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LETTER TO THE EDITOR

Case Report: Severe Immune-Related Adverse Event Under Pembrolizumab Therapy for Discoid Lupus Erythematosus-Related Squamous Cell Carcinoma

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Dear Editor,

Discoid lupus erythematosus (DLE) is an autoimmune condition and the most common subtype of chronic cutaneous lupus erythematosus, accounting for 50%–85% of cases [1]. DLE can be an individual disease only involving skin or present as part of the manifestations of systemic lupus erythematosus (SLE). DLE occurs as a localized form (80%) with lesions on the face, ears, and scalp or as a disseminated form (20%) with lesions above and below the neck [2]. In a small proportion of cases, DLE can progress to squamous cell carcinoma (SCC). It is generally accepted

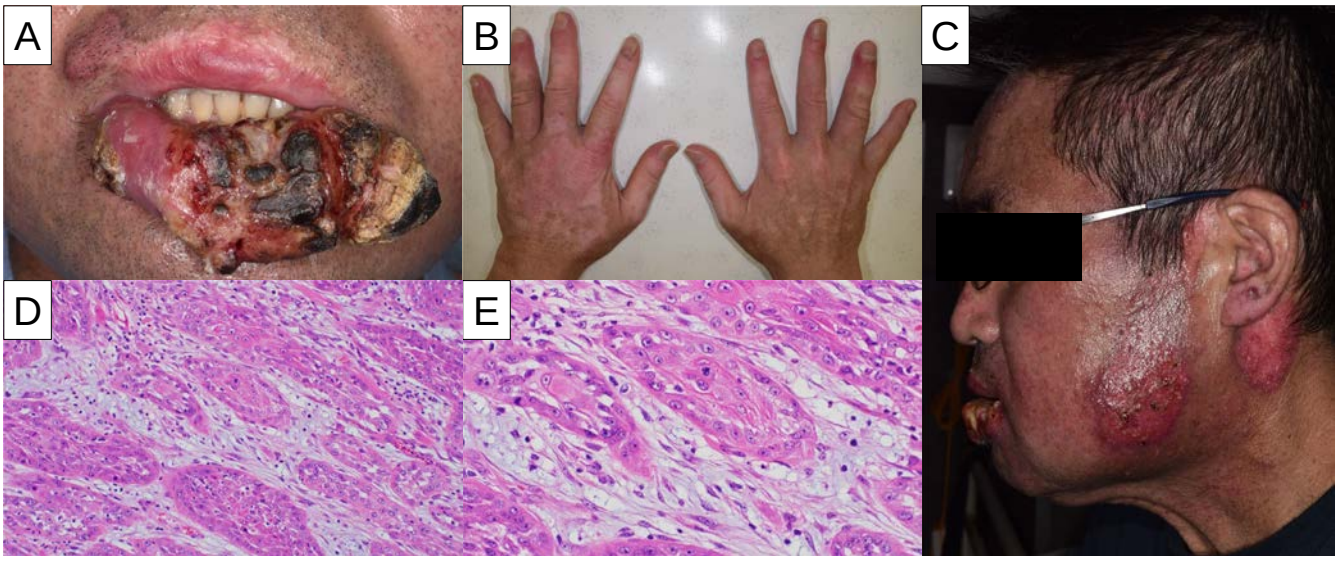

FIGURE 1 | Clinical pictures of the patient. Multiple papillomatous nodules on the lower lip (A). The erythematous scaly plaques on the dorsum of the hands (B) and on the face (C). Hematoxylin and eosin staining of the lower lip tumor biopsy. This histopathological picture demonstrated that tumor cells had round nuclei with coarse nuclear chromatin and distinct nucleoli, and eosinophilic cytoplasm with keratinization. The tumor cells proliferated in papillary to nested fashion, indicating a pathological diagnosis of squamous cell carcinoma (SCC) (D: ×200, E: ×400).

that inflammation has an important role in carcinogenesis, and consistent local inflammatory stimuli and the resulting chronic scarring seen in DLE can be contributory for the increased risk for SCC [3].

In recent years, advanced SCC has been increasingly treated with immune checkpoint inhibitors (ICIs). Immune-related adverse events (irAEs) are a range of complications associated with the use of ICIs. The risk of irAEs seems to be increased in patients with preexisting autoimmune diseases [4, 5]. Cytotoxic T lymphocyte-associated antigen 4 and programmed cell death protein 1 (PD-1) are molecules that play a crucial role in autoantigen tolerance. By inhibiting these molecules, ICIs can enhance not only anticancer immunity but also autoimmune responses, potentially exacerbating preexisting conditions or inducing new autoimmune diseases. Studies have shown that ICIs are equally effective in patients with autoimmune diseases but need close monitoring for flare-ups [6, 7]. Here, we report a case of DLE-related SCC who developed a severe irAE after introduction of pembrolizumab, an anti-PD-1 monoclonal antibody.

A 50-year-old man presented with a nine-month history of multiple lower lip papillomatous nodules (Figure 1A). He had a 25-year history of SLE. At the onset of SLE, he had erythema multiforme, polyarthritis, and recurrent lupus meningitis with positive serum antinuclear and anti-RNP antibodies, and remission was induced by high-dose prednisolone (60 mg/day). For the last 15 years, polyarthritis and meningitis had been well-controlled by maintenance therapy with prednisolone 12–13 mg/day and azathioprine 100 mg/day. However, he had refractory DLE on the dorsum of his hands and face, including his lip (Figure 1B,C). Addition of hydroxychloroquine was ineffective, and reduction of glucocorticoids was difficult. Serum anti-dsDNA antibody tests were negative and hypocomplementemia was not found in the clinical course.

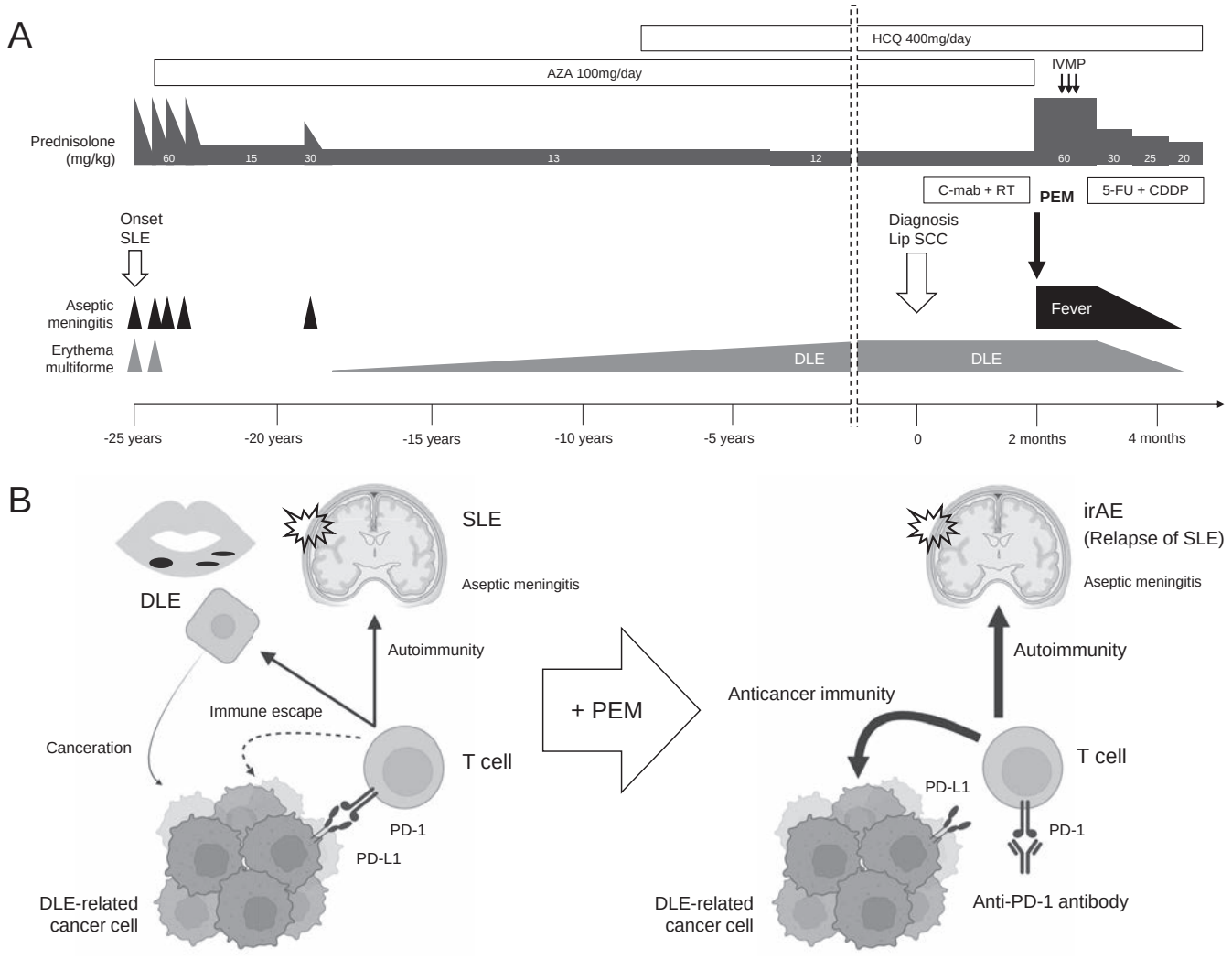

FIGURE 2 | Clinical course and suggested pathophysiology of the patient. A schema showing the clinical course of this patient (A). An illustration explaining a possible pathophysiological mechanism about the development of severe immune-related adverse event (irAE) in this patient (B). 5-FU, 5-fluorouracil; AZA, azathioprine; CDDP, cisplatin; C-mab, cetuximab; HCQ, hydroxychloroquine; IVMP, intravenous methylprednisolone pulse; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1-ligand 1; PEM, pembrolizumab; RT, radiation therapy.

During those 9 months, he underwent cryotherapy, but the lip lesions did not improve. Due to the uncertain nature, a biopsy of the lesion was performed to differentiate between benign and malignant processes. The histological examination revealed SCC (Figure 1D,E). The lip SCC was staged as T2N2M0 due to lymph node metastasis to the left submandibular region. He was treated with cetuximab, an anti-epidermal growth factor receptor monoclonal antibody, and radiation therapy, but the computed tomography scan 1 month after the treatment showed multiple lung and liver metastases. Cetuximab was withdrawn after five courses of administration over 1 month because of the progressive disease. Pembrolizumab was indicated for metastatic SCC. After the first dose of pembrolizumab 200 mg, he developed a fever of 38°C–40°C and elevated serum CRP levels around 10 mg/dL. Serum anti-dsDNA antibody test remained negative, and complement titers were unchanged. The active DLE was persistent both before and after the initiation of pembrolizumab. The elevated mononuclear cell counts in the cerebrospinal fluid, combined with the exclusion of infectious and other causes, led to the diagnosis of aseptic meningitis, suggesting a relapse of lupus meningitis as an irAE. Increasing the dose of prednisolone to 60 mg/day and methylprednisolone pulse therapy did not improve fever and elevated serum CRP levels. Pembrolizumab was withdrawn after only one dose because he developed irAE that was uncontrolled by high-dose glucocorticoids. Combined chemotherapy of 5-fluorouracil and cisplatin (FP therapy) was introduced 24 days after pembrolizumab administration with the expectation of controlling persistent inflammation as well as malignancy by cytostatic drugs. The FP therapy induced a decrease in fever and serum CRP levels and improvement of skin rash (Figure 2A). Since then, he has continued FP therapy under careful observation for the flare of SLE.

A systematic review showed that about 75% of patients with preexisting autoimmune diseases, including SLE, can experience a flare of their baseline disease or develop novel irAEs under ICI treatment [8]. Due to the small sample size and heterogeneity of the included patients, any risk factors and biomarkers to predict the irAEs have not been identified in patients with preexisting autoimmune diseases [9]. In spite of the frequency, most of the irAEs are generally controlled with glucocorticoids and manageable without ICI discontinuation: Therefore, ICI treatment is considered to have an acceptable safety profile even for patients with preexisting autoimmune diseases [10]. Nevertheless, the flare of lupus meningitis in our case could not be controlled by high-dose glucocorticoid therapy and required discontinuation of pembrolizumab. Canceration of DLE is associated with chronic inflammation by autoreactive T cells [3], and therefore, the DLE-related SCC could share an autoantigen with DLE. However, SCC can induce immune escape from the autoreactive T cells by expressing programmed cell death 1-ligand 1 (PD-L1). Pembrolizumab can restore anti-SCC immunity by inhibiting PD-1/PD-L1 binding, which could also induce cross-reactive autoimmune responses by activating the autoreactive T cells (Figure 2B). In addition, the development of irAE is associated with high levels of IFN-γ-induced cytokines [11]. The upregulated IFN-γ signature is similar to that seen in SLE, suggesting that ICI administration may have a risk of exacerbating preexisting SLE. In conclusion, immunotherapy for SCC arising from active DLE requires meticulous attention to the potential for severe irAEs.

Author Contributions

All the authors followed up the patient and collected the clinical data. Conceptualization, H.A. and H.N.; visualization, H.A., H.N., K.H., J.K., and S.S.; supervision, M.K., H.U., and H.T. H.A. and H.N. wrote the original draft, and the other authors edited it. All the authors approved the final version.

Acknowledgments

We acknowledge the patient for allowing us to publish his case and all his personal photography and information.

Consent

Informed consent was attained for the publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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LETTER TO THE EDITOR

Epstein–Barr Virus-Associated Hemophagocytic Lymphohistiocytosis in a Patient With Behçet's Disease Treated With Adalimumab

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Keywords: adalimumab | Behçet's disease | Epstein–Barr virus | hemophagocytic lymphohistiocytosis

Dear Editor,

Epstein–Barr virus (EBV) infection manifests with diverse symptoms and pathologies. B lymphocytes are the primary target of EBV. EBV infection is typically asymptomatic in most individuals, but it can occasionally result in infectious mononucleosis (IM). Furthermore, EBV may infect T or NK cells and induce EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), a life-threatening lymphoproliferative disorder requiring intensive immunosuppressive and cytotoxic treatments and, occasionally, allogenic hematopoietic cell transplantation. It is crucial to differentiate between severe IM and EBV-HLH to initiate appropriate therapeutic interventions and prevent unfavorable outcomes; however, clinical features and laboratory parameters in patients with severe IM and EBV-HLH are similar. Therefore, it is essential to identify EBV-infected cells to make a precise diagnosis.

Tumor necrosis factor (TNF) inhibitors (TNFi) are frequently employed for rheumatic diseases, such as Behçet's disease (BD). TNFi exhibit significant clinical effects in rheumatic disease treatment. However, previous studies have indicated that TNFi use is linked to an increased incidence and severity of viral infection [1]. Here, we report a case of BD complicated by EBV-HLH during adalimumab treatment. The accurate depiction of the disease pathophysiology was facilitated through the identification of EBV-infected cells in this patient through flow cytometry analysis.

A 16-year-old female was referred to us with abdominal pain and a fever for 5 days. As previously reported [2], the patient was diagnosed with BD complicated with Sweet syndrome. After adalimumab administration, her symptoms improved, and she had been in remission for 1 year. Although abdominal tenderness was detected during a physical examination, no cutaneous lesions or oral or genital aphthae were observed. The following laboratory findings were obtained: white blood cell count, 1900/μL; platelet count, 75,000/μL; aspartate transferase, 245 U/L; lactate dehydrogenase, 687 U/L; C-reactive protein, 13.3 mg/L; ferritin, 3400 ng/mL; and soluble interleukin-2 receptor, 2800 U/mL (reference range: 157–474). The whole blood EBV-DNA levels were 59,000 copies/mL. The anti-EBV VCA-IgG antibody titer was 1:160. The results for VCA-IgM and anti-EBNA antibodies were both negative. Hepatosplenomegaly was identified on contrast-enhanced computed tomography. A bone marrow aspiration revealed hemophagocytosis. Upon flow cytometry, an inverted CD4/CD8 ratio and an increased number of $CD45RO^+CD8^+$ cells were observed (Figure 1A). The identification of $EBER^+$ $CD8^+$ cells by EBV-encoded small RNA (EBER) flow-fluorescent in situ hybridization (FISH) indicated that EBV had infected $CD8^+$ cells (Figure 1B). T cell receptor (TCR)-Vβ repertoire analysis revealed

Abbreviations: BD, Behçet's disease; EBER, EBV-encoded small RNA; EBV, Epstein–Barr virus; FISH, flow-fluorescent in situ hybridization; HLH, hemophagocytic lymphohistiocytosis; IM, infectious mononucleosis; TCR, T cell receptor; TNFi, tumor necrosis factor inhibitors (TNFi).

Summary

- Accurate diagnosis and monitoring of EBV infection are required in HLH patients receiving adalimumab.

oligoclonal expansions of $CD8^+$ cells, including Vβ 5.1^+, 7.1^+, 13.1^+, and 17^+ cells (Figure 1C). Furthermore, $V\beta7.1^+CD8^+$ HLA-DR^+ cells exhibited downregulation of CD5 (Figure 1D). Based on these findings, the patient was diagnosed with a primary EBV infection and EBV-HLH. The patient was administered prednisolone (40 mg/day), and her symptoms and laboratory findings improved. Improvement in inverted CD4/CD8 ratio (Figure 1A), $CD45RO^+CD8^+$ cell numbers (Figure 1A), and oligoclonal expansions of $CD8^+$ cells (Figure 1C) was observed 1 month later. $V\beta7.1^+$ cell population with CD5 downregulation (Figure 1D) and whole blood EBV-DNA levels also became undetectable. Therefore, no additional immunosuppressive drug was initiated, and ADA was resumed. Prednisolone was tapered and discontinued 2 months after onset. The patient has not experienced a relapse of EBV-HLH and BD for 1 year.

Adalimumab is generally used for the intestinal involvement of BD. Furthermore, adalimumab is also effective for BD patients with other organ lesions refractory to colchicine and/or corticosteroids [3]. Overexpression of TNF-α is associated with the pathogenesis of not only BD but also Sweet syndrome [4]. Recent studies showed TNFi, including adalimumab, were effective for refractory Sweet syndrome [5, 6]. As we previously reported [2], our patient was refractory to colchicine and corticosteroids. After adalimumab administration, her symptoms dramatically improved, and she had been in remission for 1 year.

It is exceedingly uncommon for patients with BD to develop EBV-HLH complications [7, 8]. The use of TNFi could elevate the incidence and severity of tuberculosis and viral infections, including the hepatitis B virus [7]. Balandraud et al. [9] reported that long-term TNFi usage does not significantly impact EBV load in peripheral blood mononuclear cells in rheumatoid arthritis patients. In contrast, certain previous studies have indicated that EBV infection can induce HLH in patients receiving TNFi [10]. Although TNFi might pose a potential risk for EBV-HLH, prompt diagnosis and intervention can help avoid severe outcomes, as demonstrated in this case. Additionally, extensive research is required to validate this.

It is occasionally challenging to differentiate EBV-HLH from EBV-related disorders, such as severe IM. The monitoring of EBV-infected cells lacking expression of CD5 on $CD8^+$ T cells

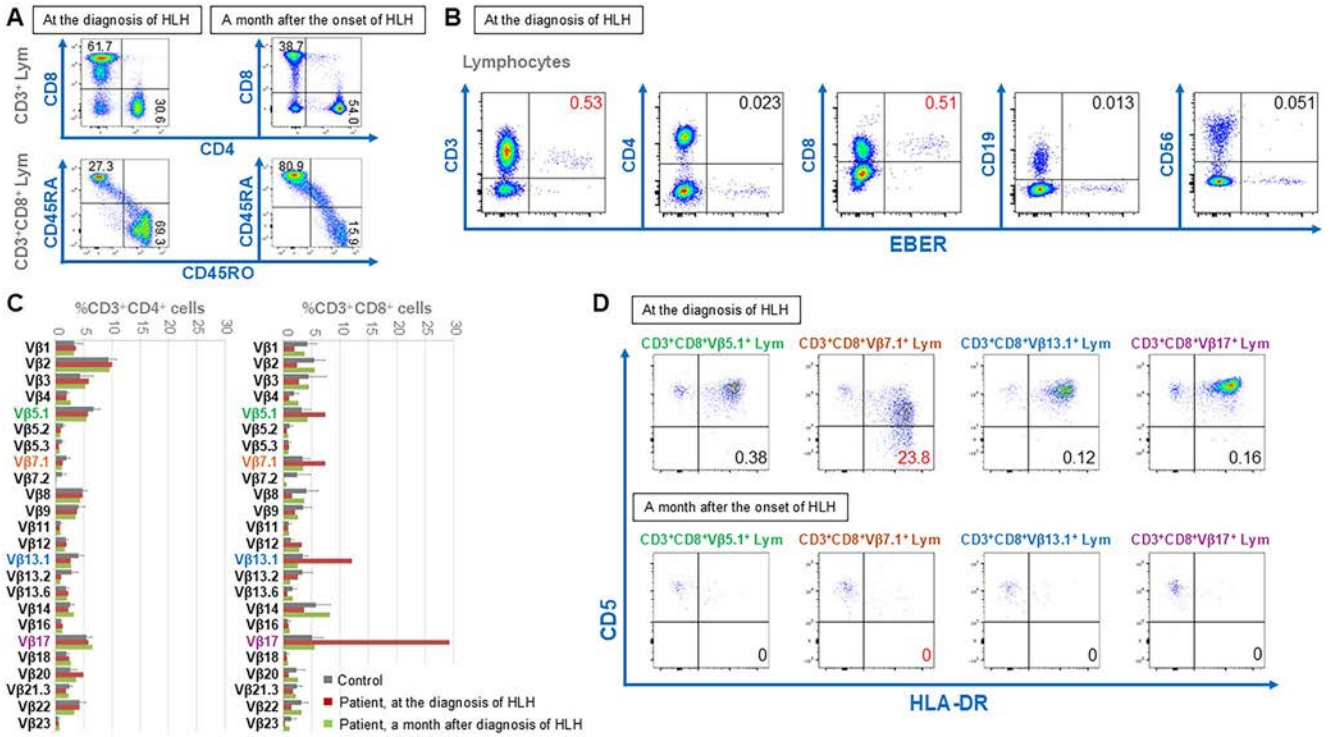

FIGURE 1 | Flow cytometry analysis results. (A) Analyses of naive and memory T cell distribution. The numbers in the upper boxes indicate the percentage of $CD4^+$ and $CD8^+$ cells among the $CD3^+$ lymphocytes, whereas the numbers in the lower boxes indicate the percentage of $CD45RA^+$ and $CD45RO^+$ cells among the $CD3^+CD8^+$ lymphocytes. (B) EBER flow FISH analysis at the diagnosis of HLH. EBV-infected cells ($EBER^+$ cells) are demonstrated in each box's top-right cell; the numbers indicate the percentage of EBV-infected cells among lymphocytes. (C) TCR-Vβ repertoire analysis of $CD4^+$ and $CD8^+$ T cells. The red bars indicate the patient's results at the time of diagnosis of HLH, and green bars indicate those 1 month after the onset of HLH. Gray bars indicate the mean percentages of healthy controls, and error bars indicate SD. (D) Analysis of HLA-DR^+ and $CD5^+$ cells in each TCR-$V\beta^+$ cell. The results at the time of diagnosis of HLH are depicted on the upper boxes, and the results 1 month after the onset of HLH are shown on the lower boxes. The numbers in the boxes indicate the percentage of HLA-DR^+CD5^- cells among each TCR-Vβ positive $CD3^+CD8^+$ lymphocytes.

with specific TCR-Vβ by flow cytometry has been revealed by previous studies to be a useful marker of dysregulated T cell activation and proliferation in EBV-HLH that aids in choosing an appropriate treatment for EBV-HLH [11]. Although the mechanism remains unclear, CD5 is a well-established negative regulator of TCR signaling, and it is suggested that a decrease in CD5 expression promotes the activation and proliferation of abnormal T cell clones in the pathogenesis of EBV-HLH [12]. Furthermore, EBER flow FISH is a direct and reliable method to characterize EBV-infected lymphocytes, which can be employed to diagnose EBV infection and elucidate the pathogenesis of EBV-associated diseases [13]. The use of conventional methods for detecting EBV-infected cells, such as cell sorting and quantitative PCR, can result in false positives and false negatives from contamination and cell loss. The flow cytometry-based method employed in our patient, including the EBER flow FISH and TCR-Vβ repertoire analysis, enabled rapid and accurate identification of EBV-infected cells.

In conclusion, we reported a BD patient who developed EBV-HLH during treatment with TNFi. Despite the ongoing debate regarding the potential for TNFi to elevate the risk of severe EBV infection, it is imperative to monitor the progression of EBV infection in patients treated with TNFi. Furthermore, accurate diagnosis and monitoring of EBV infection are required in HLH patients receiving adalimumab. In those patients, it is essential to identify EBV-infected cells. A flow cytometry-based method that combines EBER flow FISH and TCR-Vβ repertoire analysis enables rapid and accurate diagnosis of EBV-HLH.

Author Contributions

Shuya Kaneko: investigation; conceptualization; data curation; writing – original draft; writing – review and editing; project administration; formal analysis; methodology. Dan Tomomasa: investigation; data curation. Maho Hatano: investigation; data curation. Hitoshi Irabu: investigation; data curation. Yuko Hayashi: investigation; data curation. Hirokazu Kanegane: supervision; methodology; writing – review and editing. Masaki Shimizu: conceptualization; supervision; methodology; validation; writing – review and editing.

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Ethics Statement

Informed consent was obtained from the patient and her guardian for publication of this case report. This study was approved by the institutional review boards of the Institute of Science, Tokyo.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Associations of Healthcare Utilization and Health Expenditures in Older Adults With Osteoarthritis: Korean Health Panel Survey Study

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Keywords: healthcare expenditures | healthcare utilization | older persons | osteoarthritis | osteoarthritis-related cost

ABSTRACT

Background: This study investigated the association between healthcare utilization and expenditures, including non-covered services in Korean older adults with osteoarthritis (OA).

Methods: This cross-sectional study used data from the 2019 Korean Health Panel (KHP) annual data of participants aged ≥60 years who had OA. Healthcare utilization and expenditures were determined by hospitalization, outpatient, and emergency visits. A generalized linear model was used to examine healthcare utilization and expenditures associated with OA.

Results: Among the 5877 participants, 1645 (27.9%) had OA. Participants with OA had higher healthcare utilization (Increment = 6.5 visits, SE = 0.8, $p < 0.0001$) and expenditures (Increment = USD 432.8, SE = 111.8, $p = 0.0001$) compared to those without OA. The increase in utilization was primarily in outpatient visits (Increment = 6.4 visits, SE = 0.8, $p < 0.0001$), especially at clinics (Increment = 5.6 visits, SE = 0.9, $p < 0.0001$). Healthcare expenditures were also higher for both inpatient (Increment = USD 200.9, SE = 89.8, $p = 0.0254$) and outpatient visits (Increment = USD 236.6, SE = 51.7, $p < 0.0001$). Male with OA spent higher cost (USD 242.9) on outpatient visits than non-OA participants. In contrast, females with OA reported higher expenditures for both inpatient (USD 301.3) and outpatient (USD 259.6) visits than those without OA.

Conclusions: OA was associated with a significant increase in healthcare utilization and expenditure. Appropriate strategies are required to reduce the burden of OA. Further study is required to explore how various healthcare facilities might be used together to provide safe and cost-efficient treatment for OA patients within the healthcare system and in the community.

1 | Background

In 2020, the annual incidence of osteoarthritis (OA) in adults was approximately 89.7 million worldwide [1]. In 2017, the global number of years of life with disability (YLDs) for persons with OA was 9.6 million person-years, and a 31.4% increase was seen in OA YLDs worldwide over 10 years [2]. In 2018, OA accounted for 3.9% of all disability-adjusted life

Abbreviations: CVD, cardiovascular disease; DALYs, disability-adjusted life years; DM, diabetes mellitus; KHP, Korean Health Panel; OA, osteoarthritis; OOP, out-of-pocket payments; YLDs, years of life with disability.

Summary

- Even though the prevalence of osteoarthritis has increased, the relationship between OA prevalence, healthcare utilization, and healthcare expenditure has not been properly studied.
- Participants with OA visited the hospital (6.5 additional visits) and had more expenditures (USD 432.8).
- Male participants with OA had more utilization and expenditures for outpatient services; female participants with OA had more both inpatient and outpatient services.

years (DALYs) in Korea, making it the fifth leading cause of DALYs therein [3]. Korea's population is rapidly aging and is anticipated to become the second oldest after Japan by 2050. Changes in the population and its characteristics, such as aging, increased obesity, and inappropriate lifestyles, have increased the prevalence of OA [4]. Considering the aging rate, the prevalence and economic burden of OA will also consequently increase [5].

Although OA is considered to increase healthcare expenditure, the relationship between OA prevalence, healthcare utilization, and healthcare expenditure has not been properly studied in Korea, where there is a different national healthcare system. Several existing studies of OA in Korea were confined to the prevalence, patient characteristics, risk factors, and household catastrophic health expenditure in a specific region [6–8]. It is also important to study the differences in healthcare utilization and expenditures between men and women because there are differences in the prevalence and incidence of osteoarthritis between sexes due to genetic and anatomical differences [9, 10].

Generally, the prevalence and incidence of OA in women are higher than are those in men, considering genetic and anatomic differences [11]. Women over 55 years of age are more likely than men to experience OA [12]. Although there is an increasing prevalence and socioeconomic burden, especially among older women, there are few basic sociodemographic or health-economic studies of OA in some regions of Korea [8, 12–14].

Healthcare utilization and expenditure have a significant impact on controlling risk pools, medication benefit design, and care management [15]. This study (a) examined healthcare utilization and expenditures, including non-covered services, associated with osteoarthritis among older persons, and (b) examined differences in healthcare utilization and expenditures by sex using recently available data. These findings may contribute to the development of policies regarding healthcare utilization and expenditure among older people with OA in Korea.

2 | Methods

2.1 | Study Design and Data Source

This cross-sectional study used data from the 2019 Korean Health Panel (KHP). The KHP is an official statistical survey conducted annually since 2008 by the Korea Institute for Health and Social Affairs and the National Health Insurance Service. It uses stratified multistage probability sampling based on region and residence from the 2016 Korea Census to select respondents nationally. It aims to produce individual and household statistics on disease, use of healthcare services, healthcare expenditures, healthcare-related factors, and behavior as basic information for policy implementation to improve the responsiveness and accessibility of healthcare services [16].

This KHP data is accessible to the public upon request; no personally identifiable information was included. The Korea Institute for Health and Social Affairs approved the governance and ethical concerns. All participants provided informed consent when participating in the survey.

2.2 | Study Participants

The original study population consisted of 14 741 participants aged 19 years or older and under 60 years of age are excluded ($n = 5954$). The study participants were selected by the predetermined selection criteria which included older adults aged ≥60 and diagnosed with Knee OA and degenerative arthritis. The OA cases were determined by the participants responded as "yes" in the following self-reported question, "Have you ever been diagnosed with osteoarthritis by the physician?" and "no" response or "I don't know" were excluded ($n = 77$). A total of 5877 participants were included in the final analysis.

2.3 | Measures

2.3.1 | Dependent Variables

2.3.1.1 | Healthcare Utilization. Dependent variables were healthcare utilization per patient as a proxy for hospitalization, length of stay per hospitalization (LOS), outpatient visits, and emergency room (ER) visits in 2019. The number of hospitalizations, outpatient visits, and ER visits were calculated as the sum of the records for each service in 2019. The LOS was calculated by counting the number of days in hospital for each hospitalization.

2.3.1.2 | Healthcare Expenditures. Another dependent variable, healthcare expenditure per patient, was calculated for insurance charges, out-of-pocket payments (OOP), uncovered service charges, and prescription drug prices. Healthcare expenditures were classified as total, inpatient, outpatient, and ER expenditures according to each healthcare service.

2.3.2 | Independent Variables or Covariates

Covariates included sociodemographic characteristics and health-related factors. Sociodemographic characteristics were categorized as follows: age (60–69/70–79/over 80 years), sex (male/female), educational level (elementary school or less/middle school/high school/college or above), employment status (regular employee/temporary employee/employer or owner/unpaid

TABLE 1 | Distribution of demographic and socioeconomic characteristics.

	Total		OA				
			Yes ($N=1645$)		No ($N=4.232$)		
Variables	***N***	**%[a]**	***N***	**%[a]**	***N***	**%[a]**	***p*[b]**
Age							
60–69	2794	47.5	569	34.6	2225	52.6	<0.0001
70–79	2313	39.4	806	49.0	1507	35.6	
Over 80	770	13.1	270	16.4	500	11.8	
Sex							
Male	2618	44.5	384	23.3	2234	52.8	<0.0001
Female	3259	55.5	1261	76.7	1998	47.2	
Educational level							
Elementary school or less	2563	43.6	1028	62.5	1535	36.3	<0.0001
Middle school	1297	22.1	336	20.4	961	22.7	
High school	1442	24.5	223	13.6	1219	28.8	
College or above	575	9.8	58	3.5	517	12.2	
Employment status							
Regular employee	241	4.1	20	1.2	221	5.2	<0.0001
Temporary employee	1202	20.5	325	19.8	877	20.7	
Employer or owner	1077	18.3	255	15.5	822	19.4	
Unpaid family worker	407	6.9	158	9.6	249	5.9	
None	2950	50.2	887	53.9	2063	48.8	
Economic level							
Level 1 (poorest)	1173	20.0	463	28.2	710	16.8	<0.0001
Level 2	1176	20.0	390	23.7	786	18.6	
Level 3	1167	19.8	330	20.1	837	19.8	
Level 4	1184	20.2	255	15.5	929	22.0	
Level 5 (wealthiest)	1177	20.0	207	12.6	970	22.9	
Insurance type							
National Health Insurance	5552	94.5	1513	92.0	4039	95.4	<0.0001
Medical Aid	325	5.5	132	8.0	193	4.6	
With private supplementary insurance							
Yes	1490	25.4	304	18.5	1186	28.0	<0.0001
No	4387	74.6	1341	81.5	3046	72.0	
Cancer							
Yes	608	10.3	93	5.7	515	12.2	0.0453
No	5269	89.7	1552	94.3	3717	87.8	
Hypertension							
Yes	3130	53.3	978	59.5	2152	50.9	0.0001
No	2747	46.7	667	40.5	2080	49.1	

(Continues)

TABLE 1 | (Continued)

Variables	Total		OA				
			Yes ($N=1645$)		No ($N=4.232$)		
	N	%[a]	*N*	%[a]	*N*	%[a]	*p*[b]
Diabetes mellitus							
Yes	1477	25.1	403	24.5	1074	25.4	0.5769
No	4400	74.9	1242	75.5	3158	74.6	
Cardiovascular disease							
Yes	1014	17.3	272	16.5	742	17.5	0.4722
No	4863	82.7	1373	83.5	3490	82.5	
Disability							
Yes	664	11.3	235	14.3	429	10.1	< 0.0001
No	5213	88.7	1410	85.7	3803	89.9	

Abbreviation: OA, osteoarthritis.
[a]Weighted percentage.
[b]Rao-Scott chi-squared probability for comparison between osteoarthritis and non-osteoarthritis groups.

family worker/none), economic level (from level 1 [poorest] to level 5 [wealthiest]), insurance type (national health insurance/medical aid), and private supplementary insurance (yes/no).

Health-related covariates included cancer, hypertension, diabetes mellitus (DM), cardiovascular disease (CVD), and disability. These diseases were selected based on their high disease burden [3]. Each variable was classified "yes" or "no" according to whether the participant had received a diagnosis or was experiencing the relevant condition at that time.

2.4 | Statistical Analysis

Frequency distributions and the Rao-Scott chi-square test were used to identify differences between study participants with and without OA according to socioeconomic characteristics. A generalized linear model with a normal distribution and identity link function was used for segmented regression analysis based on the type of healthcare institution. Healthcare institution was classed territory hospital, general hospital, hospital (including health clinics, nursing hospitals, oriental medicine hospitals, and dental hospitals), and clinic (including health centers, oriental medicine clinics, and dental clinics). Additionally, regression analysis was conducted using two models: the first model included basic demographic variables, while the second model incorporated comorbidities to better understand the source of the observed increase. A robust standard error was used in a generalized estimating equation to prevent overestimation of the standard errors of the parameter estimates. Additionally, a subgroup analysis was performed to investigate the association between OA and healthcare utilization and expenditure according to sex. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA), and statistical significance was set at $p<0.05$. The relevant primary sampling units and sample weights were considered in the analysis because the KHP is designed as a complex sample.

3 | Results

The general characteristics of the participants are listed in Table 1. Among the 5877 participants, only 1645 (28.0%) had OA. Of the total sample, most participants were aged between 60 and 69 years (47.5%), female (55.5%), had elementary school or less education (43.6%), did not have a job (50.2%), had national health insurance (94.5%), did not have private supplementary insurance (74.7%), had comorbidity (cancer, 89.7%; DM, 74.9%; and CVD, 82.8%), and did not have disability (88.7%).

The annual healthcare utilization and expenditures according to OA are presented in Table 2. Participants with OA visited all types of healthcare institutions at an average of 26.9 times per year, which was 1.6 times more frequent than those without OA. Their healthcare utilization was primarily outpatient (26.6 visits per year), with clinics accounting for the majority (23.7 visits per year). Additionally, participants with OA incurred 1.2 to 1.3 times higher total healthcare expenditures including both inpatient and outpatient expenditures, compared to those without OA. By the type of healthcare institution, participants without OA spent more on medical expenditures at tertiary hospitals, whereas those with OA spent more at hospitals and clinics.

The associations between OA and annual incremental healthcare utilization and expenditure according to the type of healthcare institution are shown in Table 3. Participants with OA visited healthcare institutions an average of 6.5 more times annually compared to those without OA (Standard Error [SE] = 0.8, $p<0.0001$), with most of the increase attributed to clinic visits (Increment = 5.6 visits, SE = 0.9, $p<0.0001$). This increase was primarily in outpatient visits, particularly clinic outpatient visits (Increment of outpatient visit = 6.4 visits, SE = 0.8, $p<0.0001$; Increment of clinic outpatient visit = 5.6 visits, SE = 0.9, $p<0.0001$). The mean annual total healthcare expenditures were significantly higher for participants with OA than for those without OA, at USD 432.8 (SE = 111.8, $p=0.0001$). This increase

TABLE 2 | Annual healthcare utilization and expenditure according to OA ($N = 5877$).

	Osteoarthritis					
	Yes ($N = 1645$)		No ($N = 4232$)			
	Mean	SD	Mean	SD	Ratio[a]	*p*
Healthcare utilization						
Total visit	26.9	32.4	16.3	24.6	1.6	< 0.0001
Tertiary hospital	1.1	3.2	1.4	4.4	0.8	0.0040
General hospital	3.2	7.1	3.2	10.0	1.0	0.9022
Hospital	2.3	6.4	1.7	5.9	1.3	0.0027
Clinic	23.5	31.4	14.5	23.5	1.6	< 0.0001
Hospitalization	0.2	0.7	0.2	0.9	1.1	0.0128
Tertiary hospital	0.2	0.6	0.5	1.4	0.3	< 0.0001
General hospital	0.7	1.0	0.7	1.3	1.0	0.8619
Hospital	0.5	0.9	0.5	1.0	1.1	0.7177
Length of stay	3.2	15.1	3.3	23.0	1.0	0.7230
Tertiary hospital	1.2	5.9	3.5	11.2	0.3	0.0001
General hospital	8.7	18.2	7.4	23.2	1.2	0.3789
Hospital	8.6	28.1	14.4	52.5	0.6	0.0446
Outpatient visits	26.6	32.3	16.0	24.4	1.7	< 0.0001
Tertiary hospital	1.0	3.1	1.3	4.1	0.8	0.0113
General hospital	3.1	6.9	3.0	9.8	1.0	0.9046
Hospital	2.2	6.3	1.6	5.8	1.4	0.0029
Clinic	23.7	31.4	14.6	23.5	1.6	< 0.0001
Emergency room visits	0.1	0.3	0.1	0.4	0.9	0.3419
Tertiary hospital	0.2	0.5	0.4	0.9	0.7	0.1262
General hospital	0.8	0.7	0.9	1.0	0.9	0.3705
Hospital	0.2	0.5	0.2	0.5	1.2	0.6645
Healthcare expenditures ($[b])						
Total expenditures	1837.0	3693.8	1474.4	3826.3	1.2	< 0.0001
Tertiary hospital	247.0	1367.7	479.3	2612.6	0.5	< 0.0001
General hospital	647.0	2893.1	566.5	2347.5	1.1	0.3480
Hospital	362.6	1464.6	273.1	1401.8	1.3	0.0480
Clinic	797.7	1275.5	557.7	1175.6	1.4	< 0.0001
Inpatient expenditures	746.7	3183.4	631.4	3092.2	1.2	0.0547
Tertiary hospital	645.7	2610.5	1811.5	5203.4	0.4	< 0.0001
General hospital	2397.2	6085.0	1988.1	4559.7	1.2	0.3324
Hospital	1342.1	2947.7	1048.8	2931.9	1.3	0.1833
Outpatient expenditures	1077.0	1437.9	824.8	1721.3	1.3	< 0.0001
Tertiary hospital	125.5	526.4	182.2	885.5	0.7	0.0061
General hospital	204.4	575.1	235.8	1039.4	0.9	0.1829

(Continues)

TABLE 2 | (Continued)

	Osteoarthritis					
	Yes ($N=1645$)		No ($N=4232$)			
	Mean	SD	Mean	SD	Ratio[a]	*p*
Hospital	118.9	330.0	104.6	584.3	1.1	0.2842
Clinic	763.8	1199.8	535.5	1139.7	1.4	<0.0001
Emergency room expenditures	13.4	77.8	18.2	145.4	0.7	0.2222
Tertiary hospital	89.1	206.5	121.8	364.4	0.7	0.3234
General hospital	150.8	205.5	206.9	455.7	0.7	0.1376
Hospital	16.0	46.2	17.6	59.7	0.9	0.8261

Note: SD, standard deviation.
[a]Ratio between participants with and without OA.
[b]Korean won was converted to USD by applying an exchange rate of KRW 1293 per USD 1 (exchange rate on November 17, 2023).

was observed in both hospitals and clinics (Increment of total expenditures at hospitals = USD 146.2, SE = 82.1, $p = 0.0022$; Increment of total expenditures at clinics = USD 173.5, SE = 42.7, $p < 0.0001$). Participants with OA had significantly higher expenditures compared to those without OA, including inpatient and outpatient costs, particularly in outpatient clinic expenditures (Increment of inpatient expenditures = USD 200.9, SE = 89.8, $p = 0.0254$; Increment of outpatient expenditures = USD 236.6, SE = 51.7, $p < 0.0001$; Incremental of outpatient expenditure at clinics = USD 161.6, SE = 41.2, $p < 0.0001$).

Table 4 presents the results of two-model regression analysis, which explored the contributions of OA and comorbidities to increased healthcare utilization and expenditures. For healthcare utilization, the increments remained largely consistent after adjusting for comorbidities (Model 1: Increment of total visit = 6.8 visits, SE = 0.8, $p < 0.0001$; Increment of outpatient visit = 6.8 visits, SE = 0.8, $p < 0.0001$; Model 2: Increment of total visit = 6.5 visits, SE = 0.8, $p < 0.0001$; Increment of outpatient visit = 6.4 visits, SE = 0.8, $p < 0.0001$). Furthermore, participants with OA incurred higher annual expenditures, even after adjusting for comorbidities (Model 1: Increment of total expenditures = USD 342.6, SE = 113.2, $p = 0.0025$; Increment of outpatient expenditures = USD 224.8, SE = 52.2, $p < 0.0001$; Model 2: Increment of total expenditures = USD 432.8, SE = 111.8, $p = 0.0001$; Increment of inpatient expenditures = USD 200.9, SE = 89.8, $p = 0.0254$; Increment of outpatient expenditures = USD 236.6, SE = 51.7, $p < 0.0001$).

Figure 1 shows the findings of the incremental annual healthcare utilization and expenditures stratified by sex. A subgroup analysis of the association between OA and annual incremental healthcare utilization and expenditure, stratified by sex, is presented in Table 5. Males with OA had significantly more mean annual outpatient visits (Increment = 5.7 visits, SE = 1.5, $p < 0.0001$) than those without OA. Likewise, females with OA group exhibited a significantly higher association with mean annual outpatient visits (Increment = 6.8 visits, SE = 1.0, $p < 0.0001$) than those without OA. Only the mean annual expenditure according to outpatient visits was greater at USD 242.9 (SE = 106.5, $p = 0.0225$) among males with versus without OA. Females with OA had a greater mean annual expenditure on healthcare at USD 555.1 (SE = 125.0, $p < 0.0001$) for inpatient visits (Increment = USD 301.3, SE = 102.2, $p = 0.0032$) and outpatient visits (Increment = USD 259.6, SE = 55.8, $p < 0.0001$).

4 | Discussion and Conclusions

This study determined the association between healthcare utilization and expenditure in older adults with OA, including knee OA and degenerative arthritis of joints other than the knee. Our findings provide the latest incremental estimates of healthcare utilization and expenditure for OA after adjusting for sociodemographic characteristics and health-related factors. Participants with OA exhibited significantly higher incremental annual utilization of outpatient services and annual expenditures for inpatient and outpatient services than those without OA. Healthcare utilization appeared to be influenced by both OA and comorbidities, while healthcare expenditures were primarily associated with OA. These results suggest that OA, even after accounting for comorbidities, plays an important role in increased healthcare utilization, particularly for outpatient services. The higher total and inpatient expenditures observed in Model 2 compared to Model 1 may reflect the additional impact of comorbidities on healthcare costs. Meanwhile, outpatient expenditures remained consistently elevated across both models, indicating that OA continues to be a key contributor to outpatient costs. Although this is consistent with previous studies, direct comparisons could be complicated because of the health insurance system, methodologies, and data resources [4, 17–19].

Our findings revealed that senior age groups (70–79 years) and female gender were more prevalent, regardless of OA. This was consistent with the prevalent meta-analysis study, which found that knee pain is regarded as a natural consequence of aging [12, 18] and gender heterogeneity was a major contributing factor in females with likely reliable morphological radiographic structure and reproductive attributes [7, 12, 14, 18]. Moreover, a significant percentage of comorbidity between

TABLE 3 | Association between OA and annual incremental healthcare utilization and expenditures according to the type of healthcare institution.

	Increment[a]	SE	*p*
Healthcare utilization			
Total visit	6.5	0.8	<0.0001
Tertiary hospital	0.0	0.1	0.8741
General hospital	0.2	0.3	0.4310
Hospital	0.5	0.2	0.0073
Clinic	5.6	0.9	<0.0001
Hospitalization	0.1	0.0	0.0352
Tertiary hospital	−0.2	0.1	0.0495
General hospital	0.0	0.1	0.8435
Hospital	0.0	0.1	0.5690
Length of stay	0.5	0.7	0.4621
Tertiary hospital	−1.5	0.7	0.0400
General hospital	1.2	1.4	0.3962
Hospital	−2.2	4.0	0.5793
Outpatient visits	6.4	0.8	<0.0001
Tertiary hospital	0.0	0.1	0.9175
General hospital	0.2	0.3	0.4882
Hospital	0.5	0.2	0.0076
Clinic	5.6	0.9	<0.0001
Emergency room visits	0.0	0.0	0.5623
Tertiary hospital	−0.1	0.1	0.2590
General hospital	0.0	0.1	0.8124
Hospital	0.0	0.1	0.5562
Healthcare expenditures ($[b])			
Total expenditures	432.8	111.8	0.0001
Tertiary hospital	−41.3	72.9	0.5713
General hospital	145.2	82.1	0.0772
Hospital	132.2	43.3	0.0022
Clinic	173.5	42.7	<0.0001
Inpatient expenditures	200.9	89.8	0.0254
Tertiary hospital	−604.5	349.1	0.0833
General hospital	132.8	404.3	0.7425
Hospital	321.1	212.5	0.1308
Outpatient expenditures	236.6	51.7	<0.0001
Tertiary hospital	10.4	23.7	0.6602
General hospital	18.1	32.8	0.5811
Hospital	31.4	18.3	0.0855
Clinic	161.6	41.2	<0.0001
Emergency room expenditures	−4.7	3.9	0.2295
Tertiary hospital	−40.2	36.6	0.2721
General hospital	−47.2	54.1	0.3827
Hospital	−4.1	7.6	0.5868

Abbreviation: SE, standard error.
[a]Adjusted for covariates including age, sex, educational level, employment status, economic level, insurance type, private supplementary insurance, comorbidities (cancer, hypertension, diabetes mellitus, and cardiovascular disease) and disability.
[b]Korean won was converted to USD by applying an exchange rate of KRW 1293 per USD 1 (exchange rate on November 17, 2023).

OA and hypertension was found. The pathophysiological symptoms of OA have been shown to influence hypertension through a series of pain- and anxiety-related behaviors in OA patients [20, 21].

We found that the mean adjusted healthcare utilization for inpatient and outpatient services was significantly associated with OA. In particular, outpatient visits for patients with OA were 6.4 visits significantly higher than those for participants without OA. As older individuals with knee OA have limited activities of daily living, they perceive their health status and quality of life to be lower than those with other chronic diseases [20, 22]. Incremental outpatient visits might explain the need for continuous management, including healthcare and rehabilitation, to control the disease and prevent decline in physical function [21]. In addition, people with OA generally prefer non-covered outpatient services, such as traditional eastern medicine, for musculoskeletal system problems [23]. Furthermore, symptoms and their severity may increase the likelihood of outpatient visits in people with OA [24, 25]. The increase in outpatient utilization among OA patients may lead to a rise in the number of clinics specializing in outpatient care. In South Korea, OOP rates are differentiated by the type of healthcare institution to improve the efficiency of the healthcare delivery system. However, for older adults, fixed OOP rates for covered services are implemented to enhance accessibility. These policy measures would be likely to contribute to the rising expenditure associated with outpatient services, particularly in clinics. Our study focused only on knee OA and degenerative arthritis of joints other than the knee. Healthcare utilization was not directly compared with other types of OA. Although we cannot be sure of our overall OA-related healthcare utilization criteria, we believe that our work could contribute to the rationale for including pharmacological or other procedures, such as associated diagnoses and interventions, when identifying patients with OA according to the severity of their disease.

TABLE 4 | Association between OA and annual incremental utilization and expenditures by OA and comorbidities.

	Model 1[a]			Model 2[b]		
	Increment	**SE**	***p***	**Increment**	**SE**	***p***
Healthcare utilization						
Total visit	6.8	0.8	< 0.0001	6.5	0.8	< 0.0001
Hospitalization	0.0	0.0	0.2169	0.1	0.0	0.0352
Length of stay	−0.2	0.7	0.7481	0.5	0.7	0.4621
Outpatient visits	6.8	0.8	< 0.0001	6.4	0.8	< 0.0001
Emergency room visits	0.0	0.0	0.3636	0.0	0.0	0.5623
Healthcare expenditures ($[c])						
Total expenditures	342.6	113.2	0.0025	432.8	111.8	0.0001
Inpatient expenditures	123.6	90.2	0.1706	200.9	89.8	0.0254
Outpatient expenditures	224.8	52.2	< 0.0001	236.6	51.7	< 0.0001
Emergency room expenditures	−5.9	3.9	0.1320	−4.7	3.9	0.2295

Abbreviation: SE, standard error.
[a]Model 1 was adjusted by sociodemographic covariates including age, gender, employment status, economic level, insurance type, educational level.
[b]Model 2 was adjusted by sociodemographic and health-related covariates including age, gender, employment status, economic level, insurance type, educational level, comorbidities (cancer, hypertension, diabetes mellitus, and cardiovascular disease) and disability.
[c]The Korean won was then converted to USD by applying an exchange rate of KRWs 1293 per USD 1 (as of November 17, 2023).

In addition, the total annual mean expenditure on healthcare utilization was significantly higher among participants with OA than those without OA. Our findings are generally similar to those of studies conducted in other countries. The annual incremental healthcare expenditures for osteoarthritis ranged from EUR 705 to EUR 19715, depending on the specific geographic context in a systematic review study [26] and the average annual cost of OA in the US is between USD 1442 and USD 21335 [27]. Another comprehensive analysis revealed that the total annual expenses of patients with lower limb OA ranged from EUR 700 to EUR 12000 per patient [28] and also reported OA-related medical claims of USD 1926 per patient in the US [29], approximately EUR 2.5 billion per year in Italy [30], and median all-cause healthcare costs in Japan of approximately JPY 35000 for hip OA and JPY 74000 for knee OA [31]. Although previous studies have focused on healthcare expenditures according to treatment patterns and medications for patients with OA in Korea, this study focused on total expenditures on healthcare utilization, including non-covered services, using recent data. Furthermore, to the best of our knowledge, little research has been conducted on healthcare utilization expenditures for people with OA in Korea; such work is important to suggest margins to estimate the future healthcare and economic burden for patients with OA.

Among male participants, those with OA utilized outpatient services (5.7 visits), but not inpatient services, and had more outpatient expenditure (USD 242.9) than men without OA. In comparison, women with OA utilized more healthcare services related to hospitalizations (6.8 visits) and total healthcare expenditure (USD 555.1): inpatient services (USD 301.3) and outpatient services (USD 259.6). Our findings are similar to those of previous studies. In the US, the total healthcare expenditures and OOP for women with OA are higher than those for women without OA [10]. A systematic review also found that women were more likely to visit a specialist, consult an orthopedic surgeon, receive total hip replacement, and utilize other healthcare services [32, 33]. In women, the absence of activity limitation due to arthritis tends to be associated with less treatment [34]. Osteoarthritis is associated with increased wear and tear of the joints as the duration of morbidity increases, suggesting that healthcare utilization is more likely when the disease is more advanced and severe [34, 35]. Women have significantly more pain, physical difficulties, and impaired knee function than do men. Most previous studies that performed operating room morphometry at the time of arthroplasty reported worse OA scenarios in patients with end-stage OA [36]. This may partially explain why women with OA have higher hospitalization-related healthcare utilization and total healthcare expenditure.

This study had several limitations. First, the cross-sectional design precludes discussions about the causal relationships between OA and healthcare utilization and expenditures using the beta version of second generation KHP, which began in 2019. It was more suitable to use the second generation than the first because, according to the 2005 Korea Census, the first version is limited in fully reflecting rapid population changes in Korea, such as aging. Second, because OA and comorbidities were self-reported, there is a possibility of underreporting due to recall bias or the absence of medical confirmation. Participants were asked whether they had been diagnosed with specific diseases, and the data were not validated against medical records. Nevertheless, previous studies have demonstrated that self-reported questions about OA closely align with clinical findings and are considered reliable [37–39]. Additionally, healthcare utilization and expenditure were collected based

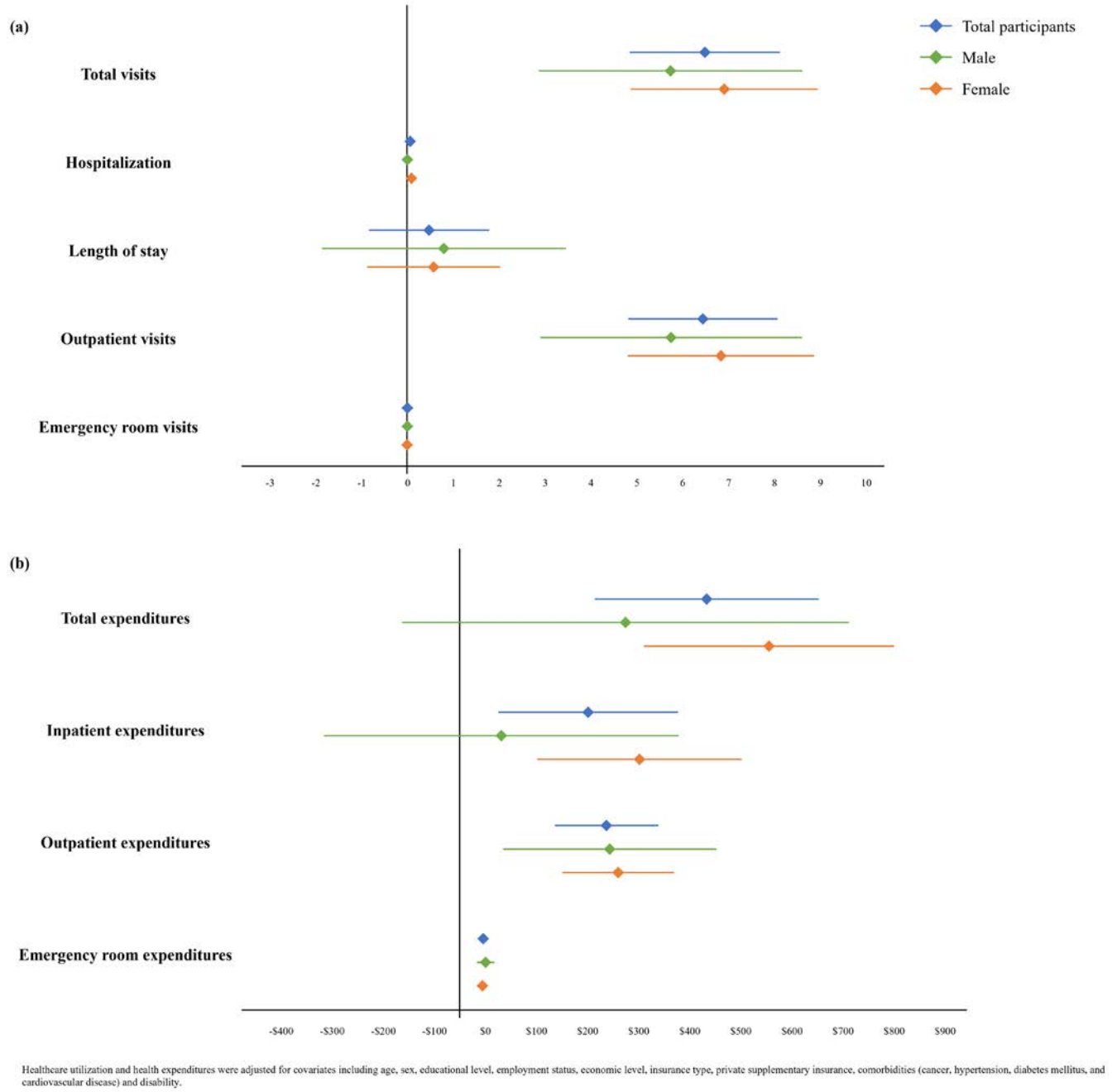

FIGURE 1 | Incremental annual healthcare utilization and expenditures associated with OA, stratified by sex. (a) Incremental mean annual healthcare utilizations among the participants with osteoarthritis ($n = 1645$) by sex. The number of hospitalizations, outpatient visits, and emergency room visits were calculated as the sum of the records for each service in 2019. The length of stay was calculated by counting the number of days in hospital for each hospitalization. (b) Incremental mean annual healthcare expenditures among the participants with osteoarthritis ($n = 1645$) by sex. Expenditure per patient was calculated for insurance charges, out-of-pocket payments, uncovered service charges, and prescription drug prices.

on receipts, which may have led to reported values being lower than the actual values. Finally, there was a lack of data regarding the healthcare utilization type used by the participants in the KHP. Nevertheless, this study analyzed healthcare utilization and expenditures associated with OA among older adults using only nationally representative data, including non-covered services. Using the KHP data is very important because musculoskeletal diseases utilize many non-covered services, such as traditional eastern medicine [23].

In conclusion, our findings suggest that OA increases healthcare utilization and expenditures in older adults. Especially for women, healthcare expenditures for hospitalization significantly increased with OA. OA is associated with morbidity, longer treatment periods, lower willingness to receive treatment and adherence to treatment, and an increased economic burden. Policymakers must enact suitable approaches to incentivize individuals to manage OA and reduce the associated burdens since it poses a significant health risk. Our study

TABLE 5 | Association between OA and annual incremental utilization and expenditures by sex.

	Male			Female		
	Increment[a]	SE	*p*	Increment[a]	SE	*p*
Healthcare utilization						
Total visits	5.7	1.5	< 0.0001	6.9	1.0	< 0.0001
Hospitalization	0.0	0.0	0.8989	0.1	0.0	0.0052
Length of stay	0.8	1.4	0.5609	0.6	0.7	0.4433
Outpatient visits	5.7	1.5	< 0.0001	6.8	1.0	< 0.0001
Emergency room visits	0.0	0.0	0.8919	0.0	0.0	0.3933
Healthcare expenditures ($[b])						
Total expenditures	273.9	223.1	0.2194	555.1	125.0	< 0.0001
Inpatient expenditures	30.8	177.2	0.8619	301.3	102.2	0.0032
Outpatient expenditures	242.9	106.5	0.0225	259.6	55.8	< 0.0001
Emergency room expenditures	0.2	8.9	0.9802	−5.9	3.8	0.1165

Abbreviation: SE, standard error.
[a]Adjusted for covariates including age, sex, educational level, employment status, economic level, insurance type, private supplementary insurance, comorbidities (cancer, hypertension, diabetes mellitus, and cardiovascular disease), and disability.
[b]Korean won was converted to USD by applying an exchange rate of KRW 1293 per USD 1 (exchange rate on November 17, 2023).

builds on a large empirical study of OA-related utilization and expenditures and may lead to further studies providing stronger evidence.

Author Contributions

Y.K. and B.K. were involved in conception of the study and statistical design, carried out the data analysis and drafted manuscript. J.S.P. was involved in conception of the study and statistical design and participated in data analysis. V.R. participated in data analysis and drafted the manuscript. H.J.C. oversaw manuscript development, and the Methods and Results sections of the manuscript, acquired funding. S.G.L. oversaw manuscript development and helped to revise the manuscript. T.H.K. was involved in conception of the study and statistical design, oversaw manuscript development, and helped to revise the manuscript. All authors revised the article critically for important intellectual content and approved the final manuscript.

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This study used the Korea Health Panel Survey 2019 Annual Data (Version 2.0.1), jointly organized by the Korea Health and Social Research Institute and the National Health Insurance Service (Version 2.0.1).

Ethics Statement

In this analysis, we used secondary data from the Korea Health Panel Survey. All data were anonymized by the Korea Institute for Health and Social Affairs and the National Health Insurance Service. As such, all ethics approvals and consent to participate were waived.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available in the Korea Health Panel Survey repository (https://www.khp.re.kr:444/web/data/data.do).

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LETTER TO THE EDITOR

Radiologic Prevalence of Kienböck's Disease in Korea: A Retrospective Analysis of Single Center Data

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Dear Editor,

Kienböck's disease (KD) is a rare condition that causes wrist pain due to lunate osteonecrosis [1–3]. It usually occurs in men aged 20–40 years and in manual workers. KD usually begins insidiously, without a traumatic event [4]. Notably, its etiology remains unknown. Mechanical and vascular factors work together and affect the blood supply to the lunate. Another study suggested that metabolic factors may also play a role in lunate osteonecrosis [2, 4, 5].

Symptoms of KD usually include central wrist pain, decreased range of motion, and reduced grip strength, which may present unilaterally or bilaterally [6]. KD is difficult to diagnose based on the symptoms alone. When no symptoms are present, a diagnosis may occur incidentally through radiographic imaging; however, the symptoms and images sometimes do not match, making it difficult to determine the prevalence of KD [7]. Therefore, some studies have retrospectively investigated the prevalence of KD using radiology reports. Although KD is rare, there are several reports on its prevalence, which ranges from 0.0066% to 1.79% [8, 9]. The significant differences in disease prevalence appear to be due to various factors, such as race, region, and imaging tools.

This study aimed to determine the prevalence of KD using plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) in Korea.

1 | Methods

This retrospective study included patients aged 18 years or older who underwent hand or wrist radiography, CT, and MRI between January 1, 2010, and December 31, 2020, at Hanyang University Seoul Hospital. Radiology reports from electronic medical records (EMR), all reported by two experienced bone and joint radiologists (YJK and SL), were searched using the picture archiving and communications system. A total of 61 903 cases were selected as subjects from 124 248 radiology reports, excluding English names, duplicate files, and patients under 18 years of age. We searched for radiology reports containing "Kienböck or osteonecrosis," confirmed the presence of KD, and performed radiographic staging by a radiologist (SL). If there were conflicting results for KD in multiple radiology reports for one patient, the presence and radiographic staging of KD were determined based on CT, MRI, or later reports [10, 11]. This study was approved by our Institutional Review Board, which waived the requirement for informed consent (IRB file No. 2021-05-001-003).

Variables are summarized as median (interquartile range) or counts (percentages), and statistical significance was set at $p < 0.05$. The continuous variables did not have equal variances; therefore, the Mann–Whitney *U* test was used to compare the two groups. Categorical variables were compared using the chi-squared test. The R statistical language (version 3.6.1; Vienna, Austria; http://www.R-project.org/) was used for statistical analysis.

2 | Results

The EMR search yielded 124 248 radiological reports. Following the exclusion of duplicate cases, there were 61 903 cases (17 913 males and 43 990 females) aged 18 years or older. Based on imaging findings, KD was confirmed in 102 patients. Therefore, the prevalence of KD was 0.17% (female: 0.17%, male: 0.16%). Among them, lunate osteonecrosis was confirmed in 106 hand images, including four patients with lunate osteonecrosis in both hands (Table 1). The median age of all patients was 59.0 (49.0–68.0) years, and females were more commonly affected (78 [73.6%]). Most cases of KD were reported on radiographs (84.0%), followed by CT (13.2%) and MRI (2.8%). There were 11 cases of wrist fractures with KD (10.4%). Among the KD stages, stage III was the most common (67.0%).

2.1 | Differences in the Left and Right Hands

Table 1 shows the differences in the clinical characteristics between the left and right hands of patients with KD. There were no statistically significant differences in clinical characteristics between the two groups; however, there was a significant difference between the left and right hands regarding the type of imaging modality used to detect KD ($p = 0.047$). KD of the right hand was more commonly observed on plain radiography (90.9% vs. 76.5%), and KD of the left hand was more commonly observed on CT (21.6% vs. 5.5%). The rate of wrist fracture was higher in the left hand than in the right hand (15.7% vs. 5.5%). Stage IV disease was found more frequently in the right hand than in the left (12.7% vs. 2.0%); however, this difference was not statistically significant.

2.2 | Stages by Modality

Most cases of KD were detected on plain radiographs ($n = 89$). Additionally, stage III was highly detectable on plain radiography, CT, and MRI (62.9%, 85.7%, and 100%, respectively). No stage I cases were identified with any of these modalities.

3 | Discussion

The prevalence of KD detected using plain radiography, CT, and MRI over 10 years was 0.17%. The ratio of males to females was similar, and there was no difference in the prevalence between the left and right hands. Most cases were found to be stage III, indicating that many cases had already progressed when confirmed through imaging.

TABLE 1 | Clinical characteristics in patients with Kienböck's disease.

	Total ($N = 106$)[a]	Left ($N = 51$)	Right ($N = 54$)	p
Age (years)	59.0 (49.0–68.0)	57.0 (46.0–67.0)	61.0 (51.0–67.5)	0.393
Female (%)	78 (73.6)	38 (74.5)	40 (72.7)	1.000
Imaging				
Plain radiograph (%)	89 (84.0)	39 (76.5)	50 (90.9)	0.047
CT (%)	14 (13.2)	11 (21.6)	3 (5.5)	
MRI (%)	3 (2.8)	1 (2.0)	2 (3.6)	
Wrist fracture (%)	11 (10.4)	8 (15.7)	3 (5.5)	0.159
Stage				
I (%)	None	None	None	0.11
II (%)	27 (25.5)	14 (27.5)	13 (23.6)	
III (%)	71 (67.0)	36 (70.6)	35 (63.6)	
IV (%)	8 (7.5)	1 (2.0)	7 (12.7)	

[a]Among the 102 patients, four had Kienböck's disease in both hands.

TABLE 2 | Prevalence of Kienböck's disease.

	Year	Country	Participants	Method	Study design	Cases	Prevalence (%)
Golay et al. [8]	2016	United Kingdom	150 912	Radiology	Retrospective	5	0.0066
This Study, 2025	2023	South Korea	61 903	Radiology	Retrospective	102	0.17
Van Leeuwn et al. [7]	2016	USA	51 071	Radiology	Retrospective	138	0.27
Mennen et al. [9]	2009	South Africa	1287	Radiology	Retrospective	23	1.79
Tsujimoto et al. [12]	2015	Japan	572	Radiology	Retrospective	7	1.2

The prevalence of KD reported in each study may vary slightly depending on the region, testing method, and characteristics of the included participants. The prevalence of 0.17% in our study was lower than the 0.27% reported in a study that retrospectively reviewed 11 years of radiologic reports from 51 071 participants (Table 2) [7–9, 12]. However, the prevalence was very high compared to 0.0066% in a radiologic study of 150 912 participants over a 5-year period by Golay et al. [8]. Given its substantially larger sample size (61903) compared to previous studies, this research serves as a valuable reference for estimating KD prevalence in Koreans [13].

The staging method introduced by Lichtman et al. [11] is widely used for the diagnosis and prognosis of KD. In brief, stage I shows a linear fracture line, and stage II shows sclerosis along the fracture line. Stages III and IV are characterized by lunate collapse, whereas radiocarpal or midcarpal degenerative changes characterize stage IV. Van Leeuwen et al. [7] reported that lunate collapse (stages III and IV) occurred in 38% of patients. In the study by Golay et al., stage II was the most common (44%) [8], and in the study by Mennen and Sithebe, stage III was the most common (48%) [9]. Taniguchi et al. reported that all cases belonged to stage IV [14]. However, in most studies, stage I was a minority or not observed.

In KD, staging can be an important factor in selecting treatment options and predicting prognosis. Conservative treatment is recommended in the early stages, such as stage I; however, when the disease progresses, surgical treatment, such as radial shortening osteotomy, revascularization procedures, core decompression, arthrodesis, or arthroplasty, is also considered [3, 4]. Moreover, the lunate status is a potential etiological and prognostic factor, and treatment options may change depending on changes in the lunate [15].

Plain radiographs are inexpensive and easy to obtain; however, it is difficult to detect early changes in KD [3], although they are helpful in determining advanced conditions, such as osteonecrosis or lunate collapse, in which the lunate density increases. CT may be advantageous in identifying lunate collapse that is not visible on plain radiography [4]. MRI can be helpful in detecting early-stage changes in the bone [3, 4, 11]; however, there are also reports that CT characterizes early-stage osteonecrosis before collapse better than MRI [1]. Our study found a predominance of stage III, meaning that CT or MRI did not appear to detect more stage I or II lesions than radiography; however, because there are few cases of CT and MRI, it is difficult to determine which test method is better for distinguishing and staging KD. Another study suggested that arthroscopy might provide additional information regarding the condition of KD [15].

This study had some limitations. First, this was a retrospective study, and KD was confirmed by reviewing radiologists' reports. Therefore, we were unable to distinguish between the symptomatic and incidental KD prevalence in patients owing to limitations in data acquisition. Moreover, identifying and comparing the KD or non-KD prevalence in the general population would be challenging, as routine imaging for asymptomatic individuals is rarely performed. Second, as there were no stage I patients, most patients included in the study had advanced disease. Therefore, the prevalence in this study should be interpreted, considering that patients in the early stages of the disease were not detected. Third, owing to limitations in data acquisition, there were no records of chronic diseases, such as rheumatoid arthritis or trauma. Depending on the comorbidity rate, there may be differences in the stage of KD. Fourth, not all patients underwent complete imaging examinations, which may be attributed to factors such as the severity and progression of symptoms or economic constraints. As a retrospective study, it was impossible to identify these reasons comprehensively, limiting the interpretation of the imaging data.

We determined the prevalence of radiographic KD in the Korean population. Although KD is a rare disease, if wrist pain persists, KD can be suspected in the early stages using various imaging tools. Active interventions for KD may prevent wrist pain and disabilities.

Author Contributions

J.B.J. had full access to all data in the study and takes responsibility for the integrity of the data, study supervision, and accuracy of the data analysis. All authors participated in the interpretation of data and the drafting, revision, and approval of the manuscript. B.S.K. and J.B.J. contributed to the study conception and/or design. B.S.K. participated in the statistical analysis. Y.J.K. and S.L. provided administrative, technical, or material support.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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EDITORIAL

Harnessing Large Language Models for Rheumatic Disease Diagnosis: Advancing Hybrid Care and Task Shifting

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Rheumatology is facing an expanding care gap, as the number of newly referred patients continues to outpace the availability of rheumatologists [1], resulting in longer diagnostic delays—often weeks to months—that lead to irreversible damage, poorer treatment outcomes, and higher societal costs [2]. Patients and physicians alike struggle with fluctuating, often nonspecific symptoms (e.g., joint pain), and this challenge is compounded by limited awareness of rheumatic diseases among both the general population and general practitioners. The poor specificity of referrals and the inability of traditional triage approaches to improve the situation widen the care gap further. Although patient education is integral to rheumatology care, it remains underutilized due to inadequate reimbursement and workforce shortages, leaving many patients feeling poorly informed about their disease. Clinicians also face a significant time burden with clinical documentation [3], especially for newly referred patients.

In response to these multifaceted challenges, digital health technologies (DHT) have emerged as a promising cornerstone to enhance diagnosis, information provision, patient education, documentation and alleviating workforce shortages. With the rapid proliferation of smartphones and advanced DHT, traditional care delivery models should be reevaluated to leverage these innovations [4]. Task-shifting is increasingly being implemented to mitigate workforce shortages, wherein tasks are delegated from physicians to nurses, medical students, or other healthcare professionals. However, task-shifting remains limited in scale and cost-efficiency and DHT could significantly leverage widespread implementation [5].

Currently increasing numbers of rheumatic patients turn to online platforms for initial symptom assessment [6], and diagnostic decision support systems (DDSS), that can empower patients to receive preliminary diagnoses within minutes. Although computer-aided diagnosis for rheumatologists has existed for decades [7], adoption has been hindered by poor usability [8], including time-intensive data entry [9] and restricted querying options. These limitations also affect patient education, as static, often printed information leaves patients scrolling through lengthy materials rather than engaging in open-ended, personalized exploration. To bridge these limitations recently made advancements in large-language-model-technology (LLM) can be used for unprecedented scalability and multimodal data processing. Therefore DHT usability, performance, and the patient-provider relationship could be significantly improved by integrating LLM-driven decision support within a collaborative digital health triad [4]. By continuously processing patient- and provider-generated data, LLMs can deliver more personalized, accessible, and dynamic support to transform care delivery aiming to close the rheumatology care gap.

LLMs have demonstrated remarkable proficiency in clinical reasoning due to their ability to process large datasets across various medical fields also including rare diseases [10]. By passively and continuously evaluating the vast amount of available clinical data, LLMs could facilitate accelerated diagnosis and the identification of at-risk individuals, enabling a more proactive approach to care without imposing additional burdens on physicians or patients. LLM capabilities have been highlighted by out-performing human experts

on standardized exams such as the United States Medical Licensing Examination (USMLE) and rheumatology exams [11]. Importantly, in a direct comparison study, ChatGPT's diagnostic accuracy was found to be not inferior to that of experienced rheumatologists [12]. Both were given the same anamnestic information from real patients presenting to a rheumatology service. Notably, the model exhibited exceptional sensitivity in identifying inflammatory rheumatic diseases (IRDs), correctly listing the accurate diagnosis among the top three options in 86% of IRD cases—surpassing the 74% success rate of rheumatologists.

Building on this, another publication by Venerito and Iannone utilized a locally fine-tuned LLM, optimized through prompt engineering, to diagnose fibromyalgia by analyzing subtle expressions of pain and emotion in patient communications [13]. This innovative approach achieved an accuracy of 87% and an AUROC of 0.86, underscoring the potential of LLMs to tackle diagnostic challenges associated with subjective and linguistically intricate conditions by broadening the scope of considerations and highlighting less obvious conditions. Additionally multiple studies have demonstrated that LLMs are capable of extracting diagnostic information from patient dialogues, even when the symptom descriptions are expressed in simple or colloquial language [14]. This linguistic adaptability allows LLMs to effectively comprehend patient narratives and identify subtle cues that might be overlooked in traditional assessments. Combined with the structured nature of multi-turn dialogues, this capability has shown significant potential for clinical applications [14].

One of these applications gaining more traction is the introduction of LLMs for documentation tasks such as summarizing clinical conversations, generating structured clinical notes, and extracting critical keywords. Research in this area has introduced improved note formats like K-SOAP and domain-specific datasets such as CliniKnote, which combine simulated doctor-patient dialogues with meticulously curated notes. Through advanced fine-tuning, prompting strategies, and sophisticated NLP methods, LLMs can enhance the efficiency and quality of clinical documentation, ultimately reducing clinician workload and enabling more effective patient care [15].

Further the potentials of LLMs can be used for educational applications, as exemplified by LLMs' ability to address patient queries with accuracy, empathy, and comprehensiveness. For instance, when ChatGPT-4 was tested with questions commonly posed by patients with systemic lupus erythematosus, its responses were not only rated more empathic but also qualitatively better than those from expert rheumatologists [16]. These capabilities stem from the transformer-based architectures underlying LLMs [17]. By integrating large, diverse knowledge sources—from clinical guidelines to authoritative research publications [18]—these models can maintain extensive contextual understanding and dynamically incorporate new information. As a result, LLMs hold the potential to improve diagnostic accuracy, streamline documentation, enhance patient education, and broaden the range of differential diagnoses considered. In doing so, they may help alleviate clinician workload, support more proactive and patient-centered care, and ultimately elevate the overall quality of healthcare delivery.

However, the clinical deployment of AI-driven diagnostic tools faces significant regulatory hurdles. Determining the intended

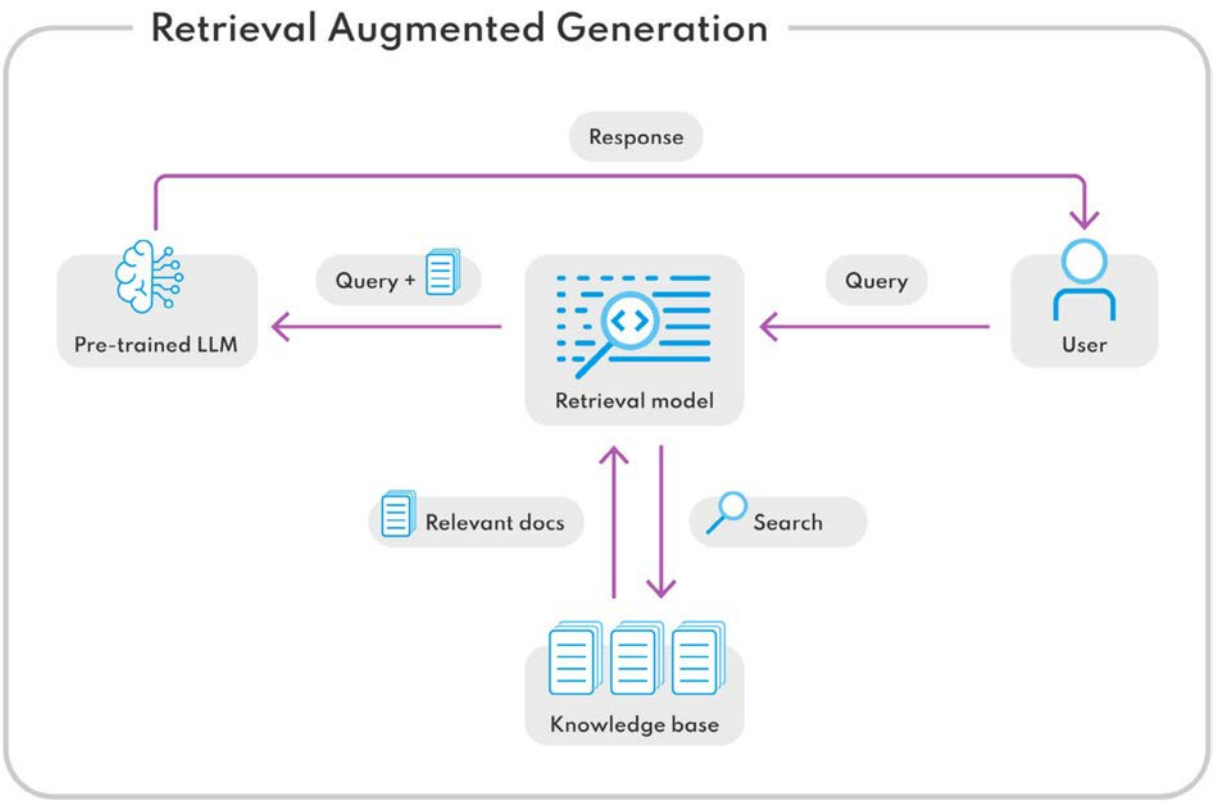

FIGURE 1 | Retrieval-Augmented Generation (RAG) to answer user queries augmented by the retrieval of relevant information.

purpose of these technologies is central to their classification as either medical or non-medical devices, a distinction that directly influences compliance requirements. Under the EU AI Act, general-purpose AI models such as LLMs supporting clinical decisions may face stringent obligations, especially regarding transparency, risk classification, and post-market monitoring. Simultaneously, regulatory requirements necessitate robust clinical evaluation, posing challenges in validating AI's predictive capabilities. Ensuring alignment with these frameworks is critical for advancing AI adoption while safeguarding patient safety and compliance with regulations.

While these regulatory challenges must be addressed, LLMs also pose inherent risks such as generating medical hallucinations—plausible yet incorrect or unverifiable information. This has been highlighted in the Med-HALT framework, where models such as GPT 3.5 were severely hallucinating given different more complex tasks. In a field where precision is paramount, such inaccuracies could misguide clinical decisions, jeopardizing patient safety [19]. Ensuring LLM transparency and explainability has become increasingly challenging, making the grounding of these models a crucial area of research. A promising grounding technique gaining significant attention is Retrieval-Augmented Generation (RAG). RAG addresses the transparency issue by first querying a database containing known information related to a user's question or input. It retrieves only semantically similar text blocks that are likely to answer the question or generate appropriate content. The model then produces an output based solely on this retrieved information, allowing it to accurately cite the source of the input. This approach enables users not only to verify the model's output against known literature but also to explore the subject further by reviewing the referenced documents, such as publications or guidelines [20]. As illustrated in Figure 1, RAG enhances both the accuracy and verifiability of LLM outputs by grounding responses in relevant, validated information from a knowledge base. While RAG systems have found widespread use in academic search engines, their effectiveness in medical contexts—particularly for patient education or diagnosis—remains largely unexplored. Collaborative efforts among AI developers, clinicians, and researchers are essential to optimize LLM utility while mitigating risks. Further exploration into grounding methods and developing specialized models tailored to rheumatology can enhance their effectiveness.

Integrating LLMs into the diagnosis of rheumatic diseases presents a transformative opportunity to reduce diagnostic delays, alleviate clinician workload, and enhance patient education. Despite existing challenges, the synergistic advancement of AI innovation and regulatory compliance can help bridge care gaps, improve patient outcomes, and elevate the professional experience of healthcare providers, ultimately fostering more efficient and patient-centered rheumatology care.

Author Contributions

Fabian Lechner and Johannes Knitza drafted the manuscript. Sebastian Kuhn provided suggestions, reviewed and edited the manuscript several times.

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Conflicts of Interest

Fabian Lechner declares honoraria from Lilly, Novo Nordisk, Siemens Healthineers, Diabetes.de, and the German Diabetes Association (DDG). Sebastian Kuhn is founder and shareholder of MED.digital GmbH. Johannes Knitza declares research support from Abbvie, GSK, Vila Health, honoraria and consulting fees from Abbvie, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, GAIA, Galapagos, GSK, Janssen, Lilly, Medac, Novartis, Pfizer, Sobi, Rheumaakademie, UCB, Vila Health and Werfen.

Data Availability Statement

The authors have nothing to report.

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ORIGINAL ARTICLE

Facilitators and Barriers to Physical Activity for Patients With Rheumatoid Arthritis and Axial Spondyloarthritis

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ABSTRACT

Background: Physical activity is important in patients with rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA). Current literature suggests they engage in less physical activity compared to healthy controls. Reasons for this discrepancy has not been well studied in Asian populations. We aimed to understand facilitators and barriers to physical activity in patients with RA and axSpA using the validated Inflammatory arthritis FAcilitators and Barriers (IFAB) questionnaire.

Methods: We conducted a cross-sectional study from 2020 to 2021 and enrolled patients diagnosed with RA and axSpA. Demographics, disease activity, comorbidities, facilitators, barriers and levels of physical activity were collected. Mean time on recreational activity, facilitators and barriers were listed.

Results: We enrolled 222 patients (109 RA, 113 axSpA). Mean (SD) age was 48.4 (14.8) years and 42.3% were males. Of all patients, 66.7% met the WHO recommendations on physical activity for health and percentage was similar between patients with RA and axSpA. Mean time spent on recreational-related activities was higher in patients with axSpA. Top three barriers to physical activity included lack of motivation (46.8%), level of symptoms (44.6%) and weather conditions (29.7%). Facilitators included knowledge of the benefits of physical activity for health (68.9%), mood (56.3%), and confidence on how to exercise safely (54.5%).

Conclusion: Overall, the facilitators and barriers to physical activity were similar between patients with RA and axSpA. Physicians could address some of these factors during consultations to promote and encourage more physical activity.

1 | Introduction

Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are some of the more common inflammatory arthropathies (IA) [1, 2]. These chronic, progressive immune-mediated rheumatic diseases lead to joint destruction and other systemic manifestations, resulting in functional impairment and a poor quality of life. The joints involved in RA and axSpA are different. RA typically affects the small joints of the hands and feet in a symmetrical distribution, resulting in decreased dexterity, [3] while axSpA typically causes inflammation of the spine, sacroiliac joint, and entheses [4]. Both conditions cause increasing pain and stiffness which can interfere with physical activity [4].

Regular physical activity is a safe and beneficial management option for the physical and mental health in people with IA [5, 6]. Physical activity helps with disease activity and outcomes, and also aids in curtailing the increase risk of comorbidities, such as slowing the atherosclerotic process in cardiovascular disease, increasing bone mineral density and muscle mass, as well as diminishing symptoms of depression, fatigue, and perceived pain [5, 7]. while not aggravating disease activity [8, 9]. In the short term, moderate intensity strength and aerobic exercises help with pain relief, improve physical ability and energy levels, result in better quality sleep and quality of life, [10, 11] while exercise in the long-term effectively reduces disease activity. In relatively early stages of RA (i.e., ≤5 years), it has also

been proven to promote clinical remission in these patients [12, 13]. Lower activity levels in those with IA on the other hand has resulted in less than ideal disease outcomes and significant morbidity, with a wider scale impact on healthcare cost and burdens worldwide [14, 15].

Despite the potential benefits, current research reported that patients with IA do not engage in regular physical activity as recommended [6, 16, 17]. These patients often cite fatigue, arthritis-related pain, and a belief that exercise may worsen arthritis as some of the barriers [6] and the confidence in the ability to exercise, the improvement in energy levels associated with exercise and knowledge of how exercise can benefit health as some of the facilitators [6, 18].

Previous studies looking into the physical activities in patients with IA were conducted in Europe, North Africa, Australia, and Korea [19, 20]. Validated questionnaires such as the International Physical Activity Questionnaire Short form (IPAQ-S), Global Physical Activity Questionnaire (GPAQ), and Inflammatory arthritis FAcilitators and Barriers (IFAB) questionnaire were used. However, differences in ethnic makeup, geographical context, working and lifestyle habits and disease course and outcomes within the Southeast Asian countries as compared to other Western and Asian counterparts could potentially affect physical activity levels as well as the factors which influence them [21].

Therefore, we aimed to understand the facilitators and barriers of physical activity in axSpA and RA patients in Singapore, and to find out if these facilitators and barriers differed between participants with different physical activity levels, diagnosis, age, and gender. This will aid in the development of targeted interventions to increase physical activity levels in patients with IA, and also further guide and optimize future clinical recommendations in the management of IA patients.

2 | Materials and Methods

2.1 | Study Design

A cross-sectional study was conducted from October 2020 to July 2021, with patients recruited from an outpatient clinic in the Department of Rheumatology and Immunology in Singapore General Hospital, a tertiary hospital in Singapore. Informed consent was obtained from participants and the study was approved by SingHealth Centralized Institutional Review Board (ref no.: 2020/2945).

2.2 | Participants

Participants were recruited based on the following criteria: (i) patients aged 21 years and above, (ii) clinically diagnosed with axSpA or RA, (iii) patients with axSpA had to fulfill Assessment of Spondyloarthritis International Society (ASAS) Classification Criteria 2009 for axSpA [22] whilst patients with RA had to fulfill ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria for RA [23]. Patients who were illiterate, cognitively impaired, wheelchair bound, or bedridden were excluded.

2.3 | Measures Collected

Patient demographics (age, gender, race, years of education, and employment status) and clinical information such as disease activity scores and comorbidities (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease) were collected. Facilitators, barriers, and levels of physical activity were also collected.

2.4 | Disease Activity

The disease activity was assessed with scales validated for use in Singapore—Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), [24] Ankylosing Spondylitis Disease Activity Score (ASDAS) [25] and Disease Activity Scale 28-Erthrocyte Sedimentation Rate (DAS28-ESR) for Rheumatoid Arthritis [26].

The BASDAI, ASDAS, and DAS28-ESR score utilized a numeric rating scale. The BASDAI included components such as severity of fatigue, back pain, joint pain, and swelling, localized tenderness and morning stiffness. The ASDAS score was calculated based on the severity of back pain, peripheral pain and swelling and duration of morning stiffness obtained through BASDAI, as well as patient global scores and CRP levels [25]. DAS28-ESR assessed the number of clinically tender or swollen joints and ESR levels for scoring. For each of these scoring systems, higher scores indicated higher disease activities. The BASDAI sum score ranges from 0 to 10, with scores of 4 or more indicating active disease [27, 28]. Having an ASDAS score of < 1.3 indicates an inactive disease, ≥ 1.3 and < 2.1 indicate a low disease activity, ≥ 2.1 and ≤ 3.5 indicate a high disease activity and a score of > 3.5 indicate very high disease activity [29]. The DAS28-ESR scores range from 0 to 9.4, where a score of 5.1 or more indicates highly active disease [30, 31].

2.5 | Facilitators and Barriers of Physical Activity

The barriers and facilitators of physical activities were categorized and documented in the use of the Inflammatory arthritis Facilitators and Barriers to Physical Activity (IFAB) Questionnaire. Each of the items fall into a category of either psychological status, social support, disease, or environmental factors. The IFAB questionnaire was validated specifically for patients with IA. There are a total of 10 items, each scored from 0 to 10, with scores of "0" meaning having no impact on participants' physical activities, and "10" meaning having maximum impact on participants' physical activities. Facilitators of physical activity are scored positively, whilst barriers to physical activities are scored negatively. The combined score ranges from −70 to 70, with a higher score indicating that the item was a greater facilitator and lower score indicating that the items was a greater barrier.

2.6 | Levels of Physical Activity

The Global Physical Activity Questionnaire (GPAQ) developed by the World Health Organization (WHO) was used to evaluate the level of physical activity as well as sedentary behavior

in participants. It contains 16 questions and estimates one's level of physical activity in terms of number of days per week and time spent per day in work, transport, and recreational-related activities and lastly, perceived time spent in sedentary behavior [32].

WHO defined those with high physical activity levels either having (1) At least 3 days of vigorous intensity activity, meeting minimum 1500 MET-minutes per week or (2) At least 7 days a combination of walking, moderate- or vigorous-intensity activities, meeting a minimum 3000 MET-minutes per week.

Participants with moderate levels of physical activity do not meet the criteria of the high activity levels group but have either (1) At least 3 days of vigorous-intensity activity for a minimum of 20 min per day or (2) At least 5 days of moderate intensity activity or walking for at least 30 min per day or (3) At least 5 days with a combination of walking, moderate- or vigorous-intensity activities, all achieving minimum 600 MET-minutes per week.

MET refers to metabolic equivalent of task. One MET is defined as the amount of oxygen consumed while at rest, which usually equals to 3.5 mL oxygen uptake/kg/min [33]. While MET-minutes refers to the number of METs of your activity multiplied by the number of minutes of the exercise performed. It is an indicator of the both the duration and intensity of the exercise [34].

Participants with low levels of physical activity do not meet any of the aforementioned criteria of each category [35].

2.7 | Statistical Analysis

Data was expressed as mean and standard deviation (SD) for continuous variables to facilitate comparison with other published studies, despite data being mostly non-parametric. While number and percentages were used for categorical variables. Patients were stratified based on their level of physical activity as defined by the Global Physical Activity Questionnaire (GPAQ) and diagnosis, age and gender. The age range was determined by taking the median age of 50 years from the participants surveyed.

The normality of data was tested using the Shapiro–Wilk test. Continuous variables were compared using Wilcoxon rank sum test or Kruskal–Wallis test as appropriate. Categorical variables were compared using chi-square test or Fisher exact test as appropriate depending on the sample size. A p-value of <0.05 was considered statistically significant. All statistical analyses were carried out using STATA SE version 15.0 for Windows (StataCorp, College Station, TX).

3 | Results

A total of 222 patients were included, of which 109 had RA and 113 had axSpA. Table 1 looks into participant characteristics. Table 2 looks into comparing facilitators and barriers between those with high and moderate physical activity levels and those with low physical activity levels based on the GPAQ. Table 3 looks into comparing facilitators and barriers between RA and axSpA patients.

The mean (SD) age of all participants surveyed was 48.4 (14.8) years, with patients with axSpA being younger than the RA group [40.1 (12.6) years vs. 57.0 (11.7) years, respectively, $p<0.01$]. There were more males ($n=82$, 72.6% vs. $n=12$, 11.0%, respectively, $p<0.01$) and Chinese ($n=105$, 92.9% vs. $n=81$, 74.3%) in patients with axSpA compared to RA. More patients with RA had hypertension ($n=36$, 33.0% vs. $n=16$, 14.2%, $p<0.01$), diabetes mellitus ($n=15$, 13.8% vs. $n=5$, 4.4%, $p=0.02$) and hyperlipidemia ($n=62$, 56.9% vs. $n=41$, 36.3%, $p<0.01$).

3.1 | Levels of Physical Activity

About two-thirds ($n=144$, 66.7%) of all patients met the WHO recommendations on physical activity for health. Mean (SD) time of total physical activity on average per day was higher in patients with RA compared to axSpA [102.2 min (137.4) vs. 88.5 min (147.9) respectively, $p=0.59$], but the difference was not statistically significant. Mean time spent on work-related physical activities and travel-related activities was similar between both disease groups. However, patients with axSpA spent significantly more time on recreational-related physical activities per day compared to patients with RA [23.2 min (39.2) vs. 11.1 min (19.5), $p<0.01$]. Majority of patients ($n=168$, 77.8%) participated in low to moderate levels of physical activity. Sixty-three ($n=63$, 57.3%) patients with axSpA had high levels of sedentary activity, which was significantly greater than that observed in patients with RA [$n=31$, 29.2%, $p<0.01$].

3.2 | Barriers to Physical Activity

The top three barriers to participation in physical activity included a lack of motivation ($n=104$, 46.8%), level of symptoms which indicates the severity of symptoms ($n=99$, 44.6%) and weather conditions ($n=66$, 29.7%) (Table 1). These were also the top three barriers identified among participants with different levels of physical activity (Table 2). When stratified by diagnosis, this was similar in patients with RA, while having a belief that physical activity will worsen symptoms instead of weather conditions was the third most common barrier in patients with axSpA ($n=30$, 26.5%) (Table 3). When grouped by age and gender, the top three barriers were similar for those age >50 and females, while the belief that physical activity will worsen symptoms instead of weather conditions, like patients with axSpA, was also the third barrier in patients age ≤ 50 ($n=37$, 32.5%) and males ($n=28$, 29.8%) (Tables S1 and S2).

3.3 | Facilitators of Physical Activity

Top three facilitators of physical activity included knowledge of the benefits of physical activity for health ($n=153$, 68.9%) and mood ($n=125$, 56.3%) as well as confidence on how to exercise safely ($n=121$, 54.5%) (Table 1). These were also the top three facilitators identified among participants with different levels of physical activity (Table 2), diagnosis (Table 3), age (Table S1) and gender (Table S2). It was also noted that more female participants rated the presence or absence of support from family and friends [$n=56$, 43.8% vs. $n=18$, 19.1%, $p<0.01$] as well as healthcare professionals [$n=55$, 43.0% vs. $n=21$, 22.3%, $p<0.01$] as being

TABLE 1 | Participant characteristics.

Characteristics	axSpA ($n=113$)	RA ($n=109$)	Total ($N=222$)	p
Current age, mean (S.D.), years	40.1 (12.6)	57 (11.7)	48.4 (14.8)	<0.01
Male sex, *n* (%)	82 (72.6)	12 (11.0)	94 (42.3)	<0.01
Race, Chinese, *n* (%)	105 (92.9)	81 (74.3)	186 (83.8)	<0.01
Body mass index, mean (S.D.), kg/m^2	25.7 (5.2)	24.9 (5.4)	25.3 (5.3)	0.15
More than 10 years of education, *n* (%)	108 (95.6)	79 (72.5)	187 (84.2)	<0.01
Employment status				
Employed, *n* (%)	89 (78.8)	65 (59.6)	154 (69.4)	<0.01
Unemployed, *n* (%)	5 (4.4)	9 (8.3)	14 (6.3)	
Student, *n* (%)	13 (11.5)	1 (0.9)	14 (6.3)	
Housewife, *n* (%)	3 (2.7)	16 (14.7)	19 (8.6)	
Retiree, *n* (%)	3 (2.7)	18 (16.5)	21 (9.5)	
Co-morbidities				
Hypertension, *n* (%)	16 (14.2)	36 (33.0)	52 (23.4)	<0.01
Diabetes mellitus, *n* (%)	5 (4.4)	15 (13.8)	20 (9.0)	0.02
Hyperlipidemia, *n* (%)	41 (36.3)	62 (56.9)	103 (46.4)	<0.01
Coronary artery disease, *n* (%)	3 (2.7)	0 (0)	3 (1.4)	0.25
Chronic kidney disease, *n* (%)	1 (0.9)	1 (0.9)	2 (0.9)	1.00
BASDAI, mean (S.D.)	2.5 (1.9)			
ASDAS[b], mean (S.D.)	2.0 (0.9)			
DAS28-ESR, mean (S.D.)		2.7 (1.3)		
Physical activity[a]				
Meets WHO recommendations on physical activity for health, *n* (%)	75 (68.2)	69 (65.1)	144 (66.7)	0.63
Mean time of total physical activity on average per day (S.D.), minutes	88.5 (147.9)	102.2 (137.4)	95.2 (142.7)	0.59
Mean time spent on work-related physical activities on average per day (S.D.), minutes	42.6 (121.3)	58.5 (124.5)	50.4 (122.9)	0.10
Mean time spent on travel-related physical activities on average per day (S.D.), minutes	22.8 (43.2)	32.6 (49.7)	27.6 (46.6)	0.08
Mean time spent on recreational-related physical activities (sport, fitness or recreational activities) on average per day (S.D.), minutes	23.2 (39.2)	11.1 (19.5)	17.3 (31.7)	<0.01
WHO level of physical activity[a]				
Low level of physical activity, *n* (%)	53 (48.2)	42 (39.6)	95 (44.0)	0.44
Moderate level of physical activity, *n* (%)	35 (31.8)	38 (35.8)	73 (33.8)	
High level of physical activity, *n* (%)	22 (20.0)	26 (24.5)	48 (22.2)	
High level of sedentary activity[c], *n* (%)	63 (57.3)	31 (29.2)	94 (43.5)	<0.01

TABLE 1 | (Continued)

IFAB Item	Total number who rated item as a facilitator, *n* (%)	Total number who rated item as a barrier, *n* (%)	Total number who rated item as having no impact, *n* (%)	*p*
Level of symptoms (pain, fatigue, lack of mobility)	33 (14.9)	99 (44.6)	90 (40.5)	
Weather conditions	16 (7.2)	66 (29.7)	140 (63.1)	
Presence or absence of support from others (friends, family)	74 (33.3)	13 (5.9)	135 (60.8)	
Presence or absence of support and/or advice from healthcare professionals	76 (34.2)	12 (5.4)	134 (60.4)	
A belief that physical activity will make symptoms worse	—	63 (28.4)	159 (71.6)	
Lack of motivation	—	104 (46.8)	118 (53.2)	
Lack of knowledge on which exercises to do and how much	—	46 (20.7)	176 (79.3)	
Knowledge of benefits of physical activity for health	153 (68.9)	—	69 (31.1)	
Knowledge of benefits of physical activity for mood	125 (56.3)	—	97 (43.7)	
Confidence on how to exercise safely	121 (54.5)	—	101 (45.5)	

[a]Three participants from both RA and SpA groups were excluded from the analysis for physical activity due to erroneous responses.
[b]Twenty-seven participants with SpA did not have results for ASDAS as they did not test for CRP levels.
[c]Defined as more than 8 h of sedentary activity.

facilitators of physical activity. However, more male participants rated these as having no impact [$n = 70$, 74.5% vs. $n = 65$, 50.8%, $p < 0.01$; $n = 65$, 69.1% vs. $n = 69$, 53.9%, $p < 0.01$] (Table S2).

4 | Discussion

In this study, we identified the facilitators and barriers to physical activity in patients with RA and axSpA. Patients with RA were older, predominantly female, and had more comorbidities than patients with axSpA. While patients with RA spent more time on average per day on work and travel-related activities, patients with axSpA spent more time on recreational-related physical activities.

Overall, the lack of motivation, level of symptoms and weather conditions were the top three barriers which discouraged participants from being involved in physical activity. Based on similar studies, level of symptoms and lack of motivation were also significant barriers to exercise, while a study in Australia noted that a proportion of respondents cited environmental and situational barriers such as weather conditions, in addition to the aforementioned factors as a significant barrier [18, 20, 36–38].

Knowledge of the benefits of physical activity for health and mood, and the confidence on how to exercise safely were the top three facilitators for patients to engage in physical activity, regardless of different levels of physical activity and diagnosis. Improvement in symptoms and health were also commonly reported as facilitators to physical activity as well in other studies [38]. However, as compared to other studies, social motivation and being aware of the benefits of physical activity was less of a facilitator for patients with RA in Western countries like London [39].

The public's perception and attitude towards health and healthcare and thus facilitators and barriers are shaped by the cultural, societal, and geographical context of Singapore being a smaller, population dense, tropical and multi-ethnic country. In Singapore, value is placed on familial and community support, yet at the same time fast-paced and high stress environments affect time with loved ones and energy levels to engage in physical activity. However, with the government's recent promotion of Healthier SG [40] and The Singapore Green Plan 2030, [41] trends are now observed on a macro level where there is now greater access to green spaces and exercise corners. Preliminary population health surveys indicate that with the implementation of these policies, overall physical activity in the local population has increased [42]. However, the longer term impact of these initiatives have yet to be fully understood.

The presence of support from friends and family, as well as reinforcement from healthcare professionals were more significant facilitators of physical activity in female patients in our population. Studies have investigated how support from healthcare professionals have facilitated greater physical activity engagement in females with other medical conditions [43]. One probability is that females, especially Asians, place greater importance in having supportive communities and peer motivation [44]. It has been highlighted in previous studies that cultural differences

TABLE 2 | Facilitators and Barriers questionnaire (IFAB), grouped by levels of physical activity based on Global Physical Activity Questionnaire (GPAQ) ($n = 216$).[a]

	Number of participants who rated item as a facilitator, *n* (%)		Number of participants who rated item as a barrier, *n* (%)		Number of participants who rated item as having no impact, *n* (%)			Score of items, mean (S.D.)		
Item	**High and moderate levels of physical activity ($n = 121$)**	**Low levels of physical activity ($n = 95$)**	**High and moderate levels of physical activity ($n = 121$)**	**Low levels of physical activity ($n = 95$)**	**High and moderate levels of physical activity ($n = 121$)**	**Low levels of physical activity ($n = 95$)**	***p***	**High and moderate levels of physical activity**	**Low levels of physical activity**	***p***
Facilitators or barriers										
Level of symptoms (pain, fatigue, lack of mobility)	19 (15.7)	13 (13.7)	54 (44.6)	44 (46.3)	48 (39.7)	38 (40)	0.91	−1.7 (4.3)	−2.2 (4.3)	0.61
Weather conditions	7 (5.8)	8 (8.4)	37 (30.6)	28 (29.5)	77 (63.6)	59 (62.1)	0.75	−1.3 (3.5)	−1.5 (3.6)	0.92
Presence or absence of support from others (friends, family)	41 (33.9)	32 (33.7)	7 (5.8)	6 (6.3)	73 (60.3)	57 (60)	0.99	2.0 (3.7)	1.9 (3.6)	0.78
Presence or absence of support and/or advice from healthcare professionals	41 (33.9)	31 (32.6)	8 (6.6)	4 (4.2)	72 (59.5)	60 (63.2)	0.71	2.0 (3.8)	1.8 (3.3)	0.77
Barriers										
A belief that physical activity will make symptoms worse			37 (30.6)	24 (25.3)	84 (69.4)	71 (74.7)	0.39	−1.7 (2.8)	−1.5 (2.9)	0.48
Lack of motivation			54 (44.6)	49 (51.6)	67 (55.4)	46 (48.4)	0.31	−2.5 (3.1)	−3.2 (3.6)	0.12
Lack of knowledge on which exercises to do and how much			24 (19.8)	21 (22.1)	97 (80.2)	74 (77.9)	0.68	−0.9 (2.1)	−1.2 (2.4)	0.33
Facilitators										

(Continues)

TABLE 2 | (Continued)

Item	Number of participants who rated item as a facilitator, *n* (%)		Number of participants who rated item as a barrier, *n* (%)		Number of participants who rated item as having no impact, *n* (%)			Score of items, mean (S.D.)		
	High and moderate levels of physical activity (*n* = 121)	Low levels of physical activity (*n* = 95)	High and moderate levels of physical activity (*n* = 121)	Low levels of physical activity (*n* = 95)	High and moderate levels of physical activity (*n* = 121)	Low levels of physical activity (*n* = 95)	*p*	High and moderate levels of physical activity	Low levels of physical activity	*p*
Knowledge of benefits of physical activity for health	87 (71.9)	62 (65.3)			34 (28.1)	33 (34.7)	0.30	4.8 (3.4)	4.4 (3.6)	0.50
Knowledge of benefits of physical activity for mood	66 (54.5)	54 (56.8)			55 (45.4)	41 (43.2)	0.74	3.5 (3.5)	3.8 (3.7)	0.45
Confidence on how to exercise safely	69 (57.0)	48 (50.5)			52 (43.0)	47 (49.5)	0.34	3.7 (3.6)	3.6 (3.8)	0.83
Global IFAB score								7.9 (15.1)	6.0 (15.8)	0.41

[a]Six participants were excluded from this analysis due to erroneous responses for GPAQ.

TABLE 3 | Inflammatory arthritis Facilitators and Barriers questionnaire (IFAB), grouped by diagnosis.

		Number of participants who rated item as a facilitator, *n* (%)		Number of participants who rated item as a barrier, *n* (%)		Number of participants who rated item as having no impact, *n* (%)			Score of items, mean (S.D.)		
Category	**Item**	**axSpA (*n* = 113)**	**RA (*n* = 109)**	**axSpA (*n* = 113)**	**RA (*n* = 109)**	**axSpA (*n* = 113)**	**RA (*n* = 109)**	***p***	**axSpA (*n* = 113)**	**RA (*n* = 109)**	***p***
Facilitators or barriers	Level of symptoms (pain, fatigue, lack of mobility)	20 (17.7)	13 (11.9)	49 (43.4)	50 (45.9)	44 (38.9)	46 (42.2)	0.48	−1.5 (4.0)	−2.3 (4.5)	0.16
	Weather conditions	6 (5.3)	10 (9.2)	29 (25.7)	37 (33.9)	78 (69)	62 (56.9)	0.16	−1.1 (2.8)	−1.7 (4.1)	0.21
	Presence or absence of support from others (friends, family)	29 (25.7)	45 (41.3)	7 (6.2)	6 (5.5)	77 (68.1)	58 (53.2)	0.05	1.4 (3.3)	2.4 (3.9)	0.03
	Presence or absence of support and/or advice from healthcare professionals	32 (28.3)	44 (40.4)	6 (5.3)	6 (5.5)	75 (66.4)	59 (54.1)	0.16	1.6 (3.0)	2.3 (4.0)	0.07
Barriers	A belief that physical activity will make symptoms worse			30 (26.5)	33 (30.3)	83 (73.5)	76 (69.7)	0.54	−1.5 (2.8)	−1.7 (2.9)	0.54
	Lack of motivation			56 (49.6)	48 (44.0)	57 (50.4)	61 (56)	0.41	−2.8 (3.3)	−2.7 (3.3)	0.63
	Lack of knowledge on which exercises to do and how much			23 (20.4)	23 (21.1)	90 (79.6)	86 (78.9)	0.89	−0.9 (2.2)	−1.1 (2.3)	0.86
Facilitators	Knowledge of benefits of physical activity for health	78 (69.0)	75 (68.8)			35 (31.0)	34 (31.2)	0.97	4.4 (3.5)	4.7 (3.5)	0.65
	Knowledge of benefits of physical activity for mood	61 (54.0)	64 (58.7)			52 (46.0)	45 (41.3)	0.48	3.4 (3.6)	4 (3.6)	0.30
	Confidence on how to exercise safely	60 (53.1)	61 (56.0)			53 (46.9)	48 (44.0)	0.67	3.5 (3.7)	3.8 (3.7)	0.42
	Global IFAB score								6.6 (14.4)	7.8 (16.2)	0.34

results in different emotional processing styles, with interdependence being a driving force for many Asians [17, 45]. Social reinforcement from healthcare professionals, involvement of caregivers in patient care and group exercise programmes which are tailored to patients' abilities may be useful to facilitate uptake. By providing an environment to promote exercising safely, this may help to increase subsequent long-term adherence to physical activity among the female population.

The lack of significance in levels of physical activity between the RA and axSpA group based on the Global IFAB score could be due to the subjectivity of understanding and thus under or overreporting of actual physical activity levels. Additionally, the score has mainly be tried and tested in European countries and are subjected to interpretation based on the geographical and cultural environment [46] The study could benefit from a larger sample size with further refinement in the validity of Global IFAB in the Southeast Asian context.

There are other limitations to our study. Firstly, given the cross-sectional nature of the study, we cannot draw causal relationships between the facilitators and barriers with the physical activity levels. Secondly, although we used GPAQ, which is a validated tool, as a measure of physical activity, it is open to recall bias as compared to other objective markers such as step trackers and metabolic equivalent of task scores (MET-min/week). A prospective longitudinal cohort study will be helpful in determining the causal association between physical activity levels and that of the respective facilitators and barriers, while correlating and quantifying time spent on physical activity in patients with axSpA and RA. Thirdly, there was no data collected on the context in which our participants received formal education on the condition from and thus perceptions on the benefits of physical exercise on clinical outcomes may differ.

Nevertheless, a better understanding of the facilitators and barriers to physical activity for patients with axSpA and RA is essential for building more targeted and personalized systems to incorporating physical activity into patients' daily lives. The early introduction of tailored and gradated exercise prescriptions including specific type and dosages of exercise [6] guided by but not limited to the recommendation of guidelines such as EULAR or American College of Sport Medicine-American Heart Association (ACSM-AHA) can be pivotal in initiating effective exercise therapy from the point of diagnosis [47, 48].

Improving patient education to correct misconceptions and highlighting the advantages of physical activity for health, mood, symptom management, and structured programmes can significantly enhance IA management, particularly for female patients. By integrating various strategies, such as wearable devices, visual exercise demonstrations to address safety concerns with exercise in IA, and group-based programmes, this approach could ultimately boost the uptake and sustained participation in physical activity among the IA population [49, 50].

Author Contributions

A.Z.Y.L., T.H.W., C.T.M.W., Y.H.K. and W.F. conceived and designed this study. T.H.W., C.T.M.W. and W.F. acquired the data for this study. A.Z.Y.L., T.H.W., Y.H.K. and W.F. performed the analyses and prepared the first draft of the manuscript. A.Z.Y.L., T.H.W., C.T.M.W., Y.H.K. and W.F. interpreted the results. All authors read, revised critically, and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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Supporting Information

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LETTER TO THE EDITOR

The Relationship Between Patient-Reported Quality of Life and Physician-Derived Clinical Outcomes in Rheumatoid Arthritis in the Australian OPAL Dataset

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Dear Editor,

We are writing to present our findings from the use of routine integration of patient-reported outcomes (PROs) in assessing the impact of rheumatoid arthritis (RA) on patient quality of life. RA is an autoimmune inflammatory condition that primarily affects the synovial joints, leading to joint damage, pain, and functional impairment [1, 2]. Fatigue is a common symptom of active disease. The disease activity score-28 (DAS28) is a common composite score used to assess RA activity and categorize patients into remission, low (LDA), moderate (MDA), or high disease activity (HDA). DAS28 evaluates inflammatory aspects of RA through swollen and tender joint counts and acute phase reactants like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), alongside patient global assessments (PtG) [1].

Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are the mainstay of RA treatment, acting on inflammatory pathways. A treat-to-target approach promoting remission or LDA is supported by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) [3, 4]. Despite b/tsDMARD effectiveness in reducing inflammation, patients often experience residual symptoms—pain, fatigue, anxiety, sleep issues, and limited social participation—that significantly affect their quality of life.

To improve RA outcomes, a holistic treatment paradigm is essential, focusing on the patient as a whole. A critical step involves understanding the full disease burden experienced by patients, best achieved through standardized measurement of PROs. PROs offer valuable insights into health and quality of life beyond clinical assessments, gaining importance in clinical management and research [5].

Although various studies have explored the relationship between PROs and clinician assessments, the integration of PROs into routine care faces challenges. Time constraints, cumbersome paper-based surveys, and a lack of awareness about software solutions hinder implementation [6]. This has resulted in studies often being limited to single centers or small patient groups. Establishing the value of PROs and integrating them with clinical data requires improved clinical workflow and training for interpreting PRO data [7, 8]. Additionally, factors beyond RA, such as social circumstances, mental health issues, and life stressors, can influence PRO scores, complicating their relationship with disease activity. A comprehensive understanding of these contextual factors is vital for accurately interpreting PROs in RA.

Optimizing patient outcomes in Australian rheumatology (OPAL) comprises 112 Australian rheumatologists using the electronic medical record (EMR) Audit4 for routine clinical practice. This EMR facilitates secure electronic PRO questionnaires

(ePROs), taking 1–2 min to complete to encourage compliance, sent to patients via email or completed in-clinic [9]. The OPAL dataset is a retrospective, non-interventional cohort study aiming to generate real-world evidence regarding pain, fatigue, mood disturbance, and physical function among a large cohort of Australian RA patients.

The aims of this study therefore were to describe the relationship between patient-reported outcomes and physician reported clinical indices in a large cohort of Australian patients with RA, using an electronic PRO integrated into routine point of care clinical assessments.

1 | Methods

1.1 | Data Source

The OPAL dataset includes clinical information captured in EMRs during routine consultations by 112 rheumatologists across 42 clinics in six Australian states/territories. The participating rheumatologists are mainly in private practice, representative of the Australian rheumatology community. Data were deidentified prior to analysis and included patient demographics, disease history, PRO measures included Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), Patient Health Questionnaire-2 (PHQ-2), pain visual analogue scale (VAS), and the Routine Assessment of Patient Index Data 3 (RAPID3) which includes the Multi-Dimensional Health Assessment Questionnaire (MDHAQ) as a measure of functional impairment. Selection and development of feasible ePROs to administer at the point of care was described previously [9]. Clinician-recorded data included medication history, and disease severity assessed using swollen and tender joint counts (SJC and TJC respectively), inflammatory markers, physician global assessment and DAS28CRP(3).

The University of New South Wales (UNSW) Human Research Ethics Committee provided overarching ethics approval for OPAL, based on an opt-out arrangement (HC17799).

1.2 | Patient Population and Eligibility Criteria

Patients included in the study were diagnosed with RA per ICD-10 codes, aged 18 or older, had completed at least one PRO between April 2020 and April 2022, and were treated with at least one DMARD for a minimum of 6 months. Exclusion criteria included being over 95 years, recorded as deceased, or lacking visit data.

1.3 | Endpoints

The study focused on a number of key PROs deemed crucial for effective disease management, such as fatigue, physical function, and pain. PRO measures included FACIT-Fatigue, pain VAS, and PHQ2. We do not report on morning stiffness or detailed psychological outcomes. Questionnaires were delivered electronically to patients and encrypted upon return for review at the next consultation. PRO scores were compared to the most recent clinician-recorded outcomes within a three-month window.

1.4 | Statistical Analysis

Descriptive statistics summarized all endpoints. Data were described using counts and percentages for categorical variables and median and interquartile range for continuous variables. Non-parametric tests were employed for hypothesis testing (Kruskal–Wallis ANOVA and Mann–Whitney *U* test), with a Bonferroni correction applied for multiple comparisons. All analyses were conducted using R version 4.1.2. Sensitivity analysis compared ePRO respondents to the total RA cohort to assess potential selection bias.

2 | Results

2.1 | Levels of Pain, Fatigue, Mood Disturbance, and Physical Function

The results indicated that although many patients reported acceptable pain levels (62.8%) and not clinically relevant fatigue (60.2%), significant portions still experienced unacceptable pain (37.2%), clinically relevant fatigue (39.8%), and moderate impairment of function (19.5%). Most patients did not show signs of depression (88.7%), but a notable percentage reported possible depressive symptoms (11.2%) (Table 1).

2.2 | Clinical Assessments

Associations were observed between individual clinical disease markers and levels of pain, fatigue, and mood disturbance. Increased swollen and tender joint counts correlated with higher pain and fatigue levels. In patients with acceptable pain

TABLE 1 | Levels of pain, fatigue, mood disturbance and physical function for patients with rheumatoid arthritis.

Feature	Category	*n* (%)
Pain VAS ($n=1397$)	Unacceptable pain (>40 mm)	519 (37.2%)
	No pain or acceptable (≤40 mm)	878 (62.8%)
FACIT-F ($n=2180$)	Clinically relevant fatigue (≤34)	867 (39.8%)
	No fatigue or not clinically relevant (>34)	1313 (60.2%)
PHQ2 Category ($n=2101$)	Possible depression (≥3)	250 (11.9%)
	Not depression (<3)	1857 (88.1%)
MDHAQ Category ($n=2243$)	Severe	14 (0.6%)
	Moderate	438 (19.5%)
	Mild	913 (40.7%)
	Minimal	878 (39.1%)

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; MDHAQ, Multi-Dimensional Health Assessment Questionnaire; PHQ-2, Patient Health Questionnaire-2; VAS, pain visual analogue scale.

the median (interquartile range [IQR]) for SJC was 0 [0–1] and for TJC was 0 [0–1], whereas for unacceptable pain the SJC was 1 [0–3] and TJC 1 [0–4]. This was highly significant ($p = 7.6e-16$ to 1e-20, using Bonferroni correction = 8.3e-o3, and Mann–Whitney U test). Similarly, in patients with acceptable fatigue the median ([IQR] for SJC was 0 [0-1] and for TJC was 0 [0–1]), whereas for unacceptable fatigue the SJC was 1 [0–3] and TJC 1 [0–3], which was also highly significant ($p = 7.9e-09$ to 6.3e-14).

The analysis also revealed that higher pain VAS scores and lower FACIT-F scores correlated with higher disease activity, aligning with DAS28CRP (3) categories (Figure 1). Among patients classified as being in DAS28CRP (3) remission or LDA, many still reported high levels of pain (32.7%) and clinically relevant fatigue (36.1%) (Figure 1). Although MDHAQ showed a significant relationship to DAS28 (CRP) categories the p values were obtained by simulation and are not likely to represent true values, hence they are not further displayed in the results.

3 | Discussion

Our study explored the relationship between PROs and clinical outcomes in a large RA cohort within the Australian OPAL dataset. Although the overall clinical characteristics indicated effective management of RA, a significant portion reported unacceptably high levels of pain and fatigue. These findings echo similar studies in other populations [10–13]. This study thus highlights that traditional clinician led clinical assessment measures in RA do not capture the total patient symptom burden, particularly those of pain and fatigue.

The complexity of pain and fatigue in RA is poorly understood and may be contributed to by a number of comorbid factors [14, 15]. Although clinician measures correlate with PROs, they may not capture the entire burden of disease experienced by patients, highlighting the need for holistic assessments in clinical practice.

4 | Study Limitations

This analysis is limited by potential selection bias regarding which patients complete questionnaires and which clinicians distribute them. Although sensitivity analysis showed similar characteristics between ePRO respondents and the broader cohort, the possibility of unmeasured bias remains. The retrospective design also presented challenges with missing data and variability in clinician data recording.

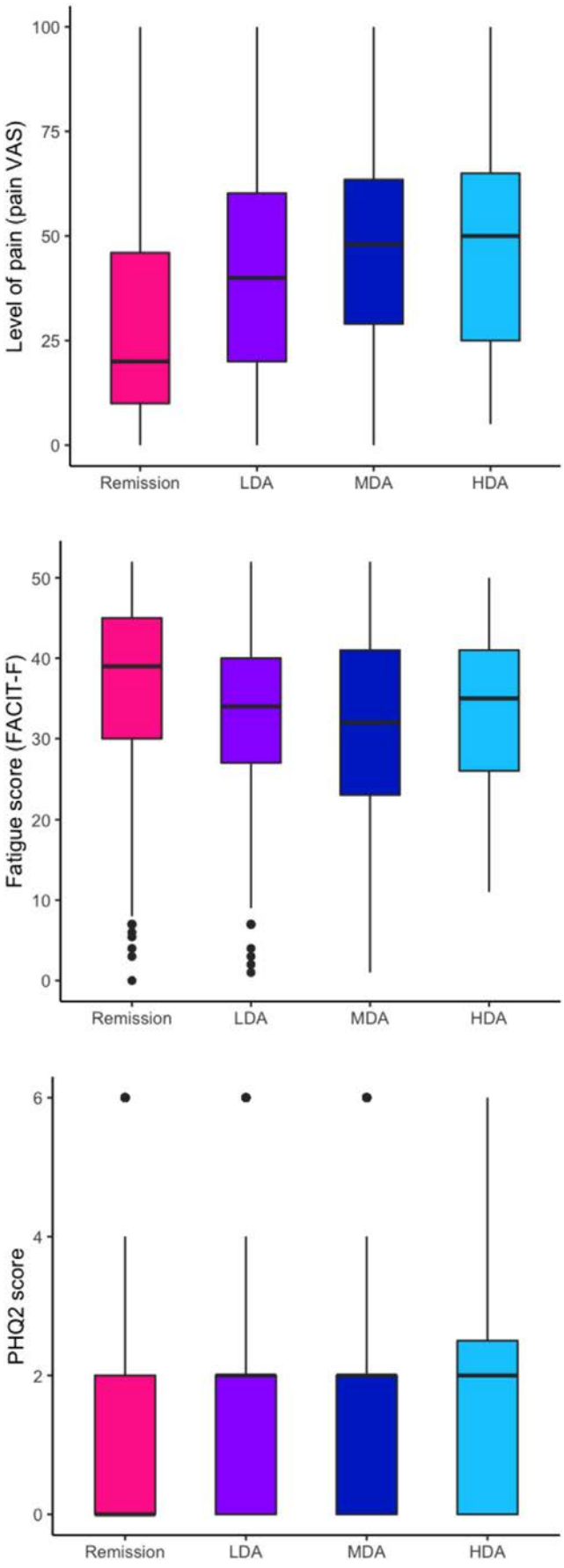

FIGURE 1 | Relationship between patient-reported outcomes and disease activity. Higher disease activity levels were associated with a higher pain VAS score ($p = 3.8e-25$), lower FACIT-F score ($p = 7.9e-15$) (i.e., higher fatigue) and a higher PHQ2 total score ($p = 9.3e-14$). Statistical tests of association used Kruskal–Wallis ANOVA with Bonferroni correction. Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F); Patient Health Questionnaire-2 (PHQ-2); pain visual analogue scale (VAS).

4.1 | Future Work

Future studies should consider non-inflammatory pain and fatigue mechanisms as possible significant factors in understanding the impact of RA on PROs. Investigating diverse RA subsets could enhance understanding of symptom patterns and disease activity, informing more targeted treatment strategies.

Author Contributions

Study design: G.L., N.A., C.O., T.S., C.T.D. Aquisition of data: G.L., T.R., P.P., S.J., L.G., N.A., C.T.D. Interpretation of data and contributed to the drafting and initial revision of manuscript: all authors. No honoraria or payments were made for authorship.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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REVIEW

Mechanisms Associated With Renal Injury in Hyperuricemia and Strategies for the Development of Natural Active Substances

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ABSTRACT

Hyperuricemia (HUA) is a metabolic condition resulting from an abnormality in the process of purine metabolism. Its occurrence has been on the rise globally. The results of relevant studies show that 5% to 12% of HUA patients will eventually develop gout, and one-third of these patients may involve the kidneys and develop kidney disease. Although the severe renal health hazards associated with excessive uric acid levels are well known, the specific molecular mechanisms remain unknown. Therefore, this paper provides insights into the mechanisms and related chain reactions of HUA leading to renal injury from three perspectives: imbalance of intestinal homeostasis, oxidative stress response, and NLRP3 inflammasome. In addition, standing against the background of the strong side effects and high tolerability disadvantages of commercially available uric acid-lowering drugs such as *allopurinol*, *benzbromarone*, and *febuxostat*, the development of a new active anti-hyperuricemic drug with fewer side effects is justified. This article reviews the progress of research on natural actives (probiotics, dietary polyphenols, peptides) with a high safety profile, multi-targeting, and integrative modulatory effects, in an attempt to provide some ideas for drug developers.

1 | Introduction

Hyperuricemia (HUA) is a condition characterized by an abnormal purine metabolism, leading to persistently elevated serum uric acid levels [1]. HUA typically manifests when the concentration of uric acid in the blood surpasses 7 mg/dL in males and postmenopausal women, or 6 mg/dL in premenopausal women [2, 3]. On a global scale, the prevalence of HUA has had a growth of over 20% and is on the rise among younger individuals [4]. China, as the largest developing nation globally, has an estimated prevalence of HUA at 16.4%, as determined through a meta-analysis of 16 research studies [5]. Furthermore, an increasing body of epidemiological research has demonstrated that uric acid can cause significant harm to the kidney, leading to the development of renal tubular lesions, interstitial fibrosis, and the accumulation of uric acid crystals [6]. Failure to address renal dysfunction can result in severe renal decompensation and the development of renal failure, leading to the accumulation of waste products in the body, a condition known as uremia.

Over the years, the number of papers on HUA leading to kidney damage has increased. An extensive study involving 444 462

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individuals in a UK biobank demonstrated a positive correlation between elevated levels of uric acid and an increased incidence of kidney cancer, particularly among women [7]. Another study, which involved 26 971 patients and utilized multivariate analysis to assess factors associated with HUA, found that serum uric acid levels tended to increase while renal function declined [8]. Nevertheless, there is a lack of consensus regarding the impact of uric acid on the advancement of chronic kidney disease (CKD). A study involving 6642 participants from the National Health and Nutrition Examination Survey 1999–2018 discovered that maintaining appropriate levels of uric acid in the blood enhances the overall well-being of individuals with CKD [9]. A research study of 34 831 participants from a Taiwanese biobank found no significant link between levels of uric acid in the blood and the chance of developing CKD, as determined by genetic risk markers and seven Mendelian randomization methods [10]. In conclusion, based on a large amount of experimental data, issues such as uric acid-related kidney diseases should not be ignored, and careful study of the mechanisms of uric acid-induced pathological changes in the kidneys will contribute to developing new therapies for preventing and treating kidney injury.

The primary treatment medications commonly used are *allopurinol* and *benzbromarone*. *Allopurinol* works by reducing the synthesis of uric acid, while *benzbromarone* promotes the excretion of uric acid. In recent years, new drugs have brought hope to patients. In December 2015, the regulatory authorities approved a medication produced by Ardea Biosciences, a subsidiary of AstraZeneca, for the treatment of individuals who do not attain the necessary levels of uric acid in their blood while using only xanthine oxidase inhibitors [11]. Regrettably, *Lesinurad* did not receive approval in China due to the potential danger of acute renal failure. Overall, the use of these new drugs is limited by high cost, lack of long-term safety data, and poor availability. In recent years, natural ingredients (probiotics, dietary polyphenols, and peptides) have attracted the attention of drug developers due to their high safety profile, multifunctionality, integrative modulation, broad clinical applications, and availability. This article aims to describe the mechanism of HUA-induced renal injury and the recent progress in the development of natural products.

2 | Overview of Uric Acid

Uric acid, a purine derivative with a molecular weight of 158 Da, was initially identified in bladder stones by the Swedish chemist Scheele in 1776 [12]. In humans and higher primates, uric acid is the final result of the breakdown of purines. It is mostly produced in the liver from both purines that are naturally present in the body and purines obtained from diet. The mechanism of synthesis includes hydrolysis of purine nucleotides, formation of hypoxanthine nucleotides, conversion of adenosine diphosphate ribose and guanosine diphosphate ribose, formation of inosine and guanosine, conversion of uracil and guanine nucleotides, and ultimately formation of uric acid [13] (Figure 1). More precisely, the ribulose-5-phosphate produced through the breakdown of sugars is transformed into ribulose phosphate pyrophosphate (PRPP) by the enzyme ribulose-5-phosphate synthase. This PRPP is then turned into inosine monophosphate. Adenosine monophosphate (AMP), guanosine monophosphate (a purine nucleotide utilized in the synthesis of DNA and RNA), and inosine are derived from this intermediate product. The enzyme purine nucleoside phosphorylase converts the latter into hypoxanthine. Xanthine oxidase (XO), an enzyme that is suppressed by *allopurinol*, transforms hypoxanthine into xanthine, which is then turned into uric acid [14].

The kidneys eliminate around 70% of uric acid, while the gastrointestinal tract eliminates the remaining 30%. A minimum of 90% of the uric acid that is filtered in the kidney is absorbed again through specific uric acid transporter proteins such as URAT1 and GLUT9 [15]. Among these proteins, URAT1 transports uric acid by countertransport and eliminates anionic organic molecules such as lactate, ketone bodies, and foreign drugs. Uricase in lower primates, like rats and mice, converts uric acid into allantoin, a substance that is 100 times more soluble in water than uric acid. This allows for efficient excretion of allantoin in the urine. Nevertheless, in humans and higher primates, the catabolism of purine ceases at the uric acid phase because of the absence of a functioning uricase gene and active uricase [12]. Uric acid exhibits modest acidity at a pH level, with a pKα value of 5.8. Uric acid mostly exists as urate, and the production of urate crystals escalates with higher levels of urate in the bloodstream. When the concentration of uric acid surpasses 6.8 mg/dL, crystals of monosodium urate (MSU) are formed [16].

3 | Mechanisms of HUA Leading to Abnormal Renal Function

3.1 | Imbalance in Intestinal Homeostasis Leads to Kidney Damage

The human gut microbiota is an exceptionally diverse ecosystem, consisting of trillions of species, including bacteria, fungi, archaea, viruses, and protozoa [17]. The collective genes of the gut microbiota form a gene pool several orders of magnitude larger than the human genome and are sometimes referred to as the "basic organ" of the human body [18, 19]. Changes in gut microbiota composition and metabolic abnormalities are strongly linked to a variety of diseases. These include neurological disorders [20], cardiovascular diseases [21], and autoimmune conditions [22].

An increasing number of studies have highlighted the significant impact of the gut microbiota on kidney function. The pathological link between the gut microbiota and kidney disease is referred to as the "gut-kidney axis" [23]. Besides the kidneys, the gut also functions as a site of uric acid excretion, with genes involved in uric acid synthesis and transport highly expressed in the gastrointestinal tract. Approximately 30%–40% of uric acid is excreted through the gut, and impaired clearance can contribute to HUA [24]. Intestinal homeostasis imbalance, which leads to renal dysfunction, manifests in three ways (Figure 2): first, metabolic disorders of the gut microbiota. In the presence of high SUA levels, dysregulation of the nitrogen cycle, increased uric acid degradation, and disruption of the hepatic urea cycle in the gut microbiota contribute to renal injury [25]. Zhou et al. demonstrated that upregulation of purine metabolism, enhanced degradation of intestinal uric acid, and improved microbial function significantly ameliorated HUA-induced renal

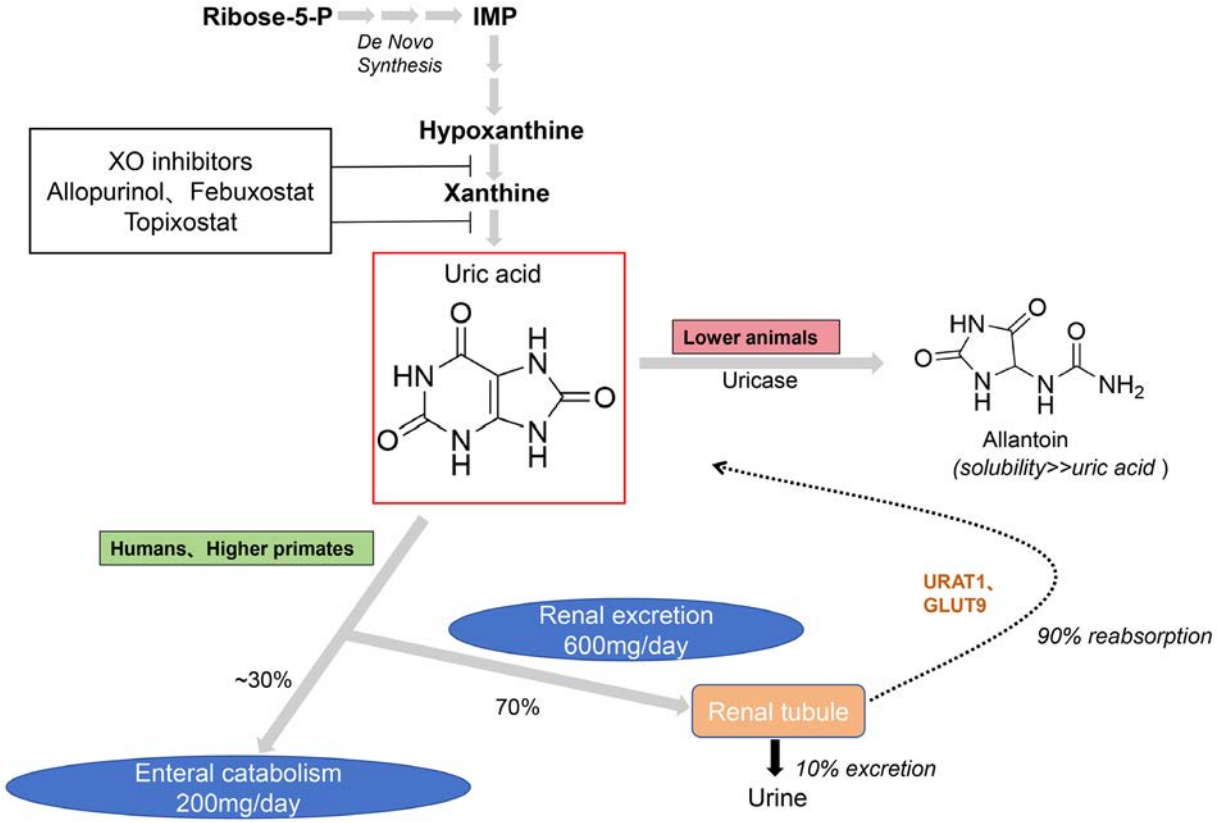

FIGURE 1 | Schematic representation of uric acid synthesis and metabolism. Uric acid is the end product of purine metabolism; only 20% of the purines in the body are from food, and 80% of the purines are produced by the body cell metabolism. In vivo purine nucleotide synthesis from scratch refers to the use of ribose phosphate, amino acids, one-carbon units and other simple substances as raw materials after a series of enzymatic reactions to synthesize purine nucleotides, nucleotides in the cell hydrolyzed into nucleosides under the action of the enzyme nucleotidase, nucleosides by the action of the enzyme nucleoside phosphorylase, the decomposition of free bases and ribose 1-phosphate, purine bases are ultimately hydrolyzed to uric acid. Uric acid is excreted mainly through the intestines (1/3) and kidneys (2/3).

injury [26]. Second, disruption of gut microbiota diversity. A large Mendelian randomization study found that changes in gut microbiota diversity not only improve host urate metabolism but also serve as a predictor of urate metabolism disorders [27]. Remodeling the gut microbiota, particularly by increasing beneficial bacteria (e.g., Lactobacillus and Ruminalococcus) and reducing pathogenic bacteria (e.g., Bacteroidetes), may alleviate HUA-associated kidney injury [28]. Third, disruption of the gut barrier. Under normal conditions, a stable, proportional relationship exists between the gut microbiota, which bind to the intestinal mucosa to form a regular microbial barrier. Impaired intestinal barrier function has been observed in the Uox-KO mouse model [29]. Specifically, uric acid disrupts the intestinal barrier by activating NLRP3 inflammasomes through transporter protein (TSPO) [30]. Furthermore, Ma's experiments showed that uric acid directly damages intestinal epithelial cells (IECs) via the TLR4/NLRP3 pathway, facilitating the transfer of microbial metabolites into systemic circulation, thereby increasing systemic inflammation [31].

The gut microbiota is a dynamic and complex ecosystem, with its balance influenced by numerous factors [32]. In addition to external factors such as diet and drug use, the host's genes, habits, lifestyle, immune status, and disease state also play a crucial role. Genetic variation influences an individual's response to microorganisms, while healthy lifestyle habits, such as a balanced diet and regular exercise, support the growth of beneficial bacteria. The immune system's health directly affects the balance of the gut microbiota, while disease induces microbial imbalances. Collectively, these factors help maintain the stability of the gut microbiota, which is crucial for human health. The development of high-throughput sequencing technologies, such as metagenomics and 16S rRNA sequencing [33], has enabled deeper investigation of the gut microbiota, helping to understand its composition and function across different populations and diseases and explore its relationship with HUA.

3.2 | Occurrence of Oxidative Stress Leading to Kidney Damage

Oxidative stress refers to the accumulation of ROS, primarily resulting from high metabolic activity and oxygen depletion [34]. Elevated intracellular ROS levels cause oxidative damage, including lipid peroxidation of cell membranes and organelles, as well as oxidation of DNA and RNA [35]. Oxidative stress is a major contributor to death and disability in many chronic and degenerative diseases [36]. Changes in uric acid levels are recognized as biomarkers of oxidative stress, and uric acid-induced oxidative stress contributes to renal dysfunction through multiple pathways (Figure 3). For instance, uric acid accumulation in the kidney triggers mast cell degranulation, thereby exacerbating

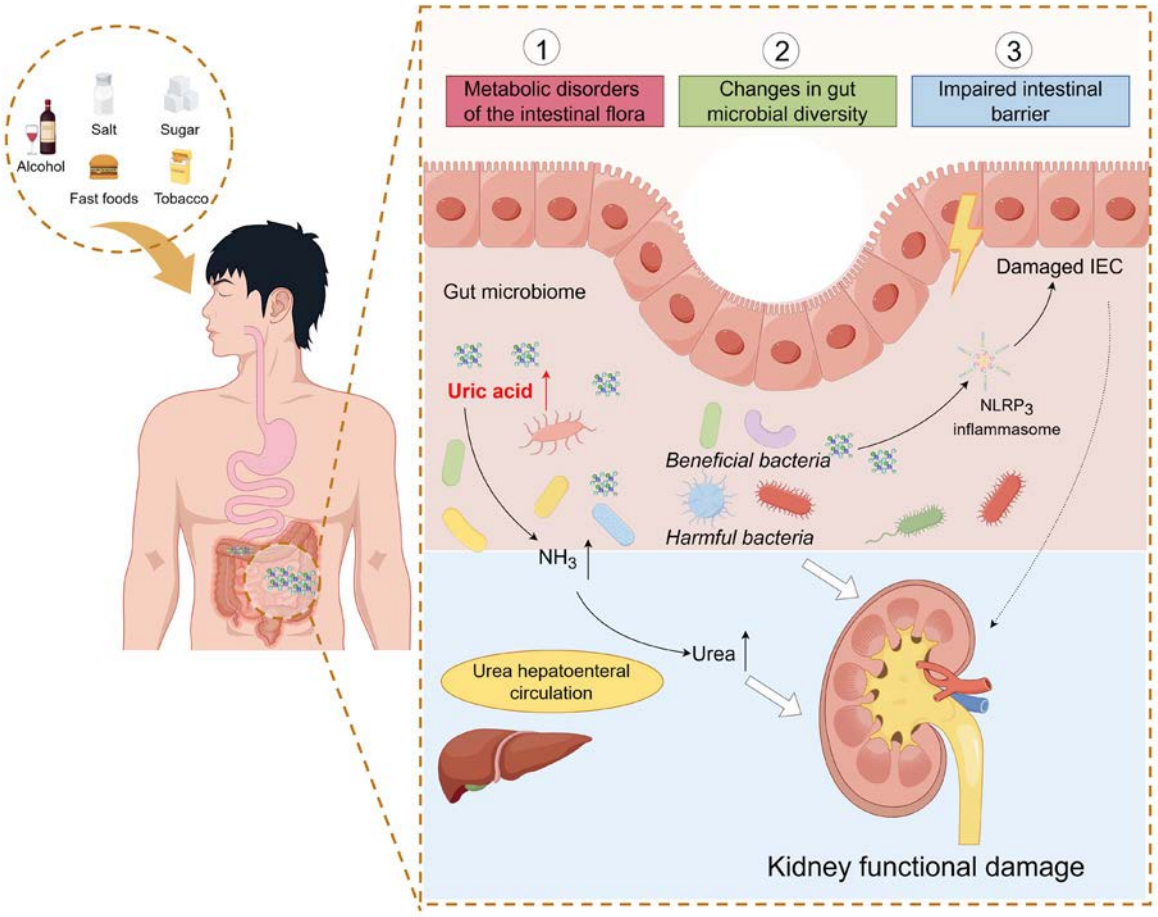

FIGURE 2 | Schematic representation of the mechanisms involved in impaired renal function due to imbalance of intestinal homeostasis. The interconnection between the gut microbiome and kidney disease is known as the "gut-kidney axis". On the one hand, high uric acid levels in HUA patients lead to imbalances in gut homeostasis. On the other hand, the imbalance of gut homeostasis leads to renal impairment in three ways: Metabolic disorders of the gut flora, alteration of gut microbial diversity, and impairment of the gut barrier.

oxidative stress [37, 38]. Additionally, uric acid induces apoptosis of human renal proximal tubular cells by activating NADPH oxidase NOX4 [39]. Zhang et al. showed that increased oxidative stress, combined with mast cell recruitment and activation of the TGF-β1/Smad2/3 pathway, accelerated renal fibrosis progression in HUA rats [40]. Endothelial dysfunction is a hallmark of mild HUA-induced renal injury. Specifically, oxidative stress plays a key role in HUA-induced endothelial dysfunction and glomerular hemodynamic alterations [37].

The kidney is the second-largest organ in terms of mitochondrial content. Dysregulation of antioxidant mechanisms and excessive ROS production can induce mitochondrial oxidative stress, exacerbating renal injury. Oxidative stress is a primary cause of apoptosis in renal tubular epithelial cells. HUA-induced oxidative stress in the kidney is linked to mitochondrial dysfunction and decreased ATP levels [41]. Oxidative stress induces apoptosis via both mitochondria-dependent and mitochondria-independent pathways [42]. For example, MSU crystals promote ROS accumulation, inflammatory cytokine expression, and mitochondrial cysteine-asparaginase-dependent apoptosis in renal cells [43]. Furthermore, studies have shown a close relationship between mitochondrial oxidative stress, ROS production, and mitochondrial autophagy, all of which contribute to various pathological conditions in acute kidney injury (AKI) [44]. These results suggest that targeted molecular therapies aimed at mitochondria may be an effective approach for treating renal damage caused by HUA.

A study found that allopurinol-induced reduction in uric acid levels slowed CKD progression during a short-term follow-up (6–12 months) [45]. A randomized, double-blind trial in stage III CKD patients showed that allopurinol reduced SUA levels but did not attenuate ROS-mediated oxidative stress [46]. These findings offer new insights into the combined use of allopurinol. The molecular mechanisms underlying the impaired redox state in the kidney are still unclear. Several antioxidant signaling pathways are known. For instance, uric acid synthesized and secreted by intestinal cells activates the Nrf2 signaling pathway, inducing downstream antioxidant factors that reduce oxidative stress [24, 47]. Further studies show that Nrf2 improves mitochondrial homeostasis and fibrosis by reducing oxidative stress, enhancing antioxidant signaling, and decreasing TGF-β1 signaling, key regulators of renal tubular cells [48]. These findings suggest that Nrf2 signaling plays a crucial role in reducing uric acid-induced oxidative stress.

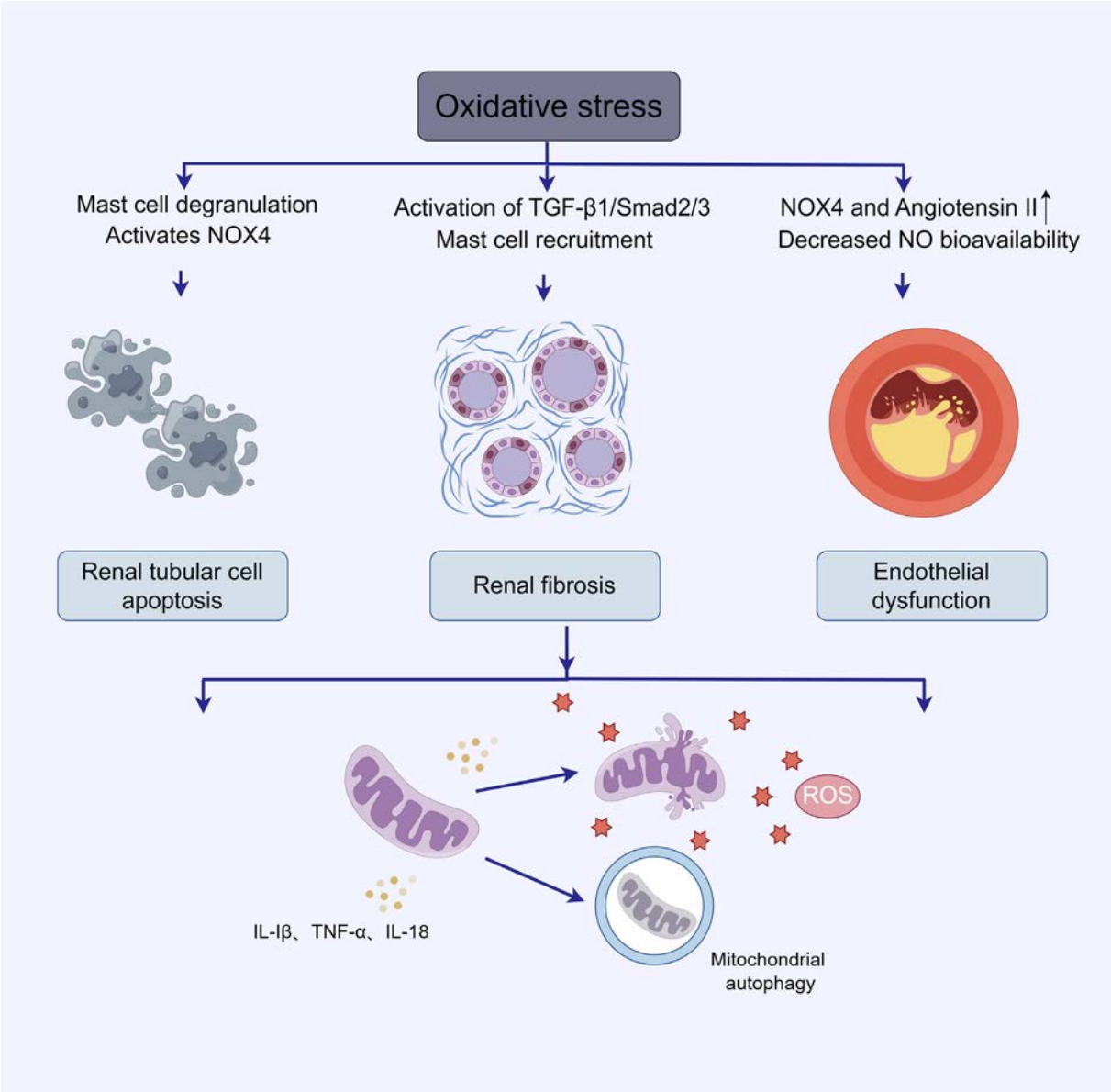

FIGURE 3 | Schematic representation of renal impairment due to HUA-related oxidative stress. Accumulation of uric acid promotes renal tubular cell apoptosis; activation of related inflammatory signaling pathways such as TGF-β1/Smad2/3 promotes the progression of renal fibrosis; in addition, oxidative stress contributes to endothelial dysfunction and changes in glomerular dynamics. Mitochondrial dysfunction as well as mitochondrial autophagy have been suggested as molecular mechanisms of redox disorders in the kidney.

3.3 | NLRP3 Inflammasome Cause Kidney Damage

Inflammasomes are components of the innate immune system [49]. Recent studies have linked abnormal inflammatory vesicles to various common and complex diseases, including metabolic disorders like diabetes, obesity, and atherosclerosis, as well as autoimmune diseases such as multiple sclerosis and lupus [50]. NLRP3 is an inflammatory protein in the innate immune system that detects pathogen invasion and intracellular damage, initiating a response through the formation of NLRP3 inflammasomes. The main components of NLRP3 inflammasomes are NLRP3, caspase-1, and ASC (apoptosis-associated speckled protein) [51]. Aberrant activation of NLRP3 can induce a chronic inflammatory state in vivo [52]. NLRP3 inflammasomes serve as molecular platforms that trigger caspase-1 activation and the lysis of IL-1β, IL-18, and Gasdermin D (GSDMD) through various mechanisms. Additionally, interactions between the NLRP3 inflammasome and endoplasmic reticulum stress, lysosomal dysfunction, mitochondrial dysfunction, as well as Golgi and extracellular vesicles contribute to cellular damage and even cell death [53].

Uric acid mediates kidney injury by activating NLRP3 inflammasomes (Figure 4). In an in vivo renal epithelial-mesenchymal transition model, uric acid activates NLRP3 inflammasomes, secretes inflammatory factors, and disrupts renal parenchymal cell morphology and function. Inhibiting NLRP3 inflammasome activation attenuates renal injury [54, 55]. Relevant studies have elucidated specific activation mechanisms. HUA leads to urate crystal formation, which is recognized by the immune system as a danger signal, stimulating macrophage activation and NLRP3 inflammasome activation, ultimately triggering

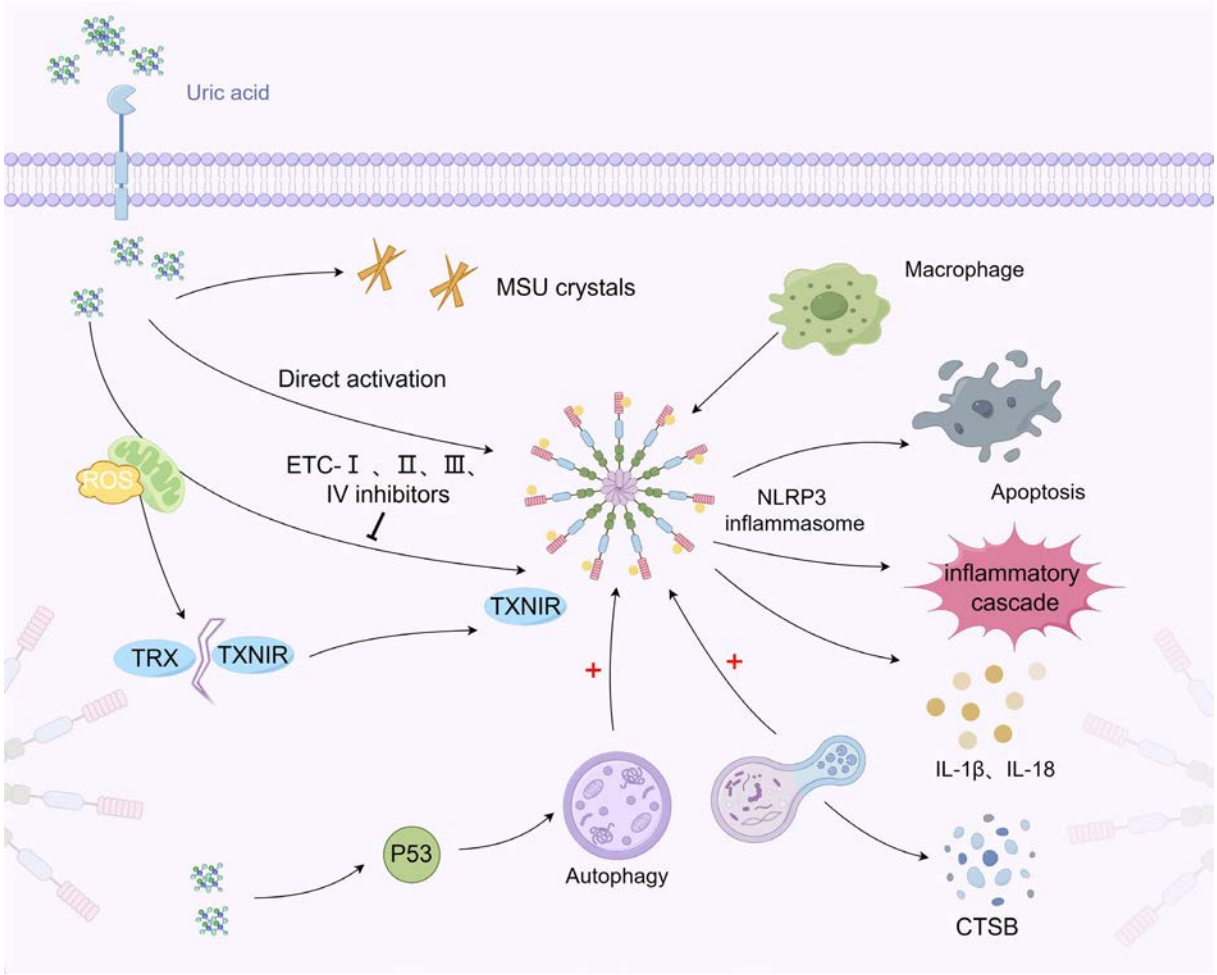

FIGURE 4 | Schematic illustration of uric acid activation of NLRP3 inflammasome-mediated inflammatory cascade response and apoptotic pathway.

inflammatory cascades and apoptosis [56]. Notably, oxidative stress and inflammasome activation have synergistic effects. Soluble uric acid triggers NLRP3 inflammasomes in a mitochondrial ROS-dependent manner, accompanied by changes in the cellular redox state, including increased mitochondrial area and ROS production [57]. Urate crystals are sensitive to thioredoxin, which induces the separation of thioredoxin-interacting protein (TXNIP) from thioredoxin-ROS to bind to NLRP3 [58]. The Keap1-Nrf2 pathway is a key defense mechanism against oxidative stress in vivo [59]. Several studies show that restoring this pathway and blocking TXNIP/NLRP3 inflammasome activation can alleviate HUA-induced kidney injury [60, 61]. This suggests the potential for combining inflammasome inhibitors and ROS scavengers to reverse renal injury in future treatments.

Recent studies have shown that NLRP3 inflammasome activation is associated with increased autophagy and lysosomal disruption. Autophagy plays a crucial role in Na-K-ATPase (NKA) signaling and increased urate reabsorption in HUA-induced renal tubular injury. Inhibiting autophagy can alleviate NKA injury-mediated NLRP3 production [62]. Additionally, inhibiting autophagy prevents HN by suppressing NLRP3 inflammasome-mediated pyroptosis [55, 63, 64]. The salvage mechanism of dysregulated mitochondrial homeostasis plays a key role in the repair and protection of renal tubular injury [65]. Mediating the mitochondrial apoptosis signaling pathway prevents uric acid-induced inflammation in renal tubular epithelial cells [66]. Moreover, the mitochondrial electron transport chain (ETC) is essential for NLRP3 inflammasome activation, and inhibitors of ETC complexes I, II, III, and V prevent this activation [67]. Uric acid modulates the NLRP3/IL-1 signaling pathway, triggering ROS activation and K+ efflux, which exacerbates vascular endothelial cell injury in early CKD [68]. These results suggest that ROS, K+ channel activation, mitochondrial disorganization, and lysosomal disruption are likely the key intermediates mediating uric acid-induced NLRP3 inflammasome activation.

4 | Treatment Strategies

4.1 | Probiotics

Probiotics are composed of yeasts and live bacteria that possess various advantageous features. They have gained attention as a potential natural treatment due to their ability to regulate the gut microbiota and enhance overall well-being [69]. After reviewing a large amount of literature, we have compiled information on probiotics that effectively relieve the symptoms of HUA, mainly from the Lactobacillus group (Table 1). In addition, three treatment options were identified. The first is to

TABLE 1 | Therapeutic strategies with natural active substances for hyperuricemia-associated renal damage.

Treatment strategy	Name	Model	Mechanism of action	Result	Reference
Probiotics	LPN1	Glycol-induced kidney stones rat model	Remodels intestinal flora and enhances intestinal barrier function	Prevents kidney stones	[56]
	Fmb14	Purine-induced HUA mouse model	Regulates the "gut-kidney axis"	Alleviates renal fibrosis	[57]
	Q7	High ticket purine, high sugar diet induced HUA mouse model	Reshapes the intestinal flora	Repairs liver and kidney damage	[58]
	LPP	Potassium oxybate and adenine-induced HUA mouse model	Regulates inflammatory pathways and the expression of renal and ileal transport proteins	Prevents kidney damage	[59]
	X11	High-ticket purine, high-sugar diet- induced HUA mouse model	Inhibits renal pro-inflammatory cytokines and restores the proportion of beneficial intestinal bacteria	Improves the inflammatory environment of the kidney	[60]
Dietary polyphenols	CUR	PO-induced HUA mouse model	Regulates NO-mediated JAK2-STAT3 signaling	Improves renal endothelial dysfunction	[71, 72]
	CPE-E	PO-induced HUA mouse model	Regulates the structure of the intestinal microbial community	Reduces serum uric acid and improves renal function	[4]
	FA	High-ticket purine, high-sugar diet-induced HUA rat model	Reshapes the intestinal flora	Reduces the inflammatory environment of the kidneys	[74]
	CGA	PO-induced HUA rat model	Regulates TMAO-associated gut microbes and inhibits the PI3K/AKT/mTOR	Alleviates renal fibrosis and prevents HN	[75, 76]
	PEC	Adenine and PO-induced HN mouse model	Reduces inflammation, fibrosis	Restores kidney damage	[77]
	API	PO-induced HN mouse model	Inhibits UA reabsorption and Wnt/β-catenin pathway	Improves HN	[78]
	PTE	Adenine and PO-induced HN mouse model	Inhibits the expression of fibrosis-related proteins	Relieves renal fibrosis	[79]
Peptide	MFPP	PO-induced HN rat model	Lowers serum UA levels and enriches beneficial intestinal bacteria	Restores kidney function and UA metabolism	[80]
	NCTX15	Adenine and PO-induced HUA mouse model	Inhibits the expression of inflammatory factors and pyroptosis-related factors	Eases the inflammatory response and kidney damage	[81]
	PEW and LLW	Adenine and PO-induced HN rat model	Regulates intestinal flora and improves oxidative stress	Reduces kidney damage	[82]
	GLPP	PO-induced HUA mouse model	Closely related to adenosine deaminase (ADA)	Reduces kidney damage	[83]

regulate the intestinal flora and maintain the intestinal microbiota balance. One instance is when the probiotic *Lactobacillus plantarum* N-1 reduces the production of kidney stones caused by ethylene glycol. It does this by changing the composition of the bacteria in the intestines and enhancing the function of the intestinal barrier [70]. *Lactobacillus rhamnosus* Fmb14 inhibits the development of HUA-induced acute kidney injury and reduces the severity of kidney fibrosis through the interaction between the gut and the kidneys [71]. *Lactobacillus plantarum* Q7 regulates the metabolism of uric acid and reduces damage to the liver and kidneys by altering the composition of the gut microbiota. This strain of probiotic bacteria shows potential in alleviating HUA [72]. Secondly, it regulates the renal inflammatory environment. Probiotic LPP has great potential in preventing HUA and HUA-related kidney injury, and its mechanism of action involves the expression of renal and ileal transport proteins [73]. In a high-fructose purine HUA model, *Lactobacillus paracasei* X11 degraded uric acid intermediates in vitro, inhibited the formation of inflammatory cytokines in the kidneys in vivo, and suppressed the expression of adenosine deaminase (ADA), XO, and transport proteins, in addition to restoring the proportion of beneficial intestinal bacteria [4].

In recent years, probiotics with uric acid-degrading properties have attracted the interest of researchers. *Lactobacillus plantarum* controls blood uric acid levels in mice by degrading nucleosides in the gastrointestinal tract [74]. Strain JL-3 showed high degradation capacity and selectivity for uric acid [75]. The study revealed a positive relationship between the concentration of uric acid in the intestines and the levels of uric acid in the blood. Additionally, when uricase was administered orally, it effectively lowered the levels of uric acid in both rats with HUA and mice without uric acid oxidase. In addition, probiotics containing uric acid-solubilizing bacteria positively affected both blood pressure and kidney disease. The results indicate that utilizing genetically modified probiotics that produce functional uricase is a promising approach for treating HUA [76].

Escherichia coli Nissle 1917 (EcN) is a probiotic bacterium that was first discovered in 1917 by the German microbiologist Dr. Ferdinand Werkmann [77]. EcN has immunomodulatory, antibacterial, anti-inflammatory, and nutritional functions, and it is often used as a key bacterium in genetic engineering [78]. Zhao et al. generated a plasmid by combining plasmids that encode two uric acid metabolizing proteins, PucL and PucM, from *Bacillus subtilis*, along with the uric acid transporter proteins YgfU and the catalase KatG from *E. coli*, and the bacterial hemoglobin Vhb from Vitreoscilla sp. The uric acid degradation capacity of this genetically modified *E. coli* strain was found to be highly effective even in low oxygen circumstances [79]. Notably, genomic isolation systems are considered an ideal strategy for modifying EcN. EcN was modified by researchers who designed a probiotic called EcN C6 by inserting the FtsP-UA enzyme gene into the "isolation site" of EcN. The segregation site is positioned between the uspG and ahpF genes. The presence of the FtsP-UA enzyme in this area does not impact the probiotic qualities and overall gene transcription of EcN. However, it notably enhances the enzyme activity involved in the degradation of uric acid [80]. In addition, Yang et al. bridged the gap in the purine-degrading enzyme pathway in strict anaerobes by introducing two hydrolases into EcN, enabling it to grow anaerobically with xanthine as the sole nitrogen source and opening the way for the development of purine-degrading probiotics [81]. Notably, the role of probiotics in the treatment of HUA is still very limited. Based on this, combinations of probiotics with other drugs or naturopathic remedies (e.g., herbs) are investigated to achieve synergistic therapeutic effects. In addition, novel drug delivery modalities, such as nanotechnology or microbial carriers, are investigated to improve the survival and bioactivity of probiotics in the gut.

4.2 | Dietary Polyphenols

Polyphenols are a class of compounds with highly diverse chemical structures that range from simple gallic acid to complex proanthocyanidins. Diets that are rich in polyphenols can prevent chronic diseases by influencing different physiological processes, including cellular redox potential, enzyme activity, cell proliferation, and signal transduction pathways [84]. It is worth noting that although insufficient polyphenol intake does not lead to specific deficiency diseases, moderately adequate polyphenols will benefit health. Dietary polyphenols have been shown to have significant therapeutic effects on HUA without any side effects.

Dietary polyphenols used to treat HUA are mainly based on plant polyphenols. Curcumin (CUR) is a naturally occurring polyphenol extracted from turmeric rhizomes. Recent research has demonstrated that CUR possesses anti-hyperuricemia properties and provides protection to the kidneys. More precisely, it arises from the activation of renal NO-mediated JAK2-STAT3 signaling and the restoration of TGF-β1 levels, which improves renal endothelial dysfunction and the renal urate transport system in this particular model [85, 86]. Interestingly, the potential of dietary polyphenols to produce clinical effects may be partially due to their reciprocal interaction with the gut bacteria. Polyphenols exert an impact on the composition of the gut bacteria, leading to the conversion of polyphenols into bioactive molecules that elicit clinical effects [87]. For example, camellia pollen polyphenols (CPE-E) modulated the gut microbiota composition in HUA mice, increasing the numbers of Lactobacillus and *Clostridium difficile* [88]. The well-known polyphenol ferulic acid (FA) had shown anti-hyperuricemic properties by inhibiting uric acid synthesis. Recently, a study found that FA affects the gut microbiota and ameliorates kidney injury associated with HUA in rats fed a high-fructose or high-fat diet [28]. Furthermore, the administration of chlorogenic acid (CGA) as a supplement can potentially hinder the development of HN by regulating the gut microbiota associated with TMAO and suppressing the PI3K/AKT/mTOR signaling pathway [89, 90].

In recent years, polyphenols in fruits and vegetables have also attracted the interest of researchers. The natural flavonoid pectin (PEC) significantly reduced serum uric acid levels, attenuated inflammation and fibrosis, and repaired damaged kidneys in HN mice [91]. Notably, renal fibrosis is the final result of long-term and irreversible kidney disorders. The most effective way to treat kidney diseases caused by high uric acid is to avoid and treat renal fibrosis. The involvement of TGF-β/Smad and Wnt/β-catenin signaling pathways is crucial in multiple renal diseases, including HN. TGF-β regulates extracellular matrix

(ECM) synthesis and degradation by activating the Smad family of proteins, thereby promoting renal fibrosis. Wnt is a glycoprotein that is released from cells and attaches to receptors on the surface of cells. This attachment triggers the activation of the β-catenin signaling pathway, which stimulates the growth and specialization of renal tubular epithelial cells. Ultimately, this process leads to the formation of fibrosis. Apigenin (API) was discovered to mitigate renal fibrosis by decreasing the reabsorption of uric acid and inhibiting the Wnt/β-catenin signaling pathway, leading to an improvement in the progression of HN [92]. Pterostilbene (PTE), a biologically active component found in blueberries, suppressed the production of fibrosis-associated proteins TGF-β1/Smad3, SRC, and STAT3 in the kidneys of HN mice. Additionally, PTE reduced renal fibrosis in a severe HN mouse model [93].

4.3 | Peptides

Peptides have garnered significant attention from the scientific community in recent years because of their potent activity, remarkable specificity, and few adverse effects. In the literature, derived peptides with urate-reducing activity are mainly derived from animal proteins. For example, marine fish protein peptides (MFPPs) have the ability to significantly decrease levels of uric acid in the blood, enhance the growth of good bacteria in the intestines, and improve kidney function and the metabolism of uric acid. Other studies have demonstrated that incorporating MFPPs into the diet decreases renal inflammation caused by HUA [94]. NCTX15, a natriuretic peptide derived from the Clavatus nematode spider toxin, was found to reduce the inflammatory response and kidney damage by suppressing the production of IL-6, IL-1β, TNF-α, NLRP3, and the coagulation-related factor gasdermin D [95]. Pro-Glu-Trp (PEW) and Leu-Leu-Trp (LLW) are peptides obtained from the breakdown of whey protein. PEW and LLW work together to enhance the body's ability to handle oxidative stress and reduce the severity of kidney injury caused by HUA [96]. It is worth mentioning that peptides containing a high amount of arginine, such as pepsin (PRTM), were found to delay the formation of sodium urate crystals and effectively prevent their formation. These peptides could potentially be used as a treatment for gout by acting as inhibitors of crystal formation [97].

Plant-derived peptides are a treasure trove of next-generation anti-hyperuricemic. Ganoderma lucidum polysaccharide peptide (GLPP) significantly reduced uric acid production and increased excretion. In addition, GLPP was found to reduce potassium oxonate (PO)-induced renal histopathological damage in a dose-dependent manner. The specific mechanism is thought to be closely related to ADA [83]. Bioactive peptides that inhibit XO function have received increasing attention due to their favorable biocompatibility and easy absorption [98]. For example, brassica peptides significantly inhibit XO activity and are a safe alternative with fewer side effects than drugs [99]. Consumption of walnut protein hydrolysate protected renal function and inhibited XO in vitro. Further experiments revealed that it was two new peptides, WPPKN (8.710 Da) and ADIYTE (7.15 Da), that played an important role [100].

However, anti-hyperuricemic therapeutic peptides still have many problems in clinical applications, such as short half-life and rapid excretion in vivo. In addition, obtaining bioactive peptides by traditional methods such as enzymatic hydrolysis, extraction, and purification is time-consuming, inefficient, and labor-intensive. Computer modeling techniques such as molecular docking are widely used to study bioactive substances' interactions and binding affinities, such as proteins and peptides. And they can be used to optimize amino acid sequences to produce more active peptides. In the experiments of Zhao et al., the inhibition of XO by GGYGIF peptide was significantly increased after replacing the N-terminal Gly with Trp. The optimization process included intermediate amino acid, bipartite amino acid, and intermediate amino acid substitutions [98]. In addition, Mao et al. performed a rapid virtual screening of seven novel XO inhibitory peptides from Pacific white shrimp based on conformational relationships using molecular docking and BLAST techniques [101].

5 | Summary

In recent years, there has been a global rise in the occurrence of HUA, a condition characterized by elevated levels of uric acid in the blood. Prolonged HUA can potentially result in various health complications, such as kidney damage. HUA is an independent influential factor that increases the risk of renal injury and is linked to higher death rates related to kidney injury [102]. While the exact cause-and-effect relationship between high levels of uric acid and CKD is still a topic of debate, it is undeniable and worrisome that there are clear renal health issues associated with HUA. As discussed, HUA is a complex physiologic process involving multiple organs (liver, kidney, and intestine), and when serum uric acid is elevated to a certain level, a series of chain reactions are stimulated that all point the finger at renal dysfunction. Numerous data show that imbalance of intestinal homeostasis, occurrence of oxidative stress, and activation of NLRP3 inflammasome are the main mechanisms leading to abnormal renal function.

The primary approach to treating HUA is to reduce blood uric acid levels. XO inhibitors and uric acid-lowering medications are commonly regarded as suitable options for decreasing serum uric acid levels. Nevertheless, there is insufficient substantial data to substantiate the claim that reducing uric acid levels can decelerate the advancement of kidney disease. Hence, it is important to devise a secure and efficient therapy methodology. We further summarize the research progress on natural active compounds and provide insights into their pharmacological effects. More specifically, natural actives are categorized into probiotics, dietary polyphenols, and peptides. The mechanisms by which they exhibit HUA effects can be broadly categorized as remodeling the intestinal flora, reducing the inflammatory environment, and promoting uric acid metabolism. Although some specific mechanisms have not yet been elucidated and many obstacles remain to be faced in drug development towards the clinic, we believe these problems will be solved soon. First, the research boom set off by 16S rRNA gene sequencing and untargeted metabolomics has provided a scientific basis for exploring relevant biomarkers, which can be combined with high-throughput technology to screen out better drugs. In addition, several techniques for extracting active substances have been developed, e.g., ultrasound-assisted extraction, microwave-assisted extraction, and supercritical fluid extraction

have increased the extraction efficiency of food polyphenols by 32%–36%, reduced energy consumption by about 15-fold, and resulted in higher quality and sustainability [103]. Overall, future work will require synergistic advances across disciplines to address HUA's renal concerns and challenges.

Author Contributions

Wanping Lv and **Huixiang Chen:** writing – original draft, data curvature, writing – review and editing. **Pan Zhou:** writing – review and editing, data cure. **Aihua Du:** funding acquisition. **Yu Lei:** administration.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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LETTER TO THE EDITOR

Investigating the Efficacy Variability of Different JAK Inhibitors in Chronic Nonbacterial Osteitis (CNO) Presenting Primarily With Pyoderma Gangrenosum

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To the Editor,

Chronic nonbacterial osteitis (CNO) represents an infrequent, chronic, and relapsing inflammatory affliction of the bone with an undetermined cause. It is distinguished by a persistent state of inflammation within the bone marrow, a condition that is not instigated by bacterial infections [1]. Necrobiosis gangrenosum, a rare inflammatory skin disease within the spectrum of neutrophilic dermatoses, is primarily characterized by painful ulcers [2]. In some instances, CNO may manifest in the form of pyoderma gangrenosum. This is predominantly attributable to the nature of CNO as an autoinflammatory disorder [1]. Previous studies have demonstrated the efficacy of Janus kinase inhibitors (JAKis) in the treatment of necrobiosis gangrenosum [2]. Here, we report a case of CNO predominantly manifested by necrobiosis gangrenosum, which showed significant improvement following treatment with abrocitinib.

The patient is a middle-aged male presenting with extensive skin rashes on the hands and trunk (Figure 1A1,A3), accompanied by pain in the upper chest and buttocks. Laboratory tests revealed a C-reactive protein (CRP) level of 17.8 mg/L, while a 99mTc bone image showed localized increased metabolic activity in the sternum and sacrococcygeal region (Figure 1B). Skin pathology confirmed the diagnosis of necrobiosis gangrenosum (Figure 1C), leading to a final diagnosis of CNO. The patient was initially treated with a nonsteroidal anti-inflammatory drug (NSAID) in combination with tofacitinib at a dosage of 5 mg twice daily for a duration of 6 months. Although there was relief from bone pain, the skin rash did not improve. Subsequently, the treatment regimen was changed to abrocitinib at a dosage of 200 mg once daily. After 6 months of this therapy, there was a marked improvement in the skin rash (Figure 1A2,A4).

Currently, JAKis have been widely utilized in treating SAPHO syndrome, consistently demonstrating favorable therapeutic outcomes [3]. Given that SAPHO syndrome's osteomyelitis is part of the CNO spectrum, we postulate that JAKis may also have comparable therapeutic effectiveness in treating CNO. Regarding the treatment of pyoderma gangrenosum, JAKis are regarded as a promising alternative therapeutic approach [4]. However, conventional literature suggests that abrocitinib can effectively treat pyoderma gangrenosum [5]. Against this backdrop, we commenced treating a patient with abrocitinib at a dosage of 200 mg once daily. After 3 months, a marked improvement was observed in the rashes on the patient's hands and trunk. After an additional 6 months of treatment, the skin lesions on the trunk showed even more significant alleviation compared to earlier evaluations. These results highlight the substantial advantage of abrocitinib in managing the skin manifestations of CNO, especially when pyoderma gangrenosum is the predominant feature. However, it is crucial to note that this is a single case report, and the limited duration of observation makes it impossible to determine whether abrocitinib can ensure sustained efficacy. Thus, continuous follow-ups and additional clinical studies are essential to validate the findings of this case report.

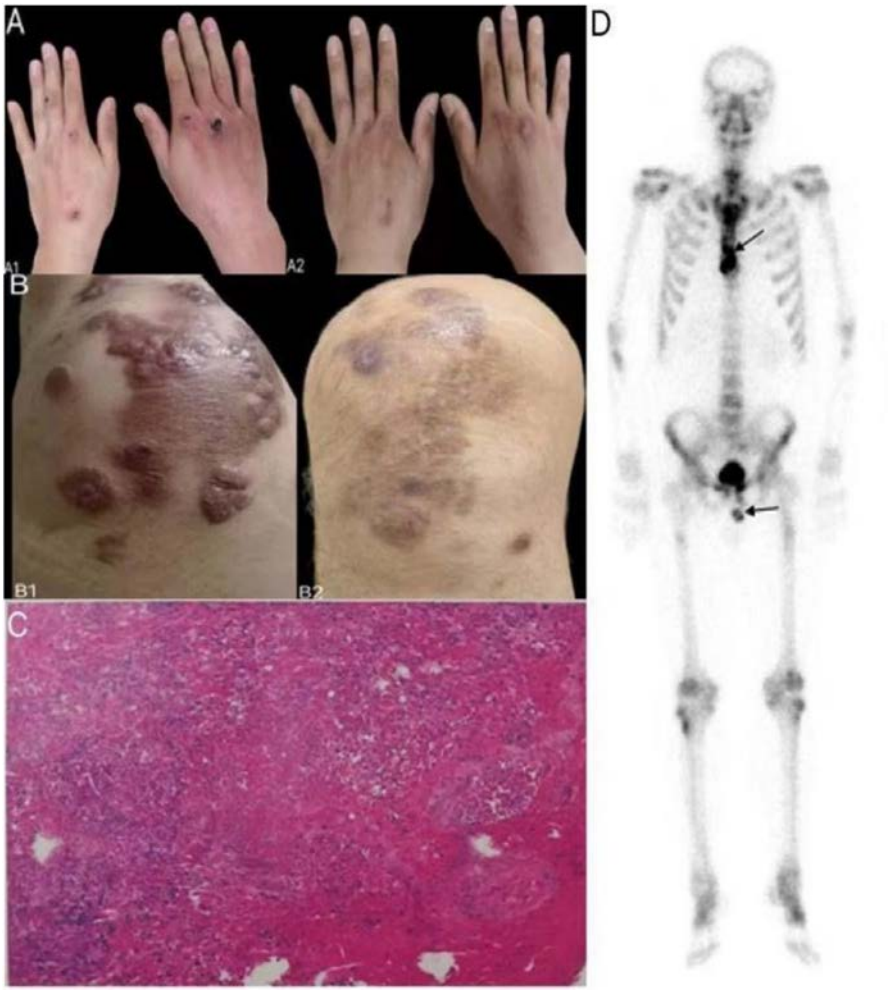

FIGURE 1 | (A1) Prior to treatment with abrocitinib, the patient was presented with significant lesions on the dorsal surfaces of both hands. (A2) Six months after initiating treatment with abrocitinib, there was a notable reduction in the lesions on the patient's hands. (B1) Before starting abrocitinib treatment, the patient exhibited skin lesions on the knees. (B2) Six months following the commencement of abrocitinib therapy, the lesions on the knees showed marked improvement. (C) Skin pathology revealed the formation of epidermal ulcers, with fibrinoid necrosis of small blood vessels and abundant neutrophilic infiltration observed beneath the ulcers, leading to the diagnosis of necrobiosis gangrenosum. (D) 99mTc bone image showing increased metabolic activity in the sternum and sacrococcygeal region (as indicated by the arrow).

Author Contributions

Ruitian Ma and Zhi Ye: drafted the manuscript; Ruitian Ma: responsible for data collection of patient samples and clinical information; Zhi Ye: was in charge of patient related picture sorting and editing; Chen Li: critically revised the manuscript for important intellectual content; Zhenhua Ying: supervised the whole research process.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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CLINICAL IMAGE

Drug Induced Autoimmunity: Propylthiouracil Induced ANCA Vasculitis

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A 57-year-old woman with a history of hypertension and hyperthyroidism presented with recurrent vomiting and loose stools since the past 7–8 months on November 8, 2017. She noticed blackish discoloration over her nasal tip and toes, along with a non-healing skin lesion on her left leg Figures 1 and 2. She had been taking an unsupervised regimen of propylthiouracil (PTU) 50 mg daily for her hyperthyroidism. On examination, she appeared delirious and pale, with large hyperpigmented patches and erythema on her skin. Laboratory tests revealed pancytopenia (hemoglobin-6.9 mg/dL, total count-3720/cubic mm, neutrophil-87%, lymphocyte-10%, monocyte-3%, platelet count-113 000/cubic mm), elevated ESR, a low serum TSH-0.03 m IU/L, and hypoalbuminemia (s. albumin-2.3 g/dL), with positive p-ANCA (22.3 RU/mL). A skin biopsy confirmed leukocytoclastic vasculitis. What is the condition affecting this patient?

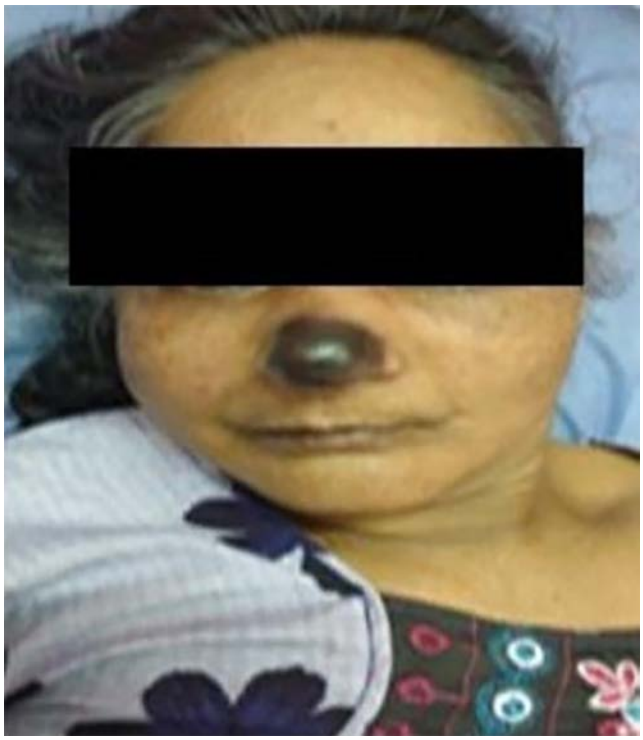

FIGURE 1 | Nasal tip ecchymosis/necrosis.

Answer:

The patient was diagnosed with PTU-induced Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis and pancytopenia. PTU, a medication commonly used for hyperthyroidism, can trigger autoimmune responses, including ANCA-associated vasculitis, which is confirmed by the positive p-ANCA and clinical findings [1, 2]. ANCA-associated vasculitis represents a group of potentially life-threatening autoimmune diseases

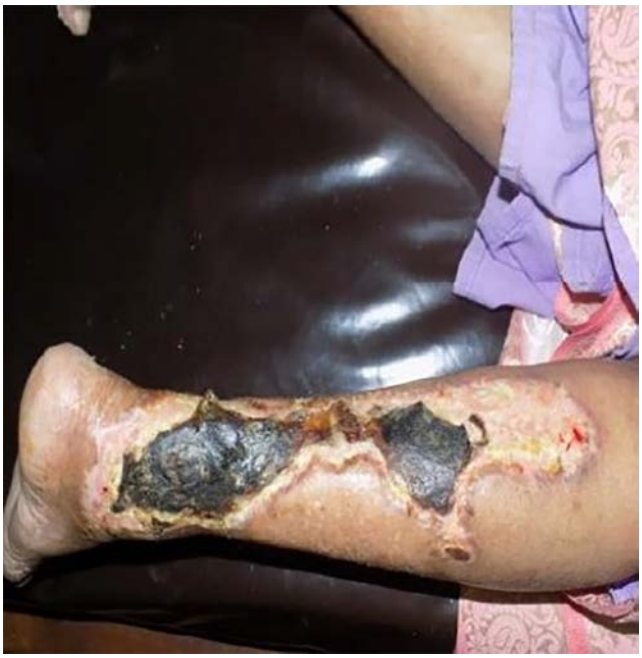

FIGURE 2 | Non-healing skin lesion on her left leg.

characterized by multi-system involvement [3]. Immediate cessation of PTU and administration of intravenous methylprednisolone significantly improved her symptoms [3]. Patient's delirium, pancytopenia resolved (hemoglobin-11.6 mg/dL, total count-5300/cubic mm, neutrophil-64%, lymphocyte-32%, monocyte-3%, eosinophil-1%, platelet count-211 000/cubic mm) and hypoalbuminemia improved (s. albumin-3.8 g/dL) by December 6, 2017. Her skin lesions began to heal. Four months later, she underwent successful nasal tip reconstruction and a split-thickness skin graft for the necrotic tissue. PTU-induced ANCA vasculitis is serious but manageable with prompt recognition and intervention [4, 5]. Physicians should suspect vasculitis in PTU-treated patients presenting with relevant symptoms, especially with systemic involvement. The positive response to the discontinuation of PTU and steroid therapy in this case underscores the importance of early and appropriate management.

Author Contributions

Authors have contributed equally to this article.

Ethics Statement

The authors have nothing to report.

Consent

We state that we obtained the patient's written informed consent to publish the material.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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LETTER TO THE EDITOR

Case Report: Dynamic Contrast-Enhanced Magnetic Resonance Imaging Depicting Intramuscular Small Vessel Vasculitis in a Patient With Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Dear Editor,

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic vasculitis predominantly affecting small vessels with potential multi-organ damage, including the lungs, kidneys, skin, and muscles [1]. Previous reports have highlighted the usefulness of MRI sequences, such as short tau inversion recovery (STIR) and contrast-enhanced T1-weighted imaging (T1WI), in evaluating muscular lesions in small to medium-sized vasculitis [2, 3]. Muscular lesions in patients with AAV and polyarteritis nodosa are identified on STIR as abnormal perivascular signals, and MRI of the skeletal muscle is crucial in estimating the size of the affected vessels [2]. Moreover, contrast-enhanced T1WI depicts areas of inflammation more accurately than STIR [3]. Furthermore, to date, only our previous case report has utilized dynamic contrast-enhanced (DCE) MRI to evaluate muscular lesions in AAV [4]. However, it did not address the pathological findings or the association between disease activity and DCE MRI. Here, we describe a patient who underwent a muscle biopsy of the lower leg following DCE MRI findings of abnormal contrast enhancement, which revealed vasculitis with fibrinoid necrosis, leading to a diagnosis of microscopic polyangiitis (MPA).

A 62-year-old man was admitted to our hospital with intermittent fever, pain, and paresthesia in the lower extremities. Five months prior to admission, the patient experienced pain in the posterior lower legs, followed by the onset of paresthesia in the same region 2 months before admission. Eleven days prior to admission, the patient sought care at another hospital due to fever. Blood tests revealed increased C-reactive protein (CRP) levels and computed tomography (CT) of the chest showed ground-glass opacities in the right inferior lung lobe. Past medical history included tonsillitis, appendicitis, and overactive bladder.

On admission, the patient's body temperature was 37.1°C, with normal blood pressure, heart rate, and oxygen saturation levels. Physical examination identified myalgia in the thighs and posterior lower legs and paresthesia in the distal lower legs. Chest auscultation revealed fine crackles on the right posterior lung, with no cardiac murmurs. Laboratory investigations demonstrated an increased white blood cell count (9300/μL), with elevated fractions of neutrophils (75.1%) and eosinophils (8.9%). Hemoglobin levels were mildly decreased at 11.5 g/L. Elevated levels of creatinine (1.16 mg/dL), CRP (6.3 mg/dL), and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA, 105 U/mL) were noted, whereas creatine phosphokinase (CPK, 89 U/L) and Krebs von den Lungen-6 (187 U/mL) levels remained within the normal range. The results for antinuclear and proteinase-3 anti-neutrophil cytoplasmic antibodies were negative. Urinalysis revealed no hematuria or casts, and a 24-h urine collection showed no significant proteinuria (0.15 g/day). Nerve conduction studies demonstrated decreased sensory nerve action potentials in the bilateral sural nerves, suggesting sensory axonopathy, consistent with a diagnosis of mononeuritis multiplex. A nerve biopsy was

not performed because of the patient's concerns regarding potential complications. Whole-body CT revealed ground-glass opacities in the bilateral inferior lung lobes without other pulmonary lesions, such as nodules, cavities, or consolidations. Bronchoscopy was not conducted, as the patient did not develop respiratory failure or worsening anemia during the clinical course, and alveolar hemorrhage was considered unlikely. No evidence of rhinosinusitis or mastoiditis was found. DCE MRI of the lower legs revealed multiple blurred dot- and nodule-like contrast enhancements within the muscles, predominantly in the posterior lower legs (Figure 1A,B, Video S1). A subsequent muscle biopsy of the left gastrocnemius muscle revealed the following histological findings: inflammatory cell infiltration was noted in the perivascular areas of the fascia and perimysium. Additionally, one arteriole in the fascia exhibited multinucleated leukocyte infiltration, nuclear debris, and fibrinoid necrosis with destruction of the arteriole wall (Figure 2), though no granuloma was identified. In contrast, no evidence of idiopathic inflammatory myopathies, such as perifascicular atrophy, lymphocytic infiltration of myofibers, or necrosis or regeneration of myofibers, was found. The patient had not used any drugs known to cause secondary AAV, such as propylthiouracil, penicillamine, hydralazine, or allopurinol. Based on the findings of MPO-ANCA positivity, mononeuritis multiplex, interstitial pneumonia, and necrotizing vasculitis, the patient was classified as MPA according to the European Medicines Agency algorithm [5] and 2022 American College of Rheumatology/European League Against Rheumatism classification criteria [6]. The patient was treated with 1 mg/kg (50 mg/day) of oral prednisolone (PSL) and 375 mg/m^2 of intravenous rituximab (RTX) weekly for 4 weeks. Clinical symptoms improved, and

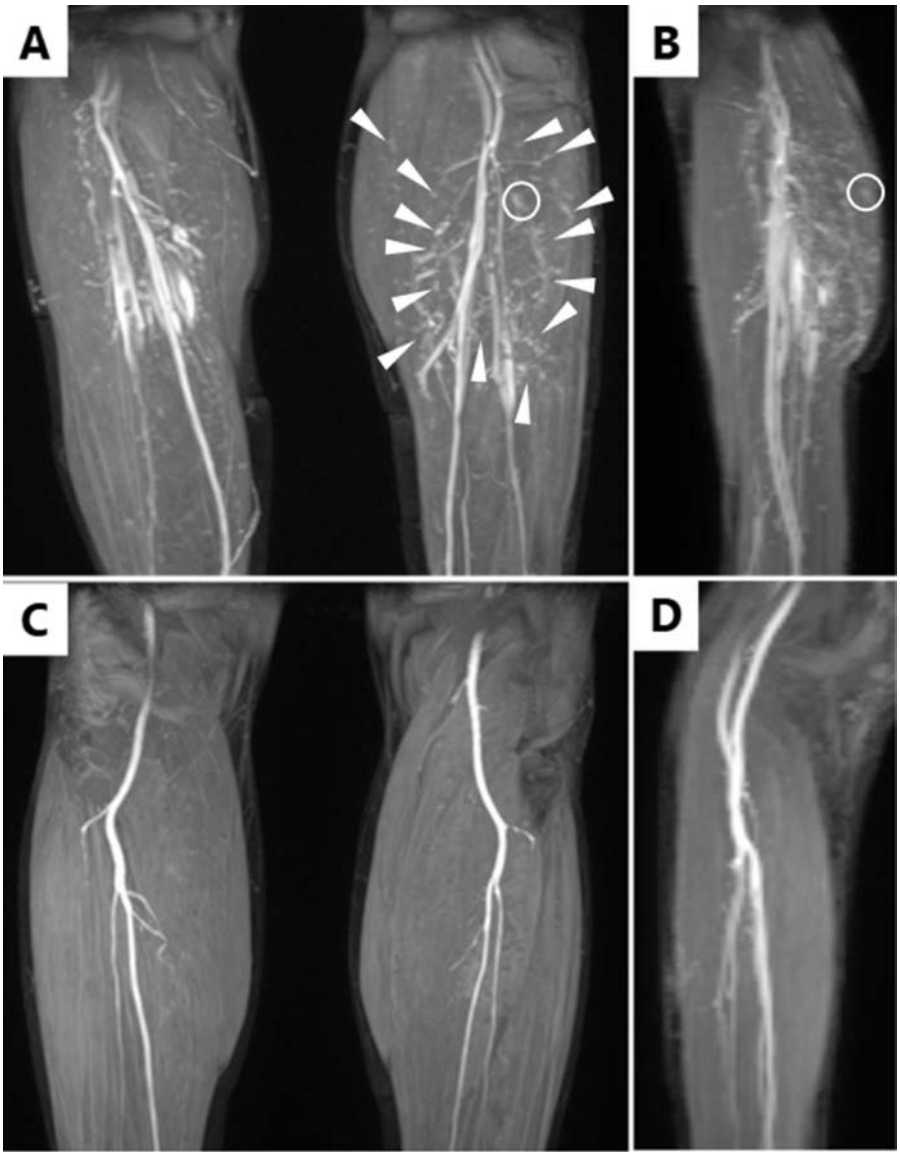

FIGURE 1 | Coronal (A) and sagittal (B) dynamic contrast-enhanced magnetic resonance imaging of the lower legs at 68.7 s, showing multiple blurred dot- and nodule-like enhancements and contrast enhancements of normal blood vessels before treatment. Circles indicate the location of the muscle biopsy. Arrowheads point to the representative abnormal findings in the left lower leg, whereas those in the right lower leg are not highlighted to maintain better image clarity. Coronal (C) and sagittal (D) dynamic contrast-enhanced magnetic resonance imaging of the lower legs at 70.6 s, showing only enhancements of normal blood vessels without abnormal contrast enhancement after treatment.

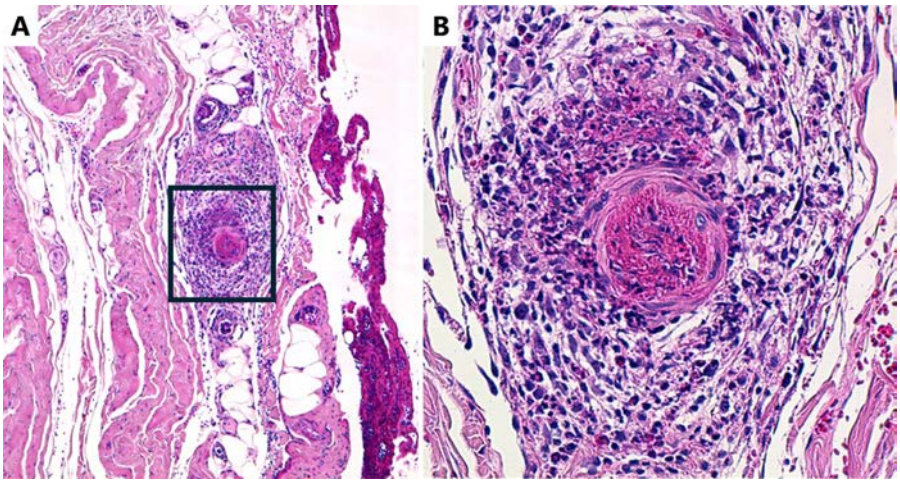

FIGURE 2 | Muscle histopathology at 50× (A) and 200× (B) magnification, showing fibrinoid necrosis with destruction of the arteriole wall in the fascia, stained with hematoxylin–eosin. The square in panel (A) indicates the region corresponding to panel (B) (200×).

CRP levels normalized by day 25 of admission. The ground-glass opacities partially resolved on chest CT performed on day 36 after admission. On day 37 after admission, follow-up DCE MRI showed complete resolution of the abnormal contrast enhancement in the lower legs (Figure 1C,D, Video S2). PSL was tapered, and the patient was discharged 41 days after admission. CPK levels remained normal, and MPO-ANCA levels normalized 65 days post-discharge, with no recurrence.

We encountered a patient whose muscle biopsy of the lower leg, following the detection of abnormal contrast enhancement on DCE MRI, revealed vasculitis with fibrinoid necrosis, leading to a diagnosis of MPA. This case underscores that the abnormal contrast enhancements observed on DCE MRI were attributable to small vessel vasculitis, and further highlights that DCE MRI may be superior to conventional sequencing in precisely identifying the location of muscular vasculitis in AAV.

Our case emphasizes two key points. Firstly, the muscle biopsy targeting areas of abnormal blurred dot- and nodule-like contrast enhancement on DCE MRI revealed pathological vasculitis with fibrinoid necrosis. Secondly, these abnormal contrast enhancements on DCE MRI resolved following treatment of AAV. These observations suggest that the abnormal contrast enhancements on DCE MRI were indicative of intramuscular small vessel vasculitis of AAV in our case. Several studies have demonstrated the use of DCE MRI to evaluate diseases affecting small vessels, similar to AAV. For example, DCE MRI has been applied in cases of atherosclerosis to assess tissue blood flow. Specifically, it has been reported that DCE MRI can evaluate reduced tissue blood flow by analyzing signal changes over time within the region of interest, as seen in arteriosclerosis obliterans [7]. However, to the best of our knowledge, no studies have used DCE MRI to perform morphological evaluations of arteriosclerosis in a manner similar to the approach presented in this case. The possible mechanisms underlying the abnormal DCE MRI findings in AAV are as follows. A review of DCE MRI applications in the musculoskeletal system indicates that malignant tumors can be distinguished from normal tissues by increased vascular permeability, with malignant tumors exhibiting early arteriole contrast enhancement compared to normal tissues [8]. DCE MRI is also useful for evaluating small vessels, including feeding and draining vessels, in vascular malformations [8]. Increased vascular permeability is involved in the pathogenesis of AAV, primarily causing inflammation in small vessels [1]. Therefore, DCE MRI may be useful in detecting AAV lesions.

To the best of our knowledge, only one previous case report of muscular lesions in AAV evaluated by DCE MRI has been published [4]. Abnormal dot- and nodule-like contrast enhancements were observed on DCE MRI at the site of the painful lesions, as in the present case. However, the previous report did not include pathological findings and assessment of MRI after treatment. Therefore, this is the first case report to demonstrate that the abnormal contrast enhancement on DCE MRI findings is consistent with pathological vasculitis and to compare these DCE MRI findings before and after treatment. Our findings strongly suggest that the abnormal contrast enhancements on DCE MRI were due to vasculitis. Furthermore, DCE MRI may be useful for evaluating disease activity in vasculitis.

DCE MRI is more effective than conventional sequencing in revealing the location of muscular vasculitis in AAV. Unlike STIR and contrast-enhanced T1WI, which capture lesions at a single time phase, DCE MRI enables continuous evaluation of lesions over time. STIR often highlights high-intensity areas in both normal and inflamed tissues, whereas contrast-enhanced T1WI exhibits high intensity in both inflamed tissues and normal blood vessels. Therefore, distinguishing truly abnormal areas based on conventional sequences is challenging. In DCE MRI, continuous temporal sequencing improves the ability to differentiate between normal blood vessels and abnormalities caused by inflammation. Consequently, DCE MRI facilitates better identification of lesion locations than conventional MRI sequences. Moreover, DCE MRI provides broader spatial coverage and allows for the visual identification of areas with high lesion density. Biopsies from areas with high lesion densities are more likely to yield vasculitis findings. Muscle involvement, which may be the initial manifestation of AAV, occurs in 48.6%

of patients [9]. In AAV with muscular lesions, a muscle biopsy at the site of abnormal contrast enhancement observed on DCE MRI can facilitate early definitive diagnosis.

In the present case, a muscle biopsy performed at the site exhibiting abnormal contrast enhancement on DCE MRI revealed the presence of necrotizing vasculitis. Post-treatment, the abnormal contrast enhancement demonstrated resolution, strongly indicating intramuscular vasculitis of AAV. These results also suggest that DCE MRI may be superior to conventional MRI sequences for detecting the location of intramuscular vasculitis. However, as this is a single case report, further studies are needed to investigate the association between DCE MRI and pathological findings in a larger cohort of patients with AAV and other inflammatory diseases involving the skeletal muscles of the lower extremities.

Author Contributions

All authors contributed to the conception and article design, manuscript drafting, and critical revision of the intellectual content. All authors approved the final version for publication and agreed to be accountable for all aspects of the work.

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Consent

Written informed consent for publication was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supporting Information

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

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LETTER TO THE EDITOR

Evaluation of Patient Information Provided by ChatGPT on Antimalarial Use in Systemic Lupus Erythematosus: Spanish Language Translation

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Dear Editor,

Inequities in healthcare access and the dissemination of medical data remain substantial challenges in chronic diseases such as systemic lupus erythematosus (SLE) [1]. For the Hispanic population, particularly Spanish speakers, linguistic barriers restrict access to critical health information. Racial and ethnic minorities—including African American (AA), Asian/Pacific Islander, and Hispanic groups—are at elevated risk of severe SLE manifestations, often associated with heavier glucocorticoid use and lower adherence to hydroxychloroquine (HCQ) [2]. These factors may lead to accelerated organ damage and diminished health-related quality of life [3].

Language hurdles frequently impede patient-provider communication, contributing to missed appointments, misunderstandings, and incomplete treatment records. Insufficient culturally and linguistically tailored resources further exacerbate low health literacy levels in these communities [4]. Culturally adapted information is thus vital for long-term SLE management, incorporating translation and alignment with beliefs and values [5]. However, many Hispanic individuals in the United States have limited English proficiency, impeding efforts to access, comprehend, and apply medical guidance [6].

Advances in artificial intelligence (AI) promise new strategies to address these gaps. Large language models (LLMs)—such as ChatGPT 3.5, 4 Omni, and Claude 3.5 Sonnet—can translate intricate medical content accurately and respectfully, promoting broader access and reducing disparities [7]. By expanding Spanish-language SLE resources, AI-driven translations may meaningfully improve health outcomes.

We conducted an observational study assessing the effectiveness of ChatGPT 3.5, 4 Omni, and Claude 3.5 Sonnet in translating 13 antimalarial use–related SLE questions from English to Spanish (Table S1). These questions were selected to address topics most pertinent to patients, drawing on two sources: (1) a survey by Garg et al. [8] on experiences and perceptions regarding lupus medications—covering information gaps ($n=4$), conflicting information, and assumptions ($n=3$)—and (2) common questions proposed by the National Health Service (NHS) ($n=6$) [9]. Institutional Review Board approval was deemed unnecessary as no human or animal subjects were involved.

Each question was entered into a "new chat" interface for ChatGPT 3.5 (gpt-3.5-2022-11-30), 4 Omni (gpt-4o-2024-05-13), and Claude 3.5 Sonnet (claude-3.5-sonnet-20240620). The AI chatbots were chosen for their advanced natural language processing capabilities and consistent translation output. Responses were generated in Spanish, and the first output provided by each model was used without further regeneration. Data collection took place in June 2024.

Summary

- GPT models and Claude 3.5 Sonnet achieved high linguistic accuracy and cultural sensitivity in translating antimalarial questions for the Spanish-speaking population.
- GPT-4o and Claude 3.5 Sonnet translations were average complexity, while GPT-3.5 translations were slightly more difficult.
- AI models like ChatGPT and Claude 3.5 Sonnet could enhance Spanish-speaking SLE patients' access to health information.

Translations were evaluated using a 5-point rubric (1 = lowest, 5 = highest) to ensure standardized assessment [10]. This rubric was divided into two dimensions:

1. *Linguistic accuracy*: Clarity and correctness of medical terminology.
2. *Cultural sensitivity*: Appropriateness of cultural references and idiomatic expressions relevant to Hispanic communities.

Two Mexican rheumatologists fluent in Spanish (PMR, CMP) independently scored each translation according to the rubric; disagreements were resolved by consensus. Cohen's kappa coefficient assessed interobserver agreement and indicated substantial concordance (0.653; CI 0.46–0.79).

Readability was analyzed with two validated Spanish instruments: the Flesch–Szigriszt (INFLESZ) and the Fernández Huerta Formula [11, 12]. The INFLESZ scale examines word count, syllables, and phrases to yield a 0–100 score, with higher values indicating lower complexity; a score ≥ 55 is considered "normal" for healthcare texts. Fernández Huerta likewise produces a 0–100 index, where lower scores signify more difficult reading levels. Both tools were selected to determine how accessible the generated translations were for Spanish speakers. Comparisons among GPT-3.5, GPT-4o, and Claude 3.5 Sonnet were performed using the Kruskal–Wallis test. Post-hoc comparisons used the Dunn test with Bonferroni correction for multiple testing. A two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed with IBM SPSS Statistics (version 26.0).

We found that the mean linguistic accuracy scores were 4.92 ± 0.28 for both GPT models and 5.00 ± 0.00 for Claude 3.5 without a statistical difference ($p = 0.611$). The mean culture sensitivity rate was 4.92 ± 0.28 for GPT-3.5, 5.00 ± 0.00 for GPT-4o, and 4.77 ± 0.44 without a statistical difference ($p = 0.33$).

The readability standard of the translated information generated by LLMs on antimalarial use in SLE was assessed. Using the Spanish version of the Flesh–Szigriszt, the mean readability of 50.97 ± 5.83 was determined for the complete set of questions created by GPT-3.5, 43.18 ± 4.90 for GPT-4o and 40.08 ± 5.62 for Claude 3.5 Sonnet ($p = 0.001$). In a post-hoc analysis, there was an evident discrepancy between GPT-3.5 and GPT-4o ($p = 0.001$) and between GPT-3.5 and Claude 3.5 ($p = 0.001$) but not among GPT-4o and Claude 3.5 ($p = 0.95$). There was no statistical difference between chatbots evaluating readability using the Fernandez–Huerta formula. Using this readability level, questions generated by Claude 3.5 Sonnet are classified as "slightly difficult." In contrast, responses created by GPT-3.5 and GPT-4o are considered "average" (Table 1).

Our study examined AI-based language models for Spanish-speaking patients seeking answers to common questions on antimalarial use in SLE. The primary finding indicates that LLMs consistently provided accurate and culturally sensitive translations, underscoring their promise to reduce health disparities for non-English-speaking communities. By furnishing reliable Spanish content, LLMs can help address linguistic obstacles and improve patient engagement, particularly for Hispanics with SLE, who often encounter communication barriers when accessing crucial health information [13].

Although patients frequently rely on popular search engines and social media for medical advice, the reliability and clarity of this content vary widely [14, 15]. High-quality, comprehensible information is critical in SLE management, where misinterpretations or inconsistencies may adversely affect treatment adherence and outcomes [16]. Our results are consistent with the growing body of literature suggesting AI's capacity to reduce language gaps. However, there remain areas for improvement: while all LLMs yielded strong scores, a few responses occasionally lacked some degree of cultural nuance. This underscores the need for ongoing refinement, particularly regarding sensitive issues that demand a more profound cultural understanding.

Readability analyses, conducted via two validated Spanish formulas (Flesch–Szigriszt [INFLESZ] and Fernández Huerta), generally rated the generated translations as "moderately difficult." Notably, Claude 3.5 Sonnet produced the most complex language. The recommended readability standard for Spanish healthcare content typically aims for a level accessible to most readers, ideally at or below sixth grade [17]. This discrepancy mirrors a broader issue in health education materials, where excessive reading complexity can diminish patient comprehension. Higher-level language structures, advanced vocabulary, or longer sentences—possibly reflective of more intricate training data—could partially explain why Claude 3.5 Sonnet was deemed less readable. Future investigations might explore modifications in model prompts and vocabulary choices to align better with typical reading levels.

Our findings also highlight some differences in how readability metrics capture text complexity. While INFLESZ revealed marked disparities among the models, Fernández Huerta was less discriminating. Each scale focuses on different linguistic characteristics; INFLESZ places emphasis on sentence construction and text structure, whereas Fernández Huerta evaluates syntactic attributes related to Spanish usage [18]. GPT-3.5 achieved the best INFLESZ readability scores, implying that its output may be simpler and thus potentially more suitable for non-expert audiences. This clarity is vital for chronic disease management, as patients need to grasp

TABLE 1 | Linguistic accuracy, cultural sensitivity, and readability ratings of antimalarial GPT questions.

Parameter	GPT-3.5	GPT-4o	Claude 3.5 Sonnet	*p*
Linguistic accuracy	4.92 ± 0.28	4.92 ± 0.28	5.0 ± 0.00	0.61
Cultural sensitivity	4.92 ± 0.28	5.0 ± 0.00	4.77 ± 0.44	0.15
Readability (INFLESZ scale)	50.97 ± 5.83	43.18 ± 4.90	40.08 ± 5.62	0.001
Readability (F-H formula)	45.85 ± 7.78	43.38 ± 4.35	45.23 ± 5.17	0.42

Abbreviations: F-H, Fernandez-Huerta Formula scores texts in Spanish; INFLESZ, Flesch-Szigriszt Readability Scale; NS, not significant.

complicated medical details to make informed decisions about their therapy [19].

These results align with a growing consensus that AI-driven tools have improved markedly in healthcare translation [20]. Previous work often criticized AI's shortcomings regarding cultural and contextual nuances, but our study demonstrates tangible progress in sophisticated models like GPT-3.5 and GPT-4 Omni. Technically accurate translations are increasingly paired with an improved capacity to incorporate relevant cultural references. Such alignment is essential for individuals who rely on health information in a language other than English, especially when managing complex conditions such as SLE.

Accurate translations foster better patient comprehension, adherence, and outcomes. A Spanish-speaking patient who receives detailed, culturally appropriate information about HCQ—including its efficacy, side effects, and practical usage tips—is more inclined to follow therapy and communicate with their healthcare providers about any complications [8]. This is particularly relevant for communities with existing socioeconomic or structural barriers to care.

Despite these promising results, our study has notable limitations. First, evaluation by human reviewers introduces subjectivity, as different individuals may have varying interpretations of cultural appropriateness and linguistic precision. Second, we focused on only three AI models, limiting the comparison scope with other emerging tools. Yet our approach facilitated a direct assessment of two GPT versions and a similarly advanced model (Claude 3.5 Sonnet), revealing only minimal differences in overall performance. A third limitation involves the evolving nature of AI applications: responses can shift depending on the specific model version, context provided, and moment of query. Hence, reproducibility over time or between updates may be inconsistent. Fourth, we relied on two native Spanish-speaking rheumatologists for translation evaluations. Although their clinical expertise ensures relevance and accuracy regarding SLE-related medical content, a multidisciplinary approach—incorporating linguists alongside medical professionals—could yield a more comprehensive assessment. Linguists would be positioned to critique syntax, grammar, and other language-specific elements, augmenting clinical insights with specialized linguistic acumen. Still, our choice of rheumatologists minimized misinterpretation of technical SLE terminology, a crucial consideration for patient-facing materials.

Additionally, our study prioritized the linguistic accuracy of translated content rather than the factual accuracy of the original English-language material. Future research may need to evaluate the reliability of both the source text and its translation, ensuring that patients not only receive culturally and linguistically precise information but also medically valid guidance. Finally, our approach did not include regenerated AI responses. Improvements or corrections made in subsequent interactions were thus not captured, potentially underestimating the models' capacity to refine their answers iteratively.

In conclusion, our research highlights the substantial potential of advanced AI-based tools—exemplified by GPT-3.5, GPT-4 Omni, and Claude 3.5 Sonnet—to mitigate language barriers in healthcare. By generating clear, contextually relevant, and culturally sensitive translations, LLMs could support health equity efforts and improve outcomes among non-English-speaking populations. While the models' outputs were generally "moderately difficult" to read, targeted strategies to reduce complexity are feasible. Future studies should explore prompt optimization, incorporate multidisciplinary feedback, and scrutinize the factual accuracy of medical data to enhance trust and effectiveness further. As AI technology continues to evolve, its role in bridging gaps between diverse communities and the healthcare system is poised to grow, offering significant benefits for patients, clinicians, and researchers.

Author Contributions

P.M.R., C.M.P., and I.E.M. were involved in the study, conception, and design. P.M.R. and C.M.P. in data collection. I.E.M., S.M.M. and E.R.L. in analysis and interpretation of results. C.M.P., J.C.S.P. and M.A.G.F. in draft manuscript preparation, editing, and completion of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The corresponding author will share the data underlying this article at a reasonable request.

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Supporting Information

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

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LETTER TO THE EDITOR

Case Report: Inflammatory Myositis Presenting as Dropped Head Syndrome in a Patient With Rheumatoid Antibodies

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Dear Editor,

Dropped head syndrome (DHS) is an uncommon clinical condition that is infrequently reported in the literature, although interest has been growing in recent years [1]. Characterized by camptocephalia (chin-on-chest deformity) that is passively correctable [2], its etiologies are varied, encompassing neuromuscular, inflammatory, and non-inflammatory causes. Characteristic magnetic resonance imaging (MRI) findings demonstrate intramuscular enhancement of the cervical extensor muscles on fluid-weighted MRI. Optimal treatment of DHS, beyond treatment of the underlying pathology, remains unclear and can include surgical, primary medical, and physical therapies. Whereas conservative treatment is successful in only 22% of patients [3], the positive response rate to immune modulating therapy in the treatment of DHS has been documented as high as 78.9% [1]. Our case represents a unique phenotype of inflammatory myositis presenting as DHS in a patient with positive rheumatoid antibodies and a maternal history of rheumatoid arthritis—raising the possibility of an overlap myositis (OM) or even of an emergent rheumatoid myositis.

A 45-year-old male hospital worker of West African descent presented with a five-month history of progressive atraumatic neck pain and head drop. He was systemically well. A full-time cleaner, his background included intermittent arthralgia mostly of the elbows and knees but no current joint pain or stiffness, hypercholesterolemia, previously treated malaria, and a maternal history of RA. An outpatient MRI was performed demonstrating cervical spondylosis, with multilevel foraminal stenosis, most severe at the C6 level bilaterally, and no cord changes. He underwent surgical review and was referred to physiotherapy for management of possible mechanical neck pain leading to neck extensor weakness.

After 6 months, the patient had not clinically improved and was referred to rheumatology for evaluation. Examination revealed camptocephalia, with the patient manually lifting his own head to meet the physician's gaze. Mild asymptomatic edema of the 3rd and 4th metacarpophalangeal (MCP) joints of the right hand was noted. This was alongside widespread muscle weakness preferentially affecting the upper limbs, including neck extensors, deltoids, wrist, and finger extensors, with a total Medical Research Council (MRC) scale for muscle strength of 44 out of 60 [4]. Tone, reflexes, and sensation were intact, and there were no ocular or bulbar symptoms. There were no cutaneous findings. The patient was not on statins.

Investigations revealed a raised creatinine kinase (CK) [2090 units/L, NR < 45–250], rheumatoid factor (92 IU/mL, NR < 30), anti-citrullinated protein antibody (ACPA)

elevation (> 200 U/mL, NR < 5), elevated IgG4 subclass (2.4 g/L, NR < 0.04) with normal IgG4: IgG ratio, and mildly elevated ESR (24 mm/h). CRP was within normal limits. ANA was 1:160 (speckled) with negative ENA and anti-dsDNA. Myositis-specific and myositis-associated antibodies were negative. HMG-CoA reductase antibodies were negative, as were serological investigations for pauci-immune vasculitis. HBV serology suggested previous Hepatitis B infection with undetectable viral DNA. Electromyography showed myopathic motor units with fibrillations, most prominent in the cervical paraspinal and deltoid muscles. No neurogenic changes were seen.

A subsequent MRI demonstrated progressive edema of multiple paravertebral and appendicular (trapezius, rhomboid, deltoid, rotator cuff and triceps) muscle groups, with relative sparing of the pectoralis and biceps brachii muscles (Figure 1A). Wrist MRI demonstrated mild non-specific synovitis of the 1st and 2nd MCP joints with no erosions. A left deltoid muscle biopsy revealed florid endomysial and perimysial inflammation (Figure 1C,D) with HLA1 upregulation consistent with an immune-mediated inflammatory myositis. The distribution was not typical of primary myositis (e.g., dermatomyositis, polymyositis), suggesting the possibility of an overlap or non-specific myositis. A diagnosis of inflammatory myositis with potential for rheumatoid arthritis overlap was made given the persistent strongly positive RA antibodies.

Pulse 1 g methylprednisolone followed by a tapering course of oral prednisolone was started, in addition to methotrexate 25 mg/week, monthly IVIG 1 g/kg and prophylactic entecavir with initial good response. Mycophenolate was started due to myositis flare when prednisone was ceased. Due to gastrointestinal intolerance, mycophenolate was subsequently ceased and 2 six-month cycles of rituximab were administered. After 24 months of immunomodulatory treatment, the patient was able to return to full-time work. Examination demonstrated resolution of the head drop and largely normal neck extensor muscle strength. A repeat MRI revealed interval improvement in intramuscular edema in the paravertebral and rotator cuff muscles, although there was new mild fatty infiltration and atrophy of the paraspinal muscles in comparison with prior imaging (Figure 1B).

The category of myositis presenting with DHS is infrequently elaborated in the literature. A systematic review of DHS describes the syndrome as largely attributable to four diagnostic categories: idiopathic neck extensor myopathy (INEM) (31.8%); Parkinson's disease (20.2%); myasthenia gravis (12.4%) and amyotrophic lateral sclerosis (7.0%) [1, p. 424]. In this review, inflammatory myopathy (mostly polymyositis) comprises only 3% of cases, and overlap myositis is not described. We note, with interest, a recently published retrospective study of inaugural dropped head syndrome and camptocormia in inflammatory myopathies [5]. In this study, Robert et al. highlight the frequency of axial deficit (28.6%) occurring as the inaugural muscular manifestation of overlap myositis [5, p. 515]. Nine cases of overlap myositis, a specific idiopathic inflammatory myopathy subtype, are described, where 5 demonstrate rheumatological manifestations of synovitis/arthritis without documented rheumatoid antibodies. Notably, only 1 of these 5 cases is documented to have presented similarly to our patient, with weakness of neck extensors, albeit without accompanying thoracolumbar weakness [5, p. 509]. DHS has also been reported in patients with systemic sclerosis and checkpoint inhibitor-related myositis [6].

Where a unifying concept of "Rheumatoid myositis" is concerned, the available literature is yet more constrained [7]. Rheumatoid factor and ACPA are not routinely tested in the workup for inflammatory myopathies; thus, little is known about the clinical implications of these antibodies in this population [8, p. 2]. While myopathy has long been described as a symptom of RA, a direct pathogenic association of the RA antibodies and inflammatory muscle disease has only been poorly characterized [8].

In summary, our case represents a rare instance of an inflammatory myositis-induced DHS. Rarer still is the co-existence of

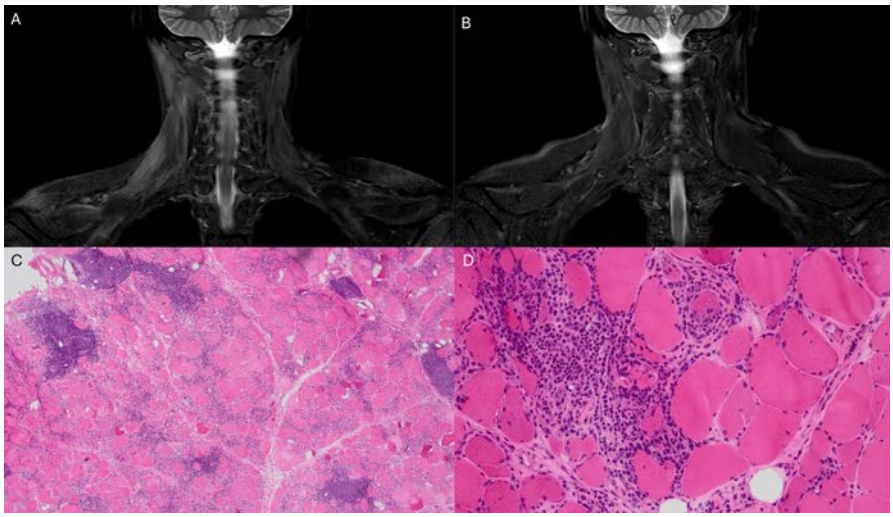

FIGURE 1 | Imaging and histopathology. (A) Pre-treatment 3 T MRI neck STIR sequence (Short Tau Inversion Recovery) demonstrates paravertebral muscle oedema. (B) Post-treatment 3 T MRI neck STIR sequence demonstrates reduction in muscle oedema. (C) Frozen section H&E (×40) demonstrates florid endomysial and perimysial inflammation. (D) Frozen section H&E (×200) demonstrates endomysial inflammation including plasma cells and infiltrating muscle fibers.

a high titer of rheumatoid arthritis antibodies in a patient "at risk" for RA [9, p. 494] due to the maternal history of RA and intermittent arthralgia. Whether this patient is suffering from a seronegative nonspecific myositis, overlap (with RA) myositis, or possible "rheumatoid myositis" cannot be definitively known. To our knowledge, our patient represents the first published report of an inflammatory myopathy presenting as DHS in a patient with strongly positive rheumatoid antibodies. This patient responded positively to treatment. Nonetheless, he endured substantial functional impairment due to the diagnostic delay in identifying the cause of his DHS. We encourage practitioners to examine for neck extensor weakness in all potential myopathies and to consider treatable inflammatory myositis among the differentials in any patient demonstrating weakness of neck extensors or "chin to chest" deformity.

Author Contributions

All authors except Estelle Noonan contributed to the diagnosis or treatment of this patient. The first draft was written by Estelle Noonan and Leticia Deveza. All authors contributed words to and edited subsequent drafts. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Exploring the Link Between Genetic Predictors of Systemic Lupus Erythematosus and Epstein–Barr Virus Infections

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Systemic lupus erythematosus (SLE) is one of the most common autoimmune diseases (ADs), has widespread clinical manifestations and a chronic relapsing–remitting course, and has different clinical courses and prognoses [1, 2]. The published data showed that AD patients have an increased danger of developing malignancies. According to relevant literature reports, viruses related to SLE include EBV, Parvovirus B19 (B19V), Retro viruses (RVs), Human Endogenous Retroviruses (HERV), Human Immunodeficiency Virus (HIV), Torque Teno Virus (TTV) and Cytomegalovirus (CMV) [3].

Epstein–Barr virus (EBV) is a lymphotripic virus, also known as Human Herpesvirus (HHV) 4 [4]. It is also considered as the most common human viruses and infects at least 90% of adults worldwide [5]. EBV is believed to be associated with the onset of a lot of ADs, such as rheumatoid arthritis (RA), multiple sclerosis (MS), and SLE [6–8].

Mendelian randomization (MR) analysis is a new-type epidemiological analysis method that uses instrumental variables (IVs) to analyze genetic variation and assess the causal association between exposures and outcomes [9]. The relevant IVs for MR research are from genome-wide association studies (GWAS).

The key point in conducting MR analysis was to select proper genetic variants from the open obtainable GWAS database as effective IVs. We selected single nucleotide polymorphisms (SNPs) from the IEU GWAS database (https://gwas.mrcieu.ac.uk/) and FinnGen database (http://www.finngen.fi) for IVs of all exposures, mediators, and outcomes. Instrumental SNPs were related with SLE and cancers at genome-wide relevance ($p < 5e\text{-}8$). Obtain genome-wide significant ($p < 1e\text{-}5$) IVs from five EBV infection databases to improve inference and computational abilities. Summary of data in this MR study can be seen in Table S1.

To make sure the facticity and correctness of the inferences regarding the causal relationship between EBV infections and SLE, we have implemented a series of quality control measures to select qualified IVs. We extracted genome-wide significantly correlated SNPs from the GWAS summary data, with linkage disequilibrium (LD) and independent ($r^2 = 0.001$, $kb = 10000$) SNPs for sorting. We followed the above steps to screen EBV infections, cancers, and SLE-related SNPs with significant correlation, linkage equilibrium, and independence from the GWAS database for MR analysis. We also estimated the *F*-statistic of SNPs to evaluate the strength of instrumental variables. If $F > 10$, it means that if the likelihood of instrumental variable bias is small, SNPs with *F*-statistic less than 10 should be removed.

In our study, the main statistical analysis was performed to use the R packages (version 4.3.2). Further, we used the "TwoSampleMR" (version 0.5.8) and "MR-PRESSO" (version 1.0) packages to conduct the MR analysis.

First, we conducted MR forward analysis using SLE as the exposures and anti-EBV IgG as the outcomes. Then, the genetic instruments selected for the five phenotypes of EBV were used as IVs, and SLE was used as the outcome of reverse MR. We used inverse-variance weighted (IVW), MR-Egger, weighted median (WM), weighted mode, and simple mode method for MR analysis to calculate the causality between SLE and EBV infections. MR analysis minimizes the impact of confusion and reverse

causal bias. In MR analysis, IVW is the standard approach for summing-up data and is the primary analysis method [10].

MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was used to further test the level of validity of the MR analysis results, and heterogeneity testing was conducted using MR Egger intercept [11]. We used Cochran *Q*-test to evaluate data heterogeneity. While $p < 0.05$, it indicates significant heterogeneity, and then using a random effects model with IVW method to infer causal relationship. Pleiotropy refers to the phenomenon where a single locus impacts on various phenotypes. We conducted the MR-Egger intercept test to appraise and regulate for horizontal pletropy, if $p > 0.05$, it implied that there is no horizontal pleiotropy, in addition to prove the stability of the research results. The results were reported as having corresponding OR and 95% CI, with $p < 0.05$ indicating statistical significance.

We passed through the two-step Mendelian randomization (TSMR) method, and performed four steps to mediation analysis. Step1: SLE to EBV (total effect β_all). Step2: EBV to SLE. Step3: SLE to cancers (βa). Step4: cancers to EBV (βb). Mediated effect βc: βa × βb. Direct effect β_dir: β_all-βa × βb.

First, select the appropriate SNP. After eliminating SNPs that were considered insignificant for both exposure and outcome, the resulting SNP sets were merged to obtain IVs for Mendelian randomization analysis.(Tables S2 and S3).

MR analysis results indicated that there was no causal association between the risk of SLE and EBV infections. IVW results suggested that there was no evidence for the effect between the two (anti-EBV IgG: $p = 0.074$; VCA IgG: $p = 0.863$; EBNA IgG: $p = 0.358$; EA IgG: $p = 0.993$). Further, the MR-Egger and WM results also proved that there was no causal association between SLE and EBV (Figure 1, Table S4).

Furthermore, when EBV infections were used as exposure, we discussed the impact of the causal effect with SLE. The IVW method suggested no significant evidence for casual relationship between EBV infections and SLE. Inefficient discoveries were validated in the evaluation by MR-Egger and WM method (Figure 2, Table S5).

In order to remove potential impacts on the MR assumption, we further conducted multiple sensitivity analyses to verify

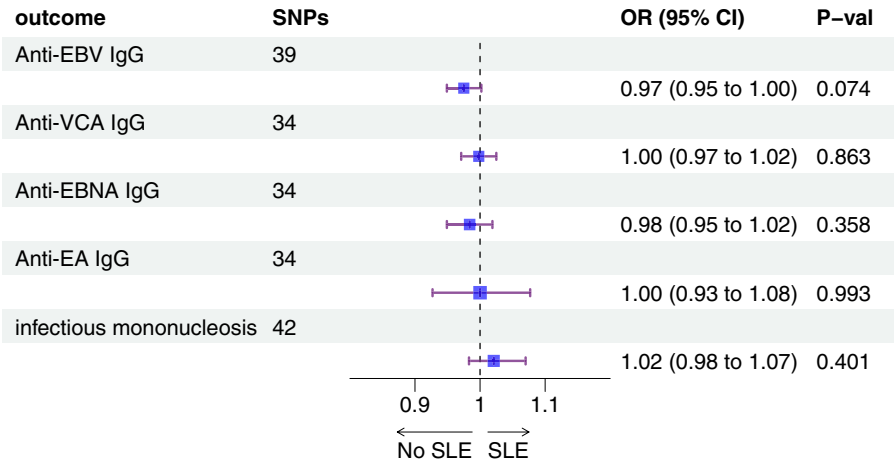

FIGURE 1 | The forest plot of existing causal effect of SLE on EBV.

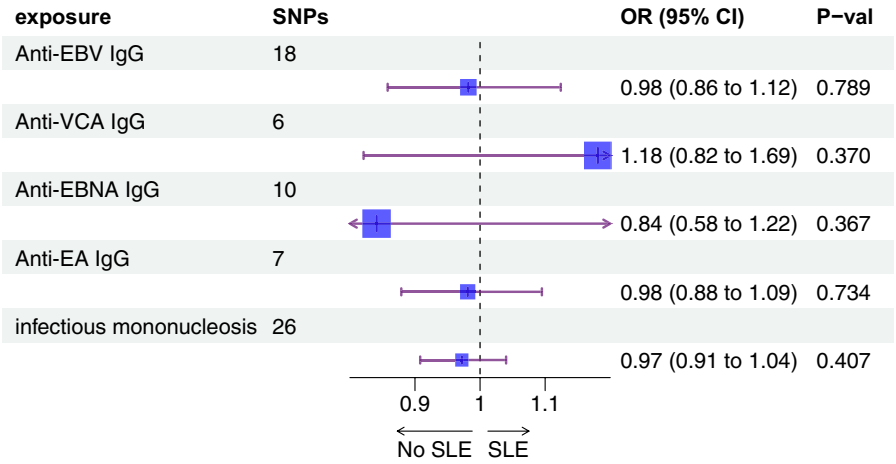

FIGURE 2 | The forest plot of existing causal effect of EBV on SLE.

whether heterogeneity and pleiotropy in the tested genetic tools would bias the MR results. According to the MR-Egger intercept analysis, the *p* values are all greater than 0.05, indicating that there is no horizontal diversity in the results, what means that the MR result analysis is effective (Tables S6 and S7).

Finally, to investigate whether cancers affect the relationship between SLE and EBV infection, further mediation analysis will be conducted. The result indicated that the five types of cancers did not affect the causal relationship between the two, and further enhance the credibility of the above results (Table S8).

For a long time, EBV has been considered as a potential trigger of SLE. A large amount of evidence suggests that viruses may be an important environmental factor in the nosogenesis of autoimmune rheumatic diseases [12], especially EBV infection, is closely related to SLE [13]. In our study, we used MR analysis to evaluate the causal association between EBV and SLE. Unexpectedly, our study indicated that there is no support for the relevance of EBV on the increased risk of SLE.

A few studies indicated that patients with SLE have an increased risk of EBV infection. An epidemiological survey in Qingdao, China, showed that SLE patients have an obviously higher danger of severe EBV infection in relation to the general population [14]. An observational study also demonstrated that SLE patients had been susceptible to viral infections, including the EBV infections [15]. In another observational study, the reactivities of IgG to EBV antigens (EBNA1) in SLE serum samples were measured, indicating that EBV EA/D IgG was significantly increase in SLE [4]. In summary, a strong correlation was found between SLE and EBV infection. However, according to our MR analysis, there is no related links between SLE and EBV infection.

Much serological evidence suggests a correlation between EBV infection and SLE. However, our reverse MR analysis shows no significant causal relationship between EBV infection and SLE, indicating that the small sample size might have influenced the results.

MR is a powerful means for studying and clarifying the causal relationship between exposure and outcomes. Currently, there are no MR studies reported on EBV infection and SLE. Our study has several important advantages. First, utilize the aggregated statistical data of the five major diseases to expand the list of EBV infections. Second, we used large-scale GWAS genetic data to study the causal association between EBV-related antibody titers in serum and SLE, improving statistical efficacy. Third, large sample sizes and robust SNPs can help detect causal effects with high precision. Forth, we conducted mediation analysis to further exclude the influence of cancers on the results of our study.

However, our study still has some shortcomings. Above all, the IVs used mostly came from the European population; therefore, the results in our article may not apply to other populations. Then, there is heterogeneity in the analysis results, as the GWAS data used were not grouped, making it impossible to proof whether there is a causal association between EBV infection and SLE in individuals of different genders, physical conditions, and age groups, such as, whether adults and elderly people are at risk of SLE when infected with EBV. Finally, as our IVs were selected based on a relaxed significance threshold of 1e-05 instead of the classical 5e-08 to ensure that all study participants had IVs, confounding factors appeared in our results.

A lot of research has suggested a potential causal relationship between SLE and EBV infections, but according to our study using Mendelian randomization in this article, there is no causal relationship between EBV infections and genetically predicted SLE. Further follow-up studies may be needed to determine whether the results are influenced by factors such as age and gender in order to obtain more accurate conclusions.

Author Contributions

Yanying Piao: writing – original draft, writing – review and editing, methodology, formal analysis, visualization, conceptualization. **Lei Li and Rongxian An:** writing – review and editing, visualization, methodology, formal analysis. **Xinying Cui** and **Long Jiang:** software, formal analysis, data curation. **Dinglu Cui:** supervision, data curation, conceptualization. **Jingchun Jin:** supervision, funding acquisition, data curation, conceptualization.

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Ethics Statement

The datasets generated during and/or analyzed during the current study are publicly available. Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data are available upon request.

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Supporting Information

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

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ORIGINAL ARTICLE

Causal Association Between Chronic Inflammatory Arthropathies and Sarcopenia and the Mediation Role of Inflammatory Factors

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Keywords: chronic inflammatory arthropathies | inflammatory factors | prospective study | sarcopenia

ABSTRACT

Background: Although chronic inflammatory arthropathies (CIA) are associated with sarcopenia, sarcopenia plays a role in their pathogenesis remains unknown. This study investigated the causal relationship between sarcopenia and CIA and to identify potential mediating factors.

Methods: We examined data from 458 910 participants in the UK Biobank to analyze the association between sarcopenia-related traits and CIA. Associations between hand-grip strength, muscle mass, walking pace, and CIA were analyzed using Cox regression models. Then, we performed a mediation analysis to explore the underlying mechanisms.

Results: Individuals with low hand-grip strength exhibited a 1.88-fold (95% CI 1.73–2.05), 2.22-fold (95% CI 2.02–2.45), and 1.36-fold (95% CI 1.32–1.41) increased risk of rheumatoid arthritis (RA), spondyloarthritis (SpA), and osteoarthritis (OA), respectively. The HRs for sarcopenia were 1.64 (95% CI 1.15–2.32) for RA, 1.83 (95% CI 1.21–2.77) for SpA, and 1.26 (95% CI 1.09–1.45) for OA. Additionally, individuals with a slow walking pace exhibited a 1.83-fold (95% CI 1.66–2.02), 3.58-fold (95% CI 3.25–3.95), and 1.82-fold (95% CI 1.77–1.88) increased risk of RA, SpA, and OA, respectively. Furthermore, we identified inflammatory markers as possible mediators of the causal effects of low hand-grip strength on the development of CIA.

Conclusions: Our findings suggest that sarcopenia is independently associated with an increased risk of CIA, which is partially mediated by inflammation factors.

1 | Introduction

Chronic inflammatory arthropathies (CIA) are a group of diseases that include inflammatory arthritis (IA) and osteoarthritis (OA). Rheumatoid arthritis (RA) is the most common type of IA. Other forms of IA include ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriatic and enteropathic arthropathies [1, 2]. Adults with CIA experience progressive articular damage,

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chronic pain, functional loss, and reduced quality of life [3]. The prevalence of these conditions is expected to rise significantly as the human population ages, posing a growing demand for effective, preventive, and therapeutic interventions.

Sarcopenia is a progressive and generalized skeletal muscle disorder involving an accelerated loss of muscle strength and mass. It is associated with adverse health outcomes, including disability, frailty, and mortality [4–6]. Sarcopenia is generally considered an age-related condition; however, secondary sarcopenia is associated with chronic inflammation, immobility, or malnutrition [7]. Recent studies have reported a higher prevalence of sarcopenia in patients with CIA. The overall prevalence of sarcopenia in patients with RA ranges from 7.8% to 87.5%, owing to the different definitions, geographic regions, and age groups studied. It was significantly higher in patients with RA than in controls [8–11]. In a review of 14 studies, pre- or probable sarcopenia was frequently observed in patients with AS [12]. A cross-sectional study of 104 patients with spondyloarthritis (SpA) in Thailand indicated that sarcopenia affected approximately one-fifth of the individuals [13]. Francesco et al. conducted a systematic review and meta-analysis of 7495 patients [14]. They found that the prevalence of sarcopenia in patients with knee OA was more than two times higher than that in controls. The high prevalence of sarcopenia among patients with CIA prompts inquiries into whether sarcopenia is an independent risk factor for CIA or merely a consequence of the disease. Compared with studies on the influence of CIA on sarcopenia, fewer studies have focused on the impact of sarcopenia on CIA. Therefore, we collected longitudinal data to investigate the causal relationship between sarcopenia and CIA, aiming to reduce the risk of developing CIA or slow their progression.

The pathogenesis of sarcopenia is complex and may involve interactions among hormones, inflammatory markers, and myostatin expression [15]. The onset of chronic inflammatory arthropathy depends on various factors leading to an imbalance of proinflammatory/anti-inflammatory local mediators [16, 17]. These cells appear to share common inflammatory processes. For example, proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), cause skeletal muscle loss, and they are closely related to the development of autoimmune diseases [18]. Therefore, this study aimed to evaluate the mediating effect of inflammation on the relationship between sarcopenia and CIA.

Does sarcopenia have an association with high incident of CIA? Our study utilized a large sample of adults from the UK Biobank study to investigate the associations, with consideration of mediating role of blood inflammatory markers. The relationship of sarcopenia and CIA and mechanisms by which sarcopenia contributes to the pathogenesis of these diseases may provide new strategies for managing CIA.

2 | Method

2.1 | Study Population and Design

This investigation was based on data from the UK Biobank, a large-scale prospective cohort study that encompasses over 500000 community-dwelling adults aged between 37 and 73 years, spanning the entirety of the UK from 2006 to 2010 (https://www.ukbiobank.ac.uk/). Ethical approval for the UK Biobank was granted by the UK National Health Service, the National Research Ethics Service North West, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. All participants provided written informed consent prior to participation. Secondary analyses were approved by the UK Biobank with approval number 106397. All data pertinent to this study are accessible in the public domain of the UK Biobank Repository.

Of the 502357 participants in UK Biobank, 29794 participants were excluded as they were non-white Europeans. A further 9440 participants were excluded as their missed impedance of the whole body and hand-grip strength data. Among the participants, 4213 participants were excluded from this study because of less than 40 years, more than 70 years, or less than 150 cm height. Finally, 458910 participants were included in the final analysis. We documented the baseline characteristics of the global population and compared them with those of the RA, SpA, and OA groups against the control group (Table 1). After excluding patients with previous CIA ($n = 984$), the relationship between sarcopenia and CIA was prospectively evaluated (Figure 1). Participants in the prospective study were followed up until a symptom of chronic inflammatory arthropathy occurred. When no CIA were reported, the follow-up was censored on the date of data extraction (23/12/2023).

2.2 | Definitions

The European Working Group on Sarcopenia in Older People criteria (19) were applied to classify the participants into four subgroups: the non-sarcopenic group (normal hand grip strength [HGS] and normal skeletal muscle index [SMI]), pre-sarcopenic subgroup 1 (low HGS and normal SMI), pre-sarcopenic subgroup 2 (normal HGS and low SMI), and the group with sarcopenia (low HGS and SMI). The SMI was obtained by dividing the SMM (expressed in kg) by height [2] (expressed in meters), where the SMM was calculated using the Janssen equation. Janssen equation, which was ethnic-specific, was used to estimate skeletal muscle mass by bioelectrical impedance [19]. A detailed algorithm and cutoff points for poor HGS and low SMI in women and men have been previously published [19].

The CIA investigated in this study were classified into three distinct groups: RA, SpA, and OA. SpA included reactive arthropathies, psoriatic and enteropathic arthropathies, juvenile ankylosing spondylitis, ankylosing spondylitis, and inflammatory spondylopathy. OA included polyarthrosis, coxarthrosis, gonarthrosis, arthrosis of the first carpomethacarpal joint, and other types of arthroses. Individuals without the above diseases were included as controls. Data pertaining to CIA were extracted from the International Classification of Diseases, Tenth Revision (ICD-10), codes M02, M06, M07, M08.1, M15.00, M15.1, M15.2, M15.3, M15.4, M15.8, M15.99, M16.0, M16.1, M16.2, M16.3, M16.4, M16.5, M16.6, M16.7, M16.9, M17.0, M17.1, M17.2, M17.3, M17.4, M17.5, M17.9, M18.0, M18.1, M18.2, M18.3, M18.5, M18.9, M19.00, M19.01, M19.02, M19.03, M19.04, M19.05, M19.06, M19.07, M19.08, M19.09, M19.90, M19.91,

TABLE 1 | Characteristics of the study participants.

	Participants without CIA ($n=328889$)	RA ($n=11881$, 3.5%)	SpA ($n=6081$, 1.8%)	OA ($n=123127$, 26.8%)	p^a	p^b	p^c
Sociodemographic factors							
Women, *n* (%)	171670 (52.2%)	7856 (66.1%)	3331 (54.8%)	72743 (59.1%)	<0.001	<0.001	0.000
Age at recruitment (years), median (IQR)	56 (49;62)	61 (55;65)	60 (54;65)	61 (56;65)	0.000	0.000	0.000
Education, college graduate or above, *n* (%)	115046 (35.0%)	2545 (21.4%)	1326 (21.8%)	29886 (24.3%)	<0.001	<0.001	0.000
Townsend deprivation index, median (IQR)	−2.3 (−3.7; 0.2)	−1.9 (−3.5; 1.1)	−1.9 (−3.5; 1.1)	−2.2 (−3.6; 0.4)	0.000	0.000	0.000
Total household income before tax, *n* (%)							
Less than 18000	53265 (16.2%)	3445 (29.0%)	1795 (29.5%)	31187 (25.3%)	0.000	<0.001	0.000
18000–30999	69007 (21.0%)	2723 (22.9%)	1345 (22.1%)	29366 (23.9%)			
31000–51999	78706 (23.9%)	2010 (16.9%)	1049 (17.3%)	23596 (19.2%)			
52000–100000	66259 (20.1%)	1143 (9.6%)	651 (10.7%)	14306 (11.6%)			
Greater than 100000	18502 (5.6%)	253 (2.1%)	153 (2.5%)	2902 (2.4%)			
Others	43150 (13.1%)	2307 (19.4%)	1088 (17.9%)	21770 (17.7%)			
Different stages of sarcopenia							
Non- sarcopenia	311417 (94.7%)	9157 (77.1%)	5225 (85.9%)	110735 (89.9%)	0.000	<0.001	0.000
Only weak hand-grip strength	10318 (3.1%)	2247 (18.9%)	705 (11.6%)	9463 (7.7%)			
Only low muscle mass	6538 (2.0%)	266 (2.2%)	118 (1.9%)	2430 (2.0%)			
Sarcopenia	616 (0.2%)	211 (1.8%)	33 (0.5%)	499 (0.4%)			
Life style							
Smoking status, *n* (%)							
Never	34806 (10.6%)	1535 (12.9%)	817 (13.4%)	12116 (9.8%)	<0.001	<0.001	0.000
Former	110672 (33.7%)	4957 (41.7%)	2579 (42.4%)	49329 (40.1%)			
Current	182409 (55.5%)	5332 (44.9%)	2648 (43.5%)	61121 (49.6%)			
Others	1002 (0.3%)	57 (0.5%)	37 (0.6%)	561 (0.5%)			
Alcohol status, *n* (%)							

(Continues)

TABLE 1 | (Continued)

	Participants without CIA ($n=328889$)	RA ($n=11881$, 3.5%)	SpA ($n=6081$, 1.8%)	OA ($n=123127$, 26.8%)	p^a	p^b	p^c
Never	19490 (5.9%)	1393 (11.7%)	672 (11.1%)	10163 (8.3%)	< 0.001	< 0.001	0.000
Special occasions only	32386 (9.8%)	1906 (16.0%)	970 (16.0%)	15815 (12.8%)			
One to three times a month	36783 (11.2%)	1385 (11.7%)	680 (11.2%)	13693 (11.1%)			
Once or twice a week	87632 (26.6%)	2954 (24.9%)	1461 (24.0%)	31390 (25.5%)			
Three or four times a week	81495 (24.8%)	2226 (18.7%)	1154 (19.0%)	27076 (22.0%)			
Daily or almost daily	70899 (21.6%)	2012 (16.9%)	1136 (18.7%)	24883 (20.2%)			
Others	204 (0.1%)	5 (0.0%)	8 (0.1%)	107 (0.1%)			
Usual walking pace							
Slow pace	14981 (4.6%)	2777 (23.4%)	1405 (23.1%)	17619 (14.3%)	0.000	0.000	0.000
Steady average pace	168779 (51.3%)	5981 (50.3%)	2992 (49.2%)	67436 (54.8%)			
Brisk pace	144215 (43.8%)	2917 (24.6%)	1584 (26.0%)	36967 (30.0%)			
Others	914 (0.3%)	206 (1.7%)	100 (1.6%)	991 (0.3%)			
For walking (MET, h/week), *n* (%)							
Low (0–6.5)	79405 (24.1%)	2762 (23.2%)	1494 (24.6%)	26857 (21.8%)	< 0.001	< 0.001	0.000
Moderate (6.6–17.2)	92891 (28.2%)	2721 (22.9%)	1415 (23.3%)	30641 (24.9%)			
High (17.3–69.4)	88148 (26.8%)	2883 (24.3%)	1496 (24.6%)	32609 (26.5%)			
Others	68445 (20.8%)	3515 (29.6%)	1676 (27.6%)	33020 (26.8%)			
For moderate activity (MET, h/week), *n* (%)							
Low (0–3.9)	82576 (25.1%)	2823 (23.8%)	1491 (24.5%)	26426 (21.5%)	< 0.001	< 0.001	0.000
Moderate (4–13.9)	89093 (27.1%)	2497 (21.0%)	1352 (22.2%)	28819 (23.4%)			
High (14–84.1)	88775 (27.0%)	3046 (25.6%)	1562 (25.7%)	34862 (28.3%)			
Others	68445 (20.8%)	3515 (29.6%)	1676 (27.6%)	33020 (26.8%)			
For vigorous activity (MET, h/week), *n* (%)							

(Continues)

TABLE 1 | (Continued)

	Participants without CIA ($n=328889$)	RA ($n=11881$, 3.5%)	SpA ($n=6081$, 1.8%)	OA ($n=123127$, 26.8%)	p^a	p^b	p^c
Low (0–0)	98230 (29.9%)	4295 (36.2%)	2143 (35.2%)	38465 (31.2%)	<0.001	<0.001	0.000
Moderate (0.1–9.3)	71089 (21.6%)	1843 (15.5%)	1027 (16.9%)	22146 (18.0%)			
High (9.3–64)	84549 (25.7%)	2013 (16.9%)	1120 (18.4%)	26879 (21.8%)			
Others	75021 (22.8%)	3730 (31.4%)	1791 (29.5%)	35637 (28.9%)			
Energy intake (kJ/day), *n* (%)							
0–7487.7	17576 (5.3%)	571 (4.8%)	292 (4.8%)	5891 (4.8%)	<0.001	<0.001	<0.001
7487.7–9670.3	15537 (4.7%)	404 (3.4%)	198 (3.3%)	4652 (3.8%)			
9670.3–47523.8	15409 (4.7%)	380 (3.2%)	217 (3.6%)	4358 (3.5%)			
Protein intake (g/day), *n* (%)							
0–50	5836 (1.8%)	217 (1.8%)	94 (1.5%)	1940 (1.6%)	<0.001	<0.001	<0.001
50–100	32572 (9.9%)	890 (7.5%)	480 (7.9%)	9909 (8.0%)			
100–640	10114 (3.1%)	248 (2.1%)	133 (2.2%)	3052 (2.5%)			
Oily fish intake							
Never	35262 (10.7%)	1457 (12.3%)	754 (12.4%)	12809 (10.4%)	<0.001	<0.001	<0.001
Less than once a week	112110 (34.1%)	3750 (31.6%)	1856 (30.5%)	38040 (30.9%)			
Once a week	123805 (37.6%)	4355 (36.7%)	2270 (37.3%)	47631 (38.7%)			
2–4 times a week	53510 (16.3%)	2144 (18.0%)	1086 (17.9%)	22845 (18.6%)			
5–6 times a week	2163 (0.7%)	82 (0.7%)	53 (0.9%)	854 (0.7%)			
Once or more daily	641 (0.2%)	29 (0.2%)	10 (0.2%)	248 (0.2%)			
Time spent outdoors in winter							
<2 h/day	169744 (51.6%)	5649 (47.5%)	2756 (45.3%)	54747 (44.5%)	<0.001	<0.001	0.000
≥2 h/day	138040 (42.0%)	5221 (43.9%)	2795 (46.0%)	58504 (47.5%)			
Others	21105 (6.4%)	1011 (8.5%)	530 (8.7%)	9876 (8.0%)			
Time spent outdoors in summer							

(Continues)

TABLE 1 | (Continued)

	Participants without CIA ($n=328\,889$)	RA ($n=11\,881$, 3.5%)	SpA ($n=6081$, 1.8%)	OA ($n=123\,127$, 26.8%)	p^a	p^b	p^c
< 2 h/day	44 235 (13.4%)	1306 (11.0%)	657 (10.8%)	11 837 (9.6%)	< 0.001	< 0.001	0.000
≥ 2 h/day	256 136 (77.9%)	9323 (78.5%)	4739 (77.9%)	98 424 (79.9%)			
Others	28 518 (8.7%)	1252 (10.5%)	685 (11.3%)	12 866 (10.4%)			
BMI category, (23) (kg/m^2), *n* (%)							
Malnutrition and thinness	1697 (0.5%)	53 (0.4%)	24 (0.4%)	307 (0.2%)	0.000	< 0.001	0.000
Normal weight	115 865 (35.2%)	3045 (25.6%)	1383 (22.7%)	28 108 (22.8%)			
Overweight	142 517 (43.3%)	4760 (40.1%)	2486 (40.9%)	52 001 (42.2%)			
Class I and II obesity	64 546 (19.6%)	3560 (30.0%)	1946 (32.0%)	38 454 (31.2%)			
Class III obesity	4264 (1.3%)	463 (3.9%)	242 (4.0%)	4257 (3.5%)			
BMI (kg/m^2), median (IQR)	26.3 (23.8; 29.2)	27.7 (24.7; 31.3)	28.0 (25.2; 31.8)	28.0 (25.1; 31.4)	0.000	0.000	0.000
Others							
Grip strength (kg), median (IQR)	32 (26; 42)	25 (18; 34)	29 (22; 39)	29 (22; 38)	0.000	0.000	0.000
SMI (BIA) (kg/m^2), median (IQR)	7.7 (6.5; 9.0)	7.1 (6.3; 8.7)	7.8 (6.5; 9.1)	7.5 (6.5; 9.1)	0.000	0.000	0.000
CRP, median (IQR)	1.2 (0.6; 2.5)	2.3 (1.1; 5.3)	2.2 (1.0; 4.8)	1.7 (0.8; 3.4)	0.000	0.000	0.000
WBC, median (IQR)	6.6 (5.6; 7.8)	6.9 (5.8; 8.2)	7.0 (5.9; 8.3)	6.7 (5.7; 7.9)	0.000	0.000	0.000
Monocyte, median (IQR)	0.5 (0.4; 0.6)	0.5 (0.4; 0.6)	0.5 (0.4; 0.6)	0.5 (0.4; 0.6)	0.000	0.000	0.000
Lymphocyte, median (IQR)	1.9 (1.5; 2.3)	1.8 (1.4; 2.3)	1.9 (1.5; 2.3)	1.9 (1.5; 2.3)	0.000	0.000	0.000
Platelets, median (IQR)	247.2 (213.0; 286.0)	258.0 (220.0; 302.0)	255.1 (219.7; 297.7)	250.5 (215.0; 289.8)	0.000	0.000	0.000

[a]Comparisons between patients with RA and participants without CIA.
[b]Comparisons between patients with SpA and participants without CIA.
[c]Comparisons between patients with OA and participants without CIA.

M19.92, M19.93, M19.94, M19.95, M19.96, M19.97, M19.98, M19.99, M46.1, M46.8, and M46.9.

2.3 | Covariates

Twenty-two potential confounding factors associated with sarcopenia and CIA were selected based on previous studies [8, 9, 12, 16]. They were collected at baseline and obtained directly from the UK Biobank, including five sociodemographic factors (age, sex, education, Townsend deprivation index, and family income), 12 lifestyle factors (smoking, alcohol, walking pace, walking, moderate activity, vigorous activity, energy intake, protein intake, oily fish intake, time spent outdoors in summer and winter, and body mass index [BMI]), and five inflammatory factors (white blood cell [WBC], C-reactive protein [CRP], monocytes, lymphocytes, and platelets). Three age subgroups (40–50 years old, 51–60 years old, and 61–70 years old), six alcohol subgroups (never, special occasions only, 1–3 times a month, once or twice a week, 3–4 times a week, daily or almost daily, and others), four walking pace subgroups (slow pace, steady average pace, brisk pace, and others), four energy intake subgroups (< 7487.7, 7487.7–9670.3, 9670.3–47523.8, and others), three protein intake subgroups (below 50, 50–100, 100–640, and others), six oily fish intake subgroups (never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily, and others), and the time spent outdoors subgroups (< 2 h/day, ≥ 2 h/day, and others) were observed.

2.4 | Statistical Analyses

For all descriptive statistics, continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables were presented as frequencies. To examine the group differences in baseline characteristics, the Mann–Whitney–Wilcoxon test was used for continuous variables where appropriate, and the chi-squared or Fisher's exact test was used for categorical variables. Linear and nonlinear associations of hand-grip strength with CIA were also tested using a restricted cubic spine (RCS). Cox regression analysis was performed to predict the likelihood of occurrence of CIA based on different stages of sarcopenia, as well as sensitivity analysis. To refine our analytical model, we incorporated an expanded set of covariates sequentially. Model 0 served as the baseline, and no adjustments were made for potential confounders using the initial, unmodified dataset. Subsequently, model 1 was adjusted for age, sex, education, Townsend deprivation index, and family income, introducing basic sociodemographic variables. In model 2, we extended the adjustment to 12 lifestyle factors. In model 3, we comprehensively adjusted for diet (energy, protein, and oily fish intake) and a range of inflammatory factors, specifically WBC, CRP, monocytes, lymphocytes, and platelets. Nonadjusted and adjusted hazard ratios (HR), along with their 95% confidence intervals (95% CI), were reported. Reference subgroups for regression analyses were non-sarcopenic participants, age > 60 years, male, higher education, brisk pace, normal BMI, current smoking, no alcohol intake, low walking, low moderate activity, low vigorous activity, high Townsend deprivation index, and high family income (greater than 100 000 dollar/year), high energy intake, high protein intake, high oily fish intake (once or more daily), long time spent outdoors in summer and winter (≥ 2 h/day).

Finally, mediation analyses were performed to determine the role of inflammation in the relationship between hand-grip strength and the occurrence of CIA. We reported the following in Appendix S1: (1) baseline characteristics and comparisons between groups in the global population, (2) multiple imputations, and (3) sensitivity analyses.

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0) and R (version 26.0). Forest plots were generated using GraphPad Prism (version 9.0). Statistical significance was set at $p < 0.05$. 3. All statistical tests were conducted using a two-sided approach.

3 | Results

3.1 | Baseline Characteristics of Study Participants

The demographic and baseline characteristics of the study participants are presented in Table 1. Among the 458 910 participants, 11 730 had RA, 6081 had SpA, and 123 127 had OA. Patients diagnosed with RA, SpA, or OA at baseline were excluded. The demographic and baseline characteristics of the prospective study participants are shown in Table 1. Participants with RA, SpA, and OA were more likely to be older, female, have a lower education level, and have a lower total household income than the general population. Unhealthy lifestyle factors such as obesity, smoking history, slow pace, less activity, less energy intake, less protein intake, less oily fish intake, and less outdoor activity were notably higher in individuals with CIA at baseline compared to controls. Additionally, inflammation-related factors among patients with CIA at baseline were higher than those in controls. The dysregulation of myokines is relevant to the development and progression of OA. Sarcopenia-related factors at baseline in patients with CIA, such as low hand-grip strength and muscle mass, were lower than those in the general population.

The media follow-up period for RA, SpA, and OA patients were 8 (IQR: 5–11) years, 9 (IQR: 5–11) years, and 8 (IQR: 4–11) years. The media follow-up period for controls was 15 (IQR: 14–16) years. Of the new CIA diagnoses, 5695 (1.4%) were RA, 5168 (1.2%) were SpA, and 72 812 (17.4%) were OA. The incidence of CIA was higher in the low hand-grip strength group than in the control group: RA (12.4% vs. 3.4%), SpA (11.0% vs. 3.4%), and OA (6.1% vs. 3.4%). The difference in muscle mass between patients with CIA and the controls was less pronounced. The incidence of CIA was higher in the slow-pace group than in the control group: RA (17.6% vs. 4.8%), SpA (21.2% vs. 4.8%), and OA (11.0% vs. 4.8%). Individuals with low hand-grip strength and slow pace in RA, SpA, and OA were 2–4 times more than the controls.

3.2 | Dose–Response Analysis of the Association Between Low Hand-Grip Strength and CIA

We evaluated the association between low hand-grip strength and CIA. After adjusting for sociodemographic factors, smoking

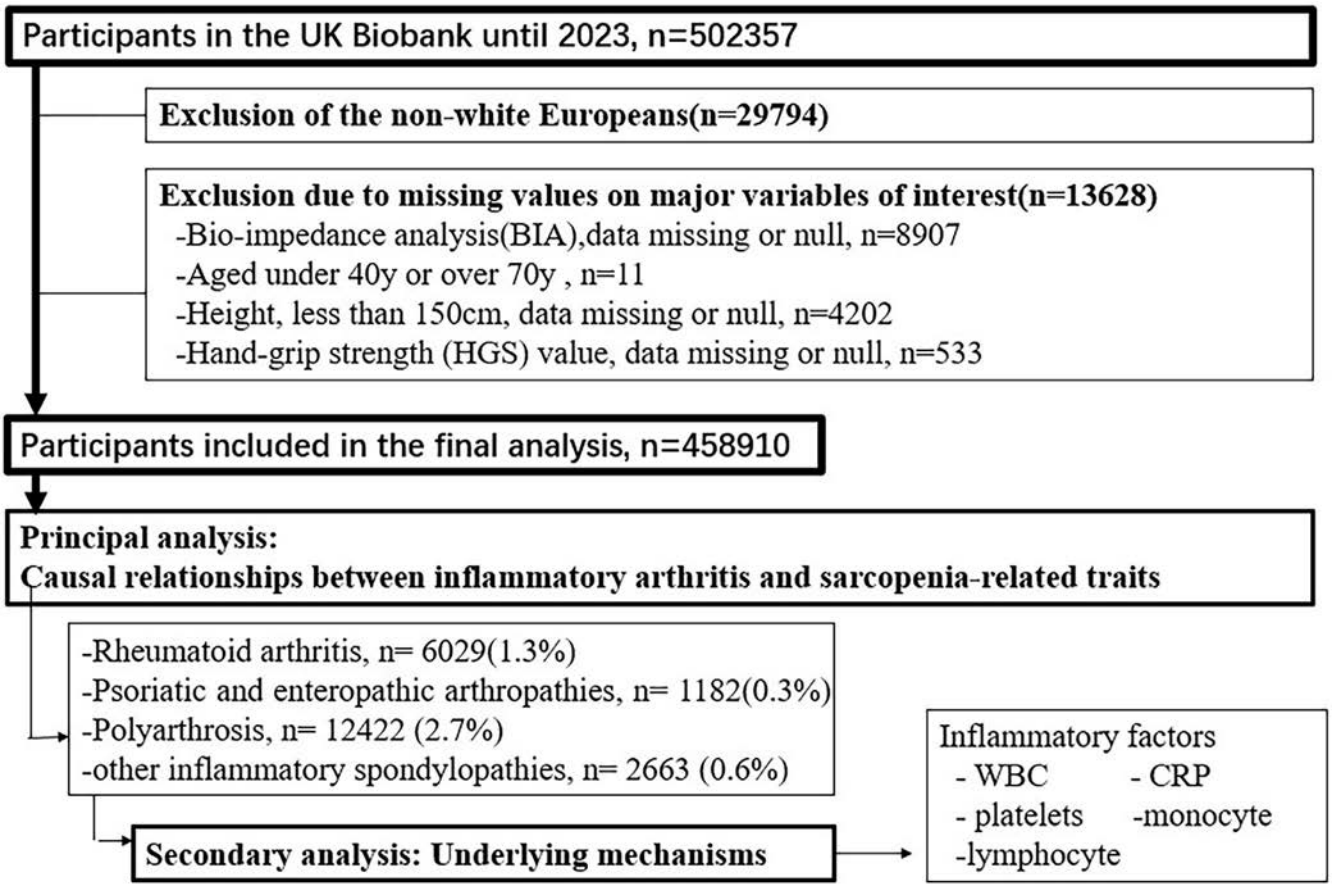

FIGURE 1 | Flowchart of CIA cohort study.

status, and alcohol status, dose–response analysis suggested that hand-grip strength had a linear association with RA, a reverse j-shaped association with SpA (p for non-linearity <0.001), and a non-linear association with OA (p for non-linearity <0.01) (Figure 2).

3.3 | Associations Between Sarcopenia and the Incidence of CIA

Cox regression analysis was used to investigate the causal relationship between sarcopenia-related factors and the incidence of CIA. Forest plots and cumulative risks of RA, SpA, and OA are shown in Figure 3. In the fully adjusted model 3, compared to normal controls, low hand-grip strength was associated with an 88% increased risk of RA (HR, 1.88; 95% CI, 1.73–2.05), a 122% increased risk of SpA (HR, 2.22; 95% CI, 2.02–2.45), and a 36% increased risk of OA (HR, 1.36; 95% CI, 1.32–1.41). Furthermore, the incidence of RA, SpA, and OA among participants with sarcopenia was associated with a 64% (HR, 1.64; 95% CI, 1.15–2.32), 83% (HR, 1.83; 95% CI, 1.21–2.77), and 26% (HR, 1.26; 95% CI, 1.09–1.45) increased risk. However, no significant association was noted between low muscle mass and OA risk in the fully adjusted model 3. Additionally, individuals with a slow walking pace exhibited a 1.83-fold (95% CI 1.66–2.02), 3.58-fold (95% CI 3.25–3.95), and 1.82-fold (95% CI 1.77–1.88) increased risk of RA,

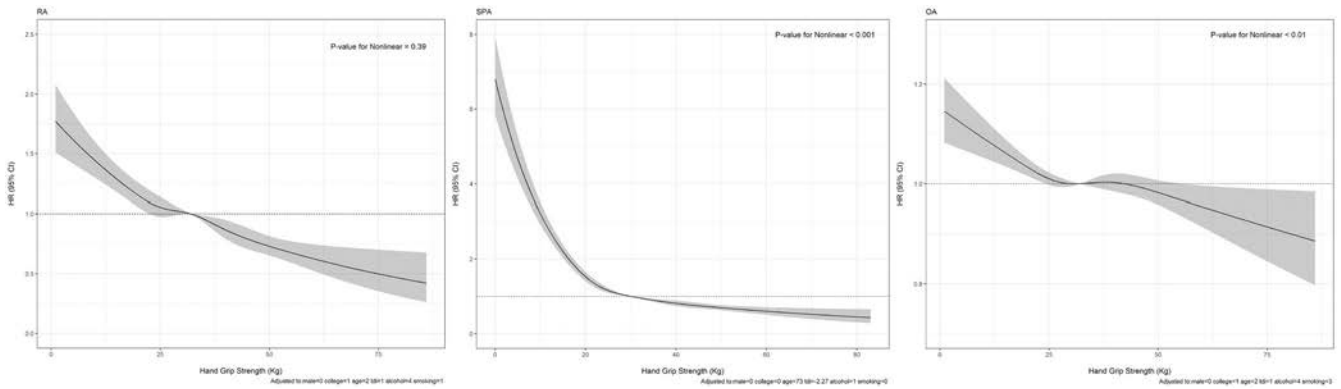

FIGURE 2 | Associations between sarcopenia and incidence of CIA by RCS.

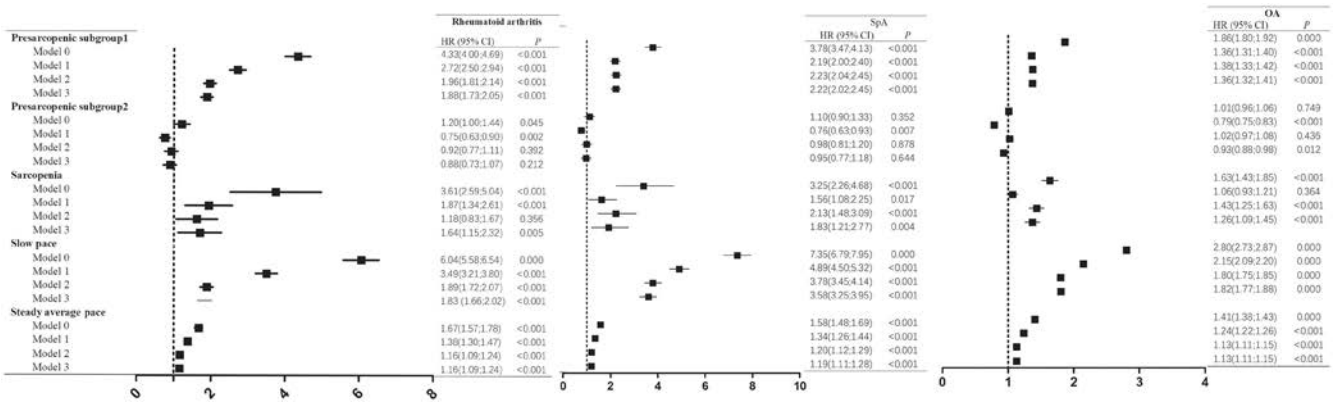

FIGURE 3 | Forest plot and cumulative risk of the incidence of CIA.

SpA, and OA, respectively. In conclusion, sarcopenia-related traits were independently associated with an increased risk of CIA. Developing targeted interventions to prevent or mitigate their progression may have important implications for reducing the incidence of CIA.

3.4 | The Mediating Role of Blood Inflammatory Markers

The six inflammatory markers were further studied for their mediating effects on the relationship between low hand-grip strength and CIA. Mediation analysis revealed that all six inflammatory markers had a mediating effect on the relationship between hand-grip strength and the risk of RA, SpA, and OA. The link between low hand-grip strength and the incidence of CIA is partially mediated by monocytes, lymphocytes, platelets, WBC, and CRP (Figure 4).

3.5 | Sensitivity Analysis

In the sensitivity analyses among women, similar conclusions were drawn regarding the causal relationship. In the analysis focusing on RA, weak HGS (HR, 1.96; 95% CI, 1.76–2.18), sarcopenic (HR, 1.75; 95% CI, 1.23–2.48), slow pace (HR, 1.88; 95% CI, 1.67–2.12), and steady average pace (HR, 1.16; 95% CI, 1.07–1.26) showed increased risk. In the analysis focusing on SpA, weak HGS (HR, 2.61; 95% CI, 2.32–2.94), sarcopenic (HR, 2.00; 95% CI, 1.32–3.04), slow pace (HR, 3.92; 95% CI, 3.44–4.47), and steady average pace (HR, 1.23; 95% CI, 1.11–1.35) showed increased risk. In the analysis focusing on OA, weak HGS (HR, 1.47; 95% CI, 1.40–1.52), sarcopenic (HR, 1.27; 95% CI, 1.10–1.47), slow pace (HR, 1.75; 95% CI, 1.69–1.83), and steady average pace (HR, 1.12; 95% CI, 1.09–1.15) showed increased risk. Notably, low SMI was associated with decreased OA among women (HR, 0.92; 95% CI, 0.87–0.98).

In the sensitivity analyses among controls and patients who developed CIA 2 years after enrollment, similar conclusions were obtained regarding the causal relationship. In the analysis focusing on RA (784 RA patients were exclued), weak HGS (HR, 1.78; 95% CI, 1.62–1.95), sarcopenic (HR, 1.51; 95% CI, 1.03–2.22), slow pace (HR, 1.77; 95% CI, 1.60–1.95), and steady average pace (HR, 1.14; 95% CI, 1.06–1.22) showed increased risk. In the analysis focusing on SpA (597 SpA patients were exclued), weak HGS (HR, 2.12; 95% CI, 1.91–2.35), sarcopenic (HR, 1.79; 95% CI, 1.15–2.80), slow pace (HR, 3.37; 95% CI, 3.03–3.74), and steady average pace (HR, 1.17; 95% CI, 1.08–1.26) showed increased risk. In the analysis focusing on OA (12932 OA patients were excluded), weak HGS (HR, 1.34; 95% CI, 1.29–1.39), sarcopenic (HR, 1.24; 95% CI, 1.06–1.46), slow pace (HR, 1.71; 95% CI, 1.66–1.77), and steady average pace (HR, 1.11; 95% CI, 1.09–1.13) showed increased risk. Notably, low SMI was associated with decreased OA (HR, 0.94; 95% CI, 0.88–1.00).

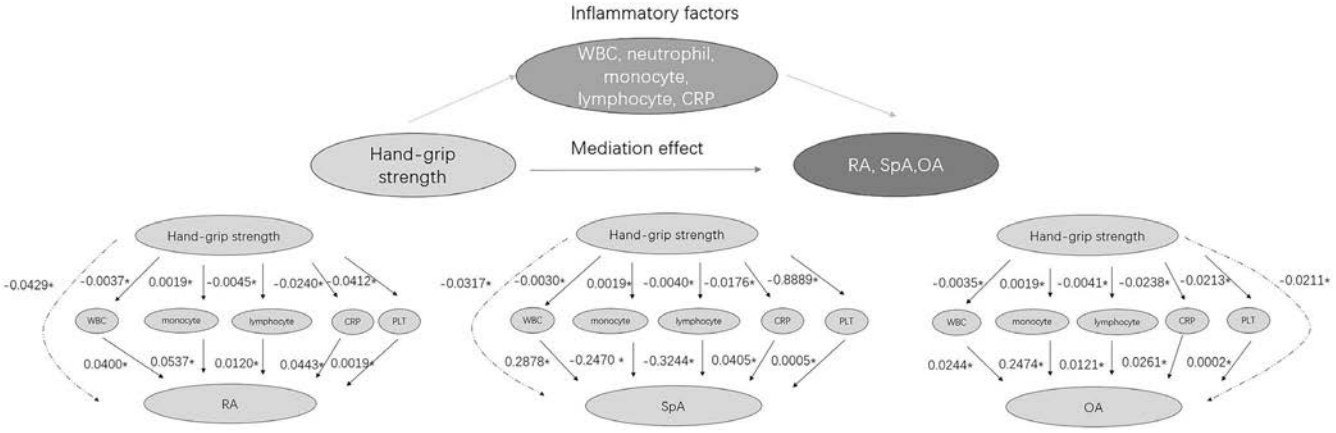

FIGURE 4 | Inflammatory markers in the association between hand-grip strength and chronic inflammatory arthropathies.

4 | Discussion

In our study, the incidence of CIA was higher in individuals with low hand-grip strength and slow pace than in controls. Almost all the studies reported the risk of sarcopenia in patients with RA, SpA, and OA. Fewer studies have focused on the impact of sarcopenia on the incidence of CIA. Therefore, it was not easy to compare the incidence of CIA in individuals with sarcopenia-related traits with previous studies. We would keep focusing on the research in this field. The incidence of RA in individuals with a low hand-grip strength was 12.4%. This is higher than the age-standardized prevalence of 3.2% in males and 2.0% in females [20]. A higher incidence of SpA and OA was also observed in individuals with low hand-grip strength and slow pace than in controls. The elevated prevalence rates observed in our study support the hypothesis that sarcopenia or pre-sarcopenia influences the incidence of CIA.

To our knowledge, this is the first study to demonstrate the causality between sarcopenia-related traits and CIA in a prospective cohort. First, we evaluated the association between hand-grip strength and CIA. The results demonstrated a linear association with RA, a reverse J-shaped association with SpA, and a nonlinear association with OA. Cox regression analysis suggested causal associations between the different stages of sarcopenia and CIA. We found that individuals with low hand-grip strength, sarcopenia, and slow pace have an increased risk of RA, SpA, and OA. For example, the HR for the three characteristics associated with sarcopenia and RA were low hand-grip strength (1.88, 95% CI, 1.73–2.05), sarcopenia (1.64, 95% CI 1.15–2.32), and slow walking pace (1.83, 95% CI 1.66–2.02). This indicated that the prevalence of RA in patients with sarcopenia-related traits was nearly twice that in the control group. Low muscle mass had little causal effect on CIA, which is consistent with the results of a meta-analysis of 2240 middle-aged and older adults with RA [21]. A recent study involving 5201 patients with RA and 45 732 controls showed that some sarcopenia-related traits have causal effects on RA [22]. However, due to limitations in Mendelian randomization analysis, some important potential confounders were not adjusted for. Most patients with RA do not engage in sufficient physical activity: an international study of 5235 patients with RA found that in 19 out of 21 countries, ≥60% performed no regular weekly exercise [23]. Moreover, the two studies that used Mendelian randomization analysis did not clarify the specific mechanisms underlying this causality. The detrimental effects of sarcopenia-related traits were more pronounced in individuals with SpA than in those with RA or OA. Compared to controls, individuals with a slow pace had a nearly fourfold increased risk of SpA. Few studies have focused on the impact of sarcopenia on SpA. In our study, the HR of low hand-grip strength, sarcopenia, and slow pace in OA were 1.372, 1.360, and 1.804, respectively. Consistent with our findings, Zhang et al. showed that patients with sarcopenia are more susceptible to developing OA [24]. The possible reason may be that enhanced muscle strength may better preserve joint stability, thus offering joint protection. Previous studies exploring the association between sarcopenia and OA have found conflicting results, partly attributable to variations in study designs and sarcopenia definitions. In another prospective cohort study involving 2779 patients without OA at baseline, low muscle mass in men showed a trend toward a protective effect against knee OA, although this effect was not significant in the entire OA cohort [25]. In our study, Cox regression analysis of 213 881 women in the cohort showed a protective effect of low muscle mass against OA. First, the participants were older, with a mean age of approximately 74 years. Second, ALM, the sum of the lean masses from all four extremities, was used to identify individuals with sarcopenia. Third, important confounding factors, such as physical activity and nutritional status, were not considered.

After gaining a primary understanding of the effects of sarcopenia-related traits, we investigated the underexplored mediators of sarcopenia in CIA. IA is characterized by autoimmune-mediated joint inflammation and is associated with systemic inflammation promoted by cytokines, such as TNF, IL-1, IL-6, and IFN-γ [26–28]. Given that the roles of the immune system and cytokines in the pathogenesis of sarcopenia and CIA have been comprehensively covered [7, 29], they seem to share systemic inflammatory consequences that affect vital organs. We then applied mediation analysis to explore the role of inflammation in CIA. Part of the total effect of sarcopenia on CIA may be mediated by inflammatory factors, including monocytes, lymphocytes, platelets, WBC, and CRP. The mediating effects of inflammatory factors have not been previously reported. These findings suggest that changes in muscle composition may play a crucial role in the muscle-bone crosstalk.

Although we identified the causal relationship and underlying mediators between sarcopenia and CIA in a large prospective cohort with good-quality data collection, our findings should be reviewed in the context of a few limitations. First, due to the relatively limited number of individuals with sarcopenia, further classification was not performed based on obesity or gait speed. Future studies focusing on these subtypes may provide a better understanding. Second, diagnosis of RA, SpA, and OA in UKB was defined by ICD-10, and very early silent phase of underlying CIA may be failed to diagnose. However, appropriate remedial measures were taken to make up for the inadequacy. In the sensitivity analysis, we excluded patients who developed CIA within 2 years of enrollment and obtained consistent conclusions. Third, UK Biobank provides limited specific cytokines. Future studies focus on IL-6, which was produced by muscle tissue, may show a higher percentage of mediating effects and may have a better interpretation [20]. We failed to analyze the effect of rheumatoid factor (RF) on RA due to the limited sarcopenia individuals with RF. Anticyclic citrullinated peptide antibody, an early inflammation factor, was not available in UK Biobank. Although peripheral blood counts were not specific indicators, they were useful in clinic and researches. The mediation effect of blood-cell-based inflammatory biomarkers had been reported widely, such as sedentary exposure on the risk of sleep disturbance, obesity to neurological and psychiatric disorders, and diet and behavioral disinhibition [30–33]. In our study, the mediation effect of blood-cell-based inflammatory biomarkers on CIA had been found, which may provide new strategies for managing CIA.

In conclusion, individuals with low hand-grip strength and slow pace are susceptible to CIA. These findings underscore the clinical importance of recognizing early warning signs of sarcopenia. Identifying sarcopenia-related traits associated with a high risk of developing CIA could facilitate interventions that prevent the

disease, including progressive resistance training. We demonstrated the mediating role of blood inflammatory markers in the relationship between hand-grip strength and CIA. This may provide clues regarding the mechanisms and development of new therapeutic approaches.

Author Contributions

Y. Q. :investigation, methodology, formal analysis, data curation, and writing – original draft. S.Z.: investigation, methodology, validation, formal analysis, data curation, and writing – original draft. X.W.: investigation, methodology, validation, formal analysis, data curation, and writing – original draft. C.Z.: investigation, formal analysis, data curation, and software. J.Z.: investigation, supervision, project administration, and funding acquisition. Q.T.: investigation, supervision, project administration, and funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data are publicly available in the UKB repository.

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Supporting Information

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

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REVIEW

Efficacy and Safety of Tocilizumab in Polymyalgia Rheumatica: A Systematic Review and Meta-Analysis

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ABSTRACT

Aims: No meta-analysis has holistically analyzed and summarized the efficacy and safety of tocilizumab in polymyalgia rheumatica (PMR). We undertook this meta-analysis to address this knowledge-gap.

Methods: Electronic databases were searched for RCTs involving patients living with PMR receiving tocilizumab in intervention arm, and placebo/active comparator in control arm. Primary outcome was to evaluate percentage of patients able to achieve C-reactive protein PMR assessment score (CRP-PMR-AS) < 10 or prednisolone dose < 5 mg/day or > 10 mg/dL decline in prednisolone from baseline. Secondary outcomes were to determine percentage of patients able to totally stop prednisolone and adverse-events.

Results: From initially screened 115 articles, data from 2 RCTs (136 patients) was analyzed. In addition, a descriptive analysis of 8 observational studies (356 patients) was also done. After 24-weeks of clinical use, patients with PMR receiving tocilizumab had significantly higher chances of achieving composite primary end-point defined as CRP-PMR-AS < 10 and either prednisone dosage < 5 mg/day or decrease in prednisolone dosage by > 10 mg/day compared to baseline [odds ratio (OR) 4.89 (95% CI: 2.34–10.23); $p < 0.001$; $I^2 = 0\%$], compared to placebo. Patients with PMR receiving tocilizumab also had significantly higher chances of being able to stop prednisolone compared to placebo [OR 4.45 (95% CI: 2.06–9.61); $p < 0.001$; $I^2 = 0\%$]. Occurrence of total adverse-events [risk ratio (RR) 1.24 (95% CI: 0.50–3.12); $p = 0.64$; $I^2 = 0\%$], adverse-events leading to treatment discontinuation [RR 0.45 (95% CI: 0.10–2.02); $p = 0.29$; $I^2 = 17\%$], and infections [RR 1.71 (95% CI: 0.83–3.52); $p = 0.14$; $I^2 = 6\%$] were comparable in patients receiving tocilizumab as compared to placebo. Observational studies have noted lung infections, neutropenia and increased cholesterol with tocilizumab use.

Conclusion: Tocilizumab is well tolerated and is effective for managing PMR. Tocilizumab is an effective glucocorticoid sparing agent in PMR.

1 | Introduction

Polymyalgia rheumatica (PMR) is the second most common debilitating rheumatologic disorder in people > 50 years-age, characterized by pain and stiffness of shoulders and hips with increased circulating inflammatory markers, having a lifetime risk of 2.4% for women and 1.7% for men [1, 2]. Glucocorticoids have been the drug of choice and the primary therapeutic option for managing PMR, having very good clinical response [3]. Most patients need at least 1 year of glucocorticoid therapy.

Relapse following glucocorticoid cessation has been common in PMR, with many patients needing chronic long term glucocorticoid therapy over many years for adequate disease control [3]. Metabolic (diabetes, dyslipidemia, hypertension, weight gain), infections, ocular (cataract, glaucoma) and bone mineral side effects of long-term glucocorticoid use has necessitated development of steroid sparing therapies for PMR. Tumor necrosis factor α based therapies have been noted to be ineffective for managing PMR in trials [4, 5]. Methotrexate and azathioprine have been noted to have only small benefit on reducing daily glucocorticoid dose in PMR [6, 7].

Interleukin (IL)-6 is believed to have a major role in the pathogenesis of PMR [4]. Several studies and randomized controlled trials (RCTs) have been published evaluating the role of humanized anti–IL-6 receptor antibody tocilizumab for managing PMR [8–12]. Tocilizumab has previously been found to be effective in managing rheumatoid arthritis, Takayasu arteritis, giant cell arteritis (GCA) and adult-onset Still's disease. However, to date no meta-analysis is available which has holistically analyzed and summarized the clinical efficacy and safety of tocilizumab in PMR. Hence the aim of this meta-analysis was to evaluate the efficacy and safety of tocilizumab for managing PMR.

2 | Methods

2.1 | Methodology

The meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [13]. The predefined protocol has been registered in PROSPERO having registration number of CRD42024497874. All randomized controlled trials (RCTs) published till December 2023 were considered for this meta-analysis. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the filled checklist of which can be found at the end of the manuscript [13]. Since ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required for this study.

The PICOS criteria was used to screen and select the studies for this meta-analysis with patients (P) being people living with PMR; intervention (I) being use of tocilizumab for managing PMR; control (C) being patients either on placebo or any other approved medication for managing PMR; outcomes (O) being evaluated were impact on PMR assessment score (PMR-AS), C-reactive protein PMR assessment score (CRP-PMR-AS) <10, prednisolone dose requirements <5 mg/day or >10 mg/dL decline in prednisolone dose from baseline, percentage of patients being able to totally stop prednisolone and adverse events. Only patients with PMR were considered for this meta-analysis. Studies needed to have at least five patients with PMR in the treatment receiving tocilizumab to be considered for evaluation in this meta-analysis. Isolated case reports were excluded. Patients with PMR and giant cell arteritis (GCA) were analyzed separately. Patient with other coexisting autoimmune disorders were excluded. Also, patients who have previously received biologic therapies like tocilizumab were excluded.

Primary outcome was to evaluate the impact on PMR assessment score (PMR-AS) or C-reactive protein PMR assessment score (CRP-PMR-AS). Secondary outcomes were to determine percentage of patients being able to reduce their daily prednisolone requirements to <5 mg/day or >10 mg/dL decline in prednisolone dose from baseline or being able to totally stop prednisolone and adverse events.

A detailed electronic databases of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health and Google scholar were searched using a Boolean search strategy: (tocilizumab) AND (polymyalgia rheumatica).

Data extraction was carried out independently by two authors using standard data extraction forms. In cases where more than one publication of a single study group was found, results were grouped and relevant data from each report were used in the analyses. Data on the primary and secondary outcomes as stated above was extracted. All disagreements were resolved by the third and fourth authors. Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 (The Cochrane Collaboration, Oxford, UK) software. We subsequently used the Risk of Bias-2 (ROB2) online tool for estimating the updated risk of bias [14]. Details have been elaborated in previous publications from our group [15, 16].

For continuous variables, the outcomes were expressed as mean differences (MD). Conventional units were used for analysis, and all studies reporting results in SI units were converted to conventional units for analysis. For dichotomous outcomes (treatment success) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). For adverse events, results were expressed as post treatment absolute risk differences. RevMan 5.4 was used for comparing MD of the different primary and secondary outcomes between the tocilizumab and the control groups of the included studies.

Heterogeneity was initially assessed by studying the forest plot generated for the primary and secondary outcomes of this study. Subsequently heterogeneity was analyzed using a chi squared test on $N-1$ df, with an alpha of 0.05 used for statistical significance and with the I^2 test [17]. Details have been elaborated in previous publications from our group [15, 16].

Data was pooled as random effect model for the analysis of primary and secondary outcomes. The outcomes were expressed as 95% confidence intervals (95% CI). Forrest plots were plotted with the left side of the graph favoring tocilizumab and the right side of the graph favoring control using RevMan 5.4 software. $p<0.05$ was considered statistically significant.

3 | Results

A total of 115 articles were found after the initial search (Figure 1). Ten duplicates were removed. Following the screening of the titles, the search was reduced down to 48 studies. Following further review of the abstracts, the search was reduced to 35 articles which were evaluated in detail for inclusion

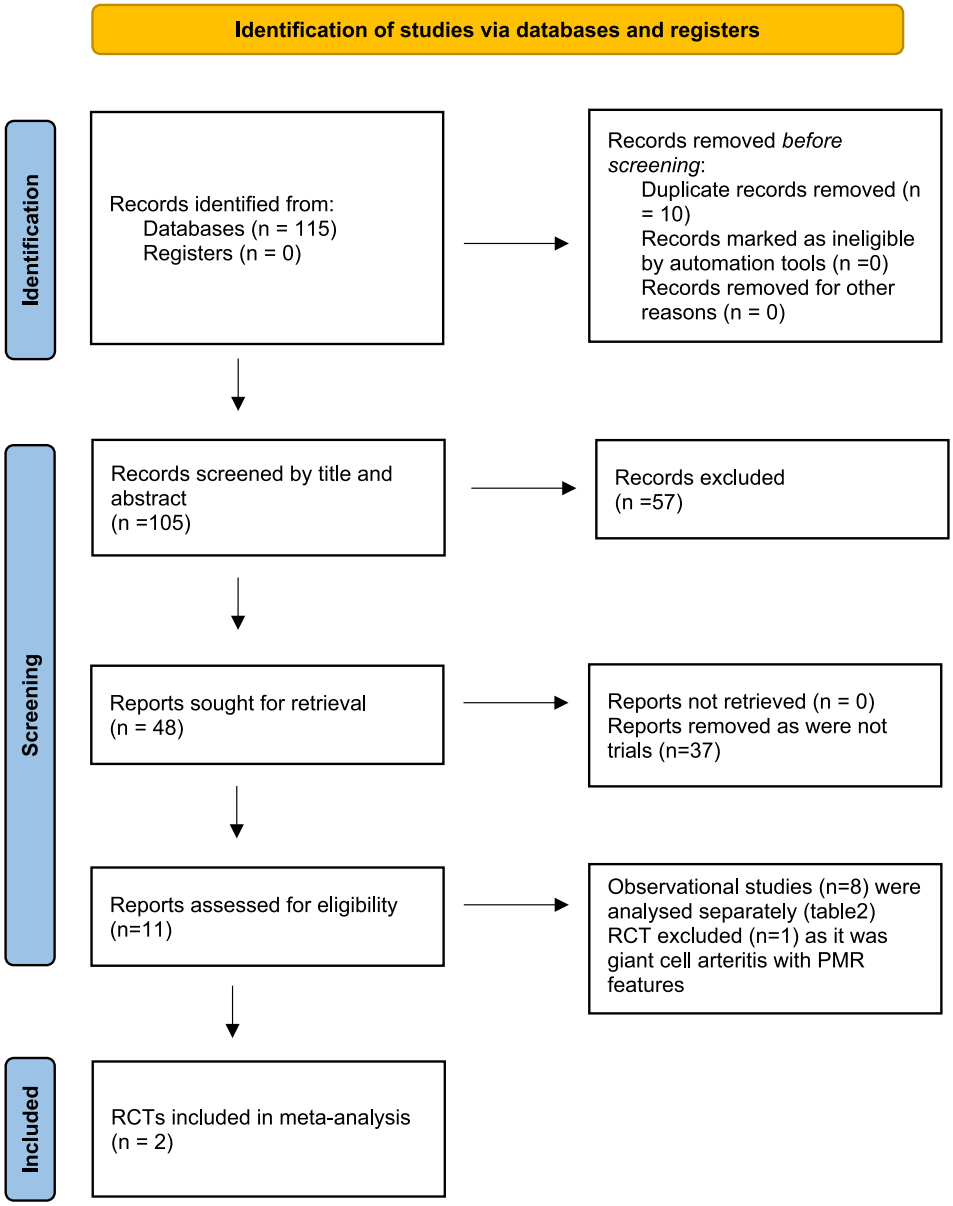

FIGURE 1 | Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: randomized controlled trial.

in this meta-analysis (Figure 1). A total of three RCTs were found [8, 9, 18]. The RCTs by Devauchelle-Pensec V et al. (2022) [8] and Bonelli et al. (2022) [9] were included in the meta-analysis as they fulfilled all criteria. The details of 136 patients analyzed from these two RCTs have been elaborated in Table 1. The RCT by Spiera et al. [18] was excluded from analysis as it evaluated the role of tocilizumab in patients with giant cell arteritis (GCA) having PMR symptoms. The studies by Chino et al. (2019) [10], Lally et al. (2016) [11], Devauchelle-Pensec et al. (2016) [12], Assaraf et al. (2023) [19], Alegria et al. (2021) [20], Izumi et al. (2015) [21] and Toussirot et al. (2016) were excluded from the meta-analysis as they were open-labeled single arm studies. The study by Izumi et al. (2021) is an observational study having three arms of patient with PMR receiving prednisolone, methotrexate and tocilizumab respectively [22]. The details of 356 patients with their outcomes from the above observational studies have been elaborated separately for a descriptive analysis in Table 2.

The summaries of ROB2 of the two studies included in the meta-analysis have been elaborated in Figure 2. Bias arising from the randomization process, deviations from the intended intervention, missing outcome data, measurement in the outcome and selective reporting, all were found to be low.

3.1 | Effect of Tocilizumab on Primary and Secondary Outcomes

After 24 weeks of clinical use, patients with PMR receiving tocilizumab had significantly higher chances of achieving composite primary end point defined as CRP-PMR-AS <10 and either prednisone dosage <5 mg/day or decrease in prednisolone dosage by >10 mg/day as compared to baseline [odds ratio (OR) 4.89 (95% CI: 2.34–10.23); $p<0.001$; $I^2=0\%$ (low heterogeneity); Figure 3a], as compared to placebo. Patients with PMR receiving tocilizumab also had significantly higher chances of

TABLE 1 | Profile of baseline characteristics of patients with side effect profile analyzed in this meta-analysis.

Study	Groups	Age (years) median (IQR)	Disease duration	CRP-PMR-AS	CRP (mg/L)	ESR (mm/h)	Prednisolone dose (mg/d)	Methotrexate		Side effects
								Current use	Prior use	
Devauchelle-Pensec et al. (2022) [8]	TCZ ($n=49$)	68.0 (63.0–75.0)	21.0 (10.0–48.0) months	20.3 (15.6–29.0)	9 (4–17)	28.3 (33.0)	10.0 (10.0–15.0)	20	11	Herpes = 1; headache = 7; hyperlipemia = 6; cytopenia = 4
	Placebo ($n=51$)	67.0 (61.0–72.0)	16.0 (8.0–35.0) months	19.7 (15.4–28.6)	9 (4–18)	24.3 (23.0)	10.0 (10.0–15.0)	11	10	Herpes = 1; headache = 1; hyperlipemia = 2; cytopenia = 2; influenza = 1; colitis = 1
Bonelli et al. (2022) [9]	TCZ ($n=19$)	68.8 ± 9.0	8 ± 5 days	—	16 ± 24	24.3 ± 16.4	16.7 ± 3.9 (100% pts)	—	—	GI disorder = 3
	Placebo ($n=17$)	71.1 ± 9.0	6 ± 3 days	—	9.8 ± 15	24.1 ± 18.7	17.2 ± 3.1 (94% pts)	—	—	GI disorder = 4; musculoskeletal disorder = 7; pancreatitis = 1; duodenal ulcer = 1

Abbreviations: AS, assessment score; continuous variables have been expressed as median (IQR) or mean ± standard deviation; CRP, C-reactive protein; ESR, erythrocytic sedimentation rate; GI, gastrointestinalh, hour; IQR, inter quartile range; PMR, polymyalgia rheumatica: pts, patients; TCZ, tocilizumab.

TABLE 2 | Profile and outcomes of patients with polymyalgia rheumatica treated with tocilizumab in observational studies.

Study	Number of patients	Age (years)	PMR duration	PMR-AS (mean)	CRP (mg/L) (mean)	ESR mm/h (mean)	Tocilizumab regimen; study duration	Outcomes	Side effects
Chino et al. (2019) [10]	13	71	4 months	33.3	4.3	67	TCZ (8 mg/kg) fortnightly for first 8 weeks (5 infusions); then every 4 weeks for the next 40 weeks (10 infusions); 104 weeks	RemR: 31% (12 weeks); 69% (52 weeks)	NTM = 1; atypical lung infiltrates = 1; neutropenia = 1; raised LDL-C = 13; mild neutropenia = 12
Lally et al. (2016) [11]	10	68	1 month	5.3	3.8	63.2	TCZ (8 mg/kg) monthly for 1 year; tapering GC with stoppage by 12 weeks	Percent patients in relapse-free remission without GC at 6 months = 90%	Neutropenia = 7; raised LDL-C: 2; oral herpes = 1; upper respiratory infection = 5; anemia = 1
Devauchelle-Pensec et al. (2016) [12]	20	67	99 days	36.65	6.5	51	TCZ (8 mg/kg) monthly for 3 months without GC; then oral prednisone from weeks 12–24 (0.15 mg/kg if PMR-AS ≤ 10 and 0.30 mg/kg otherwise)	85% patients achieved very low disease activity (PMR-AS < 7) by week 12	Neutropenia = 5; Raised LDL-C = 4
Assaraf et al. (2023) [19]	53	72.8	18 months	—	14	—	TCZ (8 mg/kg) monthly for 1 year; tapering GC; 13 months follow-upS	GC requirement < 5 mg/day: 77% at 6 months; 97% at 12 months; GC-free: 22.5% at 6 months; 58.3%at 12 months	Severe infections = 5; severe neutropenia ($< 1000/mm^3$) = 1; myocardial infaction = 2
Carvajal-Alegria et al. (2021) [20]	18	68	—	—	82	—	TCZ (8 mg/kg) monthly for first 12 weeks	Leukocytes, neutrophils and platelets were higher in early PMR HCs but hemoglobin was decreased. These parameters correlated with IL-6 levels. Quickly after tocilizumab therapy, leukocytes, neutrophils and platelets decreased and hemoglobin increased	No significant adverse event reported

(Continues)

TABLE 2 | (Continued)

Study	Number of patients	Age (years)	PMR duration	PMR-AS (mean)	CRP (mg/L) (mean)	ESR mm/h (mean)	Tocilizumab regimen; study duration	Outcomes	Side effects
Izumi et al. (2015) [21]	13	74	8 months	—	3.35	49	TCZ (8 mg/kg) monthly for 1 year	All patients had intractable PMR not responding to GC and methotrexate; CRP reduce to 0.24 mg/L at 4 weeks; ESR reduced to 6 mm/h at 4 weeks; prednisolone requirement reduced from 6 mg/d at baseline to 1 mg/d at 12 weeks	Thrombocytopenia = 1; leucopenia = 1; phlegmone = 1
Toussirot et al. (2016) [22]	7	73	2.3 years	32.3	5.7	—	TCZ (8 mg/kg) monthly for 12 months	Four patients achieved low disease activity by 8 weeks therapy	No significant adverse event reported
Izumi et al. (2021) [23]	13 (TCZ) 32 (MTX) 177 (PRED)	74.7	21.3 months	Relapse ($n = 12$); LOR ($n = 1$)	2.3	46	TCZ (8 mg/kg) monthly for 21 months	80% patients on TCZ could discontinue prednisolone as compared to only 27.7% and 18.8% in methotrexate and GC groups respectively at 2 years	Phlegmone = 1

Abbreviations: CRP, C-reactive protein; ESR, erythrocytic sedimentation rate; GC, glucocorticoids; h, hour; LDL-C, low density lipoprotein cholesterol; LOR, lack of response; MTX, methotrexateNeutropenia defined as absolute neutrophil count $< 1500/mm^3$; NTM, non-tuberculosis mycobacteria; PMR, polymyalgia rheumatica; PMR-AS, polymyalgia rheumatica- activity score; PRED, prednisolone; Remission was defined as a PMR-AS < 1.5; RemR, remission rate; TCZ, tocilizumab.

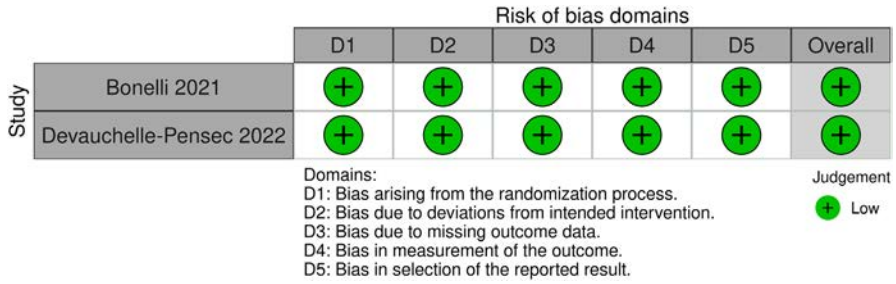

FIGURE 2 | (a) Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies. (b) Risk of bias summary: Review authors' judgments about each risk of bias item for each included study. D: domain; Low implies low risk of bias.

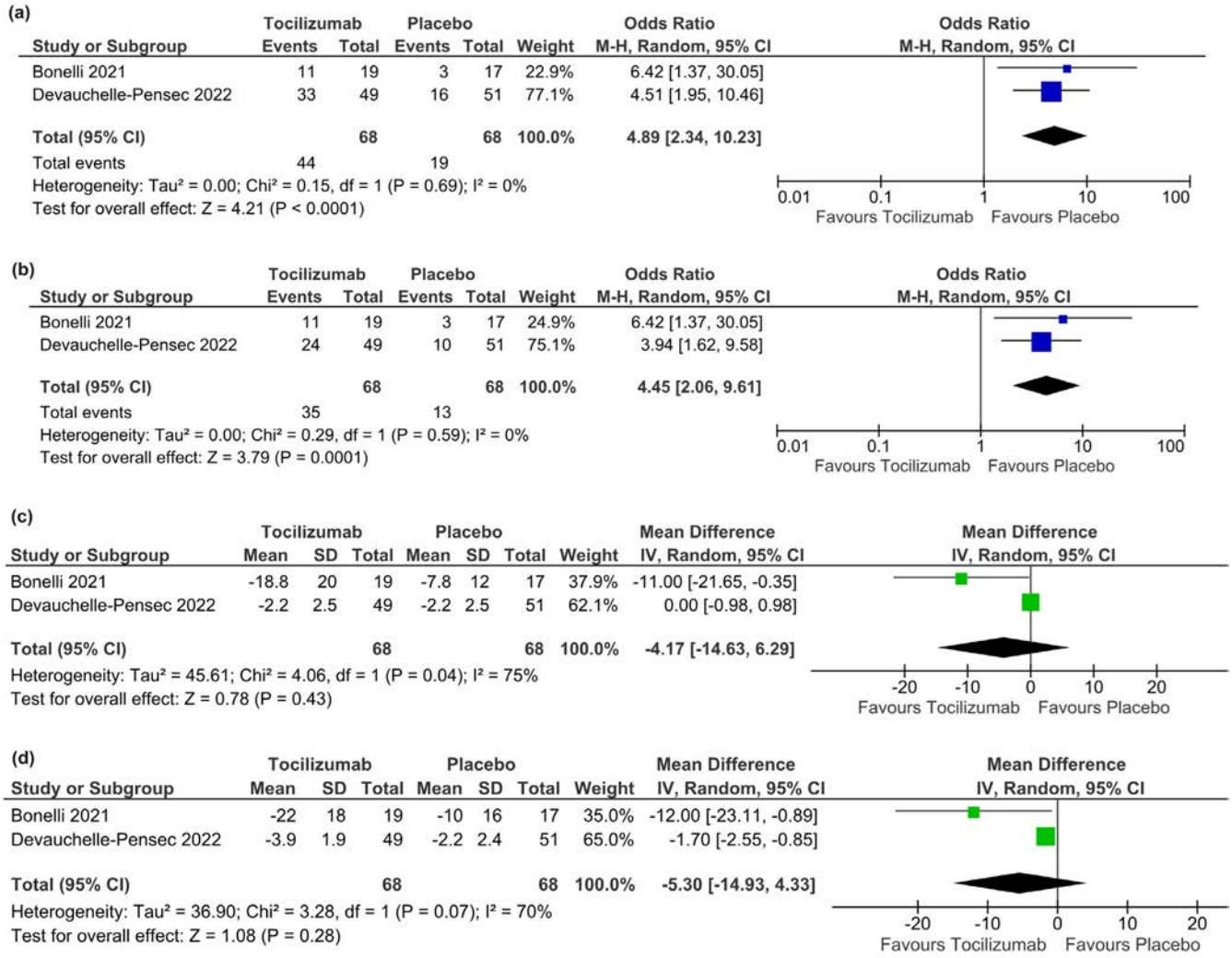

FIGURE 3 | Forest plot highlighting the impact of tocilizumab as compared to placebo on (a) Composite primary end-point defined as C-reactive protein polymyalgia rheumatica assessment score (CRP-PMR-AS) < 10 and either prednisone dosage < 5 mg/day or decrease in prednisolone dosage by > 10 mg/day as compared to baseline; (b) Chances of total stoppage of prednisolone; (c) Pan as per visual analog scale; (d) Global assessment as per visual analog scale.

being totally able to stop prednisolone as compared to placebo [OR 4.45 (95% CI: 2.06–9.61); $p < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 3b].

Pain assessed by visual analog scale (VAS) [mean difference (MD) −4.17 mm (95% CI: −14.63 to 6.29); $p = 0.43$; $I^2 = 75\%$ (moderate heterogeneity); Figure 3c] and global assessment of disease activity using VAS [MD −5.3 mm (95% CI: −14.93 to 4.33); $p = 0.28$; $I^2 = 70\%$ (moderate heterogeneity); Figure 3d] was comparable in the tocilizumab group as compared to placebo group after 24 weeks of therapy.

The occurrence of total adverse events (TAEs) [risk ratio (RR) 1.24 (95% CI: 0.50–3.12); $p = 0.64$; $I^2 = 0\%$ (low heterogeneity); Figure 4a], adverse events leading to treatment discontinuation [RR 0.45 (95% CI: 0.10–2.02); $p = 0.29$; $I^2 = 17\%$ (low heterogeneity);

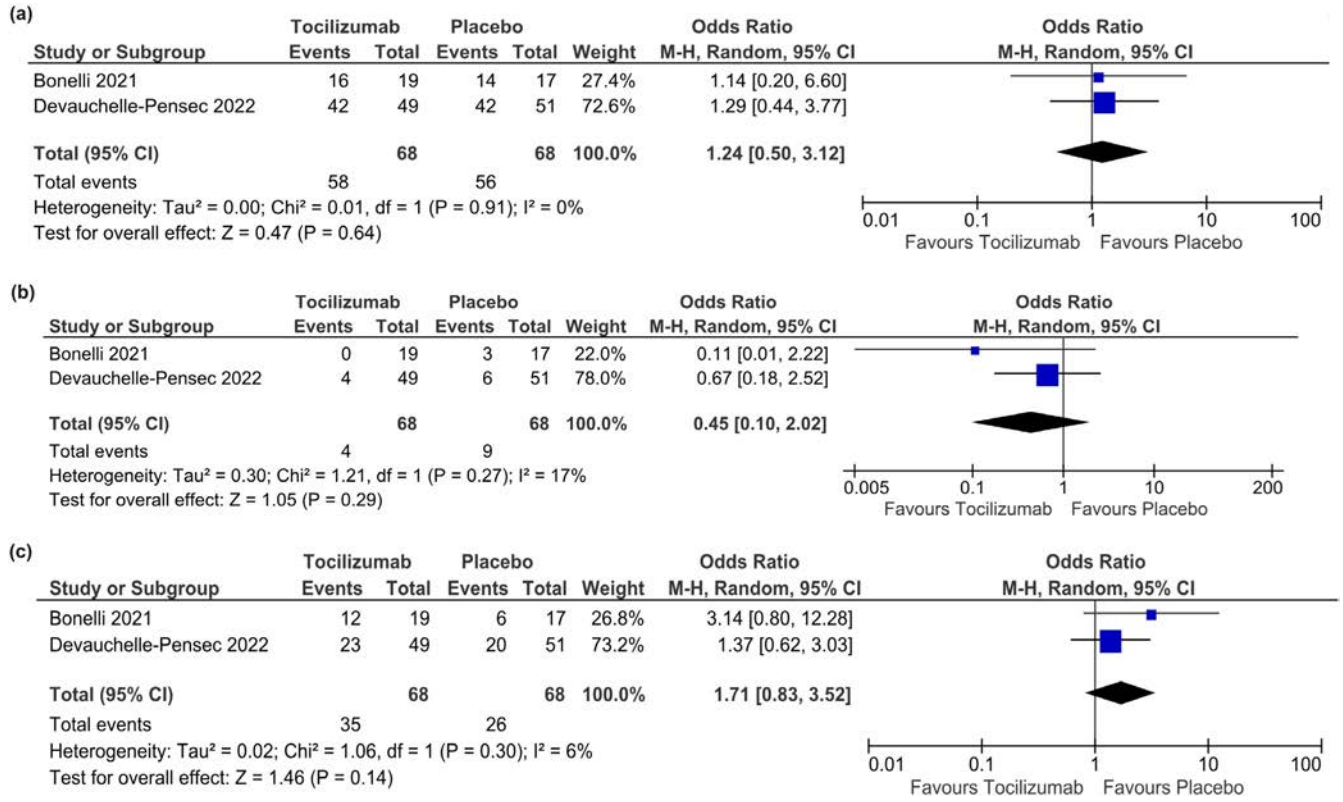

FIGURE 4 | Forest plot highlighting the impact of tocilizumab as compared to placebo on (a) Total adverse events; (b) treatment discontinuation because of side effects; (c) infections.

Figure 4b], and infections [RR 1.71 (95% CI: 0.83–3.52); $p = 0.14$; $I^2 = 6\%$ (low heterogeneity); Figure 4c] were comparable in patients receiving tocilizumab as compared to placebo. No gastrointestinal perforations, anaphylaxis, myocardial infarctions, malignancies or death were Reported in any of the RCTs.

3.2 | Key Messages From Observational Studies

The main outcomes from the eight different observational studies (356 patients) have been elaborated in Table 2. Tocilizumab has been primarily studied as second line agent along with glucocorticoids for managing PMR (Table 2). Only one prospective uncontrolled observational study has evaluated tocilizumab as a first line agent for managing PMR for 12 weeks in GC naïve patients, showing good clinical efficacy [12]. However, outcomes in general were more impressive when tocilizumab was added to glucocorticoids. Addition of tocilizumab to glucocorticoids resulted significant reduction in total daily dose of glucocorticoid requirement. Reduction in daily prednisolone requirement to < 5 mg/day was possible in almost each patient, with a good percentage of patients having opportunity to totally stop glucocorticoids (Table 2). Observational studies have noted lung infections, neutropenia and increased cholesterol with tocilizumab use (Table 2).

4 | Discussion

This meta-analysis shows reassuring data of efficacy and safety of tocilizumab in managing PMR. Novelty of this study is it being the first quantitative assessment of tocilizumab in PMR. In both the RCTs and most of the observational studies, tocilizumab has been used as an add on therapy to patients who have already received and are on GCs. Current data from RCTs shows that addition of tocilizumab to GCs in patients with PMR will result in nearly 4.89 times greater likelihood of having disease remission with 4.45 times greater likelihood of total stoppage of GCs. Hence tocilizumab becomes an ideal second like agent after GCs for managing PMR. Tocilizumab is an ideal second line agent for managing PMR in patients who do not tolerate GC, who have very high requirements of GC dose, in whom tapering of GC results in flare of PMR [24]. The main advantage of tocilizumab is its steroid sparing role, protecting the patients from long term deleterious side effects of GCs. Based on literature review, the efficacy data of tocilizumab is much better than other agents which have been tried as steroid sparing agents in PMR like methotrexate, azathioprine, hydroxychloroquine and anti-TNF therapies [4–7].

Based on current data, tocilizumab cannot be recommended as a first line agent for managing PMR. This is because we have no RCT which has evaluated the same. There is only one prospective observational study by Devauchelle-Pensec et al. (2016) [12] which evaluated once monthly tocilizumab infusion for 3 months in patients with GC free PMR, and found it to be effective in reducing PMR-AS after 12 weeks therapy, with none of the patients needed GC rescue therapy over the 3 months. In these patients also after 3-months (12 weeks), the patients were put on low dose GC for maintaining remission till 24 weeks [12].

Risk of infections, reactivation of herpes and neutropenia/leucopenia remains a concern with tocilizumab use in PMR as has

been reported previously in other autoimmune disease also. However, most of these side effects were mild in the RCTs and observational studies, and it was possible to continue treatment in most of the patients. Limitations of this meta-analysis include the small number of patients analyzed. Data was available only from two studies for analysis. Strengths of this meta-analysis include the high quality of the studies analyzed as they had low risk of bias and low data heterogeneity. This meta-analysis highlights the paucity of RCTs evaluating the role of tocilizumab on different aspects of PMR. There remains need for large multicentric multi-ethnic RCTs evaluating the role of tocilizumab as a first line agent for managing PMR. Direct head-to-head comparison of tocilizumab with GCs is also lacking and warrants evaluation.

To conclude, this first meta-analysis evaluating the efficacy and safety of tocilizumab in PMR, provides us with reassuring data on the good efficacy with good tolerability of this medicine as a second line steroid sparing agent for managing PMR with data available up to 2 years of clinical use.

Author Contributions

The study was conceptualized by M.S. Literature search was done by M.S., S.K.D. and D.D. Data analysis was done by D.D. and R.M. All authors contributed equally to the preparation of the manuscript.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

An Innovative Anoikis Signature With Inflammatory Infiltrates in Osteoarthritis

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Keywords: anoikis | GEO | immune infiltration | osteoarthritis | subchondral bone

ABSTRACT

Aim: To explore the relationship between an innovative anoikis-related gene signature and inflammatory infiltrates in patients with osteoarthritis.

Methods: Gene expression profiles (GSM1248759 and GSE200843) were curated from the Gene Expression Omnibus database, followed by the construction of a protein–protein interaction network. Functional and genomic enrichment analyses were conducted using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. The CIBERSORT method was employed to investigate immune cell infiltration differences between osteoarthritic and control tissues. Additionally, the ConsensusClusterPlus package in R software was utilized to identify distinct anoikis patterns (Cluster C1 and Cluster C2) and conduct molecular biological investigations.

Results: Analysis revealed two distinct anoikis patterns (Cluster C1 and Cluster C2), with Cluster C2 patients exhibiting varying immune cell levels compared to Cluster C1 patients. Molecular investigations identified 84 DEGs enriched in specific pathways such as adipocytokine signaling, cytokine–cytokine receptor interaction, ECM–receptor interaction, and the PPAR signaling pathway. qPCR experiments confirmed the elevated expression levels of specific genes, including *SOD2*, *MAPK14*, *CEACM3*, *LAMB3*, *COL13A1*, *TLR3*, *NOTCH3*, and *KLF12*, in the IL-1β-induced group compared with the osteoarthritis group.

Conclusion: This study highlights the role of anoikis-related genes and immune infiltration differences in osteoarthritis, enhancing our understanding of its development.

Abbreviations: ANRGs, anoikis-related genes; CD14, cluster of differentiation 14; CD16+, cluster of differentiation 16 positive; CD19+, cluster of differentiation 19 positive; CD4+, cluster of differentiation 4 positive; CD56+, cluster of differentiation 56 positive; CIBERSORT, A computational method to estimate immune cell composition; COL-2A-FITC, type II collagen conjugated with fluorescein isothiocyanate; DEGs, differentially expressed genes; DMEM, Dulbecco's modified eagle medium; ECM, extracellular matrix; FBS, fetal bovine serum; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GEO, Gene Expression Omnibus; GO, Gene Ontology; HVGs, highly variable genes; IL-1β, interleukin 1 beta; KEGG, Kyoto Encyclopedia of Genes and Genomes; LASSO, least absolute shrinkage and selection operator; MAP K14, mitogen-activated protein kinase 14; NK, natural killer; PI3K-Akt, phosphoinositide 3-kinase-Akt; PPAR, peroxisome proliferator-activated receptor; PPI, protein–protein interaction; qPCR, quantitative polymerase chain reaction; SCTransform, a normalization method for single-cell RNA sequencing data; SOD2, superoxide dismutase 2; TCF4, T-cell factor 4; TIMP-1, tissue inhibitor of metalloproteinase 1.

Ze-Hao Sheng and Xin-Yi Gong contributed equally to this work.

1 | Introduction

The burden of disabilities resulting from hip and knee osteoarthritis (OA) has witnessed a significant escalation over time. Specifically, the number of years lived with disabilities due to these conditions surged from 10.5 million in 1990 to 17.1 million in 2010. Examining the disability impact caused by the disease, the measure known as disability-adjusted life years (DALYs) illustrates a noteworthy trend. In 1990, hip/knee OA accounted for 0.42% of the total DALYs across all age groups. However, by 2010, this percentage had risen to 0.69%. These statistics unequivocally demonstrate the increasing prevalence of OA-related disabilities and the substantial burden they impose on affected individuals and society [1, 2].

OA predominantly affects the elderly population [3], representing a degenerative condition that leads to joint impairment. This debilitating disease is characterized by the progressive deterioration of cartilage and the fragmentation of bone within the affected joints [4]. Physical strain on joints and persistent mild inflammation contribute to the development of OA, which can be triggered by previous joint trauma, atypical joint or limb formation, hereditary inclination, or engaging in occupations involving heavy lifting [5]. Aging is a crucial factor associated with the escalating prevalence of OA, a chronic joint ailment that unfortunately eludes prevention [6, 7]. Consequently, the treatment expenses for OA pose substantial financial burdens on both patients and society, posing a grave threat to overall human well-being. Despite these challenges, the etiology and pathogenesis of this disease remain elusive.

Hence, in order to create successful therapeutic approaches, exploring the fundamental mechanisms governing OA progression is essential. Anoikis, a Greek term meaning "without home," is a specialized form of apoptosis triggered by the loss of cell–matrix interactions. It begins with the disruption of cytosolic connectors, such as integrin-ECM and cadherin cell, ultimately leading to intracellular cytoskeleton and signaling pathway alterations, culminating in the activation of caspases and the initiation of programmed cell death [8, 9]. This intricate process serves as a crucial mechanism by which cells uphold tissue integrity and homeostasis, preventing aberrant cell survival in unsuitable environments and facilitating normal cell turnover, tissue remodeling, and embryonic development. In contrast, OA, characterized by the gradual loss of cartilage primarily composed of chondrocytes, presents a captivating and multifaceted area of study [10]. The interplay between anoikis and the chondrocytes' ability to maintain their attachment to the extracellular matrix holds significant potential in understanding OA, yet research on the role of anoikis in this context remains surprisingly limited.

In this research, we employed gene expression patterns and bioinformatics analysis to contrast gene expression between OA patients and healthy controls. Identifying genes with altered expression patterns and unique anoikis-related genes will deepen our understanding of the molecular mechanisms behind OA-related responses on a systems biology scale.

2 | Materials and Methods

2.1 | Data Preparation and Preprocessing

Our gene expression profiles analysis featured 5 normal samples and 20 OA samples that were acquired from the Gene Expression Omnibus (GEO) (GSM1248759) [11] data portal. The OA single-cell sequencing dataset GSE200843 [12] was also included in the study. A total of 415 anoikis-related genes (ANRGs) were downloaded from the GeneCard database [13] (https://www.genecards.org/) and Harmonizome portals [14]. Further, 84 differentially expressed genes (DEGs) were identified in GEO-OA cohort via the "limma" R package, comparing the expression of 415 ANRGs between OA and normal subchondral bone.

2.2 | Identifification of Anoikis-Related Differentially Expressed Genes

Gene expression analysis was performed using the "limma" package to identify differences in gene expression between OA and healthy samples in the combined dataset, aiming to investigate the impact of gene expression levels on anoikis-related genes in OA. DEGs were defined with the criteria $|\log2FC| > 1$ and $p < 0.05$, indicating both upregulated and downregulated DEGs. Visualization of differential gene expression was achieved through volcano plots and heat maps. Anoikis-related genes showing differential expression were identified by overlapping DEGs with genes associated with anoikis.

2.3 | Forest Plot and Risk Model Construction

The model was trained using the least absolute shrinkage and selection operator (LASSO) method to predict the likelihood of OA occurrence. Anoikis genes potentially exhibiting differential expression were incorporated into the model and analyzed using LASSO. The ensuing algorithm aimed to identify characteristic genes linked to OA risk. The Lasso regression model was chosen for its ability to perform both variable selection and regularization, which helps prevent overfitting and enhances model interpretability, especially with high-dimensional data. Lasso is particularly effective when there are many predictors, as it shrinks some coefficients to zero, excluding irrelevant variables.

Following this, the frequency of OA among patients was approximated using columnar line graph models, integrating the chosen Ano-DEGs. Comparative examination was conducted by aligning the predicted values with the established standards via calibration curves. To assess the practical value of the model-derived decisions in aiding patients, a decision curve analysis was performed, and clinical impact curves were plotted.

2.4 | Functional Enrichment Analysis

Gene Ontology (GO) analysis stands as a conventional approach for conducting comprehensive large-scale functional enrichment investigations, encompassing assessments of biological

processes, molecular functions, and cellular components [15]. Meanwhile, Kyoto Encyclopedia of Genes and Genomes (KEGG) serves as a widely adopted database repository housing valuable information about genomes, biological pathways, diseases, and pharmaceuticals [16]. To carry out the analysis of GO annotations and the enrichment assessment of KEGG pathways for DEGs, the R clusterProfiler package was employed [17]. For gene set enrichment analysis (GSEA), we followed the GSEA method (DOI: 10.1073/pnas.0506580102, http://software.broadinstitute.org/gsea/index.jsp) and utilized the GSEA software (version 3.0).

2.5 | Protein–Protein Interaction Network (PPI)

The establishment of PPI networks elucidates how individual proteins participate in various life processes, encompassing biological signaling, gene expression regulation, energy and material metabolism, and cell cycle control. A methodical examination of these interactions in biological systems is vital for understanding protein functionality within such systems. Additionally, systematic analysis aids in understanding the mechanisms underlying biological signaling and energy matter metabolism, particularly in disease contexts, and reveals functional links between proteins. To construct this extensive protein interaction network, we utilized the STRING database [18], a widely utilized tool for identifying known proteins and predicting their relationships. This PPI network was specifically constructed by interlinking DEGs, referred to as Ano-DEGs, and potential differentially expressed anoikis-related genes. To visualize this network, we employed Cytoscape (v3.8.2) [19] and further elucidated the functions of the genes within the network using closeGO [20]. The PPI network analysis was conducted using Cytoscape software. Hub genes were identified using the CytoHubba plugin based on the MCC algorithm, selecting the top 40 hub genes. The screening parameters were set as degree cutoff ≥ 2, K-core ≥ 2, and edge weight threshold ≥ 0.7, according to the STRING database confidence scores. Node size and edge width were adjusted to enhance network visualization.

2.6 | Detection and Correlation of Immune Infiltrating Cells in Disease

Evaluating immune cell infiltration is crucial for predicting disease progression and treatment responses. We utilized the CIBERSORT algorithm, which employs linear support vector regression to analyze gene expression profiles from RNA-sequencing data, to estimate immune cell quantities within samples [21]. In our investigation, we evaluated 22 different immune cell types in patients, each exhibiting distinct immunological patterns, using the CIBERSORT algorithm in the R software. These findings were visually depicted using box plots, effectively highlighting differences in immune cell composition among patients with varying immune profiles.

2.7 | Primary Cell Extraction From Mice

C57 mice (3–5 days old) were euthanized by cervical dislocation, disinfected in 75% ethanol, and their femoral head cartilage caps were removed and placed in PBS with 2% antibiotics. After washing and mincing into ~1 mm^3 fragments, tissues were digested in 3 mL Collagenase D (1.5 mg/mL) at 37°C for 2 h. The suspension was filtered, centrifuged, and resuspended in DMEM-F12. Cells were counted, seeded in 24-well plates, and a second digestion was performed. Primary chondrocytes were identified by flow cytometry after 5 days. All procedures followed the Guidelines for Animal Experimentation of People's Hospital of Hangzhou Medical College and were approved by the Animal Ethical and Welfare Committee of ZPPH.

2.8 | Single Cell Transcriptomic Analysis Showed the Heterogeneity of OA Sample

We performed single-cell RNA sequencing on OA mice samples using the Illumina NextSeq 500 platform (GSE200843) and integrated datasets with the MergeSeurat function. Cells were filtered based on gene counts, UMI, and mitochondrial gene percentage. After normalization, highly variable genes were identified and confounding factors controlled using SCTransform. Cell clustering and differential expression analysis were performed, focusing on genes with logFC > 1, enhancing our understanding of the biological landscape.

2.9 | Validation of Hub Genes via qPCR

We utilized IL-1β to stimulate chondrocytes from both normal individuals and those with OA to mimic this inflammatory microenvironment. Quantitative PCR (qPCR) was used to validate the expression levels of hub genes. C-28/I2 Chondrocytes from healthy donors (Pricella, China) and primary mouse chondrocytes were cultured in DMEM/F12 medium (HyClone, USA) supplemented with 10% fetal bovine serum (FBS, Thermo Fisher Scientific, USA), Carbon dioxide at 37°C, and were divided into control and IL-1β-treated (20 ng/mL) groups. The mRNA expression levels of *SOD2*, *MAPK14*, *CEACAM3*, *LAMB3*, *COL13A1*, *TLR3*, *NOTCH3*, and *KLF12* were assessed after 48 h of incubation. Total RNA from OA samples was extracted and converted into cDNA using the HiScript II 1st Strand cDNA Synthesis Kit (Vazyme, China). qRT-PCR was performed using Real-Time PCR Mix (Vazyme, China). Gene expression levels relative to GAPDH expression were determined using the $2^{-\Delta\Delta ct}$ method. (The qPCR gene primers are detailed in Table S1).

3 | Results

3.1 | Expression of Anoikis-Related Genes in Osteoarthritis Samples

The analysis was conducted as outlined in Figure 1 (flow chart). In the lateral subchondral bone, there were 3898 DEGs identified in OA samples compared to control samples, whereas in the medial subchondral bone, 3708 DEGs were detected (Figure 2A). The volcano plot in Figure 2B highlights the most significant DEGs.

Furthermore, Figure 2C illustrates the intersection of anoikis-related genes from both datasets and the overlap with DEGs specific to OA, resulting in the identification of 28 Ano-DEGs. The

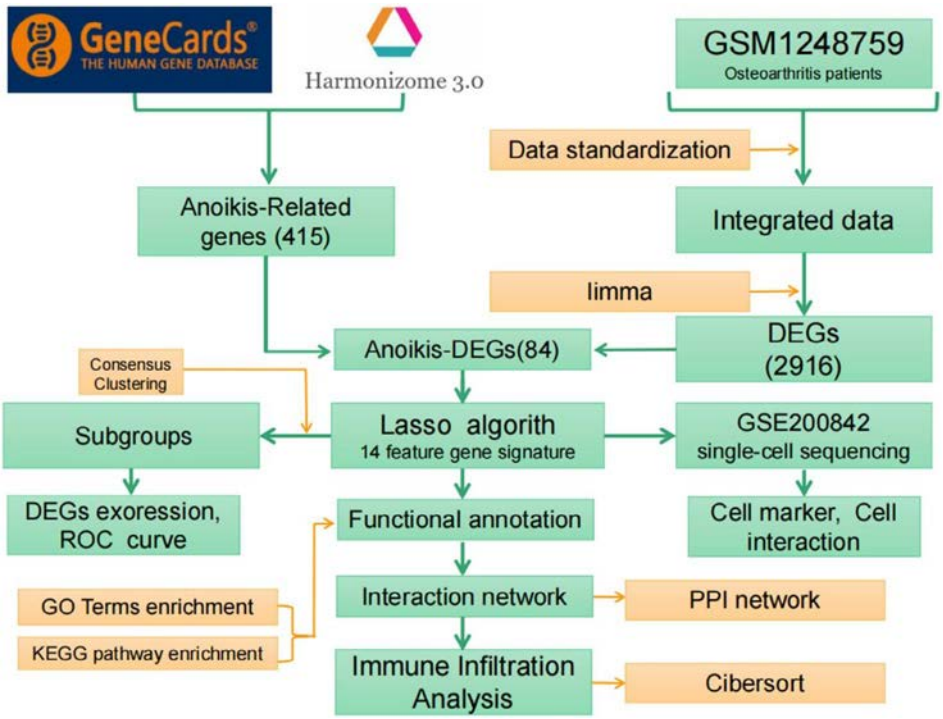

FIGURE 1 | Flowchart of the study. The flowchart depicted the identification and validation of anoikis-related gene signatures. DEGs, differentially expressed genes. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

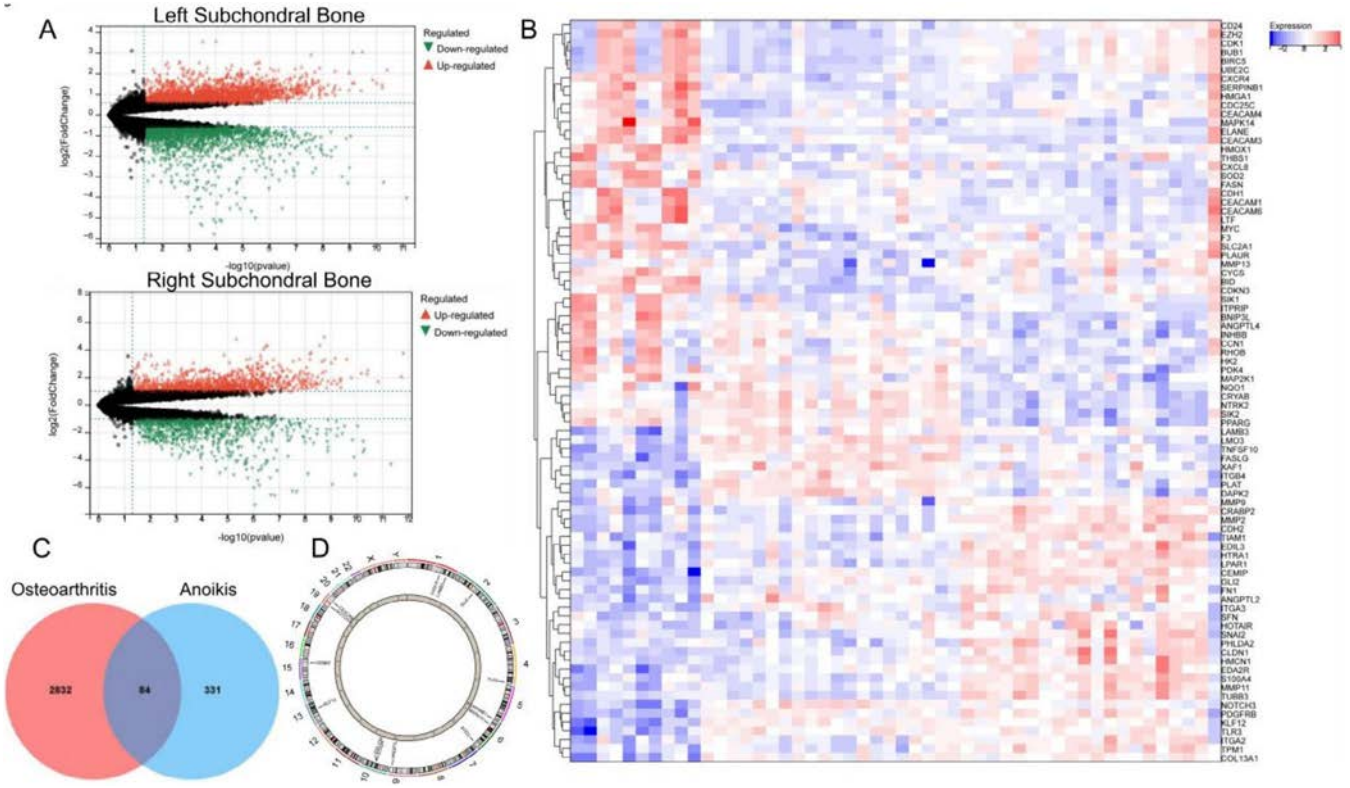

FIGURE 2 | Osteoosteoarthritis-related genes and differentially expressed Ano-DEGs. (A) OA-related DEGs volcano plot with log10FoldChange in the horizontal and vertical coordinate. Red nodes indicate upregulated DEGs, blue nodes indicate downregulated DEGs, and gray nodes indicate genes that are not significantly differentially expressed. TWO volcano plot charts were made from left and right subchondral bone gene signatures. (B) Heat map of overall expression of Ano-DEGs in OA patients: Blue for control samples, red for disease samples, red for high expression, blue for low expression. (C) Gene Venn diagram: The red represent Osteoosteoarthritis-related differentially expressed genes; the blue represent represent anoikis-related differentially expressed genes. (D) Overall expressionl histogram of immune-related genes in osteoarthritis patients: Blue for control samples, red for disease samples, horizontal axis indicates genes, vertical axis indicates gene expression levels.

genomic locations of these Ano-DEGs are annotated on human chromosomes, as depicted in Figure 2D.

3.2 | The Risk Model

The LASSO method identified 14 key genes from 28 Ano-DEGs that significantly influence OA, as shown in Figure S1A,B. Using their coefficients, an arthritogenic score was calculated (Figure S1C). We assessed the prognostic value of each gene through survival data, visualized in a forest plot (Figure S1D). A nomogram model, incorporating the 14 genes and risk scores, predicted arthritis prevalence (Figure 3A,B). Calibration curves confirmed the model's accuracy (Figure 3C), and decision curve analysis showed the model outperformed random predictions (Figure 3D). Functional associations among the 14 genes were explored (Figure S2A), with strong correlations observed, particularly between GLI2 and EDA2R (0.79) in OA samples, and SERPINE and MAPK14 (0.92), as well as CEMIP and SOD2 (−0.83) (Figure S2B,C). In healthy samples, the GLI2-EDA2R correlation remained high at 0.66 (Figure S2D).

3.3 | PPI Network of Anoikis Genes

To investigate the connections among differentially expressed anoikis genes, we constructed PPI networks for DEGs, Ano-DEGs, and gene signatures. Using Cytoscape, the network of DEGs comprised 40 genes, with CDK1 and BIRC5 showing strong correlations with 31 DEGs (Figure 4A). The network of Ano-DEGs included 30 genes, with PIK3CA closely linked to 24 differentially expressed anoikis genes (Figure 4C). The network of the gene signatures consisted of 18 interaction pairs and 10 genes, with MAPK14 closely connected to 10 Ano-DEGs (Figure 4E). To gain insights into the functions of genes within these PPI networks, we conducted functional enrichment analysis using ClueGO. The results revealed significant enrichment in various pathways. In the PPI network of DEGs, genes were enriched in pathways related to mitotic cytokinesis, mitotic spindle assembly checkpoint signaling, sister chromatid segregation, organelle fission, G2/M transition of mitotic cell cycle, and the regulation of mitotic nuclear division, among others (Figure 4B). Furthermore, gene enrichment for anoikis genes was observed in pathways involving the regulation of the actin cytoskeleton, thyroid hormone signaling, PI3K-Akt signaling, Human papillomavirus infection, and more (Figure 4D). The GSEA analysis revealed specific pathway activations in OA, such as the "Adipocytokine signaling pathway," "Response to oxygen levels," and others in Figure S4C,D.

3.4 | Differential Analysis of Two Different Anoikis Patterns

In our analysis of the differences between two distinct anoikis patterns, we identified 488 DEGs differentiating between clusters C1 and C2. This set included 169 upregulated DEGs and 319 downregulated DEGs in cluster A in Figure S3A. Heat maps provided visual representation of the capacity of these DEGs to accurately differentiate between the two anoikis patterns in Figure S3B. Subsequently, we delved into the biological relevance of these DEGs in patient outcomes. In the same way, we assessed the ROC curves for the 14 gene signatures independently for each category, and the results indicated that all 14 gene signatures demonstrated strong classification performance (as illustrated in Figure S3C).

First, the DEGs were subjected to functional annotation. Second, the functional analysis revealed that these DEGs were enriched in terms of extracellular region, leukocyte migration, extracellular matrix, collagen-containing extracellular matrix, and other functions in the GO database. Moreover, the DEGs exhibited enrichment in pathways related to adipocytokine signaling, cytokine–cytokine receptor interaction, ECM–receptor interaction, the PPAR signaling pathway, and other pathways in the KEGG database (Figure S4A,B). These findings underscore the importance of these DEGs in shaping the different anoikis patterns and their potential implications in various biological functions for patients.

3.5 | Discrepancies in Immune Attributes Between Two Models

The CIBERSORT method revealed immune cell infiltration differences between clusters C1 and C2. Cluster C2 had lower levels of B cells, plasma cells, monocytes, and activated mast cells, but higher levels of M2 macrophages, eosinophils, and CD4 memory resting T cells compared to cluster C1 (Figure 5A,B). In cluster C1, M2 macrophages were positively correlated with eosinophils and negatively with dendritic cells ($p < 0.05$, Figure S5A). In cluster C2, several immune cells, including activated mast cells and monocytes, showed negative correlations with CD8 T cells and positive correlations with eosinophils ($p < 0.05$, Figure S5B). We also explored the correlations between the 14 gene signatures and immune cells in all OA patients, cluster C1, and cluster C2 (Figure 5C, Figure S6A). Notably, LAMB3 showed no correlation with immune cells in cluster C1, whereas activated mast cells and resting memory CD4 T cells were correlated with gene signatures in cluster C2 (Figure S6B). These findings highlight the complex relationships between immune cell infiltration and gene signatures in OA.

3.6 | Single Cell Transcriptomic Analysis Showed the Heterogeneity of OA

Gene expression profiles from cells obtained from OA mice samples were extracted from the GSE200842 dataset. To identify genes of interest, we singled out highly variable genes for further investigation. Using the "RunPCA" function, we successfully reduced dimensionality, leading to the identification of 8 distinct clusters. Subsequent annotation and visualization, performed using the "SingleR" function, allowed us to uncover the presence of six cell types, including B cells, endothelial cells, erythrocytes, fibroblasts, granulocytes, macrophages, monocytes, NK cells, and T cells (Figure S7A). The relationships among these six immune cell types were depicted, highlighting a significant positive correlation among CD4 T cells, CD8 T cells, and T cells (Figure S7B). Furthermore, the application of cell phone, drawing on single-cell transcriptomic data, facilitated predictive inference regarding

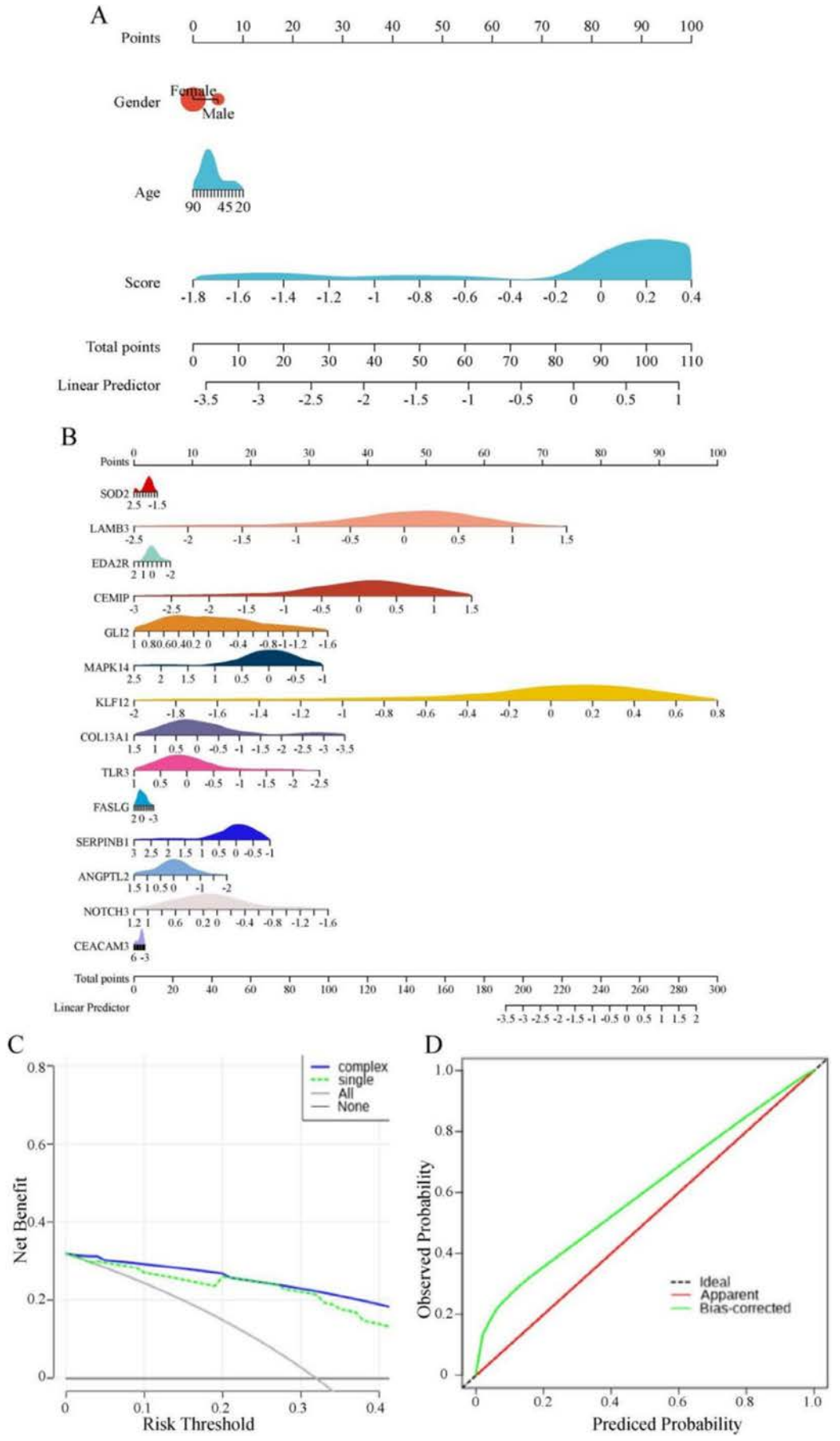

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FIGURE 3 | Line graphs (nomogram plots). (A) Nomogram of predicted risk scores in the diagnosis of osteoosteoarthritis patients. (B) Nomogram of 14 trait genes in the diagnosis of osteoarthritis patients. (C) Nomo model evaluation, where the diagnostic model is in better agreement with the ideal model. (D) Model evaluation curves: Gray indicates the follow-on diagnosis, blue indicates the complex diagnostic model with 14 trait genes, and blue indicates the simple diagnostic model with predicted risk score.

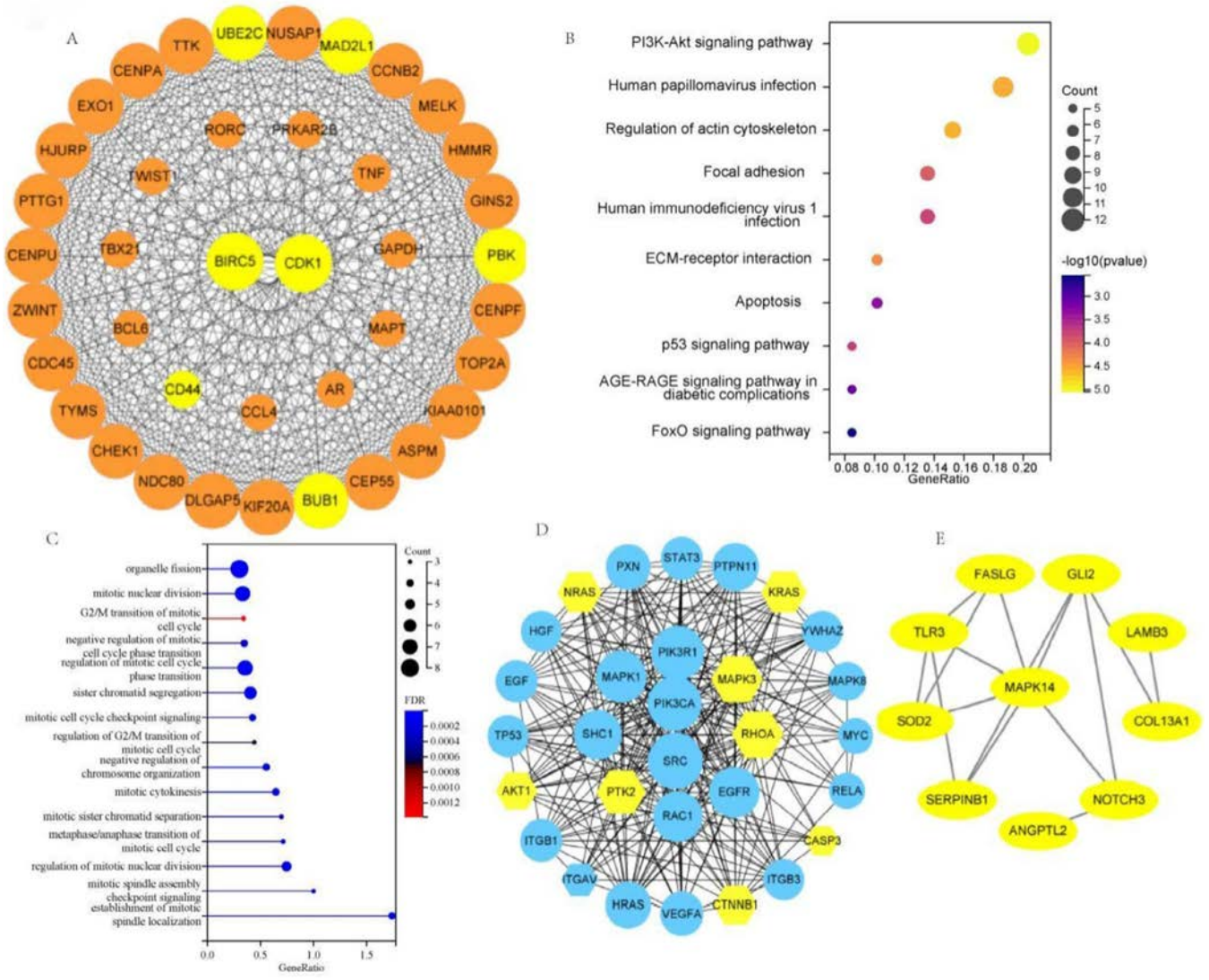

FIGURE 4 | Ano-related gene protein–protein interaction (PPI) network. (A) Differentially expressed gene PPI network: Yellow nodes indicate Ano-DEGs. (B) Results of gene enrichment analysis in DEG PPI network. (C) Differentially expressed anoikis-related genes PPI network: Yellow nodes indicate gene signatures. (D) Results of gene enrichment analysis in Ano-DEG PPI network. (E) Results of gene signatures.

potential cytokine receptor interactions. This comprehensive analysis offers valuable insights into the cellular composition and potential signaling interactions within OA mouse samples.

3.7 | Identification of Primary Cell From Mice

The flow cytometry results showed that the extracted primary chondrocytes from mice had a positivity rate greater than 95% (COL-2A-FITC positive cells) in Figure 6A,B.

3.8 | qPCR Validation of Data

To verify the bioinformatics findings, we conducted qPCR experiments. The outcomes of these experiments validated the credibility and potential research worth of the data mining results. Specifically, the mRNA expression levels of *LAMB3*, *TLR3*, and *KLF12* were notably elevated in the IL-1β-induced group, with *TLR3* demonstrating the most substantial difference in expression. However, the variance in *COL13A1* expression between the two groups did not achieve statistical significance. These

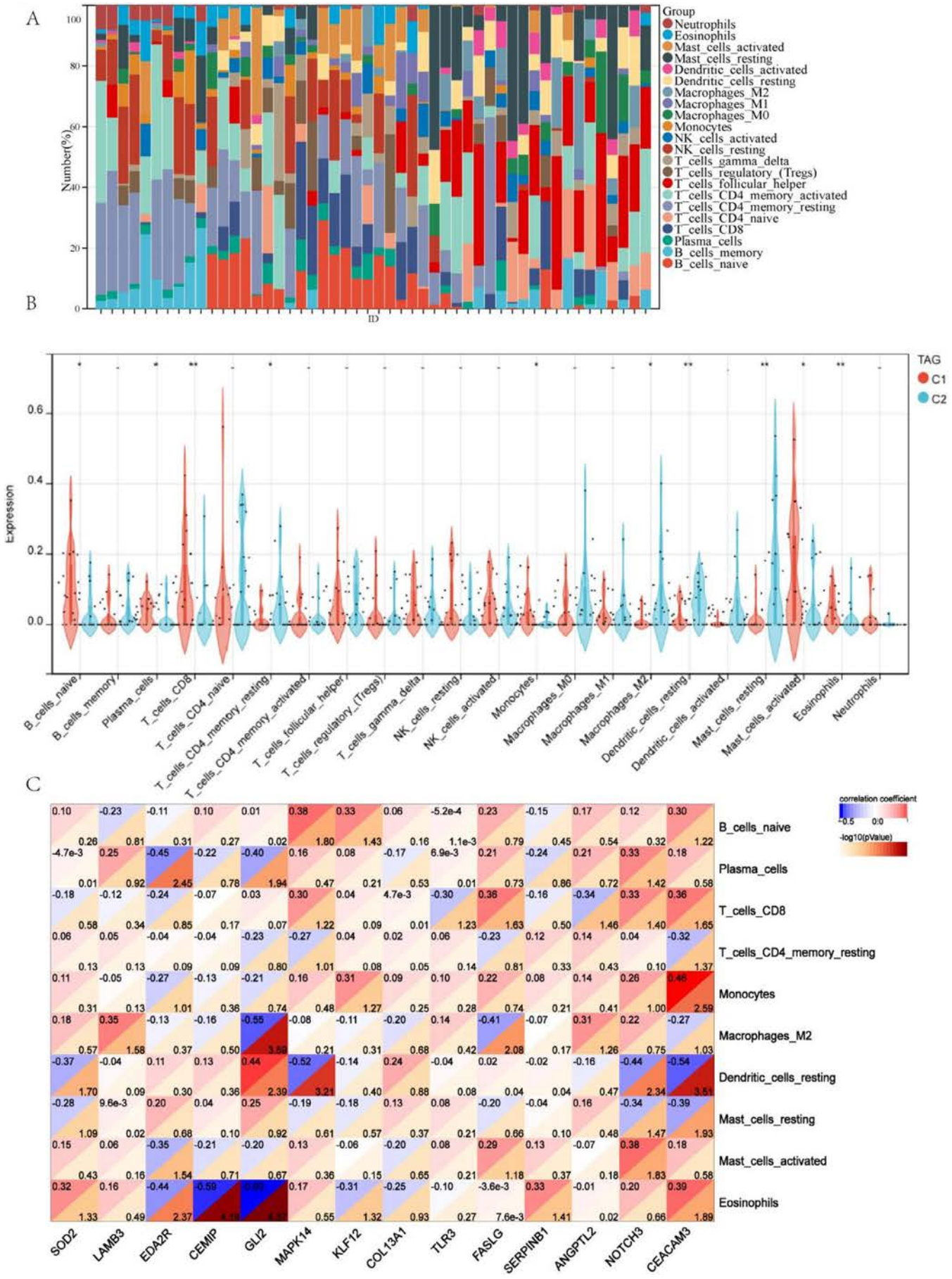

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FIGURE 5 | Immune characteristics between two different anoikis patterns. (A) Immune cell content stacking plot between cluster C1 and cluster C2: Different colors indicate different immune cells; the horizontal axis is the patient ID. (B) Immune cell content histogram: The horizontal axis indicates 22 immune cells; the vertical axis indicates cell content; pink indicates cluster C1 samples; blue indicates cluster C2 samples. (C) Correlations in OA patients. Correlation analysis of 14 gene signatures and immune cell content in all osteoosteoarthritis patients, horizontal axis indicates immune cells, vertical axis indicates 14 gene signatures, node color indicates the correlation size, and node size indicates the signifificance level. ($^{-}p > 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

observations are depicted in Figure 6C,D, further highlighting the coherence and significance of the bioinformatics findings.

4 | Discussion

OA affects 10%–15% of young individuals and up to 60% of the elderly, making it a significant global health issue [22]. Despite its prevalence, effective early detection and therapeutic options remain limited, necessitating the discovery of novel biomarkers and therapeutic targets. In our study, gene expression profiling of arthritis and control samples revealed 2916 DEGs, of which 84 were associated with various biological processes. GO analysis indicated enrichment in pathways related to mitotic cytokinesis, spindle assembly checkpoint signaling, sister chromatid segregation, and the G2/M transition of the cell cycle. KEGG pathway analysis further highlighted significant involvement of DEGs in pathways such as actin cytoskeleton regulation, thyroid hormone signaling, PI3K-Akt signaling, and human papillomavirus infection.

Our analysis identified two distinct clusters (C1 and C2) among OA patients. Cluster C2 showed lower levels of B cells, plasma cells, monocytes, and activated mast cells compared to cluster C1. Single-cell RNA sequencing revealed six cell types, including B cells, endothelial cells, fibroblasts, macrophages, monocytes, NK cells, and T cells, providing insights into their roles in OA progression. PPI network analysis highlighted key genes such as *KRAS, MAPK13*, *RHOA*, *PTK2, AKT1*, and *CTNNB*1, which were significantly linked to differentially expressed anoikis-related genes. Previous studies suggested XLGB capsules could inhibit the MAPK/AKT pathway to reverse OA. Disrupted cell traction forces in OA are linked to F-actin reorganization via the RhoA/ROCK pathway. Additionally, pathways like TNF signaling, KRAS, and IL-2/STAT5 were implicated in OA. Single-cell RNA sequencing under IL-1β-induced inflammation revealed apoptosis, reactive oxygen species, and WNT/TGF-beta/BMP signaling, suggesting alterations in bone remodeling processes, potentially explaining sex differences in OA incidence.

GO and KEGG analyses showed enrichment of DEGs in several key pathways, including adipocytokine signaling, cytokine–cytokine receptor interaction, ECM–receptor interaction, PPAR signaling, and regulation of lipolysis in adipocytes. Notably, the PPAR signaling pathway, which involves the PPARα, PPARγ, and PPARβ/δ isoforms, plays a crucial role in the progression of OA [23,24]. These ligand-dependent transcription factors regulate various cellular processes, including stem cell and chondrocyte differentiation, metabolism, and inflammation. Moreover, the identified cytokine receptor interactions were also relevant to rheumatoid arthritis, emphasizing the role of inflammatory cytokines like TNF and IL-1 in both diseases [25,26]. These findings underscore the importance of immune system regulation in OA and its potential as a therapeutic target.

In our study, consensus clustering was employed to analyze transcriptomics, proteomics, and molecular data, effectively categorizing samples into distinct clusters. This method highlighted transcriptomic and proteomic patterns across these clusters, enabling a deeper understanding of the molecular mechanisms underlying OA. For instance, previous research on squamous cell lung cancer classified tumors into molecular subtypes using proteomic data, leading to valuable insights into the disease. Similarly, our analysis revealed two immune patterns in OA, further confirming the heterogeneity among patient subgroups [27,28].

In recent years, innate immunity has been recognized as a key factor in the chronic inflammatory response associated with OA. For example, in a mouse model, IL-13, produced by synovial macrophages, has been shown to upregulate calcitonin receptors, with calcitonin gene-related peptide implicated in arthritis-related pain. Other studies have demonstrated that macrophage biomarkers in synovial fluid and blood can predict inflammatory phenotypes in knee OA patients. These studies revealed correlations between CD14 and CD163 in synovial fluid, as well as elevated macrophage activity in OA [29]. Additionally, natural killer (NK) cells have been detected in the synovial tissue of patients undergoing joint replacement, comprising approximately 30% of CD45+ cells. Monocyte infiltration, particularly CD14+ macrophages, was also noted in the synovial tissue of knee OA patients [30]. Although the precise role of NK cells in OA remains unclear, these findings highlight their potential involvement in disease pathogenesis.

Adaptive immunity also plays a role in OA, with T cells isolated from OA patients' peripheral blood and synovial fluid showing immune responses to autologous cartilage components. T-cell factor 4 (TCF4), for example, promotes chondrocyte apoptosis by enhancing apoptotic protease activity. In OA cartilage, TCF4 mRNA is significantly upregulated, driving cartilage degradation [31]. Additionally, in a mouse model, CD8+ T cells in the synovium were found to express tissue inhibitor of metalloproteinase 1 (TIMP-1), which correlates with the severity of OA, further underscoring the involvement of adaptive immunity in disease progression [32].

This study has some limitations. Firstly, the biological functions of OA were examined in vitro, and extending these findings to in vivo systems is necessary to gain a more comprehensive understanding of OA processes. The sample size was also limited, and the study did not include other rheumatic conditions. Future studies should include a broader range of samples and employ single-cell analysis to deepen

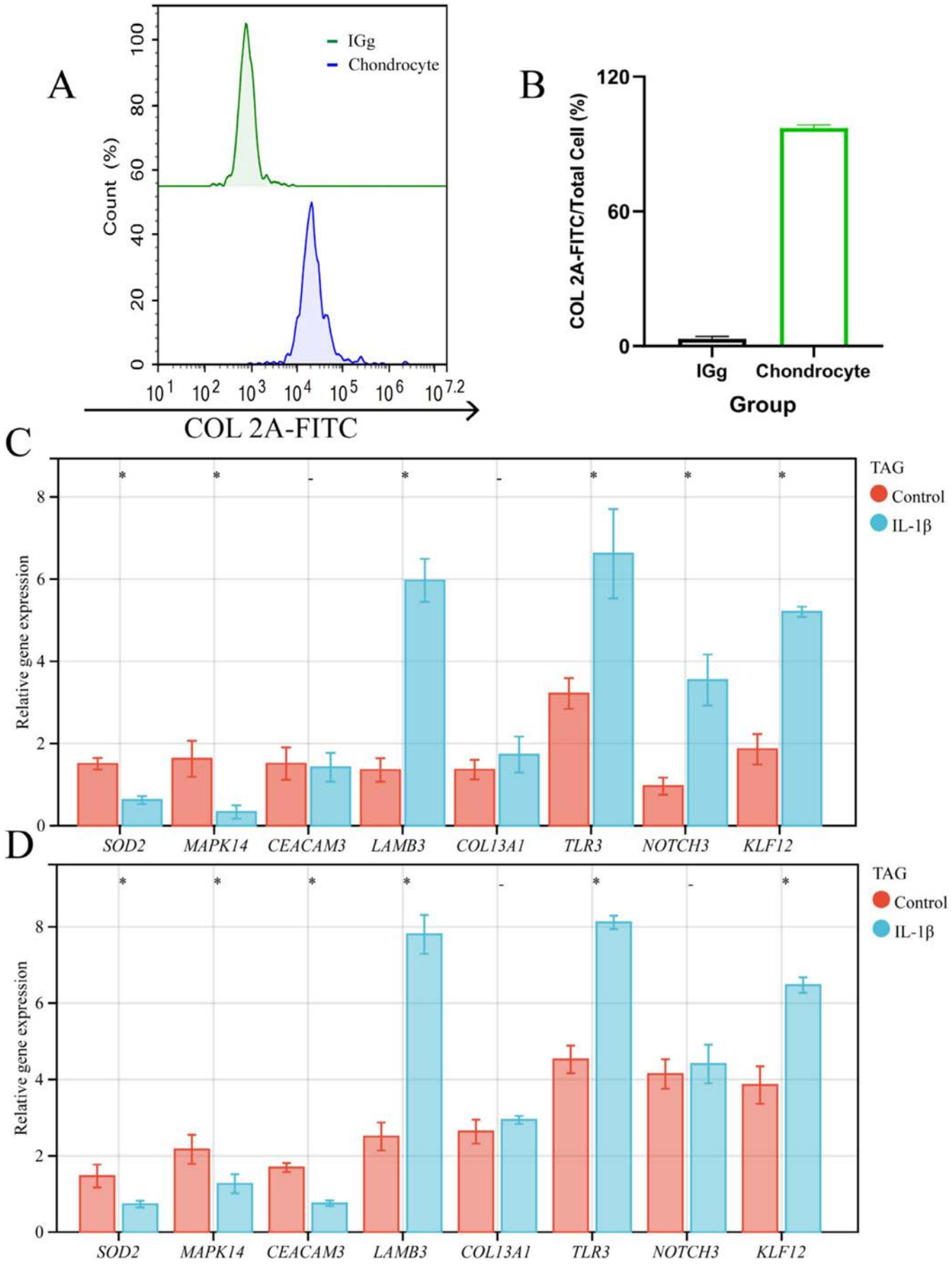

FIGURE 6 | Legend on next page.

FIGURE 6 | (A) Primary mouse chondrocytes were identified by flow cytometry. (B)The ratio of COL 2A-FITC(+) to total cells. qPCR validation. After IL-1β-induced, the mRNA expression levels of *SOD2*, *MAPK14*, *CEACAM3*, *LAMB3*, *COL13A1*, *TLR3*, *NOTCH3*, and *KLF12* were significantly higher both in C28/I2 cell (C) and primary mouse chondrocytes (D). ($^{ns}p \geq 0.05$, $^{*}p < 0.05$).

our understanding. Additionally, integrating other omics approaches such as lipidomics and metabolomics with experimental studies may provide a more thorough understanding of OA's underlying mechanisms.

In conclusion, our bioinformatics analysis revealed differences in immune infiltration between OA and control groups. Notably, higher expression levels of *SOD2*, *MAPK14*, *CEACM3*, *LAMB3*, *COL13A1*, *TLR3*, *NOTCH3*, and *KLF12* were observed in the IL-1β-induced group. Pathways like PI3K-Akt, PPAR, and inflammatory responses were implicated in OA progression. This study offers new insights into the role of anoikis in arthritis and identifies potential therapeutic targets for future interventions. Further research is needed to clarify the roles of key genes and immune infiltration patterns in OA.

5 | Conclusion

This study investigates the differences in anoikis-related genes and immune infiltration between OA and normal tissues, using microarray analysis and risk models, offering new insights into OA etiology and progression.

Author Contributions

Among the authors in the list, D.-C.Z., Z.-H.S., and X.-Y.G. conceived of the study, and participated in its design and coordination and drafted the manuscript. P.-P.H. carried out the cell experiments and the molecular studies. Z.-H.S. and K.-Y.S. performed the statistical analysis. W.-J.Z., F.-B.S., and Q.-Y.X. were responsible for the operation and verification of the algorithm.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data sets used and/or analyzed in the present study are available from the corresponding author upon request.

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Supporting Information

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EDITORIAL

Dyslipidemia and Cardiovascular Risk in Psoriatic Arthritis: The Role of JAK Inhibitors and the Need for Lipid Monitoring

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Janus kinase (JAK) inhibitors have demonstrated significant efficacy, particularly in patients with psoriatic arthritis (PsA) who have not responded to conventional biologic agents [1]. Despite their therapeutic benefits, the use of JAK inhibitors, especially in older patients, requires caution due to potential risks of immunocompromised infection, malignancy, and cardiovascular disease (CVD) [2, 3]. Most studies conducted in patients with rheumatoid arthritis (RA) have reported a slightly higher incidence of herpes zoster infection associated with the use of JAK inhibitors. This risk appears to be dose-dependent and extends to other adverse events, including an increased risk of infection, malignancy (excluding non-melanoma skin cancer), major adverse cardiovascular events (MACE), and venous thromboembolism (VTE) [2, 3]. However, whether the use of JAK inhibitors in patients with PsA carries a similar CVD risk remains unclear and needs further clarification from long-term studies.

The prevalence of CVD and metabolic disorders is higher in patients with PsA than in the general population [4–6]. A key contributing factor is dyslipidemia, a metabolic derangement commonly observed in patients with PsA, as chronic inflammation mediated by T cells contributes to both psoriasis and metabolic syndrome [7]. Dyslipidemia exacerbates systemic inflammation and accelerates atherosclerosis, increasing the likelihood of cardiovascular events. Despite the risk, the Opal Balance study showed no significant increase in CVD risk among PsA patients [5, 6]. Most studies conducted in RA patients, along with the Oral Surveillance trial, have shown an elevated risk of MACE and blood clot with tofacitinib compared to tumor necrosis factor (TNF) inhibitors, particularly in adults aged 65 or older, as well as those with a long history of smoking or preexisting heart disease [2, 3]. In PsA, no study has directly compared tofacitinib with TNF inhibitors. However, data from clinical trials indicate that younger patients without CVD risk factors have a lower risk of these complications when using tofacitinib [8]. Based on the available data, inference could be drawn that effective control of inflammation and addressing CVD risk factors are crucial for managing the risk of MACE and VTE [9].

Janus kinase inhibitors are effective in PsA treatment because of their anti-inflammatory properties. However, these agents can exacerbate dyslipidemia, as clinical studies have shown significant increases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides following JAK inhibitor therapy [4, 5]. The underlying mechanism may involve altered lipid metabolism because of the inhibition of cytokines such as interleukin-6 (IL-6) and interferons. JAK inhibitors may inadvertently affect hepatic lipid synthesis and clearance, leading to elevated levels of total cholesterol, LDL cholesterol, and triglycerides [10]. This dual action accentuates the complexity of JAK inhibitors; while they alleviate joint inflammation, they simultaneously increase CVD risk. As the maximum increase in lipid parameters is generally observed within 6 weeks of treatment initiation, lipid parameters should be monitored after 8 weeks of treatment initiation [4, 5].

The potential of JAK inhibitors to worsen dyslipidemia highlights the importance of CVD risk management in patients with PsA. Elevated lipid levels promote oxidative stress and inflammatory mediators, leading to endothelial dysfunction and an increased risk of myocardial infarction and stroke. To mitigate these risks, it is crucial to conduct pretreatment CVD risk assessments and implement regular lipid monitoring throughout therapy. Preventive strategies, such as lifestyle modifications and lipid-lowering therapies, should be employed as needed.

While JAK inhibitors provide substantial benefits for PsA management, their impact on lipid metabolism necessitates careful monitoring. A proactive approach, including comprehensive cardiovascular risk assessment and regular lipid profile monitoring, is essential to minimize the potential cardiovascular complications associated with JAK inhibitor therapy in patients with PsA.

Author Contributions

All authors critically revised the manuscript for important intellectual content.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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EDITORIAL

Glycemic Control and Fracture Risk in Patients With Type 2 Diabetes Mellitus

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1 | Introduction

Type 2 diabetes mellitus (T2DM) is a long-term metabolic disorder marked by persistent hyperglycemia, mainly due to insulin resistance and impaired insulin production. Rising rates of obesity and sedentary behavior have fueled a global increase in T2DM. While complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy are well known, recent research highlights a notable link between T2DM and bone health. Patients with T2DM face a higher risk of fractures, even with normal or increased bone mineral density (BMD), primarily due to compromised bone quality and a greater likelihood of falls.

2 | The Association Between T2DM and Bone Fragility

In a study conducted in Finland using rat bone marrow, short-term hyperglycemia (lasting 1 or 3 days) was found to stimulate osteoblast activity. However, when hyperglycemia persisted for a longer duration (10 days), it led to increased production of reactive oxygen species (ROS), which ultimately impaired osteoblast function [1], highlights the dual effects of hyperglycemia on bone health, with transient elevations possibly supporting bone formation, while prolonged exposure contributes to oxidative stress and compromised osteoblast performance.

In a longitudinal study conducted in the United States, Ballato et al. examined 169 T2DM male patients and found that poor glycemic control over 1 year was linked to reduced bone turnover and impaired bone microarchitecture [2]. Further analysis of 51 male T2DM patients indicated that poorly managed long-term blood sugar levels were associated with an increase in circulating osteogenic progenitor (COP) cells, potentially hindering the maturation of these cells into osteoblasts [3]. This disruption in cellular development may contribute to weakened bone formation and structure, underscoring the impact of glycemic control on bone health in T2DM patients.

Chronic hyperglycemia leads to the accumulation of advanced glycation end products (AGEs), which impair bone formation by promoting osteoblast apoptosis [4]. A systematic review of 66 studies found that hyperglycemia decreases osteoblast and osteoclast activity, also resulting in reduced bone turnover and increased fracture risk in T2DM [5]. However, the BMD of patients with T2DM is generally normal to higher compared to non-diabetics [4]. The elevated risk of fractures may not directly correlate with BMD in T2DM.

3 | Factors Influencing Fracture Risk in Diabetic Patients

Older patients had a higher osteoporosis fracture risk. This finding suggests that factors beyond BMD may contribute to the

heightened fracture risk in patients with T2DM. Here, we explore some of these potential reasons.

Reduced physical activity causes sarcopenia through loss of type II fast-twitch muscle, which impairs glucose uptake by skeletal muscle, and T2DM is associated with sarcopenia [6]. A UK study found reduced proximal leg muscle strength in 20 T2DM patients with diabetic polyneuropathy compared to 20 healthy individuals, creating a vicious cycle [7]. With aging, sarcopenia leads to functional impairment and disability, increasing the risk of falls in elderly individuals with diabetes. This elevated fall risk raises the likelihood of fractures, including major osteoporotic fractures [6, 7].

A Canadian retrospective population-based cohort study involving 82,094 individuals (both type 1 and type 2 DM) demonstrated that those with a long disease duration had a higher risk of osteoporotic fractures [8]. Insulin therapy is associated with an increased risk of hypoglycemic episodes, which can manifest with neurological symptoms such as dizziness, confusion, or altered consciousness. A population-based study conducted in Sweden, involving 79 159 patients with T2DM with a mean age of 80.8 years, compared to 343 603 non-diabetic individuals, demonstrated that insulin use was significantly associated with an elevated risk of hip fractures [9]. Following a fracture, higher serum glucose levels, increased AGEs, and the generation of reactive oxygen species can hinder fracture healing. This often results in patients being unable to engage in weight-bearing physical activity, leading to prolonged bed rest and perpetuating a vicious cycle.

About the novel glucose-lowering agent including dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium glucose cotransporter 2 (SGLT2) inhibitors, a meta-analysis combining 177 randomized controlled trials (RCTs) suggested that the use of DPP-4i, GLP-1 RAs, or SGLT2 inhibitors is unlikely to increase the risk of fractures in T2DM patients compared to treatments such as insulin, metformin, or sulfonylureas [10, 11].

4 | The Impact of Blood Sugar Control on Fracture Risk in Patients With T2DM

Studies of T2DM patients have shown that hyperglycemia (HbA1c > 9) is associated with peripheral neuropathy [12, 13]. For instance, research involving 20 025 T2DM patients aged 65 and older in Taiwan and another study of 10 572 diabetic patients in Tennessee, USA, using ICD-9 electronic medical records, revealed this connection. Similarly, a patient-based cohort study in Sweden involving 429 313 individuals, including 79 159 with T2DM [8], reported comparable findings. T2DM patients often experienced sensory impairment, motor function deficits, reduced muscle mass, loss of pressure sensitivity, and poor balance [9, 13], all of which increase the risk of falls [13].

5 | The Potential Impact of Osteoporosis Medications on Fracture Reduction and Blood Sugar Control

Managing bone health in diabetes requires a multifactorial approach; older patients also had higher osteoporosis fracture rates. Currently, osteoporosis medications fall into three categories: antiresorptive, anabolic, and drugs with a mixed mechanism of action. Research has shown that these medications either improve blood glucose control or have no change in glucose metabolism [14–19]. Table 1 highlights the effects of various osteoporosis medications on blood glucose levels from multiple studies. Bisphosphonates are the recommended first-line treatment for osteoporosis in patients with T2DM, despite the characteristic low bone turnover often observed in this population. This reduced bone turnover may be further suppressed by antiresorptive therapies, potentially impacting bone health. In elderly patients or those with renal impairment, denosumab is favored due to its safety profile and efficacy. For severe osteoporosis, anabolic agents are considered appropriate to address significant bone loss [14–19].

6 | The Impact of Daily Physical Activity

A population-based study in Canada from 1995 to 2005 indicated that successful treatment of diabetes reduces mortality rates. However, inadequate lifestyle-changing programs have contributed to rising obesity and a higher incidence of diabetes. A US study that recruited 77 206 postmenopausal women found that increased sedentary behavior was associated with a higher risk of total fractures and mortality [20]. Prolonged sedentary behavior diminishes physical function, reduces leg blood flow, and, with age, leads to a reduction in type II fast fibers [6], contributing to sarcopenia and an elevated risk of falls and fractures.

7 | Other Medication in Elderly Patients

Elderly individuals often have multiple comorbidities and are frequently prescribed medications such as antihypertensives, statins, anticoagulants, and sedatives. As we move towards an aging society, future research should include RCTs to better understand the risk of fractures associated with polypharmacy.

8 | Conclusions

The risk of fractures in patients with T2DM arises from a complex interplay of factors. To reduce this risk, it is essential to promote regular physical activity, optimize antidiabetic treatments, and consider early intervention with osteoporosis therapies. In elderly patients, the risk is heightened by the potential for drug interactions, especially in those managing multiple chronic conditions. Careful monitoring and adjustments to medication regimens can help minimize adverse effects. A coordinated approach to care, involving specialists in rheumatology, endocrinology, orthopedics, and nutrition, is necessary. This multidisciplinary strategy ensures comprehensive management, addressing both diabetes and fracture risk to improve patient outcomes.

Author Contibutions

S.-T.S.: wrote and revised manuscript. Y.-H.L.: assist with revising the manuscript. Y.-C.T and P.-C.S.: supervise and revised the manuscript. All the authors are responsible for the manuscript.

TABLE 1 | Effects of osteoporosis medications on blood glucose levels.

Author	Drug	Times	Population	Study	Effects	Level of evidence
Toulis et al. [14]	Bisphosphonates	42 months		UK	50% reduction incident T2DM	Level II
Karimi Fard et al. [15]	Oral alendronate 70 mg/week	12 weeks	Postmenopausal women	Iran	Improve fasting glucose, HbA1c	Level I
Maugeri D et al. [16]	Alendronate 10 mg/day	12 months, 24 months	Elderly women	Italy	Reduction the daily insulin requirement, improvement of glucose metabolism	Level I
Napoli et al. [17]	Denosumab 60 mg/6 months	36 months	Osteoporotic postmenopausal women with prediabetes or T2DM	FREEDOM	No changes in fasting plasma glucose	Level I
Passeri et al. [18]	Denosumab single dose of 60 mg	4 week, 12 week	Postmenopausal severe osteoporotic nondiabetic women	Italy	No variation in fasting glucose and insulin, reduction hepatic insulin resistance at 4 weeks, decrease in HbA1c levels at 12 weeks	Level II
Atteritano et al. [19]	Oral strontium ranelate 2 g/day	12 months	Postmenopausal osteoporosis women	Italy	No changes in fasting glucose concentrations	Level II

Abbreviations: FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months was an international randomized, placebo-controlled trial; HbA1C, glycated hemoglobin; T2DM, Type 2 diabetes mellitus.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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LETTER TO THE EDITOR

Case Report: Multiple Autoimmune Syndrome—A Multidisciplinary Clinical Approach to a Spectrum of Organ Involvement

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Dear Editor,

Autoimmune polyglandular syndrome (APS), also called polyglandular autoimmune disease, was proposed in 1980 to describe the concurrence of at least two autoimmune endocrinopathies [1]. In 2008, Betterle et al. extended the conception to multiple autoimmune syndrome (MAS), in order to include other non-endocrine and nonglandular autoimmune diseases in it [2]. Based on varying classification methods, APS/MAS could be divided into different types [1, 3, 4]. The concept of APS/MAS provides a framework for defining and categorizing a spectrum of relevant autoimmune diseases. This facilitates clinicians in more accurately identifying and differentiating these conditions, and aids in devising comprehensive clinical management strategies based on multidisciplinary collaboration. Furthermore, the introduction of APS/MAS has spurred relevant epidemiological researches as well as investigations into the genetic underpinnings of such autoimmune diseases. Herein, we report a rare case of a patient who was diagnosed with autoimmune pancreatitis (AIP), Guillain-Barre syndrome (GBS), immune thrombocytopenia (ITP), primary biliary cholangitis (PBC), type 1 diabetes mellitus (T1DM), and autoimmune thyroid disease (AITD), and therefore, APS/MAS was finally ascertained. This case report fully demonstrates the importance of multidisciplinary collaboration in managing these complex situations.

A 53-year-old male Chinese patient visited the gastroenterology outpatient clinic with the chief complaint of diarrhea for 4 months and epigastric pain for 2 months along with vomiting, anorexia, and zonesthesia. The complete blood count (CBC) result was normal. The abdominal enhanced computed tomography (CT) showed diffuse enlargement of the whole pancreas with multiple nodular convex margin and delayed enhancement, indicating inflammatory lesions (Figure 1A). The endoscopic ultrasonography showed that the pancreatic parenchyma was diffusely hypoechoic with patchy echo enhancement ("honeycomb" appearance, Figure 1B). The serum amylase (7 U/L, reference: 25–115 U/L) and lipase (31 U/L, reference: 73–393 U/L) were below normal. The serum immunoglobulin G4 (IgG4) was 1690 mg/L (reference: 80–1400 mg/L). According to the international consensus diagnostic criteria for autoimmune pancreatitis [5], AIP was suspected and Creon 300 mg three time daily was prescribed.

Two days later, the patient was referred to the emergency room for acute palpitation. Blood test showed hyperpotassemia (potassium: 7.0 mmol/L), hyponatremia (sodium: 117 mmol/L), and severely hyperglycemia (glucose: 71.0 mmol/L). Abnormal creatinine (196 μmol/L, reference: 59–104 μmol/L) and elevated high-sensitivity C-reactive protein (83.39 mg/L, reference:

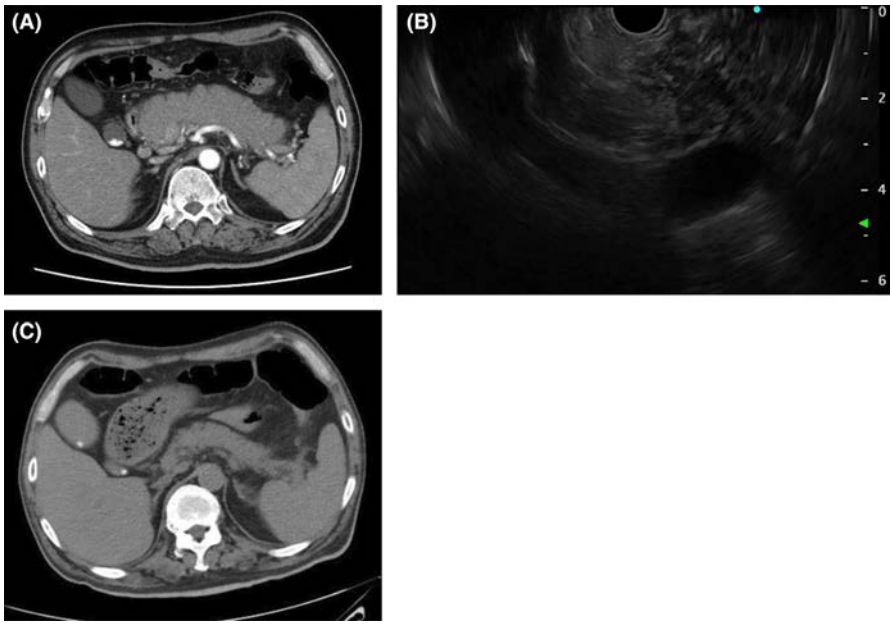

FIGURE 1 | Pancreatic imaging results of the patient. (A) Abdominal enhanced CT performed at the patient's first visit shows diffuse enlargement of the whole pancreas with multiple nodular convex margin and delayed enhancement. (B) Endoscopic ultrasonography shows that the pancreatic parenchyma was diffusely hypoechoic with patchy echo enhancement ("honeycomb" appearance). (C) Abdominal CT performed after the treatment of IVIG and prednisone shows that the diffuse enlarged pancreas was partially mitigated.

< 8 mg/L) were also noticed. The arterial blood gas analysis indicated metabolic acidosis with a pH level of 7.12. Intravenous insulin was pumped immediately along with calcium gluconate injection. The acid–base imbalance and electrolyte disturbance of the patient were improved soon after. The patient denied previous history of diabetes. However, positive serum insulin autoantibody, islet cell antibody, and glutamic acid decarboxylase antibody were detected meanwhile, leading to the diagnosis of T1DM. Glycated hemoglobin level and glycated albumin level were 6.0% and 23.7% (reference: 10.8%–17.1%), respectively.

One week later, new symptoms of extremities numbness, bilateral lower limbs weakness, dysarthria, and dysgeusia were developed. Electromyography showed peripheral nerve injuries in both upper and lower limbs with unelicited sympathetic skin response. The past history of the patient was remarkable that the patient had suffered from recurrent GBS in last 2 years, with two episodes of numbness and weakness of extremities, which were relieved after glucocorticoid and intravenous immunoglobulin (IVIG) treatment. The most recent episode took place 20 months prior to the current presentation. The patient had no history of smoking, only moderate social alcohol consumption, and denies any antecedent history of infection or other medication use.

Subsequently, the patient was admitted to hospital for further evaluation and treatment. After admission, the CBC showed mild anemia (hemoglobin level: 97 g/L) and thrombocytopenia (platelet count: 68×10^9/L). On the 3rd day after admission, the patient experienced a transient syncope while sitting up. A drop of systolic blood pressure from 110 mmHg to 80 mmHg and a reduced heart rate of 40–50 beats per minute were detected with raising the head of his bed at 60° angle. Meanwhile, the platelet count of the patient dropped to 9×10^9/L. Platelet transfusion was inefficacious and the platelet count fluctuated around $5–15 \times 10^9$/L with occurrence of persistent epistaxis and transient gastrointestinal bleeding. Bone marrow smear showed no sign of leukemia and was consistent with ITP. Therefore, autonomic nerve involvement of GBS and autoimmune thrombocytopenia were suspected. Infusion of IVIG 30 g once-daily (qd) for 5 days with oral prednisone 75 mg qd were prescribed. The platelet count recovered to normal level gradually.

Notable results of other examinations conducted immediately after admission are listed below. The serum alkaline phosphatase (436 U/L, reference: 45–125 U/L) and gamma-glutamyl transpeptidase (158 U/L, reference: 10–60 U/L) were abnormal with reduced serum complement 3 level (0.502 g/L, reference: 0.730–1.460 g/L). Both antinuclear antibody and anti-extractable nuclear antigen were negative, but anti-mitochondrial antibody-M2 was positive (28.51 RU/mL, reference: < 20 RU/mL). According to the American Association for the Study of Liver Diseases (AASLD) diagnostic criteria for PBC [6], the diagnosis of PBC was established. Positive Coomb's test and a weak positivity of anti-Ro-52 antibody, and a low titer of perinuclear antineutrophil cytoplasmic antibody (1:10) were noticed. A positivity of antibodies against thyroperoxidase (39 IU/mL, reference: < 34 IU/mL) and thyroglobulin (220 IU/mL, reference: < 115 IU/mL) were displayed with hypothyroidism (Triiodothyronine: 0.50 ng/mL, reference: 0.66–1.92 ng/mL; thyroid stimulating hormone: 4.412 μIU/mL, reference: 0.380–4.340 μIU/mL). Serum adrenocorticotrophic hormone and cortisol levels were both in normal range. Immunoglobulin levels were all within the normal range: IgG 7.85 g/L (reference: 7.00–17.00 g/L), IgA 3.58 g/L (reference: 0.70–4.00 g/L), and IgM 1.05 g/L (reference: 0.40–2.30 g/L). Peripheral blood immunophenotyping results: B lymphocyte 266/μL (reference: 180–324/μL), natural kill cell 166/μL (reference: 175–567/μL), CD4+ T lymphocyte 1108/μL (reference: 561–1137/μL), CD8+ T lymphocyte 530/μL (reference: 404–754/μL), naïve CD4+ T lymphocyte 26.9% (reference: 31.6%–54.4%). Cerebrospinal fluid (CSF) examination showed

TABLE 1 | A few representative case reports describing combinations of several autoimmune diseases.

Year	Authors	Patient characteristics	Autoimmune diseases	Treatment
2007	Kohli et al. [11]	21 yo female	ITP, GBS, and HT	Glucocorticoid, IVIG, WinRho (Anti-D), rituximab, and laparoscopic splenectomy
2010	Dogan et al. [12]	2 yo female	Celiac disease, ITP, and AITD	IVIG and gluten-free diet
2014	Li et al. [13]	65 yo male	AIP and PBC	Glucocorticoid and ursodeoxycholic acid
2015	von Laer Tschudin et al. [14]	13 yo male; 4 yo male	T1DM and ITP	Anti-CD20 therapy
2017	Lee et al. [15]	17 yo female	Psoriasis, vitiligo and Crohn's disease	Infliximab and excimer laser therapy
2018	Niknezhad et al. [16]	41 yo male	Mucous membrane pemphigoid, vitiligo, and AITD	Glucocorticoid and mycophenolate mofetil
2021	Cifuentes-González et al. [17]	43 yo female	Ocular cicatricial pemphigoid, Sjögren's Syndrome, and HT	Glucocorticoid, azathioprine, cyclophosphamide, methotrexate, and hydroxychloroquine
2022	Poli et al. [18]	65 yo male	ADEM, myasthenia gravis, and AITD	Glucocorticoid, IVIG, and plasma exchange
2022	Nori et al. [19]	7 yo female	SLE, APS, and AITD	Glucocorticoid, hydroxychloroquine, aspirin, and azathioprine

Abbreviations: ADEM, acute disseminated encephalomyelitis; AIP, autoimmune pancreatitis; AITD, autoimmune thyroid disease; APS, antiphospholipid syndrome; GBS, Guillain-Barre syndrome; HT, Hashimoto's thyroiditis; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; PBC, primary biliary cholangitis; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; Yo, years old.

higher CSF protein (0.86 g/L, reference: 0.15–0.45 g/L), elevated intrathecal IgG synthesis rate of 24 h (18.2 mg/day, reference: −9.9 to 3.3 mg/day) and a positivity of CSF anti-GM1 ganglioside antibody. Whole exome sequencing (WES) did not reveal any pathogenic/likely pathogenic variants which could potentially explain the patient's clinical features.

According to the above manifestations and laboratory findings, the patient was diagnosed with AIP, GBS with secondary orthostatic hypotension, ITP, PBC, T1DM, and AITD. A comprehensive final diagnosis of APS/MAS was made. After the usage of IVIG and adequate glucocorticoid, tapered glucocorticoid and supplement of tacrolimus 2 mg twice daily along with Creon 600 mg three times daily, ursodeoxycholic acid 500 mg twice daily, and midodrine hydrochloride 5 mg three times daily were provided. Insulin glargine and insulin lispro were carefully tuned to control blood glucose. The clinical symptoms of the patient gradually improved and midodrine hydrochloride was successfully tapered to stop. The CT showed that the diffuse enlarged pancreas was partially mitigated (Figure 1C). And the patient demonstrated no recurrence and exhibited favorable functional ability during the 1-year follow-up period.

It is generally known that several autoimmune diseases could coexist in a same patient, such as AITD which can appear with many other autoimmune diseases. For example, it was reported that the prevalence of AITD in T1DM patients was 3.9%–24% [7]. And T1DM was found in 3%–8% of chronic autoimmune thyroiditis patients and 1%–5% of Graves' disease patients [7]. A recent study evaluated the prevalence of extrahepatic autoimmune diseases in 1554 patients with PBC. AITD was diagnosed in 165 (10.6%) patients and ITP was diagnosed in 4 (0.3%) patients [8]. In a study including 248 ITP patients, 36 patients were diagnosed with AITD (13 for Graves' disease and 23 for chronic lymphocytic thyroiditis) [9]. However, it is relatively rare for the same patient to have more than two autoimmune diseases or a combination of several autoimmune diseases during the same period. In a multicenter study encompassing 1463 childhood-onset systemic lupus erythematosus (SLE) patients, 144 patients (9.8%) were found to have concurrent autoimmune diseases at diagnosis, with the most prevalent being Hashimoto thyroiditis and antiphospholipid syndrome, each constituting 29% [10]. And only 10 patients (0.7%) presented with more than two concurrent autoimmune diseases, with the most common combination being T1DM and autoimmune hepatitis diseases (6/10) [10]. Table 1 presents some case reports exhibiting the coexistence of several autoimmune diseases. The patient presented in this case report is notable for the rare involvement of a spectrum of organs, which may contribute to the advancement of future research and clinical practice in the field of autoimmune diseases.

The mechanism by which the patient developed these autoimmune diseases is not known. Genetic factors may play a significant role in the etiology of APS/MAS. APS/MAS-1, a specific subtype of APS/MAS, has been validated as a result of *AIRE* gene mutations [2]. Utilizing WES, multiple genome-wide loci were identified to be associated with one or more autoimmune diseases [20]. Genes such as *IL2RA*, *IL12B*, and *TENM3* are found to be related to various autoimmune diseases, including AITD and SLE [20]. However, WES of the patient didn't show results of suggestive significance. Further researches are

needed to clarify the pathogenesis of the concurrence of these autoimmune diseases. Fortunately, the patient responded well to the treatment of IVIG + glucocorticoid + immunosuppressant. The patient had a past history of recurrent GBS and was treated with glucocorticoid and IVIG 20 months prior to the current presentation. Because the elimination half-life of IVIG is 24–28 days [21], we believe that the previous usage of IVIG would not affect the results of the laboratory tests of autoantibodies in the current presentation. Similarly, we conducted autoantibodies testing immediately after admission, and prior to the initiation of IVIG therapy, ensuring that the autoantibodies results remain unaffected by the IVIG intervention. After reviewing the case, we think that, for these patients, plasma exchange might be beneficial in the acute phase to remove pathogenic autoantibodies from the circulation so as to gain time for glucocorticoid and immunosuppressant to take effect. And rituximab can be considered for treatment in recurrent cases.

In conclusion, we present a case of APS/MAS with a myriad of organs involvement and complications including ketoacidosis, orthostatic hypotension, bleeding, etc. APS/MAS is a relatively rare disease and should not be overlooked as a possible diagnosis when patients present with multiple autoimmune diseases simultaneously. Screening for possible coexisting autoimmune diseases should be considered in cases of suspected APS/MAS. Additionally, in the treatment of critically ill cases of APS/MAS with multiple organs involvement, symptomatic treatment, etiological treatment, and clinical care are all important and active multidisciplinary cooperation should be emphasized. For instance, endocrinologists are highly needed in the glycemic management of T1DM patients receiving adequate glucocorticoid therapy. Further researches are needed to explore the underlying mechanisms of APS/MAS in the future.

Author Contributions

J.T. participated in the management of the patient and wrote the case report under the guidance of Y.F. and L.Z. L.Z. is the rheumatologist who participated in the treatment of the patient. Y.F. and X.F. are the gastroenterologists who participated in the treatment of the patient. J.F. is the hematologist who participated in the treatment of the patient. Y.L. is the cardiologist who participated in the treatment of the patient. J.Y. is the endocrinologist who participated in the treatment of the patient. H.F. is the neurologist who participated in the treatment of the patient. T.S. is the radiologist who was responsible for the interpretation of the clinical images. All authors contributed to the manuscript and approved the submitted version.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Prevalence of Human Leukocyte Antigen (HLA)-B*58:01 and Allopurinol-Induced Adverse Reactions in Filipino Patients in Hawai'i: Implications for Genotyping

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ABSTRACT

Introduction: Allopurinol, a first-line treatment for gout and hyperuricemia, is associated with severe cutaneous adverse reactions (SCAR) in individuals carrying the HLA-B*58:01 allele. Genotyping is conditionally recommended in Han Chinese, Korean, and Thai populations with an allele prevalence of 7.4%, and in African Americans at 3.8%. The prevalence in Filipino patients has not been studied. We investigate the prevalence of HLA-B*58:01 among Filipino patients in Hawai'i and evaluate the incidence of allopurinol-induced adverse reactions following genotyping.

Methods: We conducted a retrospective chart review of 312 patients who underwent HLA-B*58:01 genotyping at a primary care clinic in Hawai'i between November 2021 and July 2024. After excluding patients with missing ethnicity data, non-Filipino ethnicity, or prior allopurinol use, 237 Filipino patients were included in the analysis. The prevalence of the HLA-B*58:01 allele and the incidence of allopurinol-induced adverse reactions were calculated.

Results: Among the 237 Filipino patients, 17 (7.2%) were HLA-B*58:01 positive. A total of 97 patients were started on allopurinol after genotyping and 1 (1.0%) developed mild cutaneous reactions, 0 (0%) developed SCAR, and 2 (2.1%) experienced gastrointestinal symptoms (nausea and diarrhea).

Conclusion: The high prevalence of HLA-B*58:01 allele among Filipino patients in Hawai'i suggests that genotyping may be considered before initiating allopurinol treatment. Given no instances of SCAR were observed in patients who were administered allopurinol after undergoing HLA-B*58:01 genotyping, genotyping may play a crucial role in reducing the risk of allopurinol-induced SCAR in this population. Further studies with larger cohorts are suggested to confirm our findings and assess broader clinical utility of genotyping.

1 | Introduction

Allopurinol is a xanthine oxidase inhibitor and the first-line treatment for gout and hyperuricemia [1]. Although generally well-tolerated, the most common side effects with incidence rates between 1 to 10% are maculopapular rash (≥1%), skin rash (2%), diarrhea (≥1%), nausea (1%), vomiting (≤1%), increased hepatic enzymes (≥1%), acute gout (≥1%), and kidney failure (≤1%) [2]. In rare cases, allopurinol may cause life-threatening severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The mean estimated historical incidence of SCAR in Taiwan

Summary

- High prevalence of HLA-B*58:01 in Filipino patients in Hawai'i. This study found that 7.2% of Filipino patients in Hawai'i carry the HLA-B*58:01 allele, a prevalence similar to other high-risk Asian populations. This underscores the importance of considering genetic screening in this population before initiating allopurinol therapy.
- Clinical implications for HLA-B*58:01 genotyping. This study revealed no cases of SCAR in patients who were administered allopurinol after undergoing HLA-B*58:01 genotyping. Healthcare providers in Hawai'i may want to consider implementing HLA-B*58:01 screening as part of routine care for Filipino patients requiring allopurinol treatment in order to reduce allopurinol-induced SCAR.

was 0.30% per year (95% confidence interval: 0.28%–0.31%), based on data from over 100 000 subjects [3]. The mortality rate associated with SCAR can reach 37%, and recent multinational case–control studies have identified allopurinol as the most common cause of SCAR in Asia and Europe [4, 5].

Prior studies indicate a strong correlation between allopurinol-induced SCAR and the human leukocyte antigen (HLA)-B*58:01 allele among high-risk Asian populations [3, 6–11]. The prevalence of HLA-B*58:01 is highest among individuals of Han Chinese, Korean, and Thai descent (7.4%), lower among African Americans (3.8%), and even lower among whites and Hispanics (0.7% each) [1]. Given this correlation, the American College of Rheumatology recommends genotype screening for patients of Chinese, Thai, Korean, African American, or other ethnicities with a similarly high frequency of HLA-B*58:01 [1]. Furthermore, testing for this allele among Asians and African Americans has been reported to be cost-effective, with incremental cost-effectiveness ratios of less than $109 000 per quality-adjusted life year [12].

To date, no studies have examined the prevalence of the HLA-B*58:01 allele or the utilization of HLA-B*58:01 genotyping prior to allopurinol administration in the Filipino population. According to the 2020 US Census, 383 200 Filipino Americans reside in Hawai'i, comprising approximately 25% of the state's population [13]. By reporting the prevalence of the HLA-B*58:01 allele and the incidence of allopurinol-induced adverse reactions following genotyping among Filipino patients in Hawai'i, we aim to provide evidence for the clinical utility of HLA-B*58:01 genotyping before allopurinol administration in this population.

2 | Materials and Methods

We conducted a retrospective chart review of all patients who received HLA-B*58:01 genotyping at the Primary Care Clinic of Hawaii between November 1, 2021, and July 31, 2024 ($n = 312$). HLA-B*58:01 genotyping was ordered at the clinic and performed by a third-party medical laboratory (Clinical Labs of Hawaii or Diagnostic Laboratory Services). Ethnicity information was obtained from electronic health records, where patients self-reported their ethnicity during their initial clinic visit. Patients with missing ethnicity information ($n = 53$) or who identified as an ethnicity other than Filipino ($n = 15$) were excluded from the study. Additionally, patients who had been on allopurinol prior to receiving HLA-B*58:01 genotyping were excluded ($n = 7$). All patients were over 18 years old. A total of 237 patients were included in the study (Figure 1). R Statistical Software (version 4.3.2; R Core Team 2023) was used for data cleaning.

3 | Results

Among the 237 patients included in our study, 17 (7.2%) were found to be HLA-B*58:01 positive. Table 1 presents the clinical characteristics according to the presence of HLA-B*58:01. Both groups had similar demographic and laboratory results. Overall, 48 patients (20.3%) were using thiazide diuretics, and 123 patients (51.9%) were using systemic steroids, most commonly prednisone for acute gout flares, at the time of genotyping. The most common underlying conditions were gout (91.6%), hypertension (85.2%), and chronic kidney disease (46.4%). The most frequent indications for HLA-B*58:01 genotyping were chronic gout (72.6%), acute gout (13.0%), and chronic gout with hyperuricemia (8.4%). Less common indications included hyperuricemia (2.9%) and urolithiasis (1.3%).

Urate-lowering drug administration after genotyping is shown in Table 2. One HLA-B*58:01 negative patient and 12

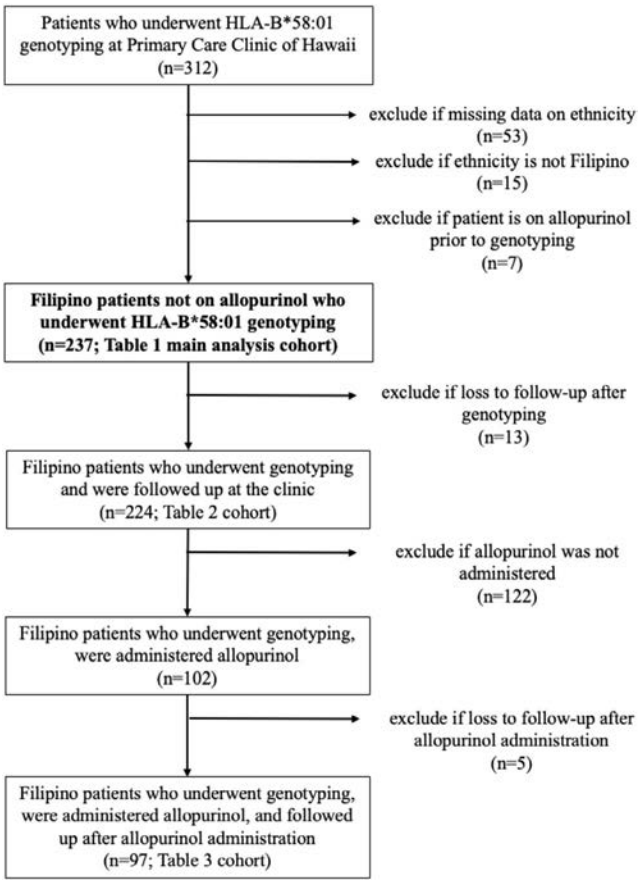

FIGURE 1 | Study participants flow.

TABLE 1 | Comparison of clinical characteristics according to the presence of HLA-B*58:01.

	HLA-B*58:01 positive	HLA-B*58:01 negative	Overall
	n **= 17**	***n*** **= 220**	***n*** **= 237**
Age (year)	62.4 (14.2)	62.8 (14.5)	62.7 (14.5)
Female sex, *n* (%)	4 (23.5)	60 (27.3)	64 (27.0)
Body-mass index, mean (SD)	28.3 ± 3.88	28.4 ± 9.25	28.4 ± 8.97
Lab tests, mean (SD)			
WBC count ($10^{9/L}$)	7.29 ± 2.52	7.84 ± 3.42	7.80 ± 3.36
Eosinophil count ($10^{9/L}$)	0.25 ± 0.15	0.34 ± 0.66	0.34 ± 0.64
AST (IU/L)	22.9 ± 8.82	25.4 ± 9.51	25.2 ± 9.47
ALT (IU/L)	24.9 ± 8.87	29.2 ± 15.6	28.9 ± 15.3
BUN (mg/dL)	20.0 ± 9.24	18.4 ± 8.27	18.5 ± 8.33
Creatinine (μmol/L)	1.26 ± 0.93	1.21 ± 1.24	1.21 ± 1.22
eGFR (mL/min/1.73 m^2)	74.1 ± 27.1	79.1 ± 25.8	78.8 ± 25.9
Uric acid (mg/dL)	7.49 ± 1.67	7.73 ± 4.01	7.72 ± 3.88
Medications, *n* (%)			
Use of thiazide diuretics	3 (17.6)	45 (20.5)	48 (20.3)
Use of systemic steroid	7 (41.2)	116 (52.7)	123 (51.9)
Underlying diseases, *n* (%)			
Hypertension	16 (94.1)	186 (84.5)	202 (85.2)
Diabetes	5 (29.4)	82 (37.3)	87 (36.7)
Chronic Kidney Disease	8 (47.1)	102 (46.4)	110 (46.4)
Malignancy	2 (11.8)	14 (6.4)	16 (6.8)
Liver disease	1 (5.9)	16 (7.3)	17 (7.2)
Asthma	1 (5.9)	10 (4.5)	11 (4.6)
Gout	14 (82.4)	203 (92.3)	217 (91.6)
Indication for genotyping, *n* (%)			
Acute gout	3 (17.6)	28 (12.7)	31 (13.0)
Acute gout with hyperuricemia	0 (0)	2 (0.90	2 (0.8)
Chronic gout	8 (47.1)	164 (74.5)	172 (72.6)
Chronic gout with hyperuricemia	3 (17.6)	17 (7.7)	20 (8.4)
Hyperuricemia	1 (5.9)	6 (2.7)	7 (2.9)
Urolithiasis	1 (5.9)	2 (0.9)	3 (1.3)
Urolithiasis with hyperuricemia	0 (0)	1 (0.5)	1 (0.4)
Chronic gout with urolithiasis	1 (5.9)	0 (0)	1 (0.4)

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; HLA, human leukocyte antigen; WBC, white blood cell count.

HLA-B*58:01 negative patient were loss to follow-up. Among HLA-B*58:01 negative patients, 101 were started on allopurinol, compared to only one HLA-B*58:01 positive patient. Additionally, 5 (29.4%) of HLA-B*58:01 positive patients were started on febuxostat compared to only 3 (1.4%) of HLA-B*58:01 negative patients.

Table 3 presents allopurinol-induced adverse reactions following drug administration. Five HLA-B*58:01 negative patient who were started on allopurinol were loss to follow-up and excluded, leaving a total of 97 patients included in Table 3. Overall, one patient (1.0%) developed mild cutaneous reactions, 0 patients developed SCAR, and two patients (2.1%) experienced

TABLE 2 | Urate-lowering drug administration after genotyping.

	HLA-B*58:01 positive	HLA-B*58:01 negative
	***n* = 17**	***n* = 220**
Loss to follow-up after genotyping, *n* (%)	1 (5.9)	12 (5.5)
No urate lowering drug administration, *n* (%)	9 (52.9)	94 (42.7)
Urate lowering drug administration		
Allopurinol, *n* (%)	1 (5.9)	101* (45.9)
Febuxostat, *n* (%)	5 (29.4)	3* (1.4)
Other**, *n* (%)	1 (5.9)	23* (10.5)

*Two patients received allopurinol and febuxostat; 11 patients received allopurinol and other urate lowering drug.
**Other includes probenecid and pegloticase.

TABLE 3 | Allopurinol-induced adverse reactions.

	HLA-B*58:01 positive	HLA-B*58:01 negative	Overall
	***n* = 1**	***n* = 96**	***n* = 97**
No adverse events	1	90	91 (93.8)
Mild cutaneous adverse events, *n* (%)	0	1	1 (1.0)
Severe cutaneous adverse events, *n* (%)	0	0	0 (0)
Other adverse events, *n* (%)	0	2	2* (2.1)
Adverse events total, *n* (%)	0	3	3 (3.1)

*Both cases were due to nausea and diarrhea.

gastrointestinal symptoms (nausea and diarrhea). In total, three patients (3.1%) developed some form of allopurinol-induced adverse reaction.

4 | Discussion

Our study demonstrates that Filipino patients in Hawai'i have a similar prevalence of the HLA-B*58:01 allele (7.2%) compared to other high-risk ethnicities, such as Han Chinese, Korean, and Thai populations (7.4%). The 2020 American College of Rheumatology Guideline for the Management of Gout states that "Testing for the HLA–B5801 allele prior to starting allopurinol is conditionally recommended for patients of Southeast Asian descent (e.g., Han Chinese, Korean, and Thai) and for African American patients, over not testing for the HLA–B5801 allele," but it does not specifically reference Filipino patients [1]. Recently, African Americans, with an HLA-B*58:01 prevalence of 3.8%, were included among the ethnicities conditionally recommended to undergo genotyping. Given our findings of a high prevalence of the allele in Filipino patients in Hawai'i, this population should be considered to similarly undergo HLA-B*58:01 genotyping prior to allopurinol administration. The prevalence of gout among US Asian adults has shown an increasing trend, with the age- and sex-adjusted prevalence doubling from 3.3% in 2011–2012 to 6.6% in 2017–2018, surpassing other racial and ethnic groups [14]. These findings suggest that, as the prevalence of gout rises in these populations, Asian individuals in the US may increasingly be considered candidates for allopurinol therapy, underscoring the relevance of our research on HLA-B*58:01 genotyping in guiding safe and effective treatment.

Our study focuses on the Filipino population in Hawai'i, which comprises approximately 25% of Hawai'i's total population. We hypothesize our findings can be applied to other Filipino American populations in the US and the general Filipino population in the Philippines. However, given that the Philippines is a multi-ethnic country with over 180 ethnic groups [15], further research on specific Filipino subgroups or regions is essential to better understand genetic variability across the broader Filipino population.

In our retrospective chart review, 1.0% of patients developed mild cutaneous reactions, none developed SCAR, and 2.1% experienced other adverse reactions (nausea and diarrhea). Overall, 3.1% of patients developed some form of allopurinol-induced adverse reaction. We hypothesized that allopurinol-induced adverse reactions would decrease with pre-administration genotyping, as HLA-B*58:01 positive patients could either avoid allopurinol or receive reduced doses with close monitoring. The incidence rate of mild cutaneous reactions, nausea, and diarrhea were comparable to reported incidence rates for the drug's most common adverse reactions [2]. Compared to the mean estimated historical incidence of SCAR in Taiwan at 0.30% per year (95% confidence interval: 0.28%–0.31%), our study found no incidence of SCAR in patients who were administered allopurinol after genotyping, suggesting the potential clinical utility of genotyping in reducing allopurinol-induced SCAR.

However, several limitations should be considered. First, our study's small sample size limits the statistical power to make meaningful comparisons between patients who underwent HLA-B58:01 genotyping and those who did not. Additionally, the absence of data on patients who experienced side effects but did not undergo HLA-B58:01 genotyping represents a critical limitation. Without this data, the true prevalence of severe adverse reactions in the Filipino patient population receiving allopurinol remains unknown. If the prevalence of severe reactions is low in the Filipino population, even among those who test positive for HLA-B58:01, the utility of routine HLA-B58:01 testing in this group may not be justified.

Future studies should include larger retrospective analyses with a comparative control cohort, such as a historical cohort, to more accurately assess the clinical implications of HLA-B*58:01 genotyping. Although prospective studies could better capture adverse reaction incidence and establish a clearer cause-and-effect relationship, providing stronger evidence to guide clinical

practice, their feasibility may be limited by the large sample size and high costs of genotyping required for specific ethnic groups.

5 | Conclusion

This study confirmed that Filipino patients in Hawai'i exhibit a high 7.2% prevalence of the HLA-B*58:01 allele which was comparable to other high risk Asian ethnicities, suggesting that they may benefit from HLA-B*58:01 genotyping prior to allopurinol administration. Among those who were administered allopurinol following genotyping, the incidence of allopurinol-induced adverse reactions was 3.1%, with no cases of SCAR. Further research is necessary to evaluate the clinical utility of HLA-B*58:01 genotyping in reducing allopurinol-induced adverse reactions, including SCAR, specifically within the Filipino population in Hawai'i.

Author Contributions

Among the authors in the list, R.T. and A.J.P.M. designed the study. R.A.B. conducted data extraction and communicated with third-party genotyping companies. A.J.P.M., H.J.F.D.M., R.S.S.B., J.A.B.A., E.M.Q., and Y.M.S. performed manual data extraction and annotation from electronic health records. R.T. carried out the statistical analysis and drafted the manuscript. C.Y.S. and S.Y. oversaw the entire project, coordinated the IRB application, and contributed to manuscript editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Genetically Predicted Plasma Metabolome Mediates the Causal Link Between Immune Cells and Risk of Gout

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Keywords: gout | immune cells | mediation | Mendelian randomization | plasma metabolome

ABSTRACT

Background: Gout is a prevalent metabolic disorder characterized by a multifaceted process of development. Recent research has emphasized a robust correlation between the immune response and gout. Nevertheless, it is still uncertain if this connection is causative. Hence, the objective of this study was to investigate the causal relationship between immune cells and gout, while also analyzing the role of the plasma metabolome as metabolic mediators in this biological process.

Methods: This study explored the causal link between different subtypes of immune cells and gout using two-sample Mendelian randomization (MR). To confirm the reliability of the findings, reverse MR analysis, steiger test and sensitivity tests were conducted. A two-step mediation analysis was used to gain insight into the role of plasma metabolites as intermediate mediators.

Results: This two-sample, bidirectional, two-step MR analysis found a nominal causal link between 33 immune cells as well as 47 known plasma metabolites and gout. Reverse MR analysis and sensitivity tests demonstrated the reliability of the MR results. In addition, we found that Tetradecadienedioate (C14:2-DC) played a partially mediating role in the CD4 on activated CD4 regulatory T cell and gout pathways, with a mediating proportion of 13.16%, (95% CI = 0.65%–25.67%, $p = 0.034$).

Conclusion: The objective of our research was to investigate the possible causative connection between immune cells and gout. Our findings indicate that certain plasma metabolites may play a role in mediating this association. This study offers novel insights and sources of information that may contribute to the early detection and proactive measures to avoid gout in the future.

1 | Introduction

Gout is the most prevalent inflammatory arthritis worldwide, with a prevalence of 1%–4% and an incidence of 0.1%–0.3%. An elevated serum uric acid concentration represents the most significant risk factor for the onset of gout, and plays a pivotal role in the pathogenesis of this condition [1, 2]. The clinical manifestations of gout include severe pain in the joints of the lower limbs, which is mainly attributed to the deposition of monocrystalline sodium urate (MSU). Large amounts of MSU lead to the formation of gouty stones and further damage to articular cartilage [3]. The prevalence of gout has continued to rise globally since the 20th century. This trend is likely to be related to changes in lifestyle, living environment, and diet [4]. Therefore, there is an urgent need to develop more effective strategies for the treatment of gout.

An increasing number of scholars have tried to understand the development of gout by studying the immune system and inflammatory cytokines. Gout is hypothesized to be a prototypical inflammatory condition caused by the activation of the innate immune system [5]. The primary contributors to acute gout episodes are macrophages and neutrophils, with innate immune mechanisms playing a significant role. Specifically,

Summary

- We found a nominal causal link between different immune cell subtypes and gout.
- Specific plasma metabolites partially mediate the causal link between immune cells and gout.
- This study offers novel insights that may contribute to the early detection and proactive measures to avoid gout in the future.

NLRP3 inflammatory vesicles, believed to be the primary route for MSU crystals to initiate cellular inflammatory reactions, can also result in the secretion of interleukin (IL)-1β, a crucial mediator of gout inflammation, along with other inflammatory cytokines. This process then triggers a series of cascading inflammatory amplification responses [6, 7]. Furthermore, several researchers have using single-cell RNA sequencing technologies and bioinformatics techniques to detect distinct subgroups of immune cells in both the blood and synovial fluid of individuals with gout. The findings indicated that individuals with gout had markedly elevated amounts of naïve CD4 T cells and classical monocyte populations [8]. Wang et al. performed a clinical study utilizing single-cell mass spectrometry flow cytometry to examine the distribution of immune cell subpopulations in the peripheral blood of gout patients. They discovered significant alterations in the NK and T cell subpopulations in gout patients compared to healthy individuals. This finding suggests that targeting these subpopulations could be a potential new therapeutic approach [9]. Nevertheless, there is a dearth of research examining the existence of a causal relationship between immune cells and gout.

Metabolic disorders are closely related to gout. With the continuous development of metabolomics, differential metabolites in gout can be effectively identified, and these metabolites can be used as potential biological markers for disease diagnosis and prognostic assessment [10]. Zhang et al. used metabolomics technology to analyze sera from 49 gout patients and 50 healthy controls, and found that there were significant alterations in a variety of metabolites involving multiple metabolic pathways such as lipid metabolism, carbohydrate metabolism, and amino acid metabolism [11]. By summarizing the changes in metabolites in gout-related literature, Li et al. found that specific metabolites play an important role in the development of gout, including uric acid, guanosine, hypoxanthine, xanthine, and adenosine, after systematic review and meta-analysis [12]. In addition, metabolites act synergistically in the pathogenesis of gout as substrates or intermediates in metabolic processes and can mediate important immunomodulatory functions [13]. Recently, genotype-dependent metabolic phenotype databases have recently been established through GWAS involving untargeted metabolomics, which also provides an effective tool to carry out further explorations [14].

Mendelian randomization (MR) is a statistical method that uses randomly assigned genetic variants as a tool to verify the causal nature of modifiable exposures on outcomes [15]. This research method is effective in reducing the effects of confounders and reverse causation [16]. In the present study, we used a two-sample, two-step MR approach to conduct a study to explore the causal link between 731 immune cells and gout risk. In addition, based on the role of metabolites in mediating disease and immune responses, we further explored the role played by plasma metabolites in the causal pathway between immune cells and gout.

2 | Materials and Methods

2.1 | Study Design and Ethnic Statement

Figure 1 displays the flowchart of our investigation. Firstly, we conducted a two-sample MR analysis with 731 immune cell phenotypes as the exposure and gout as the outcome, with the objective of elucidating the causal link between the two. Following that, a reverse MR study was conducted, using gout as the exposure variable and immune cells as the outcome variable. Next, a two-step MR analysis was conducted to investigate the potential mediating role of plasma metabolome in the relationship between immune cells and gout risk. Step 1: The effect of plasma metabolites on gout was investigated using two-sample, bidirectional MR analyses to identify plasma metabolites that were causally linked to gout. Step 2: Based on these analyses, immune cell phenotypes and plasma metabolome associated with gout risk were identified, and the association between immune cells and plasma metabolome was again assessed using the two-sample MR method.

2.2 | Data Sources

Our GWAS datasets are from separate cohorts and consortiums, thus avoiding false positive results due to sample overlap. In addition, more detailed information about the datasets can be found in Table 1.

2.3 | Data Sources for Immune Cells

The immune cell GWAS dataset comes from the SardiNIA project. In this project, peripheral blood from 3757 participants of European ancestry was immunoassayed, processed by antibody staining and analyzed by flow cytometry, resulting in 731 immune cell phenotypes [17].

2.4 | Data Sources for Plasma Metabolome

Plasma metabolome data were obtained from The Canadian Longitudinal Study of Aging (CLSA). The study involved 8299 Canadians between the ages of 45 and 85. The study was conducted through a series of rigorous quality control criteria, resulting in 1091 metabolites and 309 metabolite ratios [18].

2.5 | Data Sources for Gout

The GWAS summary-level data for gout were derived from the round 10 release by the FinnGen Consortium and included a total

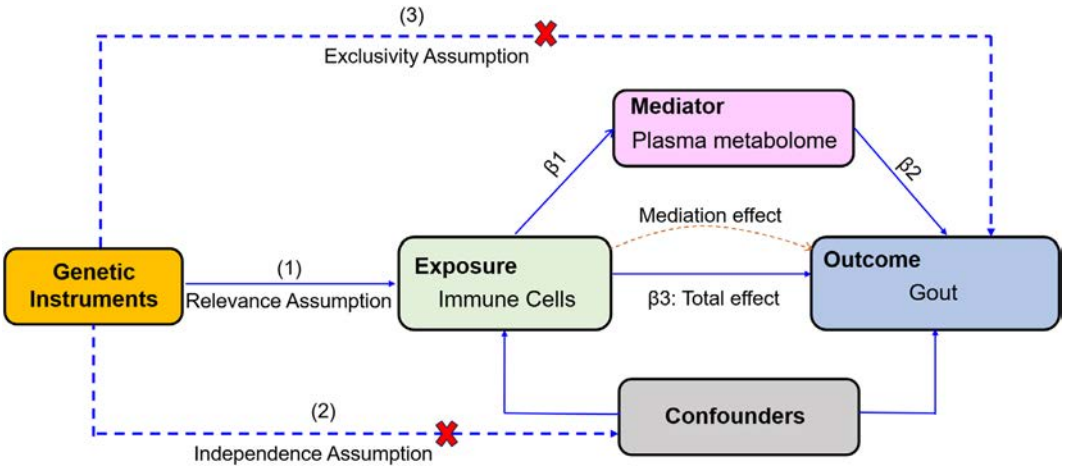

FIGURE 1 | This study strictly follows the three assumptions of MR. This includes (1) relevance assumption; (2) independence assumption; (3) exclusivity assumption. A two-step approach was used for the mediation MR analysis. The total effect between immune cells and gout (β3) can be decomposed into indirect effect (using the product method, $\beta1 \times \beta2$) and direct effect ($\beta3' = \beta3 - \beta1 \times \beta2$). The mediated effect share should be $\beta1 \times \beta2/\beta3$. 95% CI confidence intervals were calculated using the delta method.

of 9568 patients as well as 262 844 healthy controls. The FinnGen research is an extensive genomics project that has examined over 500 000 samples from the Finnish biobank. It has established connections between genetic variations and health data in order to gain insights into disease causes and susceptibility. The project includes a partnership between Finnish academic institutes and biobanks, as well as worldwide industrial partners.

2.6 | Selection of Instrumental Variables (IV)

In accordance with the three fundamental assumptions, IVs for MR studies must exhibit a robust correlation with exposure. When immune cells and plasma metabolites were employed as exposures, we elected to establish the screening threshold at $p < 5 \times 10^{-8}$. However, this resulted in an insufficient number of single-nucleotide polymorphisms (SNPs) for analysis. In light of the findings of previous studies, we opted to set the significance threshold at a more lenient level, $p < 1 \times 10^{-5}$. Subsequently, data from the European sample of the 1000 Genomes Project ($r^2 = 0.001$, LD = 10 000 kb) were used to filter SNPs in order to remove chaining imbalances. To circumvent potential bias from weak instrumental variables, we calculated the *F*-value for each IV using the following formula: $F = \text{beta}^2/\text{se}^2$. SNPs with *F*-statistics < 10 were excluded. Furthermore, palindromic SNPs were also required to be excluded from the MR analysis.

2.7 | Statistical Analysis

We used inverse variance weighted (IVW), MR-Egger, weighted median (WM), weighted model and simple model to assess the causal relationship between 731 immune cell phenotype and gout. The IVW approach was used as the major analytical technique. We used the odds ratio (OR) and their corresponding 95% confidence intervals (CI) to quantify the causal association between factors. We used the Bonferroni correction for multiple hypothesis testing. *P* values were considered statistically significant when they were below the corrected threshold. In addition, $p < 0.05$ was assumed to have a nominal causal association. In order to ensure the dependability of the results, we performed further tests to assess heterogeneity and pleiotropy. In order to identify the presence of outlier SNPs, we also went on to carry out a leave-one-out test.

2.8 | Reverse MR Analysis

In order to avoid the effects of reverse causation, we performed a reverse MR analysis using gout as the exposure. The results of the reverse MR analysis were likewise based on the IVW results.

2.9 | Two-Step MR Analysis

The current study used a two-step MR analysis method to investigate whether plasma metabolites act as mediators in the causal link between immune cells and gout. The total causal impact of immune cells on the probability of developing gout may be separated into two components: the direct impact of immune cells on gout and the indirect impact that is facilitated by plasma metabolites. The overall impact β3 represents the causal association between immune cells and gout. The causal influence of plasma metabolites on gout is represented by β2. Lastly, β1 represents the causal relationship between identified immune cells and plasma metabolites. Direct effect refers to the overall impact of a certain factor without any mediation or influence from other factors. The plasma metabolites had a mediating impact of $\beta1 \times \beta2$, and the ratio of this mediating effect to another effect, β3, was $\beta1 \times \beta2/\beta3$. The delta approach was used to examine the 95% CI.

2.10 | Statistical Software

All of this MR data was analyzed using R software (version 4.2.3). The major uses were for the TwoSampleMR and RMediation packages.

3 | Results

3.1 | Causal Link Between Immune Cells and Gout

All analyses were conducted using the IVW method as the primary analytical approach. To ensure the reliability of the results, the five MR analysis method directions were retained in order to maintain consistency. Furthermore, additional reverse MR analyses were conducted. To guarantee the reliability of the findings, immune cells without heterogeneity, pleiotropy, and exposure to reverse causality were selected. Ultimately, 33 immune cells were identified as having a nominal causal relationship with gout (Figure 2 and Table S1). We also used scatter plots (Figure S1) and forest plots (Figure S2) for the presentation of the results. The

TABLE 1 | The detailed information of the GWAS datasets using in this MR analysis.

	Smaple size	Consortium	PMID	Download sources
Immune cells	3757	SardiNIA	32929287	https://www.ebi.ac.uk/gwas/publications/32929287
Plasma metabolome	8299	CLSA	36635386	https://www.ebi.ac.uk/gwas/publications/36635386
Gout	272412	FinnGen	—	https://www.finngen.fi/en

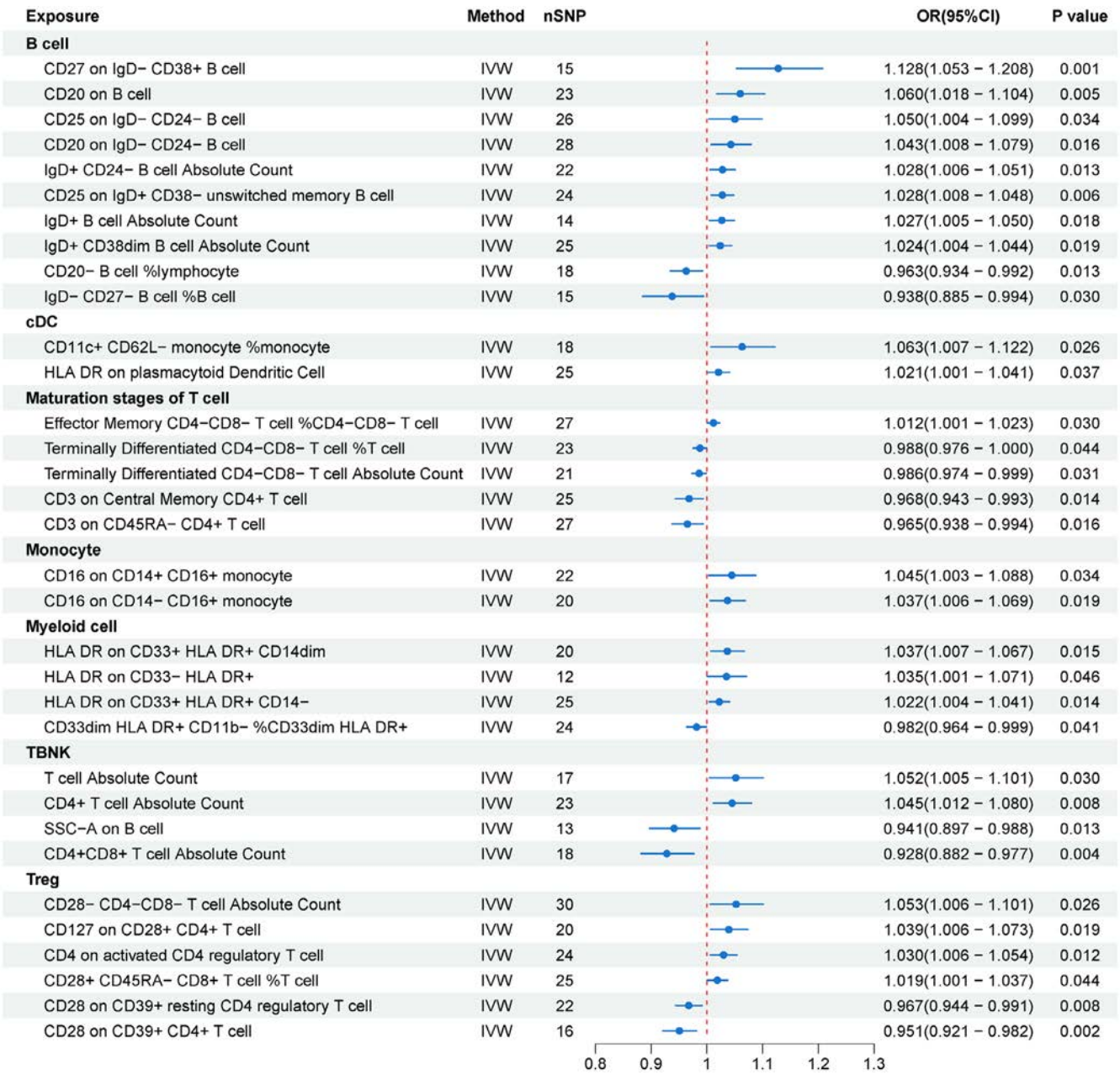

FIGURE 2 | The causal relationship between immune cells and gout.

leave-one-out method also demonstrated the absence of outlier SNPs (Figure S3). The results of the sensitivity analyses can be seen in Tables S2 and S3. Steiger test results are shown in Table S4, and the detailed results of the reverse MR analyses are referred to Table S5. Of these, 22 immune cells could be gout risk factors, although 11 immune cells are thought to be gout-protective.

3.2 | Causal Link Between Plasma Metabolome and Gout

Based on the findings from tests on directional consistency, reverse causal connection, and sensitivity, a total of 47 plasma metabolites and metabolite ratios were identified as possible factors influencing gout. These results are shown in Figure 3 and Table S6. Out of these, 24 plasma metabolites or metabolite ratios had a negative correlation with the risk of gout, while another 23 showed a potential to raise the risk of gout. The sensitivity analyses are shown in Tables S7 and S8, while the results of the Steiger test can be found in Table S9. The findings of the reverse MR analysis were shown in Table S10.

3.3 | Mediation Analysis

The mediation study was conducted using a two-step MR approach. Subsequently, we examined the intermediary function of plasma metabolites in the causative association between immune cells and gout. Using the previously mentioned MR results, we identified a causal relationship between immune cells and gout (β3), as well as between plasma metabolites and gout (β2). Additionally, we employed two-sample MR analyses to investigate the causal relationship between immune cells and plasma metabolites (β1). It is important to mention that for β1, we will only use causal linkages where the direction of the five analyses stays constant and is not influenced by reverse causality.

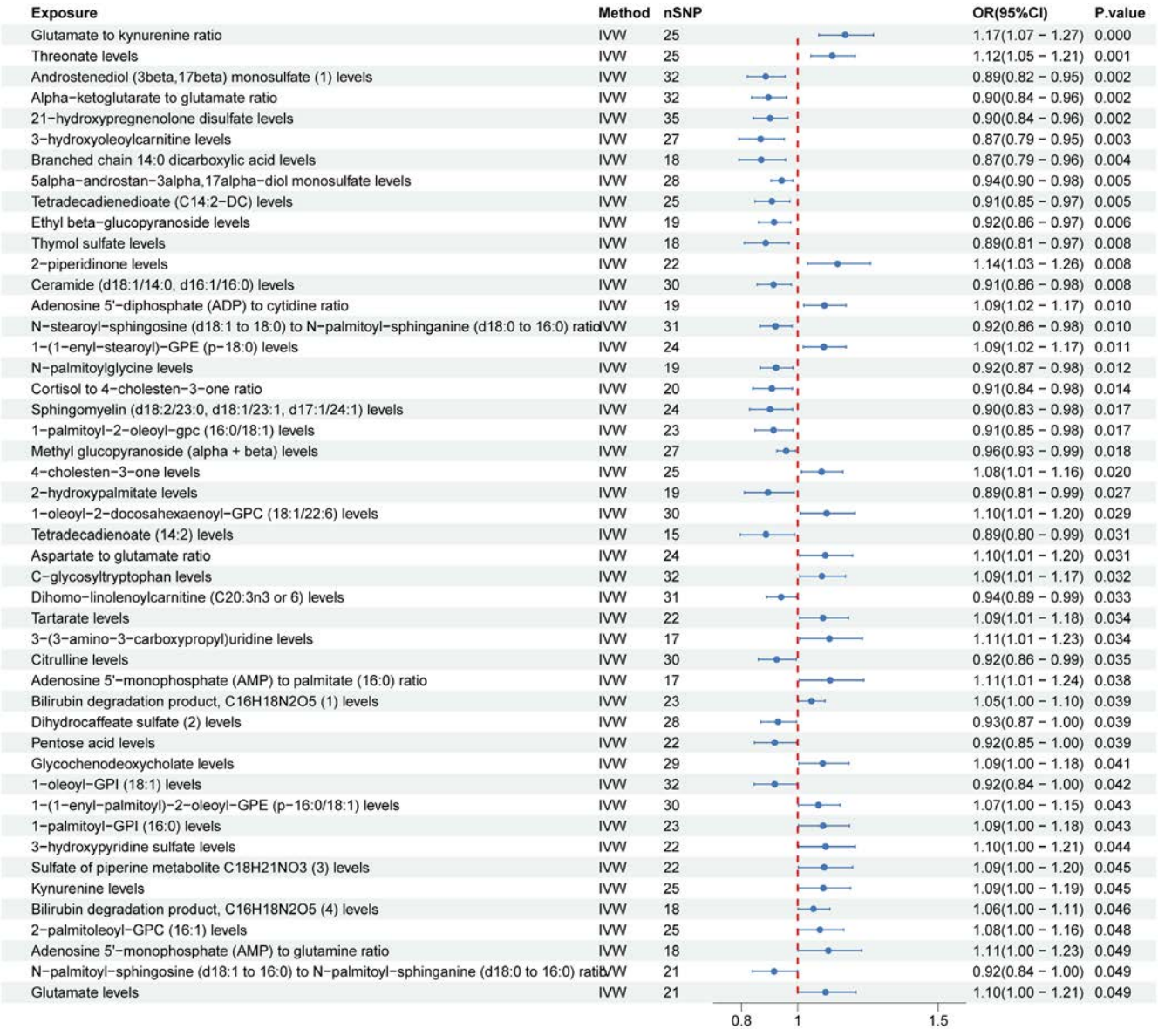

FIGURE 3 | The causal relationship between plasma metabolites and gout.

After careful analysis, we have concluded that Tetradecadienedioate (C14:2-DC) partly mediates the relationship between CD4 on activated CD4 regulatory T cell and gout. The mediating percentage is 13.16%, (95% CI = 0.65%–25.67%, $p = 0.034$). The mediation analysis findings are shown in Figure 4, providing a comprehensive and detailed overview.

4 | Discussion

Our MR study integrated large-scale GWAS datasets to thoroughly investigate the functions of the roles of different subtypes of immune cells in the progression of gout. Additionally, we investigated the intermediate activities of plasma metabolites in this process, focusing on their genetic aspects. After careful analysis, we discovered 33 different types of immune cells that are nominally associated with gout. Additionally, we found that there are 47 plasma metabolites or metabolite ratios that are known to be nominally causally linked to gout. Furthermore, we determined that Tetradecadienedioate (C14:2-DC) partially mediates the relationship between CD4 on activated CD4 regulatory T cells and gout. This mediating role accounts for 13.16% of the overall causal pathway.

Accurately identifying and differentiating distinct groups of cells is of greatest importance for immunological investigation. CD4 on activated CD4 Treg originates from the Treg panel. CD4 is a kind of glycoprotein found on the outer surface of immune cells. It plays a role in identifying antigens that are displayed by major histocompatibility complex (MHC) class II molecules [19]. CD4 also helps facilitate communication between the T-cell receptor and the antigen-presenting cell. $CD4^+$ T cells play a crucial role in starting and coordinating the immune response, as well as aiding in the activation of other immune cells. Treg, are a distinct subset of $CD4^+$ T cells which have an essential part in suppressing the immune response [20]. Researchers discovered temporal alterations in the expression levels of Treg in a rat model of acute gouty arthritis produced by MSU. The population of Treg cells exhibited a decline at the 24-h mark and a tendency towards an elevation at both the 48-h and 72-h intervals [21]. Zi et al. discovered that individuals with gout had a notably reduced number of Treg cells when comparing $CD4^+$ T cell subsets with healthy controls. Furthermore, the research team discovered a significant correlation between Treg cells in individuals with gout and the production of interleukin (IL)-2, a versatile cytokine that has a crucial role in the immune system's response [22]. Research has shown that controlling the ratio of Th17/Treg cells may decrease the symptoms of gouty arthritis [23, 24]. Yu's team used single-cell sequencing and flow cytometry to prove that Tregs expand throughout the period of gout remission and display dramatically improved ability to inhibit inflammation [25]. Additional study is required to provide greater evidence for the connection between CD4 on activated CD4 Treg and gout.

Tetradecadienedioate (C14:2-DC) is a fatty acid (FA). FAs are crucial constituents of larger lipids and serve as precursors for bioactive compounds [26]. FAs play many important roles in the human body, including energy storage, membrane synthesis and signaling molecule production. There is growing evidence that dietary FA can influence human health and disease risk. However, different types of FA can play different roles, and Saito's team found that Omega-3 polyunsaturated FA have a potentially beneficial effect in reducing the risk of hyperuricaemia and gout [27]. Low levels of omega-3 FA have also been shown to be associated with frequent gout attacks in a case-control study [28]. However, consuming too much saturated FA (SFA) may increase the risk of the disease. Previous dietary recommendations advised limiting SFA consumption to < 10% of total caloric intake [29, 30]. There are hints in the limited evidence that Tetradecadienedioate (C14:2-DC) may have a negative effect on disease. There are insufficient studies on the association between FAs, Tetradecadienedioate (C14:2-DC) and gout, and more clinical and basic studies are still needed in the future to reveal the relationship between the two.

The two-sample MR we conducted was a large sample size, statistically efficacious study analyzing both exposures and endpoints using existing publicly available, large-scale GWAS datasets as a means of increasing persuasiveness. Second, we performed a series of sensitivity analyses, reverse MR, replication and meta-analyses to increase the reliability of our results, and only those results that remained consistent in direction across the five MR analysis methods were considered potential candidate immune cells. Third, the GWAS datasets we used for exposure, mediation, and outcome were from separate cohorts, so there was no sample overlap, which also avoided the possibility of false-positive results.

However, there are some limitations to our study. Firstly, as the exposure, outcome, and mediator GWAS datasets used in this study only included participants of European ancestry, the results of this study need to be interpreted more cautiously for generalization to other ethnic groups. Secondly, the GWAS dataset used for MR analysis was pooled data and lacked classification of gout

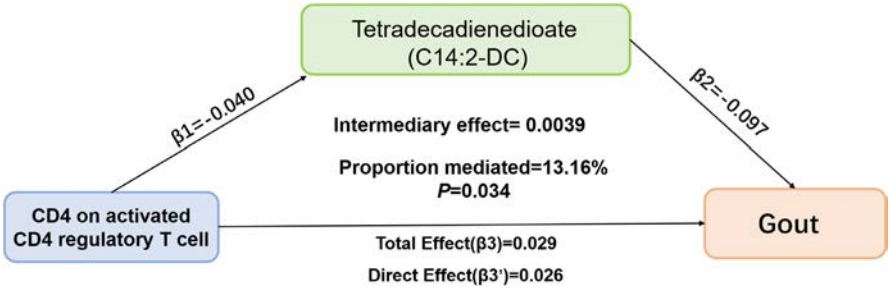

FIGURE 4 | The two-step mediation MR analysis between immune cells and gout. Tetradecadienedioate (C14:2-DC) played a partially mediating role in the CD4 on activated CD4 regulatory T cell and gout pathways, with a mediating proportion of 13.16%.

diseases such as idiopathic gout, pharmacological gout, and other secondary gout, so we could not go further to analyze the causal relationship between immune cells and different types of gout. In addition, in order to obtain sufficient SNPs for analysis, we did not choose a more stringent significance threshold ($p < 5 \times 10^{-8}$), but rather a loose threshold of $p < 1 \times 10^{-5}$. However, this loose threshold was also adjusted with reference to numerous previous studies. It is worth noting that our results do not pass rigorous multiple corrections and there is only a nominal causal link, which is an unavoidable flaw of this study. Meanwhile, this study has not yet been able to explain the association between hyperuricemia and gout. Future studies could go further to explore the role immune cells play between the two.

5 | Conclusion

In conclusion, this study provides genetic evidence that plasma metabolites act as intermediaries in the causal relationship between immune cells and gout, as established using a two-sample, two-step MR analysis. This study also has good clinical practice value. From a diagnostic point of view, it can emphasize the screening of different immune cell subpopulations in gout patients. From a preventive perspective, it can help clinicians to better identify immune cells that are protective or dangerous for gout. It also provides new targets for future clinical treatment.

Author Contributions

Yi Wei: formal analysis, methodology, investigation, supervision, validation, writing – original draft. **Jiangyi Yu:** conceptualization, project administration, writing – review and editing draft.

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Ethics Statement

As this study used publicly available summary data from previously published GWAS, ethical approval was not required. All original GWAS had obtained informed consent from participants, and the data were de-identified and publicly available for research purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets we used in this research can be downloaded from the GWAS catalogue website (https://www.ebi.ac.uk/gwas/) and FinnGen Consortium (https://www.finngen.fi/en).

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Supporting Information

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

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ORIGINAL ARTICLE

Life's Essential 8 and Risk of All-Cause and Cardiovascular Mortality in US Adults With Arthritis: A Retrospective Cohort Study Utilizing NHANES Database

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ABSTRACT

Background: Life's Essential 8 (LE8) is a recently updated algorithm for evaluating cardiovascular health (CVH). This study investigates the association between LE8 and mortality risk among individuals with arthritis in the United States.

Methods: We conducted a retrospective cohort study using data from the US National Health and Nutritional Examination Survey (NHANES) 2005–2018. Participants with arthritis were included. Mortality data, including underlying causes of death, were obtained through linkage to national death records up to December 31, 2019. LE8 components (diet, physical activity, nicotine exposure, sleep, body mass index, blood lipids, glucose, and pressure) were measured and scored from 0 to 100. The total LE8 score, calculated as the unweighted average of all components, was categorized into low (0–49), moderate (50–79), and high (80–100) CVH. We employed Kaplan–Meier curves to estimate survival probabilities and weighted Cox proportional hazards regression models to evaluate hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause and cardiovascular disease (CVD) mortality. Stratified analyses and interaction tests were performed to explore potential effect modifications.

Results: Among 4519 participants with arthritis (median follow-up: 7.67 years), we observed 793 all-cause deaths, including 213 CVD deaths. Every 10-point increase in the LE8 score was associated with a 17% lower risk of all-cause mortality (HR: 0.83, 95% CI: 0.77–0.89) and a 25% lower risk of CVD mortality (HR: 0.75, 95% CI: 0.66–0.85). Compared to the lowest CVH tertile, individuals in the highest tertile demonstrated a 38% lower risk of all-cause mortality (HR: 0.62, 95% CI: 0.41–0.92) and a 62% lower risk of CVD mortality (HR: 0.38, 95% CI: 0.18–0.80). Kaplan–Meier survival curves revealed significantly higher survival probability for patients with high CVH compared to those with lower CVH (log-rank $p < 0.05$). Stratified analyses confirmed consistent associations across various subgroups. Similar findings were observed in sensitivity analyses focusing on osteoarthritis and other arthritis subtypes.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CDC, centers for disease control and prevention; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVH, cardiovascular health; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HEI, healthy eating index; HR, hazard ratio; ICD-10, international classification of diseases, tenth revision; LE8, life's essential 8; NCHS, national center for health statistics; NHANES, national health and nutritional examination survey; OA, osteoarthritis; OR, odds ratio; SE, standard error.

Feiyu Yao, Jiafeng Zhang and Xianhua Li contributed equally to this work and share first authorship.

Conclusion: Higher adherence to LE8 recommendations is associated with reduced risks of all-cause and cardiovascular mortality among US adults with arthritis.

1 | Introduction

Arthritis, encompassing a heterogeneous group of joint disorders, is a prevalent chronic condition that significantly impacts public health, contributing substantially to disability and reduced quality of life among adults worldwide [1–3]. This group of disorders includes osteoarthritis (OA), rheumatoid arthritis, gouty arthritis, systemic lupus erythematosus, fibromyalgia, and others [4]. In the United States, the prevalence of doctor-diagnosed arthritis exhibits a pronounced age-related gradient, increasing from 24.3% in adults aged 45 years and older to 47.4% in those aged 65 years and older [5]. This age-associated increase in prevalence underscores the growing public health burden of arthritis in an aging population [6].

Substantial evidence demonstrates a significant association between arthritis and increased cardiovascular morbidity and mortality, with previous studies reporting relative risk ratios for cardiovascular events ranging from 1.49 to 4.31 in individuals with arthritis compared to those without [7, 8]. While the direct impact of arthritis on joint health and physical function is well-established, its potential influence on cardiovascular health (CVH) and mortality risk is an emerging concern that remains underrecognized in clinical practice.

The American Heart Association (AHA) has recently updated its CVH metrics, introducing "Life's Essential 8" (LE8) to encourage a comprehensive approach to cardiovascular wellness throughout the life course [9]. This new algorithm evaluates eight key components: diet, physical activity, nicotine exposure, sleep, body mass index (BMI), blood lipids, blood glucose, and blood pressure [10]. Each component is scored on a scale of 0–100, with the total LE8 score calculated as the unweighted average of these components [11]. LE8 has demonstrated significant associations with various chronic conditions, including chronic kidney disease (CKD) [12], depression [13], and sarcopenia [14]. Several studies have demonstrated that achieving a higher CVH score based on LE8 is associated with a lower risk of cardiovascular disease, cardiovascular disease (CVD) mortality, and all-cause mortality in general populations [15–18]. Such a recent nationwide study of US adults aged 30–79 years demonstrated that individuals with high LE8 scores showed significantly reduced risks of all-cause mortality (HR: 0.42, 95% CI: 0.32–0.56) and cardiovascular mortality (HR: 0.36, 95% CI: 0.21–0.59) [19]. However, the applicability and predictive capacity of LE8 in specific populations, such as individuals with arthritis, remain unclear.

Notably, many components of CVH, including physical activity, BMI, and blood pressure, are known to be affected by or have an impact on arthritis [7, 20, 21]. Moreover, individuals with arthritis often encounter challenges in maintaining optimal CVH due to pain, functional limitations, and the potential side effects of arthritis treatments [22–24]. Considering that CVH metrics are critical and modifiable factors influencing survival, it is vital to examine how mortality risks in adults with arthritis may differ based on their CVH status, as assessed by LE8. This study aimed to explore the relationship between CVH, measured by LE8 metrics, and both all-cause and cardiovascular mortalities in US adults with arthritis, using data from the National Health and Nutrition Examination Survey (NHANES).

2 | Methods

2.1 | Study Design and Data Source

This longitudinal cohort study utilized data from the NHANES, a comprehensive program conducted by the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of adults and children in the United States [25]. NHANES employs a complex, multistage probability sampling design to ensure nationally representative estimates. The NCHS has made these data publicly available (https://www.cdc.gov/nchs/nhanes/index.htm). We analyzed data from six consecutive NHANES survey cycles spanning 2005–2018. The initial cohort comprised 55 081 participants aged ≥ 20 years from the NHANES 2005–2018 cycles. Initially, 30 464 participants were excluded due to unavailable follow-up information ($n = 136$), incomplete arthritis data ($n = 5021$), or incomplete lifestyle and environmental (LE8) data ($n = 25\,307$). From the remaining 24 617 participants, we further excluded 3574 individuals for missing demographic data ($n = 1857$); unavailable information on CVD, CKD, and chronic obstructive pulmonary disease (COPD) ($n = 178$), absence of depression scores ($n = 940$); or lack of alcohol consumption data ($n = 599$). The final analytical sample consisted of 21 043 participants, stratified into two groups: those without arthritis ($n = 16\,524$) and those with arthritis ($n = 4519$) (Figure 1).

2.2 | Exposure Variable and Outcomes

The LE8 CVH score comprises eight components: four health behaviors (diet, physical activity, smoking, and sleep) and four health factors (BMI, non-high-density lipoprotein [HDL] cholesterol, blood glucose, and blood pressure), as outlined in Table S1 [9]. Dietary quality was assessed using the Healthy Eating Index (HEI) 2015, based on participants' 24-h dietary recall [26]. Physical activity was quantified as minutes of moderate or vigorous weekly exercise. Tobacco and nicotine exposure were evaluated through active consumption and secondhand smoke exposure. Sleep health was measured by total sleep duration. Diabetes status and medication history were obtained via self-reported questionnaires. Anthropometric measurements and blood pressure were assessed during physical examinations. BMI was calculated as weight (kg) divided by height squared (m^2). Blood samples were analyzed at central laboratories for lipid profiles, plasma glucose, and glycated hemoglobin (HbA1c). Each component is scored on a scale of 0–100 based

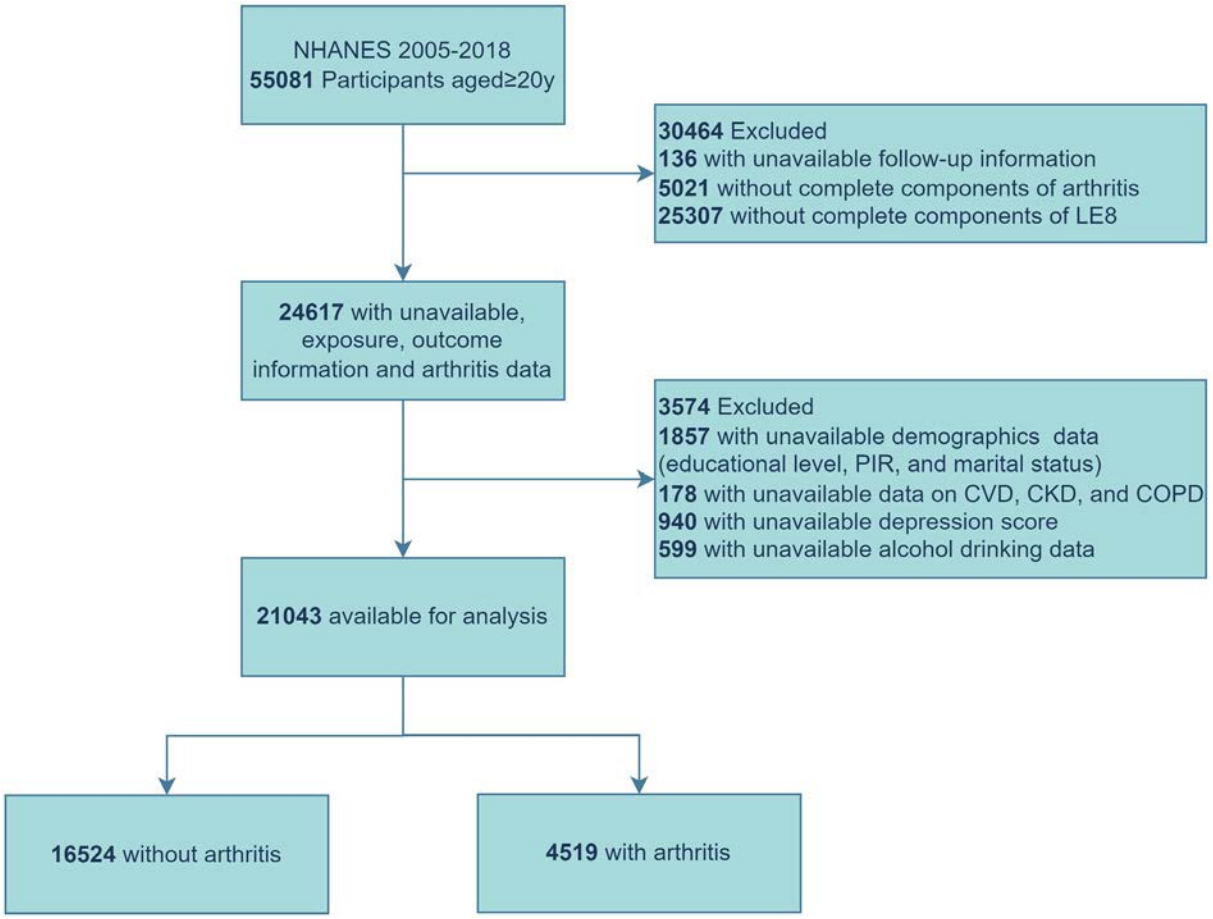

FIGURE 1 | The study's flow diagram. Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; LE8, Life's Essential 8; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio.

on predefined criteria [9]. The detailed scoring algorithms for each LE8 metric in NHANES data are provided in Table S1. The overall LE8 score was computed as the unweighted mean of the eight component scores [12]. Participants were stratified into three CVH categories: high (LE8 scores 80–100), moderate (scores 50–79), and low (scores 0–49).

Arthritis was defined based on self-reported physician diagnosis, assessed through the NHANES questionnaire item: "Has a doctor ever told you that you have arthritis?" This approach has been validated by previous research, demonstrating approximately 85% concordance between self-reported OA and clinically confirmed OA [27, 28]. So, we stratified arthritis into two main categories: OA and other forms of arthritis.

The primary outcomes of this study were all-cause and CVD mortalities. Mortality data were obtained through linkage of the NHANES database with the National Death Index, maintained by the Centers for Disease Control and Prevention (CDC). This linkage, utilizing unique subject identifiers, provided mortality information up to December 31, 2019 (Centers for Disease Control and Prevention. NCHS data linked to mortality files. Accessed August 14, 2023. https://www.cdc.gov/nchs/data_access/data_linkage/mortality.htm). Cause-specific mortality was classified using the International Classification of Diseases, Tenth Revision (ICD-10). CVD mortality was defined according to the NCHS criteria, encompassing deaths attributed to heart disease (ICD-10 codes I00–I09, I11, I13, and I20–I51) and cerebrovascular disease (ICD-10 codes I60–I69).

2.3 | Covariates

NHANES personnel used questionnaires during home interviews to collect information on age, gender, race/ethnicity, education levels, marital status, family income, smoking status, and alcohol consumption. Furthermore, race/ethnicity was classified as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race; education levels were categorized as less than high school, high school or equivalent, college, or above; drinking status was classified by whether ≥ 4 drinks/day; smoking status was categorized as daily, sometimes, and not at all. The definitions of depression, CKD, history of CVD, and COPD are all based on definitions from previously published NHANES-related literature [29, 30].

2.4 | Statistical Analysis

Data were analyzed following CDC guidelines for complex survey designs [31]. Participants were stratified into tertiles based on their CVH scores. Continuous variables are presented as

weighted means ± standard errors (SE), and categorical variables as weighted percentages. Between-group differences were assessed using χ^2 tests for categorical variables and analysis of variance (ANOVA) for continuous variables. The association between CVH levels and arthritis prevalence was examined using weighted logistic regression, adjusting for relevant covariates. Median follow-up time and confidence intervals were calculated using the reverse Kaplan–Meier method. Person-months were computed from study entry to death or the end of follow-up. Cox proportional hazards models were employed to evaluate the relationships between CVH and all-cause and CVD mortality among individuals with arthritis. CVH was analyzed both as a continuous variable (with odds ratio [OR] or hazard ratio [HR] calculated per 10 points increase) and categorically. Three models were constructed: Model 1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, and marital status; Model 3: additionally adjusted for educational level, poverty-income ratio, drinking status, CVD, CKD, COPD, and depression. Kaplan–Meier survival curves were used to estimate survival across CVH groups, with differences assessed by log-rank tests.

To assess the robustness of our findings, we conducted sensitivity analyses in two directions. We first examined whether the associations between LE8 and mortality outcomes differed by arthritis subtypes using separate Cox models for self-reported OA and other arthritis types, as identified through the NHANES Medical Conditions Questionnaire. We then investigated potential effect modifications across population subgroups by incorporating interaction terms into our Cox models. These subgroup analyses stratified participants by age, sex, race, marital status, education level, and the presence of major comorbidities including cardiovascular disease, depression, CKD, and chronic obstructive pulmonary disease.

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.5 | Ethics Statement

This study analyzed publicly available data from the NHANES. The NHANES protocol was approved by the National Center for Health Statistics Research Ethics Review Board, and all participants provided informed consent.

3 | Result

3.1 | Baseline Characteristics of the Study Population

Our study included 21 043 participants from the NHANES 2005–2018 cycles, stratified into three CVH categories based on their LE8 scores: low ($n = 2486$), moderate ($n = 14\,192$), and high ($n = 4365$) CVH (Table 1). Higher CVH status was associated with younger age, a higher proportion of females, better socioeconomic indicators (higher poverty income ratio and educational attainment), and a lower prevalence of comorbidities including depression, CVD, CKD, and COPD (all $p < 0.001$). Notably, the mean total LE8 score was 69.03 ± 0.24, with both health behavior and health factor scores improving across CVH categories ($p < 0.001$). Of particular interest, the prevalence of arthritis decreased significantly from low (37.33%) to high (11.18%) CVH groups ($p < 0.001$). However, among those with arthritis, the proportion of OA increased with improving CVH status (48.9% in low CVH vs. 64.3% in high CVH, $p < 0.001$).

3.2 | Association of LE8 With Arthritis

Table 2 revealed a significant inverse association between CVH scores and the risk of arthritis. For every 10-point increase in the total CVH score, the odds of arthritis decreased by 21% in the fully adjusted model (OR: 0.79, 95% CI: 0.76–0.83, $p < 0.001$). When categorized into CVH subgroups, a clear dose–response relationship was observed. Compared to the low CVH group, participants with moderate CVH had 36% lower odds of arthritis (OR: 0.64, 95% CI: 0.54–0.75, $p < 0.001$), while those with high CVH had 62% lower odds (OR: 0.38, 95% CI: 0.31–0.46, $p < 0.001$) in the fully adjusted model. This trend remained consistent across all three models, from the unadjusted (Model 1) to the fully adjusted model (Model 3), which accounted for various demographic, socioeconomic, and health-related factors. The p for trend was significant ($p < 0.001$) in all models.

Table 3 revealed an inverse association between CVH scores and mortality risks among individuals with arthritis. For all-cause mortality, each 10-point increase in CVH score corresponded to a 17% risk reduction (HR: 0.83, 95% CI: 0.77–0.89, $p < 0.001$), with high CVH participants exhibiting a 38% lower risk compared to those with low CVH (HR: 0.62, 95% CI: 0.41–0.92, $p = 0.019$). The association was even stronger for CVD mortality, where a 10-point CVH score increase was linked to a 25% decrease in risk (HR: 0.75, 95% CI: 0.66–0.85, $p < 0.001$), and high CVH individuals showed a remarkable 62% reduction compared to the low CVH group (HR: 0.38, 95% CI: 0.18–0.80, $p = 0.011$). These relationships persisted after adjusting for multiple confounders and demonstrated a clear dose–response pattern (p for trend < 0.001).

In Figure 2, the Kaplan–Meier survival curves demonstrate a direct association between CVH status and mortality risks in arthritis patients. For both all-cause and CVD mortalities, there is a consistent stratification among the three CVH groups, with the high CVH group showing the highest survival probabilities over time, while the low CVH group exhibits the most significant decline in survival. Notably, the separation of curves begins early and persists throughout the follow-up period. The log-rank test ($p < 0.001$ for both outcomes) confirms statistically significant differences in survival across CVH categories, suggesting the clinical relevance of CVH status in arthritis patients.

3.3 | Subgroup Analyses of CVH and Mortality Risk in Arthritis

Subgroup analysis revealed significant interactions between LE8 score and age, as well as race, in relation to all-cause mortality ($p < 0.05$). For CVD mortality, a significant interaction was

TABLE 1 | Baseline characteristics by CVH score level.

Variables	Total ($n = 21043$)	Low CVH ($n = 2486$)	Moderate CVH ($n = 14192$)	High CVH ($n = 4365$)	p
Age, years Mean ± SE	46.85 (0.26)	53.21 (0.42)	47.96 (0.26)	41.36 (0.41)	< 0.001
Age, *n* (%)					< 0.001
< 40	7393 (35.1)	414 (16.7)	4620 (32.6)	2359 (54)	
40–64	9137 (43.4)	1331 (53.5)	6302 (44.4)	1504 (34.5)	
≥ 65	4513 (21.4)	741 (29.8)	3270 (23)	502 (11.5)	
Sex, *n* (%)					< 0.001
Female	10613 (51.09)	1277 (52.58)	6751 (47.85)	2585 (59.35)	
Male	10430 (48.91)	1209 (47.42)	7441 (52.15)	1780 (40.65)	
Race/ethnicity, *n* (%)					< 0.001
Mexican American	3137 (7.65)	333 (7.13)	2219 (7.99)	585 (6.91)	
Non-Hispanic Black	4168 (9.66)	701 (15.34)	2935 (10.34)	532 (5.61)	
Non-Hispanic White	9780 (71.23)	1112 (67.88)	6558 (70.84)	2110 (73.58)	
Other Hispanic	1872 (4.88)	210 (4.49)	1269 (4.86)	393 (5.07)	
Others	2086 (6.58)	130 (5.16)	1211 (5.96)	745 (8.83)	
Marital status, *n* (%)					< 0.001
Living alone	8156 (34.71)	1127 (40.74)	5360 (34.04)	1669 (34.22)	
Living with a partner or married	12887 (65.29)	1359 (59.26)	8832 (65.96)	2696 (65.78)	
PIR, Mean ± SE	3.12 (0.04)	2.44 (0.06)	3.08 (0.04)	3.51 (0.05)	< 0.001
Education level, *n* (%)					< 0.001
Less than high school	1623 (3.81)	301 (7.12)	1134 (3.91)	188 (2.25)	
High school or equivalent	7459 (31.73)	1202 (47.68)	5363 (35.12)	894 (16.31)	
Above high school	11961 (64.46)	983 (45.20)	7695 (60.97)	3283 (81.44)	
Drinking status, *n* (%)					< 0.001
Never	2714 (10.03)	281 (8.93)	1754 (9.53)	679 (11.80)	
Former	3287 (12.76)	656 (24.11)	2296 (13.42)	335 (6.56)	
Mild	7319 (37.75)	690 (29.82)	4841 (36.61)	1788 (43.93)	
Moderate	3412 (18.26)	332 (15.71)	2225 (17.33)	855 (21.79)	
Heavy	4311 (21.20)	527 (21.42)	3076 (23.11)	708 (15.92)	
Depression, *n* (%)					< 0.001
No	19374 (93.11)	2045 (82.32)	13127 (93.15)	4202 (97.19)	
Yes	1669 (6.89)	441 (17.68)	1065 (6.85)	163 (2.81)	
CVD, *n* (%)					< 0.001
No	18992 (92.29)	1921 (79.51)	12835 (92.14)	4236 (97.63)	
Yes	2051 (7.71)	565 (20.49)	1357 (7.86)	129 (2.37)	
CKD, *n* (%)					< 0.001
No	17644 (87.03)	1663 (71.15)	11933 (87.09)	4048 (93.02)	

(Continues)

TABLE 1 | (Continued)

Variables	Total ($n = 21\,043$)	Low CVH ($n = 2486$)	Moderate CVH ($n = 14\,192$)	High CVH ($n = 4365$)	p
Yes	3399 (12.97)	823 (28.85)	2259 (12.91)	317 (6.98)	
COPD, *n* (%)					< 0.001
No	20 109 (95.80)	2232 (89.76)	13 565 (95.55)	4312 (98.82)	
Yes	934 (4.20)	254 (10.24)	627 (4.45)	53 (1.18)	
AHA LE8 scores, mean (SE)					
Total CVH score	69.03 (0.24)	42.33 (0.18)	66.29 (0.12)	86.84 (0.11)	< 0.001
Health behaviors score	67.15 (0.32)	39.36 (0.45)	64.70 (0.23)	84.58 (0.23)	
Diet score, Median (IQR)	39.56 (0.46)	20.11 (0.56)	35.04 (0.45)	59.42 (0.66)	< 0.001
PA score, Median (IQR)	73.19 (0.49)	28.44 (1.19)	71.94 (0.56)	93.92 (0.37)	< 0.001
Nicotine exposure score, Median (IQR)	71.85 (0.52)	42.05 (1.17)	68.61 (0.54)	92.19 (0.41)	< 0.001
Sleep health score, Mean ± SD	84.00 (0.29)	66.85 (0.84)	83.20 (0.29)	92.81 (0.31)	< 0.001
Health factors score	70.91 (0.25)	45.29 (0.39)	67.87 (0.20)	89.10 (0.21)	
BMI score, Median (IQR)	61.21 (0.44)	31.16 (0.77)	56.56 (0.41)	85.52 (0.46)	< 0.001
Blood lipids score, Median (IQR)	64.63 (0.35)	41.75 (0.83)	61.00 (0.39)	83.38 (0.51)	< 0.001
Blood glucose score, Mean ± SD	86.98 (0.25)	61.81 (0.81)	86.59 (0.26)	97.80 (0.20)	< 0.001
BP score, Median (IQR)	70.81 (0.35)	46.45 (0.71)	67.34 (0.39)	89.71 (0.40)	< 0.001
Arthritis, *n* (%)					< 0.001
No	16 524 (79.22)	1535 (62.67)	11 067 (78.06)	3922 (88.82)	
Yes	4519 (20.78)	951 (37.33)	3125 (21.94)	443 (11.18)	
Arthritis Type, *n* (%)					< 0.001
Osteoarthritis	2503 (55.4)	465 (48.9)	1753 (56.1)	285 (64.3)	
Others	2016 (44.6)	486 (51.1)	1372 (43.9)	158 (35.7)	

Note: CVH scores range from 0 to 100 and are classified into low CVH (0–49), moderate CVH (50–79), and high CVH (80–100).
Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVH, cardiovascular health; PIR, poverty income ratio.

observed only with age. No interactions were observed between LE8 score and sex, marital status, poverty-income ratio, education level, depression, CVD, CKD, or COPD in either group (Table S2).

3.4 | Sensitivity Analyses

Sensitivity analyses reinforced our primary findings. By dividing arthritis into OA and other types, we found the same conclusions: after adjusting for multiple confounders, each 10-point increase in CVH score was associated with a reduction in all-cause mortality risk of 16% and 20% in the two groups, respectively (Tables S3 and S4). A similar association was observed for CVD mortality (OA: HR: 0.73, 95% CI: 0.63–0.86, $p < 0.001$, other: HR: 0.78, 95% CI: 0.63–0.96, $p = 0.021$). The Kaplan–Meier survival curves for both groups also demonstrated that the high CVH group had the highest survival probability over time, while the low CVH group showed the most significant decline in survival. The log-rank test ($p < 0.001$ for both outcomes) confirmed statistically significant differences in survival across CVH categories (Figure S1).

4 | Discussion

In this large, population-based retrospective cohort study, the results demonstrate that higher LE8 scores are significantly associated with reduced risks of all-cause and CVD mortalities among US adults with arthritis. These associations remain robust after adjusting for a wide range of potential confounders, underscoring the independent protective effect of optimal CVH in this population.

TABLE 2 | Association between Life's Essential 8 and the risk of Arthritis.

Variable	Cases/ participants (%)	Model 1 OR (95% CI)	*p*	Model 2 OR (95% CI)	*p*	Model 3 OR (95% CI)	*p*
Total CVH score (per 10-unit increase)	4519/21 043 (21.5)	0.7 (0.68–0.73)	< 0.001	0.76 (0.73–0.79)	< 0.001	0.79 (0.76–0.83)	< 0.001
Subgroups							
Low CVH	951/2486 (38.3)	1 (Ref)		1 (Ref)		1 (Ref)	
Moderate CVH	3125/14 192 (22.0)	0.47 (0.41–0.55)	< 0.001	0.55 (0.47–0.64)	< 0.001	0.64 (0.54–0.75)	< 0.001
High CVH	443/4365 (10.1)	0.21 (0.18–0.25)	< 0.001	0.31 (0.25–0.37)	< 0.001	0.38 (0.31–0.46)	< 0.001
p for Trend			< 0.001		< 0.001		< 0.001

Note: Model 1: Crude model. Model 2: Adjusted for age, sex, race/ethnicity, and marital status. Model 3: Adjusted for age, sex, race/ethnicity, marital status, educational level, PIR, drinking status, CVD history, CKD, COPD, and depression. Total CVH score was entered as a continuous variable per 10 points increase. CVH scores range from 0 to 100 and are classified into low CVH (0–49), moderate CVH (50–79), and high CVH (80–100).
Abbreviations: CI, confidence interval; CVH, cardiovascular health; OR, odd ratio.

TABLE 3 | Association of Life's Essential 8 with all-cause and CVD mortality in Arthritis.

Variable	Cases/ participants (%)	Model 1 HR (95% CI)	*p*	Model 2 HR (95% CI)	*p*	Model 3 HR (95% CI)	*p*
All-cause mortality							
Total CVH score	793/4519 (17.5)	0.77 (0.73–0.83)	< 0.001	0.73 (0.68–0.78)	< 0.001	0.83 (0.77–0.89)	< 0.001
Subgroups							
Low CVH	213/951 (22.4)	1(Ref)		1(Ref)		1(Ref)	
Moderate CVH	533/3125 (17.1)	0.62 (0.50–0.79)	< 0.001	0.53 (0.43–0.66)	< 0.001	0.75 (0.60–0.95)	0.015
High CVH	47/443 (10.6)	0.37 (0.26–0.53)	< 0.001	0.33 (0.23–0.47)	< 0.001	0.62 (0.41–0.92)	0.019
p for trend			< 0.001		< 0.001		0.009
CVD mortality							
Total CVH score	213/3939 (5.4)	0.71 (0.63–0.79)	< 0.001	0.63 (0.57–0.71)	< 0.001	0.75 (0.66–0.85)	< 0.001
Subgroups							
Low CVH	70/808 (8.7)	1(Ref)		1(Ref)		1(Ref)	
Moderate CVH	132/2724 (4.8)	0.41 (0.29–0.57)	< 0.001	0.31 (0.23–0.44)	< 0.001	0.47 (0.33–0.67)	< 0.001
High CVH	11/407 (2.7)	0.21 (0.10–0.45)	< 0.001	0.18 (0.09–0.35)	< 0.001	0.38 (0.18–0.80)	0.011
p for trend			< 0.001		< 0.001		< 0.001

Note: Model 1: Crude model. Model 2: Adjusted for age, sex, race/ethnicity, and marital status. Model 3: Adjusted for age, sex, race/ethnicity, marital status, educational level, PIR, drinking status, CVD history, CKD, COPD, and depression. Total CVH score was entered as a continuous variable per 10 points increase. CVH scores range from 0 to 100 and are classified into low CVH (0–49), moderate CVH (50–79), and high CVH (80–100).
Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio.

Our findings extend previous observations of inverse associations between CVH metrics and mortality outcomes in general populations to individuals with arthritis, a group known to have elevated cardiovascular risk [32, 33]. Notably, individuals in the highest CVH tertile exhibited a 38% lower risk of all-cause mortality and a 62% lower risk of CVD mortality compared to those in the lowest tertile. These substantial risk reductions highlight the potential for CVH improvement to mitigate mortality risk in this vulnerable population, despite the challenges posed by pain, functional limitations, and potential side effects of arthritis treatments.

Several mechanisms may underlie these observed associations. The components of the LE8 metrics, including physical activity,

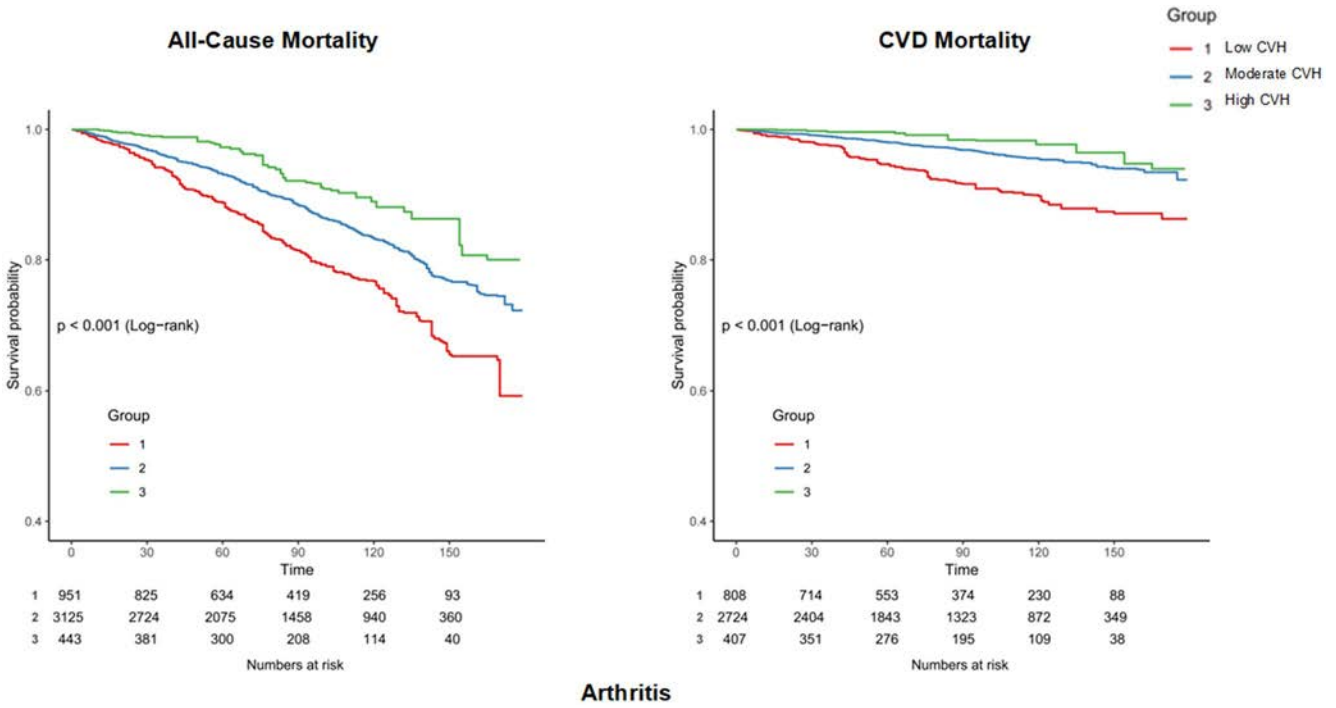

FIGURE 2 | Kaplan–Meier survival curve for all-cause and CVD mortality of individuals.

diet, and sleep duration, likely exert direct beneficial effects on cardiovascular function and overall health [34–37]. Additionally, improved CVH may attenuate the systemic inflammation associated with arthritis, a known contributor to cardiovascular risk [38, 39]. Furthermore, enhanced CVH may bolster individuals' capacity to manage the physical and psychological challenges of arthritis, potentially leading to improved overall health outcomes. Further mechanistic studies are warranted to elucidate these underlying pathways.

Our study's strengths include the use of data from the NHANES, which is a large, nationally representative dataset, enhancing the generalizability of our findings [40]. The comprehensive LE8 metrics provided a nuanced assessment of CVH, capturing the multifaceted nature of cardiovascular risk in individuals with arthritis [41]. Moreover, our analysis adjusted for a wide range of potential confounders, including demographic characteristics and comorbidities, reinforcing the robustness of our results.

Despite these strengths, several limitations merit consideration. The observational nature of our study precludes causal inferences regarding the relationship between LE8 scores and mortality outcomes. Despite adjusting for multiple confounding factors, potential residual confounding from unmeasured variables cannot be ruled out, limiting our ability to establish causality. Future prospective cohort studies and randomized controlled trials focusing on LE8 components in arthritis patients could help establish causality while accounting for this population's unique challenges, such as mobility limitations and pain management needs. The assessment of LE8 scores at baseline, without accounting for potential temporal changes in CVH status, may have led to some exposure misclassification. Additionally, the reliance on self-reported arthritis diagnosis might have introduced misclassification bias, potentially affecting the precision of our estimates. However, the consistency of our findings across different arthritis subtypes suggests that this limitation is unlikely to have substantially altered our main conclusions. Several external factors may have influenced our findings. Although we adjusted for the poverty–income ratio and education level, other socioeconomic factors such as neighborhood environment and healthcare accessibility could affect CVH maintenance in our study population. Arthritis patients face additional challenges in healthcare utilization, which might influence both their CVH metrics and mortality outcomes. Further research incorporating more comprehensive socioeconomic and healthcare access data would enhance our understanding of these relationships. Lastly, while our median follow-up of 5.83 years provided valuable insights into medium-term mortality risks, longer-term studies may be necessary to fully elucidate the impact of CVH on life expectancy in individuals with arthritis.

5 | Conclusion

The current study demonstrates a significant association between higher LE8 scores and lower risks of all-cause and cardiovascular mortality in the US adult population with arthritis. These findings underscore the importance of promoting CVH in individuals with arthritis and offer a novel perspective on early prevention and management strategies for this high-risk group.

Author Contributions

F.Y. and J.Z. collected and analyzed the data, and wrote the first draft. X.L. and M.S. participated in managing the research and agreed to the final version of the manuscript. T.L. and J.Z. designed the study. T.L.,

J.Z., and P.-C.S. critically revised the paper and approved the final version. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Publicly available datasets are available online for this study. The repository/repositories name and accession numbers are available online at http://www.cdc.gov/nchs/nhanes.htm

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Supporting Information

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

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LETTER TO THE EDITOR

Reduced Health-Related Quality of Life in Patients With Systemic Sclerosis: A Cross-Sectional Analysis of PROMIS Global Health Data From the International COVAD-2 e-Survey

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Dear Editor,

Systemic sclerosis (SSc) is a multisystem disorder characterized by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy [1–3]. SSc is associated with altered physical function, pain, and psychological consequences including depression and anxiety [4–7], leading to impaired health-related quality of life (HRQoL) [8]. However, there remains an unmet need for a thorough evaluation of the HRQoL status and its determinants in SSc patients.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centered measures that evaluate and monitor physical, mental, and social health in individuals living with or without chronic conditions [9]. As for HRQoL, PROMIS global physical health (GPH) and global mental health (GMH) scores have demonstrated favorable reliability in evaluating physical and mental health [10]. In this study, we investigated PROMIS GMH and GPH scores in a global cohort of patients with SSc compared to those with non-SSc autoimmune inflammatory rheumatic diseases (AIRDs), non-rheumatic autoimmune diseases (nrAIDs), and individuals without autoimmune diseases using PROMIS global health data obtained through the second COVID-19 vaccination in autoimmune disease (COVAD-2) survey.

The complete list of authors part of the COVAD Study Group, as well as their affiliations, are provided in Supporting Information.

Vikas Agarwal and Masataka Kuwana are co-senior authors.

The COVAD-2 study is an international, multicenter, self-reported e-survey designed to evaluate several facets covering COVID-19 infection and vaccination as well as validated patient-reported outcome measures (PROMs) in a variety of autoimmune diseases including SSc, which was conducted between February and June 2022. The detailed study design was published elsewhere [11]. Data on demographics, diagnosis of autoimmune diseases including the subtypes of SSc [12], clinical characteristics, patient-reported disease activity assessed using a 4-point scale (inactive, active but stable, active and improving, active and worsening), and PROMs including PROMIS global health items were extracted from the COVAD-2 database. The COVAD-2 survey form questions relevant to the present study are presented in Table S1. Respondents were divided into four disease groups: SSc, non-SSc AIRDs, nrAIDs, and those without autoimmune diseases (controls). Comorbidities were grouped into several categories to avoid extreme sparsity in the design matrix (Figure S1).

The primary outcomes were PROMIS GPH and GMH scores calculated using PROMIS global health items as previously described [10], in which higher scores indicated better HRQoL. Secondary outcomes included PROMIS Short Form v2.0 Physical Function-10a (PROMIS PF-10a), pain visual analog scale (VAS), and PROMIS Short Form v1.0 Fatigue 4a (PROMIS Fatigue-4a) scores. Higher PROMIS PF-10a scores indicate better physical function, while higher PROMIS Fatigue-4a scores suggest increased fatigue. Continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (25%–75%) as appropriate, whereas categorical variables were reported as frequencies with proportions. We employed analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the chi-square test or Fisher's exact tests for categorical variables, respectively. *p*-values were adjusted using Dunnett's test for continuous variables and the Bonferroni method for categorical variables where we performed multiple comparisons. Demographics, clinical characteristics, and PROMs were compared between SSc and the other three disease groups, followed by stratification according to SSc phenotype. Factors associated with lower PROMIS GPH or GMH scores in SSc patients were identified using multivariable regression analysis. Along with clinical context, we employed the least absolute shrinkage and selection operator (LASSO) regression to address multicollinearity and select the optimal set of variables incorporated into multivariable models. Variables with non-zero coefficients in the LASSO regression model were incorporated into multivariable models. A linear regression model was employed to perform multivariable analysis. As for variables with more than 10% of missing data, we performed a sensitivity analysis excluding the variables.

A total of 9277 responses from 261 SSc, 5441 non-SSc AIRD, 465 nrAID patients, and 3110 controls as of May 2022 were included in the analysis (Figure S2). Rheumatoid arthritis (32.4%) was the most common non-SSc AIRD, followed by systemic lupus erythematosus (22.6%) and idiopathic inflammatory myopathies (17.7%). In terms of nrAIDs, autoimmune thyroid disease (58.7%) was the most common, followed by inflammatory bowel disease (21.9%) and type 1 diabetes (10.1%). Table S2 summarizes the demographics and clinical characteristics of participants in each disease group. Patients with SSc reported a higher prevalence of interstitial lung disease (ILD) and treatment with mycophenolate mofetil (MMF) compared to those in other disease groups ($p < 0.001$). Among the SSc group, diffuse cutaneous SSc (dcSSc) patients accounted for 46% and received MMF more frequently than those with limited cutaneous SSc (lcSSc) ($p < 0.001$) (Table S3).

Patients with SSc had lower GPH median scores compared to those with nrAIDs or controls (SSc: 13 [IQR 11–15] vs. non-SSc AIRDs: 13 [11–15] vs. nrAIDs: 15 [13–17] vs. controls: 17 [15–18], $p < 0.001$) (Figure 1A). The GMH median scores were also lower in SSc compared to nrAIDs or controls (SSc: 13 [IQR 10–15] vs. non-SSc AIRDs: 13 [10–15] vs. nrAIDs: 13 [11–16] vs. controls: 15 [13–17], $p < 0.001$) (Figure 1B). SSc was independently associated with lower PROMIS GPH and GMH scores in the entire cohort when adjusted for demographics and comorbidities (Table S4). Consistent with these findings, patients with SSc reported lower PROMIS PF-10a median scores (Figure 1C) and higher median pain VAS (Figure 1D) and PROMIS Fatigue-4a scores (Figure 1E) compared to those with nrAIDs or controls.

When stratified by SSc subtypes, PROMIS GPH (dcSSc: 12 [IQR 10–14] vs. lcSSc: 14 [11–16], $p < 0.001$) (Figure 2A) and PROMIS GMH (dcSSc: 12 [IQR 10–14] vs. lcSSc: 13 [10–15], $p = 0.013$) (Figure 2B) median scores were lower in dcSSc than in lcSSc. PROMIS PF-10a median scores (Figure 2C) were lower, whereas pain VAS (Figure 2D) and PROMIS Fatigue-4a (Figure 2E) median scores were higher in dcSSc.

Multivariable regression analyses were performed to identify factors independently associated with PROMIS GPH or GMH scores in SSc patients. The independent factors for lower PROMIS GPH scores in SSc included dcSSc subtype ($p = 0.046$), mental disorder ($p < 0.001$), disease activity (active and getting worse) ($p = 0.003$), and low- or medium-dose glucocorticoid (GC) use (prednisolone/prednisone-equivalent dose of < 10 mg/day: $p < 0.001$; 10–20 mg/day: $p = 0.001$) (Table S5A). On the other hand, longer disease duration ($p = 0.044$) and higher PROMIS Fatigue-4a scores ($p < 0.001$) were identified as independent factors for lower PROMIS GMH scores in SSc (Table S5B). We also performed sensitivity analyses excluding disease activity from covariates, considering more than 10% of missing data in patient-reported disease activity. The independent factors associated with lower PROMIS GPH scores or GMH scores were largely consistent with the primary analysis (Table S6A,B).

Our large-scale, global e-survey demonstrated that both mental and physical health were significantly impaired in SSc patients compared to those with nrAIDs or those without autoimmune diseases, and the level of impairment was comparable to those with non-SSc AIRDs. Patients with dcSSc had significantly lower PROMIS GPH and GMH scores than those with lcSSc, indicating considerable impairment of HRQoL in dcSSc, which is consistent with a previous report [13]. Factors associated with lower PROMIS GPH scores in SSc patients included dcSSc subtype, mental disorders, and GC use. On the other hand, only higher PROMIS Fatigue-4a scores were associated with lower PROMIS

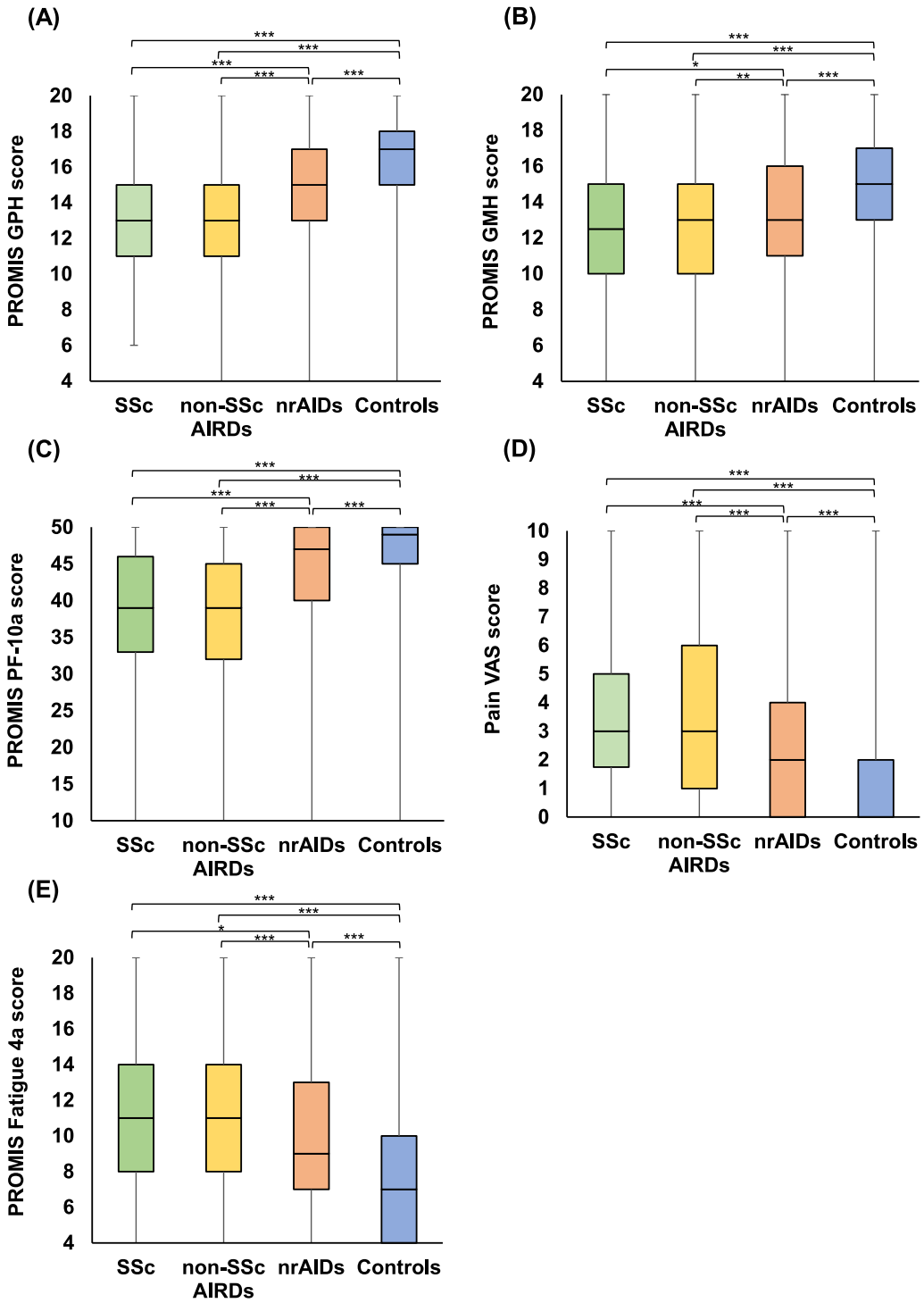

FIGURE 1 | Patient-reported outcomes in each disease group. (A) PROMIS GPH score†, (B) PROMIS GMH score††, (C) Pain VAS, (D) PROMIS PF-10a score, (E) PROMIS Fatigue-4a score, $*p<0.05$, $**p<0.01$, $***p<0.001$; AIRDs, autoimmune inflammatory rheumatic diseases; GMH, global mental health; GPH, global physical health; nrAIDs, non-rheumatic autoimmune inflammatory diseases; PF, physical function; PROMIS, Patient-Reported Outcome Measurement Information System; SSc, systemic sclerosis; VAS, visual analog scale.

GMH scores in SSc, suggesting that fatigue is the major determinant of impaired mental health and needs greater attention to optimize mental health in SSc.

Our study has the advantage of being the first, global evaluation of PROMIS global health items in SSc patients using the large-scale international COVAD-2 database. Our study has several limitations. First, we acknowledge selection bias owing to convenience sampling, as well as information bias inherent to self-reported e-surveys. Given the fluctuating disease course and inter-individual variability in disease perception, subjective bias could have affected the patient-reported disease activity. Moreover, although PROMIS-29 demonstrated reliability and construct validity in a cohort of SSc-ILD patients [14], PROMIS GPH, GMH, PF-10a, and Fatigue-4a short forms have not been validated in an academic cohort of SSc. Second, organ involvement in SSc

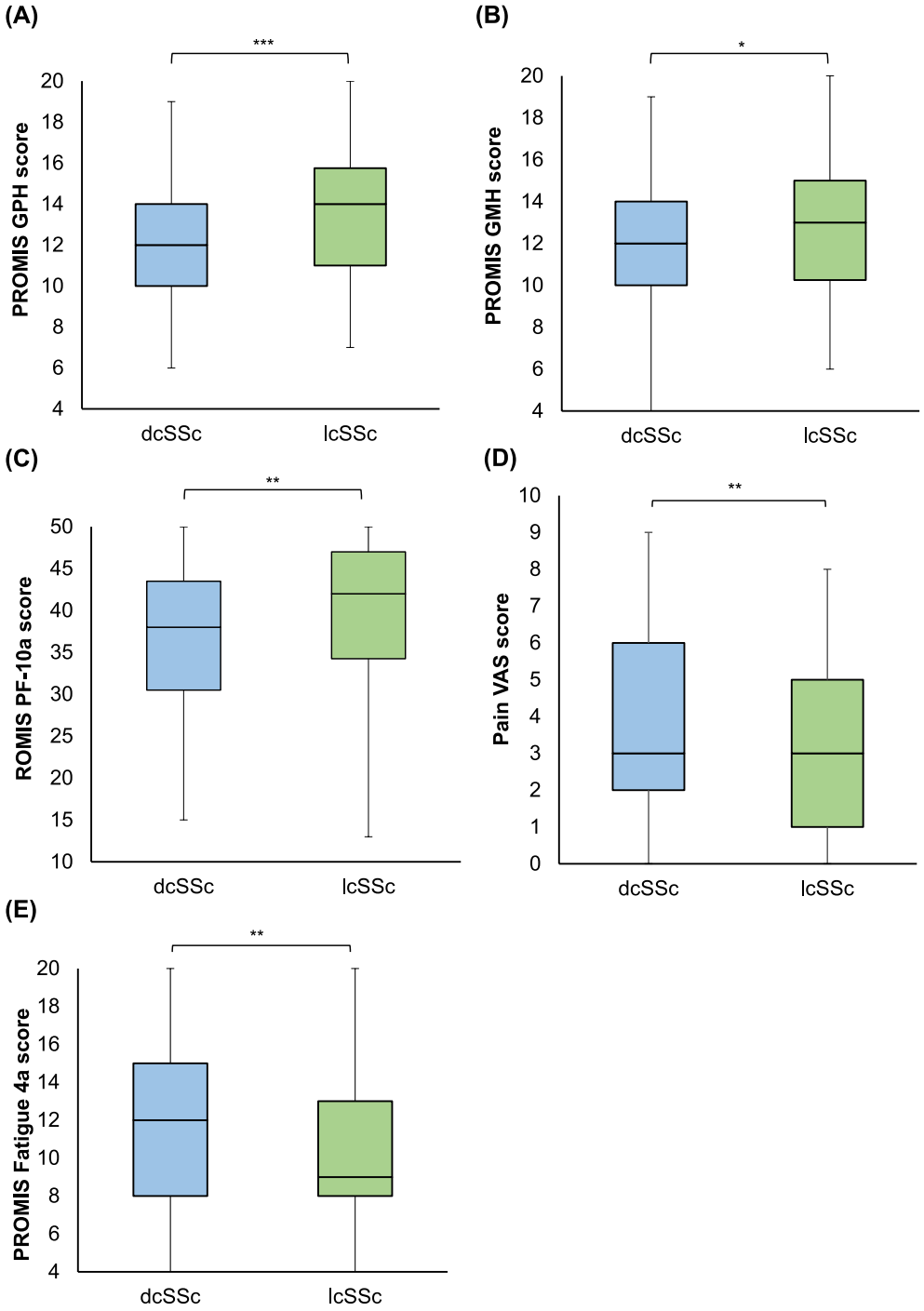

FIGURE 2 | Patient-reported outcomes stratified by SSc subtypes. (A) PROMIS GPH score†, (B) PROMIS GMH score††, (C) Pain VAS, (D) PROMIS PF-10a score, (E) PROMIS Fatigue-4a score, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; AIRDs, autoimmune inflammatory rheumatic diseases; GMH, global mental health; GPH, global physical health; nrAIDs, non-rheumatic autoimmune inflammatory diseases; PF, physical function; PROMIS, Patient-Reported Outcome Measurement Information System; SSc, systemic sclerosis; VAS, visual analog scale. †PROMIS GPH score is the sum of Global03 (physical health), Global06 (physical function), Global07 (pain), and Global08 (fatigue). ††PROMIS GMH score is the sum of Global02 (quality of life), Global04 (mental health), Global05 (satisfaction with social activities), and Global10 (emotional problems).

was not evaluated except for ILD. Furthermore, SSc respondents were at relatively late disease stages with a median disease duration of 9 years, and our results might not be generalizable to those with early SSc. Our findings need to be verified in a large, international, multicenter cohort comprising SSc patients with various disease duration and organ involvement.

In conclusion, both physical and mental health are significantly impaired in SSc patients, especially in those with dcSSc and increased fatigue. Our study is pioneering in assessing the HRQoL and its determinants in SSc patients globally using PROMIS global health items, which underscores the importance of patient-reported experiences including fatigue and warrants

future studies to investigate targeted interventions in high-risk populations to improve overall well-being in SSc patients.

Author Contributions

K.Y., A.Y., Y.L., V.M., N.R., and L.G. conceptualized the study. All authors contributed to the data curation. K.Y., A.Y., Y.L., V.M., N.R., Vik.A., and L.G. conducted the formal data analysis. P.S. and L.G. were responsible for the project administration. A.M., M.K., Vik.A. and L.G. supervised the study. K.Y., Y.L., V.M., and L.G. drafted the original letter. All authors reviewed and approved the final version of the letter for publication.

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Ethics Statement

Informed consent was obtained from all respondents electronically at the beginning of the survey form before proceeding with the questions. The COVAD study was approved by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences (IEC code: 2021-143-IP-EXP-39) and performed in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors have relevant financial activities as follows: M.K., speaker honoraria/participated in advisory boards for Abbvie, Asahi-Kasei, Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai, Corbus, Eisai, GSK, Horizon, Kissei, BML, Mochida, Nippon Shinyaku, Ono Pharmaceuticals, Tanabe-Mitsubishi; T.V., speaker honoraria from Pfizer and AstraZeneca. The other authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article is available from the corresponding author upon reasonable request.

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Supporting Information

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

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ORIGINAL ARTICLE

Fracture Risk Linked to Proton Pump Inhibitors Versus H2 Receptor Antagonists in Autoimmune Rheumatic and Gastrointestinal Disease Patients

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ABSTRACT

Objective: To understand if proton pump inhibitors (PPIs) usage associated with an increased risk of fractures among adult patients diagnosed with autoimmune rheumatic and gastrointestinal diseases, compared with H2 receptor antagonists (H2RAs) usage.

Methods: We used the TriNetX US collaborative database for the study, which includes detailed demographic information, diagnostic and procedural data, medication details, laboratory results, genomic information, and healthcare utilization metrics. We analyzed 61 healthcare organizations to compare fracture risks associated with PPIs and H2RAs in adults, particularly those diagnosed with autoimmune rheumatic and gastrointestinal diseases. Propensity score matching acted as a control for demographic and clinical variables.

Results: The study involved 1 717 598 patients, focusing on 16 299 who were new users of PPIs and 16 299 H2RAs users after propensity score matching. Over a 24-month follow-up period, no significant differences in fracture risks were observed between the PPI and H2RA groups in the overall cohort (hazard ratio, HR = 1.369, 95% confidence interval, CI = 0.933–2.009). However, subgroup analysis indicated that senior patients (≥ 65 years) who had been administered PPIs experienced a significantly higher risk of fractures (HR = 1.927 [1.153–3.221]), particularly non-vertebral fractures (HR = 2.379 [1.214–4.661]), when compared to their counterparts who had been prescribed H2RAs. Notably, the simultaneous use of PPIs and glucocorticoids further increased the fracture risk (HR = 4.273 [2.219–8.227]).

Conclusions: The study demonstrates that patients diagnosed with autoimmune rheumatic and gastrointestinal diseases who were aged 65+ face increased fracture risks when using PPIs, particularly when there is a simultaneous intake of glucocorticoids.

Miaoyu Zeng and Shiow-Ing Wang contributed equally for this work.

Summary

- Practitioner points
  - Higher fracture risk is noticed among older adults using PPIs compared to H2 receptor antagonists (H2RAs).
  - Concurrent use of glucocorticoids significantly increases the risk of fractures in PPI users.
  - Provides a comparison between PPIs and H2RAs in patients with autoimmune rheumatic and gastrointestinal diseases.

1 | Introduction

The impact of osteoporosis and its associated conditions is of substantial concern in the medical field. In the Unites States alone, approximately 10 million individuals aged 50 and older were reported to have osteoporosis, and an additional 43.3 million people were identified as having low bone mass [1]. Previous reports have demonstrated that older adults with osteoporosis experienced increased risks of suffering from depression [2], sarcopenia and frailty [3], infection and sepsis [4], osteoporotic fracture-related functional impairment [5], and even mortality [6]. Although there are effective drugs for the primary and secondary prevention of osteoporosis [7], it is important to mitigate the risks and consequences associated with the condition. Previous research has reported on the numerous dietary risk factors of osteoporosis, including alcohol consumption [8], malnutrition [9], and Vitamin D deficiency [10].

Other than diet, medication is another potential risk factor for developing of osteoporosis. There are many medications related to osteoporosis and further fractures, including glucocorticoids [11], anticonvulsants [12], thiazolidinediones (TZD) [13], selective serotonin reuptake inhibitors [14], chemotherapy, and aromatase inhibitors [15]. Recently, the question has been raised as to whether very commonly used popular drugs such as proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs) also have negative effects on bone health in middle-aged and older adults.

PPIs and H2RAs are each effective for the treatment of esophageal and gastric diseases, such as gastritis, peptic ulcer or gastroesophageal reflux disease (GERD). Both medications are popular prescriptions for older adults while PPIs are assumed to be more effective than H2RAs. However, there is concern that the two have negative effects on bone health. The first report of an association between PPI and fracture was published in 2006, and revealed that long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture [16]. In 2010, Gray et al. demonstrated that PPI use was also modestly associated with clinical spine, forearm or wrist, and total fractures [17]. An updated systematic review and meta-analysis performed by Nassar and Richter suggested that PPI use may increase fracture risk. However, there was no effect seen in PPI use on BMD [18]. For H2RA, a study using a UK primary care research database demonstrated an increased risk of fracture with the use of high H2RA doses [19]. Only a few studies have reported on a comparison of fracture risk between PPIs and H2RAs. Using a UK database, Wei et al. discovered that the initiation of PPIs was associated with a higher risk of hip fracture than the initiation of H2RA [20]. However, in a study conducted by Wang et al., the analysis of PPIs versus H2RAs did not reach statistical significance for risk of fracture among a child cohort [21].

As the world population is rapidly aging, prompt choice of medication among certain groups of patients, such as older adults, patients of different races or regions, or patients with multimorbidity and polypharmacy, is more important than before. Therefore, the principal research questions of our study were: (1) Compared with H2RAs, is PPI usage associated with an increased risk of fractures among adult patients diagnosed with autoimmune rheumatic and gastrointestinal diseases? (2) Is there any susceptible group for developing fractures while under the use of PPIs and H2RAs? We employed a retrospective study design analyzing data taken from the TriNetX dataset which includes 61 global healthcare organizations in order to answer these two important questions.

2 | Methods

2.1 | Data Source

Data for this study were obtained from the TriNetX US Collaborative Network, which encompasses 61 healthcare organizations. The TriNetX database, a major global clinical research platform, offers real-time access to comprehensive medical records. This database includes detailed demographic information, diagnostic and procedural data, medication details, laboratory results, genomic information, and healthcare utilization metrics. Previous research has extensively described the data included in this database [22]. In this investigation, the US Collaborative Network within TriNetX facilitated the establishment of a cohort comprising over 92 million participants.

2.2 | Participants

Between January 1, 2015, and December 31, 2022, a total of 1 717 598 patients diagnosed with autoimmune rheumatic and gastrointestinal diseases and being older than 18 years of age were identified from a larger cohort of 79 534 491 participants within the US Collaborative Network. The inclusion criteria led to the preliminary exclusion of several subgroups: (1) 869 083 participants who had never been prescribed either PPIs or H2 receptor antagonists (H2RAs) following their diagnosis of autoimmune rheumatic and gastrointestinal diseases; and (2) 520 630 participants who had received either PPIs or H2RAs prior to their initial autoimmune disease diagnosis. Additionally, two specific groups were selected for further analysis: 153 528 patients who were administered PPIs and 74 586 patients who received H2RAs during the study period. The index date was established as the date of first administration of either PPIs or H2RAs.

Subsequently, exclusions were made for participants who were not new users, those who had switched treatments, those who had suffered injuries or other external causes post-index date, those who were younger than 18 years at the index date, and those who

had experienced fractures or were deceased by the index date. Following these exclusions, the final analysis included 49 793 patients in the PPI group and 16 303 in the H2RA group.

2.3 | Study Variables

2.3.1 | Autoimmune Rheumatic Disease

The study encompassed a broad range of autoimmune rheumatic and gastrointestinal diseases, categorized as follows:

1. Inflammatory arthritis, which included rheumatoid arthritis [ICD-10: M05-M06] and ankylosing spondylitis [ICD-10: M45].
2. Connective tissue related conditions, encompassing vasculitis [ICD-10: M30, M31, L95], psoriasis [ICD-10: L40], systemic lupus erythematosus [ICD-10: M32], dermatomyositis/polymyositis [ICD-10: M33], systemic sclerosis [ICD-10: M34], Sjögren's syndrome [ICD-10: M35.0], mixed connective tissue disease [ICD-10: M35.1], Behçet's disease [ICD-10: M35.2], and polymyalgia rheumatica [ICD-10: M35.3].
3. Autoimmune gastrointestinal diseases, which included inflammatory bowel disease [ICD-10: K50-K52] and celiac disease [ICD-10: K90.0]. These classifications facilitated the structured investigation of disease patterns and treatment outcomes within the cohort.

2.4 | Covariates

In this investigation, propensity score matching (PSM) was employed to systematically stratify the study cohort based on multiple variables, ensuring a balanced comparison between groups. The stratification included demographic factors such as age, gender, and race; socioeconomic conditions as indicated by ICD-10-CM codes Z55-Z65; and a range of medical conditions including arterial hypertensive diseases [ICD-10-CM: I10-I16], ischemic heart diseases [ICD-10-CM: I20-I25], cerebrovascular diseases [ICD-10-CM: I60-I69], diseases of the arteries, arterioles, and capillaries [ICD-10-CM: I70-I79], chronic lower respiratory diseases [ICD-10-CM: J40-J47], type 2 diabetes mellitus [ICD-10-CM: E08-E13], chronic kidney disease [ICD-10-CM: N18], liver diseases [ICD-10-CM: K70-K77], disorders of lipoprotein metabolism and other dyslipidemias [ICD-10-CM: E78], obesity [ICD-10-CM: E66], vitamin D deficiency [ICD-10-CM: E55], malnutrition [ICD-10-CM: E40-E46], dementia [ICD-10-CM: F00-F03], and anemia [ICD-10-CM: D60-D64]. Additional considerations included medication usage (e.g., bisphosphonates, calcium supplements, magnesium supplements, NSAIDs, HMG-CoA reductase inhibitors, aspirin/acetylsalicylic acid, sex hormones, opioids, diuretics and glucocorticoids), lifestyle factors (such as tobacco use, nicotine dependence, alcohol-related disorders and mobility-related issues), surgical procedures, medical utilization (encompassing ambulatory, preventive, emergency and inpatient treatments), and certain biochemical markers related to bones (such as Calcium, Magnesium, Phosphate, Cobalamin, and Calcidiol), estimate glomerular filtration rate (eGFR), C reactive protein (CRP), and body mass index (BMI). All these variables were collected within 1 year prior to the index date, facilitating a comprehensive 1:1 matched analysis based on these criteria.

2.5 | Outcomes

The outcomes of the study included incidence of four groups of fractures: any fractures, vertebral fracture, non-vertebral fracture and fracture of the hip/femur/pelvis, which were assessed from the index date to the end of follow-up (lasting 24 months). All types of fractures in the study are defined in Table S1.

2.6 | Statistical Analyses

A built-in PSM was employed to create groups with matched baseline characteristics using a greedy nearest neighbor matching approach, with a caliper set at 0.1 pooled standard deviation. We used PSM to match the two groups at a fixed 1:1 ratio by age, gender, race, socioeconomic status, comorbidities, procedures, lifestyle factors, medication use and medical utilization. Standardized mean differences (SMD) were used to evaluate the balance of baseline characteristics in populations. In general, an SMD < 0.1 is considered a small difference. After PSM, a built-in Kaplan–Meier analysis was employed to assess the incidence of outcomes, while the log-rank test was utilized for significance testing. Additionally, a built-in Cox proportional hazard model was applied to estimate the hazard ratios between the PPI and H2RA groups. The hazard ratio (HR) for all groups of fractures was calculated. Statistical significance was evaluated using the 95% confidence interval (95% CI).

Subgroup analyses were performed to investigate how the risks of fracture outcomes in patients with autoimmune rheumatic and gastrointestinal diseases differed with respect to gender, age, use of glucocorticoids, and autoimmune disease groups. We also performed subgroup analysis among PPI users with glucocorticoids versus PPI users without glucocorticoids. Owing to the different prevalence of gastric diseases, such as gastric ulcer, gastritis or GERD, PPIs and H2RAs are more widely prescribed in Asian countries. Therefore, we performed sensitivity analysis in both the global network and APAC network, including 10 large healthcare organizations (HCOs) across five countries (Australia, India, Malaysia, Singapore and Taiwan).

3 | Results

3.1 | Study Population Characteristics

Propensity score matching was employed within the study cohort to control for age, gender, race, socioeconomic status, comorbidities, procedures, lifestyle factors, medication use and medical utilization, using a 1:1 matching ratio. Post-PSM, the matched cohort was comprised of 16 299 participants each in both the PPI and H2RA groups. Figure 1 delineates the cohort selection process through a detailed flowchart.

The demographic characteristics, socioeconomic status, comorbidities, lifestyles, medications and medical utilization of the

PPI and H2RA groups both before and after PSM are presented in Table 1. The mean age of the participants in the PPI group was 51.0 years after matching. Approximately 63.7% of the patients in the PPI group were female, with the major race being White (67.3%). The two groups were well-matched with concern to socioeconomic status, comorbidities, medications, lifestyles and medical utilization (SMD < 0.1).

3.2 | Incidence of Fractures in the Two Groups

The 24-month follow-up of the patients showed that there was no significant difference seen between the PPI and H2RA groups for all outcomes selected (Table 2). The Kaplan–Meier curve of incidence of the fracture outcomes also indicated that there was no difference of probability between the two groups (Figure 2, Log-rank test, $p = 0.107$). There was no significant difference seen for all fracture outcomes if using different durations of follow-up or when there was an adjustment of different variables, as shown in Tables S2 and S3.

3.3 | Subgroup Analyses

The risk of fractures in the subgroups was evaluated based on age, gender, glucocorticoid usage and different diagnosis of autoimmune diseases. Table 3 shows that the older (aged ≥ 65 years) subgroups in the PPI group experienced a significantly increased

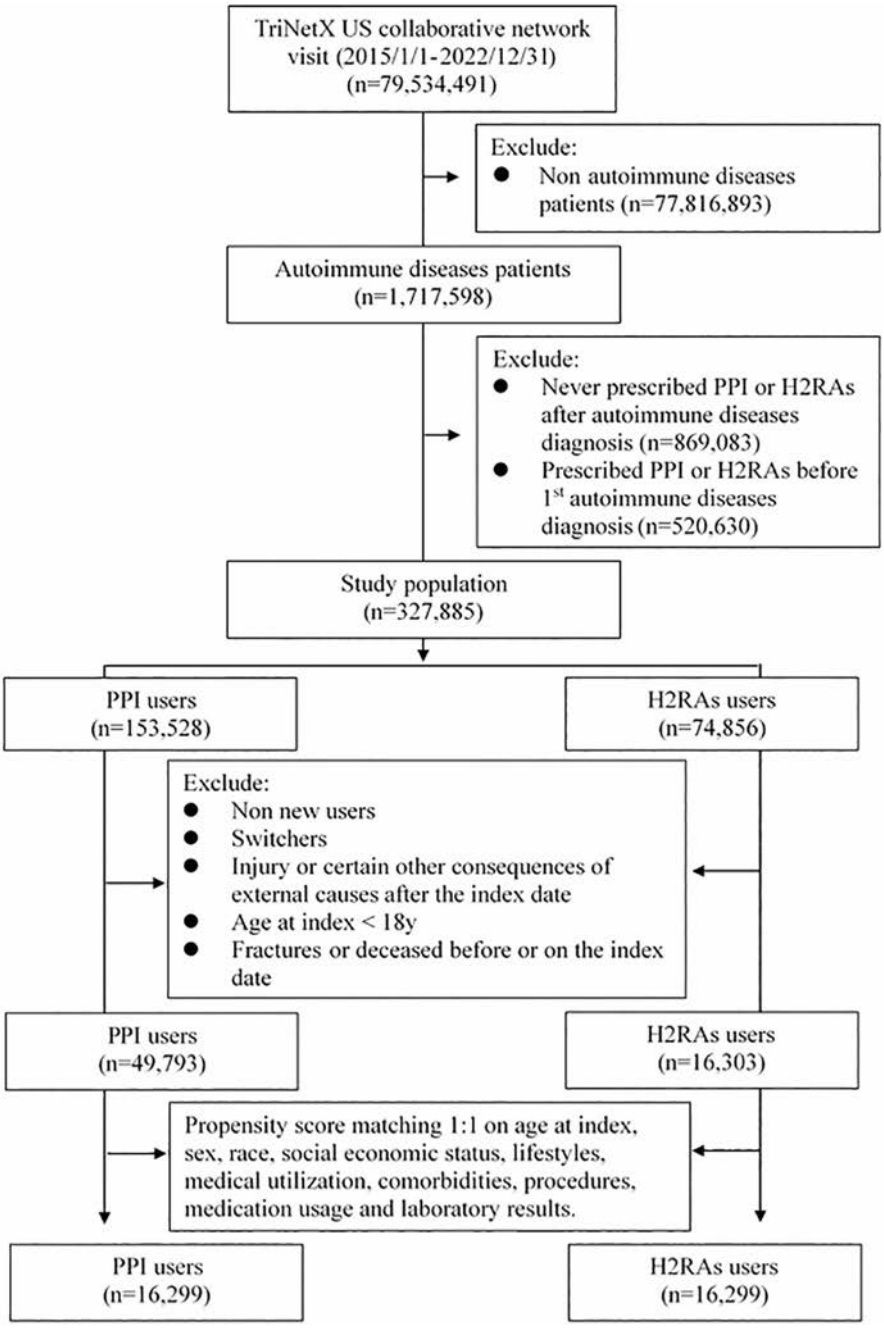

FIGURE 1 | Flowchart of study.

TABLE 1 | Baseline characteristics of the study subjects (before and after matching).

Variables	Before PSM			After PSM[a]		
	PPI users ($n = 49\,793$)	H2RAs users ($n = 16\,303$)	SMD	PPI users ($n = 16\,299$)	H2RAs users ($n = 16\,299$)	SMD
Age at index						
Mean ± SD	55.5 ± 17.2	51.2 ± 18.7	**0.244**	51.0 ± 18.1	51.2 ± 18.7	0.008
Gender, *n* (%)						
Female	29 621 (59.5)	10 420 (63.9)	0.091	10 389 (63.7)	10 416 (63.9)	0.003
Male	17 280 (34.7)	4855 (29.8)	**0.105**	4933 (30.3)	4855 (29.8)	0.010
Race, *n* (%)						
White	34 770 (69.8)	10 832 (66.4)	0.073	10 967 (67.3)	10 831 (66.5)	0.018
Black or African American	5599 (11.2)	2042 (12.5)	0.040	1980 (12.1)	2042 (12.5)	0.012
Asian	1338 (2.7)	475 (2.9)	0.014	466 (2.9)	474 (2.9)	0.003
Other	1463 (2.9)	647 (4.0)	0.056	648 (4.0)	646 (4.0)	0.001
American Indian or Alaskan Native	150 (0.3)	63 (0.4)	0.015	48 (0.3)	63 (0.4)	0.016
Native Hawaiian or Other Pacific Islander	145 (0.3)	33 (0.2)	0.018	48 (0.3)	33 (0.2)	0.018
Unknown	6328 (12.7)	2211 (13.6)	0.025	2142 (13.1)	2210 (13.6)	0.012
Social economic status, *n* (%)						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	684 (1.4)	234 (1.4)	0.005	235 (1.4)	233 (1.4)	0.001
Lifestyles, *n* (%)						
Personal history of nicotine dependence	5350 (10.7)	1360 (8.3)	0.082	1306 (8.0)	1360 (8.3)	0.012
Nicotine dependence	4949 (9.9)	1255 (7.7)	0.079	1234 (7.6)	1255 (7.7)	0.005
Tobacco use	1225 (2.5)	317 (1.9)	0.035	319 (2.0)	317 (1.9)	0.001
Alcohol-related disorders	1323 (2.7)	247 (1.5)	0.080	232 (1.4)	247 (1.5)	0.008
Reduced mobility	533 (1.1)	152 (0.9)	0.014	143 (0.9)	152 (0.9)	0.006
Difficulty in walking, not elsewhere classified	426 (0.9)	122 (0.7)	0.012	126 (0.8)	122 (0.7)	0.003
Dependence on wheelchair	150 (0.3)	40 (0.2)	0.011	47 (0.3)	40 (0.2)	0.008
Medical utilization, *n* (%)						
Office or Other Outpatient Services	28 164 (56.6)	9641 (59.1)	0.052	9563 (58.7)	9638 (59.1)	0.009
Emergency Department Services	13 681 (27.5)	3948 (24.2)	0.075	3892 (23.9)	3948 (24.2)	0.008
Hospital Inpatient and Observation Care Services	7901 (15.9)	2396 (14.7)	0.033	2365 (14.5)	2395 (14.7)	0.005
Preventive Medicine Services	3846 (7.7)	1316 (8.1)	0.013	1228 (7.5)	1316 (8.1)	0.020
Comorbidities, *n* (%)						
Hypertensive diseases	20 154 (40.5)	5278 (32.4)	0.169	5183 (31.8)	5278 (32.4)	0.012
Disorders of lipoprotein metabolism and other lipidemias	14 828 (29.8)	3806 (23.3)	0.146	3797 (23.3)	3806 (23.4)	0.001

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM[a]		
	PPI users ($n = 49\,793$)	H2RAs users ($n = 16\,303$)	SMD	PPI users ($n = 16\,299$)	H2RAs users ($n = 16\,299$)	SMD
Aplastic and other anemias and other bone marrow failure syndromes	8261 (16.6)	2538 (15.6)	0.028	2468 (15.1)	2536 (15.6)	0.012
Overweight and obesity	7463 (15.0)	2104 (12.9)	0.060	2024 (12.4)	2104 (12.9)	0.015
Chronic lower respiratory diseases	8068 (16.2)	2186 (13.4)	0.079	2113 (13.0)	2185 (13.4)	0.013
Diabetes mellitus	7945 (16.0)	2089 (12.8)	0.090	1971 (12.1)	2089 (12.8)	0.022
Vitamin D deficiency	5061 (10.2)	1762 (10.8)	0.021	1746 (10.7)	1760 (10.8)	0.003
Ischemic heart diseases	5974 (12.0)	1484 (9.1)	0.094	1444 (8.9)	1484 (9.1)	0.009
Diseases of the arteries, arterioles and capillaries	4303 (8.6)	1298 (8.0)	0.025	1296 (8.0)	1296 (8.0)	0.000
Chronic kidney disease (CKD)	4178 (8.4)	1271 (7.8)	0.022	1240 (7.6)	1270 (7.8)	0.007
Diseases of the liver	4352 (8.7)	1010 (6.2)	0.097	979 (6.0)	1010 (6.2)	0.008
Cerebrovascular diseases	2579 (5.2)	791 (4.9)	0.015	762 (4.7)	790 (4.8)	0.008
Malnutrition	2457 (4.9)	700 (4.3)	0.031	747 (4.6)	700 (4.3)	0.014
Unspecified dementia	563 (1.1)	120 (0.7)	0.041	132 (0.8)	120 (0.7)	0.008
Procedures, *n* (%)						
Surgical procedures on the pelvis and hip joint	269 (0.5)	31 (0.2)	0.058	40 (0.2)	31 (0.2)	0.012
Surgical procedures on the femur and knee joint	299 (0.6)	37 (0.2)	0.058	43 (0.3)	37 (0.2)	0.007
Surgical procedures on the spine	169 (0.3)	27 (0.2)	0.035	36 (0.2)	27 (0.2)	0.013
Comedications, *n* (%)						
Glucocorticoids for systemic use	21 781 (43.7)	7742 (47.5)	0.075	7656 (47.0)	7738 (47.5)	0.010
Opioids	18 624 (37.4)	5926 (36.3)	0.022	6020 (36.9)	5924 (36.3)	0.012
NSAIDs	12 415 (24.9)	4019 (24.7)	0.007	4131 (25.3)	4016 (24.6)	0.016
Calcium	10 882 (21.9)	3857 (23.7)	0.043	3504 (21.5)	3856 (23.7)	0.052
Diuretics	8729 (17.5)	2706 (16.6)	0.025	2534 (15.5)	2706 (16.6)	0.029
HMG-CoA reductase inhibitors	9381 (18.8)	2693 (16.5)	0.061	2511 (15.4)	2692 (16.5)	0.030
Magnesium	7052 (14.2)	2584 (15.9)	0.047	2262 (13.9)	2583 (15.8)	0.055
Aspirin	5976 (12.0)	2002 (12.3)	0.009	1665 (10.2)	2002 (12.3)	0.065
Sex hormones	3040 (6.1)	1271 (7.8)	0.067	1220 (7.5)	1270 (7.8)	0.012
Bisphosphonates	766 (1.5)	284 (1.7)	0.016	216 (1.3)	284 (1.7)	0.034
Laboratory, *n* (%)						
Calcium in serum, plasma or blood (mg/dL)						
< 8.5	8080 (16.2)	2805 (17.2)	0.026	2772 (17.0)	2803 (17.2)	0.005
8.5–10.5	31 388 (63.0)	10 741 (65.8)	0.059	10 561 (64.8)	10 737 (65.8)	0.022
> 10.5	1194 (2.4)	453 (2.7)	0.023	489 (3.0)	452 (2.7)	0.013

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM[a]		
	PPI users ($n=49\,793$)	H2RAs users ($n=16\,303$)	SMD	PPI users ($n=16\,299$)	H2RAs users ($n=16\,299$)	SMD
eGFR (mL/min/1.73 m^2)						
< 60	10 577 (21.2)	3288 (20.1)	0.026	3244 (19.9)	3287 (20.1)	0.006
60–90	19 764 (39.6)	6365 (39.0)	0.013	6282 (38.5)	6363 (39.0)	0.010
> 90	15 723 (31.5)	6132 (37.6)	0.127	6121 (37.5)	6128 (37.6)	0.000
BMI (kg/m^2)						
< 30	9604 (19.2)	3686 (22.6)	0.081	3381 (20.7)	3684 (22.6)	0.045
≧ 30	6155 (12.3)	2098 (12.8)	0.015	2051 (12.5)	2097 (12.8)	0.008
C-reactive protein in serum, plasma or Blood (mg/L)						
< 3	3889 (7.8)	1489 (9.1)	0.047	1532 (9.4)	1488 (9.1)	0.009
3–5	1672 (3.3)	750 (4.6)	0.063	630 (3.8)	749 (4.6)	0.036
> 5	6480 (13.0)	2498 (15.3)	0.066	2464 (15.1)	2496 (15.3)	0.005
Magnesium in serum, plasma or blood (mg/dL)						
< 1.5	1754 (3.5)	623 (3.8)	0.015	512 (3.1)	623 (3.8)	0.037
1.5–2.5	9494 (19.0)	3238 (19.8)	0.020	3138 (19.2)	3237 (19.8)	0.015
> 2.5	1143 (2.3)	409 (2.5)	0.013	372 (2.2)	408 (2.5)	0.014
Phosphate in serum, plasma or blood						
< 3	4018 (8.0)	1535 (9.4)	0.047	1314 (8.0)	1534 (9.4)	0.047
3–4.5	5899 (11.8)	2300 (14.1)	0.067	2018 (12.3)	2299 (14.1)	0.050
> 4.5	1743 (3.5)	741 (4.5)	0.053	627 (3.8)	741 (4.5)	0.034
Cobalamin (vitamin B12) in serum, plasma or blood (pg/mL)						
< 200	242 (0.4)	96 (0.5)	0.014	90 (0.5)	96 (0.5)	0.004
200–900	4595 (9.2)	1914 (11.7)	0.082	1690 (10.3)	1914 (11.7)	0.043
> 900	1090 (2.1)	440 (2.7)	0.033	361 (2.2)	440 (2.7)	0.031
Calcidiol (25-hydroxyvitamin D3) in serum or plasma (ng/mL)						
< 20	971 (1.9)	421 (2.5)	0.042	384 (2.3)	421 (2.5)	0.014
20–40	2105 (4.2)	921 (5.6)	0.065	851 (5.2)	921 (5.6)	0.018
> 40	1181 (2.3)	468 (2.8)	0.031	412 (2.5)	468 (2.8)	0.021

Abbreviations: BMI, body mass index; eGFR, glomerular filtration rate/1.73 square meter predicted in serum plasma or blood by creatinine-based formula; H2RAs, histamine-2 receptor antagonists; HMG CoA, hydroxy-3-methylglutaryl coenzyme A; NSAIDs, anti-inflammatory and anti-rheumatic products, non-glucocorticoids; PPI, proton pump inhibitor; PSM, propensity score matching; SD, standard deviation; SMD, standardized mean difference.

[a]Propensity score matching was performed on age at index, gender, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol-related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diabetes mellitus, chronic kidney disease (CKD), diseases of liver, disorders of lipoprotein metabolism and other lipidemias, overweight and obesity, vitamin D deficiency, malnutrition, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes), procedures (surgical procedures on the pelvis and hip joint, surgical procedures on the spine, surgical procedures on the femur and knee joint), medication usage (glucocorticoids for systemic use), and laboratory results (calcium, and estimated glomerular filtration rate).

risk of any fractures (HR = 1.927 [1.153–3.221]) and non-vertebral fractures (HR = 2.379 [1.214–4.661]). In the subgroup analysis based on gender, there was no difference seen between the outcomes of the PPI and H2RA groups, neither in the male nor the female group (Table S4).

With respect to glucocorticoid use, there was no difference seen in outcomes between the PPI and H2RA groups in either the glucocorticoid group or non- glucocorticoid group (Table S5). However, when compared with PPI users without using glucocorticoids, PPI users using glucocorticoids experienced

TABLE 2 | Risk of any fractures among PPI users and H2RA users.

	Patients with outcome				
	PPI users		H2RAs users		
Outcomes	***n*** **= 16 299**	**Risk (%)**	***n*** **= 16 299**	**Risk (%)**	**Adjusted hazard ratio (95% CI)[a]**
Any fractures	62	0.38	45	0.27	1.369 (0.933–2.009)
Vertebral fractures	20	0.12	20	0.12	0.996 (0.536–1.850)
Non-vertebral fractures	43	0.26	28	0.17	1.525 (0.947–2.454)
Hip/femur/pelvis fractures	10	0.06	10	0.06	1.498 (0.423–5.307)

Note: If the patient is less or equal to 10, results show the count as 10.
Abbreviations: CI, confidence interval; H2RAs, histamine-2 receptor antagonists; NA, not available; PPI, proton pump inhibitor.
[a]Propensity score matching was performed on age at index, gender, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol-related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of the arteries, arterioles and capillaries, chronic lower respiratory diseases, diabetes mellitus, chronic kidney disease (CKD), diseases of the liver, disorders of lipoprotein metabolism and other lipidemias, overweight and obesity, vitamin D deficiency, malnutrition, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes), procedures (surgical procedures on the pelvis and hip joint, surgical procedures on the spine, surgical procedures on the femur and knee joint), medication usage (glucocorticoids for systemic use), and laboratory results (calcium, and estimated glomerular filtration rate).

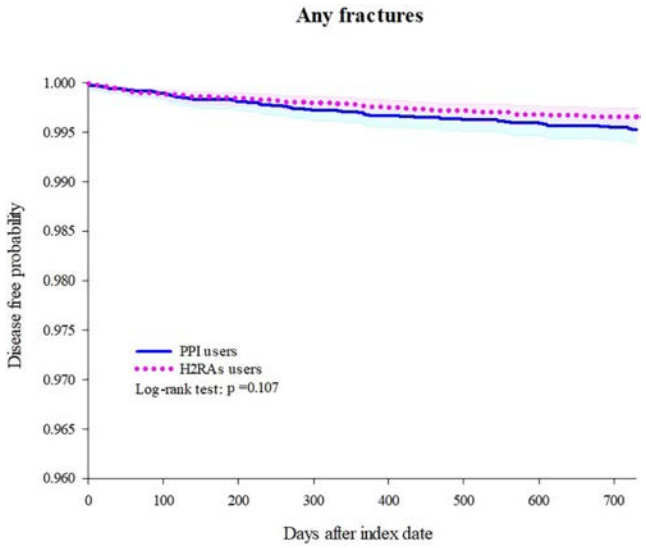

FIGURE 2 | Kaplan–Meier curve of any fracture incidence between PPI users and H2RA users.

a significantly increased risk of any fractures (HR = 4.273 [2.219–8.227]), vertebral fractures (HR = 6.876 [2.051–23.05]) and non-vertebral fractures (HR = 1.184 [1.838–9.525]) (Table 4). The Kaplan–Meier curve of incidence of fracture outcomes also indicated that PPI users who were prescribed glucocorticoids experienced a greater risk of any type of fracture as shown in Figure 3 (Log-rank test, $p < 0.001$). For subgroup analysis regarding the different diagnosis of autoimmune diseases, there was no difference in outcomes between the PPI and H2RA groups for participants diagnosed with inflammatory arthritis, connective tissue disease or intestinal-related diseases (Table S6).

3.4 | Sensitivity Analyses

The risk of fracture outcomes did not increase significantly when analyzing data from either the global network or APAC network (Table S7).

4 | Discussion

To the best of our knowledge, this is the first study to compare the fracture risk of PPIs and histamine-2 receptor antagonists in a large number of patients diagnosed with autoimmune rheumatic and gastrointestinal diseases, using the TriNetX database, while being in consideration of the concomitant use of glucocorticoids as well as among different subgroups. We found that the elderly (aged ≥ 65 years) subgroup in the PPI group experienced a significantly increased risk of fracture outcomes, including any fractures and non-vertebral fractures. Moreover, when compared with PPI users who were not prescribed glucocorticoids, PPI users taking glucocorticoids showed a significantly increased risk of any type of fracture, as well as vertebral fractures and non-vertebral fractures.

Our results are partially consistent with previous reports which had shown that PPI users experienced a higher risk of developing fractures than H2RA users among older adults. In a Korean study, Park et al. discovered that when compared with the use of H2RA alone, PPI use was associated with an increased risk of osteoporotic fractures in elderly Korean women, particularly among those who had used PPIs within the last year or for more than 1 year [23]. Miyano et al. demonstrated that PPI users had a higher risk of fractures than H2RA users among mostly advanced-age patients diagnosed with ANCA-associated vasculitis who had undergone remission induction therapy [24]. Another Korean study conducted by Park et al. showed that the risk of osteoporotic fracture in patients whose cumulative use of PPIs was longer than 1 year was higher than that seen in others. Patients who had regularly used PPIs in the recent year showed a higher risk of osteoporotic fracture than those who were exclusively H2RA users [25]. Corley et al. also found that patients with hip fractures were more likely than controls to have previously received a ≥ 2-year supply of PPIs in a case–control study [26]. Recently, Palmowski et al. found that PPIs lead to a loss of BMD rather than an impairment of bone microarchitecture in patients with inflammatory rheumatic and musculoskeletal diseases [27].

TABLE 3 | Subgroup analysis of risk of any fracture stratified by age at index date.

Outcomes (PPI users vs. H2RAs users)	18–64 years ($n = 11513$ pairs)		≧65 years ($n = 5104$ pairs)	
	Patients with outcome (PPI users/ H2RAs users)	Adjusted hazard ratio (95% CI)[a]	Patients with outcome (PPI users/ H2RAs users)	Adjusted hazard ratio (95% CI)[a]
Any fractures	24/23	1.037 (0.585–1.837)	43/22	**1.927 (1.153–3.221)***
Vertebral fractures	10/10	1.122 (0.433–2.908)	22/11	1.969 (0.955–4.061)
Non-vertebral fractures	17/15	1.125 (0.562–2.253)	29/12	**2.379 (1.214–4.661)***
Hip/femur/pelvis fractures	10/10	3.001 (0.312–28.84)	10/10	1.478 (0.247–8.845)

Note: If the patient is less or equal to 10, results show the count as 10.
Abbreviations: CI, confidence interval; H2RAs, histamine-2 receptor antagonists; NA, not available.; PPI, proton pump inhibitor.
[a]Propensity score matching was performed on age at index, gender, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol-related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of the arteries, arterioles and capillaries, chronic lower respiratory diseases, diabetes mellitus, chronic kidney disease (CKD), diseases of the liver, disorders of lipoprotein metabolism and other lipidemias, overweight and obesity, vitamin D deficiency, malnutrition, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes), procedures (surgical procedures on the pelvis and hip joint, surgical procedures on the spine, surgical procedures on the femur and knee joint), medication usage (glucocorticoids for systemic use), and laboratory results (calcium, and estimated glomerular filtration rate). * Proportionality < 0.001.

TABLE 4 | Risk of any fracture among PPI users with using glucocorticoids versus PPI users without using glucocorticoids.

Outcomes	Patients with outcome				Adjusted hazard ratio (95% CI)[c]
	PPI users with glucocorticoids[a]		PPI users without glucocorticoids[b]		
	$n = 9244$	Risk (%)	$n = 9244$	Risk (%)	
Any fracture	48	0.5	11	0.1	4.273 (2.219–8.227)
Vertebral fractures	21	0.2	10	0.1	6.876 (2.051–23.05)
Non-vertebral fractures	30	0.3	10	0.1	1.184 (1.838–9.525)
Hip/femur/pelvis fractures	10	0.1	0	0	NA

Note: If the patient is less or equal to 10, results show the count as 10.
Abbreviations: CI, confidence interval; H2RAs, histamine-2 receptor antagonists; NA, not available; PPI, proton pump inhibitor.
[a]With glucocorticoid: glucocorticoids were prescribed within one year before or on the index date.
[b]Without glucocorticoid: patients whose electronic medical records show no history of being prescribed glucocorticoids.
[c]Propensity score matching was performed on age at index, gender, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol-related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of the arteries, arterioles and capillaries, chronic lower respiratory diseases, diabetes mellitus, chronic kidney disease (CKD), diseases of the liver, disorders of lipoprotein metabolism and other lipidemias, overweight and obesity, vitamin D deficiency, malnutrition, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes), procedures (surgical procedures on the pelvis and hip joint, surgical procedures on the spine, surgical procedures on the femur and knee joint), and laboratory results (calcium, and estimated glomerular filtration rate).

The association between PPIs and increased fracture risk appears to be multifactorial, involving several biologically plausible mechanisms which affect bone health. First, PPIs are known to reduce gastric acid secretion, which is crucial for calcium absorption. Impaired calcium absorption can subsequently lead to a decrease in bone mineral density, a critical factor in bone strength and fracture risk. Additionally, PPIs have been associated with alterations in the hormone levels that regulate bone homeostasis, including parathyroid hormones, which in turn can lead to increased bone turnover and potential bone loss [28]. Moreover, the use of PPIs has been linked to vitamin B12 deficiency due to decreased gastric acid; a deficiency which could contribute to weakened bone structure, further predisposing individuals to fractures [29]. Furthermore, increased fall risk, possibly due to altered hormone levels and other systemic effects of long-term PPI use, may also contribute to the higher incidence of fractures seen among PPI users [30, 31]. Lastly, Lau et al. reported that PPI-induced hypochlorhydria could impair calcium absorption, thereby directly affecting bone mineral density and increasing fracture risk. Additionally, PPIs may disrupt the bone remodeling process by altering bone cell function, which could lead to a qualitative decline in bone architecture, further predisposing individuals to fractures [32]. The interplay of all these factors highlights the complexity of PPI's effects on bone health and the critical need for ongoing research to further clarify these associations.

Our results also show that PPI users using glucocorticoids have a significantly increased risk of any fractures, vertebral fractures and non-vertebral fractures, which is consistent with previous

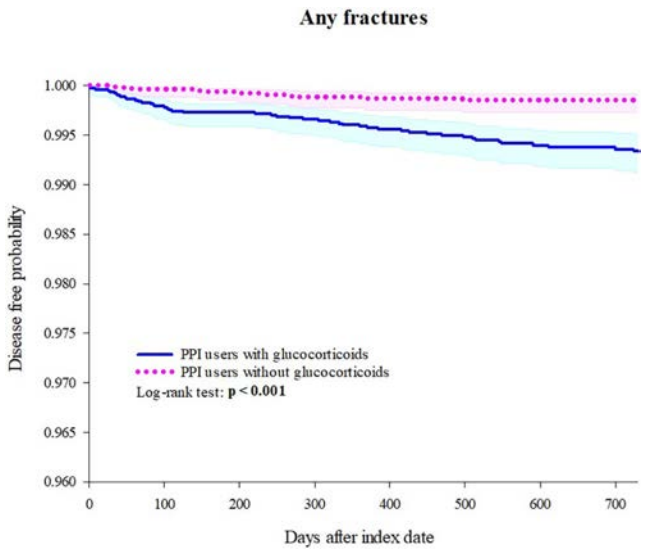

FIGURE 3 | Kaplan–Meier curve of any fracture incidence among PPI users with or without using glucocorticoids.

reports. Abtahi et al. discovered that concomitant current use of oral glucocorticoids and PPIs was associated with a 1.6-fold increased risk of osteoporotic fractures when compared with non-use in a large cohort study enrolling 12351 patients with rheumatoid arthritis [33]. Our results further prove that concomitant current use of oral glucocorticoids and PPIs not only increased the number of osteoporotic fractures but also increased the number of all fractures. The mechanisms underlying the association between PPIs and glucocorticoids with fracture risk exhibit notable similarities, particularly in their impact on bone health, despite their distinct pharmacological actions. Both PPIs and glucocorticoids contribute to an increased risk of fractures through mechanisms that involve more than just a reduction in bone mineral density (BMD). Glucocorticoids directly impair bone formation by inhibiting osteoblasts and promoting osteoclast activity, leading to decreased BMD. PPIs may indirectly affect BMD through reduced calcium absorption due to decreased gastric acidity acting as one of the mechanisms. Additionally, both drug classes are implicated in altering bone quality, which may predispose individuals to fractures even when BMD measurements do not indicate severe osteoporosis [28, 34, 35]. This suggests that both PPIs and glucocorticoids may weaken bone structure in ways not fully detectable through the use of standard BMD tests. Thus, the need for a multimodal approach to bone health assessment and management, including optimal control of disease activity, minimization of glucocorticoids, anti-osteoporotic drug treatment, advice on physical activity and nutrition, and prevention of falls, as well as the management of other risk and protective factors in patients undergoing long-term treatment with these drugs are all more important [36]. Future studies should be implemented in order to explore the molecular interplay between PPIs and glucocorticoids and its effect on bone health.

Our results also indicate that PPI users in Asian countries experience a higher risk of fractures compared to H2RA users (HR: 2.648, 95% CI: 0.514–13.64), but not of any statistical significance (possibly due to the small number of occurrences). There have been many studies exploring PPIs, H2RAs and fracture risk among the Asian population [23, 25], however, studies regarding racial differences remain scarce. Yang et al. performed a meta-analysis suggesting that there is an interaction associated with increased fracture risk among the Asian race between Bisphosphonate and PPI use [37]. Additionally, genetic differences may also play a role. PPIs are metabolized through hepatic cytochrome P450 enzymes, predominantly by CYP2C19, resulting in inactive metabolites [38]. The CYP2C19 genotype in patients significantly influences the interindividual variability in the pharmacokinetics of PPIs [39]. However, there is a recent study from Taiwan showing that the CYP2C19 poor metabolizer or intermediate metabolizers do not confer an increased risk for fractures or diminished BMD in individuals who have utilized PPIs for extended periods [40]. It is suggested that future studies delve deeper into Asian populations by exploring the interaction between Bisphosphonates and PPIs, as well as any genetic differences, for purposes of further investigation.

4.1 | Limitations

This study, while offering valuable insights, is subject to several limitations that warrant acknowledgment. First, even though the treatment initiation of PPIs and H2RAs was evaluated, PPI and H2RA dosage data could not be obtained from the database. Besides, users may get PPIs and H2RAs from over the counter (OTC) in US. Imran et al. conducted a survey in US which showed that 32% of all PPI users purchased OTC PPIs [41]. From another survey of gastroenterologists in US, for the typical acid reflux patient, 50% of gastroenterologists recommended OTC PPIs, 13% recommended an OTC H2RAs, whereas 33% recommended a prescription PPIs [42]. Future study is warranted to include the dosage of PPI and H2RA into analysis, including OTC use. Second, the number of Asian subjects involved in our study was rather small, which may have produced a racial bias in the results. However, we have performed a sensitivity analysis, which included participants from the APAC network only. Third, health insurance coverage had a significant impact on the utilization of healthcare services, however healthcare insurance status could not be obtained from TrinetX which may have produced potential confounding. Fourth, while PSM was utilized to minimize bias, it is important to acknowledge that misclassification bias and residual confounding factors remain inherent challenges. These limitations arise from the intrinsic constraints of using an electronic health record database, which may not capture all relevant variables or fully account for unmeasured confounders. Fifth, among the PPI and H2RA groups, a low number of fractures was observed. Therefore, future studies remain warranted in order to investigate the research question over a longer period of observation. Sixth, misclassification bias could have occurred due to potential loss of follow-up, while participants may also have gone to other healthcare organizations which were not represented in TrinetX. Seventh, there is a potential for selection bias, as participants with polypharmacy or higher doses of steroids may have been more likely to receive PPIs. However, as shown in Table 1 of our manuscript, both before and after PSM, there were no significant differences in the usage of comedications, including glucocorticoids, opioids, NSAIDs, and other drugs, between participants using PPIs and those using H2RAs.

5 | Conclusion

Our findings reveal that when compared with the use of H2RAs, older adults with autoimmune rheumatic and gastrointestinal diseases using PPIs experienced a significantly increased risk of fractures outcomes, including any type of fracture and non-vertebral fractures. Moreover, when compared with PPI users who were not prescribed glucocorticoids, PPI users who were given glucocorticoids experienced a significantly increased risk of any type of fracture, as well as vertebral fractures and non-vertebral fractures. These results highlight the importance of personalized guidance on acid suppression medication in order to maintain optimal bone health, particularly for those who are more susceptible to osteoporosis and bone fractures.

Author Contributions

Conceptualization: Andriko Palmowski, Frank Buttgereit. Data curation: Shiow-Ing Wang. Formal analysis: Shiow-Ing Wang. Funding acquisition: Shiow-Ing Wang. Investigation: Wei-Min Chu. Methodology: Shiow-Ing Wang, Andriko Palmowski, Frank Buttgereit. Project administration: Wei-Min Chu and Frank Buttgereit. Resources: Frank Buttgereit. Software: Shiow-Ing Wang. Supervision: Wei-Min Chu and Frank Buttgereit. Validation: Frank Buttgereit. Visualization: Shiow-Ing Wang. Roles/writing – original draft: Miaoyu Zeng and Wei-Min Chu. Writing – review and editing: Shiow-Ing Wang, Andriko Palmowski, Frank Buttgereit and Wei-Min Chu. All the authors have read and agreed to the submission of this version of the manuscript for publication.

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Ethics Statement

This study was approved by the Institutional Review Board of Chun Shan Medical University Hospital (case number: CS2-21105).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available publicly.

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Supporting Information

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

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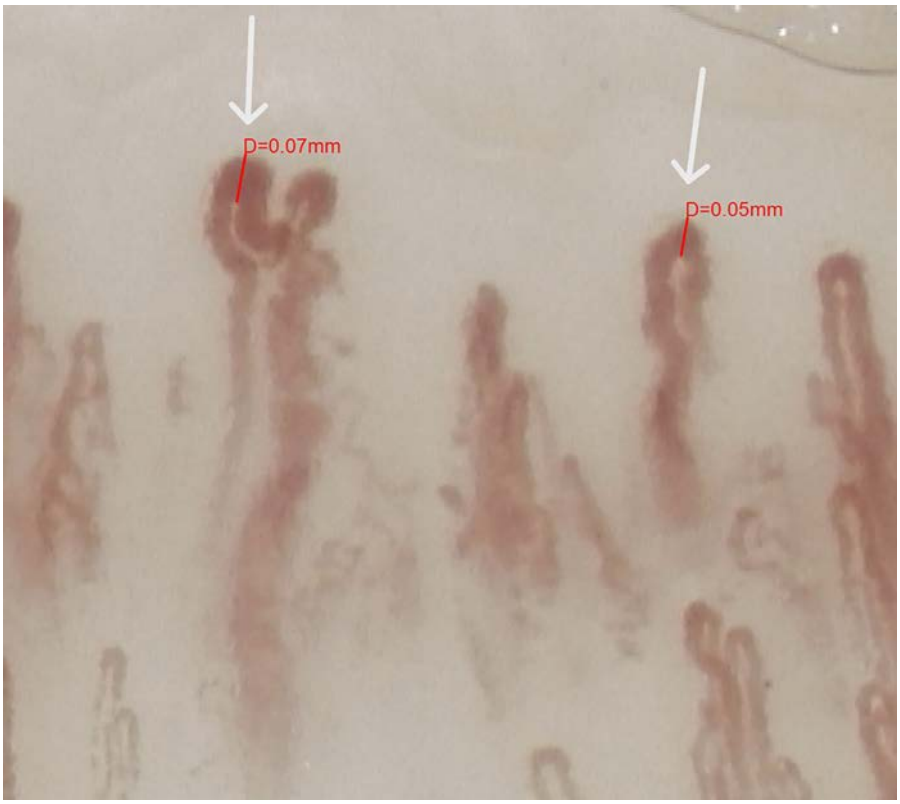
CORRECTION

Correction to "Alterations on Nailfold Videocapillaroscopy in Myelodysplastic Syndrome and Onychomycosis in a Female Smoker: Microvascular Dysfunction Without Connective Tissue Disease"

A. Nigro, "Alterations on Nailfold Videocapillaroscopy in Myelodysplastic Syndrome and Onychomycosis in a Female Smoker: Microvascular Dysfunction Without Connective Tissue Disease," *International Journal of Rheumatic Diseases* 27 (2024): e70000.

Correction for Figure 2: Revise the measurement of the apical diameter of the capillaries.



We apologize for this error.