along with posterolateral subluxation of the dens and mild to moderate joint effusion with enthesitis of the facet joints at the C2/C3/C4 levels (Figure 2).

The patient was treated with a combination therapy of intravenous pulse therapy with 500 mg methylprednisolone for 3 days, Tofacitinib 5 mg, and Sulfasalazine 1000 mg twice daily, and Etoricoxib 60 mg daily for rapid control of symptoms and to

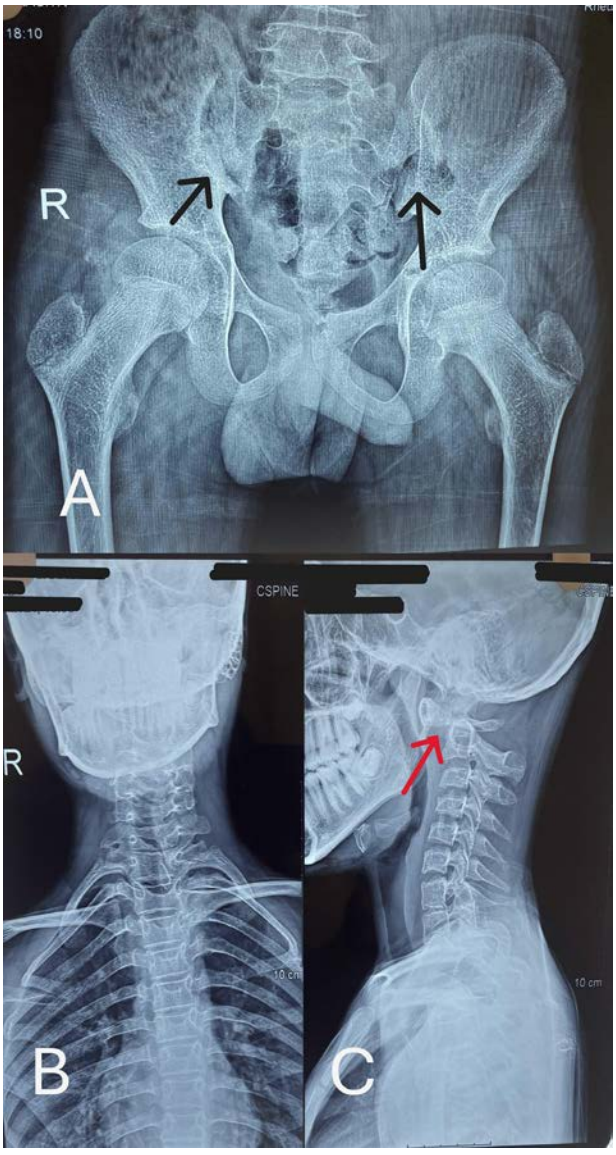

FIGURE 1 | X-ray of pelvis, AP view and X-ray of neck, AP and Lateral view. (A) X-ray of pelvis AP view showing bilateral sacroiliac joint space narrowing (black arrows) suggesting bilateral sacroiliiitis. (B) X-ray of neck, AP view. (C) X-ray of neck lateral view showing anterior subluxation (red arrow) of C1 (atlas) over C2 (axis).

prevent progression of the disease. In view of his aggressive disease, the option of biological therapy with TNF inhibitors was also offered, but relatives refused it due to financial constraints. At the 2-month follow-up, examination revealed a negative Schober's test (5 cm), and the finger-to-floor distance was 25 cm. The patient reported no pain or stiffness in the neck or lower back. Investigations showed HB 9.2 g/dL, WBC 6610 cells/mm^3, platelets 223 000 cells/mm^3, ESR 31 mm/h, and CRP level 23.7 mg/L, S. creatinine 0.53 mg/dL, SGPT 30 IU/L. Close follow-up and observation for his symptoms and a possible need for spinal fixation are planned in case of neurological deterioration, rotational instability on dynamic CT/MRI, worsening of cord compression, or recurrence of symptoms.

1 | Discussion

To our knowledge, this is the first reported case from India of early Atlantoaxial rotatory subluxation (AARS) in Enthesitis-Related Arthritis (ERA), a subtype of juvenile idiopathic arthritis (JIA) based on the International League of Associations for Rheumatology (ILAR) classification criteria [1, 2].

ERA is defined by the International League of Associations for Rheumatology as ≥ 6 weeks of arthritis and enthesitis—or one plus at least two of: sacroiliac tenderness or inflammatory lumbosacral pain; HLAB27 positivity; male onset > 6 years; acute anterior uveitis; or familial history of ankylosing spondylitis, ERA, sacroiliitis with IBD, Reiter's syndrome, or acute anterior uveitis in a first-degree relative [1, 2].

Cervical spine involvement in JIA is rare; sub-axial lesions are more common, and C1/C2 involvement is uncommon [3]. AARS in early ERAJIA is extremely rare and, if untreated, may cause fusion and radiculopathies [4]. Early axial involvement correlates with worse outcomes and enduring disability into adulthood [5]. While few cases exist, its prognostic relevance remains unclear [6].

Our case emphasizes the importance of recognizing early AARS in ERA. Usually in ERA, sub-axial lesions are more commonly reported than C1/C2 lesions. However, identifying early C1/C2

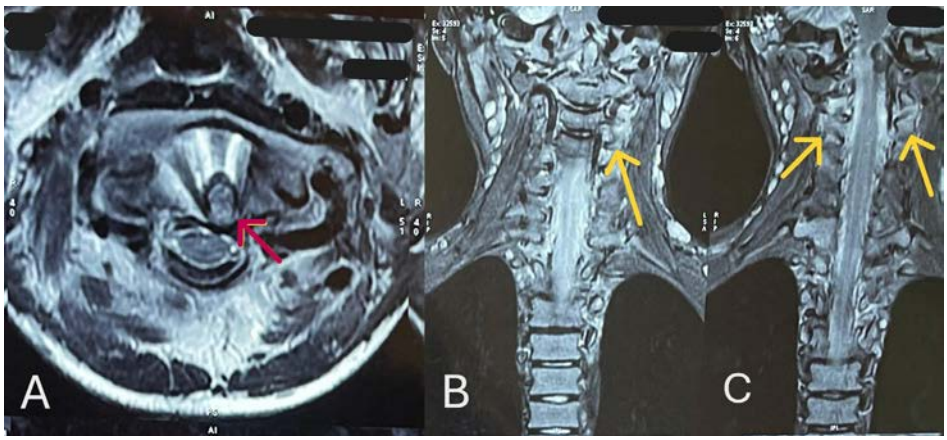

FIGURE 2 | MRI of neck. (A) Axial view at C1/C2 level showing left posterolateral subluxation of dens (Red arrow). (B and C) Coronal STIR views showing facet joint edema and costovertebral enthesitis (yellow arrows) at C2/C3/C4 levels.

instability is critical to prevent severe complications such as spinal cord compression and neurologic deficits.

The pathophysiology of ERA involves chronic synovial and entheseal inflammation, resulting in joint laxity [6]. Differential diagnoses include infection, polyarticular JIA (RF positive or negative), systemic JIA, and juvenile psoriatic arthritis. In our patient, MRI ruled out abscesses or erosions. Chronic relapsing arthritis without fever, weight loss, or systemic symptoms—and negative tuberculosis tests—but positive HLAB27, excluded infectious causes. The absence of psoriatic features (nail/scalp involvement, family history), negative anti-CCP and rheumatoid factor, and lack of C1–C2 pannus (typical in polyarticular JIA) all supported an ERA diagnosis.

Early cervical spine evaluation in ERA can be overlooked due to its rarity. Thus, routine cervical imaging—particularly MRI—should be performed early to prevent progression and neurological injury [3].

Management of AARS in ERA involves disease-modifying and anti-inflammatory therapy. In our case, high-dose glucocorticoids and DMARDs were initiated early to control inflammation and prevent progression. Regular spinal monitoring is essential to identify neurological deterioration that may require surgical intervention to fix the spine by an expert team of pediatric spine surgeons and anesthetists.

A limitation of this report is the inability to definitively exclude juvenile psoriatic arthritis. The patient had a skin rash that resolved before presentation, but no nail or scalp involvement, no family history, and no dermatologist or biopsy confirmation of psoriasis. We did not perform musculoskeletal ultrasonography for enthesitis, although it was shown to be useful for detecting subclinical enthesitis in chronic nonbacterial osteomyelitis by Sener et al. [7] Ideally, dynamic CT of the neck is the modality of choice to evaluate for AARS; however, it was not performed due to financial constraints. Hence, ERA remains the most plausible diagnosis.

2 | Conclusion

Despite its rarity, early AARS in ERA is clinically important. Comprehensive clinical and radiological cervical assessment, including prompt MRI, enables early detection and can help prevent neurological complications. Further prospective studies are needed to clarify prevalence, natural history, prognosis, and optimal management of AARS in ERA.

Author Contributions

P.P. and M.B. – designed the work, revised the manuscript. P.P. and P.D. – collected the case data, coordinated patient follow-up, reviewed literature and images, wrote the first draft. M.B. – reviewed literature, critically revised the manuscript, responsible for overall accountability. All authors approved the final version.

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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References

1. R. E. Petty, T. R. Southwood, P. Manners, et al., "International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001," *Journal of Rheumatology* 31, no. 2 (2004): 390–392.

2. M. Yıldız, F. Haşlak, A. Adroviç, S. Şahin, K. Barut, and Ö. Kasapçopur, "Juvenile Spondyloartropathies," *European Journal of Rheumatology* 9, no. 1 (2022): 42–49, https://doi.org/10.5152/eurjrheum.2021.20235.

3. M. Kotecki, P. Gietka, M. Posadzy, and I. Sudoł-Szopińska, "Radiographs and MRI of the Cervical Spine in Juvenile Idiopathic Arthritis: A Cross-Sectional Retrospective Study," *Journal of Clinical Medicine* 10, no. 24 (2021): 5798, https://doi.org/10.3390/jcm10245798.

4. M. Sae-Huang, A. Borg, and C. S. Hill, "Systematic Review of the Nonsurgical Management of Atlantoaxial Rotatory Fixation in Childhood," *Journal of Neurosurgery. Pediatrics* 27, no. 1 (2020): 108–119, https://doi.org/10.3171/2020.6.PEDS20396.

5. R. Naveen, N. Mohindra, N. Jain, S. Majumder, and A. Aggarwal, "Hip Involvement in Children With Enthesitis-Related Arthritis (ERA) is Associated With Poor Outcomes in Adulthood," *Clinical Rheumatology* 40, no. 11 (2021): 4619–4627, https://doi.org/10.1007/s10067-021-05807-3.

6. W. H. S. Siu, C. J. Wang, C. T. Wu, C. Y. Wu, and L. S. Ou, "C1-C2 Subluxation in Enthesitis-Related Arthritis: Two Case Reports and Literature Review of Ten Cases," *Pediatric Rheumatology* 21, no. 1 (2023): 77, https://doi.org/10.1186/s12969-023-00862-3.

7. S. Sener, P. Oktayoglu, F. Önder, et al., "Subclinical Enthesitis in Children With Chronic Nonbacterial Osteomyelitis," *Turkish Archives of Pediatrics* 60, no. 2 (2025): 289293, https://doi.org/10.5152/TurkArchPediatr.2025.24300.

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LETTER TO THE EDITOR

Juvenile-Onset Diffuse Systemic Sclerosis Later Developing Systemic Lupus Features: A Challenging Overlap Syndrome

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Dear Editor,

Juvenile-onset overlap connective tissue diseases (OCTDs) represent a rare incidence of 0.23 per 100 000 children's years and a heterogeneous group of autoimmune conditions distinct from their adult counterparts, both in clinical presentation and long-term outcomes [1]. These include combinations of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and inflammatory myopathies, with SLE being the most frequent phenotype [2]. Overlap between juvenile SLE and SSc is particularly rare, with limited case reports in the literature [3–5]. This report describes a rare case of juvenile-onset diffuse cutaneous SSc evolving into an overlap syndrome with SLE after 7 years of disease onset and had an aggressive and difficult-to-control disease course. Our objective is to emphasize the diagnostic and therapeutic challenges posed by this evolving phenotype, especially in the context of conflicting treatment paradigms and complications such as pulmonary hypertension and lupus nephritis.

A 20-year-old female presented with a history of Raynaud's phenomenon since the age of 14, without developing gangrene or digital ulcers. At the age of 16, she developed salt-and-pepper pigmentation over the upper and lower limbs, which later spread to the entire body. She developed progressive skin thickening over the face and limbs, restricted mouth opening, and exertional dyspnea (MMRC grade 2) without cough, chest pain, or orthopnea. Occasional polyarthralgia involving the small joints was noted. She was diagnosed with dcSSc. High-resolution CT (HRCT) of the thorax showed no evidence of interstitial lung disease (ILD), and 2D echocardiography (ECHO) revealed a right ventricular systolic pressure (RVSP) of 30 mmHg. She was initiated on tadalafil, with clinical improvement over the following year. The modified Rodnan skin score (mRSS) improved from 6/51 at presentation to 0/51 1 year later.

After 15 months of treatment for SSc, she developed new-onset hyperpigmented skin lesions over both pinnae, which were only partially responsive to low-dose oral prednisolone. Additionally, she experienced daily high-grade intermittent fever, new-onset painless oral and palatal ulcers, non-scarring alopecia, and fatigue with unintentional weight loss of three kilograms over 3 months. There was no history of renal involvement, hypertension, sicca symptoms, gastrointestinal, or neuropsychiatric complaints. She denied prior blood transfusions or history of jaundice.

On examination, she had pallor and bilateral subcentimetric, non-tender axillary lymphadenopathy. There was generalized non-scarring alopecia and a discoid lupus rash over both pinnae, preauricular, and postauricular regions, with surrounding areas of hypopigmentation. Mouth opening was restricted to two-finger breadths, and there were multiple superficial buccal mucosal ulcers along with a single palatal ulcer (Figure 1). The skin over the limbs and trunk showed salt-and-pepper pigmentation. Neuromuscular examination revealed subtle neck and proximal thigh muscle weakness. Mild hepatosplenomegaly was present. Pulmonary function tests showed a reduction in lung volumes compared to baseline; however, HRCT thorax did not show ILD, though 2D ECHO showed an increase in RVSP to 46 mmHg.

Immunological workup revealed a 4+ positive anti-nuclear antibody (ANA) with homogeneous and coarse speckled patterns, and extractable nuclear antigen (ENA) panel showed positivity for double-stranded DNA (dsDNA), Ku, and U1RNP.

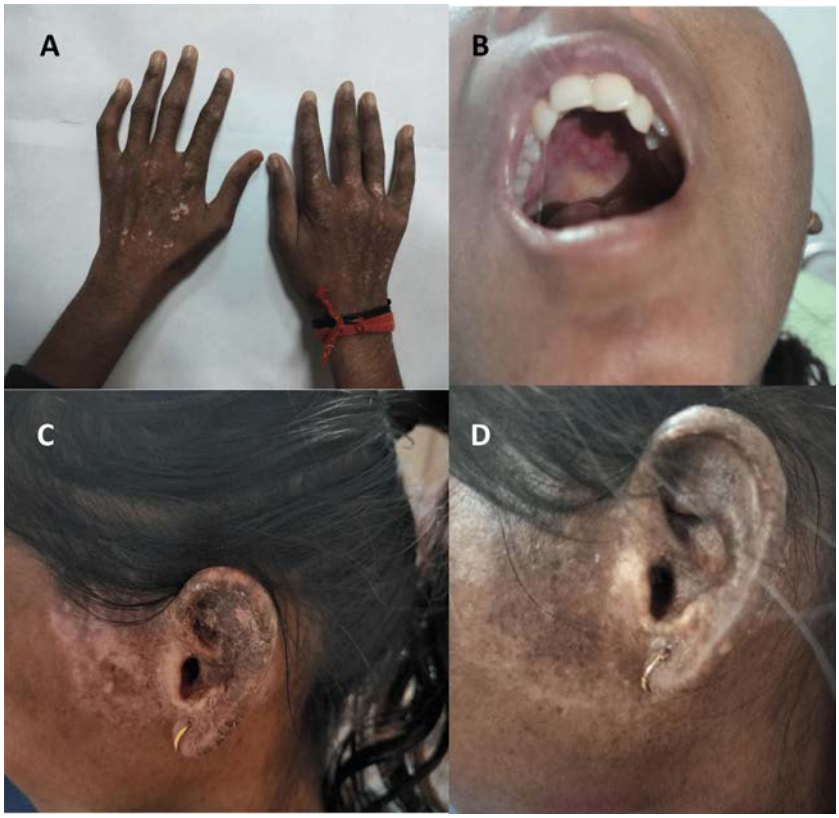

FIGURE 1 | (A) Salt and pepper pigmentation of the skin, (B) palatal ulcer, (C) discoid lupus rash over the pinna and pre auricular areas with surrounding hypopigmentation, and (D) resolving discoid rash following treatment initiation.

Complement levels were low, and IgG anti-cardiolipin antibody was positive in moderate titers. Liver function tests showed a mildly elevated aspartate transaminase (AST) level, while other muscle enzymes were within the normal range. Urine examination showed 4+ proteinuria with active sediments, and the spot urine protein-to-creatinine ratio (UPCR) was 148/151, and 24-h urine protein was 1.09 g (Table 1). Serum creatinine was normal at 0.28 mg/dL. Given the presence of significant proteinuria, a renal biopsy was performed, which showed class II lupus nephritis with a full-house immunofluorescence pattern.

Considering severe disease features, including lupus nephritis, pulmonary hypertension, and a high SLEDAI-2 K score of 33, she was initiated on the NIH cyclophosphamide (CYC) regimen. Prednisolone was maintained at a dose of 10 mg/day, and telmisartan was continued. She showed significant improvement in skin lesions and became afebrile after two doses of CYC. However, she later developed recurrent fever and new onset chest pain. Echocardiography and CT revealed moderate pericardial effusion and mild bilateral pleural effusion. Her RVSP had worsened to 64 mmHg. CRP was elevated, but workup for infection was negative. Prednisolone was increased to 12.5 mg/day, and tacrolimus and ambrisentan were added while continuing NIH CYC. However, she had recurrent culture-positive urinary tract infections; hence, tacrolimus was withheld. Due to persistent low-grade fever and cytopenia, the prednisolone dose was hiked to 0.5 mg/kg/day. Currently, she is stable on monthly cyclophosphamide and low-dose prednisolone.

Although observational studies suggest that juvenile OCTDs have a somewhat more favorable overall prognosis compared to juvenile MCTD [2], our case demonstrates that patients can present with a severe disease spectrum when two high morbidity phenotypes such as dcSSc and SLE coexist. Juvenile SLE is known to be more aggressive than adult-onset disease, with higher disease activity scores and early and damage accrual [6], while juvenile-onset dcSSc itself is associated with worse outcomes compared to limited cutaneous disease [7] and has greater cardiopulmonary involvement, consistent with the findings in our patient.

The therapeutic complexity of this overlap syndrome was further magnified by the risk of scleroderma renal crisis associated with high-dose glucocorticoid therapy, the standard first-line treatment for proliferative lupus nephritis. Although renal biopsy revealed only class II lupus nephritis, significant proteinuria and active urine sediments raised concern for proliferative disease, prompting early initiation of NIH CYC. But the patient subsequently developed pleuropericardial effusions and worsening pulmonary hypertension, necessitating additional immunosuppressive agents like tacrolimus, but later discontinued due to recurrent infections, which are a common complication in heavily immunosuppressed patients.

This case underscores the need for continuous re-evaluation in juvenile-onset connective tissue diseases due to the potential for phenotypic evolution. Overlap syndromes between SLE and SSc, though rare in children, pose significant therapeutic challenges

TABLE 1 | Biochemical and immunological investigations.

Investigations	Value	Normal range
Hemoglobin	7.5 g/dL	14–18 g/dL (M),12–16 g/dL (F)
Total leukocyte count (differential count)	3130/mm^3 ($N_{60}L_{30}E_3M_7$)	4000–11 000/mm^3
Platelet count	1.97 lakhs/mm^3	1.5–4.5 lakhs/mm^3
Peripheral blood smear	Normocytic normochromic RBCs	NA
Corrected retic count	2.4%	NA
Serum creatinine	0.28 mg/dL	0.6–1.3 mg/dL
Serum bilirubin (total/direct)	0.2/0.04 mg/dL	0.1–1.2/< 0.3 mg/dl
Total protein/albumin	5.35/1.78 g/dL	6.0–8.3/3.5–5.0 g/dL
AST/ALT	37/5 IU/L	0–35 IU/L
C reactive protein	0.48 mg/dL	< 5 mg/L
ESR	76 mm/h	0–20 mm/h (M), 0–30 mm/h (F)
Lactate dehydrogenase	368 U/L	125–220 U/L
Serum ferritin	175 mcg/L	24–336 mcg/L (M), 11–307 mcg/L (F)
IgG/IgM	1080/37 mg/dL	700–1600/40–230 mg/dL
ANA	4+ homogenous and coarse speckled	Negative
ENA	3+ dsDNA, U1RNP, nucleosome, histone	Negative
C3/C4	46.2/3.7 mg/dL	60–120 mg/dL/15–25 mg/dL
Anti-dsDNA	> 300 IU/mL	< 10 IU/mL
IgG anticardiolipin antibody	40.1 mg/dL	Negative
24-h urine protein	1090 mg	< 150 mg
Direct/indirect Coomb's test	Positive/Negative	Negative
Pulmonary function tests	July 2023	November 2024
FEV1	2.03 L, 71%	1.69 L, 67%
FVC	2.39 L, 73%	2.0 L, 66%
DLCO	4.01 L, 46%	3.01 L, 46%

Abbreviations: ALT, alanine transaminase; ANA, anti nuclear antibody; AST, aspartate transaminase; DLCO, diffusion capacity for carbon monoxide; dsDNA, double stranded deoxy ribonucleic acid; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

where treatment for one condition can worsen the other. The emergence of newer biologic and cellular therapies offers hope for targeted treatment and long-term disease control in such complex cases [8].

Author Contributions

L.M.R., M.C. and V.A. concept, data acquisition/analysis, manuscript drafting/revision, and final approval.

Consent

Written informed consent was obtained from the patient for this case report according to the regulations of the institutional ethics committee. Confidentiality of patient data was maintained.

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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Manikandan Chidambaram
Vikas Agarwal

References

1. A. Felix, L. Osei, F. Delion, et al., "Longitudinal Follow-Up of Mixed Connective Tissue Disease and Overlapping Autoimmune Diseases of Childhood Onset in the Afro-Descendant Population of the French

West Indies," *Pediatric Rheumatology Online Journal* 22, no. 1 (2024): 13, https://doi.org/10.1186/s12969-023-00951-3.

2. E. D. Batu, A. Günalp, S. Şahin, et al., "Pediatric Mixed Connective Tissue Disease Versus Other Overlap Syndromes: A Retrospective Multicenter Cohort Study," *Rheumatology International* 43, no. 8 (2023): 1485–1495, https://doi.org/10.1007/s00296-023-05300-x.

3. N. A. Popescu, D. Manea, G. Capitanescu, E. Cinteza, M. D. Ionescu, and M. Balgradean, "Respiratory Failure in a Rare Case of Juvenile Dermatomyositis–Systemic Scleroderma Overlap Syndrome," *Maedica* 15, no. 3 (2020): 394–400, https://doi.org/10.26574/maedica.2020.15.3.394.

4. M. Kaniu, D. Owende, and A. Migowa, "E58 the Rheumatologic Masquerader: A Case Report on SLE-Dermatomyositis-Systemic Scleroderma Overlap Syndrome," *Rheumatology* 62, no. suppl 3 (2023): kead323.058, https://doi.org/10.1093/rheumatology/kead323.058.

5. K. H. Lin and J. K. Kao, "Overlap Syndrome in a 12-Year-Old Girl With Systemic Lupus Erythematosus and Anti-OJ Antibody-Positive Polymyositis: A Case Report," *Pediatric Rheumatology Online Journal* 20, no. 1 (2022): 92, https://doi.org/10.1186/s12969-022-00753-z.

6. P. Ö. Avar Aydın and H. I. Brunner, "Revisiting Childhood-Onset Systemic Lupus Erythematosus," *Turkish Archives of Pediatrics* 59, no. 4 (2024): 336–344, https://doi.org/10.5152/TurkArchPediatr.2024.23300.

7. I. Foeldvari, J. Klotsche, M. Zhavania, et al., "Differences Sustained Between Diffuse and Limited Forms of Juvenile Systemic Sclerosis in an Expanded International Cohort," *Arthritis Care & Research* 74, no. 10 (2022): 1575–1584, https://doi.org/10.1002/acr.24609.

8. F. Müller, J. Taubmann, L. Bucci, et al., "CD19 CAR T-Cell Therapy in Autoimmune Disease—A Case Series With Follow-Up," *New England Journal of Medicine* 390, no. 8 (2024): 687–700, https://doi.org/10.1056/NEJMoa2308917.

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LETTER TO THE EDITOR

Case Report: A Challenging Case of Seronegative Catastrophic Antiphospholipid Syndrome

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Dear Editor,

Antiphospholipid syndrome (APS) is an immune-mediated prothrombotic state disorder characterized by circulating APS antibodies (APS-Ab) that activate endothelial cells, leukocytes, and platelets to induce thrombosis [1]. Diagnosis requires at least one clinical criterion and one APS-Ab detected on ≥2 occasions at least 12 weeks apart. APS-Ab include either anticardiolipin, lupus anticoagulant, and/or beta-2 glycoprotein [1, 2].

Catastrophic APS (CAPS) is a rare, severe manifestation of APS characterized by rapid, widespread thrombosis in multiple organs, often triggered by infection, trauma, or surgery [3]. Diagnosis of CAPS includes thrombi in ≥3 organs within 1 week, histopathological confirmation of small vessel occlusion, and APS-Ab positivity [4].

Seronegative (SN) CAPS is a recognized but rare variant lacking detectable APS-Ab. It remains a diagnosis of exclusion but carries significant mortality [4]. Herein, we present a case of seronegative CAPS.

1 | Case Presentation

A 55-year-old female with seropositive rheumatoid arthritis on disease-modifying therapy and prior transcatheter aortic valve replacement presented with hypotension, lactic acidosis (peak 9.2 mmol/L), and elevated troponin (peak 12,585 ng/L). She was treated empirically for septic versus cardiogenic shock with vasopressors, broad-spectrum antibiotics, and heparin infusion. Blood cultures grew group A streptococcus. Transthoracic echocardiogram demonstrated severely reduced left ventricular ejection fraction of 20%, patent foramen ovale, and no valvular vegetations. Her clinical course improved, and vasopressors were weaned.

On hospital day 5, she developed acute dysarthria and left facial droop. Brain MRI showed diffuse embolic shower with multiple ischemic infarcts (Figure 1). CTA of the head and neck confirmed multiple scattered bilateral acute ischemic infarcts without large vessel occlusion or mycotic aneurysm. She also developed acute bilateral upper and lower extremity pain with associated necrotic skin changes. Low-dose vasopressors were restarted for hypotension, and she was transferred to our tertiary care center. Upon arrival, heparin infusion was discontinued given low suspicion for acute coronary syndrome and risk of hemorrhagic conversion in the setting of acute stroke. Transesophageal echocardiogram was negative for valvular vegetations or thrombi and confirmed patent foramen ovale. Venous and arterial duplex ultrasounds of bilateral carotid, lower, and upper extremities were negative for acute or chronic thrombi.

On hospital day 6, hematology was consulted for a hypercoagulable workup in the setting of arterial thrombi and evaluation of

Abbreviations: APS, Antiphospholipid Syndrome; APS-Ab, Antiphospholipid Antibodies; CAPS, Catastrophic Antiphospholipid Syndrome; DIC, Disseminated Intravascular Coagulation; DITP, Drug Induced Thrombocytopenia; HIT, Heparin Induced Thrombocytopenia; IVIG, Intravenous Immunoglobulin; PF, Purpura Fulminans; SN-CAPS, Seronegative Catastrophic Antiphospholipid Syndrome; TTP, Thrombotic Thrombocytopenic Purpura.

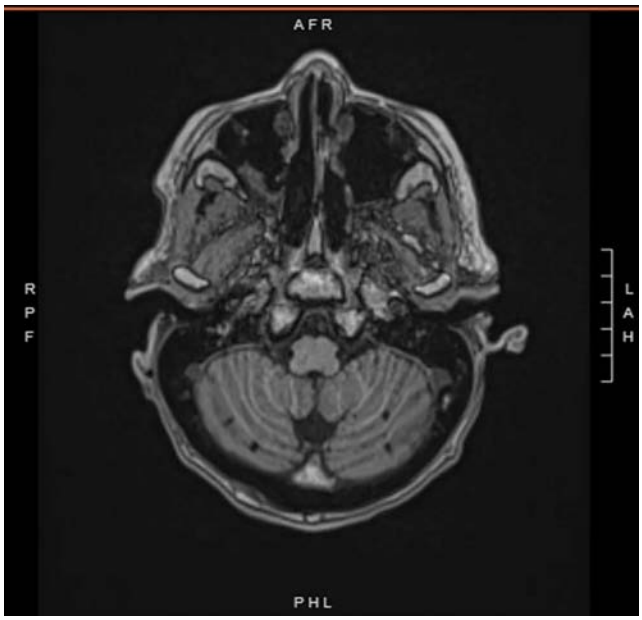

FIGURE 1 | Magnetic Resonance Imaging Head.

thrombocytopenia. Labs revealed moderate thrombocytopenia (platelet nadir 35 K/mcL, Table 1), prolonged protime (15.5 s), and partial thromboplastin time (46 s). Schistocytes were present on the peripheral smear. Subsequent workup demonstrated low-detectable haptoglobin (47 mg/dL), elevated LDH (1128 units/L), normal total bilirubin (0.4 mg/dL), and normal fibrinogen (283 mg/dL). Anticardiolipin, beta-2 glycoprotein, lupus anticoagulant, and heparin-induced platelet Ab were negative. ADAMTS13 activity was 89%, protein C functional activity 120%, and protein S functional activity 71%, all within normal limits. Anti-nuclear Ab was positive with a titer of 1:320 and a speckled pattern; rheumatoid factor was normal (11 IU/mL), and anti-cyclic citrullinated peptide was elevated (59 U). Pathology from the right acral skin biopsy showed epidermal necrosis with organized fibrin thrombi in deep dermal vessels.

Given the high clinical suspicion for SN-CAPS, heparin infusion was restarted on day 6 despite the risk of hemorrhagic conversion of known infarcts. She received 3 days of intravenous methylprednisolone 1000 mg and 2 days of intravenous immunoglobulin (IVIG) 1 g/day with improvement in platelets (Table 1). On day 9, hemoglobin acutely worsened from hemoglobin 9.0 g/dL to 7.3 g/dL (Table 1), and heparin infusion was held due to concerns for bleeding. The platelet count continued to improve. An interval CT head from earlier that morning did not demonstrate evidence of hemorrhagic conversion. The patient developed worsening shortness of breath and eventually became bradycardic and unresponsive with fixed, dilated pupils and an upward right gaze. After discussion with her family, the patient was transitioned to comfort care and died shortly thereafter.

2 | Discussion and Conclusions

Our patient met CAPS diagnostic criteria: multiorgan thrombosis, histopathological confirmation, and rapid onset. However, APS-ab were absent, leading to consideration of SN-CAPS. The differential included heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), purpura fulminans (PF), thrombotic thrombocytopenic purpura (TTP), and drug-induced thrombocytopenia (DITP). Although she was at intermediate risk for HIT based on the 4Ts score, the abrupt decline of platelet count on day 1 of hospitalization, with no known previous or recent exposures to heparin, lowered our suspicion. DIC was less likely due to normal fibrinogen. With normal protein C activity and fibrinogen, PF was thought to be unlikely despite evidence of thrombosis and rapidly progressive purpura. TTP was ruled out in the presence of normal ADAMSTS13. DITP secondary to antibiotics is a possible explanation but also less likely due to limited exposure initially and would not explain concurrent arterial thrombi.

SN-CAPS is a diagnostically challenging, life-threatening condition. Absence of APS antibodies may be due to consumption during the prothrombotic period and subsequent thrombo-occlusive episodes [4–6]. There are also emerging "non-criteria" Ab associated with APS; however, due to limited availability of standardized assays and clinical relevance, they are not routinely tested for. Further investigation of these antibodies may help elucidate variability in the clinical presentation of SN-CAPS and better risk stratify patients [1, 2, 7].

Current guidelines recommend "triple therapy" with anticoagulation, glucocorticoids, and plasma exchange, in addition to addressing the underlying trigger [3, 8]. Anticoagulation with heparin is considered the mainstay of CAPS treatment, and glucocorticoids are the most commonly used anti-inflammatory drug. Although plasma exchange is recommended and has grade 2C evidence (American Society for Apheresis), hemodynamic instability at presentation limited our ability to offer this [9, 10]. IVIG may also effectively downregulate the CAPS inflammatory response [9]. Other second-line agents include rituximab (anti-CD20 monoclonal Ab) and eculizumab (anti-C5 monoclonal Ab) [3, 8]. Despite initiating anticoagulation, glucocorticoids, and IVIG, our patient ultimately declined.

This case underscores the importance of considering SN-CAPS in the differential of patients with multiorgan thrombotic events, even when APS-Ab are absent. The diagnostic challenges inherent in SN-CAPS can delay appropriate management, and despite

TABLE 1 | Hemoglobin and Platelet Trends.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Hemoglobin (g/dL)	11.8	9.8	8.7	7.7	9.3	8.7	7.6	9.6	9.0	7.3
Platelet (K/mcL)	292	163	112	78	35	40	46	68	100	112

the initiation of treatment, prognosis can be poor, as observed in this case. Timely recognition based on clinical criteria and exclusion of other thrombotic microangiopathies remains crucial for potentially improving outcomes in this rare and life-threatening condition.

Author Contributions

All authors contributed to patient data collection, manuscript preparation, and revision.

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The authors have nothing to report.

Disclosure

Permission to Reproduce Material From Other Sources: Not applicable.

Ethics Statement

The authors have nothing to report.

Consent

Informed consent for publication was obtained from next of kin.

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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References

1. J. S. Knight, D. W. Branch, and T. L. Ortel, "Antiphospholipid Syndrome: Advances in Diagnosis, Pathogenesis, and Management," *BMJ (Clinical Research ed.)* 380 (2023): e069717, https://doi.org/10.1136/bmj-2021-069717.

2. P. Pignatelli, E. Ettorre, D. Menichelli, A. Pani, F. Violi, and D. Pastori, "Seronegative Antiphospholipid Syndrome: Refining the Value of "Non-Criteria" Antibodies for Diagnosis and Clinical Management," *Haematologica* 105, no. 3 (2020): 562–572, https://doi.org/10.3324/haematol.2019.221945.

3. V. Bitsadze, F. Yakubova, J. Khizroeva, et al., "Catastrophic Antiphospholipid Syndrome," *International Journal of Molecular Sciences* 25, no. 1 (2024): 668, https://doi.org/10.3390/ijms25010668.

4. V. Pinto, A. Ministro, N. R. Carreira, et al., "A Catastrophic Seronegative Anti-Phospholipid Syndrome: Case and Literature Review," *Thrombosis Journal* 19, no. 1 (2021): 103, https://doi.org/10.1186/s12959-021-00356-w.

5. R. Nayfe, I. Uthman, J. Aoun, E. Saad Aldin, M. Merashli, and M. A. Khamashta, "Seronegative Antiphospholipid Syndrome," *Rheumatology (Oxford, England)* 52, no. 8 (2013): 1358–1367, https://doi.org/10.1093/rheumatology/ket126.

6. C. D. Enescu, B. Basida, N. Zalavadiya, R. Akram, and H. Sarakbi, "A Diagnostic Dilemma: Catastrophic or Seronegative Antiphospholipid Syndrome," *Cureus* 13, no. 10 (2021): e18745, https://doi.org/10.7759/cureus.18745.

7. K. M. J. Devreese, "Noncriteria Antiphospholipid Antibodies in Antiphospholipid Syndrome," *International Journal of Laboratory Hematology* 46, no. Suppl 1 (2024): 34–42, https://doi.org/10.1111/ijlh.14268.

8. I. Rodríguez-Pintó, M. Moitinho, I. Santacreu, et al., "Catastrophic Antiphospholipid Syndrome (CAPS): Descriptive Analysis of 500 Patients From the International CAPS Registry," *Autoimmunity Reviews* 15, no. 12 (2016): 1120–1124, https://doi.org/10.1016/j.autrev.2016.09.010.

9. R. Cervera, I. Rodríguez-Pintó, and G. Espinosa, "The Diagnosis and Clinical Management of the Catastrophic Antiphospholipid Syndrome: A Comprehensive Review," *Journal of Autoimmunity* 92 (2018): 1–11, https://doi.org/10.1016/j.jaut.2018.05.007.

10. S. Bucciarelli, G. Espinosa, R. Cervera, et al., "Mortality in the Catastrophic Antiphospholipid Syndrome: Causes of Death and Prognostic Factors in a Series of 250 Patients," *Arthritis and Rheumatism* 54, no. 8 (2006): 2568–2576, https://doi.org/10.1002/art.22018.

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ORIGINAL ARTICLE

Get OUT: Factors Associated With a Longer Length of Stay in Patients Admitted With an Acute Gout Flare, and the Effects of Anakinra on Length of Stay

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ABSTRACT

Objective: Acute gout flares (AGF) are a significant burden to healthcare systems globally, due to the prolonged length of stay (LOS). The study's aim was to audit patients admitted to our facility with AGF, then re-audit after the introduction of interleukin-1 receptor antagonist anakinra in select patients to assess whether it would result in a reduced LOS.

Methods: A single-center retrospective audit was conducted on 62 hospitalizations for AGF in 2019 that met inclusion criteria. Data on patient demographics, comorbidities, and clinical parameters (number of joints involved, C-reactive protein (CRP), urate levels, and tophi) were analyzed using multivariable Poisson regression models to determine predictors of LOS. We then compared patients that received anakinra in 2020 ($n = 7$) with a historical control group ($n = 13$).

Results: The average LOS in 2019 for AGF was 3.36 days (1.22–4.28). CRP, prior use of allopurinol, and impaired mobility levels were significant predictors of prolonged LOS, with respective coefficients of 0.0036 (95% CI: 0.0023–0.0050, $p < 0.0001$), 0.321 (95% CI: 0.043–0.599, $p = 0.023$), and 0.708 (95% CI: 0.416–1.000, $p < 0.0001$). When CRP was treated as a controlled variable, patients treated in 2020 with anakinra demonstrated a 0.493-day reduction in LOS compared to the control group, which was statistically significant ($p = 0.043$).

Conclusion: CRP levels, allopurinol use, and impaired mobility are key predictors of prolonged LOS in AGF. Although the use of anakinra shows promise in reducing LOS and costs, larger studies are needed to confirm its efficacy.

1 | Introduction

Gout, the most common form of inflammatory arthritis, is characterized by recurrent episodes of acute arthritis resulting from monosodium urate (MSU) crystal deposition in joints and periarticular tissues. It has emerged as a public health issue, with acute flares often leading to hospital admissions. In Australia, the incidence of hospitalizations associated with an acute gout flare is increasing, with 1 gout episode per 1000 total hospital admissions [1]. Although there have been advances in treatment options, the length of stay (LOS) for patients admitted with acute gout remains a critical concern. The average LOS in Australian hospitals in 2021–2022 for patients with a primary diagnosis of gout was 5.1 days, in keeping with international studies that have noted LOS ranges of 3–5 days [1–3].

Despite this, few studies have specifically analyzed factors associated with LOS in hospitalized gout patients, and those that have primarily focus on patient-related factors rather than the severity of the gout flare itself [2–6]. A 2012 abstract presented at

Summary

- The main predictors of extended LOS for gout patients in this audit were found to be significantly increased CRP levels, previous use of urate-lowering therapy, and mobility impairment.
- Interleukin-1 inhibition using anakinra may be a promising adjuvant therapy for patients admitted to the hospital for severe or refractory gout flares.
- High CRP levels may point to the appropriateness of starting advanced anti-inflammatory treatment, such as anakinra, at an earlier stage to prevent complications of impaired mobility, prolonged hospitalization, and prolonged high inflammatory state.

the American College of Rheumatology and the Association for Rheumatology Health Professionals Annual Meeting found that a delayed diagnosis of gouty arthritis and female sex were associated with an increased LOS at their institution [4]. Similarly, Singh and Yu, who used United States (US) National Emergency Departments (ED) Sample data to search for gout admissions from EDs across the US, identified that older age, renal failure, heart failure, diabetes, or osteoarthritis were associated with a longer LOS [2].

Understanding the factors associated with increased LOS in patients hospitalized with acute gout flares can help to tailor individual treatment plans based on the presence or absence of both patient-related and gout flare-specific factors associated with an increased LOS. Current treatment options for an acute gout flare include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids (either systemic or through local injection), and interleukin-1 (IL-1) inhibitors.

IL1, an inflammatory cytokine, plays a key role in the inflammatory response associated with an acute gout flare [7]. Anakinra, an IL-1 receptor antagonist, has shown success in managing acute gout flares, serving both as an effective treatment option and as an alternative for patients with comorbidities, such as patients with diabetes or chronic kidney disease [8–18].

Pharmacologically, anakinra reaches its peak concentration within 3–7 h, and it demonstrates faster efficacy than other treatments, with significant reductions in pain typically observed by 48 h. In an analysis of 72 published cases with data on the timeframe to improvement, 41 (57% reported) reached significant improvement after 24 h, and 62 (86% reported) after 48 h [8–18]. Janssen et al. [15], in a randomized-controlled trial, showed that anakinra was noninferior to usual treatment with regard to reductions in mean pain scores on Days 2–4 of treatment during an acute gout flare, but by Day 3 there was a significant difference in favor of anakinra, with more patients achieving a $\geq 50\%$ decrease in mean pain scores (odds ratio [OR] 2.56; 95% confidence interval [CI], 1.03–6.37; $p = 0.04$).

The most common dosage of anakinra is 100 mg/day administered subcutaneously for 3–5 days, and at this dose, it appears to be as safe as other treatments used to manage acute gout flares. Janssen et al. [15] recorded 15 adverse events among 43 patients treated with anakinra, all of which were nonsevere, compared to 21 adverse events in 45 patients in patients who received conventional treatment (NSAIDs, corticosteroids, or colchicine). Furthermore, Thueringer et al. reported safely using anakinra to treat acute gout flares in critically ill patients with severe infections and included patients requiring renal replacement therapy [10].

Campbelltown Hospital is a major metropolitan hospital located in the Macarthur region of New South Wales, Australia, with a catchment of 324,000 people. As of February 2020, anakinra cost Campbelltown Hospital $53 per 100 mg syringe, compared to $0.22 per colchicine 500 μg tablet, $2.22 per vial of methylprednisolone acetate 40 mg for injection, $0.10 per prednisolone 25 mg tablet, and $0.05 per indometacin 25 mg capsule. In contrast, the approximate cost per night for a gout-related hospital admission was $1904. Therefore, while costs relative to other treatments may limit its use in the community, the evidence that anakinra may act faster at inducing remission would make its use in hospitalized patients favorable and cost-effective. Despite this, there is currently no published data on the effect it has on hospital LOS in patients with acute gout flares.

The purpose of this study was to audit the inpatient LOS and management of patients admitted to Campbelltown Hospital in 2019 with an acute gout flare as the primary reason for hospital admission. The study aimed to identify factors associated with an increased LOS at our institution to help guide clinical decisions regarding which patients may benefit from more intense therapy. The study also aimed to identify whether anakinra was an appropriate management option alongside conventional therapy for treatment of an acute gout flare in select hospitalized patients.

2 | Patients and Methods

The retrospective aspect of this audit was conducted at Campbelltown Hospital over a 12-month period, from January 2019 to December 2019. All patients admitted to the hospital for an acute gout attack were included in the study.

Eligible participants were identified through an International Classification of Diseases (ICD)-10 code search of discharge summaries using gout-specific codes where gout was the primary diagnosis for the admission. A retrospective review of the electronic and laboratory results was performed. Patients were excluded if they developed an acute gout flare while in hospital for another primary diagnosis. Patients were also excluded if they were admitted with complications of gout unrelated to an acute flare, including patients admitted with an infected tophus or joint and patients admitted for an elective gout-related surgical procedure such as tophi removal. If a patient had multiple admissions for acute gout flares, each admission was analyzed as a separate case. Patients who were classified as having two separations of admission but had not left hospital were counted as only one admission.

The length of hospital stay was calculated from date and time of admission to date and time of discharge, as recorded in the electronic medical record. The number of joints affected was

calculated based on the clinical description of joints involved and treated as a continuous variable. It was also categorized into monoarticular (one joint), oligoarticular (two to four joints), or polyarticular (five or more joints) flares. The presence of tophi, as described in the clinical notes, was also noted. Use of NSAIDs, colchicine, and systemic steroids, as well as intra-articular steroids, was recorded, as was the use of urate lowering therapy (ULT) prior to admission. Nursing documented pain scores, which are a subjective numerical rating from 0 to 10 (with 10 indicating the most severe pain), were recorded. Serum C-reactive Protein (CRP) and urate levels, and results of any arthrocentesis, were documented. Co-morbidities, including diabetes, ischaemic heart disease, heart failure, and chronic kidney disease, were also recorded.

Additional factors thought to have the potential to increase length of stay for reasons unrelated to the severity of the flare were also collected. Mobility assessments by physiotherapists or other allied health professionals were recorded, and patients were classified as having impaired mobility if it was documented that they were below their baseline level of mobility and required more time in hospital owing to this fact. If the patient was discharged prior to any allied health assessments, they were classified as having no mobility impairment. The presence of support people at home was also recorded, and patients were classified as either home alone or home with support (including those residing in aged care facilities).

Upon completion of the initial audit, a change to practice was made to include the use of anakinra as an add-on therapy in addition to conventional therapies in selected patients admitted to our facility with an acute gout flare in 2020 onward. It is important to note that not all patients admitted with a gout flare were given anakinra. The decision to use anakinra was made at the attending physicians' discretion. Reasons for using anakinra were based on the perceived severity of the flare and were influenced by the number of joints involved, inflammatory markers, and mobility impairment. Patients' comorbidities were also considered, as was failure to respond to usual treatments either during hospitalization or prior to admission. For the purposes of this audit, data collection included patients treated with anakinra through to April 2021. Anakinra was given subcutaneously at a daily dose of 100 mg. No routine screening for latent infections was performed prior to the use of anakinra. Similar data to the original audit was collected from these patients prospectively, as well as dates and number of doses of anakinra. To measure whether anakinra resulted in any difference in LOS, the senior rheumatologist in the department, who was responsible for inpatient care in both 2019 and 2020, was presented with deidentified data from the 2019 group. The rheumatologist was blinded to the actual LOS and asked which patients he would have chosen to treat with anakinra had it been available at the time, based on the patient characteristics including CRP levels, mobility impairments, and joint count.

All statistical analyses were performed using Minitab for Windows version 21.1.0. To assess factors associated with an increased LOS, Spearman's rank correlation coefficient (r_s) was used to assess for significant correlation using an initial univariable Poisson regression model (LOS data did fit the Poisson model ($p = 0.001$)). The level of significance (alpha) was set to 0.05. Subsequently, a multivariable Poisson regression model was created with all predictors that were significant or tended towards significance ($p < 0.15$), and backwards elimination was used to assess for significant factors associated with LOS. For the anakinra subgroup, further analysis was completed by combining both the pre-anakinra and anakinra cohorts and performing multivariable analysis using a Poisson regression model with anakinra included as a covariate. Missing data were replaced using mean substitution, which included 11 missing serum urate levels and 9 missing nursing documented pain scores. Student *t*-tests were used for continuous variables, and the chi-squared test was used for categorical variables.

This audit was undertaken as a quality improvement activity by employees of the organization, and approval from the Quality Manager of the facility was granted. A formal ethics review was not required.

3 | Results

Over the initial 12-month period of the 2019 audit, 75 individual acute hospital admissions for gout were identified. Nine episodes were excluded as they were not classified as gout flares, and four additional episodes were excluded as they were different separations of the same admission. This resulted in a final cohort of 62 separate hospital admissions for an acute gout flare as the primary diagnosis in 2019, with a mean LOS of 3.36 days (1.22–4.28) and a median of 2.40 days (Figure 1). Four patients (6%) were readmitted during the study period with recurrent gout flares.

The average age of patients was 67.45 years (95% CI, 63–72), and 76% of patients were male. 29% of patients were on ULT prior to admission (allopurinol in all cases), and 29% had documented presence of tophi, as represented in Table 1. 34% had diabetes, 48% had chronic kidney disease, 39% had a history of ischemic heart disease, and 23% had a history of heart failure. Twenty-nine percent were classified as having an acute mobility impairment during their admission, and the majority (77%) had support people at home.

The mean CRP level was 109.5 mg/L (95% CI, 86.8–132.3), and mean serum urate levels at admission with an acute flare of gout were 0.48 mmol/L (95% CI, 0.34–0.60), with 42% of patients having a urate level within the normal range. The mean number of joints involved was 2.6 (95% CI, 1.9–3.2), and the majority of flares were monoarthritis (52%), followed by oligoarthritis (27%) and polyarthritis (21%). The mean nursing-assessed pain score on the day of admission was 6.1 (95% CI, 5.3–6.9).

Twenty-nine patients underwent arthrocentesis during their admission, with 28 aspirates confirming the presence of MSU crystals. Despite this, only two patients received intra-articular steroid injections. A vast majority (79%) of patients received oral corticosteroids during their admission, whereas 37% received colchicine and 18% received NSAIDs.

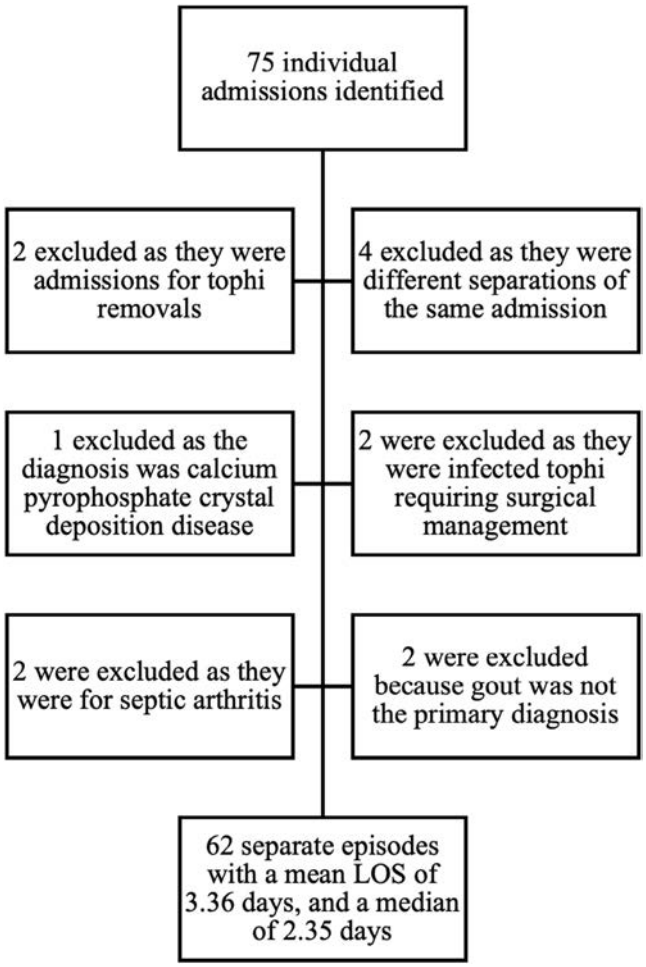

FIGURE 1 | Patient flowchart.

Among the 34 episodes without an aspirate confirming the presence of MSU crystal during their admission, 10 had previous aspirate results available on our electronic pathology records that confirmed MSU crystal deposition, and another 10 had the presence of tophi documented on clinical examination. This left 14 patients without laboratory or clinical confirmation of MSU deposition. Of these 14 patients, nine had elevated serum urate, and two were treated with allopurinol prior to admission. In total, 10 of these patients met the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Gout Classification Criteria [19] based on the available clinical information.

Univariable Poisson regression models were created to identify which variable could be significant predictors when compared with LOS. Higher joint counts (treated as a continuous variable, $r_s = 0.0762$ (95% CI: 0.04–0.11, $p < 0.0001$)), elevated CRP ($r_s = 0.005$ (95% CI: 0.004–0.006, $p < 0.0001$)) levels, impaired mobility ($r_s = 0.981$ (95% CI: 0.71–1.25, $p < 0.0001$)), presence of tophi ($r_s = 0.624$ (95% CI: 0.35–0.90, $p < 0.0001$)), allopurinol use prior to admission ($r_s = 0.523$ (95% CI: 0.25–0.80, $p < 0.0001$)), chronic kidney disease as a comorbidity ($r_s = 0.506$ (95% CI: 0.23–0.78, $p < 0.0001$)), known ischemic heart disease ($r_s = 0.32$ (95% CI: 0.05–0.59, $p = 0.02$)) and heart failure as a comorbidity ($r_s = 0.33$ (95% CI: 0.03–0.63, $p = 0.032$)) correlated with a longer LOS (Table 1). Subsequently, multivariable analysis was conducted including the above variables and other variables that approached significance (age and urate levels), and on backward elimination, three variables were found to be significant predictors including CRP ($r_s = 0.0036$ (95% CI: 0.0023–0.0050, $p < 0.0001$)), allopurinol use prior to admission ($r_s = 0.321$ (95% CI: 0.043–0.599, $p = 0.023$)), and impaired mobility ($r_s = 0.708$ (95% CI: 0.416–1.000, $p < 0.0001$)).

TABLE 1 | Analysis of correlation between variables and LOS for admissions for acute gout flares in 2019.

Characteristic	Descriptive statistics (count (percentage) or mean (95% confidence interval))	r_s	r_s 95% CI	p
Male	47 (76%)	−0.14	−0.45 to 0.17	0.37
Age	67.45 (63.39–71.52)	0.007	−0.002 to 0.015	0.138
Tophi	18 (29%)	0.624	0.35 to 0.90	**<0.0001**
CRP (mg/L)	109.5 (86.79–132.3)	0.005	0.004 to 0.006	**<0.0001**
Urate (mmol/L)	0.4810 (0.34–0.60)	0.831	−0.27 to 1.93	0.14
Allopurinol use prior to admission	18 (29%)	0.523	0.25 to 0.80	**<0.0001**
Mobility impaired	18 (29%)	0.981	0.71 to 1.25	**<0.0001**
Diabetes	21 (34%)	0.056	−0.23 to 0.34	0.70
CKD	29 (48%)	0.506	0.23 to 0.78	**<0.0001**
IHD	24 (39%)	0.32	0.05 to 0.59	**0.02**
Heart failure	14 (23%)	0.33	0.03 to 0.63	**0.032**
Presence of support at home	48 (77%)	0.057	−0.26 to 0.38	0.73
Pain score on day of admission	6.1 (5.3–6.9)	−0.013	−0.06 to 0.03	0.552
Joint count	2.5 (1.9–3.2)	0.0762	0.04 to 0.11	**<0.0001**

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; IHD, ischemic heart disease.

TABLE 2 | Baseline characteristics between anakinra group and control group.

Characteristic	Anakinra group ($n=7$, count (percentage); mean (95% confidence interval))	Control group ($n=13$, count (percentage); mean (95% confidence interval))	p
Male	7 (100%)	12 (92%)	0.25
Age	53.14 (39.08–67.2)	66.54 (57.03–76.05)	0.08
Tophi	4 (57%)	9 (69%)	0.59
CRP (mg/L)	159.8 (72.32–247.2)	205.3 (148.0–262.5)	0.32
Urate (mmol/L)	0.48 (0.37–0.58)	0.46 (0.39–0.53)	0.77
Allopurinol use prior to admission	4 (57%)	7 (54%)	0.89
Mobility impaired	6 (86%)	7 (54%)	0.15
Diabetes	1 (14%)	4 (31%)	0.41
CKD	2 (29%)	8 (62%)	0.16
IHD	1 (14%)	6 (46%)	0.15
Heart failure	2 (29%)	2 (15%)	0.48
Presence of support at home	5 (71%)	9 (69%)	0.92
Pain score on day of admission	6.3 (2.1–10)	5.4 (3.5–7.5)	0.62
Joint count (continuous variable)	20.1 (3.6–36.7)	6.5 (4.7–8.2)	0.01
Joint count (categorical variable)	Monoarthritis: 0 (0%) Oligoarthritis: 1 (14%) Polyarthritis: 6 (86%)	Monoarthritis: 0 (0%) Oligoarthritis: 2 (15%) Polyarthritis: 11 (85%)	0.95

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; IHD, ischemic heart disease.

Between January 2020 and April 2021, seven patients were treated with anakinra whilst admitted to the study site with an acute gout flare as the primary reason for hospital admission. Three patients received 3 days and four received 4 days of anakinra 100 mg daily by subcutaneous injection. The mean LOS for these patients was 5.0 days, with a mean LOS of 3.2 days calculated from the first dose of anakinra. Thirteen patients from the 2019 cohort were retrospectively selected by the senior rheumatologist as individuals they would have treated with anakinra for their acute gout flare had it been available at the time—functioning as our historical control group (Table 2). Baseline characteristics between the two groups were similar. However, the joint count, when treated as a continuous variable, was significantly higher in the anakinra group, with a mean joint count of 20.14 compared to 6.46 in the control group. When joint counts were categorized as mono-, oligo-, or polyarthritis, the results were similar (Table 2), with the majority of patients admitted having five or more joints involved. Treatment with conventional medications was also similar between the two groups (Table 3).

TABLE 3 | Conventional treatments per group.

Treatment during admission	Anakinra group ($n=7$)	Control group ($n=13$)	p
NSAIDs	2 (29%)	1 (8%)	0.21
Colchicine	3 (43%)	2 (15%)	0.18
Systemic corticosteroids	5 (71%)	13 (100%)	0.11
Intra-articular corticosteroids	1 (14%)	1 (8%)	0.64

Abbreviation: NSAIDs, nonsteroidal anti-inflammatories.

The mean LOS for patients receiving anakinra was 5 days, compared to 6.3 in the control group, which did not reach significance ($p=0.27$) (Figure 2). When the mean LOS was analyzed from the time of the first dose of anakinra to the time of discharge, a mean LOS of 3.2 days was observed compared to 6.3 days in the control group ($p=0.076$) (Figure 3). A further multivariable regression model was created using the combined populations (anakinra and historical control groups) with the anakinra group used as a covariate, which found that there was a 0.662-day difference between the cohorts ($p=0.005$), in addition to a 0.3543 day increase in length of stay for both cohorts for every 100-point increase in CRP levels ($p=0.001$). If a patient had the same CRP level in both cohorts (CRP treated as a controlled variable), there was noted to be a reduction in LOS of 0.493 days (95% CI 0.016–0.969, $p=0.043$) with $R^2=0.32$, meaning that this regression model would be significant for 32% of the population described.

No adverse events were noted in patients receiving anakinra, with no injection site reactions or infections documented. One

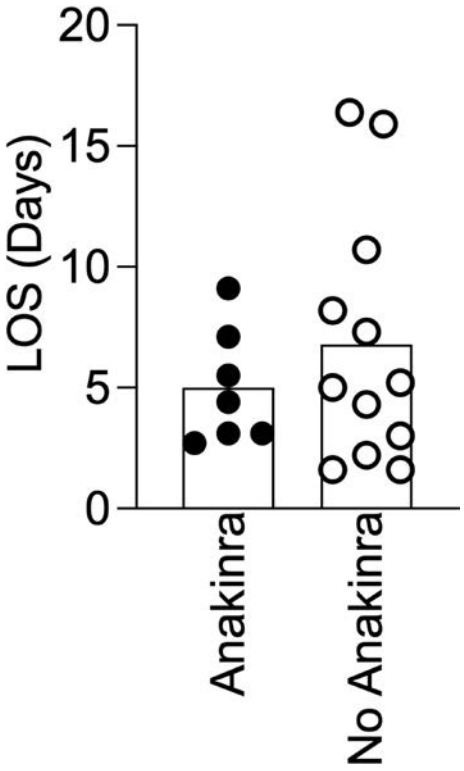

FIGURE 2 | Length of stay (LOS) for anakinra vs. control group (column graph refers to group mean). ●, Data point for patients who received anakinra. ○, Data point for historical control patients who did not receive anakinra. Height of the column graph refers to mean LOS of that particular group.

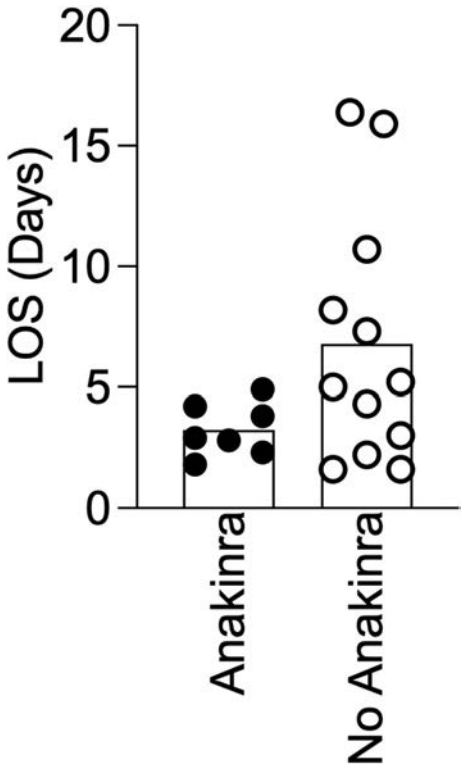

FIGURE 3 | Length of stay (LOS) from time of first anakinra dose vs. control group (column graph refers to group mean). ●, Data point for patients who received anakinra. ○, Data point for historical control patients who did not receive anakinra. Height of the column graph refers to the mean LOS of that particular group.

patient (14%) was readmitted with a relapse of his gout flare 3 weeks after discharge in the anakinra group, compared to one patient out of 13 in the control group.

4 | Discussion

This audit establishes that acute gout flares are an important cause of hospital admission in the Macarthur region, New South Wales, Australia, with 62 inpatient admissions for an acute gout flare as the primary reason for admission in 2019, comparable to published rates Australia-wide and in other regions [1, 20]. These findings highlight that gout imposes a substantial burden on both our hospital and the wider community, particularly as there is a proportionately larger population of high-risk gout ethnicities living in the multiculturally diverse region, such as New Zealand Māori and Pacific Islander ethnic groups.

The patient demographics in our cohort were similar to that of other published studies, with males being disproportionately affected, patients being of an older age, and frequently having comorbidities such as diabetes, heart failure, renal impairment, and ischaemic heart disease [1, 2, 20].

In analyzing factors associated with a longer LOS for an acute gout flare requiring hospital admission, we found higher CRP levels, allopurinol use prior to admission, and impaired mobility to be associated with longer LOS. This is in contrast to the findings of Sharim et al. [4], who observed that in a hospital inpatient population, a later diagnosis of gouty arthritis and female sex were associated with an increased LOS in their study conducted at a single center. Similarly, our results differed from those reported by Singh et al. [2], whose study focused on reasons for emergency department (ED) visits and included other critical patient and hospital characteristics such as age, sex, insurance status, location, and comorbidities. Singh et al. found that older age and the presence of renal failure, heart failure, diabetes, or osteoarthritis were associated with longer LOS. Our finding of higher CRP levels correlating with a longer LOS suggests that CRP serves as an important objective marker of disease severity during acute gout flares. This aligns with the findings from Janssen et al. [6], who reported that CRP levels exceeding 30 mg/L were associated with increased risk of a recurrence of gout flare in the first 3 months of starting ULT during an acute flare. Impaired mobility, unsurprisingly, was associated with a longer LOS, as it limits people's ability to function independently at home and in the community. This is particularly relevant for older patients, who are becoming more frequently admitted with acute gout flares. In this context, the effects of a gout flare on mobility appear to reflect the broader impact that the flare has on a patient's functioning, rather than a direct marker of disease severity. In addition to this, patients on ULT prior to admission tended to have a longer length of stay. This contrasts with data from Jatuworapruk's cohort study [21] ($n = 36\,047$), where they observed a 10% reduction in LOS with patients on ULT prior to admission.

In the analysis of LOS among patients treated with anakinra, there were no significant differences observed between patients

who received anakinra compared to the control group who would have been considered for anakinra therapy had it been available, apart from the joint count when taken as a continuous variable. When joint count was taken as a categorical variable, there was no observed difference between groups with most patients with polyarticular disease, demonstrating the loss of data clarity when clustered. Hence, this makes it an insignificant variable, noting that in the initial retrospective cohort analysis, joint count, when taken as a continuous variable, did not have a significant correlation with LOS regardless. The control group exhibited higher CRP levels, whilst the anakinra group had higher rates of impaired mobility, neither of which reached statistical significance. Patients in the anakinra group who were on ULT prior to admission tended to have a lower mean LOS compared to those in the control group who were not (5.25 (3.78–6.72) and 7.41 (4.18–10.64) days, respectively), but this difference is not statistically significant ($p = 0.449$).

Despite the use of anakinra in selected patients, no differences in the use of conventional treatments were observed between groups. While there was a reduction in mean LOS in patients who received anakinra in comparison to the control group (5.0 and 6.3 days respectively), this did not reach statistical significance. However, when the control group was compared to LOS analyzed from the time of the first dose of anakinra to the time of discharge (6.3 and 3.2, respectively), this approached statistical significance ($p = 0.076$). This 1.8-day difference may be attributable to the delay in commencing anakinra due to permission being required on each occasion for usage, and hence there would be a potentially clearer advantage if started earlier rather than waiting for an inadequate response to oral corticosteroids. However, on further multivariable analysis with the creation of a Poisson regression model, it was shown that there is a reduction in LOS of 0.493 days in the anakinra cohort ($p = 0.043$) if the only significant covariant, CRP, was taken as a controlled variable. In addition to this, as CRP was a significant variable, it was shown that for every 100-point increase in CRP levels, LOS increased by 0.3543 days, making it an important variable to note when patients are admitted to the hospital. If CRP was not taken as a controlled variable, there would be a 0.662-day difference in LOS. This would represent a cost saving of AUD $1048 per patient in 2019, and annual savings of AUD $64 976, based on the admission rate of 62 patients from our 2019 data, which considers the added cost of anakinra to the hospital. If this finding could be attributed to Australia as a whole, there would be a potential cost saving of AUD $7 440 800 based on the 2022 Australian Institute of Health and Welfare's reported 7100 gout hospitalizations in a year [22].

Anakinra appeared safe to use in our cohort, with no adverse events noted. Overall, readmissions were relatively common, with four readmissions (6.5%) from 62 admissions in 2019, which is in keeping with the 7.8% readmission rate that Kennedy et al. [20] found in their audit. There was one readmission 3 weeks following discharge in a patient treated with anakinra; however, it is important to note that this patient had a history of difficult-to-control gout. There was no significant difference in the rates of readmission between groups.

The strengths of our project are that it is the first Australian study to examine factors associated with an increased LOS, and the first to analyze the impact of anakinra on LOS. However, several limitations should be noted. The retrospective nature of the study introduces potential bias, particularly in regard to the retrospective clinical decisions for inclusion into the historical control group. Additionally, a major limitation of this study was its small sample size, which limits the applicability of this study to larger populations. If the applicable population proportion was set to 32% given $R^2 = 0.32$ of the final Poisson regression model, the minimum sample size would have to be $n = 53$ to apply to the Campbelltown Hospital area, and $n = 335$ for global application of the analyzed data [23]. Several patients were already on treatment prior to commencing anakinra, and the timing of anakinra varied during admissions, which may have affected the LOS data.

Gout represents a significant burden on the community and hospitals, and finding ways to improve the management of acute flares is justified. We found higher CRP levels, prior use of ULT, and impaired mobility to be associated with an increased LOS during hospitalization for an acute gout flare. Although the reduction in LOS observed in this study did not achieve statistical significance, the results suggest its potential economic and therapeutic utility. If validated, these findings could support the integration of anakinra as an effective adjunctive treatment, particularly in those with the highest cost savings potential, for example, patients with tophi, polyarticular gout, and mobility impairment. Clinical markers such as CRP and impaired mobility could be used to identify candidates for anakinra use. Future research should focus on larger, multicenter randomized-controlled trials to confirm these findings and establish standardized treatment protocols. Additionally, such studies could also explore the optimal timing and duration of anakinra administration to maximize its clinical benefits. Future studies could investigate the long-term outcomes of patients treated with anakinra through flare recurrence rates, as well as long-term safety in diverse patient groups, including those with significant comorbidities.

Author Contributions

Hansaja Weerawardena: further data and cost analysis, writing of the manuscript, background research, editing and liasing with authors. **Cameron Louis Adams:** study design, collecting of data, initial data analysis, drafting of manuscript. **Narainraj Kamalaraj:** study design, editing, providing feedback. **Kevin Pile:** study design, editing, providing feedback.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Deidentified data that support the findings of this study are available from the corresponding author, [H.W.], upon reasonable request.

References

1. P. C. Robinson, S. Kempe, I. Tebbutt, and L. Roberts, “Epidemiology of Inpatient Gout in Australia and New Zealand: Temporal Trends,

Comorbidities and Gout Flare Site," *International Journal of Rheumatic Diseases* 20, no. 6 (2017): 779–784.

2. J. A. Singh and S. Yu, "Gout-Related Inpatient Utilization: A Study of Predictors of Outcomes and Time Trends," *Arthritis Research & Therapy* 18, no. 1 (2016): 57–66.

3. M. I. Dehlin, V. Sigurdardottir, P. Drivelegka, A. Svard, and L. T. Jacobsson, "Trends and Costs for Gout Hospitalization in Sweden," *Annals of the Rheumatic Diseases* 76, no. S2 (2017): 164.

4. R. Sharim, M. Musselman, and M. Blum, "Factors Associated With a Prolonged Hospital Length of Stay for Patients With Acute Gout," *Arthritis & Rheumatism* 64, no. 10 (2012): S722.

5. K. Jatuworapruk, R. Grainger, N. Dalbeth, and W. J. Taylor, "Development of a Prediction Model for Inpatient Gout Flares in People With Comorbid Gout," *Annals of the Rheumatic Diseases* 79, no. 3 (2020): 418–423.

6. C. A. Janssen, M. A. H. Oude Voshaar, P. M. Ten Klooster, H. E. Vonkeman, and M. A. F. J. Van de Laar, "Prognostic Factors Associated With Early Gout Flare Recurrence in Patients Initiating Urate-Lowering Therapy During an Acute Gout Flare," *Clinical Rheumatology* 38, no. 8 (2019): 2233–2239.

7. A. So, A. Dumusc, and S. Nasi, "The Role of IL-1 in Gout: From Bench to Bedside," *Rheumatology (Oxford, England)* 57, no. 1 (2018): 12–19.

8. J. Van Wabeke, E. Dhondt, I. Peene, and Y. Piette, "Anakinra in Resistant Gout: A Case Report," *Acta Clinica Belgica* 72, no. 4 (2017): 293–295.

9. A. So, T. de Smedt, S. Revaz, and J. Tschopp, "A Pilot Study of IL-1 Inhibition by Anakinra in Acute Gout," *Arthritis Research & Therapy* 9, no. 2 (2007): R28.

10. J. T. Thueringer, N. K. Doll, and E. Gertner, "Anakinra for the Treatment of Acute Severe Gout in Critically Ill Patients," *Seminars in Arthritis and Rheumatism* 45, no. 1 (2015): 81–85.

11. S. E. Petite, "Effectiveness of Anakinra in Acute Gout: A Retrospective Review of Initial and Refractory Therapy," *American Journal of Therapeutics* 24, no. 5 (2017): e592–e596.

12. P. Ghosh, M. Cho, G. Rawat, P. A. Simkin, and G. C. Gardner, "Treatment of Acute Gouty Arthritis in Complex Hospitalized Patients With Anakinra," *Arthritis Care and Research* 65, no. 8 (2013): 1381–1384.

13. D. McGonagle, A. L. Tan, S. Shankaranarayana, J. Madden, P. Emery, and M. F. McDermott, "Management of Treatment-Resistant Inflammation of Acute on Chronic Tophaceous Gout With Anakinra," *Annals of the Rheumatic Diseases* 66, no. 12 (2007): 1683–1685.

14. C. Loustau, N. Rosine, M. Forien, et al., "Effectiveness and Safety of Anakinra in Gout Patients With Stage 4–5 Chronic Kidney Disease or Kidney Transplantation: A Multicenter, Retrospective Study," *Joint, Bone, Spine* 85, no. 6 (2018): 755–760.

15. C. A. Janssen, M. A. H. Oude Voshaar, H. E. Vonkeman, et al., "Anakinra for the Treatment of Acute Gout Flares: A Randomized, Double-Blind, Placebo-Controlled, Active-Comparator, Non-Inferiority Trial," *Rheumatology* 58, no. 8 (2019): 1344–1352.

16. S. Ottaviani, A. Moltó, H. K. Ea, et al., "Efficacy of Anakinra in Gouty Arthritis: A Retrospective Study of 40 Cases," *Arthritis Research & Therapy* 15, no. 4 (2013): R123.

17. K. Chen, T. Fields, C. A. Mancuso, A. R. Bass, and L. Vasanth, "Anakinra's Efficacy Is Variable in Refractory Gout: Report of Ten Cases," *Seminars in Arthritis and Rheumatism* 40, no. 3 (2010): 210–214.

18. J. Desmarais and C. Q. Chu, "Utility of Anakinra in Acute Crystalline Diseases: A Retrospective Study Comparing a University Hospital With a Veterans Affairs Medical Center," *Journal of Rheumatology* 46, no. 7 (2019): 748–750.

19. T. Neogi, T. L. Jansen, N. Dalbeth, et al., "2015 Gout Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative," *Arthritis and Rheumatology* 67, no. 10 (2015): 2557–2568.

20. N. J. Kennedy, P. J. Healy, and A. A. Harrison, "Inpatient Management of Gout in a New Zealand Hospital: A Retrospective Audit," *International Journal of Rheumatic Diseases* 19, no. 2 (2016): 205–210.

21. K. Jatuworapruk, R. Grainger, N. Dalbeth, and W. J. Taylor, "Regular Pre-Admission Urate-Lowering Therapy and Serum Urate Testing Are Associated With a Shorter Hospital Length of Stay in People With Gout: A Nation-Wide Population-Based Cohort Study," *International Journal of Rheumatic Diseases* 25, no. 2 (2021): 154–162.

22. Australian Institute of Health and Welfare, *Gout – National Hospital Morbidity Database* (Australian Institute of Health and Welfare, 2022).

23. Australian Bureau of Statistics, *Sample Size Calculator* (Australian Bureau of Statistics), Abs.gov.au, 2024.

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LETTER TO THE EDITOR

Cases Report: Spontaneous Intramuscular Hemorrhage in Anti-MDA5 Positive Dermatomyositis

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Dear Editor,

Anti-melanoma differentiation-associated gene 5 (anti-MDA5)-positive Dermatomyositis (DM) is a relatively rare subtype of idiopathic inflammatory myopathies, distinguished by clinically amyopathic dermatomyositis, cutaneous manifestations such as skin ulcers and palmar papules, and rapidly progressive interstitial lung disease (RP-ILD) [1]. Spontaneous intramuscular hemorrhage (SIH) is one of the rare complications of DM and carries an extremely high risk of mortality [2]. It involves non-traumatic muscle bleeding or hematoma formation, potentially leading to disseminated intravascular coagulation and even hemorrhagic shock.

A 60-year-old female patient was admitted to our center, presenting with 20 days of exertional dyspnea, productive cough, and low-grade fever with a maximum temperature of 37.8°C. Physical examination revealed notable features such as mechanic's hands and velcro rales upon chest auscultation. Laboratory tests indicated elevated erythrocyte sedimentation rate (ESR at 45 mm/H; upper limit of normal [ULN]: 20 mm/H), C-reactive protein (8.65 mg/L; ULN: 3.14 mg/L), and ferritin (623.42 ng/mL; ULN: 336 ng/mL). Creatine kinase, platelet count, and coagulation tests were within normal limits. Antinuclear antibody and MDA5-IgG were strongly positive. Pulmonary high-resolution computed tomography (HRCT) revealed multiple ground-glass opacities and consolidation in bilateral lung lobes (as shown in Figure 1). The partial pressure of oxygen in arterial blood gas analysis (PaO2) was 62.5 mmHg on room air.

She was subsequently diagnosed with anti-MDA5 positive DM complicated by ILD. Due to the active nature of the disease, immunosuppressive treatment was initiated, including intravenous methylprednisolone at 80 mg per day. However, 7 days after admission, she experienced a sudden increase in dyspnea, with PaO2 at 60.7 mmHg while receiving oxygen at 5 L/min. HRCT revealed multiple ground-glass opacities and consolidations without any further aggravation. Computed tomographic angiography of the pulmonary and coronary arteries showed no signs of pulmonary embolism or myocardial infarction. Considering the ongoing disease activity, the immunosuppressive regimen was adjusted to include intravenous methylprednisolone (80 mg twice daily), oral tofacitinib sustained-release tablets (11 mg per day), and intravenous immunoglobulin (20 g per day for 5 days). Prophylactic anticoagulant therapy with low molecular weight heparin (6000 IU every 12 h) was initiated due to an elevation in troponin I levels to 0.92 ng/mL one week later.

Thirteen days after admission, she suddenly experienced pain without any trauma, localized to the right elbow and the left upper abdominal region. Ultrasound examination revealed mixed echoes within the muscles of the right elbow and the upper left abdomen, measuring 2.7 × 0.9 cm and 5.4 × 2.3 cm, respectively. A CT scan identified a new-onset hematoma in the left rectus abdominis muscle, as shown in Figure 1. Coagulation tests indicated a significant prolongation of thrombin time (TT at 32.6 s; ULN: 14–21 s). Consequently, low-molecular-weight heparin was discontinued, and the patient received an infusion of 400 mL of plasma and a total of 10 units of cryoprecipitate. The tofacitinib was switched to upadacitinib, one tablet per day. Immunosuppressants, including tacrolimus at 1 mg twice daily and cyclophosphamide at 0.4 g administered twice with a one-week interval, were added. The steroid dosage was gradually reduced to 12 tablets administered orally once a day. During this period, four coagulation parameters were monitored (detailed in Table 1, assessed on the second and tenth days post-hemorrhage), and fibrinogen declined to 1.19 g/L (ULN: 1.93–4.19 g/L), hyperfibrinolysis was considered, and 1.5 g of fibrinogen was transfused

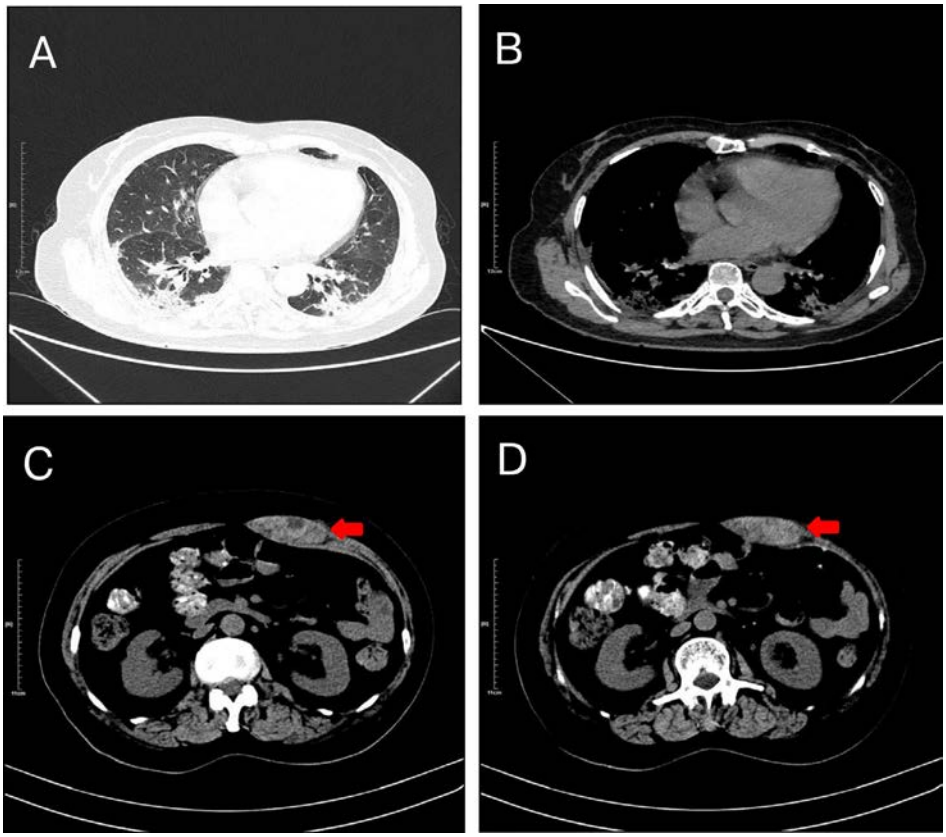

FIGURE 1 | (A, B) Pulmonary high-resolution computed tomography (HRCT) revealed interstitial lung disease characterized by inflammation in both lungs. (C, D) An abdominal CT scan revealed a new-onset hematoma in the left rectus abdominis muscle.

TABLE 1 | The four coagulation function parameters were assessed on the second and tenth days following the onset of the intramuscular hemorrhage.

The coagulation parameters	The second day	The tenth day	Reference range
TAT	7.3	4.2	
TM	10.2	9.8	3.8–13.3Tu/mL
PIC	0.949	0.917	< 0.8ug/mL
t-PAic	17.0	17.5	Male < 17 ng/mL Female < 10.5 ng/mL

accordingly. Subsequently, the bleeding gradually resolved, and no further hemorrhages occurred (the key process in the form of a timeline in Figure 2). She successfully recovered and was discharged after a brief rehabilitation period. She continues to be followed at our center with stable disease.

SIH is a rare but potentially fatal complication of DM, associated with a notably high mortality rate. In a study by Döndü Üsküdar Cansu, only 1 out of 42 DM patients (2.4%) developed SIH [3]. Meanwhile, Zhangling Xu's study reported an SIH incidence rate of 1% [4]. The overall mortality in these studies ranged from 50% to 60.9%. It is well established that SIH affects not only the limb girdle muscles but also the non-palpable deep muscles, such as the abdominal and pelvic muscles [5]. Superficial muscles are more commonly involved; however, patients with hematomas in deep muscles exhibit a higher mortality rate [6].

The detection of myositis-specific antibodies (MSAs) is crucial for the diagnosis, categorization, and prognostication of DM. Among DM patients with SIH, the presence of anti-MDA5 antibodies is commonly associated with a distinct subset characterized by significant cutaneous and pulmonary involvement. Other MSAs, such as JO-1, Mi2, TIF1, and NXP-2, have also been detected in individual patients [4–6].

SIH can occur with either thrombocytopenia or normal platelet counts, as well as with normal coagulation function. In our case, the platelet count was normal, but TT was prolonged and fibrinogen (Fbg) levels decreased, indicating abnormal coagulation function. We evaluated four coagulation parameters; our analysis (refer to Table 1) indicated that a decline in TAT reduced thrombosis risk. However, the persistent increase in PIC and concurrent decrease in fibrinogen suggested that continuous hyperfibrinolysis was the primary issue, with an elevated risk of bleeding [7, 8]. Consequently, fibrinogen infusion therapy was administered, leading to better control of bleeding and normalization of coagulation. The t-PAIC may relate to vascular endothelial injury, and hyperfibrinolysis might be linked to endothelial damage from the primary disease activity [9, 10]. The pathogenesis of SIH in anti-MDA5 positive DM may involve vascular damage, highlighting the potential of monitoring these four coagulation parameters to assess vascular endothelial injury and guide anticoagulant therapy timing.

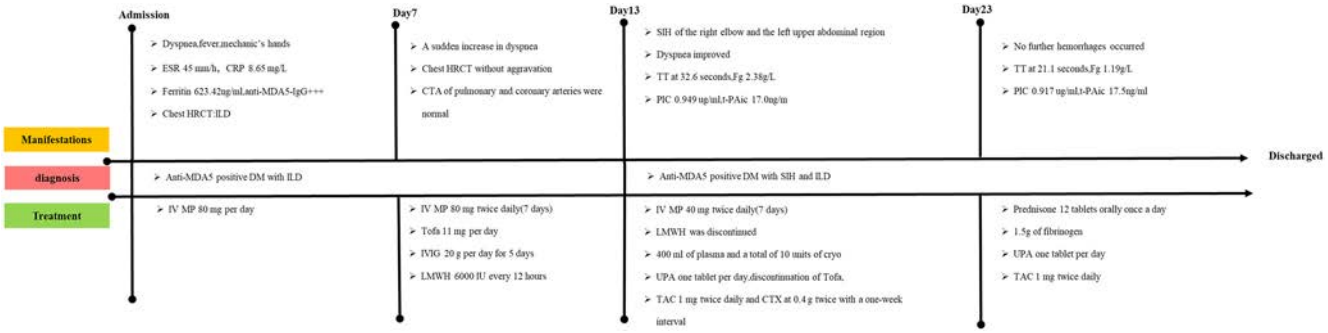

FIGURE 2 | The key diagnostic and therapeutic process in the form of a timeline. Cryo, cryoprecipitate; CTX, cyclophosphamid; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LMWH, low-molecular-weight heparin; TAC, tacrolimus; Tofa, tofacitinib; UPA, upadacitinib.

Glucocorticoids are the first-line drugs for treating DM. Intravenous immunoglobulin is also considered one of the most effective treatments available for DM. Research indicates that JAK/STAT inhibitors can be used to treat DM, showing benefits in improving rash and ILD, as well as reducing mortality rates [11]. Early diagnosis and standardized treatment are crucial. There is an urgent need for larger-scale prospective studies to thoroughly describe the disease's characteristics and identify effective treatment methods.

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 from the corresponding author upon reasonable request.

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References

1. X. Lu, Q. Peng, and G. Wan, "Anti-MDA5 Antibody-Positive Dermatomyositis: Pathogenesis and Clinical Progress," *Nature Reviews Rheumatology* 20, no. 1 (2024): 48–62.

2. J. M. Yang and B. Yan, "Rare Complications of Anti-Melanoma Differentiation—Associated Gene 5 Antibody-Positive Dermatomyositis: Time to Nip Them in the Bud," *Frontiers in Immunology* 13 (2022): 1009546.

3. D. Ü. Cansu, R. Yildirim, B. C. Uludoğan, M. Bilgin, and C. Korkmaz, "Evaluation of the Frequency and Risk Factors of Spontaneous Intramuscular Hemorrhage Associated With Dermatomyositis," *Rheumatology International* 44, no. 7 (2024): 1327–1335.

4. Z. Xu, X. Lv, W. Xu, et al., "Spontaneous Intramuscular Hemorrhage in Anti-MDA5 Positive Dermatomyositis: A Case Series and Literature Review," *Frontiers in Medicine* 8 (2022): 802753.

5. T. Fukumoto, S. Fujiwara, M. Sakaguchi, M. Oka, and C. Nishigori, "A Case of Malignant Melanoma With Multiple Metastases After Switching From Interferon-Beta to Pegylated Interferon-Alpha-2b as Adjuvant Therapy," *European Journal of Dermatology* 28, no. 1 (2018): 115–116.

6. M. Bartl, J. G. G. Casanovas, C. E. Loftis, et al., "A Case of Hemorrhagic Myositis Associated With Prophylactic Heparin Use in Dermatomyositis," *Cureus* 15, no. 5 (2023): e39540.

7. Y. Ji, Y. Qin, Q. Tan, Y. Qiu, S. Han, and X. Qi, "Development of a Chemiluminescence Assay for Tissue Plasminogen Activator Inhibitor Complex and Its Applicability to Gastric Cancer," *BMC Biotechnology* 24 (2024): 30.

8. K. Huang, Q. Mo, C. Liao, et al., "The Clinical Significance of TAT, PIC, TM, and t-PAIC in Vascular Events of BCR/ABL-Negative Myeloproliferative Neoplasms," *Clinical and Experimental Medicine* 24, no. 1 (2024): 107.

9. D. Lemmer, J. Schmidt, K. Kummer, et al., "Impairment of Muscular Endothelial Cell Regeneration in Dermatomyositis," *Frontiers in Neurology* 13 (2022): 952699.

10. A. Nombel, N. Fabien, and F. Coutant, "Dermatomyositis With Anti-MDA5 Antibodies: Bioclinical Features, Pathogenesis and Emerging Therapies," *Frontiers in Immunology* 12 (2021): 773352.

11. W. L. Wu, B. P. Guo, W. J. Sun, et al., "Effectiveness and Safety of Tofacitinibversuscalcineurin Inhibitor in Interstitial Lung Disease Secondary to Anti-MDA5-Positive Dermatomyositis: A Multi-Centre Cohort Study," *European Respiratory Journal* 65 (2025): 2401488.