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LETTER TO THE EDITOR

A Case Report of Atypical Presentation of Systemic Lupus Erythematosus in a Young Child

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ABSTRACT

Systemic lupus erythematosus is a chronic multisystem autoimmune disorder with varied etiology and clinical presentation. It is unusual during infancy. We describe a 2-year-old boy who presented with progressive mucocutaneous lesions with arthralgia and limb pain. He had hepatomegaly, Raynaud's phenomenon, brisk deep tendon reflexes, and bilateral upper and lower limb weakness. On evaluation, he was positive for ANA and SSA only without any complement activation and was subsequently diagnosed with mixed features of both subacute and chronic cutaneous lupus erythematosus. Infantile onset lupus is rare and should be suspected in children with mucocutaneous and musculoskeletal involvement.

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder with varied etiology and clinical presentation [1]. SLE usually manifests at 9–14 years of age with a 3–11 times preponderance for the female sex [2]. The female preponderance for the disease is mainly due to an increase in the number of genes involved in innate and adaptive immune responses, increasing the production of type 1 interferons and disease risk in females [3]. Various genetic as well as epigenetic factors are responsible for influencing the risk of developing disease and even the outcomes [4]. Here, we present the case of a young infant with a relatively atypical presentation of SLE.

The child was a 2-year-old boy who presented to us with symptoms starting from 8 months of life. He had a smooth perinatal transition, was completely immunized, and was developmentally normal for his age. Till 8 months of life, the child was otherwise well when he developed ulcerative lesions over the gluteal region and feet. Similar lesions appeared over the head and face by the next month. These lesions healed after the application of topical steroids for 2 weeks. These lesions continued to recur every once or twice per month, along with intermittent epistaxis. By 18 months of age, he started developing oral ulcers along with severe gingivostomatitis and angular cheilitis, accompanied by 1–2 high-grade fever spikes every month. Intermittently, indigenous treatments were also tried at home without any improvement. Two months later, he developed an erythematous rash over bilateral palms and soles, which healed with residual hyperpigmentation. At the same time, the mother also gave a history of Raynaud's phenomenon occurring in the winter season. By 22 months, the boy developed difficulty raising his arms above the shoulder and getting up from a supine position without support. This was associated with pain in bilateral lower limbs. There was no drug history before the onset of the illness. For these complaints, he was admitted to a local hospital for 2 weeks with only partial improvement in symptoms. Upon referral to our center, the child was already on prednisolone at 1 mg/kg/day and tofacitinib. Upon examination, he weighed 13 kg (−0.14 *z*-score), had sparse hair, severe gingivostomatitis, multiple hyperpigmented residual lesions, and atrophic scarring over his face, sparing the nasolabial folds and eyelids, healed ulcers over the hard palate, vasculitic rash over bilateral palms and soles along with residual hyperpigmented lesions (Figure 1). On systemic examination, he had hepatomegaly, brisk deep tendon reflexes, and proximal muscle weakness of bilateral upper and

Summary

- Early infants with mucocutaneous and musculoskeletal involvement should be evaluated for potential underlying autoimmune conditions.
- Various autoantibodies against extractable nuclear antigens can be present in Lupus, highlighting their non-specific nature.
- Musculoskeletal involvement is not exclusive to inflammatory myopathies and can also occur in Lupus.

lower limbs. The ophthalmic examination was unremarkable. A dermatology consultation was also sought, and the possibility of small vessel vasculitis or a connective tissue disorder such as SLE was considered due to the presence of chronic cutaneous lesions with acute flare and the presence of fever and musculoskeletal involvement (polyarthralgia and myopathy).

Upon initial workup, the child had microcytic hypochromic anemia (hemoglobin—10 g/dL), inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), and creatine phosphokinase within normal limits, no proteinuria or hematuria, or low C3 levels. His antinuclear antigen (ANA—8.6 IU/mL by immunoassay) and anti-SS-A/Ro-52 were positive, while his anti-double-stranded deoxyribonucleic acid antibodies (anti-dsDNA Ab), antineutrophilic cytoplasmic antibodies, antiphospholipid antibodies, and lupus anticoagulant were negative. MRI of the thigh and shoulder revealed altered signal intensity in bilateral gluteal muscles, bilateral vastus muscles, right adductor muscles, right long head of biceps femoris, muscles of bilateral legs, right subscapularis, bilateral supraspinatus, and infraspinatus muscles, suggestive of inflammatory myositis. Other causes for inflammatory myopathies were ruled out based on the absence of any skin manifestations or dysphagia, the absence of myositis-specific and myositis-associated antibodies, and a normal creatine phosphokinase or lactate dehydrogenase. Congenital causes were not considered clinically, as the child could perform all motor activities as per age before the onset of the disease. We did not do aldolase levels, electromyography, or muscle biopsy as the myopathy was clinically evident. The child fulfilled the European League Against Rheumatism/American College of Rheumatology classification criteria for SLE (score—14). SLE disease activity index—2000 (SLEDAI-2 K) score was 19, indicating a severe disease. Subsequently, a skin biopsy was done, which was consistent with Lupus and showed IgM and IgG deposition at the dermoepidermal junction and fibrinogen deposition in the superficial dermal vessels (Figure 2). The child was started on methylprednisolone pulse at 30 mg/kg/day for 5 days, followed by prednisolone at 1 mg/kg/day, along with hydroxychloroquine and oral methotrexate. He responded well and is now on maintenance therapy with a weight gain of 3 kg in the last 6 months and no active cutaneous lesions.

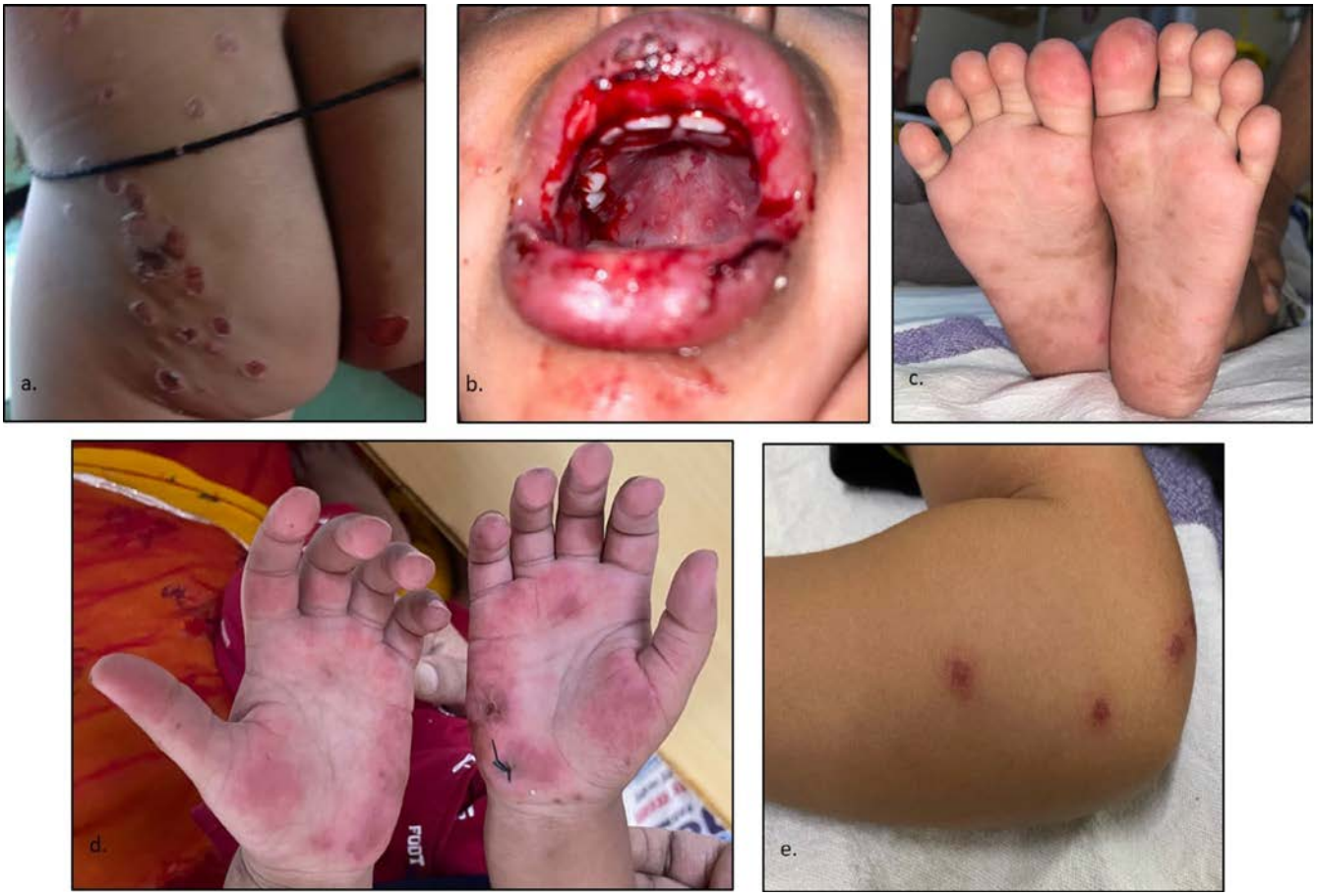

FIGURE 1 | Multiple scarring lesions over the forehead, nasal bridge, and cheek with old post-inflammatory hyperpigmentation sparing the eyelids and nasolabial folds. (b) Oral mucosal ulceration at presentation. (c) Erythematous non-blanchable macules over palms. (d) Erythematous non-blanchable macules over soles with old hyperpigmented lesions. (e) Macules with central duskiness over the extensor aspect of the right forearm.

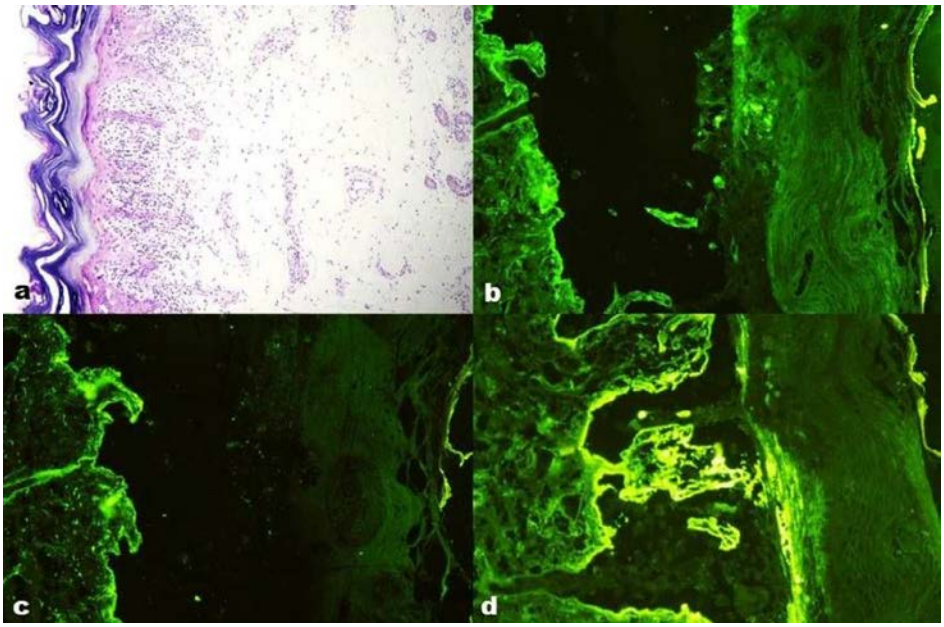

FIGURE 2 | (a) H&E stained section shows crusting of the epidermis with hypo and hypergranulosis with dyskeratosis, basal cell vacuolization, and diffuse interface dermatitis (H&E 100X). On direct immunofluorescence, the dermo-epidermal junction shows continuous granular deposition of (b) IgG & (c) IgM. (d) Fibrinogen is also highlighted in the superficial dermal vessels.

This child presented with an acute flare of chronic cutaneous lupus erythematosus with musculoskeletal involvement. A similar presentation can be seen in acute porphyria overlap with SLE; however, due to the rarity of this entity and the child's good response to treatment, including hydroxychloroquine, it seemed unlikely in our case. There have been previous reports of infantile-onset disease occurring in male infants, but not with predominant cutaneous involvement [5]. It is known that early-onset disease usually presents with mucocutaneous and musculoskeletal involvement without cytopenia or low complement levels and atypical serology with negative anti-dsDNA antibody and a positive anti-SS-A/Ro-52 Ab, as was seen in our case [3]. This case underscores the need to consider autoimmune diseases in early infancy and to investigate a potential genetic basis when such conditions present early.

Author Contributions

P.K. and J.P.G. conceptualized the idea, conducted a literature search, and prepared the initial manuscript. S.A. and K.P.: data collection, literature search, and initial draft preparation. A.N.: data collection, literature search, and initial draft preparation. It was critically reviewed and approved for publication by all authors. A.N.: data collection, literature search, and initial draft preparation. P.K. will act as a guarantor for this manuscript.

Acknowledgments

We also thank the parents for permitting us to publish his images.

Ethics Statement

Ethical approval is not required for letter to editor/case report at our institute.

Consent

Taken from the parents and they have permitted us to publish the clinical images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Since this study does not generate any data, so it is not applicable.

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LETTER TO THE EDITOR

The PROMIS-29 and SF-36 Quality of Life Scales Are Not Interchangeable in Systemic Sclerosis

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Dear Editor,

Systemic sclerosis (SSc, scleroderma) patients experience poor health-related quality of life (HRQoL), often measured using the Medical Outcomes Study 36 Short Form (SF-36), a generic outcome measure validated in SSc [1]. An Australian study demonstrated the construct validity of a new such instrument in SSc, the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29), but did not assess the global summary scores [2]. Instruments such as the SF-36 attempt to measure underlying constructs that cannot be directly observed, such as HRQoL. The construct validity of an instrument is the degree of certainness that the instrument measures that underlying construct. There are several ways to assess the construct validity of an instrument, and a common one is to demonstrate that the new instrument correlates well with another instrument that is already widely accepted as a good measure of the construct or that it correlates well with other measures that should also reflect the underlying construct. A good correlation between measures, however, does not mean that the scores on the two instruments are almost identical. Therefore, a novel question to be asked of these two instruments, the SF-36 and the PROMIS-29, is whether they may be interchangeable as well as well correlated with each other. Interchangeability of two instruments would be useful if a newer instrument becomes available with fewer restrictions on its use, such as cost or its availability in more languages. Knowing that a cohort already followed for many years using one instrument could switch to a new instrument and that scores from both instruments could be used interchangeably in data analyses would be very useful. Also, interchangeability would allow comparison of older studies with the SF-36 and more recent ones using the PROMIS. As each measure uses a standardized score where 50 is the mean for the normal population and 10 is one standard deviation, if both measures are measuring the exact same underlying construct, that is, HRQoL, then not only should the scores correlate, but they should "agree" with each other.

We assessed the construct validity of the global summary scores of the PROMIS-29 in SSc and also determined whether these global score measures agree with each other, suggesting interchangeability of one with the other.

Data were collected from subjects in The Canadian Scleroderma Research Group (CSRG) registry. We collected SF-36 data since the onset of the cohort in 2004, and during a changeover to the PROMIS-29, we have 136 patients who filled in both forms at the same visit.

The PROMIS-29 consists of 29 questions addressing several domains (Table 1) [3]. Global Physical and mental health scores summary scores were calculated. The SF-36 measures eight health domains (Table 1), and summary scores include the Physical Component Score (PCS) and the Mental Component Score (MCS) [4]. We report results of the Health Assessment Questionnaire (HAQ) Disability Index and the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) as these measures represent function and disease damage, which are likely related to the level of HRQoL [5].

TABLE 1 | Intraclass correlation coefficients and Spearman's correlations between PROMIS-29 and SF-36.

			In CSRG cohort ($n = 136$)		Australian cohort ($n = 477$)[a]
	PROMIS-29	SF-36	ICC (95% CI)	Spearman's rho[b]	Spearman's rho[b]
Overall scores	Physical health	PCS	0.76 (0.68, 0.82)	0.80	N/A
	Mental health	MCS	0.55 (0.42, 0.66)	0.64	N/A
Matched sub-domain scores	Physical function	Physical function	0.67 (0.56, 0.75)	0.75	0.84
	Physical function	Role physical	0.52 (0.38, 0.63)	0.60	0.64
	Anxiety	Emotional well-being	−0.54 (−0.75, −0.25)	−0.65	−0.71
	Depression	Emotional well-being	−0.63 (−0.79, −0.42)	−0.66	−0.76
	Fatigue	Vitality	−0.55 (−0.74, −0.31)	−0.66	−0.80
	Satisfaction with social	Social function	0.59 (0.47, 0.69)	0.66	0.58
	Pain interference	Bodily pain	−0.63 (−0.80, −0.25)	−0.82	−0.85
	Global pain	Bodily pain	−0.65 (−0.80, −0.25)	−0.83	−0.88

Abbreviation: CSRG, Canadian Scleroderma Research Group (current study).
[a]Data from reference [2].
[b]All Spearman correlation results were significant $p = 0.001$.

Correlation was assessed with Spearman correlation coefficients. Agreement was assessed with the two-way mixed effects, absolute agreement, single rater intraclass correlation coefficient (ICC). ICC values for agreement of < 0.5 were considered poor; 0.5–0.75 moderate; 0.75–0.9 good; > 0.90 excellent [6]. Lin's concordance correlation coefficient and Bland–Altman limits of agreement were also determined. If agreement between the measures was excellent, then the mean difference of the measures as determined by the Bland–Altman plot should fall within values of the minimal clinically important differences (MCID) of the SF-36 PCS in SSc, which are 2.18 and −1.74 for improvement and worsening, respectively [7]. As well, they should fall within values of MCID of the PROMIS-29, which unfortunately has not been calculated in SSc.

The median age of the 136 participating patients was 61 years, with females making up 92.7% of cases. Median (IQR) disease duration from first non-Raynaud's sign or symptom was 7.6 (3.6; 13.2) years; 31.1% of patients had dcSSc; 35.8% had ILD; and 5.3% had PAH. The median (IQR) HAQ-DI was 1.25 (1; 1.88), which indicates moderate functional disability. Disease damage measured by the SCTC-DI (5 (3; 9)) was low moderate [5]. The median (IQR) scores for the SF-36 and PROMIS summary scores were as follows: SF-36 PCS = 41.6 (32.8, 49.7); SF-36 MCS = 47.8 (35.8, 55.3); PROMIS-29 physical = 44.8 (38.9, 56.1); and PROMIS-29 mental health = 49.2 (42.1, 55.4).

We compared the correlation coefficients of the domain scores in our CSRG subjects to those noted in the Australian cohort study [2]. All correlation coefficients between the SF-36 and the PROMIS-29 in the CSRG cohort were significant, with a rho > 0.60 (Table 1). The coefficients were very similar in the CSRG and Australian cohorts for each domain. The physical health summary score correlation in the CSRG between the 2 measures was good (rho = 0.80) but only moderate for the mental health summary scores (rho = 0.64).

The agreement by ICC between the SF-36 MCS and the Mental health summary score of the PROMIS was 0.55 (95% CI 0.42, 0.66), which is moderate; and between the SF-36 PCS and the physical health summary score of the PROMIS, the ICC was 0.76 (95% CI 0.68, 0.82), which is good [6]. The ICC between domains of the SF-36 and similar domains of the PROMIS-29 was all ≥ 0.52 and fell into the moderate range for agreement.

The value (95% CI) of Lin's concordance coefficient for the physical health measures of the SF-36 and PROMIS-29 was 0.69 (0.61; 0.77), and was 0.52 (0.41; 0.62) for the mental health measures, and both were significant ($p < 0.001$). Bland–Altman analysis was carried out for the physical health summary measures of the SF-36 and PROMIS-29. It showed a mean difference of 4.43 units and the limits of agreement, which are calculated as (±1.96*SD), are −9.84 and 18.92 units (Figure 1). That is greater than the MCID of the SF-36 PCS in SSc, which are 2.18 and −1.74 for improvement and worsening, respectively [7]. Although most values fall between the limits of agreement in the plot, those limits are far wider than the MCID values. To our knowledge, the MCID for the PROMIS-29 has not been calculated in any systemic rheumatic disease.

Our data of good correlation between the SF-36 PCS and the PROMIS physical health summary score supports the construct validity of that PROMIS summary scale in SSc. Although the mental health summary scores of both instruments correlated with each other, both scores were very close to the general population mean of 50. We have shown similar findings for the SF-36 MCS before [8], which attests to the orthogonal scoring method that tends to normalize the SF-36 MCS score when the SF-36

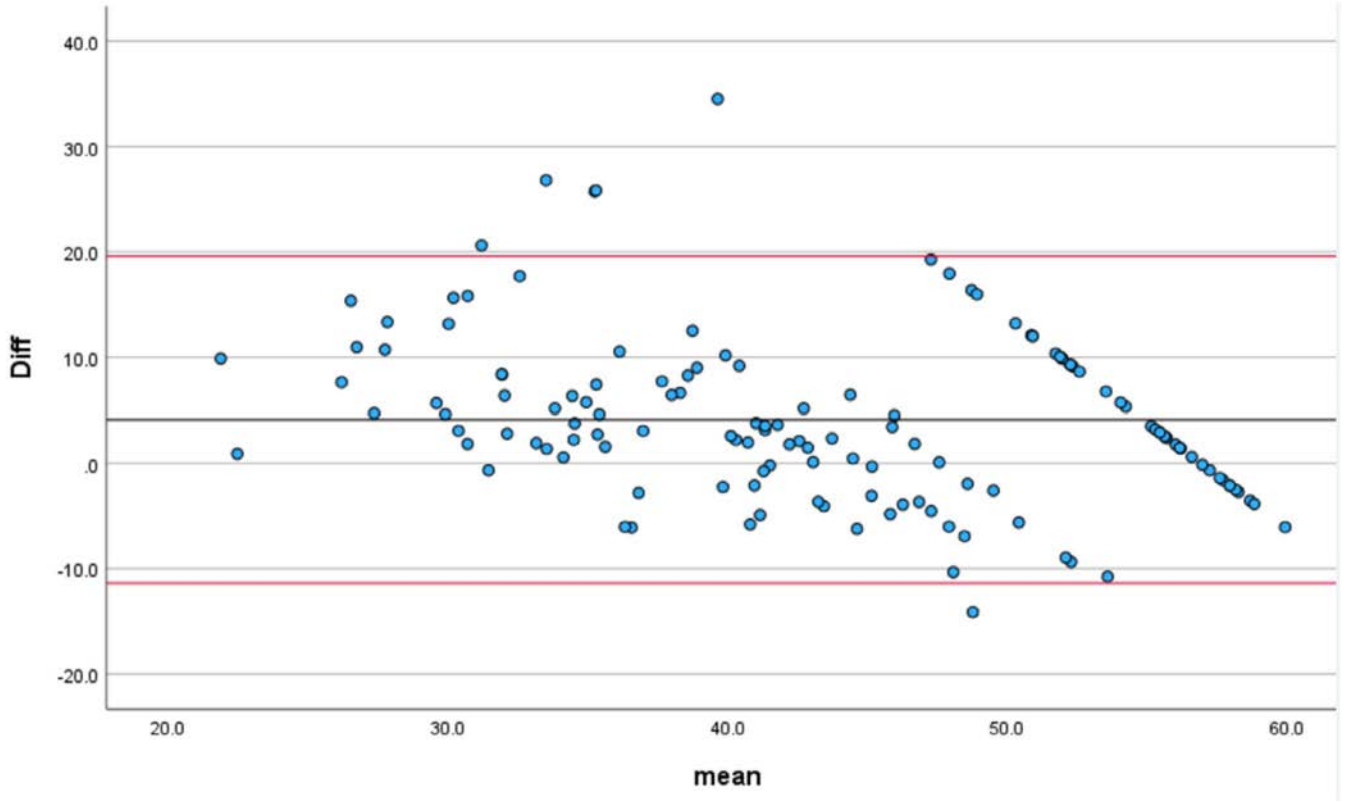

FIGURE 1 | Bland–Altman Plot. The *x* axis represents the mean values of SF-36 PCS and Promis-29 physical summary T-scores for each patient. The *y*-axis demonstrates the difference between the 2 T-score values for each *x*-axis value. The solid line is the mean value of the T-score difference scores, and the dashed lines represent the limits of agreement, which are 1.96 SDs from the mean.

PCS is quite abnormal, but unexpectedly it appears to be similar for the PROMIS-29. Thus, the validity of both mental health summary scores in SSc is in doubt.

Agreement between the SF-36 PCS and PROMIS-29 physical health summary scores by ICC was good, but it was only moderate by Lin's concordance coefficient, and Bland–Altman analysis showed a relatively large mean difference and limits of agreement, and the mean difference of the measures is greater than the MCIDs of the SF-36 PCS. As only one of the three methods showed good agreement between the measures, we have concluded that there is not enough support to call the summary scores interchangeable.

This suggests that the SF-36 PCS and the PROMIS may be measuring somewhat different aspects of the underlying construct of HRQoL.

Author Contributions

Murray Baron, Charmaine van Eeden and Mohamed Osman substantially contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; drafting the work or reviewing it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Mianbo Wang substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All members of the Canadian Scleroderma Research Group acquired the data, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

Murray Baron
Charmaine van Eeden
Mohamed Osman
Mianbo Wang
the Canadian Scleroderma Research Group

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LETTER TO THE EDITOR

Case Report: Fecal Impaction in an Atypical Localization at the Proximal Sigmoid Colon in a Patient With Systemic Sclerosis Recovered After Surgical Resection

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Dear Editor,

Systemic sclerosis (SSc) is a multisystem autoimmune connective tissue disease characterized by vasculopathy and progressive skin and internal organ fibrosis. Gastrointestinal system (GIS) involvement is frequent in both limited and diffuse SSc patients, up to 90%. While the esophagus is the most commonly affected area, any part of the gastrointestinal tract can be involved [1, 2]. Patients with SSc may experience reduced colonic contractions and prolonged colonic transit time [3]. Although alternating constipation–diarrhea episodes and pseudo-obstructions are the fairly well-defined symptoms of SSc patients with GIS involvement, mechanical obstructions are rare [2, 3]. Herein, we present a case of a patient with limited SSc who developed atypical mechanical obstruction of the proximal sigmoid colon due to fecal impaction.

A 67-year-old woman with limited SSc was admitted with a 2-week history of abdominal pain, nausea, and constipation. Prior to the constipation, she had diarrhea and was treated with ciprofloxacin and rifaximin for 2 weeks. The patient was diagnosed with SSc in 2011, presenting with Raynaud's phenomenon, skin thickening, and positive centromere antibodies. Following her diagnosis, the patient was initially treated with hydroxychloroquine and methotrexate, which were replaced by azathioprine and later by mycophenolate mofetil. She has not received any immunosuppressive therapy since 2019. The patient's medical history was also positive for gastroesophageal reflux disease (GERD) and pulmonary arterial hypertension (PAH), and she was on macitentan treatment (World Health Organization functional capacity II). There is no evidence of interstitial lung disease. She had a history of bowel perforation during a colonoscopy procedure 16 years ago but denied any hematemesis, melena, or hematochezia. On physical examination, she had sclerodactyly (MRSS: 3). Normoactive bowel sounds were heard in all four quadrants, and her abdomen was distended and tender without rebound. Laboratory tests revealed mild anemia, leukocytosis, and hypoalbuminemia [Hemoglobin: 11.6 g/dL (13.5–16.9), white blood cells: $13.78 \times 10^3/\mu L$ (4.49–12.68), albumin: 3.06 g/dL (3.5–5.2)] with elevated acute phase reactants [C-reactive protein: 126 mg/L (0–5), erythrocyte sedimentation rate: 54 mm/h (0–20)]. The abdominal X-ray showed no air-fluid levels. An abdominal computed tomography (CT) scan was performed for further evaluation, confirming colonic obstruction at the proximal sigmoid colon level, accompanied by colonic dilation (Figure 1A). After consulting with the surgical team, oral intake was restricted, and a nasogastric tube was inserted to alleviate vomiting and facilitate bowel rest. Domperidone and ondansetron were added to her treatment regimen, while macitentan remained uninterrupted during this period. The patient underwent daily abdominal X-rays and an attempted colonoscopy, which was not completed due to a blockage in the sigmoid colon. The distal segments observed during the procedure showed normal findings. Although the patient experienced partial relief in abdominal pain and distention following the colonoscopy, constipation persisted without improvement. During follow-up, a multidisciplinary committee comprising specialists in surgery, gastroenterology, and rheumatology determined that surgery was warranted due to prolonged treatment-resistant symptoms. Intraoperative exploration revealed dilatation of approximately 10 cm at the level of the sigmoid colon, with areas of necrosis and

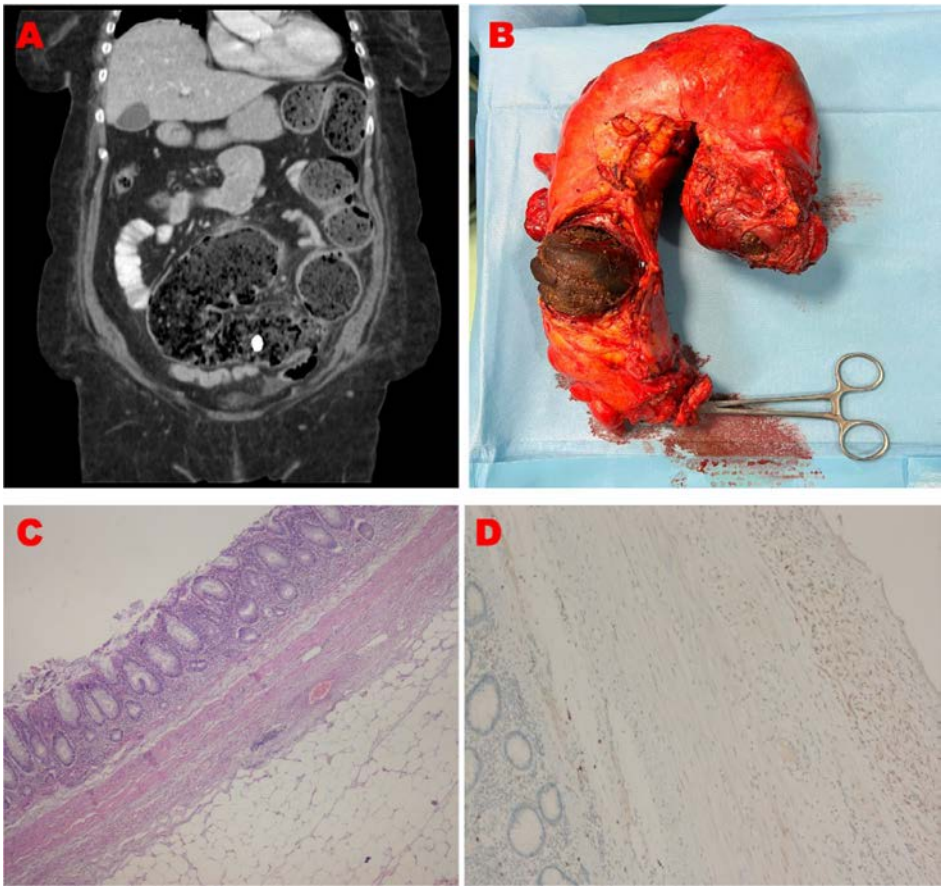

FIGURE 1 | (A) Colonic dilatation at sigmoid level, (B) Fecal impaction and perforation on the surgical specimen, (C) Atrophic muscle layers, (D) Relatively preserved neural networks in Calretinin staining.

spontaneous perforation occurred intraoperatively. Initially, segmental colon resection and anastomosis were planned but could not be performed due to the risk of fecal contamination. Instead, segmental colon resection with end colostomy was performed (Hartmann's procedure). After surgery, an abscess developed at the anastomosis site, necessitating treatment with drainage and antibiotics. During the follow-up, the patient's abdominal pain and nausea improved, leading to the resumption of oral intake. Fecal impaction and perforation were noted on the gross examination of the surgical specimen (Figure 1B). Pathological evaluation of the colon showed extensive fibrosis and atrophic smooth muscle bundles, especially at the circular muscular layer (Figure 1C). The atrophic muscle bundles exhibited vacuolated cells. Trichrome staining emphasized the presence of fibrosis. Immunohistochemical analysis with calretinin indicated relatively preserved neural networks compared to muscle tissue (Figure 1D). CMV testing yielded negative results. The findings indicated myopathic involvement rather than neuropathic plexus destruction, aligning with the manifestations observed in systemic sclerosis. During her outpatient follow-up, she tolerated oral intake well and her colostomy functioned properly. Therefore, we decided to close the colostomy after 3 months. Following the colonic anastomosis, she remained in good condition, although she experienced some distension complaints. Her follow-up abdominal CT revealed no intra-abdominal collection or abscess, and the anastomosis line was intact.

Gastrointestinal system involvement is the most common internal organ manifestation in SSc, and it is the third leading cause of disease-associated mortality [1, 4]. Colonic involvement, with a prevalence of 30%–50%, represents the least common subtype among gastrointestinal organs. Rectal involvement is more prevalent and can lead to symptoms such as constipation, fecal incontinence, and rectal prolapse [1–3]. Esophageal strictures and intestinal pseudo-obstruction are well-known causes of GIS obstruction in SSc. However, mechanical colonic obstruction is uncommon in SSc, with reported occurrences of volvulus, diverticulosis, and megacolon in this patient population [1–3]. Fecal impaction is frequent in the geriatric population, especially in patients who live in nursing homes and have multiple comorbidities. Patients with low fiber intake, dehydration, spinal cord injury, stroke, and dementia are at increased risk for the occurrence of fecal impaction. In severe cases, fecal impaction can lead to the development of ulcers and/or colonic ischemia [5–7]. Fecal impaction may occur in patients with SSc due to gastrointestinal hypomotility. Sarnoff et al. described a patient with diffuse cutaneous systemic sclerosis who developed fecal impaction due to a bezoar, which was successfully managed via colonoscopic disimpaction [8]. Additionally, other reports have documented acute colonic obstruction, intestinal atony, and volvulus in systemic sclerosis patients, emphasizing the diverse and potentially severe gastrointestinal manifestations of the disease [9–11]. There have also been reports of fecal

impaction in scleroderma patients in association with the use of barium and verapamil [12, 13]. In our patient, who was admitted to the hospital with complaints of abdominal pain and constipation, we determined fecal impaction in an atypical location at the proximal sigmoid colon. She also had a history of GERD, alternating periods of constipation and diarrhea, and had received treatment for small intestinal bacterial overgrowth, all suggestive of extensive GIS involvement. During her follow-up, despite supportive treatment, she did not show any improvement, leading us to opt for surgical intervention. Although an intraoperative perforation was noted, her symptoms improved after surgery, and she tolerated oral intake well. Three months later, we performed a second operation for colonic anastomosis. The possibility of fecal impaction in an SSc patient with colonic obstruction should be kept in mind. A timely decision to operate is essential in this patient group due to the increased risk of perforation without any change in symptoms, as in our patient.

Fecal impaction in systemic sclerosis may result from multiple pathophysiological mechanisms. Vasculopathy and enteric neurogenic damage are pivotal in the pathogenesis of SSc-associated GIS involvement, leading to smooth muscle atrophy and/or fibrosis in the gastrointestinal tract. Both autoantibodies (such as anti-muscarinic receptor 3 antibodies) and cell-mediated damage play roles in the development of GIS involvement in patients with SSc [1, 2]. Autonomic neuropathy and smooth muscle atrophy lead to colonic hypomotility, impairing effective peristalsis. Fibrosis and loss of enteric neurons further disrupt gastrointestinal transit [14]. Additionally, pelvic floor dysfunction and dyssynergic defecation can hinder stool evacuation. In our patient, pathological evaluation revealed severe smooth muscle atrophy and fibrosis, despite a preserved enteric nervous system. While these findings, coupled with PAH, may support a severe vasculopathic process in GIS involvement in our patient, we could not exclude the possibility of functional impairment of the enteric nervous system. Certain medications commonly used in SSc, such as calcium channel blockers or opioids, may exacerbate constipation. We have not seen any reported cases of fecal impaction related to the patient's current medications (colchicine, macitentan, acetylsalicylic acid, and methylprednisolone), but there have also been reports of fecal impaction in SSc patients in association with the use of barium and verapamil [12, 13]. Prior abdominal surgeries, particularly those involving colonic perforation, as in our patient's history, can also contribute through altered motility or adhesions. Reduced dietary fiber and fluid intake, often secondary to dysphagia or gastrointestinal symptoms, may further aggravate bowel dysfunction. Together, these factors create a high-risk environment for fecal stasis and subsequent impaction.

In this report, we have documented that although GIS involvement is prevalent in SSc, the severity of involvement can vary even within the same part of the gastrointestinal tract. Notably, our patient's quality of life improved significantly following the colonic anastomosis. On the other hand, this decision was made clinically, addressing the need for feasible and objective methods to evaluate the severity of GIS involvement in SSc.

Author Contributions

B.B., B.F.-Y., and A.A. contributed to data analysis and drafting of the original manuscript. O.C. and A.A. reviewed and revised the manuscript. All authors read and approved the final version for submission.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Case Report: Cryptococcal Meningitis During Tofacitinib Therapy in Ulcerative Colitis: A Rare Opportunistic Infection

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Keywords: cryptococcal meningitis | tofacitinib | ulcerative colitis

Dear Editor,

Tofacitinib, a Janus kinase (JAK) inhibitor, is increasingly used in patients with moderate to severe ulcerative colitis (UC) who fail anti-TNF therapy. However, its immunosuppressive effects may predispose patients to rare opportunistic infections. Here we report a 47-year-old man with a history of severe UC was hospitalized 1 month prior due to an acute severe flare (Figure 1). He was under oral prednisolone 15 mg daily treatment before admission. During this episode, his treatment regimen was switched from infliximab to oral tofacitinib due to a loss of response. After 1 month of tofacitinib therapy, he presented with a 7-day history of headache, accompanied by fever, drowsiness, and neck stiffness. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (82 cells/μL), an elevated protein level (192.2 mg/dL; reference range: 15–45 mg/dL), and a decreased glucose level (25 mg/dL; reference range: 40–70 mg/dL). A meningitis and encephalitis panel detected *Cryptococcus neoformans* /gattii DNA, and CSF cryptococcal antigen testing was positive with a titer of 1:80. A human immunodeficiency virus test was negative. Brain computed tomography showed no significant intracranial abnormalities. A diagnosis of cryptococcal meningitis was established.

The patient received antifungal induction therapy with intravenous amphotericin B deoxycholate, which was later transitioned to liposomal amphotericin B due to renal toxicity. Oral flucytosine (1500 mg every 6 h) was coadministered and continued throughout the 28-day induction phase. During hospitalization, UC treatment was maintained with oral tofacitinib (11 mg once daily) and mesalazine. After achieving clinical stability, consolidation therapy with oral fluconazole (750 mg daily) was initiated and continued for 2 months. The patient remained stable and was scheduled to continue oral fluconazole maintenance therapy (200 mg daily) for 1 year. Follow-up endoscopy performed 6 months after starting tofacitinib demonstrated improvement in UC (Figure 2).

Janus kinase inhibitors—such as tofacitinib, upadacitinib, and filgotinib—have been approved for the treatment of adults with moderate to severe UC who have failed or are intolerant to anti-tumor necrosis factor (TNF) therapies [1, 2]. Tofacitinib, a pan-JAK inhibitor with activity against JAK1, JAK3, and to a lesser extent JAK2, was the first approved JAK inhibitor for UC. In the OCTAVE Induction 1 and 2 trials, the rates of overall infection and serious infection were higher with tofacitinib than with placebo [3]. Notably, opportunistic infections—including herpes zoster [4, 5], tuberculosis [6], esophageal candidiasis, Pneumocystis jirovecii, cytomegalovirus (CMV), and cryptococcal infections—have been reported [7], although much of the early safety data originated from rheumatoid arthritis cohorts.

To the best of our knowledge, only five cases of cryptococcal infection have been reported in patients receiving tofacitinib therapy. Among these, three involved pulmonary infection and two presented with disseminated disease [8–10]. Notably, none of the cases were associated with treatment for inflammatory

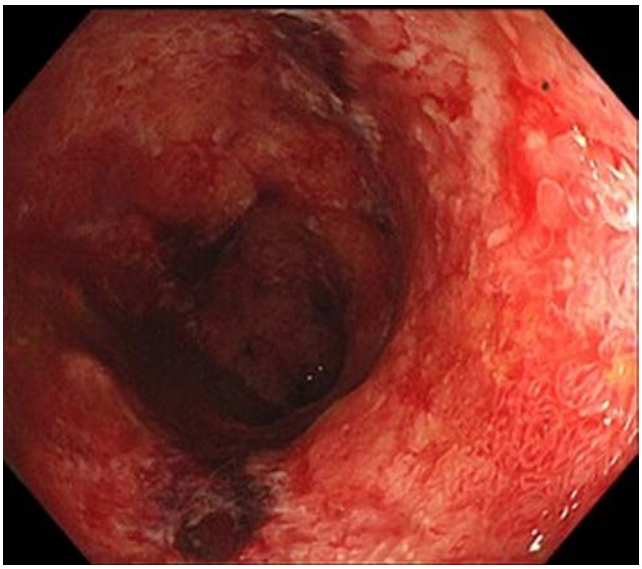

FIGURE 1 | Colonoscopy at admission revealed severe mucosal inflammation, corresponding to a Mayo endoscopic subscore of 3.

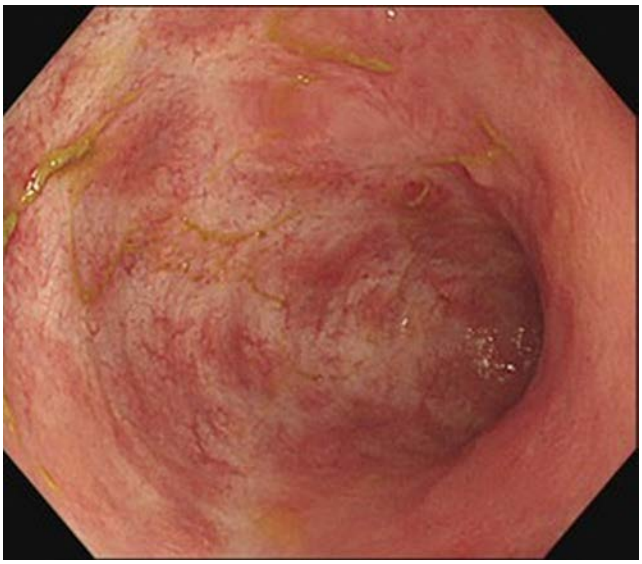

FIGURE 2 | Colonoscopy at 6-month follow-up showed mucosal healing, corresponding to a Mayo endoscopic subscore of 0.

bowel disease. In this case, the patient developed cryptococcal meningitis within 1 month of initiating tofacitinib—a rare but potentially life-threatening opportunistic infection if left unrecognized. This underscores the importance of a comprehensive evaluation of the patient prior to and during treatment. Pretreatment screening for latent infections, timely administration of recommended vaccinations, and ongoing clinical monitoring are essential to minimize the risk of serious infectious complications—particularly when immunosuppressive therapy is initiated or escalated.

Author Contributions

Chien-Ming Chen: writing and final approval of the manuscript. **Hsu-Heng Yen:** conception, care of the patient, writing, and final approval of the manuscript. **Yang-Yuan Chen:** final approval of the manuscript.

Disclosure

Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work, the authors used Copilot software and ChatGPT to enhance language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Discordance in Patient and Physician's Perception of Disease Activity Among Idiopathic Inflammatory Myopathy Patients: Insights From the COVAD Study

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Dear Editor,

Disease activity assessment forms the cornerstone of the management of patients with idiopathic inflammatory myopathies (IIMs), and is crucial for titrating the dose of immunosuppressants for optimal disease control and improving patient's physical function and quality of life [1]. Traditional methods of assessing disease activity in IIMs primarily rely on in-person clinical examination techniques, such as manual muscle testing, and laboratory investigations, particularly muscle enzyme levels [2]. However, during circumstances where in-person evaluations are limited, such as the COVID-19 pandemic, disease activity may be gauged through patient-reported symptoms. Patients and physicians have differences in perception of symptoms, prioritization of different parameters, and hence, discordance can occur in their assessment of disease activity [3].

The specific factors contributing to this disparity may vary depending on the subtype of IIMs and patient population, which remains an underexplored aspect [4]. This discordance has important implications, as it may lead to underestimation of disease severity by the physician and inadequate treatment, which in turn can impact patient outcomes such as function and quality of life. While studies have shown that patients with higher self-reported disease activity compared to their physicians'

Abbreviations: ASyS, antisynthetase syndrome; COVAD, COVID-19 Vaccination in Autoimmune Diseases; DM, dermatomyositis; GC, glucocorticoid; HCs, healthy controls; HDI, human development index; IBM, inclusion body myositis; ICC, interclass correlation; IIMs, idiopathic inflammatory myopathies; NAM, necrotizing autoimmune myopathy; OM, overlap myositis; PA, patient assessment; PM, polymyositis; PROMIS SF10, Patient Reported Outcome Measurement Information System Scale v1.2 (Global Health); PROs, patient reported outcomes; PRPA, patient-reported physician assessment; QoL, quality of life; VAS-F, visual analogue scale-fatigue; VAS-P, visual analogue scale-pain.

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For affiliations refer to page 4.

assessments have poorer long-term outcomes, there is a lack of consensus on how to integrate patient-reported outcomes in the assessment of disease activity to guide treatment decisions [5]. In this study, we explored the level and predictors of disparity in patient-physician-reported disease activity in a global sample of patients with IIMs from the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study.

The COVAD study is a global, multicenter survey assessing COVID-19 vaccination, infection, and disease activity in autoimmune diseases. The survey was administered through SurveyMonkey from April to December 2021, with ethical approval and informed consent obtained from all participants [6].

The survey gathered data on participant demographics, disease details (diagnosis, duration, treatment history, and current symptom status), infection history, vaccination details, and patient-reported outcomes (PROs) such as physical function, pain, and fatigue, using established PRO tools such as the Patient-Reported Outcome Measurement Information System (PROMIS) Short Form v1.2 for global health, the visual analogue scale (VAS) for pain (VAS-P), and the VAS for fatigue (VAS-F).

Disease activity was assessed from two perspectives: patient assessed (PA) and patient reported physician-assessed activity (PRPA). PA was measured using a 5-point Likert scale in which patients reported their disease as "active," "improving," "stable," "worsening," or "inactive/remission." PRPA was determined by the patient reported physician's assessment based on patient-reported symptoms such as joint swelling, active rash, muscle weakness, and the use of glucocorticoids (GC) greater than or equal to 10 mg/day of prednisolone equivalent. Discordance was based on whether patients perceived their disease activity as active, while their physicians considered it inactive, or vice versa.

Statistical analysis was performed to assess the level of agreement between PRPA and PA using the Phi coefficient for concordance and multivariable logistic regression models to identify factors influencing discordance. A range of covariates, including age, gender, VAS-P, VAS-F, and PROMIS Physical Function (PF-10a) scores, were adjusted for in these models. The internal consistency of the PROMIS scores and other PROs was evaluated using interclass correlation (ICC), and the associations between categorical variables were measured using Cramér's Phi coefficient. A p-value of 0.05 was considered significant and a 95% confidence interval was used for precision.

The survey sample included 1217 IIM patients with a median age of 59 years (IQR 45–73), 70% of which were female. Of these patients, 30.9% had DM, 26.7% had IBM, and 12.5% had PM, with IBM patients being older on an average and having a higher proportion of Hispanic individuals compared to other subtypes (Table S1). The disease activity assessment showed that 52.8% ($n=643$) of respondents were classified as PRPA active, while 76.7% ($n=933$) were classified as PA active. Concordance between patient and physician assessments was observed in 61.2% ($n=745$) of cases, with discordance noted in 38.8% ($n=472$) of patients. Discordance was most common in IBM patients, where a significant proportion of patients reported active disease despite physician assessments of inactivity.

The agreement between patient and physician assessments of disease activity was moderate overall ($\phi=0.23$, $p<0.001$), with the greatest discordance observed in IBM ($\phi=0.12$, $p=0.03$), overlap myositis (OM) ($\phi=0.11$, $p=0.17$), and necrotizing autoimmune myopathy (NAM) ($\phi=0.001$, $p=0.99$) subgroups. By contrast, subgroups such as dermatomyositis (DM) ($\phi=0.33$, $p<0.001$), polymyositis (PM) ($\phi=0.25$, $p=0.002$), and antisynthetase syndrome (ASyS) ($\phi=0.27$, $p=0.001$) exhibited lower levels of discordance. The internal consistency of the PROMIS, VAS-P, and VAS-F scales demonstrated a high correlation (interclass correlation >0.9). The PROMIS scores were highest and pain and fatigue scores were lowest when there was concordance on inactive disease, and a worsening of these scores (lower PROMIS, higher pain, and fatigue) was noted in the discordant groups ($p<0.001$) (Table 1). Discordant pairs, where only physicians perceived disease activity (PRPA-active), exhibited higher levels of pain and fatigue compared to pairs in which patients reported active disease (PA-active) (Table 2). Lower PROMIS scores (poorer physical function) were similarly reflected in the discordant pairs of the individual disease subgroups, except IBM (Figure S1).

Multivariable analysis revealed that lower PROMIS scores were associated with a higher likelihood of classification into discordant PA-active group in patients with DM ($p=0.02$), PM ($p=0.001$), and ASyS ($p=0.009$) subgroups, but not in the IBM and OM subgroups (Table S2). Furthermore, higher pain levels were predictive of discordance in DM patients (OR [95% CI]: 1.27 = [1.01–1.16], $p=0.04$).

PROMIS scores also varied by country HDI, with significant differences between medium, high, and very high HDI groups (27.7 ± 11.4 vs. 30.9 ± 10.6 vs. 25.4 ± 10.4 respectively, $p<0.001$). On multivariate analysis after adjusting for other covariates significance of this effect did not persist (Table S3).

Receiver operating characteristic (ROC) curves were drawn to identify cut-off values for PROMIS scores that could distinguish

TABLE 1 | Patient reported outcomes among the four groups of perceived disease activity in the entire dataset.

Parameters	Concordance: inactive	Discordance: PRPA-active	Discordance: PA-active	Concordance: active	p
Fatigue VAS	3.34 ± 2.985	5.2 ± 2.76	4.4 ± 2.65	5.329 ± 2.34	<0.001
Pain VAS	1.8 ± 2.439	3.51 ± 2.89	2.658 ± 2.655	3.45 ± 2.64	<0.001
PROMIS PF10a	41.546 ± 9.56	35.04 ± 9.327	34.67 ± 10.54	31.03 ± 9.67	<0.001

Note: PRPA active: patient-reported physician assessment where only physician's perceives disease as active, and patient does not; PA-active: patient assessment where only patient perceives disease as active, and physician does not; PF10a: physical function 10a; PROMIS: Patient-Reported Outcome Information System; VAS: visual analogue scale (0–10).

TABLE 2 | Pairwise comparisons of concordance and discordance states across different patient reported outcomes (fatigue/pain/PROMIS PF10a respectively).

	Concordance: inactive	Discordance: PRPA-active	Discordance: PA-active	Concordance: active
Concordance: inactive	N/A	<0.001/<0.001/<0.001	<0.001/<0.001/<0.001	<0.001/<0.001/<0.001
Discordance: EA	<0.001/<0.001/<0.001	N/A	0.01/0.003/0.98	0.98/0.93/<0.001
Discordance: PA	<0.001/<0.001/<0.001	0.01/0.003/0.98	N/A	<0.001/<0.001/<0.001
Concordance: active	<0.001/<0.001/<0.001	0.98/0.93/<0.001	<0.001/<0.001/<0.001	N/A

Note: PRPA active: patient-reported physician assessment where only physician's perceives disease as active, and patient does not; PA-active: patient assessment where only patient perceives disease as active, and physician does not; PF10a: physical function 10a; PROMIS: Patient-Reported Outcome Information System; VAS: visual analogue scale (0–10); N/A: not applicable.

between active and inactive disease (Figure 1). The following PROMIS scores were used as cut-offs to distinguish inactive disease subgroups in patients: DM− 43.5 (sensitivity 71.9%, specificity 71.5%, the area under the curve [AUC]: 0.76 [95% CI: 0.7–0.82], $p < 0.001$); PM− 36.5 (sensitivity 81.6%, specificity 60.5%, AUC: 0.75 [0.67–0.84], $p < 0.001$); ASyS− 43.5 (sensitivity 65.2%, specificity 70.2%, AUC: 0.78 [95% CI: 0.68–0.88], $p < 0.001$) and OM− 35.5 (sensitivity 84.2%, specificity 50%, AUC: 0.69 [95% CI: 0.57–0.82], $p = 0.006$). These cut-offs demonstrated good sensitivity and specificity, particularly in the DM, PM, ASyS, and OM subgroups.

This study highlights the significant disparity between PRPA and PA in IIMs. The highest discordance was observed in the IBM subgroup. Discordance was largely due to patients perceiving their disease as active, while physicians did not, possibly due to the subjective nature of symptoms such as pain (muscle pain and diffuse pain), skin lesions, and fatigue, which were more pronounced in the discordant groups due to the level of agreement between patients and physicians being 41% [7]. Physician assessments were more closely tied to functionality loss, ensuring an optimal quality of life, and attaining disease remission. Thus, PRPA of active disease may be guided largely by the patient-reported pain and fatigue, while the PA may be colored by their experience of pain, fatigue, overall quality of life (QoL), and additional comorbidities that may confound the accurate assessment of disease activity. This may explain our observation of the highest discordance in the IBM group, where individuals had the highest average age of all subgroups, with older age contributing to a worse QoL in these patients. Discordance between patient-reported and physician-reported assessments may also arise from clinical nuances, such as comorbid fibromyalgia, depression, or other overlapping pain and fatigue syndromes, rather than misjudgment. Stratification of discordant cases by patient-reported outcomes or comorbid burden in future analyses may provide a better understanding of these discrepancies.

The discordance with PA-active disease perceived inactive by the physician was the least predominant in DM, PM, and ASyS groups, plausibly due to the systemic involvement of multiple organs in these diseases leading to more rigorous monitoring of patient-reported symptoms and disease activity by the physician [8, 9]. In contrast, the highest disparity was present in the IBM, OM, and NAM subgroups, possibly due to the predominantly muscular involvement of these diseases, where the physician has to depend on patient reports and their interpretation of physical examination tools to ascertain disease progression. Another possible explanation may be the inclusion of GC use as a marker for PRPA-active disease, a practice typically not applied in the context of IBM.

The concordant groups in this study were largely homogeneous and effectively modeled using linear scales like fatigue VAS, pain VAS, and PROMIS PF10a scores, particularly in DM, PM, ASyS, and OM patients. PROMIS scores demonstrated high sensitivity and specificity in distinguishing active from inactive disease, as supported by ROC curves with AUC > 0.5. These findings suggest that the physician's empiric assessment of active disease could be replaced with simple PROMIS PF10a cut-offs, enabling reliable remote disease monitoring. However, discordant groups with intermediate scores may represent a "grumbling disease" continuum, requiring closer follow-up to track progression. Although the PROMIS PF10a cut-off points are promising, but

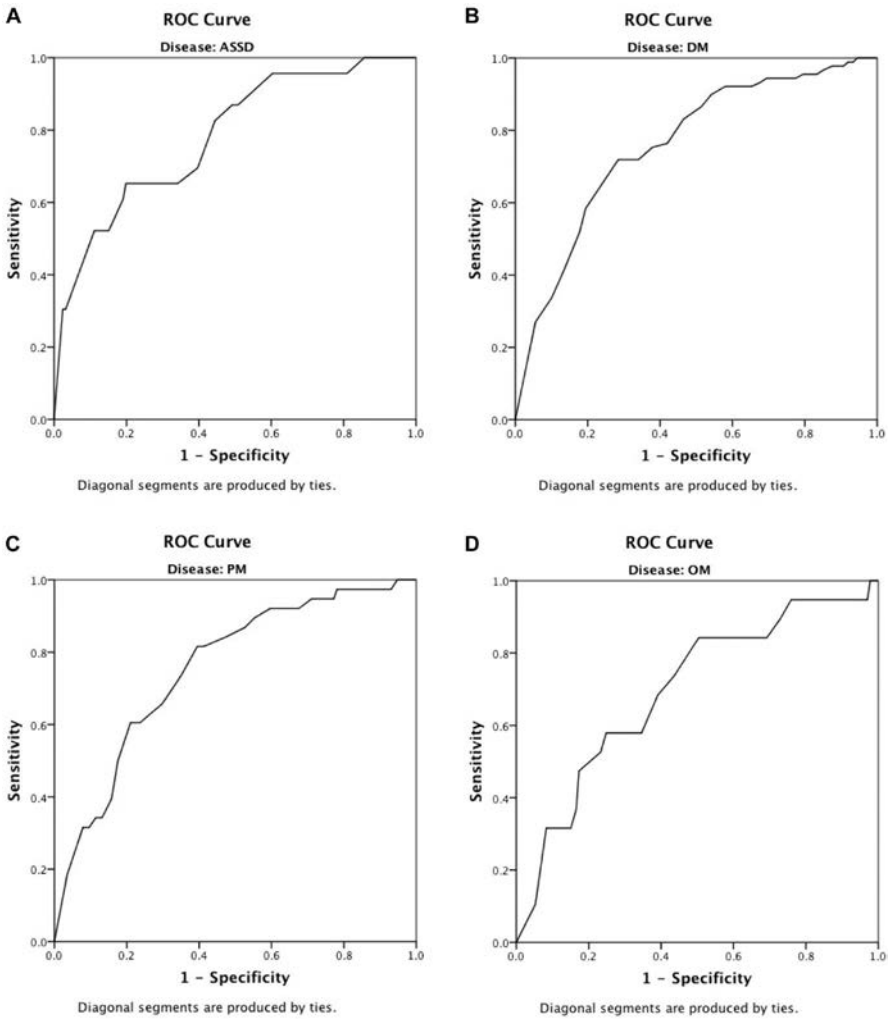

FIGURE 1 | ROC curves for differentiating concordance between patient and physician's perception of inactive disease from any perception of active disease in different types of idiopathic inflammatory myopathies: ASyS (panel A), DM (panel B), PM (panel C) and OM (panel D) by PROMIS PF10a scores. ASyS, antisynthetase syndrome; DM, dermatomyositis; OM, overlap myositis; PF: physical function; PM, polymyositis; PROMIS, Patient-Reported Outcome Information System; ROC, receiver operating characteristic.

further external validation is required, including assessment of measurement error and potential floor or ceiling effects, to confirm their reliability and clinical utility.

This study underscores the need to integrate PROs with reliable markers into routine clinical practice to capture patient perspective. However, PROs are not well established by global studies, primarily due to a lack of matched physician data in specific cohorts [10, 11].

This study's strengths include its large, multinational sample and analysis of patient-physician disparity across IIM subgroups using PROMIS scores. These findings must be interpreted considering certain limitations, including reliance on self-reported diagnoses, absence of disease duration data, and the cross-sectional design, which precludes causal inferences. Importantly, PRPA is based on patient recall rather than medical records, introducing a potential risk of recall or misclassification bias. Additionally, due to the cross-sectional design, the findings can only be interpreted as associative and do not imply causation. Longitudinal studies will be required to confirm these observations and assess their stability over time.

The discordance between PRPA and PA is an important challenge, but integrating PROs could help improve disease monitoring and patient care. Simple cut-off values based on PROMIS scores may offer an effective means of distinguishing between active and inactive disease, which could facilitate remote disease monitoring and reduce the need for in-person consultations, ultimately improving patient outcomes.

Author Contributions

Conceptualization: R.P.G., Z.Z.F., P.S., and L.G. Data curation: All authors. Formal analysis: R.P.G.; Funding acquisition: N/A. Investigation: R.P.G., L.G., Z.Z.F., and P.S. Methodology: L.G., V.A., and R.N.; Software: L.G. Validation: V.A., and J.B.L. Visualization: V.A., and L.G. Writing-original draft: R.P.G., Z.Z.F., P.S., and L.G. Writing-review and editing: all authors.

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Disclosure

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Ethics Statement

Ethical approval was obtained from the Institutional Ethics Committee of SGPGIMS, Raebareli Road, Lucknow.

Consent

All participants consented electronically.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apl70428-sup-0001-supinfo.docx.

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EDITORIAL

Helicobacter pylori and Immune-Mediated Diseases: A Complex Interplay

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1 | Introduction

Helicobacter pylori (*H. pylori*) is a bacterium that commonly infects the human stomach, causing various gastrointestinal diseases, including gastritis, peptic ulcers, and gastric cancer. Despite often being asymptomatic, its potential role in immune-mediated diseases has garnered significant attention. Immune-mediated diseases arise from abnormal immune responses targeting the body's own tissues, leading to chronic inflammation and damage. This editorial explores the current understanding of this complex relationship, its implications, and directions for future research [1–3].

2 | Prevalence of *H. pylori* and Immune-Mediated Diseases

Globally, *H. pylori* infection remains prevalent despite its decreasing incidence over the last three decades, dropping from 52.6% before 1990 to 43.9% between 2015 and 2022. Over 40% of the world's population is affected, with higher prevalence in developing countries. Notably, the "African and Asian enigma" highlights lower incidences of gastric carcinoma and peptic ulcer disease in regions with high *H. pylori* prevalence, suggesting that bacterial strain variations and host genetics may influence disease outcomes [1].

Immune-mediated diseases are increasingly common, affecting an estimated 5%–7% of the population in Western societies. In 2019, approximately 67.6 million cases of immune-mediated inflammatory diseases were reported globally. The rise in these conditions, potentially driven by environmental changes like pollution, diet, and infections, underscores the importance of understanding *H. pylori*'s role in their development [4, 5].

3 | Mechanisms Linking *H. pylori* to Immune-Mediated Diseases

Several mechanisms may explain how *H. pylori* contributes to immune-mediated diseases, which are shown as Table 1.

4 | Current Evidence

Research on the link between *H. pylori* and immune-mediated diseases remains mixed. Table 2 is a summary of current evidence.

5 | Implications for Prevention and Treatment

5.1 | Early Detection and Eradication

Early identification and eradication of *H. pylori* may help prevent associated immune-mediated diseases, particularly in high-risk individuals [3, 6]. Implementing appropriate screening

Yen-Chu Huang and Meng-Che Wu are contributed equally to this work.

TABLE 1 | Mechanisms linking *H. pylori* to immune-mediated diseases.

Mechanism	Description	Example
Molecular Mimicry	*H. pylori* antigens resemble human proteins, leading to immune responses targeting both the bacteria and host tissues.	In autoimmune gastritis, CD4+ T cells cross-react with H+, K+-ATPase and *H. pylori* antigens [3, 4].
Chronic Inflammation	Persistent *H. pylori* infection induces chronic inflammation, disrupting immune regulation.	*H. pylori* infection causes immune cell infiltration and inflammatory cytokine production in gastric mucosa [5].
Immune Modulation	*H. pylori* alters host immune responses, leading to dysregulation and autoimmunity.	Virulence factors like VacA and CagA modulate dendritic cell function and cytokine secretion [6].
Genetic Susceptibility	Host genetic factors influence susceptibility to *H. pylori* infection and immune-mediated diseases.	Polymorphisms in immune-related genes may heighten autoimmune disease risks in *H. pylori* infection [7].

TABLE 2 | Current evidence with *H. pylori* to immune-mediated diseases.

Autoimmune condition	Evidence	Overall association
Immune Thrombocytopenic Purpura (ITP)	Strong association; eradication improves platelet counts in some patients [3].	Likely association
Autoimmune Gastritis	*H. pylori* is a known trigger [4].	Definite association
Chronic Urticaria (CU)	Conflicting evidence; eradication may benefit some patients [6].	Possible association
Psoriasis	Some evidence suggests symptom improvement after eradication [8].	Possible association
Alopecia Areata	Limited evidence suggests a possible link [7].	Possible association
Rheumatoid Arthritis	Conflicting findings [5].	Uncertain association
Systemic Lupus Erythematosus (SLE)	Conflicting findings [5].	Uncertain association
Autoimmune Thyroid Diseases	Conflicting findings [9].	Uncertain association
Primary Biliary Cirrhosis (PBC)	Limited evidence of association via molecular mimicry [10].	Possible association
Primary Sclerosing Cholangitis (PSC)	Limited evidence; *H. pylori* DNA detected in liver samples [6].	Uncertain association
Inflammatory Bowel Diseases (IBD)	Conflicting findings [11–13].	Uncertain association
Ankylosing Spondylitis (AS)	Limited evidence; the AS and uSpA incidences were lower in the follow-up after UBT in the previously *H. pylori* positive individuals than in the *H. pylori* negative individuals [14].	Uncertain association
Sjögren's Syndrome	Inconclusive evidence [15].	Uncertain association

and intervention strategies for at-risk populations could mitigate its long-term effects on the host immune system.

5.2 | Targeted Therapies and Immune Regulation

A deeper understanding of *H. pylori* 's mechanisms may facilitate the development of targeted therapies aimed at modulating immune responses or blocking molecular mimicry [4, 5]. Recent research has focused on precision medicine approaches, including novel therapeutic regimens [such as vonoprazan (a potassium-competitive acid blocker)] [16] and the use of biomaterials, protecting drugs against stomach acid and target lesions, controlling drug release, and destroying biofilms, to enhance treatment efficacy [17]. These approaches have the potential to provide more precise treatment strategies for *H. pylori* -associated immune disorders like immune thrombocytopenic purpura [17] and autoimmune gastritis [16].

5.3 | Personalized Medicine and Genetic Susceptibility

Identifying host genetic susceptibility factors may enable the development of personalized treatment approaches [7, 9]. Genetic screening could help determine individual risk profiles, allowing for tailored eradication strategies that minimize potential adverse effects.

5.4 | The Dual Role of *H. pylori* in Immune Regulation

Interestingly, *H. pylori* may exert protective effects against certain autoimmune and allergic diseases, highlighting its dual role in immune regulation. Studies have reported potential therapeutic benefits of *H. pylori* eradication in autoimmune dermatological conditions, such as chronic urticaria and psoriasis [10].

However, the debate over whether *H. pylori* should always be eradicated remains unresolved. While eradication may be beneficial for certain autoimmune conditions, emerging evidence suggests that the absence of *H. pylori* could negatively impact the gut microbiome, potentially increasing the risk of allergic or metabolic disorders [3, 18]. This complex interplay underscores the need for a balanced approach, with treatment strategies tailored to individual patient profiles based on clinical and genetic risk factors.

6 | Future Research Directions

Robust, large-scale studies are essential to confirm associations and establish causality between *H. pylori* and specific immune-mediated diseases [8, 11]. Further research into the pathogen's virulence factors and host immune responses is crucial for elucidating the underlying mechanisms of infection and immune modulation [4]. Understanding host-pathogen interactions, particularly the genetic and environmental factors influencing susceptibility to *H. pylori* and autoimmunity, is vital in identifying at-risk populations [7]. Additionally, exploring novel therapeutic strategies targeting *H. pylori* virulence factors or immune dysregulation may pave the way for more effective treatments [10]. Continued efforts in vaccine development, including the identification of novel antigen candidates and the advancement of delivery systems, remain a priority in preventive strategies [19]. Furthermore, longitudinal studies observing the effects of *H. pylori* over time are necessary to comprehensively assess its dual role in immune regulation, shedding light on both its protective and pathogenic influences [18].

7 | Conclusion

The interplay between *H. pylori* and immune-mediated diseases is complex, involving multifaceted mechanisms. While evidence supports an association with certain autoimmune conditions, further research is essential to elucidate these relationships fully. Early detection, eradication, and novel therapeutic approaches may hold promise for managing and preventing these conditions. However, the dual role of *H. pylori* in influencing immunity—both as a potential pathogen and a contributor to immune homeostasis—should not be overlooked [1, 6].

Given the global prevalence of both *H. pylori* infection and autoimmune diseases, advancing our understanding of this interaction is a critical priority in modern medicine. Precision medicine strategies that consider individual genetic, environmental, and microbial profiles will be pivotal in optimizing prevention and treatment for patients impacted by both *H. pylori* and immune-mediated diseases [5, 7].

Author Contributions

Y.-C.H. and M.-C.W. drafted the manuscript. P.-Y.L. provided suggestions, reviewed, and edited the manuscript several times. All authors approved the final version of the manuscript.

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Ethics Statement

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Conflicts of Interest

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EDITORIAL

Are Pharmacological Interventions for Adults With Low Back Pain Effective and Safe? An Overview of Cochrane Reviews Summary With Commentary

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The aim of this commentary is to discuss the Cochrane Overview of Reviews "Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews" [1] by Cashin AG, Wand BM, O'Connell NE, Lee H, Rizzo RRN, Bagg MK, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH,[1] published by the Cochrane Back and Neck and Cochrane Musculoskeletal Groups. This Cochrane Corner is produced in agreement with the *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation with views[2] of the review summary authors in the "implications for practice" section.

1 | Background

In 2020, low back pain (LBP) affected approximately 619 million people globally, making it the leading cause of years lived with disability (YLDs) worldwide [2]. The global burden is expected to rise significantly, with projections showing that by 2050, over 800 million people will be living with LBP. This ever-increasing prevalence highlights the urgent need for tailored strategies to manage the condition in different settings. A key challenge lies in aligning healthcare practices with clinical guidelines to curb excessive opioid use and avoid unnecessary, costly surgical interventions [2]. Guidelines recommend mostly a comprehensive clinical assessment and tailored rehabilitation, although medication may be considered for certain indications [3, 4]. Current guidelines for the pharmacological management of LBP recommend initiating treatment with oral nonsteroidal anti-inflammatory drugs (NSAIDs), using the lowest effective dose for the shortest possible period, and tailoring the choice to each patient's risk factors [3, 4]. If NSAIDs are contraindicated, not tolerated, or ineffective, weak opioids (with or without paracetamol) may be considered for acute low back pain; however, routine use of opioids is discouraged, particularly for chronic LBP. Additionally, the guidelines advise against offering paracetamol alone, or the use of SSRIs, SNRIs, tricyclic antidepressants, gabapentinoids, or antiepileptics for managing LBP. However, the evidence for the pharmacological treatment of LBP is rather weak, and the advantages must be carefully weighed against the disadvantages [5].

2 | Pharmacological Treatments for Low Back Pain in Adults: An Overview of Cochrane Reviews

(Cashin AG, Wand BM, O'Connell NE, Lee H, Rizzo RRN, Bagg MK, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH, 2023)

2.1 | What Is the Aim of This Cochrane Review?

This Cochrane Overview of Reviews aimed to summarize the evidence from Cochrane Systematic Reviews (CSRs) of randomized controlled trials on the efficacy, effectiveness, and safety of systemic pharmacological interventions for adults with non-specific low back pain.

2.2 | What Was Studied in the Cochrane Review?

The population addressed in this review was adults, 18 years or older, with non-specific LBP (e.g., non-radicular LBP, with or without non-specific degenerative changes), of any duration. Systematic reviews that included participants with spinal stenosis, LBP caused by known structural or pathological or specific medical conditions were excluded. The interventions studied were systemic pharmacological interventions used with the intent to improve pain and function for people with LBP, considered broadly as any medicine that affects the body as a whole, rather than individual parts or organs. There was no restriction on routes of administration or dose, and combinations of pharmacological interventions were also included. Comparisons were the following:

- Pharmacological intervention versus placebo or sham intervention (efficacy).
- Different forms of the same pharmacological intervention (e.g., selective NSAID versus a non-selective NSAID) (effectiveness).
- Pharmacological intervention versus a different type of pharmacological intervention (effectiveness).
- Pharmacological intervention versus a non-pharmacological intervention (effectiveness).

The major outcomes studied were pain, physical function, and safety. Minor outcomes were participant ratings of improvement, health-related quality of life, and workplace participation. The outcomes were grouped into a short-term period (≤ 3 months postintervention), an intermediate-term period (3–12 months postintervention), and a long-term period (> 12 months postintervention).

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

The review authors searched for Cochrane Reviews in the Cochrane Database of Systematic Reviews that had been published from inception to June 3, 2021, without restriction. They used a combination of Medical Subject Headings (MeSH) and keywords on low back pain.

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

Seven reviews were included with 22 238 participants across 103 unique randomized controlled trials (RCTs), with two to 32 RCTs in each review. Sample sizes ranged from 722 to 5540 participants. Six CSRs were published before 2017 and one in 2020. The reviews reported on six pharmacological intervention classes: paracetamol, NSAIDs, muscle relaxants, benzodiazepines, opioids, and antidepressants. Very few reviews reported data for intermediate-term follow-up and no reviews reported data for long-term follow-up; so, unless otherwise stated, outcome data are presented below for short-term follow-up.

2.4.1 | Acute Low Back Pain

- For pain intensity, there is moderate certainty evidence that NSAIDs (MD −7.29 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI −10.98 to −3.61) and muscle relaxants (RR 0.58, 95% CI 0.45 to 0.76) probably slightly improve pain, and high-certainty evidence for no difference between paracetamol and placebo (MD 0.49 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI −1.99 to 2.97).
- For physical function, there is high-certainty evidence that NSAIDs provide a small improvement (MD −2.02 on a 0–24 scale (higher scores indicate worse disability), 95% CI −2.89 to −1.15), moderate-certainty evidence that muscle relaxants provide a small improvement (RR 0.55, 95% CI 0.40 to 0.77), and high-certainty evidence for no difference between paracetamol and placebo (MD 0.05 on a 0 to 24 scale (higher scores indicate worse disability)).
- For NSAIDs there was very low-certainty evidence for no evidence of an increased risk of adverse events (RR 0.86, 95% CI 0.63 to 1.18), but moderate certainty evidence was found for an increased risk of adverse events (RR 1.50, 95% CI 1.14 to 1.98) for muscle relaxants.
- None of the included Cochrane Reviews aimed to identify evidence on the efficacy of opioids for acute LBP, whereas for antidepressants no evidence was identified by the included reviews for acute LBP.

2.4.2 | Chronic Low Back Pain

- There is moderate-certainty evidence that selective NSAIDs (MD −6.97 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI −10.74 to −3.19), and strong opioids (SMD −0.43, 95% CI −0.52 to −0.33) provide a small improvement, high-certainty that tapentadol (opioid) provides a small improvement (MD −8.00 on a 0 to 100 scale (higher scores indicate worse pain), 95% CI −1.22 to −0.38), and low-certainty evidence for no difference between placebo and SSRIs (antidepressants) on pain intensity (SMD −0.04, 95% CI −0.25 to 0.17). There was low-certainty evidence for a small between-group difference favoring benzodiazepines compared to placebo for a higher chance of pain relief (RR 0.71, 95% CI 0.54 to 0.93).
- There is moderate-certainty evidence that both strong opioids (SMD −0.26, 95% CI −0.37 to −0.15) and tramadol (opioid) (SMD −0.18, 95% CI −0.29 to −0.07) provide a small improvement in physical function.
- There is low-certainty evidence for no evidence of an increased risk of adverse events for NSAIDs (RR 1.04, 95% CI −0.92 to 1.17), and low-certainty evidence for no evidence of difference

between muscle relaxants and placebo in the risk of adverse events (RR 1.02, 95% CI 0.67 to 1.57). However, low-certainty evidence was found for a small between-group difference for an increased risk of adverse events for opioids (all types) compared to placebo, in particular nausea (RD 0.10, 95% CI 0.07 to 0.14), headaches (RD 0.03, 95% CI 0.01 to 0.05), constipation (RD 0.07, 95% CI 0.04 to 0.11), and dizziness (RD 0.08, 95% CI 0.05 to 0.11). Regarding the efficacy of paracetamol, no evidence was identified by the included reviews for chronic LBP.

2.5 | What Did the Authors Conclude?

The authors concluded that NSAIDs and muscle relaxants may provide a small improvement in pain and function, and there is no evidence of a difference between paracetamol and placebo for acute LBP. They did not find evidence for the use of opioids or any other medicines for acute LBP. For chronic LBP, they found evidence that NSAIDs and opioids may provide a small improvement in pain. Six of the seven reviews were published more than 5 years ago, and some of the evidence from these reviews is more than 10 years old, so an update of the CSRs is needed.

The available evidence suggests that pharmacological interventions for adults with non-specific LBP appear to be only marginally or not effective and carry an increased risk of adverse events. Besides the needed updates of CSRs, the authors also call for new RCTs investigating pharmacological interventions using common outcome sets to improve the synthesis of results and compatibility between trials. Trialists should clearly and comprehensively describe the characteristics of the included participants, as currently, it is unclear to whom the available evidence is applicable. Additional comparative studies for pharmacological interventions would enable us to draw firmer conclusions about which treatments are most effective. The use of network meta-analysis could also offer information.

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

Painkillers are a first-line treatment for acute pain, while their use in chronic pain is frequently questioned in favor of more active rehabilitation treatments, particularly in cases of LBP [4–6]. This overview of Cochrane Reviews provides a summary of the existing Cochrane evidence, characterized by the rigorous GRADE approach for assessing the certainty of evidence. The overview highlights the absence of not only long-term but also medium-term results regarding the efficacy and harms of these drugs. Although randomized controlled trials (RCTs) with short-term outcomes are easier to perform and less expensive, one must consider the potential influence of publication bias in the lack of long-term evidence. Alternatively, researchers might not be in equipoise and convinced that painkillers might not be worthwhile studying through medium- and long-term RCTs, also because for some drugs the known harms may outweigh the potential benefits. Whatever the reason, this represents the knowledge gathered from the overview, even though the included Cochrane Reviews urgently need updating. Overall, this evidence supports current guidelines [3–6]: NSAIDs are recommended as a first-line treatment for acute LBP to complement preventive measures against recurrence or the progression to chronicity and may provide short-term small relief in chronic LBP, where additional rehabilitation treatments are necessary.

Endnotes

[1] This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2023, Issue 4, Art. No.: CD013815, DOI: 10.1002/14651858.CD013815.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

[2] The views expressed in the summary with commentary are those of the Cochrane Corner authors [different than the original Cochrane Review authors] and do not represent the Cochrane Library or Wiley.

Author Contributions

Both authors contributed equally to all sections of the paper.

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Conflicts of Interest

Stefano Negrini declares ownership of stocks in ISICO srl, Milan (Italy).

Data Availability Statement

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

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LETTER TO THE EDITOR

Trends in Self-reported Sleep Disturbance and Unhealthy Sleep Duration Among US Adults with Arthritis, 2005–2018

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Dear Editor,

Many individuals with arthritis often suffer from poor sleep, impairing their daily functioning as well as overall physical and mental well-being [1]. Sleep disturbance and sleep duration are the primary dimensions used to assess sleep quality [2]. However, the temporal trends in these sleep characteristics among arthritis patients remain unclear. Therefore, we comprehensively estimated the temporal trends in the prevalence of self-reported sleep disturbance and unhealthy sleep duration in adults with arthritis, with stratification across demographic and socioeconomic variables.

We used the publicly available data from the National Health and Nutrition Examination Survey (NHANES), which conducted a complex, multistage probability sampling design to provide representation of the non-institutionalized US civilian population [3]. Our analysis was conducted from 2005–2006 to 2017–2018 with the sleep disturbance and sleep duration data only systematically collected during this period. We identified adults aged 20 years and older with arthritis and excluded those who were pregnant. After separately addressing missing values in the measurements of sleep disturbances and sleep duration, the final analytical datasets comprised 10 678 and 10 637 participants, respectively.

Participants were classified as having arthritis and sleep disturbance if they responded "yes" to the question "Has a doctor ever told you that you have arthritis?" and "Have you ever told a doctor or other health professional that you have trouble sleeping?". Sleep duration was assessed using questionnaires. According to the recommendations of the National Sleep Foundation in the US, sleep duration was categorized into three groups (< 7, 7–9, > 9 h), with < 7 and > 9 h classified as unhealthy sleep duration and < 7 h defined as insufficient sleep [4].

We estimated the weighted prevalence and 95% confidence intervals (CIs), with stratification across age groups, gender, race/ethnicity, education, poverty income ratio (PIR), body mass index (BMI), smoking, alcohol use status, depression status, and arthritis types. All covariates were self-reported except for BMI, which was measured through standardized physical examinations. Tests for trends were assessed using weighted logistic regression models, treating the survey cycle as a continuous variable. Joinpoint regression was employed to calculate the average annual percentage change (AAPC). Chi-square tests were utilized to evaluate between-group comparisons. A two-tailed $p < 0.05$ was the threshold for statistical significance. Data were analyzed using R, version 4.3.1.

The overall weighted prevalence of sleep disturbance among adults with arthritis was 47.46% (95% CI: 45.28%, 49.64%), and the overall weighted prevalence of unhealthy sleep duration was 43.90% (95% CI: 41.84%, 45.97%) (Tables 1 and 2). The prevalence of sleep disturbance was substantially higher in participants

Yuxin Lai and Huiting Liang contributed equally.

TABLE 1 | Weighted prevalence of sleep disturbance among adults with arthritis, NHANES 2005–2018.[a]

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
Overall	452 (40.47) [34.76–46.44]	677 (40.63) [35.88–45.56]	671 (46.21) [40.25–52.29]	546 (48.24) [41.68–54.87]	682 (49.42) [44.62–54.23]	708 (54.87) [49.22–60.40]	740 (50.11) [43.87–56.35]	**< 0.001***	23.83	**5.03*** (**2.56, 8.07**)	4476 (47.46) [45.28–49.64]
Age category, years											
20–44	69 (40.77) [31.05–51.26]	97 (42.10) [34.32–50.30]	97 (51.37) [41.76–60.89]	86 (50.87) [39.38–62.28]	98 (52.08) [43.27–60.76]	95 (57.90) [47.63–67.53]	85 (50.33) [40.18–60.45]	**0.022***	23.47	4.70 (–1.18, 11.95)	627 (49.62) [45.89–53.36]
45–64	201 (45.65) [37.80–53.72]	307 (41.87) [36.27–47.68]	312 (45.31) [38.42–52.39]	251 (51.76) [42.98–60.44]	330 (51.03) [42.29–59.71]	324 (55.75) [48.84–62.44]	335 (53.38) [48.10–58.59]	**0.002***	16.94	**4.24*** (**0.54, 8.99**)	2060 (49.55) [46.81–52.29]
≥ 65	182 (30.51) [26.22–35.18]	273 (34.20) [30.53–38.07]	262 (32.91) [29.90–36.08]	209 (34.47) [30.33–38.87]	254 (38.91) [33.80–44.28]	289 (44.59) [40.50–48.75]	320 (43.74) [38.72–48.89]	**< 0.001***	43.34	**6.91*** (**2.47, 11.98**)	1789 (37.52) [35.85–39.22]
Gender											
Male	173 (30.52) [24.33–37.52]	243 (33.67) [28.26–39.55]	247 (41.56) [33.63–49.96]	196 (44.86) [36.19–53.86]	236 (46.71) [41.12–52.39]	263 (51.00) [43.23–58.72]	297 (42.73) [35.58–50.20]	**< 0.001***	39.98	**7.26*** (**2.50, 13.03**)	1655 (41.86) [39.14–44.64]
Female	279 (47.43) [38.97–56.05]	434 (46.04) [40.51–51.67]	424 (49.74) [43.16–56.33]	350 (50.47) [43.23–57.69]	446 (50.98) [44.09–57.84]	445 (57.23) [49.54–64.59]	443 (55.95) [47.10–64.43]	**0.023***	17.95	**3.77*** (**1.32, 6.31**)	2821 (51.39) [48.56–54.22]
Race/ethnicity											
Non-Hispanic White	287 (41.63) [34.42–49.22]	387 (40.42) [34.48–46.65]	389 (49.33) [41.70–56.98]	280 (50.03) [42.22–57.85]	389 (50.52) [44.68–56.34]	317 (54.40) [46.35–62.22]	359 (53.50) [46.23–60.63]	**0.001***	28.51	**4.93*** (**1.67, 8.84**)	2408 (48.70) [45.99–51.42]

(Continues)

TABLE 1 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
Non-Hispanic Black	104 (41.56) [32.93–50.75]	150 (51.06) [41.89–60.16]	137 (38.73) [30.38–47.80]	148 (46.01) [35.98–56.38]	134 (41.55) [28.66–55.72]	143 (53.38) [46.73–59.91]	174 (42.89) [34.12–52.14]	0.672	3.20	1.99 (−4.98, 11.53)	990 (44.94) [41.27–48.68]
Hispanic[d]	44 (29.78) [20.47–41.14]	124 (35.01) [26.83–44.18]	124 (32.89) [26.67–39.78]	80 (41.18) [29.98–53.37]	105 (36.89) [28.65–45.97]	175 (48.86) [38.04–59.79]	121 (38.74) [27.45–51.39]	0.095	30.10	6.55 (−2.96, 17.56)	773 (38.59) [34.56–42.79]
Other[e]	17 (33.18) [23.91–43.97]	16 (32.63) [16.91–53.55]	21 (46.53) [25.42–68.95]	38 (38.68) [27.59–51.09]	54 (70.71) [59.95–79.57]	73 (65.57) [53.87–75.65]	86 (48.16) [32.28–64.42]	**0.018***	45.16	**13.18*** (**3.70, 27.85**)	305 (50.44) [44.28–56.59]
Education											
Less than high school	123 (39.76) [32.68–47.31]	237 (44.33) [36.45–52.51]	207 (54.32) [43.91–64.37]	148 (46.26) [37.40–55.36]	166 (41.04) [31.85–50.90]	182 (47.44) [37.25–57.85]	149 (45.52) [32.78–58.86]	0.689	14.46	1.40 (−3.26, 5.71)	1212 (45.59) [41.98–49.25]
High school	108 (38.46) [32.11–45.23]	182 (42.43) [31.89–53.70]	174 (46.55) [35.25–58.22]	127 (54.34) [42.17–66.01]	178 (60.20) [52.62–67.32]	150 (53.80) [42.43–64.80]	191 (53.39) [43.84–62.71]	**0.003***	38.83	**6.81*** (**1.85, 13.01**)	1110 (49.73) [45.92–53.54]
College	125 (44.01) [32.89–55.77]	174 (46.08) [37.22–55.20]	201 (47.73) [40.18–55.39]	194 (50.09) [41.07–59.12]	225 (52.84) [45.35–60.21]	224 (60.13) [49.10–70.23]	272 (53.31) [41.19–65.04]	**0.050***	21.11	**4.81*** (**2.56, 7.25**)	1415 (51.34) [47.51–55.16]
College graduate or above	96 (37.35) [27.60–48.24]	84 (25.34) [17.12–35.81]	89 (38.06) [27.46–49.93]	76 (43.09) [33.16–53.61]	112 (36.17) [26.18–47.51]	152 (53.77) [42.84–64.34]	126 (43.96) [31.91–56.77]	**0.015***	17.71	7.20 (−2.96, 22.06)	735 (40.72) [36.53–45.06]

(Continues)

TABLE 1 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
BMI											
< 18.5 (underweight)	5 (47.29) [18.81–77.65]	10 (50.95) [21.92–79.35]	11 (51.33) [34.85–67.52]	4 (68.93) [40.43–87.88]	11 (64.42) [42.37–81.69]	4 (81.19) [54.77–93.90]	8 (34.56) [22.32–49.24]	0.807	−26.93	2.67 (−10.19, 23.13)	53 (55.01) [45.42–64.24]
18.5 ≤ and < 25 (healthy weight)	83 (40.41) [27.29–55.07]	133 (35.13) [25.99–45.50]	120 (43.39) [35.50–51.63]	109 (45.97) [34.17–58.24]	105 (40.80) [31.23–51.11]	109 (42.12) [30.86–54.25]	99 (41.70) [31.01–53.24]	0.603	3.19	1.14 (−2.55, 4.86)	758 (41.28) [37.08–45.61]
25 ≤ and < 30 (overweight)	116 (36.29) [27.19–46.50]	192 (36.91) [29.84–44.59]	191 (42.41) [33.76–51.56]	132 (49.23) [37.52–61.03]	185 (44.41) [33.90–55.45]	183 (50.75) [38.78–62.64]	187 (51.96) [42.35–61.42]	**0.005***	43.16	**6.45* (3.26, 9.83)**	1186 (44.82) [40.97–48.74]
≥ 30 (obesity)	210 (41.18) [32.99–49.88]	310 (45.68) [39.35–52.14]	326 (49.73) [41.46–58.02]	262 (47.65) [39.31–56.12]	350 (52.31) [45.85–58.69]	380 (62.79) [56.50–68.67]	395 (51.87) [42.18–61.42]	**0.004***	25.97	**6.36* (2.73, 11.25)**	2233 (50.91) [47.91–53.90]
PIR											
≤ 1	83 (52.44) [45.10–59.67]	152 (50.19) [44.13–56.24]	169 (61.57) [50.16–71.83]	163 (55.06) [46.17–63.65]	190 (57.80) [50.89–64.42]	151 (58.98) [49.05–68.22]	136 (50.21) [36.25–64.14]	0.824	−4.25	2.08 (−0.83, 4.77)	1044 (55.26) [51.59–58.88]
1 < and ≤ 3	176 (39.34) [31.08–48.26]	305 (46.53) [38.63–54.60]	253 (40.30) [33.51–47.48]	220 (46.97) [38.64–55.48]	260 (53.09) [41.17–64.68]	291 (57.14) [47.99–65.83]	298 (52.09) [43.27–60.78]	**0.003***	32.41	5.48 (−0.26, 12.17)	1803 (48.13) [44.70–51.59]
> 3	161 (37.49) [29.87–45.78]	157 (31.52) [24.69–39.25]	189 (44.99) [36.87–53.40]	130 (44.89) [31.54–59.02]	188 (42.55) [36.18–49.19]	195 (52.87) [43.60–61.94]	200 (44.80) [35.26–54.75]	**0.013***	19.51	5.47 (−2.42, 15.78)	1220 (43.17) [39.72–46.69]

(Continues)

TABLE 1 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b] 2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
Smoke											
Never	200 (42.04) [32.80–51.88]	284 (37.39) [30.54–44.79]	267 (39.81) [33.55–46.41]	220 (38.46) [29.61–48.14]	298 (44.87) [38.49–51.41]	314 (48.84) [40.91–56.83]	313 (47.82) [37.04–58.81]	0.072	13.74	**4.40*** (**1.00, 8.29**)	1896 (43.21) [39.95–46.52]
Former	147 (37.97) [24.57–53.49]	212 (31.22) [24.62–38.68]	229 (44.42) [33.85–55.51]	183 (46.24) [32.00–61.11]	220 (53.60) [42.34–64.50]	240 (65.32) [54.20–74.98]	260 (49.71) [41.22–58.22]	**<0.001***	30.93	**9.76*** (**3.34, 18.47**)	1491 (47.55) [43.33–51.81]
Current	105 (38.92) [32.03–46.27]	181 (52.88) [44.20–61.39]	175 (56.26) [49.23–63.05]	143 (60.73) [51.99–68.84]	163 (51.76) [39.99–63.33]	153 (57.68) [50.66–64.40]	167 (53.52) [46.65–60.26]	**0.020***	37.54	2.68 (−2.17, 8.62)	1087 (53.00) [49.81–56.17]
Alcohol											
Never	55 (42.08) [27.83–57.78]	104 (51.32) [38.88–63.59]	74 (30.26) [19.09–44.37]	60 (38.72) [20.46–60.83]	83 (49.25) [26.75–72.06]	92 (47.91) [32.04–64.21]	43 (20.03) [10.76–34.21]	0.438	−52.40	−3.99 (−26.93, 17.34)	511 (41.67) [35.14–48.50]
Former	131 (49.98) [38.25–61.72]	198 (42.37) [35.01–50.08]	151 (56.07) [47.73–64.09]	141 (61.14) [45.44–74.82]	170 (52.73) [36.98–67.95]	162 (63.17) [52.48–72.70]	NA	NA	NA	NA	953 (53.77) [48.98–58.50]
Current	222 (37.74) [31.83–44.05]	302 (39.34) [33.91–45.06]	371 (46.10) [38.47–53.92]	280 (46.66) [39.32–54.14]	370 (48.37) [43.36–53.41]	393 (54.54) [47.81–61.11]	422 (50.90) [43.93–57.83]	**<0.001***	34.85	**5.96*** (**3.24, 9.50**)	2360 (46.93) [44.43–49.45]
Depression											
No	321 (36.34) [30.80–42.28]	440 (35.68) [31.00–40.64]	453 (42.13) [34.53–50.11]	354 (44.38) [36.88–52.14]	454 (43.42) [38.67–48.29]	486 (48.88) [43.29–54.50]	499 (43.55) [37.50–49.79]	**0.003***	19.82	**4.76*** (**1.24, 8.40**)	3007 (42.27) [39.96–44.60]

(Continues)

TABLE 1 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
Yes	82 (75.71) [68.95–81.39]	157 (68.38) [61.79–74.31]	140 (73.64) [67.58–78.92]	119 (74.18) [63.23–82.77]	169 (80.55) [75.59–84.70]	148 (81.71) [71.37–88.89]	153 (78.82) [64.32–88.48]	0.070	4.11	2.36 (−0.20, 5.00)	968 (76.61) [73.32–79.61]
Arthritis types											
Osteoarthritis	152 (40.14) [30.06–51.13]	202 (39.73) [32.31–47.65]	201 (41.72) [29.45–55.11]	236 (54.28) [46.46–61.90]	300 (51.63) [46.42–56.80]	329 (63.94) [55.91–71.25]	334 (50.39) [40.56–60.19]	**0.003***	25.53	**7.61* (1.36, 17.57)**	1754 (50.46) [47.12–53.80]
Rheumatoid arthritis	87 (40.03) [26.41–55.38]	139 (50.12) [37.43–62.79]	137 (46.19) [34.96–57.81]	103 (44.03) [32.65–56.07]	119 (46.28) [35.14–57.80]	142 (53.40) [40.95–65.43]	145 (42.29) [30.40–55.15]	0.777	5.65	0.87 (−6.15, 9.33)	872 (46.05) [41.32–50.85]
Gout	NA	76 (50.69) [32.67–68.54]	70 (56.26) [31.02–78.63]	47 (59.21) [33.04–81.02]	68 (60.82) [40.97–77.63]	92 (75.99) [63.36–85.27]	93 (38.90) [23.95–56.27]	0.655	−23.27	5.90 (−4.38, 25.53)	446 (55.65) [47.57–63.45]
Others	65 (34.99) [25.34–46.04]	90 (44.92) [38.00–52.05]	104 (51.60) [39.74–63.28]	47 (55.57) [37.72–72.09]	77 (43.70) [31.58–56.63]	77 (49.45) [35.96–63.02]	92 (52.43) [33.64–70.56]	0.171	49.86	3.91 (−6.96, 12.66)	552 (47.38) [42.18–52.63]

[a]All estimates were age-standardized excepted age category.
[b]Counts were unweighted and examination weights were used to calculate weighted prevalence estimates and 95% CIs. The rare strata with single sampling units in the data were treated as certainty units to perform variance estimation.
[c]All between-group comparisons yielded $P < 0.001$.
[d]Mexican American or other Hispanic race.
[e]Other non-Hispanic races, including non-Hispanic multiracial.
*$P < 0.05$. The values in bold indicate statistical significance.

TABLE 2 | Weighted prevalence of unhealthy sleep duration among adults with arthritis, NHANES 2005–2018.[a]

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
Overall	566 (49.83) [43.42–56.24]	831 (45.20) [40.87–49.62]	800 (49.42) [42.60–56.25]	646 (45.32) [38.74–52.07]	669 (45.99) [41.02–51.04]	577 (37.34) [32.66–42.28]	647 (36.97) [32.73–41.42]	**< 0.001***	−25.80	−4.32 (−9.96, 1.25)	4736 (43.90) [41.84–45.97]
Age category, years											
20–44	100 (59.14) [47.21–70.08]	122 (47.33) [40.65–54.11]	115 (54.23) [41.90–66.07]	78 (48.02) [38.26–57.92]	106 (53.47) [44.84–61.90]	74 (40.79) [32.18–50.01]	73 (37.58) [28.49–47.63]	**0.004***	−36.45	−4.24 (−11.53, 2.70)	668 (48.14) [44.46–51.83]
45–64	219 (43.35) [38.20–48.65]	359 (44.46) [38.33–50.77]	362 (48.68) [43.07–54.32]	296 (45.70) [39.30–52.25]	304 (42.11) [36.34–48.10]	252 (35.50) [30.96–40.31]	292 (39.98) [34.28–45.96]	**0.020***	−7.78	−2.98 (−6.93, 0.99)	2084 (42.54) [40.38–44.73]
≥ 65	247 (34.33) [29.00–40.10]	350 (40.37) [34.63–46.38]	323 (36.83) [32.97–40.86]	272 (36.88) [32.36–41.65]	259 (31.24) [28.54–34.07]	251 (30.63) [24.52–37.50]	282 (29.92) [26.00–34.15]	**0.005***	−12.86	−4.48 (−10.38, 2.04)	1984 (34.04) [32.21–35.93]
Gender											
Male	242 (51.60) [44.28–58.85]	343 (44.17) [38.33–50.18]	339 (50.63) [40.64–60.57]	252 (44.29) [34.05–55.04]	245 (46.13) [38.26–54.20]	237 (37.10) [32.44–42.01]	290 (38.69) [29.22–49.10]	**0.001***	−25.02	−4.73 (−10.48, 1.05)	1948 (44.22) [41.05–47.45]
Female	324 (48.66) [38.25–59.18]	488 (46.05) [41.48–50.68]	461 (48.89) [43.09–54.72]	394 (45.97) [39.06–53.04]	424 (45.68) [41.27–50.15]	340 (37.44) [30.37–45.08]	357 (35.56) [32.60–38.63]	**0.012***	−26.92	−5.31 (−9.61, −0.43)	2788 (43.67) [41.29–46.09]

(Continues)

TABLE 2 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b] 2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
Race/ethnicity											
Non-Hispanic White	294 (48.04) [41.31–54.85]	406 (41.82) [35.32–48.62]	406 (48.51) [41.22–55.86]	265 (42.71) [33.81–52.12]	318 (44.72) [38.81–50.78]	224 (37.07) [31.18–43.37]	257 (35.66) [30.90–40.72]	**0.003***	−25.77	**−4.26*** (−7.76, −0.40)**	2170 (42.44) [39.93–45.00]
Non-Hispanic Black	178 (63.02) [49.37–74.86]	221 (71.49) [65.56–76.76]	194 (60.73) [48.04–72.11]	216 (56.71) [48.85–64.24]	171 (51.64) [39.55–63.54]	140 (46.68) [40.25–53.21]	187 (50.59) [41.83–59.32]	**0.001***	−19.72	**−7.61* (−11.75, −4.45)**	1307 (56.83) [53.07–60.51]
Hispanic[d]	70 (49.55) [35.04–64.15]	180 (53.36) [44.56–61.95]	178 (48.99) [38.94–59.12]	111 (51.83) [42.42–61.10]	129 (44.34) [34.42–54.73]	157 (41.60) [31.67–52.27]	112 (35.19) [25.70–46.01]	**0.008***	−28.99	**−5.75* (−8.67, −3.03)**	937 (45.22) [41.25–49.25]
Other[e]	24 (56.89) [33.82–77.32]	24 (33.83) [26.43–42.11]	22 (34.13) [15.95–58.58]	54 (38.88) [26.82–52.47]	51 (61.77) [46.21–75.25]	56 (26.87) [18.31–37.60]	91 (35.44) [24.68–47.91]	0.147	−37.70	−0.85 (−18.95, 21.57)	322 (39.10) [33.78–44.69]
Education											
Less than high school	181 (57.83) [50.41–64.92]	331 (57.88) [48.45–66.77]	270 (58.94) [43.76–72.59]	202 (53.36) [41.54–64.82]	190 (62.97) [57.17–68.41]	195 (49.02) [39.14–58.98]	148 (47.42) [37.03–58.05]	0.099	−18.00	−0.84 (−5.34, 3.79)	1517 (55.81) [51.80–59.73]
High school	144 (55.64) [45.94–64.93]	215 (46.17) [36.94–55.67]	201 (48.77) [40.22–57.39]	150 (52.18) [40.22–63.89]	165 (51.77) [44.30–59.16]	117 (42.76) [32.54–53.64]	173 (44.39) [35.48–53.68]	0.148	−20.22	−2.41 (−9.85, 5.71)	1165 (48.54) [44.92–52.17]
College	151 (51.10) [40.46–61.63]	183 (42.85) [35.51–50.51]	236 (53.69) [43.38–63.69]	197 (42.50) [31.81–53.93]	209 (42.93) [34.39–51.91]	170 (38.99) [32.56–45.82]	219 (35.22) [30.14–40.65]	**0.002***	−31.08	**−5.42* (−8.97, −1.25)**	1365 (43.07) [39.86–46.33]

(Continues)

TABLE 2 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b]							*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018				
College graduate or above	88 (33.21) [22.79–45.58]	101 (33.13) [24.57–42.97]	92 (37.24) [26.91–48.89]	95 (38.33) [27.82–50.06]	104 (35.20) [24.99–46.98]	95 (22.32) [14.51–32.74]	106 (26.09) [18.75–35.07]	**0.056***	−21.43	−4.79 (−18.73, 9.86)	681 (31.43) [27.69–35.43]
BMI											
< 18.5 (underweight)	11 (46.92) [19.00–76.92]	15 (77.12) [63.51–86.71]	12 (28.45) [10.60–57.16]	6 (38.12) [14.98–68.30]	12 (81.39) [63.92–91.52]	4 (73.42) [48.81–88.89]	6 (26.07) [14.88–41.57]	0.774	−44.44	−2.54 (−28.19, 30.95)	66 (52.50) [43.84–61.01]
18.5 ≤ and < 25 (healthy weight)	118 (56.34) [45.87–66.27]	169 (43.55) [34.63–52.90]	142 (49.30) [40.86–57.77]	119 (40.15) [29.01–52.42]	104 (42.57) [27.36–59.31]	96 (40.84) [32.36–49.90]	115 (39.55) [24.82–56.47]	0.066	−29.79	−5.30 (−9.17, −2.36)	863 (44.63) [40.20–49.14]
25 ≤ and < 30 (overweight)	152 (46.96) [40.11–53.93]	229 (42.08) [33.02–51.71]	244 (50.24) [38.01–62.44]	162 (42.73) [30.34–56.10]	177 (42.78) [35.27–50.64]	152 (33.36) [26.21–41.37]	162 (32.40) [21.15–46.14]	**0.013***	−31.00	−4.84 (−10.57, 0.39)	1278 (41.13) [37.29–45.08]
≥ 30 (obesity)	253 (47.17) [37.37–57.19]	366 (46.37) [41.36–51.44]	374 (50.11) [38.63–61.57]	311 (49.34) [42.74–55.97]	346 (47.17) [41.97–52.43]	287 (35.33) [28.39–42.96]	316 (38.31) [31.85–45.21]	**0.011***	−18.78	−3.19 (−12.20, 6.19)	2253 (44.19) [41.31–47.10]
PIR											
≤ 1	116 (65.57) [52.33–76.77]	199 (64.02) [56.54–70.87]	184 (65.19) [53.91–75.00]	177 (56.78) [47.47–65.64]	185 (54.15) [49.08–59.13]	142 (51.34) [38.09–64.41]	121 (35.34) [27.41–44.17]	**< 0.001***	−46.11	**−7.22* (−11.69, −2.47)**	1124 (55.25) [51.58–58.86]
1 < and ≤ 3	229 (50.34) [41.23–59.43]	358 (49.21) [43.24–55.20]	313 (47.67) [39.38–56.09]	268 (47.67) [39.49–55.98]	258 (49.79) [43.44–56.15]	227 (41.60) [35.05–48.46]	242 (38.99) [32.42–45.99]	**0.022***	−22.55	**−3.38* (−6.30, −0.38)**	1895 (46.50) [43.71–49.30]

(Continues)

TABLE 2 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b] 2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
> 3	179 (42.71) [34.19–51.68]	189 (34.83) [27.52–42.93]	228 (44.11) [34.03–54.71]	155 (39.28) [29.00–50.61]	173 (38.08) [28.73–48.41]	131 (26.36) [20.61–33.04]	182 (34.43) [27.92–41.57]	**0.020***	−19.40	−4.39 (−9.32, 0.71)	1237 (36.70) [33.48–40.03]
Smoke											
Never	263 (49.89) [40.58–59.21]	375 (44.25) [36.47–52.32]	344 (43.11) [33.43–53.35]	289 (43.59) [33.89–53.79]	305 (41.76) [36.16–47.57]	265 (33.39) [28.44–38.73]	304 (33.98) [27.51–41.10]	**0.001***	−31.90	**−6.07* (−9.74, −1.37)**	2145 (40.86) [37.95–43.84]
Former	160 (41.60) [28.82–55.62]	248 (31.50) [26.32–37.19]	266 (52.78) [43.99–61.39]	204 (39.63) [24.61–56.90]	189 (38.87) [28.99–49.76]	180 (30.49) [21.17–41.74]	198 (34.51) [27.52–42.23]	0.148	−17.04	−2.23 (−10.84, 7.28)	1445 (38.11) [34.14–42.24]
Current	142 (57.44) [48.35–66.06]	206 (54.63) [49.40–59.76]	190 (57.03) [48.75–64.94]	153 (53.65) [42.31–64.63]	175 (57.64) [50.62–64.36]	130 (49.93) [42.92–56.95]	145 (43.57) [35.69–51.78]	**0.017***	−24.15	−2.54 (−6.46, 1.06)	1141 (53.23) [50.17–56.27]
Alcohol											
Never	86 (57.85) [50.23–65.12]	111 (45.21) [33.89–57.06]	111 (40.98) [26.23–57.55]	93 (45.58) [29.09–63.10]	98 (48.69) [37.72–59.78]	96 (30.28) [19.36–44.01]	46 (38.89) [18.17–64.60]	**0.033***	−32.77	−6.87 (−19.66, 1.16)	641 (44.25) [39.03–49.59]
Former	169 (58.33) [46.65–69.14]	248 (44.25) [36.91–51.85]	177 (61.57) [47.91–73.62]	166 (52.44) [32.53–71.61]	142 (47.66) [29.22–66.76]	124 (47.20) [34.03–60.78]	NA	NA	NA	NA	1026 (51.58) [45.64–57.48]
Current	254 (44.56) [37.47–51.87]	374 (44.66) [39.22–50.24]	410 (47.14) [39.03–55.40]	307 (42.45) [33.43–52.01]	368 (43.74) [38.23–49.40]	292 (34.42) [29.45–39.76]	342 (34.27) [29.63–39.23]	**<0.001***	−23.09	**−4.72* (−8.61, −0.48)**	2347 (41.04) [38.60–43.51]

(Continues)

TABLE 2 | (Continued)

Characteristic	Unweighted no. (weighted %) [95% CI][b] 2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend	Percentage change (%)	AAPC (95% CI)	Total unweighted no. (weighted %) [95% CI][c]
Depression											
No	426 (48.64) [42.08–55.25]	557 (40.26) [36.09–44.57]	561 (46.94) [39.21–54.82]	433 (41.03) [33.54–48.96]	461 (41.07) [35.58–46.78]	399 (31.28) [25.93–37.18]	461 (34.19) [29.16–39.61]	**< 0.001***	−29.71	**−4.96* (−10.60, −0.06)**	3298 (40.05) [37.75–42.40]
Yes	75 (55.23) [40.10–69.45]	170 (68.21) [58.75–76.37]	132 (65.61) [56.64–73.59]	124 (71.95) [61.63–80.39]	145 (63.82) [54.25–72.40]	94 (50.50) [36.50–64.42]	94 (46.41) [33.61–59.70]	**0.025**	−15.98	−3.33 (−13.86, 6.36)	834 (59.80) [55.33–64.12]
Arthritis types											
Osteoarthritis	159 (38.07) [30.47–46.32]	242 (41.59) [30.91–53.12]	229 (49.53) [39.71–59.39]	251 (39.36) [33.01–46.10]	272 (44.90) [37.50–52.54]	231 (38.86) [30.98–47.36]	261 (36.88) [27.64–47.20]	0.470	−3.13	−0.69 (−6.27, 5.48)	1645 (41.03) [37.69–44.46]
Rheumatoid arthritis	117 (60.02) [51.26–68.18]	188 (58.67) [51.80–65.22]	165 (53.81) [44.04–63.30]	136 (60.78) [45.38–74.30]	125 (52.59) [40.88–64.02]	138 (39.58) [32.60–47.01]	140 (35.24) [27.64–43.68]	**< 0.001***	−41.29	**−7.72* (−13.89, −2.79)**	1009 (50.93) [47.25–54.61]
Gout	NA	90 (65.24) [55.12–74.14]	85 (52.36) [32.88–71.15]	71 (41.23) [30.08–53.37]	66 (54.25) [33.65–73.50]	70 (35.16) [19.66–54.59]	85 (53.43) [32.79–72.96]	0.323	−18.10	−7.63 (−11.34, −22.59)	467 (50.57) [42.90–58.21]
Others	87 (49.30) [36.05–62.66]	97 (41.94) [34.57–49.69]	113 (43.88) [34.06–54.21]	60 (43.79) [30.37–58.18]	84 (50.12) [39.70–60.54]	47 (24.36) [15.87–35.46]	77 (35.74) [26.23–46.53]	**0.019***	−27.51	−3.67 (−11.00, 3.39)	565 (40.85) [36.81–45.01]

[a]All estimates were age-standardized excepted age category.
[b]Counts were unweighted and examination weights were used to calculate weighted prevalence estimates and 95% CIs. The rare strata with single sampling units in the data were treated as certainty units to perform variance estimation.
[c]All between-group comparisons yielded $P < 0.001$ excepted gender subgroup.
[d]Mexican American or other Hispanic race.
[e]Other non-Hispanic races, including non-Hispanic multiracial.
*$P < 0.05$. The values in bold indicate statistical significance.

aged 20 to 44 years (49.62%), females (51.39%), indicated "other" race/ethnicity (50.44%), with a college degree (51.34%), underweight (55.01%), lower PIR (55.26%), current smokers (53.00%), former alcoholics (53.77%), and individuals with depression (76.61%) and gout (55.65%) than their counterparts (Table 1). The higher prevalence of unhealthy sleep duration was observed in participants aged 20 to 44 years (48.14%), males (44.22%), non-Hispanic Blacks (56.83%), with less than a high school degree (55.81%), underweight (52.50%), lower PIR (55.25%), never smokers (40.86%), former alcoholics (51.58%), and individuals with depression (59.80%) and rheumatoid arthritis (50.93%) than their counterparts (Table 2).

From 2005–2006 to 2017–2018, the prevalence of sleep disturbance among adults with arthritis increased from 40.47% (95% CI: 34.76%, 46.44%) to 50.11% (95% CI: 43.87%, 56.35%) (P for trend <0.001), while the prevalence of unhealthy sleep duration decreased from 49.83% (95% CI: 43.42%, 56.24%) to 36.97% (95% CI: 32.73%, 41.42%) (P for trend <0.001), with the AAPC of 5.03 (95% CI: 2.56, 8.07) and −4.32 (95% CI: −9.96, 1.25), respectively (Tables 1 and 2). The prevalence of insufficient sleep duration decreased from 49.83% (95% CI: 43.42%, 56.24%) to 33.94% (95% CI: 29.70%, 38.46%) (p for trend <0.001), with the AAPC of −5.64 (95% CI: −9.98, −1.10) (Table S1).

We observed significantly increasing trends in sleep disturbance prevalence among those aged 45 and 64 years and over 65 years, males, non-Hispanic White, indicated "other" race/ethnicity, those with high school education and college degree, overweight and obese, former smokers, and current alcoholics and patients with osteoarthritis (all p for trend <0.05) (Table 1). The significantly decreased prevalence of unhealthy sleep duration was observed among non-Hispanic Whites, non-Hispanic Blacks, and Hispanics, those with a college degree, lower and median PIR, never smokers, and current alcoholics and patients with rheumatoid arthritis (all p for trend <0.05) (Table 2).

This study found that the estimated prevalence of unhealthy and insufficient sleep duration decreased significantly among US adults with arthritis between 2005 and 2018. Meanwhile, we concurrently revealed an increasing trend in the prevalence of self-reported sleep disturbance among this population, particularly in older individuals, males, non-Hispanic Whites, and those who indicated "other" race/ethnicity, those with moderate educational levels, overweight and obese, former smokers, and current alcoholics, compared with their respective counterparts. These results collectively indicate that sleep quality was compromised and sleep efficiency decreased among adults with arthritis.

Previous research consistently reported that the prevalence of sleep disturbance was significantly higher in arthritis patients than in non-arthritis populations [5]. The sleep quality of arthritis patients was influenced by multiple factors, including disease-related symptoms (e.g., pain, stiffness, fatigue) and comorbid conditions. For example, symptoms of anxiety and depression, cardiovascular diseases and their risk factors, inflammation, and disease activity severity of arthritis and its resulting pain, as well as the use of glucocorticoids may collectively contribute to poor sleep quality in individuals with arthritis [6, 7]. Furthermore, patients with arthritis exhibit a higher prevalence of fibromyalgia comorbidity, which also constitutes a common etiology of sleep disturbance [8, 9]. Additionally, smoking may also contribute to sleep disturbances through respiratory diseases [10]. There exists a bidirectional mechanistic link between sleep disturbance and arthritis. Poor sleep quality, in turn, activates peripheral inflammatory responses, which subsequently exacerbate disease activity in arthritis and intensify pain in peripheral joints [11]. Therefore, better targeted management is urgently needed to control the aforementioned risk factors for sleep quality in patients with arthritis, especially in the specific populations where the prevalence of sleep disturbance has been observed to increase [1, 12].

The measurement of arthritis, sleep disturbance, and sleep duration was based on self-reported questionnaires from NHANES, which may be susceptible to recall bias. The lack of objectively measured data makes these findings be interpreted with caution.

Author Contributions

Concept and design: Y. Lai, H. Liang, C. Ding, Z. Zhu. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Y. Lai, H. Liang, H. Chen. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Y. Lai, H. Liang, H. Chen. Supervision: C. Ding, Z. Zhu.

Disclosure

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics Statement

This study is a secondary analysis of the publicly available database and did not involve human participants or animal subjects. Ethical approval is not applicable for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available in a public, open access repository. The data used for the analyses are publicly available from https://www.cdc.gov/nchs/nhanes/index.htm.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** apl70430-sup-0001-AppendixS1.docx.

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LETTER TO THE EDITOR

Dual Outcomes of *Schnurri-3* Inhibition in Psoriasis: Skeletal Rescue and Dermatological Aggravation

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Dear Editor,

Psoriasis is a chronic autoimmune inflammatory disease characterized by scaly erythematous patches or plaques [1]. These skin fragments or scales aggravate during the pathological process and eventually fall off and lead to bleeding, leaving irreversible scars. Thirty percent of patients with psoriasis will eventually develop psoriatic arthritis (PsA) [2]. In addition to skin lesions around the joints, psoriatic arthritis involves bone tissue lesions, similar to other forms of arthritis [3]. The pathogenesis of psoriasis entails both innate and adaptive immunity, with the IL-17/IL-23 axis playing a central role by triggering a persistent autoimmune response and subsequent skin and vascular inflammation [4]. In psoriatic synovium, upregulated RANK/RANKL and reduced OPG expression disrupt bone signaling, while RANK activation and a TNF-α/IL-17-rich environment drive synovitis and bone erosion [5].

Schnurri-3 (Shn3), a zinc finger nuclear protein, regulates skeletal metabolism by suppressing osteoblast activity via WWP1-mediated RUNX2 degradation, promoting osteoclast formation by upregulating the key osteoclastogenic factor receptor activator of nuclear factor-κB ligand (RANKL) expression [6, 7]. *Shn3*-deficient ($Shn3^{-/-}$) mice exhibit high bone mass [6], and mesenchymal-specific deletion of *Shn3* ($Shn3^{Prrx1}$) impairs osteoclast differentiation [7]. Osteoblast-specific *Shn3* inhibition also reduces rheumatic arthritis (RA)-associated joint damage via ERK–MAPK signaling [8]. Given shared autoimmune and osteoimmunological features between PsA and RA—including periarticular inflammation, impaired bone remodeling, and enhanced osteoclastic resorption—we hypothesized that targeted inhibition of *Shn3* in osteoblasts may exert comparable osteoprotective effects in PsA. Therefore, in this study, we established osteoblast lineage-specific *Shn3* knockout models using $Shn3^{Bglap\text{-}Cre}$ and $Shn3^{Bglap\text{-}CreERT}$ mice. A psoriasis model was established through imiquimod (IMQ), a synthetic agonist of Toll-like receptors (TLRs), that is widely employed to recapitulate psoriatic pathology in murine models [9]. Disease progression was longitudinally monitored to investigate the potential significance of *Shn3* inhibition in the management of psoriasis.

1 | Methods

4-week-old male C57BL/6 *Bglap-Cre* mice (Stock No. 019509), *Bglap-CreER* mice (Stock No. 023827), and *Shn3-floxed* mice (Stock No. 027794) were acquired from The Jackson Laboratory (USA) and bred in Xiamen University Laboratory Animal Centre. To induce Cre activity, $Shn3^{Bglap\text{-}CreERT}$ mice were administered tamoxifen (TMX, 10 mg/mL in corn oil, 50 mg/kg) for five consecutive days (i.p.). To generate a psoriasis model, mice were shaved and 40–45 mg of 5% IMQ/day was applied for 5 consecutive days per week for 6 weeks (Figure 1A,C). $Shn3^{f/f}$ littermate control groups underwent dorsal hair removal and received either IMQ or not. Daily

Ying Liu and Li Lin contributed equally to this work.

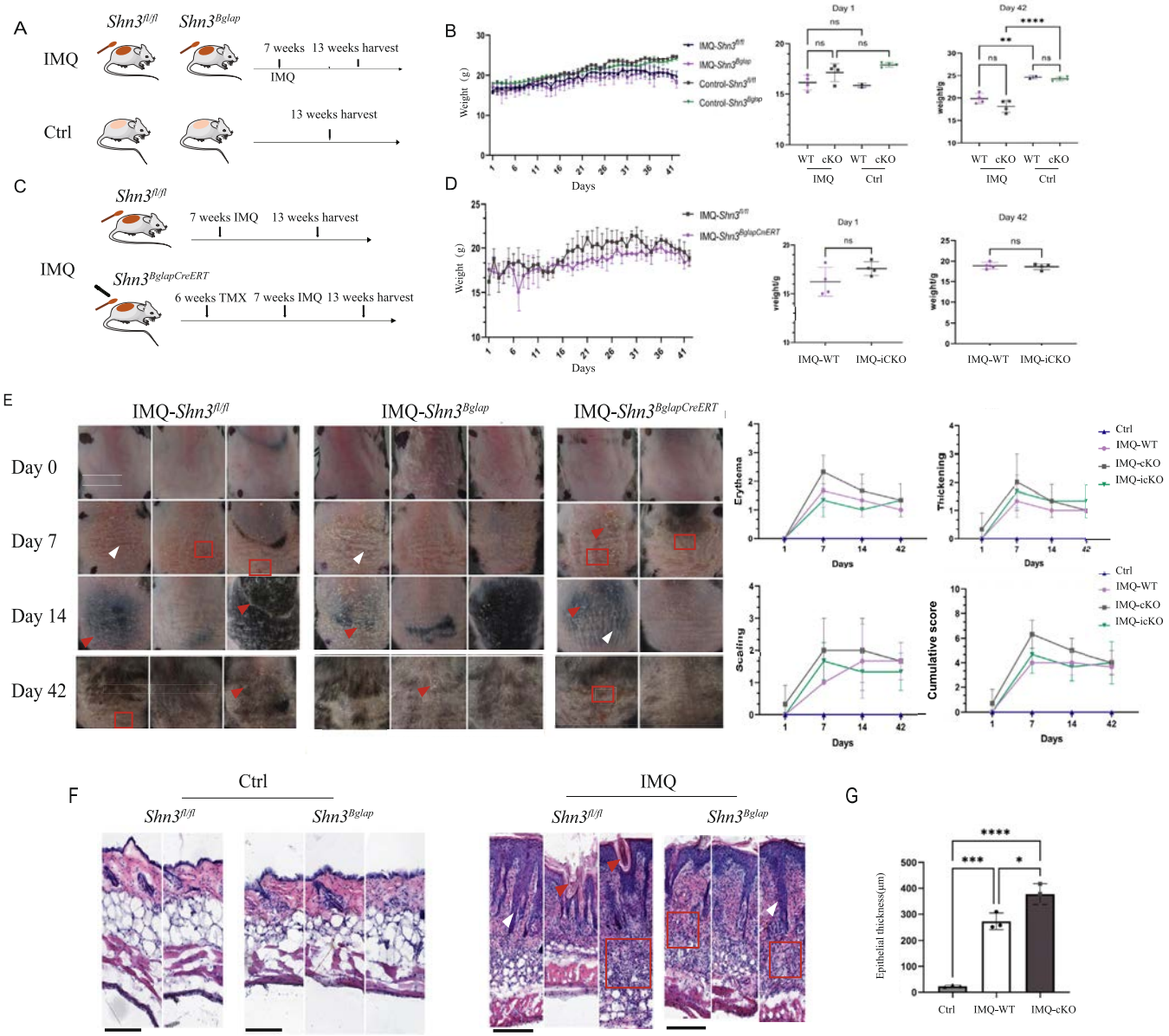

FIGURE 1 | *Shn3* depletion in osteoblast exacerbates weight loss and skin inflammation. (A, C) Schematic diagram of *Shn3* depletion by cre activity induction and IMQ-induced psoriasis model establishment. (B, D) The line graphs illustrating the body weight change trends in $Shn3^{fl/fl}$, $Shn3^{Bgalp}$, $Shn3^{BgalpERT}$ mice and untreated control groups during IMQ administration ($n = 4$/group), with statistical analysis for each group on Day 1 and Day 42 respectively. (E) Representative photographs of skin lesions at each time point and the line graphs of symptom scores, where the cumulative score is the sum of erythema, thickening, and scaling scores ($n = 4$/group). Red arrows indicate scaling, white arrows indicate thickening, and red boxes indicate erythema. (F) Representative H&E stained skin sections (Scale bar = 50 μm). (G) Statistical analysis of epidermal thickness in control mice, IMQ-treated $Shn3^{fl/fl}$ and $Shn3^{bglap}$ mice ($n = 4$/group). Red arrows indicate parakeratosis, white arrows indicate acanthosis, and red boxes indicate inflammatory cell infiltration. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

photography of the dorsal skin, measurement of toe joint swelling, and body weight recording were performed. Skin inflammation severity was assessed using a modified Psoriasis Area and Severity Index (PASI) scoring system which excluded the evaluation of affected area. Erythema, scaling, and thickening were each graded on a 0–4 scale (0: none; 1: slight; 2: moderate; 3: marked; 4: very marked) [10]. The PASI assessments were performed by two independent trained researchers who were blinded to the genotype of the mice. The final PASI score for each mouse was taken as the average of the scores from the two assessors. Mice were sacrificed at Day 42 post-IMQ first treatment, and back skin tissue was fixed in 4% paraformaldehyde solution. Hematoxylin and eosin (H&E) staining was performed following standard procedures on Optimum Cutting Temperature (OCT)-embedded tissues, which were cut into 12-μm sections. Femurs were evaluated by Micro-CT scanning (Bruker, Belgium). Quantification parameters included bone volume/tissue volume (BV/TV, %), trabecular number (Tb.N, mm^{-1}), trabecular separation (Tb.Sp, μm), trabecular thickness (Tb.Th, μm), and cortical thickness (Ct.Th, μm). For epithelial thickness comparisons at the endpoint, an unpaired two-tailed t-test was used. For longitudinal

data (body weight, PASI scores, psoriasis mouse, and affected toes measured over multiple time points), a two-way analysis of variance (ANOVA) was performed. Sidak's multiple comparisons test was used as a post hoc analysis to compare the genotypes at Days 1 and 42. For micro-CT parameters from different genotypes, a one-way analysis of variance (ANOVA) was performed, followed by Sidak's multiple comparisons test. All data are presented as mean ± SEM. Statistical analyses were performed using GraphPad Prism software (version 9.0) $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

2 | Results

2.1 | *Shn3* Depletion in Osteoblast Exacerbates Psoriatic Skin Inflammation

Baseline body weights were comparable across groups before IMQ treatment (Figure 1B), but diverged during the IMQ-induced psoriasis. By Day 42, IMQ-treated mice showed significant weight loss versus untreated controls ($p < 0.01$), whereas no statistical intergroup differences were observed between IMQ-KO and IMQ-WT cohorts ($p = 0.1355$), indicating *Shn3* deletion failed to mitigate IMQ-induced cachexia (Figure 1D). IMQ-treated mice developed typical psoriatic lesions by Day 5, confirming successful model induction. Unexpectedly, cKO ($Shn3^{Bglap}$) and icKO ($Shn3^{BglapCreERT}$) mice showed worsened skin symptoms compared to WT, manifested by elevated PASI scores both at Day 7 and experimental termination (Figure 1E). After 6 weeks of IMQ treatment, histological analysis revealed markedly increased epidermal thickness in cKO mice relative to WT controls ($p < 0.05$) (Figure 1F,G). Correspondingly, $Shn3^{Bglap}$ mice displayed reduced subcutaneous adipose layer relative to littermate controls, and the IMQ-KO group showed near-complete fat loss (Figure 1F), suggesting *Shn3* deficiency in osteogenic cells may exacerbate psoriasis by impairing the skin's immunometabolic barrier.

2.2 | *Shn3* Depletion in Osteoblast Increases PsA Incidence but Reduces Bone Loss

Following sequential IMQ application, cKO mice developed toe swelling and stiffness (Figure 2A) at Day 20, with 50% mice involvement by Day 23 and 100% incidence at Day 29, consistently earlier compared to the WT mice (Figure 2A). The icKO cohort also exhibited accelerated arthritic pathogenesis and elevated incidence of toe joint involvement relative to the WT group (Figure 2B). These collective findings imply that conditional *Shn3* inhibition in the osteogenic lineage may accelerate PsA onset. Femoral μCT analysis showed significant trabecular bone loss in both IMQ-treated WT and cKO mice compared to controls, indicating bone erosion in PsA (Figure 2 C,D). The cKO mice displayed distinct IMQ-induced trabecular deterioration patterns marked by decreased Tb.Th ($p < 0.0001$) but without a statistic difference in Tb.N compared to IMQ-untreated controls (Figure 2D). Notably, osteoblast-specific *Shn3* inhibition conferred a constitutive high-bone-mass phenotype with increased trabeculation and reduced Tb.Sp, and no statistic difference in Cs.Th (Figure 2D), mirroring $Shn3^{-/-}$ murine characteristics [6]. Crucially, IMQ-induced cKO mice maintained superior bone volume versus both IMQ-WT and untreated WT controls, indicating *Shn3* deletion protects against psoriatic bone loss despite worsening skin symptoms. icKO mice showed similar bone traits (Figure 2C,E), demonstrating the similar effects of transient depletion of *Shn3* in osteoblast lineage.

3 | Discussion

Cutaneous immune disorders demonstrate a significant association with the homeostasis of the musculoskeletal system. A cross-sectional study revealed that more than 80% of the psoriasis patients were affected by at least one musculoskeletal disorder [11]. In PsA, cytokines—primarily TNF-α and the IL-23/IL-17A axis—drive the bone remodeling process. TNF-α promotes osteoclast differentiation and activation, and IL-17A enhances bone resorption via RANKL activation and activates synovial cells while inducing matrix metalloproteinases, thereby promoting cartilage and matrix destruction [12]. The progression of PsA to complications including bone erosion, joint stiffness, or structural deformities correlates with marked deterioration in the quality of life. Notably, this population also exhibits heightened osteoporosis risk mediated by a persistent inflammatory response and chronic glucocorticoid therapy [11]. While current biologics demonstrate partial efficacy against osteolytic progression, the development of novel agents still remains a clinical need due to adverse reactions and non-response issues [13].

In this study, we investigated whether increased bone mass via *Shn3* conditional knockout could alleviate PsA and modulate immune-related skin inflammation. We found that *Shn3* deletion in osteoblasts did not improve PsA symptoms and, in fact, exacerbated psoriatic skin lesions. Histological analysis revealed reduced subcutaneous adipocyte thickness and disrupted adipose architecture in cKO mice. We have previously demonstrated that *Shn3* deficiency in osteoblasts increases C-terminal fragment of SLIT2 (SLIT2-C) release and thereby activates white adipose tissue browning in mice [14]. Osteoblast-specific deletion of *Shn3* causes thinning of the subcutaneous fat layer, which may contribute to the exacerbated psoriatic skin lesions observed in $Shn3^{Bglap}$ and $Shn3^{BglapERT}$ mice, but further verification is needed. Our findings in this study verify bone as a pivotal regulator that modulates multiorgan crosstalk. This implies that osteocentric therapeutic interventions may unexpectedly exert far-reaching metabolic and immunological effects.

A limitation of this study is the lack of characterization of immune responses in the *Shn3* conditional knockout IMQ-induced psoriatic mice. Consequently, the precise link between *Shn3* deficiency and psoriasis pathogenesis requires further elucidation. In the future, we will measure the levels of IL-17A, IL-17F, IL-22, IL-23, and TNF-α in mouse serum and skin homogenates and characterize immune cell infiltrates in the skin lesions and draining lymph nodes, including quantifying the percentages and absolute numbers of Th17 cells, neutrophils, macrophages, and dendritic cells. To understand the spatial distribution of these key players, we will perform immunofluorescence staining on skin sections using antibodies against IL-17 and CD4. Nevertheless, our findings suggest that skin lesion status should be monitored in patients undergoing osteoporosis treatments or prevention strategies.

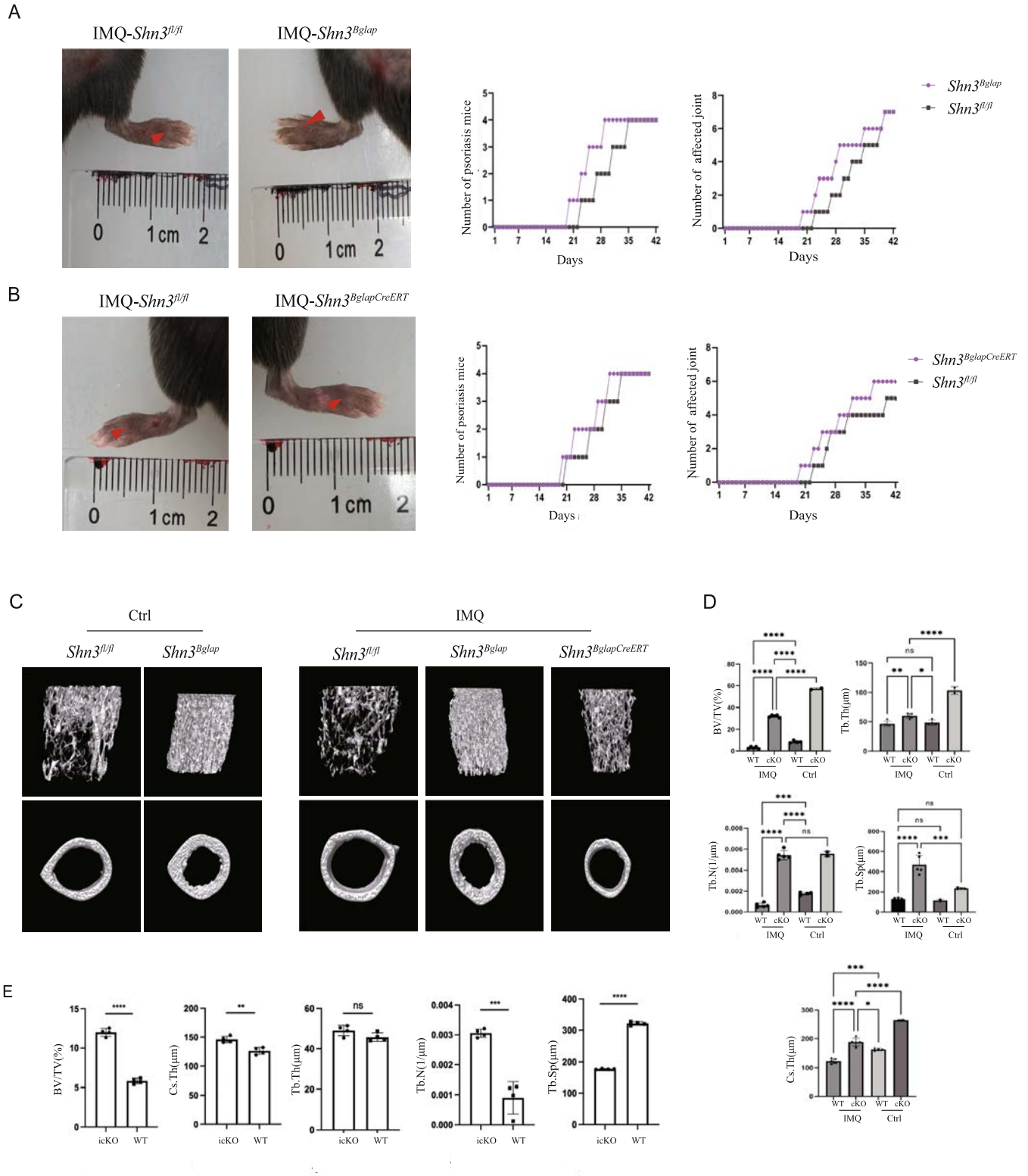

FIGURE 2 | *Shn3* depletion in osteoblasts increased PsA incidence but reduced bone loss. (A) Representative images of affected joints in mice, with red arrows indicating swelling toes. (B) Line graphs showing temporal changes in the number of mice developing arthritic symptoms and the total number of affected toe joints ($n = 4$/group). (C) Representative images of femur μCT reconstruction. (D, E) Quantitative analysis of bone parameters including bone volume/tissue volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), and trabecular separation (Tb. Sp) in $Shn3^{fl/fl}$, $Shn3^{Bgalp}$, $Shn3^{BgalpERT}$ mice and untreated control groups during IMQ administration ($n = 4$–5/group). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

Author Contributions

Y.L. and L.L. conducted the experiments and drafted the manuscript. X.L. edited the manuscript, and G.Y. and R.X. coordinated the research.

Ethics Statement

All experimental procedures were conducted under approved protocols (XMULAC20190084).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data supporting this study is available within the article. Raw datasets are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Prevalence of Metabolic Syndrome in Gout Patients and Its Relationship With Metabolic Markers: A Propensity Score Matching Study

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Keywords: gout | metabolic markers | metabolic syndrome | propensity score matching

ABSTRACT

Objective: To evaluate the association between metabolic markers and metabolic syndrome (MetS) in gout patients, and to assess the predictive performance of the triglyceride-glucose (TyG) index and triglyceride/high-density lipoprotein cholesterol (THR) ratio.

Methods: In this cross-sectional study, 502 gout patients (97.8% male) admitted between February 2023 and February 2024 were enrolled. MetS was defined according to the International Diabetes Federation criteria. Four metabolic markers—TyG, THR, serum uric acid/creatinine (SUA/Cr) ratio, and C-reactive protein/HDL-C ratio—were measured. Multivariate logistic regression identified independent predictors of MetS, while receiver operating characteristic (ROC) curves evaluated diagnostic accuracy. Propensity score matching and restricted cubic spline analyses were also performed to adjust for confounders and explore dose–response relationships.

Results: The prevalence of MetS was 62.4%. Patients with MetS exhibited significantly higher weight, systolic blood pressure (SBP), TyG, and THR values compared to non-MetS subjects (all $p < 0.05$). After adjustment, TyG (OR = 3.94, 95% CI: 2.60, 5.98) and THR (OR = 1.66, 95% CI: 1.33, 2.07) remained independently associated with MetS. ROC analysis revealed AUCs of 0.771 for TyG and 0.776 for THR; a combined model achieved an AUC of 0.820. A non-linear dose–response relationship was also observed.

Conclusion: Elevated TyG and THR indices are robust, independent predictors of MetS in gout patients. These cost-effective markers may facilitate early screening and risk stratification in clinical practice.

Abbreviations: AMPK, AMP kinase; ASO, anti-streptococcal "O"; AUC, area under the curve; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; HUA, Hyperuricemia; MetS, metabolic syndrome; PSM, propensity score matching; RCS, restricted cubic spline; RF, rheumatoid factor; ROC, receiver operating characteristic; SBP, systolic blood pressure; SUA/Cr, serum uric acid/creatinine; THR, triglyceride/high-density lipoprotein cholesterol; TyG, triglyceride-glucose; VIF, variance inflation factor; WBC, white blood cell.

1 | Introduction

Metabolic syndrome (MetS) encompasses a range of metabolic disorders such as abdominal obesity, high blood pressure, dyslipidemia, and insulin resistance. These disorders often stem from overnutrition and a sedentary lifestyle [1]. MetS is now a significant global public health issue, closely linked to obesity and type 2 diabetes mellitus, affecting about one-fourth of the global population. It contributes to two-thirds of the mortality from non-communicable diseases [2, 3]. Studies show that the prevalence of MetS has consistently increased from 27.4% to 39.0% over the past decade [4–7]. Scholars now describe MetS as the "developmental origin of health and disease," emphasizing its significant future healthcare challenges worldwide. Gout, another metabolic disease, arises from purine metabolism disorders, leading to high blood uric acid levels and subsequent deposition of urate crystals in joints and surrounding tissues [8]. Hyperuricemia (HUA) leads to gout. Due to population growth and aging, an estimated 55.8 million people worldwide suffered from gout as of 2020, with projections suggesting a rise to 95.8 million by 2050, an increase of over 70% [9].

Hypertriglyceridemia has been recognized as a metabolic abnormality since the mid-1960s and remains a key component of metabolic risk assessment today. Gout is closely linked to MetS. Elevated uric acid levels are shown to promote gluconeogenesis and insulin resistance by inhibiting AMP kinase (AMPK) activity [10]. Furthermore, HUA and gout are closely linked to dyslipidemia, including conditions like hypertriglyceridemia and low HDL-C. Uric acid is known to encourage adipogenesis and lipid metabolism disorders by inhibiting AMPK activity [11]. In gout patients, elevated serum uric acid (SUA) levels can damage the vascular endothelium and alter renal function, leading to increased blood pressure [12]. Feig et al. reported that allopurinol significantly reduces blood pressure in hypertensive adolescents [13]. Therefore, monitoring the development of MetS in populations with gout is crucial.

A cross-sectional study of 409 adults with a body mass index (BMI) $> 24\,kg/m^2$ found no significant link between elevated SUA levels and MetS components such as hypertension, dyslipidemia, and type 2 diabetes [14]. Similarly, a study in an elderly Chinese cohort detected no significant differences in SUA levels between MetS and non-MetS patients [15]. Some studies attribute this paradox to renal clearance functions significantly affecting endogenous SUA levels, leading to abnormal fluctuations [16]. Due to the limited accuracy of single biomarkers in identifying MetS, several ratios, including triglyceride/high-density lipoprotein cholesterol (THR), serum uric acid/creatinine (SUA/Cr), triglyceride-glucose (TyG), and CRP/HDL-C, have been proposed as more effective indicators [16, 17]. THR and TyG are straightforward indicators of lipid and glucose metabolism, linked to cardiovascular disease and insulin resistance [18, 19]. SUA/Cr is a superior indicator of net uric acid production [20]. CRP/HDL-C, a marker of chronic inflammation and lipid metabolism, is closely associated with cardiovascular disease and MetS [21]. Compared with other commonly used metabolic indicators—such as fasting glucose, HDL-C, BMI, or waist circumference—TyG and THR integrate multiple metabolic parameters and offer enhanced predictive utility. Multiple studies have demonstrated that the TyG index is superior to HOMA-IR in identifying insulin resistance and predicting MetS, while requiring only routine biochemical tests and avoiding insulin assays [22]. Likewise, THR has been consistently shown to be closely associated with cardiometabolic risk and MetS beyond individual lipid parameters [23]. Although inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) have been proposed for metabolic risk assessment, their validation in gout-specific populations remains sparse and less established [24]. These four markers were therefore selected as they represent distinct and complementary dimensions of metabolic dysfunction—namely insulin resistance, dyslipidemia, uric acid handling, and chronic inflammation—allowing for a comprehensive assessment of metabolic risk in gout patients.

2 | Method

2.1 | Study Population

In this cross-sectional study, we screened 523 gout patients admitted to a rheumatology specialty hospital in Chengdu, Sichuan Province, from February 2023 to February 2024 using questionnaire interviews. The inclusion criteria included gout patients who voluntarily participated and signed an informed consent form. Exclusion criteria were designed to ensure accurate questionnaire responses, excluding patients with communication or mental disorders, pregnant women, those with malignant tumors or severe organ failure, and those missing data on fasting plasma glucose (FPG) or SUA levels. After applying these criteria, 502 patients were enrolled in the study (Figure 1). The study received approval from the hospital's Ethics Committee. All participants provided written informed consent and were registered in the National Medical Research Registration and Filing Information System (MR-51-25-007763).

2.2 | Metabolic Markers

This study involved four metabolic markers. The TyG index, combining TG and FPG levels, is a simple method to assess insulin resistance and is widely used to predict cardiovascular disease risk. The SUA/Cr ratio assesses net uric acid production and reflects kidney efficiency in uric acid excretion. The THR index, which combines TG and HDL-C levels, evaluates lipid metabolism disorders. The CRP/HDL-C ratio is a composite indicator used to evaluate both inflammation and lipid metabolism disorders. The calculations for these indices are as follows [21, 25–27]:

$$\mathrm{TyG} = \ln\left[(\mathrm{TG(mg/dL)}) \times (\mathrm{FPG(mg/dL)})/2\right]$$

$$\mathrm{SUA/Cr} = \mathrm{SUA(mg/dL)}/\mathrm{Cr(mg/dL)}$$

$$\mathrm{THR} = \mathrm{TG(mg/dL)}/\mathrm{HDL-C(mg/dL)}$$

$$\mathrm{CRP/HDL-C} = \mathrm{CRP(mg/L)}/\mathrm{HDL-C(mg/dL)}$$

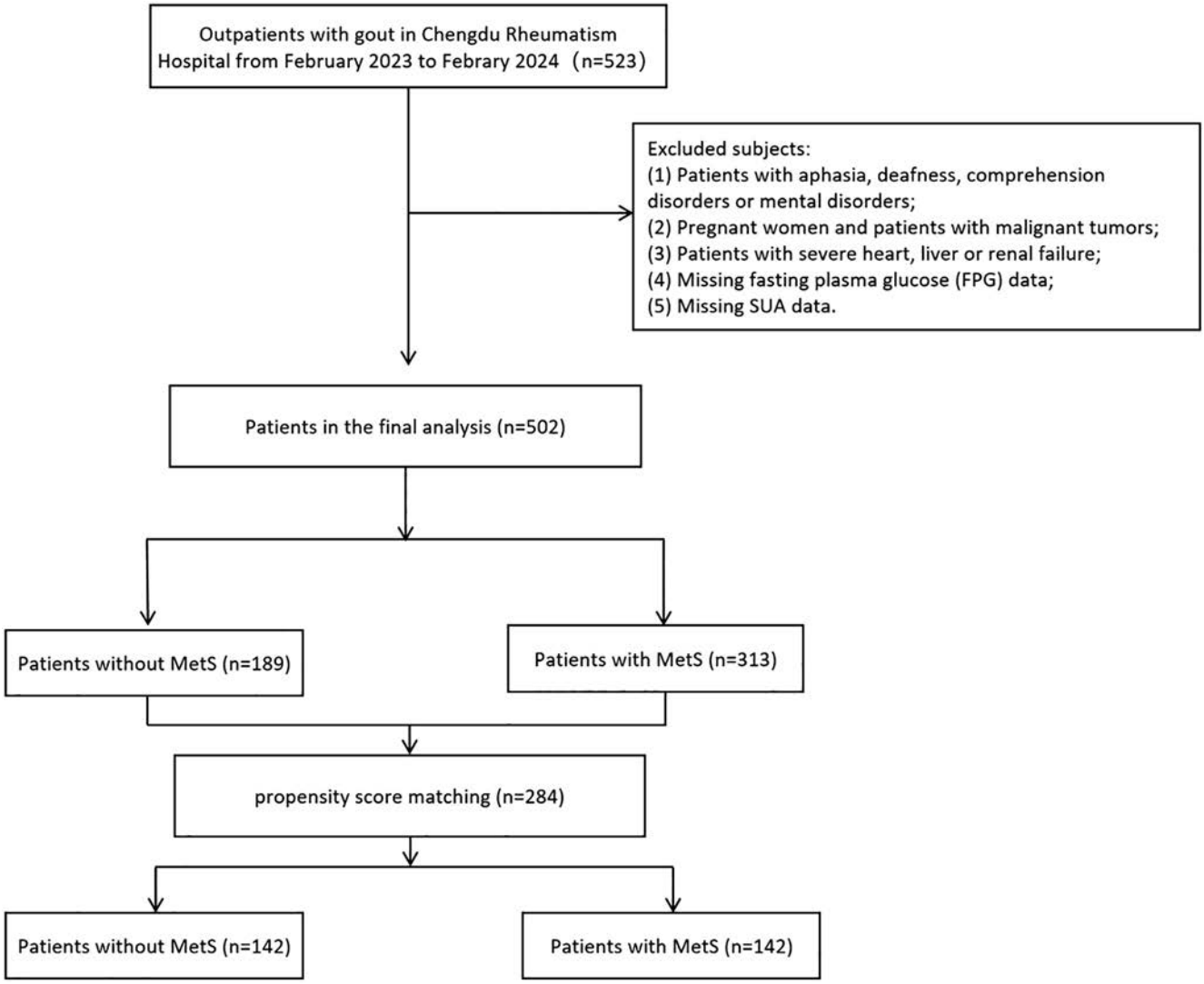

FIGURE 1 | Flowchart for inclusion and exclusion of study participants. MetS, metabolic syndrome; SUA, Serum uric acid.

2.3 | Diagnosis of Diseases

2.3.1 | Diagnosis of Gout

Gout was diagnosed based on the 2015 ACR/EULAR classification criteria [28].

2.3.2 | Assessment of the Metabolic Syndrome

The International Diabetes Federation's definition of MetS was applied to assess whether participants met the criteria for MetS: central obesity (Chinese guidelines: waist circumference ≥90 cm in men and ≥80 cm in women) plus any two of the following: (1) TG >150 mg/dL (1.7 mmol/L); (2) HDL-C <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women; (3) systolic blood pressure (SBP)/DBP ≥130/85 mmHg, or a prior diagnosis of hypertension; (4) elevated fasting glucose: FPG ≥100 mg/dL (5.6 mmol/L) or a prior diagnosis of type 2 diabetes [29]. According to the Chinese Guidelines for the Prevention and Control of Overweight and Obesity in Adults, a BMI between 18.5 and 23.9 kg/m^2 is considered normal [30]. Additionally, the following indicators were defined according to relevant guidelines and medical reference values: normal triglyceride level <150 mg/dL (1.7 mmol/L), normal HDL-C level ≥60 mg/dL (1.55 mmol/L), normal blood pressure values (SBP ≥130 mmHg, DBP ≥80 mmHg), and normal FPG level <100 mg/dL (<5.6 mmol/L).

2.4 | Covariates

Potential confounding variables were collected at baseline, including general information, biochemical indicators, medical history, and medication history. General information included sex (male or female), age (years), marital status (married: married or living with a partner; unmarried: never married, separated, divorced, or widowed), drinking status (drinking: more than once a month; non-drinking: no more than once a month or never), height (cm), body weight (kg), SBP (mm Hg), and DBP (mm Hg). Biochemical indicators included blood uric acid concentration (μmol/L), anti-streptococcal "O" (ASO) (IU/mL), erythrocyte sedimentation rate (ESR) (mm/h), rheumatoid factor (RF) (IU/mL), white blood cell (WBC) count (10^9/L), and

estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2). Medical history included hypertension, diabetes mellitus, fatty liver, kidney stones, and hyperlipidemia. Medication history included uric acid-lowering drugs, antihypertensive drugs, hormonal drugs, diuretics, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs.

2.5 | Data Collection

2.5.1 | Basic Characteristics and Lifestyle Behavior of Research Subjects

This was a cross-sectional study, and all information was collected by face-to-face interviews with study participants using a structured questionnaire by uniformly trained specialists to collect (1) general demographic characteristics: gender, age, and marital status; (2) health status: hypertension, hyperglycemia, and other medical histories; and (3) lifestyle and behavior: alcohol consumption.

2.5.2 | Laboratory Tests

Fasting blood was collected from participants who had fasted for over 8 h to measure glucose, SUA, TG, total cholesterol, LDL-C, and HDL-C. Data on height, weight, and waist circumference were also recorded.

2.6 | Statistical Analysis

A total of 502 patients were included in the study. Quantitative data were assessed for normality using the Kolmogorov–Smirnov test. Continuous variables that followed a normal distribution were expressed as $\bar{X} \pm S$ (Mean ± SD), while those that did not follow a normal distribution were presented as M(P25, P75) [median (quartiles)]. Comparisons between two groups of continuous variables with a normal distribution were made using the independent samples t-test, while comparisons between two groups of continuous variables with a non-normal distribution were conducted using the Mann–Whitney *U*-test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test. Variables with $p < 0.05$ in the one-way analysis of variance were included in the multifactorial logistic regression analysis. Factors for the differential diagnosis of MetS were derived and quantified using receiver operating characteristic (ROC) curves to assess their discriminative ability. Statistical analyses were performed using SPSS software (version 25.0). The propensity score of the subjects was calculated, and nearest-neighbor matching was performed with a matching tolerance of 0.02 to compare the differences before and after matching. Statistical analysis was conducted using R 4.3.0 (http://www.R-project.org), with the "MatchIt" and "optmatch" packages. All statistical tests were two-sided, and differences were considered statistically significant at $p < 0.05$. For the dose–response analysis, nonlinear dose–response models for metabolic markers and MetS risk were constructed using generalized least squares estimation and a four-node restricted cubic spline (RCS) function with nodes at 5%, 35%, 65%, and 95%. The Wald test was used to assess nonlinearity, with a nonlinear dose–response relationship considered significant if $p < 0.05$. If not, a linear relationship was assumed, and the model's fit was evaluated.

3 | Results

3.1 | Characteristics of the Study Population

This study included 502 patients diagnosed with gout, of whom 491 (97.81%) were male and 11 (2.19%) were female. The patients were categorized into two groups based on the presence or absence of MetS. Among the patients, 189 did not have MetS, while 313 had MetS, resulting in an incidence of 62.4%. Statistically significant differences were observed between the MetS and non-MetS groups in terms of body weight, drinking status, SBP, WBC, eGFR, antihypertensive medication history, diuretic history, diabetes mellitus history, hyperlipidemia history, THR, and TyG (all $p < 0.05$) (Table 1). Compared to the non-MetS group, the MetS group had a higher body weight, higher SBP, lower eGFR, a greater likelihood of alcohol consumption, a higher tendency to take antihypertensive medications, and higher THR and TyG indices. Tables S1 and S2 summarize the general characteristics of the study participants, grouped by quartiles of THR and TyG indices, respectively. The incidence of taller height, SUA/Cr levels, and hyperlipidemia was higher in groups Q3–Q4 than in group Q1 ($p < 0.05$). Significant differences were observed between group Q1 and the other groups in terms of weight, SUA levels, and TyG ($p < 0.05$). However, no significant differences were found in age, gender, SBP, DBP, ESR, RF, WBC, eGFR, and CRP/HDL-C ($p > 0.05$). No significant differences were found in medication history or the incidence of kidney stones, diabetes, and hypertension among the four groups ($p > 0.05$). In Table S2, group Q3 had significantly higher body weight than group Q1 ($p < 0.05$). The incidence of hyperlipidemia in groups Q2–Q4 was higher than in group Q1 ($p < 0.05$). However, no significant differences were found in SUA/Cr levels, CRP/HDL-C, medication use, or complication rates ($p > 0.05$). The incidence of hyperlipidemia in groups Q2–Q4 was higher than in group Q1.

3.2 | TyG and THR Can Predict the Risk of Developing MetS

Multivariate logistic regression was performed to identify independent correlates. The independent variables included drinking status, weight, WBC, SBP, eGFR, history of diabetes mellitus, use of hypoglycemic, antihypertensive, and diuretic medications, as well as THR and TyG. The results indicated that weight, THR, TyG, and eGFR were independent risk factors for MetS (Figure 2). A covariance diagnosis was performed to assess multicollinearity among independent variables. The variance inflation factor (VIF) was used to quantify multicollinearity. Higher VIF values indicate greater covariance issues. A VIF of less than 5 suggests minimal collinearity (Table S3). These findings suggest that THR and TyG indices are useful predictors of MetS after adjusting for confounders. To further evaluate the predictive performance of THR and TyG, ROC curves were constructed (Figure S1) to assess their diagnostic ability for MetS. The differences in the area under the curve (AUC) for THR and TyG were statistically

TABLE 1 | Baseline characteristics of the non-MetS and MetS groups before and after propensity score matching [$\bar{X} \pm SM\ (Q_L, Q_U)$, n (%)].

	Before PSM			After PSM		
	Non-MetS	MetS		Non-MetS	MetS	
Variable names	***N* = 189**	***N* = 313**	***p***	***N* = 142**	***N* = 142**	***p***
General clinical data						
Age, (years)	42.00 (32.50, 49.00)	42.00 (33.00, 50.50)	0.740	41.34 ± 12.05	42.33 ± 12.41	0.494
Gender, (male, %)	184 (97.4%)	307 (98.1%)	0.821	138 (97.2%)	138 (97.2%)	1.000
Marital status, (yes, %)	151 (79.9%)	266 (85.0%)	0.141	118 (83.1%)	111 (78.2%)	0.293
Drink status, (yes, %)	22 (11.6%)	70 (22.4%)	0.003	21 (14.8%)	17 (12.0%)	0.486
Height, cm	170 (165.00, 175.00)	170 (168.00, 175.00)	0.075	170.00 (165.00, 175.00)	170.00 (168.00, 175.00)	0.743
Weight, kg	72.00 (64.00, 82.00)	78.00 (71.25, 87.00)	0.000	74.25 (66.75, 84.25)	75.00 (70.00, 85.00)	0.187
SBP, mmHg	128 (115.00, 141.00)	131 (121.00, 144.00)	0.024	130.00 (117.75, 144.00)	128.00 (120.00, 140.00)	0.922
DBP, mmHg	89 (78, 98.50)	90 (81, 98)	0.254	90.00 (80.00, 99.00)	88.00 (81.00, 96.25)	0.597
Biochemical indicators						
SUA, μmol/L	572.03 ± 131.30	590.42 ± 127.70	0.087	579.24 ± 126.21	574.71 ± 131.00	0.767
ASO, IU/ml	38.60 (24.00, 73.20)	41.70 (23.70, 70.75)	0.841	36.10 (23.33, 57.85)	41.80 (25.90, 76.23)	0.122
ESR, mm/h	11.00 (4.00, 27.00)	10.00 (5.00, 20.00)	0.692	10.50 (4.75, 23.75)	12.00 (5.00, 26.00)	0.276
RF, IU/mL	8.00 (5.45, 11.15)	8.60 (4.85, 11.55)	0.525	8.10 (5.50, 11.33)	8.00 (5.08, 11.23)	0.753
WBC, 10^9/L	7.05 (5.80, 9.34)	6.75 (5.54, 8.13)	0.046	6.96 (5.87, 9.11)	7.20 (5.92, 8.68)	0.930
eGFR, mL/min/1.73 m^2	91.16 ± 30.35	85.19 ± 30.05	0.033	90.75 ± 30.12	93.39 ± 28.14	0.444
Medicine						
Hypouricemic agents, (yes, %)	183 (96.8%)	310 (99.0%)	0.143	59 (41.5%)	55 (38.7%)	0.628
NSAID, (yes, %)	127 (67.2%)	216 (69.0%)	0.672	91 (64.1%)	85 (59.9%)	0.463
Hormonal drugs, (yes, %)	37 (19.6%)	81 (25.9%)	0.107	62 (43.7%)	62 (43.7%)	1.000
Blood pressure lowering, (yes, %)	3 (1.6%)	24 (7.7%)	0.003	16 (11.3%)	13 (9.2%)	0.557
Diuretic, (yes, %)	2 (1.1%)	18 (5.8%)	0.009	2 (1.4%)	0 (0.0%)	0.487
Proton pump inhibitors, (yes, %)	9 (4.8%)	7 (2.2%)	0.119	4 (2.8%)	1 (0.7%)	0.367
Complications						
Hypertension, (yes, %)	37 (19.6%)	81 (25.9%)	0.107	32 (22.5%)	28 (19.7%)	0.561
Diabetes, (yes, %)	3 (1.6%)	24 (7.7%)	0.003	3 (2.1%)	5 (3.5%)	0.720

(Continues)

TABLE 1 | (Continued)

	Before PSM			After PSM		
	Non-MetS	MetS		Non-MetS	MetS	
Variable names	***N*** **= 189**	***N*** **= 313**	***p***	***N*** **= 142**	***N*** **= 142**	***p***
Kidney stone, (yes, %)	65 (34.4%)	111 (35.5%)	0.807	50 (35.2%)	41 (28.9%)	0.252
Hyperlipidemia, (yes, %)	50 (26.5%)	123 (39.3%)	0.003	45 (31.7%)	42 (29.6%)	0.699
Fatty liver, (yes, %)	34 (18.0%)	80 (25.6%)	0.050	29 (20.4%)	24 (16.9%)	0.446
Metabolic markers						
SUA/Cr	6.15 (4.68, 7.54)	6.02 (4.87, 7.56)	0.696	6.43 ± 2.16	6.47 ± 2.15	0.877
THR	1.28 (0.816, 2.22)	2.52 (1.79, 3.91)	0.000	1.34 (0.89, 2.34)	2.32 (1.66, 3.37)	0.000
TyG	8.82 (8.46, 9.44)	9.53 (9.19, 10.04)	0.000	8.99 (8.49, 9.52)	9.51 (9.18, 10.05)	0.000
CRP/HDL-C	0.009 (0.003, 0.033)	0.012 (0.004, 0.030)	0.287	0.007 (0.003, 0.029)	0.016 (0.005, 0.046)	0.021

significant ($p < 0.001$). The AUC values for THR and TyG in predicting MetS were 0.776 and 0.771, respectively (both $p < 0.001$). The TyG index exhibited a larger AUC than THR. When combined, TyG and THR achieved an AUC of 0.820, with 93% sensitivity and 62.4% specificity.

3.3 | Propensity Score Matching

To minimize confounding effects, propensity score matching (PSM) was performed using a 1:1 ratio. In this study, 142 MetS patients were successfully matched. The standardized mean difference after PSM was < 0.02 (Figure 3), indicating a well-balanced baseline between groups. Table 1 presents the baseline clinical characteristics after PSM. Similar to the pre-matching period, TyG and THR remained statistically significant ($p < 0.01$) between groups after PSM (Table 1). Before PSM, alcohol consumption, weight, SBP, WBC, eGFR, CRP/HDL-C, antihypertensive medication use, diuretic use, diabetes, and hyperlipidemia significantly differed between the MetS and Non-MetS groups ($p < 0.05$). After adjusting for confounders with PSM, differences in these variables were eliminated, except for CRP/HDL-C, which became statistically significant. This may be because the CRP/HDL-C ratio, a novel biomarker, is strongly associated with systemic inflammation and lipid metabolism. MetS patients often exhibit low-grade chronic inflammation and lipid metabolism disorders, and the CRP/HDL-C ratio effectively reflects these pathological changes [31]. Elevated CRP levels, a hallmark of low-grade inflammation, are frequently observed in MetS patients and are linked to insulin resistance and obesity [32, 33]. Moreover, decreased HDL-C levels impair reverse cholesterol transport, further aggravating metabolic dysfunction [21]. Despite advances in the application of the CRP/HDL-C ratio in inflammatory and metabolic diseases, its underlying mechanisms require further investigation. One study found that the AUC of THR was superior to CRP/HDL-C in predicting MetS among African Americans and non-Hispanic whites. Thus, CRP/HDL-C was not included as an independent risk factor in this analysis [34].

3.4 | Association of TyG, THR, and MetS

Three models were constructed to adjust for confounders and evaluate the association between TyG, THR, and MetS (Table 2). The results demonstrated a strong positive correlation. In Model 1 (unadjusted), elevated TyG and THR levels were significantly associated with a higher risk of MetS (TyG: OR = 5.056, 95% CI = 3.542, 7.218; THR: OR = 2.057, 95% CI = 1.704, 2.483). Model 2 adjusted for variables that were significant in univariate analysis. After adjusting for all confounders in Model 3, the positive association remained statistically significant in both partially and fully adjusted models (Model 2: TyG: OR = 5.056, 95% CI = 2.388, 5.211; THR: OR = 1.518, 95% CI = 1.256, 1.836; Model 3: TyG: OR = 3.939, 95% CI = 2.595, 5.980; THR: OR = 1.660, 95% CI = 1.330, 2.072). To explore whether MetS prevalence increased with higher TyG and THR values, these variables were dichotomized based on their optimal cutoff values for further analysis. The positive association between MetS and both TyG and THR remained stable across all models. (Model 1: TyG: OR = 3.682, 95% CI = 2.507, 5.407; Model 2: TyG: OR = 2.250, 95% CI = 1.426, 3.551; Model 3: TyG: OR = 2.409, 95% CI = 1.488, 3.899). (Model 1: THR: OR = 4.418, 95% CI = 2.986, 6.537; Model 2: THR: OR = 2.101, 95% CI = 1.305, 3.381; Model 3: THR: OR = 2.372, 95% CI = 1.377, 4.086).

3.5 | Dose–Response Relationship Between MetS and TyG and THR

Building on the above model, this study further investigated the dose–response relationship between MetS and TyG/THR using RCS analysis (Figure 4). The continuous variations in TyG and THR were plotted on the *x*-axis, while the risk of MetS

	Pvalue	OR (95%CIs)
Weight	<0.001	1.038(1.019–1.058)
SBP	0.915	0.999(0.998–1.011)
WBC	0.085	0.921(0.838–1.012)
eGFR	<0.001	0.984(0.976–0.993)
Diabetes, (yes)	0.051	3.720(0.997–13.882)
Diuretic, (yes)	0.119	3.872(0.707–21.190)
Drinking alcohol, (yes)	0.095	1.718(0.911–3.240)
Antihypertensive drug, (yes)	0.584	0.823(0.410–1.652)
THR	<0.001	1.518(1.256–1.836)
TyG	<0.001	3.528(2.388–5.211)

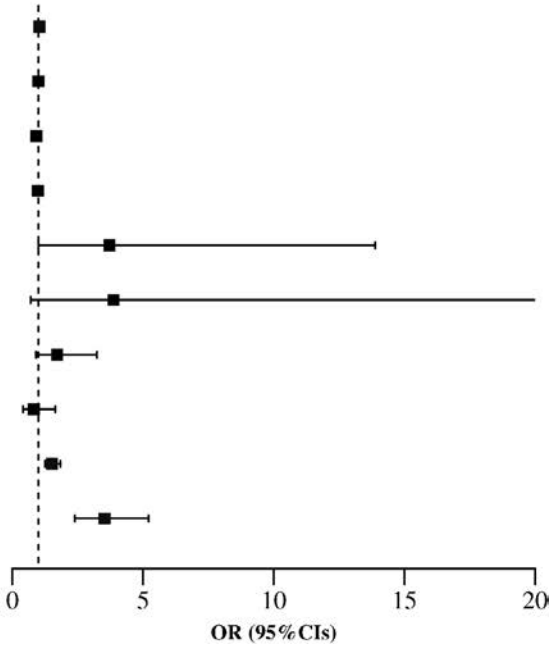

FIGURE 2 | Forest plot of indicators associated with multifactorial logistic regression analysis of the relationship with gout risk. CIs, confidence intervals; eGFR, estimated glomerular filtration rate; OR, odds ratio; SBP, systolic blood pressure; WBC, white blood cell count.

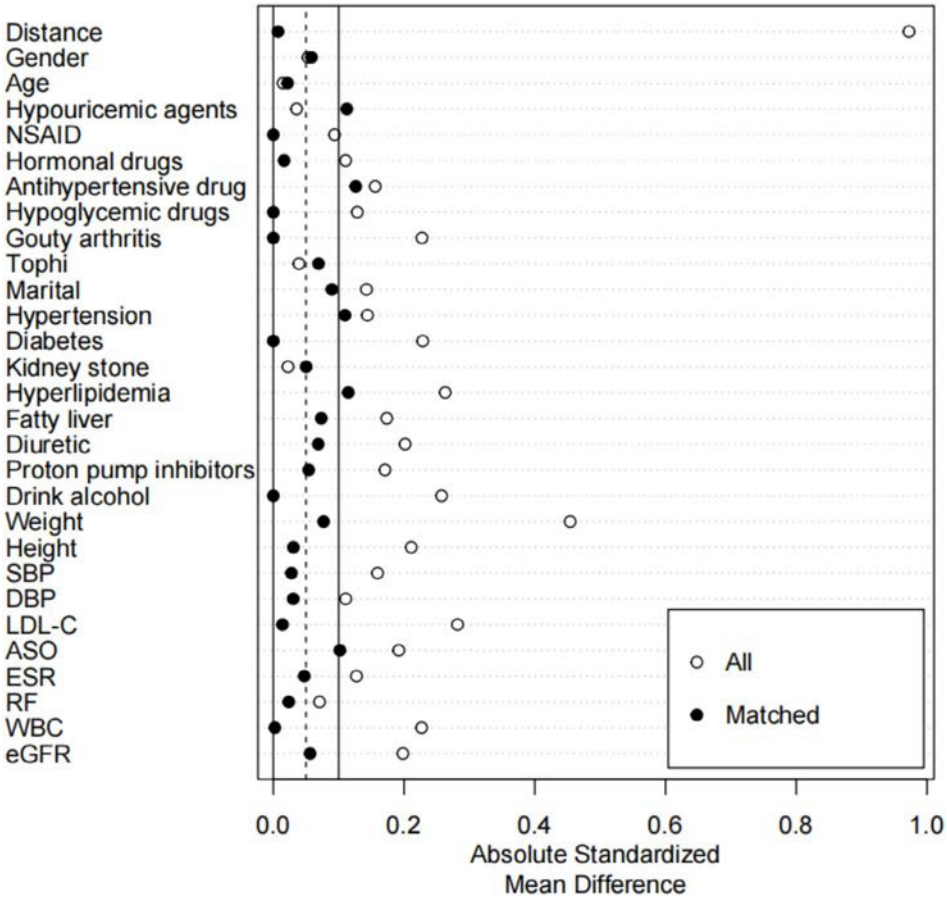

FIGURE 3 | After propensity score matching, the absolute standardized mean difference (AMD) for all variables was <0.02, indicating that the two groups were well balanced on each covariate after matching.

TABLE 2 | The association between the TyG index and THR index with MetS.

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
TyG						
Continuous	5.056 (3.542, 7.218)	0.000	3.528 (2.388, 5.211)	0.000	3.939 (2.595, 5.980)	0.000
Categories						
<9.34	Reference		Reference		Reference	
≥9.34	3.682 (2.507, 5.407)	0.000	2.250 (1.426, 3.551)	0.000	2.409 (1.488, 3.899)	0.000
THR						
Continuous	2.057 (1.704, 2.483)	0.000	1.518 (1.256, 1.836)	0.000	1.660 (1.330, 2.072)	0.000
Categories						
<2.09	Reference		Reference		Reference	
≥2.09	4.418 (2.986, 6.537)	0.000	2.101 (1.305, 3.381)	0.002	2.372 (1.377, 4.086)	0.000

Note: Model 1: evaluated the basic connection between TyG and THR and the occurrence of MetS was assessed without adjustment; Model 2: further controlled for Drink status, Weight, SBP, WBC, eGFR, Blood pressure lowering, Diuretic, Diabetes, Hyperlipidemia, THR, TyG; Model 3 is Model 2 plus further adjustment for age, gender, marital status, height, DBP, SUA, ASO, ESR, RF, NSAID, Hypouricemic agents, Hormonal drugs, Proton pump inhibitors, Hypertension, Kidney stone, Fatty liver, SUA/Cr, CRP/HDL.

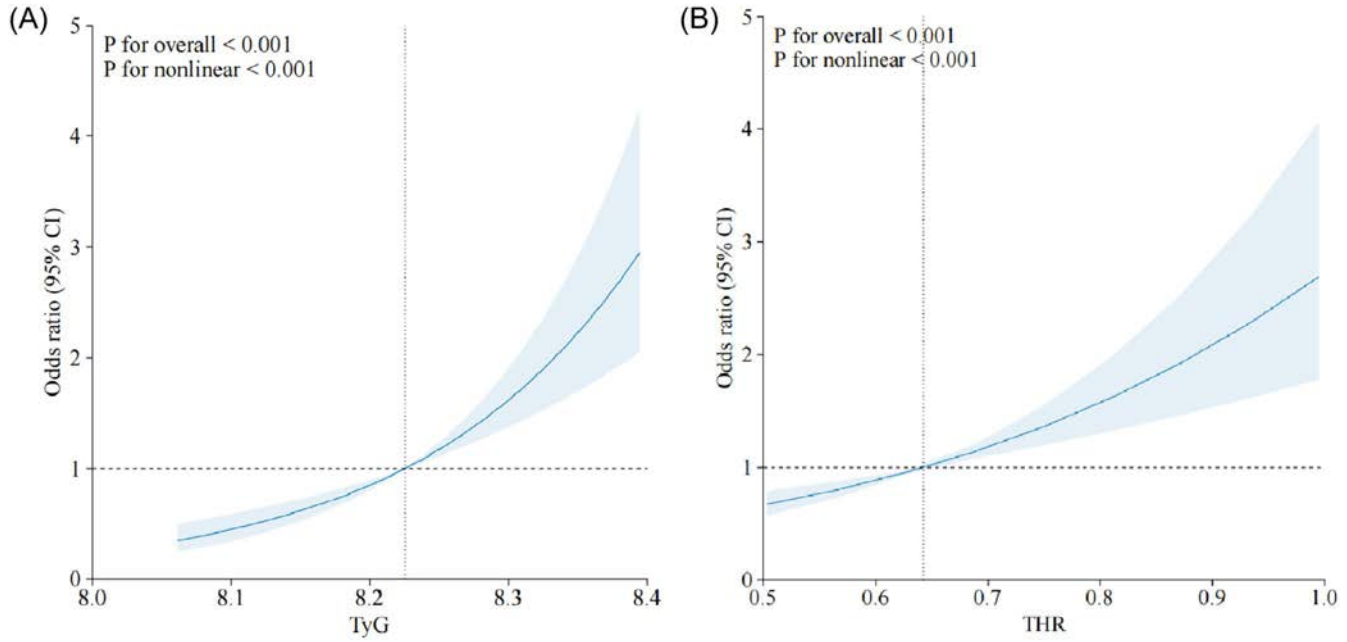

FIGURE 4 | Dose–response relationship between metabolic composite index (TyG and THR) and MetS in gouty patients. (A) Dose-response analysis of TyG and MetS in patients with gout; (B) Dose-response analysis of THR and MetS in patients with gout.

(expressed as OR values) was plotted on the *y*-axis. The results revealed a significant nonlinear association ($p < 0.001$) between TyG and THR levels and the risk of MetS in the fully adjusted model (Model 3). Specifically, the risk of MetS increased with higher TyG and THR levels.

4 | Discussion

MetS is a complex metabolic disorder that has been increasingly linked to HUA in recent years [35]. This study comprehensively investigated the risk of MetS in gout patients and analyzed potential mechanisms using metabolic markers, based on data from a rheumatology specialty hospital in Sichuan Province. The results indicated a high prevalence of MetS among gout patients, with metabolic markers such as the TyG index and THR showing predictive value for MetS. These findings offer new insights into early screening and intervention strategies.

Gout is strongly associated with insulin resistance, lipid metabolism disorders, and hypertension [36]. In this study, the prevalence of MetS among gout patients reached 62.4%, aligning with global research findings [37]. Elevated SUA levels exacerbate metabolic disorders by inhibiting AMPK activity and promoting

hepatic gluconeogenesis and lipogenesis [38]. Additionally, urate deposition in gout patients impairs vascular function, contributing to increased blood pressure. In this study, SBP was significantly higher in the MetS group than in the non-MetS group, consistent with previous findings [39].

In this study, the TyG index and THR were significantly and positively associated with MetS risk. The TyG index, a composite marker of fasting blood glucose and triglyceride levels, is strongly associated with insulin resistance and serves as a predictor of type 2 diabetes and MetS [40]. In this study, patients with a higher TyG index exhibited a significantly elevated risk of MetS, consistent with previous findings [41]. THR is a sensitive marker of lipid metabolism disorders, with elevated levels often indicating an increased risk of insulin resistance, atherosclerosis, and cardiovascular disease [42]. This study further validated the predictive value of THR for MetS, suggesting its potential as an auxiliary marker for early assessment in gout patients.

Additionally, the TyG index (OR = 3.939, $p < 0.001$) and THR (OR = 1.660, $p < 0.001$) remained statistically significant in the fully adjusted model, indicating their potential as independent predictors of MetS. ROC curve analysis demonstrated that the TyG index had a larger AUC (AUC = 0.719) than THR (AUC = 0.677), suggesting a superior ability of TyG in identifying MetS. Notably, while both TyG and THR reflect components of metabolic dysfunction, they capture partially distinct physiological processes. TyG integrates fasting glucose and triglyceride levels and serves as a robust surrogate for insulin resistance, whereas THR emphasizes lipid abnormalities—particularly elevated triglycerides and low HDL-C—commonly seen in MetS. Their combination, therefore, provides a more comprehensive risk profile, as supported by our ROC analysis, where the joint model achieved a higher AUC (0.820) than either marker alone. In contrast, although the CRP/HDL-C ratio remained significantly different after PSM, its predictive power was relatively weak, likely due to its complexity as a composite marker of inflammatory lipids [21]. By comparison, TyG and THR, as single indicators or simple ratios, are more accessible, cost-effective, and feasible for implementation in primary care settings.

Regarding the relationship between SUA and MetS, a previous study suggested that the SUA/Cr ratio could account for the influence of creatinine on uric acid excretion, potentially providing a more accurate reflection of the impact of uric acid metabolism abnormalities on MetS [43]. However, a study conducted in an overweight Chinese population reported no significant association between SUA and MetS components [44]. Similarly, the present study found no significant relationship between the SUA/Cr ratio and MetS. This discrepancy may be attributed to variations in study populations or differences in selected metabolic markers. Despite the valuable findings of this study, several limitations should be acknowledged. First, the cross-sectional nature of this study precludes the establishment of a causal relationship between gout and MetS. Future longitudinal cohort studies are required to validate the predictive value of these metabolic markers [45]. Secondly, as the study population was recruited from a specialized hospital, 97.81% of the participants were male, reflecting the well-documented higher epidemiological prevalence of gout in men compared to women. Sex-related differences in hormone levels, metabolic responses, and comorbidity profiles may influence the manifestation of MetS and the diagnostic performance of metabolic markers such as the TyG index and THR.

Building on the aforementioned limitations, future studies should explore the following directions in greater depth. First, a longitudinal cohort study should be conducted to track the dynamic changes in metabolic markers in gout patients, with a focus on clarifying the predictive timeliness of TyG and THR for MetS. Second, a multicenter, large-sample study should include populations from various regions, genders, and races to validate the generalizability of the markers and establish more precise cutoff values. Notably, future studies should aim to include a larger proportion of female participants or perform subgroup analyses to evaluate the influence of sex on clinical outcomes. Third, the combination of markers should be optimized, and the joint application of TyG and THR with other indicators (e.g., inflammatory factors or genetic markers) should be explored to develop a comprehensive predictive model. Fourth, mechanistic studies should be conducted to elucidate the molecular mechanisms by which TyG and THR influence insulin resistance and lipid deposition, utilizing animal models or cell-based experiments. Fifth, given their availability in routine biochemical testing and ease of calculation, both TyG and THR indices could be readily integrated into primary care and rheumatology clinics as cost-effective tools for early screening of MetS among gout patients. Incorporating these markers into annual metabolic risk assessments may help identify high-risk individuals earlier, enabling timely lifestyle or pharmacological interventions to prevent complications [46].

5 | Conclusion

The present study revealed that the prevalence of MetS in gout patients was 62.4%. TyG and THR were independent predictors of MetS. Even after adjusting for confounders, the association remained significant. The combined model exhibited good diagnostic efficacy, and a nonlinear dose–response relationship was observed, which was beneficial for early screening. However, owing to the limitations of cross–sectional design, sample size, incomplete indicator inclusion, and unclear mechanism, longitudinal cohort studies, multicenter large–sample research, optimized indicator combinations, mechanism exploration, and clinical translational research are required to enhance the study findings.

Author Contributions

Wanping Lv, Huixiang Chen, and Hongmei Zhu: writing – review and editing. **Yu Lei and Dong Han:** data collection. **Yu Lei:** conceptualization. **Yu Lei:** funding acquisition. **Yu Lei:** administration.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** apl70424-sup-0001-AppendixS1.docx.

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REVIEW

Decoding the Spontaneous Resolution Nature of Gout: Molecular Crosstalk Between Immune Cells, Neutrophil Extracellular Traps, Non-Coding RNAs, and Inflammatory Factors

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Keywords: immune cells | inflammatory factors | NETs | non-coding RNAs | spontaneous resolution nature of gout

ABSTRACT

Gout, a prevalent rheumatic disorder, arises from purine metabolic dysfunction characterized by elevated uric acid levels, which culminates in hyperuricemia, crystallization of sodium urate, and subsequent deposition of these crystals in joints, synovium, and other tissues or organs. Spontaneous resolution of gout is defined as the self-resolution of acute gouty arthritis observed in some patients within 7–10 days without pharmacological intervention, with no residual sequelae. The mechanistic basis underlying this spontaneous resolution remains incompletely understood, involving a spectrum of biological entities including immune cells, RNA, neutrophil extracellular traps, inflammatory mediators, and pattern recognition receptors. This review synthesizes current research progress on the spontaneous resolution of gout, with the objective of delineating directions for future investigations.

1 | Introduction

Gout is an inflammatory arthritis caused by the formation of monosodium urate crystals secondary to chronic hyperuricaemia [1]. The prevalence of this disease exhibits a marked upward trend across all socioeconomic groups [2]. Notably, the prevalence of gout is significantly associated with an increased burden of comorbidities, including cardiovascular diseases and diabetes [3]. Furthermore, recent studies have demonstrated that the age of onset of gout is gradually trending younger,

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and the rapid and substantial increase in the incidence of gout among young populations has emerged as a public health concern across both developed and developing regions and countries worldwide [4].

The pathological mechanism underlying gout flares involves an aseptic inflammatory response triggered by monosodium urate (MSU) crystals [5]. Upon recognition and phagocytosis of MSU crystals by macrophages, the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome is activated [6], culminating in the release of pro-inflammatory mediators such as interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). Subsequent production of chemokines including IL-8 and monocyte chemoattractant protein-1 (MCP-1) recruits a massive influx of neutrophils and monocytes to the inflammatory foci, ultimately precipitating severe inflammatory reactions and joint pain [7, 8]. Clinical studies have demonstrated that MSU crystals are detectable in some patients with asymptomatic hyperuricemia and gout, while gout flares can undergo spontaneous resolution within 7 to 10 days in the absence of clinical intervention [9]. Currently, research into inflammatory resolution pathways remains limited; however, multiple mechanisms are hypothesized to participate in the resolution of acute gout attacks. This review aims to systematically synthesize and elaborate on the key mechanisms governing the spontaneous resolution of acute gouty arthritis, with a focus on the dual roles of immune cells (e.g., macrophages and neutrophils) in both initiating and resolving inflammation, the generation and regulatory mechanisms of neutrophil extracellular traps (NETs) and aggregated neutrophil extracellular traps (AggNETs), as well as the regulatory roles of microRNAs (miRNAs)/long non-coding RNAs (lncRNAs) and various inflammatory factors in this process. Furthermore, this review intends to highlight existing research gaps and controversies, explore potential therapeutic targets, and provide a theoretical foundation and practical guidance for further elucidating the mechanisms underlying gout flares and their self-limiting nature, optimizing clinical treatment strategies, and improving patient prognosis.

2 | Immune Cells Involved in Gout Flares and Spontaneous Resolution

2.1 | Macrophages

Macrophages, among the earliest identified and extensively investigated immune cells, exert a pivotal role not only in the initiation of acute gout but also in its spontaneous resolution. Accumulating evidence indicates that M1/M2 polarization of macrophages predominates in the regulation of gout inflammation and spontaneous resolution [10]. Specifically, M2-polarized macrophages contribute significantly to promoting inflammation regression, whereas M1-polarized macrophages are primarily involved in amplifying the inflammatory response [11]. Studies have demonstrated that during the spontaneous resolution phase of acute gouty arthritis, there is a marked increase in resident synovial macrophages within the synovial tissue. These cells are capable of facilitating M2 macrophage polarization and initiating a "programmed" resolution process at the early stage of MSU crystal-induced inflammatory responses [12].

Macrophages can also facilitate the spontaneous resolution of inflammation through alternative mechanisms. Activated macrophages suppress the production of pro-inflammatory cytokines and initiate the synthesis of anti-inflammatory cytokines—such as transforming growth factor beta 1 (TGF-β1)—as well as the secretion of TNF-α receptors, via upregulation of intracellular regulatory pathways including the suppressor of cytokine signaling 3 (SOCS3) pathway. TGF-β1 can potentiate the termination of inflammatory functions in macrophages and neutrophils, which includes inhibiting IL-1β signal amplification and downregulating IL-1R expression [13]. Macrophages are also capable of directly phagocytosing MSU crystals; naive macrophages exhibit a propensity to differentiate into mature macrophages upon crystal exposure, concomitantly producing substantial amounts of the anti-inflammatory cytokine TGF-β [14]. Experimental data demonstrate a positive correlation between TGF-β production and the duration of spontaneous gout resolution. Furthermore, macrophages can mitigate inflammatory responses through direct phagocytosis of apoptotic neutrophils, a process termed "efferocytosis" [15].

2.2 | Neutrophils

Neutrophils exhibit a dual role in gout pathogenesis [16]. In one hand, they are intricately involved in the inflammatory response during acute gout flares [17]. On the other hand, neutrophils contribute to and facilitate the spontaneous resolution of gout, primarily via the release of NETs to exert anti-inflammatory effects; numerous targets have been reported to be implicated in MSU crystal-induced NET formation [16].

Hyperuricemia serves as a crucial basis for the precipitation of sodium urate crystals [18]. During an acute gout attack, the inflammatory cascade is initiated [5, 18]. However, studies have demonstrated that this inflammatory response spontaneously attenuates over time, a phenomenon closely linked to the self-regulatory capacity of neutrophils.

A pivotal mechanism underlying spontaneous gout resolution involves the capacity of human neutrophil-derived AggNETs to degrade inflammatory mediators. Accumulating evidence confirms that AggNETs can degrade pro-inflammatory mediators including IL-1β, IL-6, and TNF-α, thereby facilitating spontaneous inflammatory resolution [19]. This observation explains why an elevated neutrophil count in the early phase may actually herald the onset of spontaneous gout resolution. Neutrophils can also directly phagocytose MSU crystals to promote inflammation resolution [15]. Experimental evidence demonstrates that neutrophils undergoing MSU crystal phagocytosis enter a specialized functional state, characterized by reduced pro-inflammatory factor release and increased anti-inflammatory mediator production. In the presence of MSU crystals, the C-type lectin domain family 12 member A (Clec12a)—a member of the C-type lectin receptors (CLRs) family—can downregulate neutrophil activation by inhibiting reactive oxygen species (ROS) production. Additionally, Clec12a exerts regulatory effects on neutrophils, indirectly suppressing MSU-induced aseptic inflammation [20].

3 | The Role of NETs and AggNETs in Spontaneous Gout Resolution

3.1 | NETs

NETs, reticular structures extruded by neutrophils, exert a pivotal role in the spontaneous resolution of acute gouty arthritis [21]. During the inflammatory process of gout, MSU crystals deposited in joints or local tissues are recognized, thereby recruiting neutrophils to the inflammatory site. These neutrophils release cytokines and mediators, amplify the inflammatory response, trigger oxidative bursts, release DNA, and ultimately produce NETs. The active release of NETs is referred to as NETosis, a unique form of neutrophil death that differs from the suicidal modes of necrosis and apoptosis. NETosis encompasses two forms: suicidal and survival-oriented. Suicidal NETosis relies on NADPH oxidase and leads to neutrophil death, whereas survival-oriented NETosis does not depend on NADPH oxidase and can maintain cellular viability [22]. Among these, the activation of protein arginine deiminase 4 (PAD4) and chromatin decondensation are key steps in this process [23].

NETs exert a dual role in gout, encompassing both pro-inflammatory and anti-inflammatory functions [13]. In the context of pro-inflammatory effects, aberrant release of NETs or impairment in their timely degradation and clearance may result in excessive accumulation [24], which can induce vascular occlusion, tissue injury, and sustained inflammatory responses. Such processes consequently contribute to the progression and exacerbation of multiple pathological states [25]. Regarding their anti-inflammatory role, following MSU crystal-induced NETosis, neutrophil recruitment may persist until neutrophils at the inflammatory site reach a critical concentration, leading to the formation of AggNETs. Subsequently, AggNETs interrupt the inflammatory cycle by degrading chemokines and pro-inflammatory cytokines, thereby terminating NETosis and resolving inflammation [26]. Furthermore, accumulating evidence has confirmed that NET formation increases significantly following the peak of gout flares, which aligns with the clinically observed self-limiting nature of gout. Experimental studies have demonstrated that pharmacological inhibition of NET formation results in a significant prolongation of the duration of gout-like arthritis, further validating the critical role of NETs in facilitating spontaneous gout resolution [16]. Moreover, during the spontaneous resolution phase of gout, NETs can degrade pro-inflammatory factors via specific protease activity, thereby forming a negative feedback regulatory loop [27].

3.2 | AggNETs

In inflamed tissues with high neutrophil density, MSU crystal-induced NETs undergo aggregation to form AggNETs via serine proteases, a process that is strictly dependent on ROS production [22]. Accumulating evidence indicates that IL-1β [6], ATP, and lactoferrin—a specific inhibitor of neutrophil migration—can potentiate the formation of AggNETs [26]. These aggregated NETs represent a core mechanism underlying spontaneous gout resolution, as they effectively block neutrophil recruitment and activation and promote inflammatory resolution by encapsulating MSU crystals [16, 20]. Emerging studies further suggest that serine proteases within AggNETs can specifically degrade key pro-inflammatory cytokines and chemokines, with the efficiency of this degradation positively correlated with the rate of spontaneous gout resolution [25]. AggNETs exhibit striking analogies to tophi, featuring extracellularly dispersed MSU crystals and DNA extensions modified by neutrophil granule components [28]. They may serve as a structural basis for tophus formation and influence the disease course of gout [16]. Notably, the capacity of AggNETs to degrade inflammatory mediators aligns with the clinical observation that tophi in some patients with chronic gouty arthritis remain in a prolonged state of inflammatory quiescence [28]. This phenomenon explains why certain patients, despite extensive MSU crystal deposition in joints, do not necessarily manifest active inflammation—a state attributed to long-term spontaneous resolution. However, depending on the site of AggNETs formation (e.g., tubular structures such as blood vessels or ducts), these large and adhesive aggregates may induce various types of obstructions. These occlusions contribute to the pathogenesis of multiple diseases, exacerbating disease severity by driving pathophysiological processes [29]. Therefore, in the clinical practice of diagnosing and treating gout, emphasis should be placed on avoiding its adverse effects.

4 | Involvement of Regulatory Networks in Spontaneous Gout Resolution

4.1 | miRNAs/lncRNAs

Numerous studies have demonstrated that miRNAs and lncRNAs are involved in acute gouty inflammation and could serve as therapeutic targets for spontaneous resolution of gout [15]. Non-coding RNAs (ncRNAs), including lncRNAs, regulate the transcription of downstream target genes (mRNAs) through interactions with miRNAs via the competing endogenous RNA (ceRNA) network [30]. This mechanism allows the lncRNAs antisense noncoding RNA at the INK4 locus (ANRIL) to bind to miRNA-122-5p, upregulating the expression of BRCA1-BRCA2-containing complex, subunit 3 protein (BRCC3), thereby initiating NLRP3 inflammasome activation [31] and accelerating urate-induced inflammatory progression [15]. Interfering with this process may contribute to spontaneous gout resolution.

miRNA-142-3p has been confirmed to facilitate spontaneous gout resolution. It is enriched in NET-containing supernatants and transferred to macrophages via NET-mediated carriage, exerting its effect by downregulating TNF-α production through the inhibition of protein kinase C expression [32]. miR-143-3p can also reduce urate reabsorption by suppressing its downstream target gene, glucose transporter 9 (GLUT9) [33]. miR-146a negatively regulates gouty arthritis by downregulating pro-inflammatory factors. Deficiency of miR-146a exacerbates gouty arthritis through the upregulation of TNF receptor-associated factor 6 (TRAF6), interleukin-1 receptor-associated kinase 1 (IRAK-1), and NALP3 inflammasome activity [13, 34]. Additionally, miR-3146 expression in neutrophils is significantly upregulated upon MSU stimulation, coinciding with NET formation, and thus represents a potential target for promoting spontaneous gout resolution [35]. Upregulation of miR-328-3p, miR-375-5p, and miR-299a positively regulates cellular

apoptosis via the p53 signaling pathway. Meanwhile, miR-203a, miR-3085, and miR-19b-2-5p indirectly mediate the inflammatory response in gout by modulating the mitogen-activated protein kinase (MAPK) signaling pathway [13], and may therefore participate in the spontaneous resolution of gout.

4.2 | Interleukin-1 Family

Interleukin-1 (IL-1) is a cytokine with potent pro-inflammatory and immune-amplifying properties [36]. IL-1β-mediated inflammation is central to the pathogenesis of gout [37], and attenuation of IL-1β activity contributes to spontaneous gout resolution. Toll-like receptors 2/4 (TLR2/4) and CD14 can mediate crystal phagocytosis and initiate Pro-IL-1β production, a process promoted by pattern recognition receptors upon sensing MSU crystals. During the late phase of inflammation, these molecules undergo shedding, which impairs crystal uptake and inhibits the release of active IL-1β, thereby suppressing the inflammatory response [7]. This mechanism provides one plausible explanation for the spontaneous resolution of gout.

The phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin signaling pathway, recognized to negatively regulate autophagy activation, can prevent NLRP3 inflammasome activation and IL-1β production by modulating autophagic clearance of ROS [38], thereby promoting inflammation resolution. IL-1Ra, an endogenous competitive inhibitor of IL-1R signaling, can block the pro-inflammatory activity of IL-1 released by MSU crystal-stimulated macrophages, indicating its regulatory role in inflammation [20]. Anakinra, a recombinant IL-1Ra, has demonstrated efficacy in the management of refractory and complex gout as well as long-term gout treatment; however, its safety profile requires further evaluation [39]. It may thus contribute to gout therapy and shorten the acute phase in the future.

IL-33, a member of the IL-1 cytokine family, exerts multiple functions in immune defense [40] and may facilitate spontaneous gout resolution. Elevated IL-33 expression is observed in patients with gout, and exogenous IL-33 can reduce MSU-induced neutrophil recruitment and IL-1β production [5]. In a murine gout model, the IL-33/Suppression of tumorigenicity 2 (ST2) axis mediates pain hypersensitivity and inflammation by promoting neutrophil-dependent ROS production and transient receptor potential ankyrin 1 (TRPA1) channel activation. Targeting the IL-33/ST2 signaling pathway may thus represent a novel therapeutic target [41].

IL-37, a cytokine belonging to the IL-1 family, participates in inflammatory resolution by inhibiting the secretion of pro-inflammatory mediators and cytokines [42], as well as suppressing immune responses and inflammation [43], thereby emerging as a potential mediator of spontaneous gout resolution. The production of human IL-37 can be regarded as a self-protective mechanism that counteracts uncontrolled inflammation while preventing tissue damage [43]. When rare variants occur in the gene encoding IL-37, the anti-inflammatory properties of this cytokine are abrogated, leading to increased gout susceptibility, whereas recombinant IL-37 may hold therapeutic potential [37]. The Mer receptor, a soluble "bridging protein" capable of independently binding to phosphatidylserine (PtdSer) [44], partially mediates the inhibitory effect of IL-37 in MSU-induced acute inflammation [10].

4.3 | Transforming Growth Factor β1

TGF-β1, an anti-inflammatory cytokine exerting both intracellular and extracellular functions [20], is likely to play a facilitative role in spontaneous gout resolution. During the advanced phase of a gout flare, activated neutrophils promote TGF-β1 production and resolve the inflammatory response through phagocytosis of apoptotic neutrophils [5]. Additionally, under the regulation of the intracellular mediator cytokine-inducible SH2-containing protein (CIS), the production of TNF-α and IL-1β is reduced, while TGF-β1 is increased in MSU-induced murine macrophages, thereby promoting the spontaneous resolution of acute gouty arthritis [20].

5 | Reduction of Pattern Recognition Receptors Promotes Spontaneous Gout Resolution

Human monocyte differentiation antigen CD14, a pattern recognition receptor that amplifies innate immune responses [45], triggers innate immune responses to pathogens and tissue damage in macrophages and monocytes [46]. MSU crystals primarily enter cells via CD14 [5], diminished CD14 production may contribute to the resolution of MSU-induced inflammation [14]. The chimeric monoclonal antibody IC14, as a prospective anti-CD14 therapeutic agent, holds potential for therapeutic efficacy in gout. It exerts this effect by blocking the interaction between CD14, damage-associated molecular patterns (DAMPs), and MSU, thereby attenuating the NLRP3/IL-1β signaling cascade [5].

6 | Other Substances Involved in Spontaneous Gout Resolution

6.1 | Ferroptosis

Previous studies have demonstrated that genetic susceptibility to a hyperferric state is associated with an elevated risk of gout [47], suggesting that ferroptosis may contribute to spontaneous gout resolution. Serum iron and ferritin levels are positively correlated with the frequency of gout flares, and serum ferritin levels in patients with gout are higher than those in the control group. The mechanism by which iron is involved in gout pathogenesis may involve the role of xanthine oxidase (XO) in uric acid production [48]. Reducing iron stores helps prevent gout recurrence and significantly decreases the frequency and severity of flares [49].

6.2 | Apolipoproteins

Apolipoproteins may facilitate spontaneous gout resolution through multiple pathways. Studies have demonstrated that upon binding to apolipoprotein B (Apo B) and apolipoprotein E (Apo E), MSU crystals can prevent neutrophil activation and the

production of an as-yet-unidentified soluble mediator. This mediator interferes with the formation of Immunoglobulin G (IgG) coating on MSU crystals, thereby attenuating the driving force behind the inflammatory response [5]. Lipoproteins containing Apo B-100 and Apo E bind to MSU crystals, inhibiting crystal-neutrophil interactions [50]. Additionally, Apo E and Apo B may suppress crystal-induced phagocytosis [17].

6.3 | Omega-3 Fatty Acids

Currently, omega-3 fatty acids are recognized to exert anti-inflammatory effects by inhibiting MSU crystal-induced inflammatory mediators, including NLRP3 inflammasome assembly and neutrophil chemotaxis [51]. Low intake of seafood rich in omega-3 fatty acids is associated with an elevated risk of gout [52]. In patients with gout, increasing the consumption of fish rich in omega-3 fatty acids, on the basis of adjusting total purine intake, can reduce the risk of gout recurrence [53]; however, their use as a standalone dietary supplement appears to be ineffective [54]. Furthermore, omega-3 fatty acids can inhibit urate transporter 1 (URAT1), thereby preventing the reabsorption of glomerular-filtered urate back into the bloodstream [55], suggesting that this pathway may also contribute to the facilitation of spontaneous gout resolution by omega-3 fatty acids.

7 | Conclusion and Future Direction

In summary, the spontaneous resolution of acute gouty arthritis involves multiple mechanisms and substances, among which immune cells, inflammatory factors, RNA, and NETs play indispensable roles (Figure 1). It is noteworthy that NETs and AggNETs play key roles in all stages of gout, participating in the initiation, exacerbation, resolution of inflammation, and maintenance of the chronic phase. The complex mechanisms underlying the spontaneous resolution of gout may explain why the symptoms of acute gouty arthritis can be alleviated to a certain extent despite the persistent presence of MSU crystals. Currently, research into the spontaneous resolution of gout remains fragmented and has not yet been fully integrated into a coherent mechanistic framework. Many hypotheses remain at the speculative stage, lacking supporting research data, and further studies are needed to explore the relationships. In order

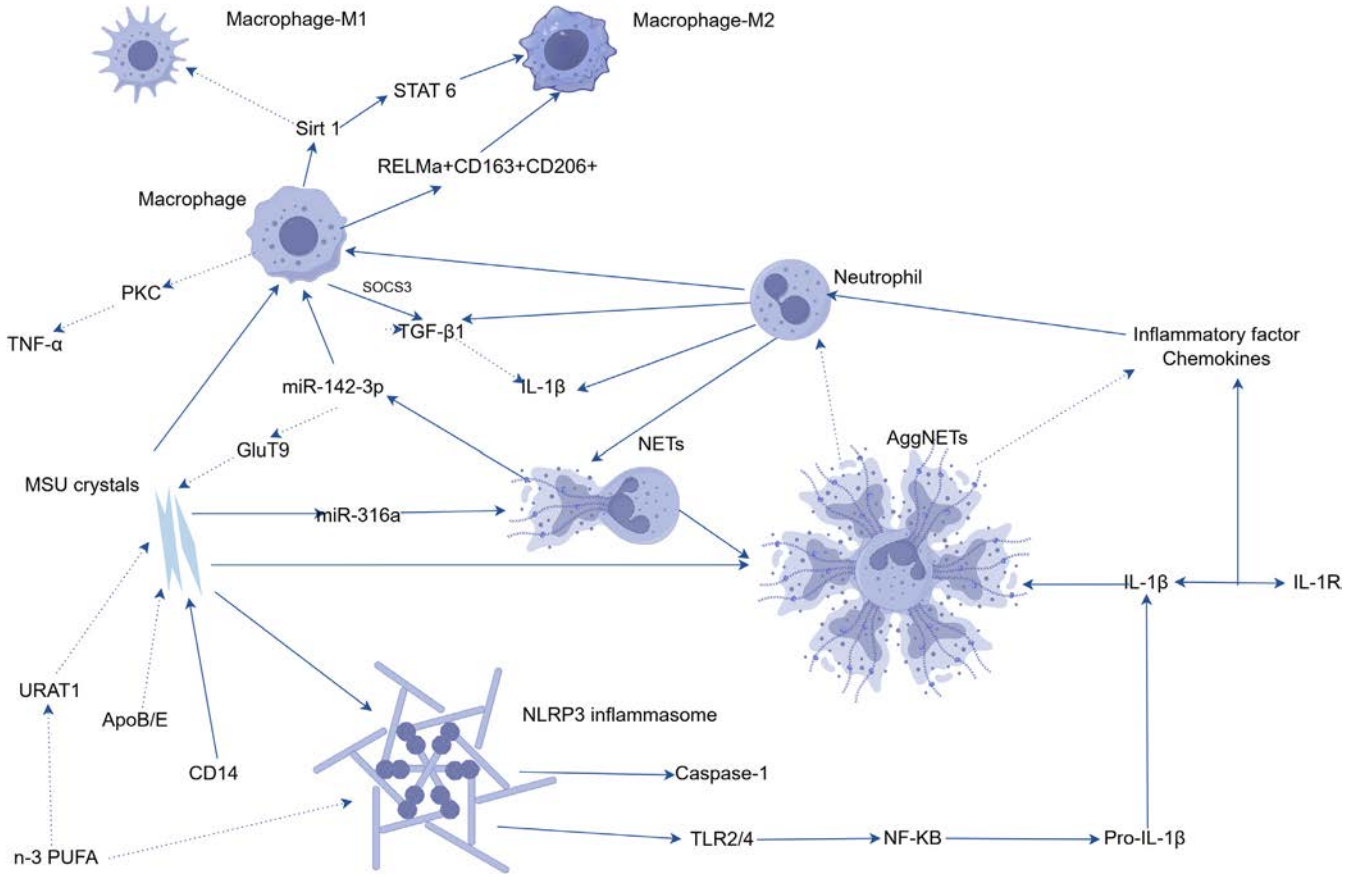

FIGURE 1 | Mechanisms potentially involved in the onset and spontaneous resolution of acute gouty arthritis. (By Figdraw) The pathological mechanism underlying gout flares involves urate crystal recognition and phagocytosis by macrophages via CD14 mediation, which activates the NLRP3 inflammasome. This subsequently induces the release of pro-inflammatory mediators (e.g., IL-1β), recruits inflammatory cells (e.g., neutrophils), and triggers an inflammatory response. During the acute inflammatory phase, neutrophils release NETs to exert anti-inflammatory effects and further form AggNETs to promote inflammation resolution. The spontaneous resolution process involves multiple components, including immune cells (macrophages and neutrophils), RNAs, and inflammatory factors. Targeting any of these pathways may facilitate inflammation resolution. AggNETs, Aggregated neutrophil extracellular traps; IL, Interleukin; MSU, Monosodium urate; NETs, Neutrophil extracellular traps; NLRP3, NOD-like receptor pyrin domain-containing protein 3; TGF-β1, Transforming growth factor β1; TNF, Tumor necrosis factor.

TABLE 1 | Summary of the possible components of the spontaneous resolution mechanism of acute gouty arthritis.

Component	Core role	Key mechanistic	Implications and research gaps
Macrophages (M1/M2 Polarization)	M1: trigger and sustain inflammation M2: promote inflammation resolution	M1: release proinflammatory cytokines M2: produce anti-inflammatory mediators, efferocytosis, intracellular regulators (e.g., SOCS3), phagocytosis MSU crystals	Clarify M1/M2 balance triggers/ pathways for therapeutic modulation
Neutrophils, NETs and AggNETs	Trigger the inflammatory response Promote inflammation resolution	NETs: formed via PAD4/chromatin decondensation AggNETs: encapsulate MSU crystals, degrade cytokines/chemokines, limit neutrophil recruitment	Elucidate precise roles/regulatory mechanisms for targeting NETs/AggNETs formation
miRNAs/lncRNAs and Inflammatory Mediators	Regulation of cytokine expression Promote inflammation resolution	RNA networks regulate pro/anti-inflammatory cytokines as well as gene expression	Identify specific RNAs as targets Clarify detailed regulatory mechanisms
Overall Research Gaps and Controversies	Immune component interplay	Incomplete understanding of cross-talk between cells, NETs/AggNETs, and RNAs Contradictory findings	Resolve existing controversies Translate mechanisms into clinical interventions

to express it more intuitively, we have sorted out a table of the elements that may be involved in the spontaneous resolution of gout (Table 1).

Gout is a prevalent chronic disease, with its affected population expanding in parallel with rising living standards. Like other chronic disorders, it is characterized by the need for long-term pharmacotherapy and lifelong management. Notably, multiple factors exert a "double-edged sword" effect in gout pathogenesis and progression. Therefore, during clinical management, a balanced approach should be pursued by carefully accounting for individual patient variability and treatment adherence. Integrating patient-specific clinical profiles, interventions such as health education, pharmacotherapeutic regimens, and, when indicated, tophus resection can be implemented to reduce flare frequency, mitigate the risk of disability, and improve patients' quality of life.

However, exploring the mechanisms underlying spontaneous resolution of gout and fundamentally addressing gout flares remains an urgent clinical challenge. Building on existing research, future studies should focus on designing intervention strategies targeting specific molecules or pathways based on the mechanisms of spontaneous gout resolution. These strategies may include accelerating resolution and shortening the acute phase through promoting M2 polarization and anti-inflammatory functions of macrophages, regulating the functions of neutrophils and NETs/AggNETs, inhibiting pro-inflammatory pathways while enhancing the effects of anti-inflammatory factors, and targeting pattern recognition receptors and metabolic pathways. Simultaneously, it is essential to enrich monitoring approaches to predict disease progression. Biomarkers such as macrophage polarization markers, neutrophil function markers, cytokines, and inflammatory mediators should be utilized for monitoring disease course, evaluating prognosis, and predicting therapeutic responses in gout patients. Furthermore, novel drugs should be developed based on substances that facilitate resolution, aiming to provide more precise and efficient treatment regimens for patients. Nevertheless, the achievement of this objective remains a protracted and arduous endeavor in the current context.

Author Contributions

Jing Ma, Xinru Liu, Yuewang Li, Jing Zhao, Chunlei Li, Dafu Man, Huilin Li, Gula Da, Yan Chen, Yu Yang, Hongbin Li, Cheng Wang and Yong Wang: contributed to the conception and design of the study. Ma Jing collected and analyzed the data. **Yong Wang, Cheng Wang:** provided critical revisions to the manuscript. **Yong Wang and Cheng Wang:** supervised the study and provided administrative, technical, and material support. All authors participated in the drafting of the manuscript, interpretation of data, and approval of the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Diverse Joint Manifestations in Anti-MDA5 Antibody-Positive Juvenile Dermatomyositis: A Unique Case Report

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Dear Editor,

Anti-melanoma differentiation associated gene 5 (MDA5) antibody-positive juvenile dermatomyositis (MDA5-JDM) is a distinct subtype of dermatomyositis characterized by anti-MDA5 antibody seropositivity, minimal or absent muscle weakness, skin ulceration, and rapidly progressive interstitial lung disease. Joint symptoms can also occur in some patients. However, their clinical characteristics remain unclear, and no specific therapeutic strategy has been established. Here, we report a case of MDA5-JDM presenting with unique joint manifestations as the main symptom during both disease onset and relapse.

A 5-year-old Japanese girl with a two-month history of bilateral leg pain, recurrent fever, anorexia, and weight loss was referred to our hospital. Physical examination revealed symmetrical joint swelling and tenderness in wrists, knees, ankles, proximal interphalangeal (PIP) joints of the second to fourth digits, and the left hip, along with Gottron's and inverse Gottron's signs on her fingers. Laboratory tests showed normal serum creatine kinase and matrix metalloproteinase-3 (MMP-3) levels. Antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide antibody were negative, while anti-MDA5 antibody was positive. Musculoskeletal ultrasound demonstrated peritendinitis around the extensor tendon in the left second PIP joint (Figure 1A). (Alt text: Musculoskeletal ultrasound showing hypoechoic area with power Doppler signals around the extensor tendon of the left second finger (A). Lower limb STIR MRI showing suprapatellar joint effusion (B), mild synovial proliferation (B), patellar tendon insertions (B), and hyperintensity lesions around the medial and lateral collateral ligaments (C). Thigh STIR MRI showing hyperintense lesions in the adductor muscle group (D). Coronal STIR MRI of both hips demonstrating joint effusion and bone marrow edema in the femoral heads and acetabula (E). Musculoskeletal ultrasound showing hypoechoic area with power Doppler signals in the left wrist joint (F).) Magnetic resonance imaging (MRI) with short tau inversion recovery (STIR) sequences of the left knee showed suprapatellar joint effusion, mild synovial proliferation at the patellar tendon insertions (Figure 1B), and hyperintensity around the medial and lateral collateral ligaments (Figure 1C). In contrast, synovial effusion and proliferation in the left knee were mild. These findings indicated synovitis, bursitis, and enthesitis. Although the patient had no muscle weakness or respiratory symptoms, MRI revealed myositis in the bilateral adductor muscles (Figure 1D), and chest CT demonstrated consolidation with surrounding ground-glass opacity in the peripheral region of the left lower lobe. Collectively, she was diagnosed with MDA5-JDM.

Methotrexate (MTX, 8.2 mg/m^2/week) was initiated. However, erythema on the eyelids and cheeks worsened and arthralgia persisted. Prednisolone (PSL, 1.2 mg/kg/day) and tacrolimus (0.12 mg/kg/day) were subsequently administered, resulting

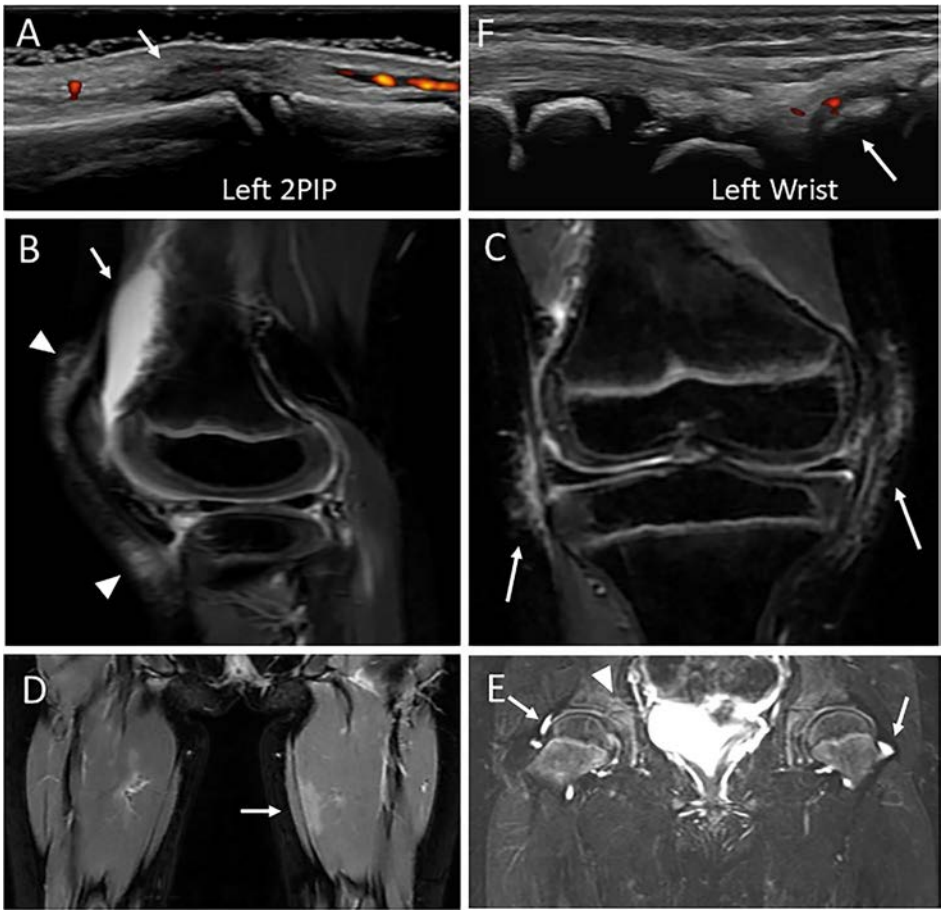

FIGURE 1 | Musculoskeletal ultrasound and MRI findings in our case. (A) Musculoskeletal ultrasound showing hypoechoic area with power doppler signals around the extensor tendon of the left second finger (arrow). (B, C) Lower limb STIR MRI showing suprapatellar joint effusion, mild synovial proliferation (B, arrow), patellar tendon insertions (B, arrow heads), and hyperintensity lesions around the medial and lateral collateral ligaments (C). (D) Thigh STIR MRI showing hyperintense lesions in the adductor muscle group (arrow). (E) Coronal STIR MRI of both hips demonstrating joint effusion and bone marrow edema in the femoral heads (arrow) and acetabula (arrow head). (F) Musculoskeletal ultrasound showing hypoechoic area with power Doppler signals in the left wrist joint (arrow).

in improvement in skin rash, arthralgia, and interstitial pneumonia. Anti-MDA5 antibody levels became negative, and PSL was discontinued after 8 months. However, 1 month after PSL cessation, arthralgia recurred in the hips and knees. STIR MRI revealed hip joint effusion and hyperintensity of the femoral head, suggesting bone marrow edema (Figure 1E). Ultrasound revealed active synovitis in the left wrist (Figure 1F). Following treatment with ibuprofen (400 mg/day) and MTX (7.0 mg/m^2/week), joint symptoms improved.

The incidence of joint involvement in MDA5-JDM and adult MDA5-DM is reported to be 30%–80% [1]. A Japanese multicentre study demonstrated that nearly half of MDA5-JDM patients developed arthritis, and the incidence of arthritis was significantly higher than in JDM patients positive for other myositis-specific antibodies [2]. Furthermore, almost 90% of MDA5-JDM patients in North America developed arthritis and arthralgia [3]. These findings indicate that joint involvement is not a rare manifestation in MDA5-JDM. Cluster analyses of adult MDA5-DM have identified distinct subgroups characterized by arthritis. In a Chinese cohort, one cluster was defined by articular involvement in more than 70% of patients, supporting arthritis as a key clinical phenotype of MDA5-DM [4].

Joint involvement in MDA5-JDM is typically described as a symmetrical, small-joint predominant polyarthritis resembling rheumatoid arthritis (RA). However, large joints are also frequently affected in MDA5-JDM. Vignesh et al. reported that patients with MDA5-JDM are affected by both small and large joints, with the knee joints being the most common site of the disease [1].

Extensor tenosynovitis has also been reported in MDA5-DM [5]. Importantly, our patient did not show synovial hypertrophy on imaging or elevated serum MMP-3 levels. Previous reports of joint involvement in MDA5-JDM have also highlighted the absence of bone erosions [6]. Taken together, these results indicate that arthritis in anti-MDA5 dermatomyositis differs from RA-like destructive synovitis. To our knowledge, no previous studies have documented bursitis, collateral ligamentitis, or patellar tendon enthesitis in either MDA5-JDM or MDA5-DM. In our case, we presumed that inflammation of the prepatellar and infrapatellar bursae, as well as bursae near the collateral ligaments, led to secondary inflammation of adjacent ligaments and tendons. Rather than RA-like erosive synovitis, MDA5-JDM may involve non-erosive synovitis, bursitis, and enthesitis. Our unique case expands the musculoskeletal phenotype of

anti-MDA5 disease by demonstrating periarticular-dominant inflammation beyond the synovium.

Treatment of MDA5-JDM generally targets myositis and interstitial lung disease severity, with no established regimen for joint manifestation. In this case, arthritis relapsed during tacrolimus monotherapy but improved with the addition of MTX. Saito et al. reported a case of MDA5-DM with arthritis and tenosynovitis successfully treated with moderate-dose corticosteroids [5] and adalimumab has also been reported effective in a case of refractory arthritis in MDA5-JDM [6]. More recently, biologic therapies and JAK inhibitors have shown promise in MDA5-DM, particularly for systemic inflammation and interstitial lung disease [7]. However, their efficacy for joint manifestations, especially periarticular inflammation, remains poorly documented, and further studies are required to establish optimal strategies.

In conclusion, our case highlights the diverse joint involvements in MDA5-JDM, including synovitis, bursitis, enthesitis, and collateral ligament inflammation—features rarely documented in the literature. MDA5-JDM should be considered in the differential diagnosis of children with multifocal joint inflammation. Further investigation is needed to clarify the underlying mechanism and develop treatment strategies tailored to joint involvement in MDA5-JDM.

Author Contributions

Futaba Miyaoka: investigation; conceptualization; data curation; writing – original draft; writing – review and editing; formal analysis; methodology. **Hitoshi Irabu:** investigation; data curation. **Shuya Kaneko:** investigation; data curation. **Tomoya Kaneda:** data curation; writing – review and editing. **Yuko Akutsu:** data curation; writing – review and editing. **Yuko Hayashi:** investigation; data curation. **Masaki Shimizu:** conceptualization; project administration; supervision; methodology; validation; writing – review and editing.

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Consent

Informed consent was obtained from the patient and her guardian.

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

Effect of Pilates Exercise on Health-Related Outcomes in Patients With Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Knee osteoarthritis (KOA) is a chronic, progressive condition characterized by cartilage degeneration, synovial inflammation, and bone changes leading to pain and functional impairment. Despite the availability of various treatment options, including multidisciplinary approaches and muscle strengthening exercises, there remains uncertainty regarding the efficacy of Pilates as a therapeutic intervention for KOA. This highlights the need for a systematic review to synthesize current evidence on the effects of Pilates on health-related outcomes in this population.

Objective: This systematic review aimed to analyze the effects of Pilates compared to no exercise or conventional exercises on pain in individuals with knee osteoarthritis, as well as on secondary outcomes including function, quality of life, range of motion, balance, and adverse events. A secondary aim is to characterize the key components and implementation characteristics of the Pilates interventions applied in the included studies.

Methods: The review protocol has been registered in PROSPERO under the number CRD42024532727. Searches were conducted in PubMed/MEDLINE, Embase, CINAHL, CENTRAL, Scopus, Web of Science, and SPORTDiscus. Eligible studies included randomized controlled trials (RCTs) that investigated the impact of Pilates exercises in patients aged ≥ 18 years, diagnosed with KOA according to the Kellgren and Lawrence criteria or the American College of Rheumatology. Studies including participants with systemic arthritis, knee joint surgery within the past 12 months, lower extremity arthroplasty, intra-articular steroid injections within the past 6 months, or any neurological conditions were excluded. The risk of bias was assessed using the RoB 2 tool, and the quality of evidence was evaluated using the GRADE approach. Meta-analyses used random-effects models, with standardized mean differences (SMDs) and heterogeneity analyzed using I^2 statistics.

Results: Eleven studies involving 476 participants were included, of which seven contributed to the quantitative synthesis. Based on this analysis, Pilates exercises reduced pain compared to no intervention (SMD −1.09; 95% CI −2.04 to −0.14; $I^2 = 66\%$; $p = 0.02$; 3 studies; $n = 66$; low-quality evidence), but did not demonstrate superiority over conventional exercises (SMD −0.28; 95% CI −1.06 to 0.50; $I^2 = 86\%$; $p = 0.49$; 5 studies; $n = 210$; very low-quality evidence). No significant improvement in knee health, assessed by the WOMAC total score, was found when compared to conventional exercises (SMD −0.14; 95% CI −1.12 to 0.85; $I^2 = 91\%$; $p = 0.78$; 4 studies; $n = 202$; very low-quality evidence), but knee range of motion increased

with Pilates (SMD 1.07; 95% CI 0.56 to 1.57; $I^2 = 0\%$; $p = 0.0001$; 2 studies; $n = 70$; low-quality evidence). The qualitative analysis revealed evidence of improvements in balance, proprioception, and quality of life in some individual studies. However, the quality of the evidence was considered very low to low.

Conclusion: The Pilates method may be an effective alternative for the rehabilitation of patients with KOA, particularly in reducing pain compared to no intervention. However, it did not demonstrate superiority over conventional exercises in pain reduction or knee health improvement. Pilates was more effective in increasing range of motion compared to conventional exercises and showed benefits in proprioception, dynamic balance, and quality of life. The heterogeneity among the studies and the low quality of the evidence suggests caution in the interpretation of the results, with new RCTs potentially impacting the findings of this review.

1 | Introduction

Knee osteoarthritis (KOA) is the most common chronic joint disease, characterized by degeneration and loss of cartilage, synovial inflammation, alteration of periarticular bone with osteophyte formation, and subchondral sclerosis [1]. The global prevalence of KOA among individuals aged 40 years and over is estimated to be 22.9%, affecting approximately 654 million people worldwide. Additionally, by 2020, around 86 million adults aged 20 years and over were diagnosed with KOA annually [2]. In the United States, annual direct healthcare costs exceed $185 billion [3]. KOA symptoms include pain, muscle weakness, stiffness, decreased physical function, mobility, range of motion, and quality of life [4, 5]. The management of KOA is a challenge and requires multidisciplinary approaches that combine pharmacological therapy, surgical interventions, and non-pharmacological strategies [6]. Of these, muscle strengthening is the strategy most recommended according to guidelines, which can be achieved through resistance exercises [7]. In this context, the Pilates method stands out as being a therapeutic option that can influence increased muscle strength [8].

Developed in the early 20th century, Pilates is based on principles such as breathing control, balance, flexibility, proprioception, and strengthening of the powerhouse—a muscular unit that includes the core, abdominal muscles, lumbar muscles, pelvic floor, and hip region [9, 10]. Studies suggest that Pilates exercises may outperform traditional strengthening programs in reducing pain and disability in individuals with KOA [11]. Furthermore, Pilates has been shown to reduce pain and improve quality of life in patients with rheumatological conditions [12, 13]. Such versatility allows routines to be personalized according to the needs of the patients, highlighting the potential of this method for managing KOA [11, 14].

Despite the growing interest in Pilates as a therapeutic intervention for KOA, the available evidence remains fragmented, hindering its practical application in clinical settings. Therefore, the aim of this systematic review is to synthesize the available evidence on the effects of the Pilates method on pain in individuals with knee osteoarthritis, as well as on secondary outcomes including function, quality of life, range of motion, balance, and adverse events. A secondary aim is to characterize the key components and implementation characteristics of the Pilates interventions applied in the included studies.

2 | Methods

2.1 | Study Design

This systematic review was prospectively registered with the international prospective register of systematic reviews (PROSPERO) (Registration number: CRD42024532727, December 2024). It was conducted according to the guidance provided in the Cochrane Handbook [15] and reported in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16].

2.2 | Search Strategy

The search was carried out in November 2024 using the following databases: PubMed/MEDLINE, Embase, CINAHL, CENTRAL, Scopus, Web of Science, and SPORTDiscus. Search strategies were designed based on the specific recommendations of each database, incorporating descriptors and their variations, combined with the Boolean operator "AND." No limitations were imposed with regard to publication date or language. Furthermore, the reference lists of articles identified through the search process were manually screened to identify additional studies. The full search strategy is provided in the Supporting Information S1.

2.3 | Eligibility Criteria

Studies including both men and women, aged 18 years or over, diagnosed with unilateral or bilateral KOA, as confirmed by either the Kellgren and Lawrence grading system [17] through radiographic evaluation, the American College of Rheumatology classification [18] or by an orthopedist, were included. This expansion of the diagnostic criteria, relative to the original protocol, was implemented to maximize the inclusion of relevant randomized controlled trials and ensure that all eligible evidence addressing the review objectives was captured. Studies were excluded where the participants had systemic arthritis, knee joint surgery within the past 12 months, lower extremity arthroplasty, intra-articular steroid injections within the past 6 months, any neurological conditions, as well as studies with mixed populations (e.g., knee osteoarthritis combined with other conditions such as low back pain, neck pain, or osteoporosis), unless data for participants with knee osteoarthritis were reported separately and met the eligibility

Summary

- The Pilates method has shown a significant reduction in pain in patients with knee osteoarthritis (KOA) compared to the absence of intervention. These findings reinforce the potential of Pilates as a complementary therapeutic approach in the management of chronic pain associated with KOA.
- Pilates resulted in a significant increase in knee range of motion compared to conventional exercises and exhibited similar effects on pain reduction and improvement in knee health. Therefore, as a modality that offers lower-impact exercise options, it may serve as a viable alternative for individuals with mechanical restrictions or difficulty adhering to traditional exercise regimens. Additionally, according to qualitative evidence, Pilates has shown benefits in proprioception and dynamic balance.
- This systematic review employed a robust methodological approach, including the assessment of evidence quality using the GRADE system and quantitative analysis through meta-analysis. The identification of substantial heterogeneity and the low quality of evidence underscores the need for future randomized clinical trials to strengthen the scientific foundation regarding the efficacy of Pilates in KOA.

criteria. The intervention of interest is the Pilates method, a body conditioning technique developed by Joseph Pilates [19], which aims to improve posture, stability, and movement awareness through controlled exercises, emphasizing the isometric contraction of core muscles. Pilates exercises may include both mat- and apparatus-based routines targeting deep stabilizing muscles such as the multifidus and transversus abdominis. Randomized controlled trials were included that compared the effects of Pilates exercise with other exercise methods, or no exercise, including conventional treatments for KOA. Conference abstracts were eligible for inclusion if they met all predefined eligibility criteria and provided sufficient and usable data.

2.4 | Outcome Measures

The primary outcome for this review was pain. Secondary outcomes included function, quality of life, range of motion, balance, and adverse events. These outcomes were considered eligible for inclusion if they were assessed using validated measurement instruments or standardized clinical scales [15].

2.5 | Study Selection and Data Extraction

Two authors (TMDO and RQC) exported the studies identified through the search strategy into EndNote X9 software (Thomson Reuters, Philadelphia, USA) for the purpose of removing duplicates. Subsequently, these two authors independently screened the titles and abstracts to assess the potential eligibility of the studies. The full text of selected articles was then reviewed to confirm final inclusion in the review. Any disagreements between reviewers were resolved through discussion or, if necessary, arbitration by a third reviewer (C.M.). Data extraction, including information on author names, year of publication, study design, age, population characteristics, sample size, exercise protocol, duration, main outcomes, and adverse events, was carried out by two reviewers (TMDO and RQC). Specifically, data on adverse events were systematically extracted from the descriptions presented in the Results and Discussion sections, as well as from the study flowchart, to ascertain whether participant withdrawals were attributable to these events. Any discrepancies between reviewers were resolved through consensus or arbitration by a third reviewer (C.M.).

2.6 | Risk of Bias

The methodological quality of studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized clinical trials. The RoB 2 tool evaluates quality across five key domains: the randomization process, deviations from the intended interventions, missing data, outcome measurement, and the reporting of results. Studies were classified as having a low risk of bias if all domains are rated as "low-risk," a moderate risk of bias if one or more domains are marked as presenting "some concerns," and a high-risk of bias if any domain is judged to be "high-risk" [20].

The tool relied on a consensus-based approach achieved through independent evaluation by two reviewers (T.M.D.O. and J.E.F.). Any disagreements were resolved by consulting a third reviewer (C.M.) for arbitration.

2.7 | Quality of Evidence

The quality of the evidence included was evaluated using the grading of recommendations, assessment, development and evaluation (GRADE) system [21]. This approach considers five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. For each domain, the reasons for downgrading were as follows: [1] study design: one level of non-randomized study; [2] risk of bias: one level if the overall assessment presented some concerns; two levels if the overall assessment was high risk of bias; [3] inconsistency: one level if there was minimal overlap in the effect estimates among the studies; two levels if the confidence intervals of the effect estimates did not overlap; [4] indirectness: one level if there was indirectness from one source (population, intervention, comparison, outcome); two levels if there was indirectness from more than one source; [5] imprecision: one level if the total sample size (sum of both groups) did not meet the optimal information size (OIS) criterion, defined as fewer than 400 participants; two levels when the CI around the effect estimate included meaningful effect and no effect; [6] publication bias: one level if publication bias was suspected. Quality of evidence will be classified into four categories: very low, low, moderate, and high. The assessment was conducted independently by two reviewers using the GRADEpro software (https://gradepro.org/).

2.8 | Statistical Analysis

A random-effects meta-analysis was performed. Continuous outcomes were presented as standardized mean differences (SMD) with 95% confidence intervals (95% CI). Effect sizes were classified as minimal, small, medium, or large, corresponding to SMD values of <0.2, 0.2–0.5, 0.5–0.8, and >0.8, respectively [22]. Studies with multiple treatment groups were treated as independent studies. In instances where the control group sample was used more than once within the same forest plot, the sample size was halved. When more than one instrument was used to assess the same outcome (e.g., for pain, both SF-36 and WOMAC), preference was given to the instrument specifically validated for assessing symptoms of the health condition under investigation, rather than a generic instrument applicable to any condition [23]. Assessment timepoints were categorized as short-term ($\leq$12 weeks), medium-term (6 months), and long-term (12 months) [24]. If multiple post-intervention timepoints had been reported, the data closest to the timepoints of interest (12 weeks, 6 months, or 12 months) would have been selected.

Heterogeneity was evaluated through visual inspection of the forest plots and quantified using the I^2 statistic [15]. I^2 values were interpreted as follows: 0%–40% indicates minimal heterogeneity; 30%–60% reflects moderate heterogeneity; and 50%–90% indicates substantial heterogeneity, with significance set at $p<0.10$. To examine the influence of individual studies on the pooled outcomes, a leave-one-out sensitivity analysis was applied. When sufficient data were available, subgroup analyses were planned according to participant age (adults vs. older adults).

Publication bias was assessed through inspection of funnel plots and Egger's test when ten or more studies were included for the same outcome. Statistical significance was defined as $p<0.05$. All analyses were conducted using RevMan 5.4 software.

3 | Results

3.1 | Study Selection

The literature search identified 1166 articles. The PRISMA flow diagram summarizes the results of the literature search (Figure 1). Eleven studies [11, 14, 25–33] were included in the qualitative analysis, of which seven studies [11, 14, 25, 28, 29, 32, 33] provided sufficient information for inclusion in the meta-analysis. No subgroup analyses were conducted because none of the included studies provided outcome data stratified by age group.

3.2 | Population and Study Characteristics

A total of 476 participants were included in the studies, with ages ranging from 43 to 68 years. The majority of participants were diagnosed with KOA according to the Kellgren and Lawrence criteria, ranging from levels 1–3, or by the American College of Rheumatology criteria. Eight of the included studies were two-arm trials [25, 27–33], and three were three-arm trials [11, 14, 26]. The studies were conducted in Brazil, Egypt, India, Iran, Nigeria, Pakistan, and Turkey. The publications of the studies ranged from 2013 to 2023. All studies are randomized clinical trials, with one of them being a conference abstract (Table 1).

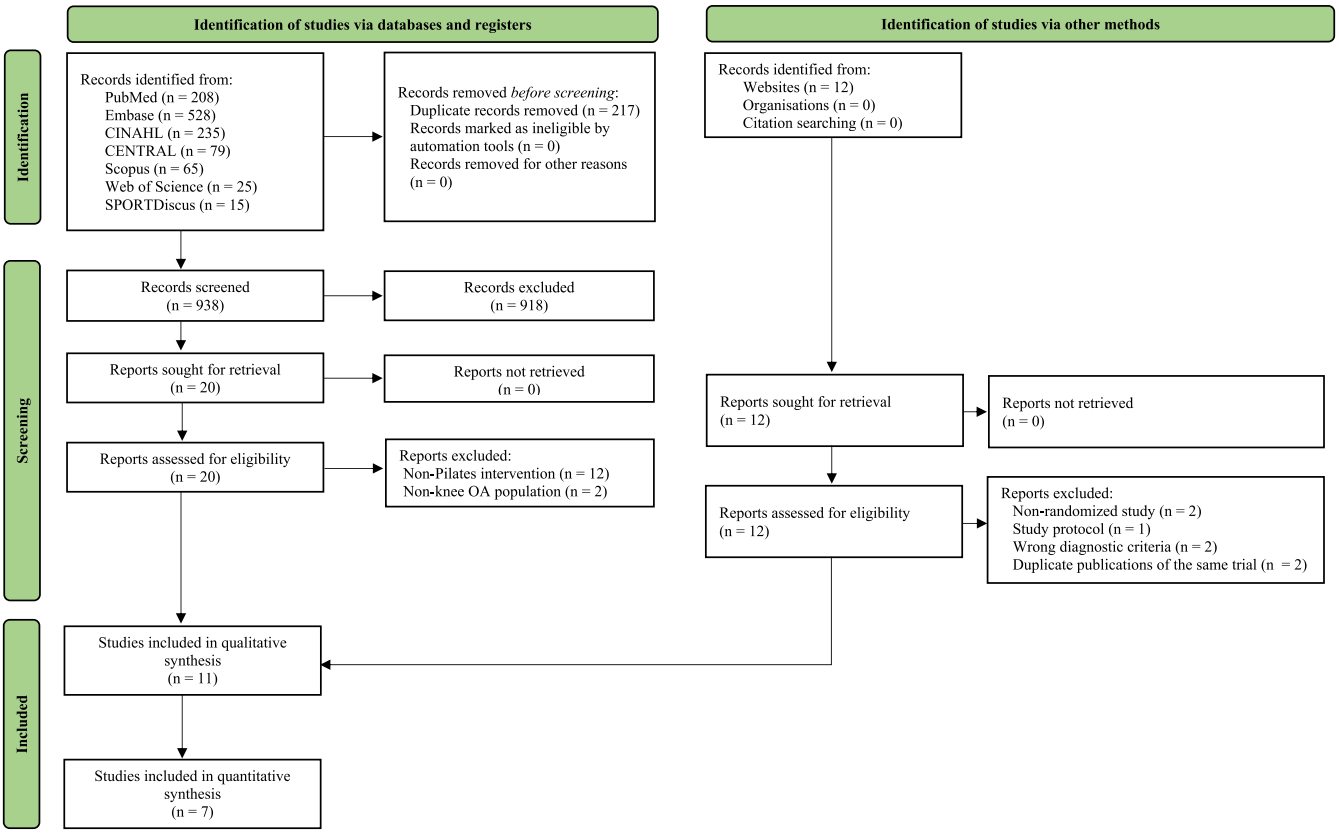

FIGURE 1 | PRISMA flow diagram which included searches of databases, registers and other sources.

TABLE 1 | Characteristics of the included studies.

Study	Design	Sample size and profile	Diagnostic criteria	Pilates intervention	Comparison	Outcomes
Karimi 2021	RCT	$n = 30$ Country: Iran Setting: Outpatient Age (years): 61.4% ± 4.8% females: 100 BMI (kg/m^2): NR Baseline pain: NR	Kellgren and Laurence	Pilates: seven exercises aimed at muscle strengthening, endurance, postural stability, proprioception and mobility 8 weeks (3×/week)	1. Suspension training: seven TRX suspension exercises targeting muscle strengthening, endurance, and stability 2. Control group: no intervention	Static balance Stork test (seconds; ↑ = better) Dynamic balance Y test (centimeters; ↑ = better) Knee range of motion Goniometry (degrees) Knee function WOMAC (0–100; ↑ = worse)
Rêgo 2023	RCT	$n = 17$ Country: Brazil Setting: Outpatient Age (years): 52.1% ± 8.9% females: 100 BMI (kg/m^2): 30.5 ± 2.5 Baseline pain: 8.4 ± 2.6 (WOMAC)	Kellgren and Laurence (grade 2 or 3)	Mat Pilates: seven exercises divided into stretching, core exercises and relaxation. Exercises included movements such as leg raises, sidekicks, swimming, spine twists, and bridges 7 weeks (2×/week)	Control group: no intervention	Knee function WOMAC (0–100; ↑ = worse) Quality of life SF-36 (0–100; ↑ = better)
Mazloum 2018	RCT	$n = 41$ Country: Iran Setting: NR Age (years): 52.1% ± 8.9% females: 32 BMI (kg/m^2): NR Baseline pain: 10.4 ± 1.8 (Lequesne index)	American College of Rheumatology	Pilates: protocol based on pilates rehabilitation program after total hip and knee arthroplasty (Levene et al., 2007) 8 weeks (3×/week)	1. Conventional therapeutic exercise: isometric and concentric contractions aimed at strengthening specific muscles, while promoting stability and control 2. Control group: no intervention	Joint position sense Biodex 60° flexion (↓ error = better) Functional performance AFPT (time to complete walk, chair rise, stairs; ↓ = better) Pain and disability Lequesne index (0–24; ↑ = worse)
Saleem 2022	RCT	$n = 40$ Country: Pakistan Setting: NR Age (years): 56.6% ± 6.8% females: 100 BMI (kg/m^2): 26.3 ± 4.2 Baseline pain: 8.0 ± 1.5 (VAS)	Kellgren and Laurence (grade 2 or 3)	Pilates: postural training, balance, breathing, and strength, focusing on quadriceps and gluteus strengthening, hip flexibility, and motor control, incorporating exercises such as bridging, squats, and specific stretches 8 weeks (3×/week)	Conventional therapeutic exercises: hot compresses, TENS, followed by isometric quadriceps strengthening and hamstring stretching exercises	Pain NPRS (0–10; ↑ = worse) Knee function WOMAC (0–100; ↑ = worse) Knee range of motion Goniometry (degrees)

(Continues)

TABLE 1 | (Continued)

Study	Design	Sample size and profile	Diagnostic criteria	Pilates intervention	Comparison	Outcomes
Rabiei 2023	RCT	$n = 54$ Country: Iran Setting: Outpatient Age (years): 60.5% ± 5.6% females: 41 BMI (kg/m^2): 29.5 ± 4.4 Baseline pain: 54.1 ± 13.2 (VAS 0–100)	American College of Rheumatology classification and Kellgren and Lawrence (grade 2 or 3)	Pilates: exercises were guided by six core principles: centering, control, precision, concentration, breath, and flow, ensuring mindful, coordinated, and fluid movements that emphasize spinal protection, core engagement, and full-body integration 8 weeks (3×/week)	Pilates + pain neuroscience education: reframe negative beliefs about pain, reduce fear-avoidance behaviors, and increase self-efficacy by teaching participants about the mechanisms of pain using accessible explanations, visual aids, and recorded materials	Pain **WOMAC** (0–20; ↑ = worse) Physical function WOMAC (0–68; ↑ = worse) Pain catastrophizing PCS (0–52; ↑ = worse) Kinesiophobia TSK (17–68; ↑ = worse) Pain self-efficacy PSEQ (0–60; ↑ = better) Functional performance TUG (seconds; ↑ = worse)
Akodu 2017	RCT	$n = 33$ Country: Nigeria Setting: Outpatient Age (years): 56.4% ± 11.6% females: 85 BMI (kg/m^2): 29.7 ± 5.4 Baseline pain: 7.7 ± 1.2 (VAS)	Kellgren and Laurence	Pilates: exercises + TENS 8 weeks (2×/week)	1. Isometric exercise + TENS 2. Usual care: diet education, losing weigth, knee care education, joint protection measures and TENS	Pain VAS (0–10; ↑ = worse) Knee range of motion Goniometry (degrees) Knee function WOMAC (0–100; ↑ = worse)
Bakk 2023	RCT	$n = 30$ Country: Egypt Setting: Outpatient Age (years): 51.9% ± 3.7% females: 0 BMI (kg/m^2): < 30 Baseline pain: 8.3 ± 0.8 (VAS)	Diagnosed by an orthopedist (unspecified criterion)	Pilates: Pilates-based exercises targeting abdominal muscles, core stability, spinal muscle stretching and postural control + the same procedures as the usual care group 8 weeks (3×/week)	Usual care: traditional exercise programme, infrared therapy, and US application	Pain VAS (0–10; ↑ = worse) Knee range of motion Goniometry (degrees) Knee function WOMAC (0–100; ↑ = worse)

(Continues)

TABLE 1 | (Continued)

Study	Design	Sample size and profile	Diagnostic criteria	Pilates intervention	Comparison	Outcomes
Meenakshi 2021	RCT	$n = 68$ Country: India Setting: Outpatient Age (years): 49% females: NR BMI (kg/m^2): NR Baseline pain: 5.9 ±1.2 (VAS)	American College of Rheumatology classification and Kellgren and Lawrence (grade 1 and 2)	Pilates: exercises focused on core strengthening, movement control, body alignment, and functional mobility, including the hundred, one leg stretch, double leg stretch, clams, side leg kick, and one leg circle 6 weeks (3×/week)	Closed kinematic chain exercises: balance training on hard and soft surfaces, retro walking, stair climbing, heel raises, single-leg stance with dynamic leaning, and sit-to-stand transitions	Pain VAS (0–10; ↑ = worse) Knee flexor isometric strength Hand held dynamometer (kg) Knee function WOMAC (0–100; ↑ = worse)
Meenakshi 2021a	RCT	$n = 64$ Country: India Setting: Outpatient Age (years): 53% females: NR BMI (kg/m^2): NR Baseline pain: 6.0 ±1.6 (VAS)	American College of Rheumatology classification and Kellgren and Lawrence	Pilates: exercises focused on core strengthening, movement control, body alignment, and functional mobility, including the hundred, one leg stretch, double leg stretch, clams, side leg kick, and one leg circle (same of Meenakshi 2021) 8 weeks (3×/week)	Neuromuscular exercises: balance, coordination, and dynamic postural control through exercises such as tandem walking, side and crossover stepping, modified grapevine, and variations of forward and backward marching	Pain VAS (0–10; ↑ = worse) Knee function WOMAC (0–100; ↑ = worse)
Kisacik 2016	RCT (Conference abstract)	$n = 39$ Country: Turquia Setting: NR Age (years): 55.9% ± 5.5% females: NR BMI (kg/m^2): NR Baseline pain: NR	Kellgren and Lawrence (grade 1 and 2)	Clinical Pilates exercise 10 weeks (3×/week)	Control group: no intervention	Kinestesia and position sense PMS-1000; degrees (↓ error = better)
Rajinder 2016	RCT	$n = 60$ Country: India Setting: NR Age (years): 55.7% ± 3.2% females: NR BMI (kg/m^2): 26.9 ± 1.7 Baseline pain: 5.4 ±0.9 (VAS)	Kellgren and Lawrence (grade 1 and 2)	Pilates: increasing complexity and repetitions weekly with exercises such as hundreds, adding one-leg stretch, double-leg stretch, clams, one-leg kick, side kick, and one-leg circle, with repetitions increasing from 5 to 10 6 weeks (3×/week)	Proprioceptive exercises: one-leg balances, leg swings, toe and heel walking, and cross-body swings, progressing to advanced one-leg balances, maximum swings, squats, runner's poses, blind balances, bicycle swings, and partial squats	Pain NPRS (0–10; ↑ = worse) Knee function WOMAC (0–100; ↑ = worse) Joint position sense Goniometer 30° flexion (↓ error = better)

Note: Data are presented as mean ± standard deviation or as percentages.

Abbreviations: AFPT, aggregate functional performance time; KOA, knee osteoarthritis; NPRS, numeric pain rating scale; NR, not reported; PCS, pain catastrophizing scale; PSEQ, pain self-efficacy questionnaire; RCT, randomized controlled trial; SF-36, Short-Form 36; TENS, transcutaneuous electrical nerve stimulation; TRX, total resistance exercise; TSK, tampa scale for kinesiophobia; TUG, timed up and go; US, ultrasound; VAS, visual analog scale; WOMAC, Western Ontario & McMaster University osteoarthritis index.

3.3 | Summary of the Pilates Interventions

The intervention period and frequency were substantially consistent across most studies, ranging from 6 to 10 weeks (short-term) with sessions conducted 2–3 times per week. Protocols followed the core principles of Pilates (centering, control, precision, concentration, breathing, and flow), incorporating a progressive structure and emphasizing core strengthening, flexibility, postural control, and breathing. While specific exercises and progression schemes varied, common movements included "the hundred", "single leg stretch", "double leg stretch", "clam", and "shoulder bridge". Some studies also introduced more advanced or combined modalities (e.g., clinical Pilates, Pilates plus TENS), with adaptations based on participant capacity. For further details of the interventions, see Supporting Information S2.

3.4 | Adverse Events

Only two studies provided data on adverse events. Rêgo et al. (2023) stated that no participant experienced adverse effects related to the intervention, such as pain or musculoskeletal discomfort, during the treatment or between sessions [32]. Rabiei et al. (2023) reported no serious adverse events in the pain neuroscience education followed by Pilates exercises group or in the Pilates exercises group [30].

3.5 | Meta-Analysis

3.5.1 | Effect of Pilates on Pain

Based on 3 studies [11, 14, 32], Pilates exercises reduced pain compared with no intervention in the short-term (SMD −1.09; 95% CI −2.04 to −0.14; $I^2 = 66\%$; $p = 0.02$; 3 studies; $n = 66$; low-quality evidence) (Figure 2). Based on 5 studies [11, 14, 25, 28, 29], Pilates exercises did not reduce pain compared with conventional exercises in the short-term (SMD −0.28; 95% CI −1.06 to 0.50; $I^2 = 86\%$; $p = 0.49$; 5 studies; $n = 210$; very low-quality evidence) (Figure 3).

3.5.2 | Effect of Pilates on Knee Health

Based on 4 studies [25, 28, 29, 33], Pilates exercises did not increase knee health assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) compared with conventional exercises in the short-term (SMD −0.14; 95% CI −1.12 to 0.85; $I^2 = 91\%$; $p = 0.78$; 4 studies; $n = 202$; very low-quality evidence) (Figure 4).

3.5.3 | Effect of Pilates on Knee Range of Motion

Based on 2 studies [25, 33], Pilates exercises increased knee range of motion compared with conventional exercises in the short-term (SMD 1.07; 95% CI 0.56 to 1.57; $I^2 = 0\%$; $p = 0.0001$; 2 studies; $n = 70$; low-quality evidence) (Supporting Information S3).

3.6 | Descriptive Synthesis

3.6.1 | Balance and Proprioception

Three trials [11, 26, 27], comprising 110 participants, investigated the effects of Pilates on balance and proprioception. These studies could not be included in the meta-analysis due to heterogeneity in outcome measures and lack of standardized effect size reporting. Two of these studies demonstrated low methodological quality and were classified as having a high risk of bias [26, 27], while one study was classified with some concerns [11].

The study by Karimi et al. (2021) analyzed the effects of suspension training and Pilates on the balance of patients with KOA [26]. A significant increase in dynamic balance was observed in the anterior ($p \leq 0.04$), posteromedial ($p \leq 0.05$), and posterolateral ($p \leq 0.04$) directions in both experimental groups, with no improvement in the control group ($p \geq 0.09$). Static balance also improved significantly in the intervention groups ($p = 0.001$) while the control group presented no difference ($p = 0.50$).

Mazloum et al. (2018) assessed Target Angle Reproduction Error (TARE) to measure knee proprioception, comparing the effects of Pilates and conventional therapeutic exercises [11]. A significant improvement in proprioceptive accuracy was found in both experimental groups, with a significant reduction in target angle reproduction error ($p < 0.001$). However, there was no statistically significant difference between the intervention groups ($p = 0.727$).

The study by Kisacik et al. (2016) found a significant improvement in kinesthetic perception (the ability to perceive body movement and position in space) in the exercise group ($p < 0.05$) [27]. However, no significant improvement was observed in position sense (the ability to perceive the position of a joint without visual

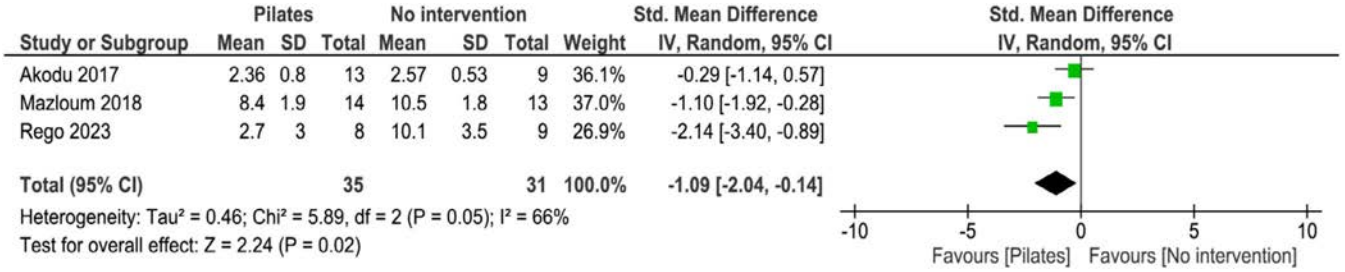

FIGURE 2 | Forest plot of comparison: Pilates versus no intervention; outcome: Pain (short-term). CI, confidence interval; SD, standard deviation; STD, standardized.

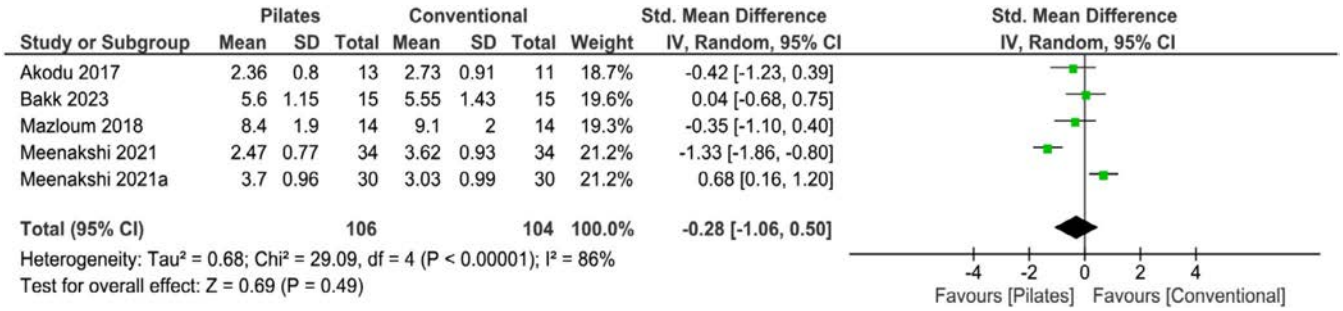

FIGURE 3 | Forest plot of comparison: Pilates versus conventional exercise; outcome: Pain (short-term). CI, confidence interval; SD, standard deviation; STD, standardized.

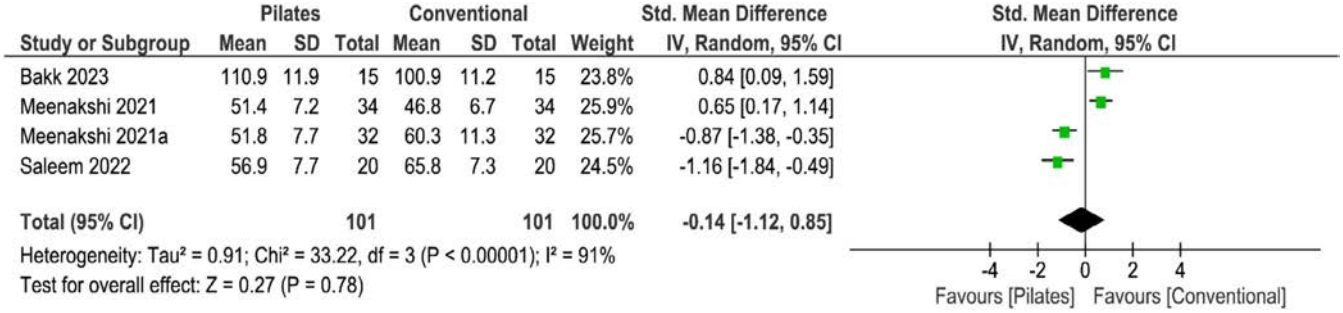

FIGURE 4 | Forest plot of comparison: Pilates versus conventional exercise; outcome: Knee health (short-term). CI, confidence interval; SD, standard deviation; STD, standardized.

aid) in the same group ($p > 0.05$). Additionally, the control group, which did not perform the exercises, showed no changes in kinesthetic and position sense values before and after treatment.

3.6.2 | Quality of Life

One trial [32], comprising 41 participants, investigated the effects of Pilates on quality of life. Because this was the only study evaluating this outcome, it could not be included in the meta-analysis. This study demonstrated low methodological quality and was classified as having a high risk of bias due to the lack of blinding of outcome assessors.

The study conducted by Rêgo et al. (2023) evaluated the quality of life of older women with KOA using the SF-36 questionnaire [32]. The experimental group, which performed mat Pilates, showed a significant improvement in functional capacity (33.12 $\pm$ 22.03 to 69.37 $\pm$ 22.43; $p < 0.05$) and in the pain domain (39.50 $\pm$ 12.89 to 71.75 $\pm$ 18.66; $p < 0.05$). Furthermore, overall health status also improved in the Pilates group (59.44 $\pm$ 18.07 to 82.75 $\pm$ 12.03; $p < 0.05$), whereas no significant changes were observed in the control group, which did not receive any physical intervention or therapeutic guidance.

3.7 | Risk of Bias

Many studies exhibited a high risk of bias, particularly in the domain of outcome measurement, mainly due to the lack of blinding of outcome assessors when evaluating subjective outcomes such as pain and function. On the other hand, in the majority of studies, greater methodological quality was observed in the domains of missing outcome data and deviations from intended interventions (Figure 5).

3.8 | Quality of Evidence

Although all analyzed outcomes derived from randomized clinical trials, the quality of the evidence was downgraded due to methodological limitations. Most studies exhibited a high risk of bias, leading to a reduction in confidence in the results. Additionally, two comparisons showed high inconsistency among the included studies, resulting in a further downgrading of the quality of evidence. However, for the domain of indirectness, no limitations were identified that would justify an additional downgrade. Conversely, all the studies had sample sizes below the Optimal Information Size (OIS) and possessed wide confidence intervals, leading to a downgrading in the quality of evidence due to imprecision. Consequently, the overall confidence in the findings ranged from low to very low (Supporting Information S4).

4 | Discussion

The results of this systematic review indicate that Pilates exercises may provide benefits for individuals with KOA. The analysis of the included studies revealed that Pilates might help reduce pain compared with no intervention and may improve knee range of motion compared to conventional exercises, both having a large effect size. Additionally, the evidence supporting a positive impact of Pilates practice on proprioception and dynamic balance is very uncertain. No significant differences were observed in knee health improvement, as assessed according to

FIGURE 5 | Summary plots of the risk of bias.

the WOMAC scale, when compared with other conventional exercise methods; however, the evidence is also very uncertain. These findings suggest that Pilates may be a viable alternative for the rehabilitation of patients with KOA, particularly in terms of pain reduction and motor control improvement. Most of the included studies involved middle-aged adults, a participant profile that should be taken into account when interpreting the results, given the limited investigation of older adults. Although these results are promising, the quality of the evidence ranged from very low to low, indicating that the findings should be interpreted with caution.

The present systematic review highlights the benefits of Pilates as an intervention for KOA while its effectiveness is comparable to that of other conventional exercises, although this evidence is very uncertain. Raposo et al. (2021) reported that both aerobic and strengthening exercises effectively reduce pain and improve function in individuals with KOA [34]. Similarly, the findings of the present review indicate that Pilates may reduce pain when compared with no intervention. Moreover, the results suggest, with a high degree of uncertainty in the evidence, that its effectiveness is similar to that of conventional exercise protocols. Likewise, Denham-Jones et al. (2022) concluded that Pilates is as effective as other exercises in managing pain and functional impairment in older adults with chronic musculoskeletal conditions, without evidence of significant differences between approaches [35]. In comparison, the present review focused specifically on knee osteoarthritis, included additional outcomes such as range of motion, balance, proprioception, and adverse events, and incorporated several recent randomized controlled trials. Furthermore, we conducted quantitative meta-analyses and assessed the certainty of the evidence using GRADE, providing a more robust and up-to-date synthesis of the available literature.

Additionally, our review identified potential improvements in knee range of motion and both dynamic and static balance, reinforcing previous findings that Pilates may enhance proprioception and postural stability. In contrast to Denham-Jones et al. (2022), who reported broad quality-of-life benefits across

various musculoskeletal conditions [35], our synthesis highlighted more specific gains in functional capacity, pain, and overall health status measured by the SF-36 in elderly women with KOA, although this evidence remains very uncertain. Taken together, these findings support Pilates as a potential therapeutic modality for KOA, while also suggesting that its benefits relative to other exercise interventions may depend on the outcomes assessed and the characteristics of the target population.

For clinical practice, the Pilates method may be a strategy for the rehabilitation of patients with KOA, particularly in reducing pain and improving range of motion, although the evidence regarding pain compared with conventional treatment is very uncertain. Although Pilates has shown effects on knee health comparable to conventional exercises, as well as potential additional benefits in proprioception and dynamic balance, the quality of evidence for these outcomes is very low. Therefore, while its incorporation into clinical practice may be a viable alternative for patients with deficits in these areas, these findings should be interpreted with caution. Furthermore, the progressive and adaptable nature of Pilates exercises allows for personalization in keeping with the condition and progression of the patient, which may enhance adherence to treatment. However, due to the heterogeneity of intervention protocols and variability in outcomes, healthcare professionals are encouraged to customize the prescription of Pilates based on a comprehensive physical-functional assessment and integrate it with other established therapeutic approaches for KOA management.

Future studies on the impact of the Pilates method on KOA should adopt more robust methodological designs, with larger sample sizes and longer follow-up periods to assess the sustainability of intervention effects, identify potential adverse events, and evaluate long-term adherence. Additionally, standardization of intervention protocols is recommended, including a detailed description of the exercises performed, frequency, and progressive intensity, in order to enhance replicability. Further research should also explore the effects of Pilates in subgroups of adults and older adults, incorporate complementary outcomes such as knee extensor and flexor strength, quality of life, and functional capacity measures, such as gait speed and sit-to-stand performance, to better elucidate the action mechanisms of the method and identify patient profiles that may derive the greatest benefit from this intervention.

This systematic review is not without its limitations. Although the included studies adequately described the prescribed exercises, most did not specify the target intensity, the criteria for its definition, or whether progression occurred throughout the sessions, all of which may compromise the accuracy of the results. Additionally, some outcomes, such as balance, proprioception, and quality of life, could not be pooled for analysis using statistical methods due to the scarcity of investigations into these variables and the heterogeneity among the studies. Furthermore, most investigations assessed the effects of Pilates only in the short-to-medium term, making it difficult to extrapolate the findings to longer periods. For outcomes such as pain and knee health, the high statistical heterogeneity observed indicates considerable variability among the pooled studies. Finally, although most risk of bias assessment domains were rated as having a low risk, the majority of the studies were assessed as having a high overall risk of bias, indicating that the results of this review should be interpreted with caution.

This systematic review presents several strengths. The study was conducted following internationally recognized guidelines, such as the Cochrane Handbook and PRISMA criteria, ensuring transparency, methodological rigor, and reproducibility in the synthesis of evidence. Additionally, the search strategy was comprehensive, including multiple relevant databases without restrictions as to language or publication date, thereby minimizing the risk of publication bias. The inclusion in the study of exclusively randomized clinical trials enhances the quality of evidence and reduces potential biases associated with other study designs, for example, non-randomized studies. Furthermore, the quality of evidence was assessed using the GRADE tool, permitting an evaluation of whether future studies may impact the findings of this review.

5 | Conclusion

The Pilates method may be an effective alternative for the rehabilitation of patients with KOA, particularly in reducing pain when compared with no intervention. However, Pilates did not demonstrate superiority over conventional exercises in reducing pain or improving knee health as assessed by the WOMAC. On the other hand, the method may enhance knee range of motion compared with conventional exercises and may also provide benefits in proprioception and dynamic balance, although the evidence for these outcomes is very uncertain. Furthermore, Pilates exercises had a positive impact on quality of life, particularly in functional capacity, pain perception, and the overall health of older women with KOA, with the evidence for this outcome also being very uncertain. The heterogeneity among the included studies, as well as the predominance of short-term investigations, limits the generalizability of the findings to medium- and long-term interventions. The very low to low quality of the evidence indicates that the results should be interpreted with caution and that new randomized clinical trials may modify the findings of this review.

Author Contributions

T.M.D.O.: conceptualization, methodology, software, formal analysis, writing of the original draft, and visualization; D.C.F.: conceptualization, writing – review and editing, supervision, project administration, and funding acquisition; J.E.F.: writing of the original draft, visualization, and formal analysis; RQC: writing of the original draft, and visualization; F.J.S.G.: methodology, writing of the original draft, and visualization; L.F.P.P.: methodology, writing of the original draft, and visualization; D.S.F.: resources, writing – review and editing, supervision, and visualization; C.M.: conceptualization, methodology, resources, writing – review and editing, supervision, project administration, and funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This study is a systematic review and meta-analysis. All data analyzed are included in the published articles cited in the reference list. Additional data extraction sheets and analysis files are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** apl70434-sup-0001-AppendixS1.docx. **Appendix S2:** apl70434-sup-0002-AppendixS2.docx. **Appendix S3:** apl70434-sup-0003-AppendixS3.docx. **Appendix S4:** apl70434-sup-0004-AppendixS4.docx.

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CLINICAL IMAGE

Asymmetric Sacroiliitis as the Presenting Manifestation of Axial Gout

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1 | Case Summary

A 29-year-old man from North India presented with a 7-year history of episodic inflammatory low back pain and alternating buttock pain, associated with morning stiffness lasting up to 45 min. His symptoms used to improve with NSAIDs. Over the past 3 years, he developed episodic inflammatory polyarthritis that gradually became persistent. He had a fluctuant swelling near the right first metatarsophalangeal joint and dactylitis of the left second and third toes. He was not obese, diabetic, hypertensive, and did not have enthesitis, psoriasis, IBD, oral ulcers, or uveitis. There was no family history of gout or hyperuricemia. Laboratory findings revealed hyperuricemia (10.9 mg/dL, normal 3.5–7.2 mg/dL in males), elevated CRP (271 mg/L, normal < 6 mg/L), and negative HLA-B27 status.

Microscopy of aspirated fluid from the first metatarsophalangeal joint revealed negatively birefringent monosodium urate crystals (Figure 1B). He had multiple tophi in all his toes. Radiographs showed erosions and soft tissue calcifications of the metacarpophalangeal and proximal interphalangeal joints of fingers, as well as asymmetric sacroiliitis (Figure 1A,C). Ultrasound showed erosions and double contour (DC) sign in bilateral MTPs and hyperechoic aggregates in all toes. Dual energy CT (DECT) confirmed urate deposition in the sacroiliac joints, hip joints, and spine (Figure 1D). On direct questioning, he stated that his back pain used to worsen with alcohol and high protein meals.

Axial skeleton involvement is uncommon in gout but is increasingly being recognized, with reported sacroiliac joint or spinal involvement ranging from 14% to 17% [1, 2]. Clinical features

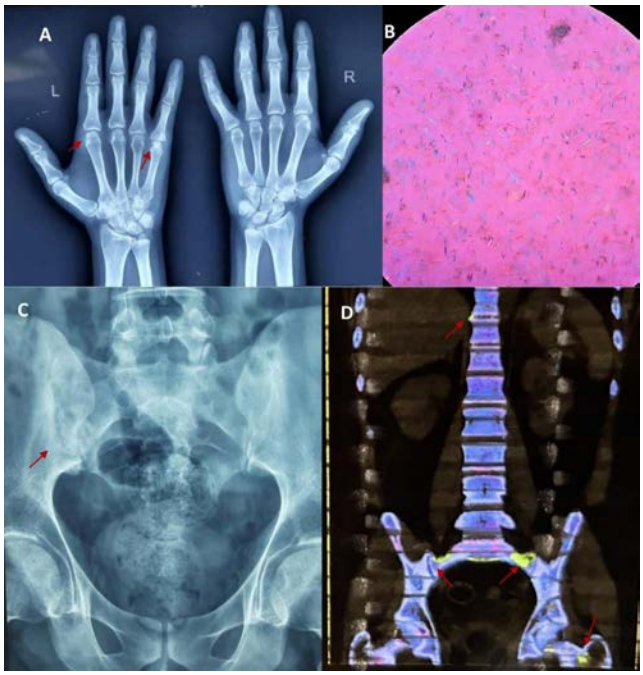

FIGURE 1 | (A) Plain radiograph of the hands showing erosions and soft tissue calcifications, (B) Needle shaped negatively birefringent monosodium urate crystals in the fluid aspirated from soft tissue swelling over the right first metatarsophalangeal joint, (C) Plain radiograph of the pelvis showing asymmetric right sacroiliitis, (D) DECT showing urate deposition in the sacroiliac joints, hip joints, and spine (green deposits, pointed by red arrows).

often mimic spondyloarthropathies, leading to diagnostic delay and inappropriate use of biologic agents. DECT is a valuable diagnostic tool that can detect urate crystal deposition in both peripheral and axial sites with high specificity, especially when joint aspiration is not feasible [3].

The patient was treated with NSAIDs, colchicine, and allopurinol, with marked symptomatic improvement and reduction in serum uric acid to 7.2 mg/dL after 1 month. He had no flares at the current 2 years follow-up, with a reduction in the size of tophi. Uric acid is stabilized at 5–6 mg/dL (normal 3.5–7.2 mg/dL); he is on allopurinol 400 mg/day and colchicine 0.5 mg/day. This case highlights the importance of considering gout in the differential diagnosis of axial inflammatory arthritis. Early recognition using crystal analysis and advanced imaging can avoid misclassification and guide appropriate therapy.

Author Contributions

L.M.R., S.S.J., K.C., and A.A. were involved in the diagnosis and management of the patient. L.M.R. wrote the original manuscript, K.C. and A.A. reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Consent

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

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Retinoid-Associated Severe Posterior Ligamentous Predominant Soft Tissue Inflammation: A Phenotype Beyond Diffuse Idiopathic Skeletal Hyperostosis

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Dear Editor,

Retinoids are synthetic vitamin A analogs including isotretinoin, alitretinoin, and acitretin used to treat keratinization disorders such as ichthyosis, psoriasis, and severe acne. Musculoskeletal side effects following retinoid exposure including peripheral enthesitis, tendonitis, and a diffuse idiopathic skeletal hyperostosis (DISH) phenotype with inflammatory back pain (IBP) are well reported [1]. DISH phenotype typically affects the annulus and anterior longitudinal ligament (ALL) territory [2]. Herein, we present a 16-year-old female who developed severe IBP after 12 years of acitretin use for lamellar ichthyosis. Surprisingly, imaging showed inflammatory changes confined to the posterior spinal ligamentous elements such as interspinous and posterior longitudinal ligaments (PLL).

We present a case of a 16-year-old female with a documented history of autosomal recessive congenital ichthyosis, characterized by the lamellar ichthyosis phenotype and associated with a heterozygous novel nonsense mutation (c.4070C>A) and a known missense mutation (c.4139A>G) in exon 28 of the ABCA12 gene, who presented with persistent inflammatory back pain (IBP) and morning stiffness of 18 months' duration. Her symptoms manifested insidiously, with axial pain primarily involving the thoracic and lumbar regions, demonstrating amelioration with physical activity but marked exacerbation during the second half of the night. The patient had no personal or familial indicators suggestive of spondyloarthropathy spectrum disorders, including the absence of uveitis, psoriasis, recent infectious triggers or vaccinations, or inflammatory bowel disease. Additionally, there is no evidence that the ABCA12 mutation-related lamellar ichthyosis mutation itself is associated with skeletal phenotypes. Since age two, she had been maintained on acitretin (10–25 mg daily) alongside vitamin D supplementation for ichthyosis management.

On physical examination, there was no synovitis, enthesitis, or dactylitis, and spinal mobility was preserved. Laboratory analysis revealed normal blood count parameters, renal and hepatic functions, calcium, phosphate, and immunoglobulins. C-reactive protein and erythrocyte sedimentation rate were normal. Immunologic assays, including HLA-B27 and autoantibody panels, were negative. Spinal magnetic resonance imaging (MRI) demonstrated marked inflammation within the ligamentous structures of the lower thoracic and upper lumbar spine, specifically in interspinal and posterior ligaments, along with facet joint effusions and adjacent bone oedema in the lower thoracic region. Notably, there was no evidence of sacroiliac or peripheral joint involvement or new bone formation on X-rays (Figure 1).

In view of these findings, a diagnosis of “acitretin-induced spinal enthesitis” was established, recognizing this as an uncommon manifestation secondary to retinoid exposure. Given the patient's optimal dermatologic control, she expressed reluctance to discontinue acitretin. Consequently, treatment with naproxen 500 mg twice daily was initiated, and acitretin was substituted

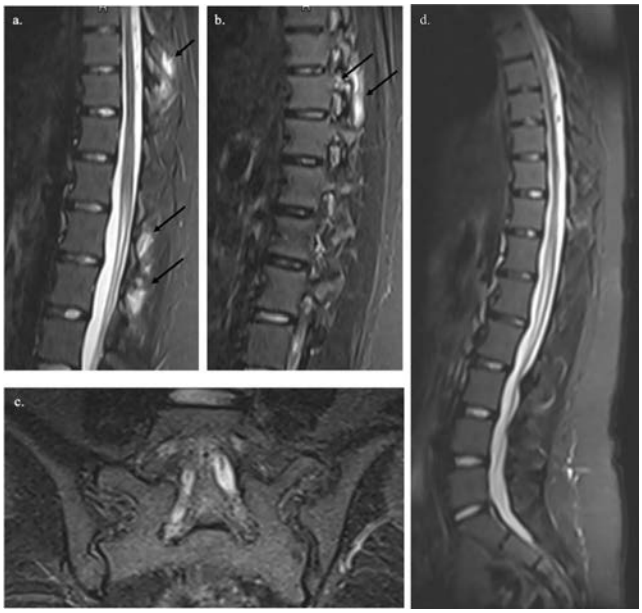

FIGURE 1 | Distinctive spinal ligamentous involvement detected by MRI. All images in this figure show the involvement pattern of the sacroiliac joint and spine in a 16-year-old female patient following acitretin treatment. Whole spine MRI demonstrated involvement confined to soft tissue, primarily affecting the interspinous and posterior spinal ligaments, with no evidence of ossification (a, b) T2 Short Tau Inversion Recovery (STIR) sequences demonstrate signal hyperintensity in the posterior longitudinal ligament and interspinous ligament, as indicated by arrows. The sacroiliac joint remained unaffected, with no osteitis or enthesitis lesions (c). Spinal MRI obtained six months after discontinuation of acitretin, during an asymptomatic period, showed no evidince of soft tissue involvement (d).

with isotretinoin, an alternative retinoid. Following these adjustments, the patient reported significant improvement in axial pain and nocturnal discomfort. After reducing the NSAID dosage to less than half of the initial amount, a reduction in her Bath Ankylosing Spondylitis Disease Activity Index from 6.9 to 3.7 was observed at her 3-month follow-up, indicating sustained clinical benefit and stabilization.

Acitretin is commonly prescribed for keratinization disorders such as ichthyosis and psoriasis due to its stronger effect among the retinoids [1]. It has been shown to reduce keratinocyte proliferation, modulate Treg and Th17 cells, and inhibit IL-6, all of which are beneficial in managing IL-17-driven ichthyosis [3]. Supporting the anti-inflammatory properties of retinoids, a study demonstrated that coculturing CD3/CD28-activated peripheral blood mononuclear cells (PBMCs) with mesenchymal stem cells (MSCs) pretreated with retinoids led to a reduction in Tregs, an increase in the Th17 subgroup, and elevated IL-6 production while reducing IL-17A, IFN-γ, and TNF-α production, which are significant mediators in AS pathogenesis [4]. Furthermore, retinoic acid significantly decreased CD14, MHC II expression in MSC-stimulated PBMCs, and suppressed ROR-γt transcripts/protein, a key transcription factor required for Th17 differentiation, leaving the precise mechanism behind the inflammatory lesions unclear [5]. A theoretically plausible mechanism by which retinoic acid may promote inflammation is its ability to drive IL-22 expression (while inhibiting IL-17) from γδ T cells and type 3 innate lymphoid cells (ILC3) in the gut [6]. It can also increase expression of α4β7 integrin on ILC3s [7] and promotes dendritic cells to drive expression of β7 integrins on T cells [8] which classically directs cells to the gut, but its ligand MAdCAM-1 has been found expressed in synovial tissue/bone in rheumatoid arthritis (RA) [9] and is upregulated when inflamed. Dirk Elewaut also found α4β7-expressing T cells were upregulated in SpA synovial tissue compared to RA, supporting a putative link between mucosal immune trafficking and axial inflammation [10]. Although these pathways have not been directly studied in the context of retinoid exposure, they offer a conceptual framework for understanding how retinoids might, under certain conditions, contribute to entheseal or spinal ligament inflammation.

Common musculoskeletal disorders related to retinoid exposure are bone abnormalities (hyperostosis, DISH, osteophytes), ossification of the tendons along with anterior and posterior longitudinal ligaments of the spine, sacroiliitis, peripheral enthesitis, arthralgia, and myalgia [11]. This case report presents a rare instance of acitretin-induced spinal enthesitis involving elements of the interspinous and posterior spinal ligaments. No evidence of ossification was noted, and this pattern of soft tissue involvement is more characteristic of axial psoriatic arthritis (PsA) than HLA-B27-positive ankylosing spondylitis or DISH [2, 12]. Prior studies have reported peripheral enthesitis, including greater trochanter or patellar tendon enthesopathy [13] as well as plantar ligamentitis and ossification as adverse effects after retinoid exposure. Long-term follow-up in our case will determine whether these prominent soft tissue inflammatory changes may evolve into radiographically detected new bone formation.

Additionally, while we attribute this presentation to retinoid exposure, the concomitant initiation of NSAID therapy following drug cessation raises the possibility of a confounding effect. However, upon resolution of the back pain, we gradually reduced the NSAID dosage to less than half of the initial amount. Notably, after substituting acitretin with isotretinoin and reducing the NSAID dosage, the persistence of symptom improvement, along with a follow-up MRI showing no spinal soft tissue inflammation (Figure 1), further supports the association between acitretin and the observed inflammatory response as a side effect, rather than indicating de novo spondylitis. Given the potential confounding factors and limited precedent for this presentation, we emphasize that this interpretation remains at the hypothesis-generating level and warrants careful longitudinal observation.

Clinical trials have demonstrated that 26% of the patients treated with isotretinoin showed progressive formation of small bony spurs arising from the front side of the vertebral bodies [1]. Another trial focusing on acitretin exposure in psoriasis found that 5% of the patients experienced progression in their diseases like PsA, DISH, and degenerative arthritis [1]. A cross-sectional study demonstrated the distribution of the symptoms after isotretinoin treatment as 47.9% arthralgia, 53.2% myalgia, 70.2% low back pain, 11.7% sacroiliitis, and 4.3% tendinopathy [14]. In regard to other drugs causing tendinopathy, quinolones, statins, glucocorticoids, and aromatase inhibitors are reported to provoke tendinitis, especially in peripheral tendons [15].

In conclusion, among the rheumatologic adverse events caused by retinoids, hyperostosis, DISH-like symptoms, and sacroiliitis are common. However, enthesitis in the posterior and interspinous spinal soft tissues without ossification has not been reported as an adverse effect of retinoid usage. This case highlights that physicians should always consider spinal enthesitis in the posterior and interspinous ligaments as a potential adverse event of retinoids when a patient treated with retinoids presents with IBP and positive imaging findings. As a final observation, longitudinal follow-up will be necessary to determine whether this presentation is associated with posterior element ossification or with the development of a more classical radiographic DISH phenotype elsewhere in the spine.

Author Contributions

Sena Uslu: conducted the literature review, drafted the letter, and compiled the case presentation; **Kerem Abacar:** contributed to manuscript preparation and figure design; **Harun Gupta:** performed the patient MRI imaging; **Mike Green:** provided clinical patient information; **Benjamin Walker:** contributed dermatology expertise; **Tom Macleod:** provided immunological literature insights and formulated related hypotheses; **Dennis McGonagle:** supervised the project, conducted the final patient assessment, and provided overall oversight throughout manuscript preparation.

Consent

The authors affirm that the patient in this case report provided informed consent for the publication of the images in Figure 1. Written informed consent was obtained from the patient.

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.

Sena Uslu
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Mike Green
Benjamin Walker
Tom Macleod
Dennis McGonagle

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EDITORIAL

Mendelian Randomization in Autoimmune Disease Research

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Autoimmune diseases (ADs) constitute a diverse array of disorders marked by the disruption of immune tolerance and the aberrant activation of the immune system. Recent research has revealed a progressive annual increase in both the prevalence and incidence of ADs, impacting 5%–10% of the global population [1]. Drawing on Mendelian inheritance laws and instrumental variable estimation techniques, Mendelian Randomization (MR) harnesses genetic variations linked to particular exposures to investigate the causal impacts of modifiable exposures—such as potential risk factors—on health, society, and economy. MR has been widely used in the medical field for a multitude of applications. For example, it can not only confirm and reveal the causal relationships between clinically relevant risk factors, behavioral traits, and environmental elements with associated diseases, but also be employed to simulate drug targets and investigate genetic susceptibilities [2]. As current research struggles to pinpoint the causal risks of ADs, the emerging technique of MR aids in hypothesizing risk factors, pathogenesis, potential drug targets, and the potential causal relationships with other diseases, offering a fresh perspective on understanding these conditions.

Epidemiological research indicated that environmental influences are critical risk factors contributing to the breakdown of immune tolerance [3]. Wen et al. [4] conducted a MR study that identified a causal link between air pollutants and an increased risk of developing hypothyroidism, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ulcerative colitis (UC). Conversely, they found a decreased risk of coeliac disease associated with air pollution. Additionally, another MR study [5] supported the role of environmental pollution in AD, which revealed a causal association between PM2.5 and psoriasis in European populations. Research has established a correlation between Body Mass Index (BMI) and the risk of developing various ADs, with obesity increasing the risk of AD onset [6]. When exploring the relationship between diet and disease, existing observational studies on the association between folate and vitamin B12 with ADs present conflicting findings [6]. In a MR analysis conducted by Yang et al. [7] discovered that genetically elevated circulating folate levels are linked to a lower risk of vitiligo, suggesting that folate supplementation might serve as a preventative strategy against this condition. Moreover, Zhao et al. [8] reported similar findings, which showed that higher levels of 25-hydroxyvitamin are causally associated with a reduced risk of psoriasis and SLE. Additionally, attention must also be paid to the relationship between individual factors (such as mental health, education) and ADs. Emotional instability was considered a modifiable risk factor for hypothyroidism and SLE [9]. Furthermore, higher levels of education-related factors have a protective effect against ADs such as RA, UC, Crohn's disease (CD), and irritable bowel syndrome (IBS) [10]. In summary, MR can provide relatively convincing evidence for studying the potential causal relationships between relevant risk factors and ADs.

In recent years, the role of the gut microbiota in the pathogenesis of ADs has emerged as a focal point in medical research. While cross-sectional studies have indicated associations between dysbiosis of

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gut microbiota and the development of ADs, they have not yet established a causal link [11]. Xu et al. employed a two-sample MR analysis to investigate the potential causal relationships between the gut microbiome and six prevalent ADs, including SLE, RA, inflammatory bowel disease (IBD), multiple sclerosis (MS), type 1 diabetes (T1D), and coeliac disease. Their findings revealed a causal association between an increased relative abundance of the Bifidobacterium genus and the risk of developing T1D and celiac disease, offering novel perspectives on the mechanisms by which the gut microbiota may mediate the onset of ADs [11].

Moreover, MR is a valuable tool in drug treatment. Genetic variations in gene coding regions can influence target gene expression, acting like drug interventions on these targets [12]. MR integrates data on SNP gene expression and disease associations to establish causality between exposures and outcomes [13], which allows the use of genetic variations to identify new drug targets for diseases. For instance, researchers used MR analysis to integrate multi-omics data including DNA methylation, gene expression, and protein abundance, along with SMR and collocation analyses, to reveal potential targets such as TNFAIP3, BTN3A1, and PLAU for Sjögren's syndrome [14]. Cao et al. [13] identified seven potential drug targets for RA, suggesting that drugs targeting these genes may have a higher chance of success in clinical trials. Moreover, MR can provide evidence for emerging treatment strategies. An increasing amount of evidence highlights the interplay between lipid metabolism and immune regulation, yet the causal relationship between lipids and AD, as well as their potential as drug targets for AD, still lacks substantial evidence. Hu et al. [12] conducted a study on the association between lipid traits (such as cholesterol and triglycerides) and AD, and assessed the possibility of lipid-lowering drug targets for AD treatment. The results showed no evidence of a causal effect of these lipid traits and lipid-lowering drug targets on AD. However, a causal relationship was found between HMGCR-mediated LDL-C reduction and decreased HMGCR expression with a lower risk of RA, indicating that HMGCR could be a promising therapeutic target for RA. Xie et al. [15] also found through MR that lipid-lowering drug PCSK9 inhibition significantly reduced the risk of SLE but increased the risk of asthma and CD. This discovery offered a new perspective on the role of PCSK9 inhibitors in different diseases.

MR has emerged as a valuable causal inference tool, revealing potential causal links between ADs and a range of other health conditions, including respiratory system diseases [16, 17] (bronchiectasis, sinusitis), central nervous system diseases [18] (Alzheimer's disease), urinary system diseases [19] (prostate cancer), gynecological diseases [20, 21] (premature ovarian insufficiency, endometriosis), pain-related conditions [22, 23] (chronic pain in multiple sites, migraine), skin diseases [24] (psoriasis), eye diseases [25] (age-related macular degeneration), kidney tumors [26] and so on. These findings were crucial for clinical practice, highlighting the need for vigilant screening and management of potential risk factors and complications associated with ADs. For instance, SLE patients might require regular ovarian function assessments, while those with POI should be screened for CD [20].

MR is becoming increasingly popular in biomedical research to identify risk factors for various diseases. Unlike correlation analyses like differential expression analysis or weighted gene co-expression network analysis that only show associations, MR provides deeper insights into the causal relationship between gene expression and disease. Currently popular methods like machine learning and deep learning focus on the process of fitting predictive models to data or identifying informative groupings within data, with the interest being in the description and prediction of the data [27, 28]. Many articles pursue the combination of the two, screening feature genes with high predictive performance through machine learning algorithms, obtaining causal genes through MR, and finally confirming key biomarkers [29, 30], contributing to the value of prediction. As methodological and bioinformatics innovations progress, coupled with the development of computational tools and the availability of extensive Genome-Wide Association Studies (GWAS) datasets, the automation of MR analysis has become feasible, which has greatly facilitated the conduct of MR studies.

Although ADs are considered relatively rare, their incidence and mortality rates cannot be ignored. Our comprehension of ADs remains incomplete. With its strengths in elucidating causality, MR has risen as an innovative and indispensable tool for advancing our understanding of ADs. Relying on fixed genetic variations to minimize ascertainment bias and unmeasured confounders, MR has been employed to identify potential factors in disease progression, conduct drug trials, forecast the causal impacts of interventions on long-term clinical outcomes, and elucidate molecular mechanisms [2, 31]. Nevertheless, MR faces certain limitations, such as insufficient sample sizes in GWAS, the lack of diversity in study populations, and the potential for horizontal pleiotropy. Thus, there is a continued need to improve MR studies to ensure their robustness and reproducibility [2, 31]. It is anticipated that MR will further facilitate the translation of observational findings into clinical practice in future research, contributing to the prevention, diagnosis, and treatment of ADs.

Author Contributions

Chen Li and Yuanhao Wu conceived and designed the study. Yunuo Wang and Hanjing Huang wrote the paper. Mengjiao Gu participated in the literature search. All authors approved the final manuscript. Yunuo Wang and Hanjing Huang contributed equally to this work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Circulating Galectins and Risk of Dermatopolymyositis: A Mendelian Randomization Study

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Dear Editor,

Dermatopolymyositis (DPM) is a group of idiopathic inflammatory myopathies (IIMs), including dermatomyositis (DM), polymyositis (PM), juvenile dermatomyositis (JDM), and other DM [1]. The etiology of DPM is complex, mainly caused by abnormal autoimmune function, characterized by diffuse skeletal muscle inflammation and fibrosis involving proximal limbs, cervical, and pharyngeal muscles, and may be accompanied by multiple organ damage [2]. Although the incidence is low, DPM patients face significantly increased risks of interstitial lung disease, cardiovascular events, and mortality [3–5].

The galectin (Gal) family includes 15 endogenous lectins that have a high affinity for polysaccharides containing β-galactoside residues [6]. Galectins are widely expressed in epithelial and immune cells and regulate cell growth, differentiation, adhesion, signaling, and apoptosis [7]. Gal-1, -3, -7, -9, and -12 are involved in the disease process of skin tumors, wound healing, psoriasis, scleroderma, systemic lupus erythematosus, atopic dermatitis, vitiligo, and other skin diseases, and are expected to serve as biomarkers for disease development and prognosis [8, 9]. Previous studies have identified elevated Gal-3 levels correlated with severity in IIMs, suggesting involvement in inflammatory and fibrotic processes [10]. Similarly, Gal-1 and Gal-9 levels are associated with disease severity and predict treatment responses in juvenile DM [11]. Nonetheless, there are few studies on the association between the Gal family and DPM.

Mendelian randomization (MR) is an epidemiological approach that uses genetic variants as instrumental variables (IVs) to assess causal relationships between exposures and outcomes, mimicking randomized controlled trials and minimizing confounding biases [12]. We conducted a bidirectional two-sample MR analysis to evaluate causal relationships between circulating galectins and DPM, aiming to elucidate the mechanisms of the occurrence and development of DPM based on gene aspect analysis, and to provide new evidence-based support for strengthening the prevention and treatment measures of DPM.

MR studies rely on three assumptions: relevance (strong association between IVs and exposure), independence (IVs unrelated to confounders that affect the outcome), and exclusion restriction (IVs influence outcomes exclusively through exposures) [13]. Figure 1 shows a diagram of the present MR study.

Exposure data for SNPs related to Gal-1, Gal-2, Gal-4, Gal-7, Gal-8, Gal-9, and Gal-10 were extracted from the GWAS data of 3301 European individuals, and for Gal-3 were from the GWAS data of 30,931 European individuals [14]. Outcome data for DPM, dermatopolymyositis (FG), polymyositis, and other DM were

Ke Xue and Ruilian Lin these authors contributed equally to this work.

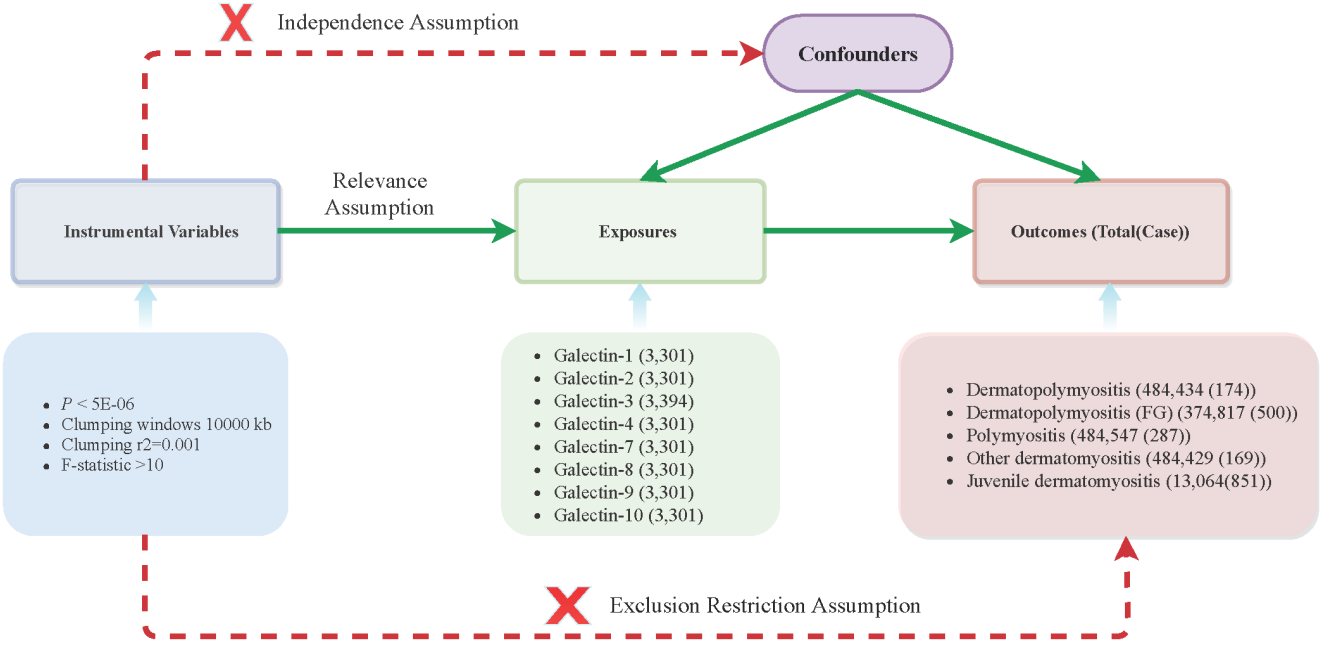

FIGURE 1 | The directed acyclic graph between exposures and outcomes.

extracted from the FinnGen consortium (https://www.finngen.fi/fi), with 225,419, 38,598, 38,903, and 38,871 Europeans, respectively; while data for JDM were obtained from the GWAS Catalog (https://www.ebi.ac.uk/), with 17,663 participants of European ancestry (Table S1). Ethical approvals were obtained by the original studies.

The screening flowchart of IVs is illustrated in (Figure S1), using a threshold of $p < 5 \times 10^{-6}$, linkage disequilibrium (LD) criteria ($r^2 = 0.001$, and clumping distance = 10,000 kb), and removing palindromic SNPs to ensure allele consistency. MR-Egger regression, MR pleiotropy residual sum and outlier (MR-PRESSO) test, and Cochran's Q assessed the potential horizontal pleiotropy effect and heterogeneity. The F-statistics > 10 reflects a small likelihood of weak bias between IVs [15].

The MR analysis was estimated by the inverse variance weighting (IVW) with odds ratios (ORs) and 95% confidence intervals (CIs), which is the primary method for unbiased assessment of causal association in the absence of horizontal pleiotropy between IVs (random effects model in heterogeneity scenarios, fixed effects otherwise). Two-sided p-value < 0.05 was significant. Sensitivity analyses included potential horizontal pleiotropy between IVs, which was assessed with the intercept of MR-Egger regression ($p > 0.05$ shows no horizontal pleiotropy). Cochran's Q test was utilized to assess the heterogeneity of included IVs, and $p < 0.05$ was considered to be heterogeneous. Outlier SNPs were tested by MR-PRESSO global test. Reverse MR analysis was conducted to validate the causal relationships between the exposures and outcomes. Additionally, multiple sensitivity analyses based on leave-one-out and MR steiger were conducted to assess whether the causal relationships between circulating Gal and DM remain robust. Analyses utilized R version 4.3.3 (2023-03-15 ucrt) with the R package "TwoSampleMR".

Seven to twenty SNPs for Gal families were screened out (Table S2), R^2 of each IVs ranged from 7.45% to 13.92%. Horizontal pleiotropy between other DM and Gal-4 and Gal-7, while the direction between exposures and outcomes is true based on MR Steiger test. No horizontal pleiotropy was detected between DPM, DPM (FG), and PM and IVs for each exposure factor (all $p > 0.05$). There was heterogeneity between IVs that are associated with Gal-7 and DPM (Cochran's $Q = 25.072$, $p = 0.009$; IVW $Q = 25.168$, $p = 0.014$). No heterogeneity was found among DPM (FG), PM, other DM, and IVs of individual exposure factors (all $p > 0.05$) (Table S3).

Forward MR analyses (Table S4) revealed a causal relationship between genetically predicted Gal-3 (OR = 1.442, 95% CI: 1.091–1.905) and Gal-1 (OR = 1.782, 95% CI: 1.042–3.048) with PM and other DM, respectively. No significant causal relationships were found between DPM and DPM (FG) with exposures (all $p > 0.05$). The forest plot of exposures and outcomes suggests the consistent causal relationships (Figure 2).

Reverse MR analyses showed no evidence of bidirectional causality (Table S5). There was no evidence to suggest the bidirectional causal relationship between the Gal family and DPM (FG), other DM as well as PM.

Several sensitivity analyses were further conducted to verify the causal relationship between Gal-3 and Gal-1 with PM and other DM, respectively. The scatter plot showed that the weighted median and weighted mode were consistent with the IVW test direction (Figure S2). The results of leave-one-out analysis showed that no single SNP has an effect on the overall causal estimate (Figure S3). The above sensitivity analyses indicated that the causal relationships between Gal-3 and PM and between Gal-1 and other DM were robust.

The Gal family is hailed as an ancient family of carbohydrate-binding proteins with modern functions, and its members are present in almost every lineage of multicellular life [16]. Based on their molecular structure, the Gal family can be roughly divided into three categories: (1) prototype Gal (including Gal-1,

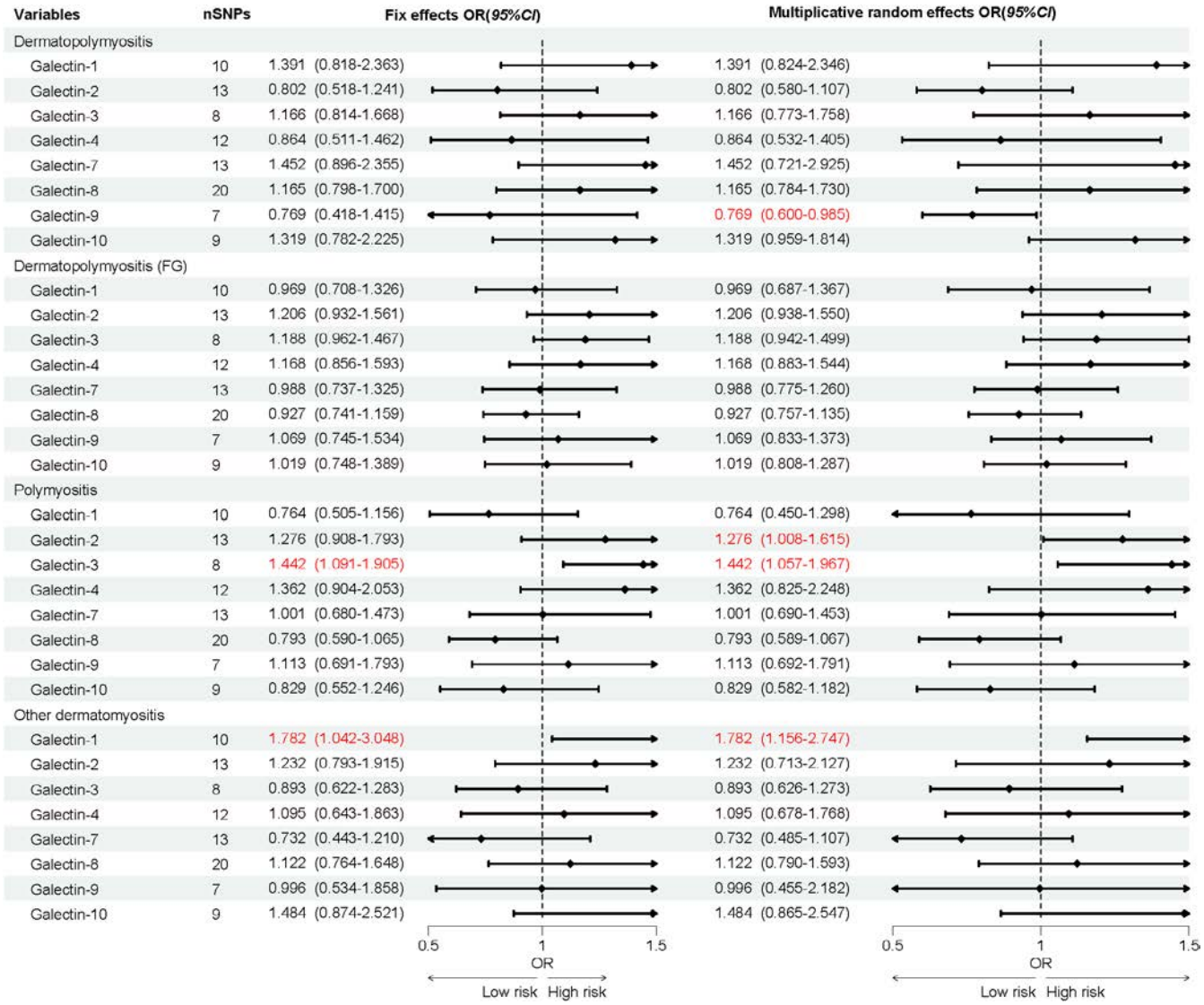

FIGURE 2 | The forest plot of causal association between exposures and outcomes.

-2, -7, and -10); (2) chimeric Gal formed by the fusion of a single sugar recognition domain and a collagen repeat domain (including Gal-3); (3) tandem repeat Gal (Gal-4, -8, and -9) formed by the fusion of two tandem single sugar recognition domains. Gal binds to sugar complexes on the cell surface, causing intracellular signal transduction, thereby participating in the interaction between cells themselves or between cells and between cells and matrix, and ultimately plays a role in regulating cell growth, cell–cell adhesion, autoimmune response, inflammation, apoptosis, and other physiological activities [17]. Several previous epidemiological observations have suggested that the Gal family may be associated with the risk of autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis [12–15]. However, due to the nature of traditional observational studies being susceptible to confounding factors, it is difficult to clarify the causal relationship between circulating Gal family and DPM based on observational studies alone.

The results of suggest that Gal-3 and Gal-1 were associated with increased risk of PM and other DM, respectively. Our study partially validates the findings of observational studies. A prior study suggested that Gal-3 is highly expressed in epithelial cells including keratinocytes and is involved in the pathogenesis of inflammatory skin diseases by affecting the function of immune cells [18]. By regulating dendritic cell (DC) and T cell function, Gal-3 promotes the polarization of Th2 immune response, thereby promoting the occurrence of atopic dermatitis. Additionally, Gal-3 may participate in the occurrence of contact hypersensitivity by regulating the migration ability of antigen-presenting cells [19] PM is an autoimmune disease characterized by massive T cell infiltration into muscle tissue. Histopathological evidence suggested that $CD8^+$ T cells are cytotoxic to the muscle fibers of PM patients [20]. Moreover, inflammatory response is also an important mechanism of Gal-3 related to the occurrence and development of PM [10].

Several strengths of our study need to be highlighted. First, MR reduces the confounding caused by environmental factors and avoids the bias caused by reverse causality. Secondly, the genetic data in the GWAS data of MRC-IEU and FinnGen database have a large sample advantage and can improve the statistical power of causal relationships. Our findings provide new evidence that

elevated levels of circulating Gal-3 and Gal-1 increase the risk of PM and other DM, supporting further exploration into their mechanisms. Clinically, these findings suggest monitoring Gal levels may aid in predicting and managing DPM.

However, several limitations should be noted. Firstly, some heterogeneity was observed in the analysis. Potential nonlinear relationships or stratification effects that vary by age, gender, or health status could not be explored using GWAS data. Secondly, causal relationships between galectin levels and JDM could not be explored due to insufficient SNPs being screened out. Thirdly, the GWAS data utilized were limited to people of European ancestry, which may limit the generalizability of our findings to other populations. Lastly, GWAS can provide new insights into the genetic relationship between circulating Gal levels and PDM, but future mechanistic studies are needed to confirm these relationships.

In conclusion, we found elevated circulating Gal-3 level increased the risk of PM, and Gal-1 level increased the risk of other DM. These findings provide supportive evidence for the diagnosis and prevention of DPM, but future animal experiments and clinical trials are needed to prove these conclusions.

Author Contributions

K.X., R.L., J.C. designed the study, K.X., R.L., J.C. wrote the manuscript, K.X., R.L., L.M., L.Q., J.Q., and J.C. collected, analyzed, and interpreted the data, J.C. critically reviewed the manuscript, and all authors read and approved the manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** The flowchart of IV selection. **Figure S2:** The scatter plot: (a) Gal-3 with PM; (b) Gal-1 with other DM. **Figure S3:** Leave-one-out sensitivity analysis: (a) Gal-3 with PM; (b) Gal-1 and PM. **Table S1:** The detailed information of exposures traits and outcomes in the present study. **Table S2:** The screening procedure of SNPs in forward MR analysis. **Table S3:** The pleiotropic and heterogeneity test of exposures instrument variables in forward MR analysis. **Table S4:** The forward MR analysis of circulating galectin and dermatopolymyositis. **Table S5:** The reverse MR analysis of circulating galectin and dermatopolymyositis.

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ORIGINAL ARTICLE

Long-Term Prognostic and Hemodynamic Outcomes of Intensive Immunosuppressive Therapy in Patients With Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

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ABSTRACT

Background: Intensive immunosuppressive therapy (IIT) is recommended for PAH associated with connective tissue disease (CTD-PAH). However, the long-term effects of IIT on pulmonary hemodynamics in this population remain unexplored. Additionally, its effectiveness in patients with systemic sclerosis (SSc)-associated PAH (SSc-PAH) is poorly understood.

Methods and Results: This retrospective analysis included 69 consecutive patients with CTD-PAH treated at our institution (men/women: 9/60, mean age 55.3 ± 14.0 years). Patients were divided into two groups, wherein 41 patients received IIT (IIT group) and 28 did not (non-IIT group). Both groups received conventional vasodilator therapy. The prognosis and pulmonary hemodynamics were evaluated in all patients. The IIT group exhibited significantly lower rates of PAH-related mortality ($p < 0.001$) compared with the non-IIT group. The mean PAP (mPAP) improved significantly in the IIT group during the follow-up (baseline: 38.7 ± 12.2 mmHg; 1 year: 27.0 ± 8.2 mmHg; 5 years: 26.8 ± 7.3 mmHg, $p < 0.05$), while it remained unchanged in the non-IIT group. None of the patients with CTD-PAH required IIT retreatment. Among the 27 patients with SSc-PAH, the IIT group ($n = 9$) showed a significantly greater improvement in mPAP compared with the non-IIT group ($n = 18$) (ΔmPAP at 1 year: −13.4 ± 6.5 mmHg in IIT group vs. −3.0 ± 6.2 mmHg in non-IIT group, $p < 0.001$).

Conclusions: This study's findings suggest that IIT may lead to sustained improvements in pulmonary hemodynamics and better long-term outcomes in patients with CTD-PAH, including potential benefits in those with SSc-PAH.

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; CTD, connective tissue disease; ERA, endothelin receptor antagonist; IIT, intensive immunosuppressive therapy; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase inhibitor; PGI2, prostacyclin; PVR, pulmonary vascular resistance; RAP, right arterial pressure; sGC, soluble guanylate cyclase; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SvO_2, mixed venous oxygen saturation.

Summary

- PAH-related death was significantly lower in patients with CTD-PAH who received IIT (IIT group) than in those who did not receive IIT (non-IIT group).
- Pulmonary hemodynamics of CTD-PAH including SSc-PAH were significantly improved in the IIT group but remained unchanged in the non-IIT group over a median follow-up period of 5.3 years.
- IIT might have potential effectiveness in patients with SSc-PAH whose pulmonary hemodynamics was improved with acute vasoreactivity test.

1 | Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening condition caused by obstruction of the small pulmonary arteries due to vascular remodeling [1–3]. It is defined as a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest and pulmonary vascular resistance (PVR) exceeding 160 dyne s/cm^5 [4]. Among the various subtypes of pulmonary hypertension (PH), PAH associated with connective tissue disease (CTD-PAH) has a poor prognosis, partly owing to its recalcitrance to conventional vasodilator therapy [5]. Immunological and inflammatory mechanisms are implicated in the progression of PAH in patients with CTD [6]. Therefore, the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend the addition of immunosuppressive therapy to pulmonary vasodilator therapy for the treatment of CTD-PAH [4].

Intensive immunosuppressive therapy (IIT), which typically includes glucocorticoids and cyclophosphamide, has been shown to improve symptoms, pulmonary hemodynamics, and prognosis in patients with PAH associated with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and Sjögren syndrome (SjS) [7–9]. However, these studies were limited by short follow-up periods and the investigation of only the prognosis, rather than the long-term pulmonary hemodynamics, leaving the long-term effects of IIT on pulmonary hemodynamics unclear. Furthermore, since previous studies indicated that IIT may not be effective in patients with PAH associated with systemic sclerosis (SSc) [4, 9], the ESC guidelines advised against IIT for patients with SSc-PAH [4]. However, these studies were small, engendering uncertainty about the effectiveness of IIT for all patients with SSc-PAH.

Therefore, the present study aimed to assess the long-term effectiveness of IIT on pulmonary hemodynamics and prognosis in patients with CTD-PAH and to examine its effect in patients with SSc-PAH.

2 | Material and Methods

This study was approved by the Institutional Review Board of Tohoku University, Sendai, Japan, and the Medical Ethics Review Committee (approval no. 2021-1-208), which waived the requirement for informed consent owing to its retrospective design. The opt-out method was used to obtain patient consent for participation in this study.

2.1 | Cohort of PH Patients

The cohort comprised 69 consecutive patients with CTD-PAH who underwent right heart catheterization (RHC) at Tohoku University Hospital between 2005 and 2022 (Figure 1) [8, 10]. These patients were regularly followed up every 6–12 months with RHC [8, 10].

2.2 | Diagnosis of PH Subtypes

All 69 patients underwent RHC, with PH defined as an mPAP ≥ 25 mmHg at rest [11]. The diagnosis of PAH was contingent upon an additional criterion of pulmonary arterial wedge pressure ≤ 15 mmHg [11]. Acute pulmonary vasoreactivity testing was performed during right heart catheterization (RHC), where nitric oxide (NO) was inhaled for 5 min to assess changes in pulmonary hemodynamics [12]. A positive response to the acute pulmonary vasoreactivity test was defined as a reduction in mean pulmonary artery pressure (mPAP) ≥ 10 mmHg and mPAP ≤ 40 mmHg, with either an increased or unchanged cardiac output [4]. CTD-PAH and liver disease-associated PAH were diagnosed clinically and through blood tests, according to established criteria [4]. We defined SLE, MCTD, SjS, and SSc based on each of the classification criteria [13–16]. Overlap syndrome was defined as meeting classification criteria for two connective tissue diseases. Patients with overlap syndrome involving systemic sclerosis (SSc) were classified as having SSc-PAH. All

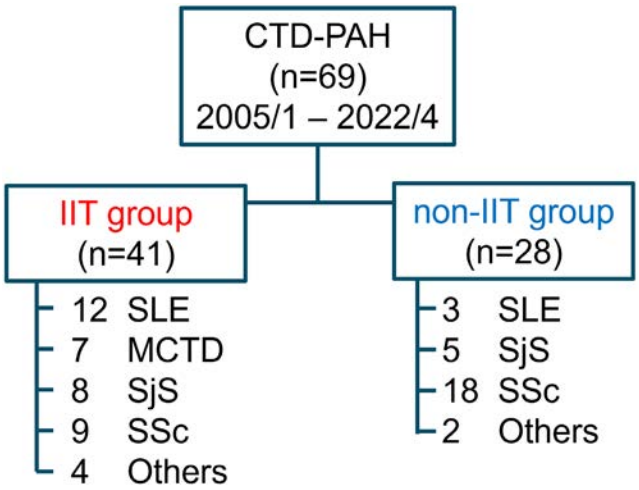


FIGURE 1 | Enrollment algorithm. In our pulmonary hypertension cohort, 69 patients were diagnosed with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) between 2005 and 2022. Among them, 41 consecutive patients received intensive immunosuppressive therapy (IIT) in conjunction with conventional vasodilator therapy (IIT group), whereas 28 patients received only conventional vasodilator therapy (non-IIT group). CTD, connective tissue disease; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

connective tissue diseases were diagnosed by rheumatologists using established criteria [13–16]. Congenital heart disease-associated PH was identified via echocardiography, whereas chronic thromboembolic PH was diagnosed using ventilation-perfusion scans and computed tomography (CT). Lung disease and hypoxia were diagnosed using pulmonary function testing, arterial blood gas analysis, chest radiography, and CT. Patients without these abnormalities were diagnosed with idiopathic PAH [4].

2.3 | Data Collection

Baseline characteristics, such as age, sex, height, weight, use of pulmonary vasodilators, clinical diagnosis, comorbidities (CTDs, interstitial lung disease), plasma B-type natriuretic peptide levels, and pulmonary hemodynamic data from catheterization before and after acute pulmonary vasoreactivity testing [12] were extracted from the medical records. The pulmonary hemodynamic parameters included pulmonary arterial wedge pressure, pulmonary artery pressure (PAP), right atrial pressure, cardiac output, cardiac index (CI), PVR, and mixed venous oxygen saturation. All-cause mortality and PH-related mortality (defined as lung transplantation or death due to worsening of right heart failure) were investigated in each patient. Safety outcomes during the follow-up period were also investigated. Infection was defined as the number of patients requiring hospitalization for treatment. Severe infection was defined as the number of patients whose infection resulted in death. Malignancy was defined as newly diagnosed malignant tumors during the follow-up period.

2.4 | IIT for CTD-PAH

The IIT regimen consisted of cyclophosphamide (500 mg intravenous, 10 times over 1 year, administered monthly for the first 3 months, and once every 1–3 months thereafter) combined with glucocorticoids (1 mg/kg/day per oral for the first month, with gradual tapering to 5–10 mg/day every 2–4 weeks until a maintenance dose of 5–10 mg/day was reached) [8, 10]. RHC was performed at baseline and every 6–12 months during the follow-up [8, 10].

2.5 | Statistical Analysis

The data were presented as the mean ± SD for normally distributed continuous variables, and as medians with interquartile ranges (25th–75th percentiles) for continuous variables with non-normal distribution and categorical variables. Paired *t*-tests were used to compare continuous variables, and Fisher's exact test was used for categorical variables. Survival outcomes, including all-cause mortality, cardiovascular mortality, and lung transplantation, were estimated using the Kaplan–Meier method; the differences between the survival curves were assessed using the log-rank test. The association between groups and time-to-event outcomes was assessed using Cox regression analysis adjusted for age and sex. Similar analyses were conducted for PH-related death in each group. All statistical analyses were conducted using GraphPad Prism 9.0E (GraphPad Software Inc., La Jolla, CA, USA). p values < 0.05 were considered statistically significant.

3 | Results

3.1 | Study Population and Baseline Characteristics

This study enrolled 69 consecutive patients with CTD-PAH who underwent RHC between 2005 and 2022. Forty-one patients received IIT in conjunction with conventional vasodilator therapy (IIT group), while 28 patients received conventional vasodilator therapy alone (non-IIT group) (Figure 1). Among the non-IIT group, 11 of 28 patients received maintenance doses of glucocorticoids or immunosuppressive agents as follows: prednisolone 1–5 mg/day ($n = 5$), prednisolone 6–10 mg/day ($n = 4$), mycophenolate mofetil 500 mg/day ($n = 1$), and tacrolimus hydrate 1 mg/day ($n = 1$). The median follow-up period was 4.3 years. There were no differences in the study enrollment period between the groups. Although four patients in each group were lost in the follow-up periods (Table S1), there were no differences in disease severity between these patients. The baseline clinical characteristics of the IIT and non-IIT groups are presented in Table 1. Patients in the IIT group were younger than those in the non-IIT group (49.1 ± 12.8 years vs. 64.3 ± 49.1 years, $p < 0.001$). In the IIT group, the proportion of patients with SLE and those with MCTD was higher and that of patients with SSc was lower compared to the non-IIT group. Renal function was lower in the non-IIT group, although no significant differences were evident in the baseline hemodynamic parameters between the groups (mPAP: 38.6 ± 12.0 mmHg [IIT] vs. 35.4 ± 8.1 mmHg [non-IIT], $p = 0.313$; PVR: 678.7 ± 484.2 vs. 516.4 ± 256.3 dyne s/cm^2, $p = 0.389$; Table 1).

3.2 | Long-Term Prognosis of CTD-PAH

All CTD-PAH patients in the IIT group received IVCY 10 times, with a cumulative cyclophosphamide dose of 5000 mg. During the follow-up period, 14 CTD-PAH patients died (7 in each group). In the IIT group, the causes of death were interstitial pneumonia in five patients, bacterial pneumonia in one patient, and PH-related death in one patient. In the non-IIT group, the causes of death were PH-related in six patients and trauma in one patient.

Patients in the IIT group demonstrated significantly better long-term survival than those in the non-IIT group (Figure 2A,B). Although the difference in all-cause mortality did not attain statistical significance ($p = 0.098$), PH-related mortality was significantly lower in the IIT group ($p < 0.001$). The 1-, 3-, 5-, and 10-year survival rates in the IIT group were 95.0%, 91.9%, 88.3%, and 76.7%, respectively, compared with 96.0%, 91.0%, 63.2%, and 54.3%, respectively, in the non-IIT group. An adjusted Cox regression analysis for age and sex showed that the IIT group tended to have a lower risk of PH-related death compared with the non-IIT group (hazard ratio [HR] 0.09; 95% CI 0.01–1.36; $p = 0.082$). After further adjustment for age, sex, the presence

TABLE 1 | Baseline characteristics of patients with pulmonary arterial hypertension associated with connective tissue disease treated with and without intensive immunosuppressive therapy.

	IIT ($n=41$)	Non-IIT ($n=28$)	p
Age (years)	49.1 ± 12.8	64.3 ± 10.4	< 0.001
Female (%)	38 (92.7)	22 (78.6)	0.087
Follow-up period (month)	64.0 (30.0–119.5)	46.0 (31.3–66.0)	0.092
Underlying CTDs (%)			
SLE	12 (29.3)	3 (10.7)	0.067
MCTD	7 (17.1)	0 (0.0)	0.021
SjS	8 (19.5)	5 (17.9)	0.863
SSc	9 (30.0)	18 (64.3)	< 0.001
Others	4 (9.8)	2 (7.1)	0.705
Time from diagnosis of CTD to diagnosis of PAH	84.0 (0.0–132.0)	23.0 (0.0–114.0)	0.403
Simultaneous diagnosis of PAH and CTD	15 (36.6)	8 (30.8)	0.625
Baseline measurement			
Hb (g/dL)	12.7 ± 2.0	12.3 ± 1.9	0.456
Creatinine (mg/dL)	0.6 ± 0.3	1.1 ± 1.4	0.030
CRP (mg/dL)	0.0 (0.0–0.2)	0.0 (0.0–0.2)	0.597
BNP (pg/mL)	65.2 (12.5–280.0)	79.9 (29.2–207.0)	0.325
NYHA			
I	6 (14.6)	1 (3.6)	0.135
II	21 (51.2)	18 (65.3)	0.282
III	11 (26.8)	7 (25.0)	0.865
IV	3 (7.3)	2 (7.1)	0.978
Pulmonary hemodynamic			
mPAP (mmHg)	38.6 ± 12.0	35.4 ± 8.1	0.313
PVR (dyne s/cm^2)	678.7 ± 484.2	516.4 ± 256.3	0.389
CI (L/min/m^2)	2.5 ± 0.6	2.5 ± 0.4	0.886
PAWP (mmHg)	8.1 ± 3.3	8.3 ± 6.9	0.467
RAP (mmHg)	6.0 ± 3.8	4.7 ± 3.7	0.167
SvO_2 (%)	66.5 ± 9.4	65.8 ± 8.8	0.362

Note: Continuous variables are expressed as the mean ± SD, except for the follow-up period. The eGFR and BNP levels are expressed as medians with interquartile ranges. The parameters were compared using the Mann–Whitney *U* test.

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; CTD, connective tissue disease; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right arterial pressure; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SvO_2, mixed venous oxygen saturation.

of systemic sclerosis, and NYHA functional class, IIT was associated with a significantly lower risk of PH-related death (HR 0.02; 95% CI 0.00–0.63; $p=0.027$). These findings indicate that IIT is associated with improved long-term prognosis in patients with CTD-PAH, as reported previously [7].

3.3 | Pulmonary Hemodynamics of CTD-PAH

Next, we examined the changes in pulmonary hemodynamics during the follow-up period (baseline, 1 year, and 5 years: $n=69$, 61, 30, respectively). In the non-IIT group, the mPAP initially improved at 1 year but increased again by year 5 (baseline, 1 year, and 5 years: 35.4 ± 8.1, 31.5 ± 9.5, 33.6 ± 12.0 mmHg, respectively). In contrast, the mPAP in the IIT group showed significant improvement throughout the follow-up period (baseline, 1 year, and 5 years: 38.6 ± 12.0, 30.0 ± 8.2, 26.8 ± 7.3 mmHg, respectively, $p<0.001$) (Figure 3A). Additionally, a significantly higher proportion of patients in the IIT group achieved an mPAP < 25 mmHg during the follow-up period than those in the non-IIT group (68.4% vs. 34.6%, $p=0.008$) (Figure 3B) [17], Furthermore, more patients in the IIT group avoided being administered the pulmonary vasodilators during the follow-up period compared with the non-IIT group (IIT group vs. the non-IIT group: 12/41 [29.3%] vs. 2/28 [7.1%], $p=0.025$). Notably, none of the patients in the IIT group required a second round of IIT due to worsening pulmonary hemodynamics during follow-up, and there were no interruptions of IIT due to any adverse events. Furthermore, during the follow-up period, the incidence of safety outcomes (infections, infection-related mortality, newly diagnosed malignancy, bleeding, bone marrow suppression) did not increase in the IIT group (Figure 3C). These results suggest that IIT not only improves pulmonary hemodynamics but also maintains them in the long term in patients with CTD-PAH.

3.4 | IIT for SSc-Associated PAH

While previous studies have reported that IIT is ineffective in patients with SSc-PAH [4, 9], they were marred by the small sample size. This study included 27 patients with SSc-PAH, of whom 9 received IIT and 18 did not receive IIT. The baseline characteristics of these patients are shown in Table 2, which showed blood collection data, interstitial lung disease comorbidity, pulmonary hemodynamics, disease duration, and disease subtype were comparable between the IIT-SSc-PAH and non-IIT-SSc-PAH groups. The proportion of patients with other CTDs was significantly higher in the IIT-SSc-PAH group than that in the non-IIT group. Additionally, although no SSc-PAH patients met the positive criteria for the acute vasoreactivity test, the IIT-SSc-PAH group showed a significantly greater reduction in mPAP and PVR during the acute pulmonary vasoreactivity test (Table 2). Notably, the improvement in mPAP was significantly more pronounced in the IIT-SSc-PAH group (Figure 4A,B). Furthermore, changes in the PVR and mPAP during the vasoreactive test at diagnosis were strongly correlated with mPAP improvement following IIT in the IIT-SSc-PAH group (PVR: $r=0.835$, $p=0.0386$; mPAP: r = 0.842, $p=0.0355$) (Figure 4C,D), but no such improvement was apparent in the non-IIT group (Figure S1A,B).

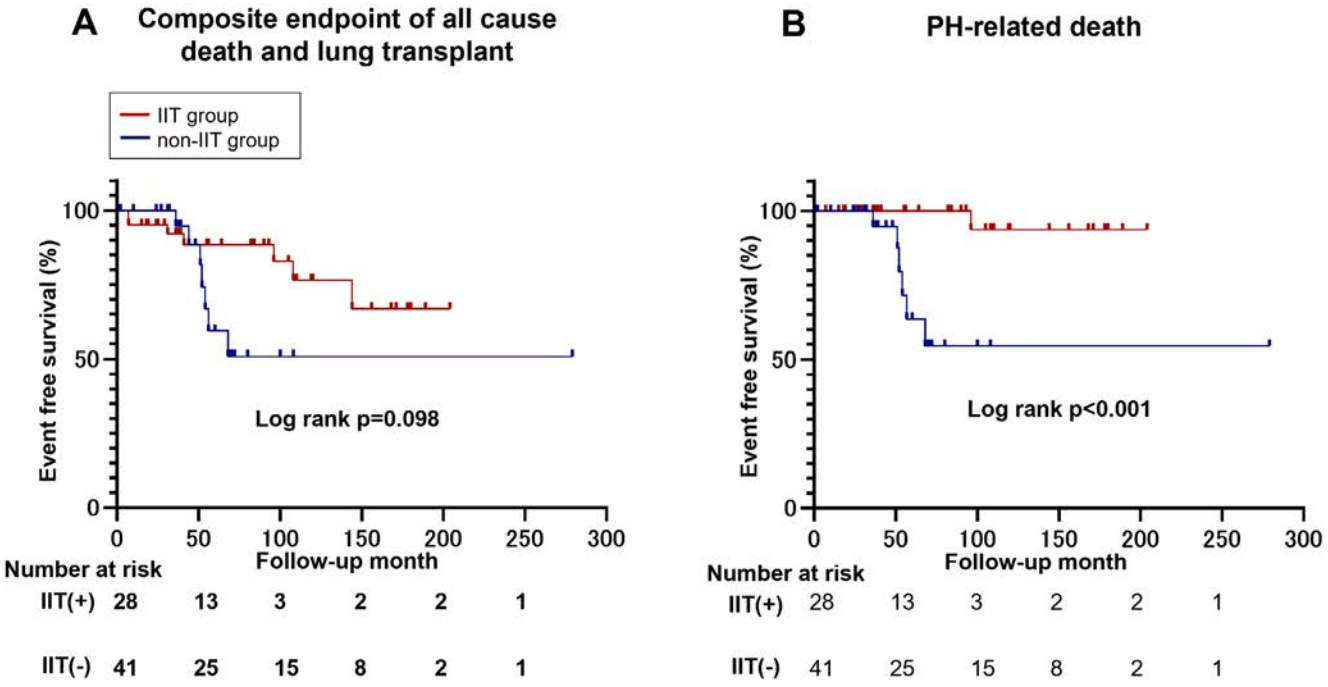
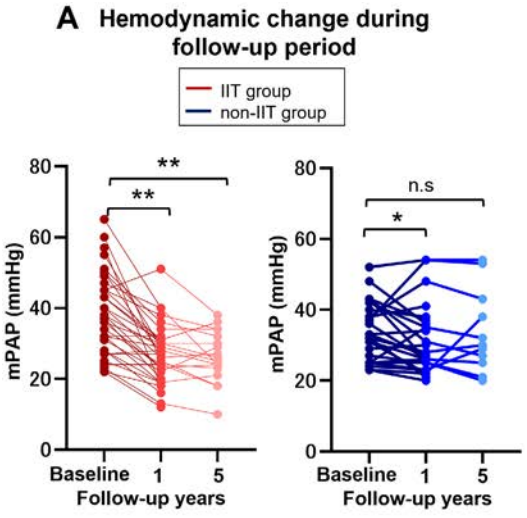
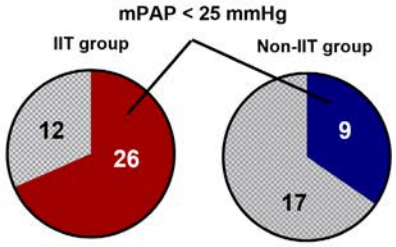


FIGURE 2 | Effects of IIT on long-term prognosis. (A) Kaplan–Meier curves for the composite endpoint of all-cause mortality and lung transplantation. (B) Kaplan–Meier curves for pulmonary hypertension (PH)–related mortality. The curves compare patients treated with intensive immunosuppressive therapy (IIT group: $n = 41$) and conventional vasodilator therapy with those who received only conventional vasodilator therapy (non-IIT group: $n = 28$) during the follow-up period.



B Number of patients who achieved mPAP < 25 mmHg after IIT

	IIT(+)	IIT(-)	P value
mPAP < 25 mmHg	n=26 (68.42%)	n=9 (34.62%)	0.0076



C Safety outcomes

	IIT(+)	IIT(-)	P value
Infection	n=7 (17.07%)	n=4(14.29%)	0.7561
Infection death	n=1 (2.44%)	n=0(0.00%)	0.4052
Malignancy	n=0 (0.00%)	n=1 (3.57%)	0.2229
Bleeding	n=1 (2.43%)	n=1 (3.57%)	0.7969
Bone marrow suppression	n=0 (0.00%)	n=0 (0.00%)	1.0000

FIGURE 3 | Effects of IIT on pulmonary hemodynamics. (A) Effect of intensive immunosuppressive therapy (IIT) on pulmonary hemodynamics in patients with CTD-PAH after 1 and 5 years. The red bars represent the IIT group, while blue bars represent the non-IIT group. (B) Number of patients who achieved a mean pulmonary artery pressure (mPAP) < 25 mmHg following intensive immunosuppressive therapy or conventional treatment during the follow-up period. (C) Safety outcome during the follow-up period. Infection was defined as the number of patients requiring hospitalization for treatment. Severe infection was defined as the number of patients whose infection resulted in death. Malignancy was defined as newly diagnosed malignant tumors. Bleeding was defined as BARC type 3 or higher. Bone marrow suppression was defined as the occurrence of grade 3 or higher hematologic adverse events in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 during the follow-up period. The results are presented as mean ± SEM. Statistical comparisons were performed using the paired *t*-test, two-tailed Student's *t*-test, or Welch's *t*-test, as appropriate. The significance levels are as follows: $^{*}p < 0.05$, $^{**}p < 0.01$. CTD-PAH, pulmonary arterial hypertension associated with connective tissue disease.

TABLE 2 | Baseline characteristics of patients with pulmonary arterial hypertension associated with systemic sclerosis treated with or without intensive immunosuppressive therapy.

	IIT ($n=9$)	Non-IIT ($n=18$)	p
Age (years)	59.7 ± 8.8	64.2 ± 10.7	0.172
Female (%)	8 (88.9)	13 (72.2)	0.326
Follow-up period (month)	36.0 (15.5–70.0)	51.0 (30.0–74.0)	0.395
Diffuse type of SSc	2 (22.2)	5 (27.8)	0.756
Limited type of SSc	7 (77.8)	13 (72.2)	0.756
Anti-centromere	4 (44.4)	6 (33.3)	0.573
Anti-Scl70	1 (11.1)	1 (5.6)	0.603
Time from diagnosis of CTD to diagnosis of PAH	24.0 (0.0–132.0)	90.0 (0.0–80.5)	0.526
Disease duration at end of follow-up	136.0 (81.0–300)	120.0 (75.5–204.0)	0.554
Simultaneous diagnosis of PAH and CTD	3 (33.3)	6 (35.3)	0.920
ILD	3 (33.3)	10 (55.6)	0.276
Underlying CTDs overlapped with SSc (%)			
Any CTDs overlapped with SSc	4 (44.4)	2 (11.1)	0.050
SLE	1 (11.1)	0 (0.0)	0.149
SjS	3 (33.3)	2 (11.1)	0.161
Medications after 1 year (n, %)			
PDE5i or sGC stimulator	4 (44.4)	16 (88.9)	0.013
ERA	3 (33.3)	10 (55.6)	0.276
Oral PGI_2 analogs	4 (44.4)	5 (27.8)	0.387
Treprostinil or epoprostenol	0 (0.0)	1 (5.6)	0.471
Mono therapy	3 (33.3)	7 (38.9)	0.778
Dual therapy	4 (44.4)	8 (44.4)	1.000
Triple therapy	0 (0.0)	3 (16.7)	0.050
Baseline measurement			
Hb (g/dL)	13.2 ± 1.4	12.4 ± 2.1	0.358
Creatinine (mg/dL)	0.6 ± 0.1	0.8 ± 0.4	0.298
CRP (mg/dL)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.967
BNP (pg/mL)	127.3 (7.3–441.6)	75.0 (26.3–454.5)	0.602
NYHA			
I	1 (11.1)	2 (11.1)	1.000
II	4 (44.4)	9 (50.0)	0.785
III	4 (44.4)	6 (33.3)	0.573
IV	0 (0.0)	2 (11.1)	0.298
Pulmonary hemodynamic			
mPAP (mmHg)	35.9 ± 14.5	33.8 ± 7.2	0.898
PVR (dyne s/cm^2)	689.5 ± 480.5	480.7 ± 246.1	0.520
CI (L/min/m^2)	2.3 ± 0.4	2.4 ± 0.3	0.571

(Continues)

TABLE 2 | (Continued)

	IIT ($n=9$)	Non-IIT ($n=18$)	p
PAWP (mmHg)	7.5 ± 2.9	8.8 ± 8.0	0.965
RAP (mmHg)	4.7 ± 2.2	4.9 ± 4.3	0.875
SvO_2 (%)	68.8 ± 6.7	65.7 ± 8.0	0.365
Hemodynamic change after the acute vasoreactive test			
ΔmPAP (mmHg)	−6.9 ± 6.3	−3.0 ± 3.8	0.029
ΔPVR (dyne s/cm^2)	−189.1 ± 166.0	−50.3 ± 86.4	0.034
ΔCI (L/min/m^2)	−0.06 ± 0.39	−0.08 ± 0.38	1.000

Note: Continuous variables are expressed as the mean ± SD, except for the follow-up period. The eGFR and BNP levels are expressed as medians with interquartile ranges. The parameters were compared using the Mann–Whitney *U* test.
Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; CTD, connective tissue disease; ERA, endothelin receptor antagonist; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase inhibitor; PGI2, prostacyclin; PVR, pulmonary vascular resistance; RAP, right arterial pressure; sGC, soluble guanylate cyclase; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SvO_2, mixed venous oxygen saturation.

4 | Discussion

The salient findings of this study were as follows: (1) the favorable effect of IIT on both prognosis and hemodynamics in CTD-PAH was sustained over prolonged periods without the need for additional IIT due to worsening of PH, and (2) IIT could be potentially effective in patients with SSc-PAH. These results indicate that IIT can be effective for patients with CTD-PAH in the long term.

4.1 | Long-Term Benefits of IIT: CTD-PAH

The first key finding of this study is that IIT not only improved pulmonary hemodynamics, but also sustained these improvements over an extended follow-up and yielded a positive effect on prognosis. While earlier studies have confirmed that IIT benefits patients with CTD-PAH, they primarily focused on short-term outcomes (improvement in hemodynamics or WHO functional class after 3 months to 1 year) [7, 8, 18, 19], without examining the persistence of pulmonary hemodynamic improvements. This fostered uncertainty regarding the durability of the effects of IIT. In this study, sustained improvements in both prognosis and pulmonary hemodynamics were confirmed over a prolonged median follow-up of 5.3 years. Importantly, no patient required repeat IIT owing to worsening of PH, indicating that once pulmonary hemodynamics improved, the effects were sustained. Previous studies have reported an infection incidence of approximately 10%–15% with IIT [20], which is consistent with our findings. This study further revealed that adverse events and adverse event-related mortality did not significantly increase during long-term follow-up after IIT. These findings suggest that IIT is both effective and safe over the long term for patients with CTD-PAH. However, in this study, the treatment of patients with CTD-PAH was individualized rather than randomized. Further randomized studies are needed to confirm these findings while minimizing individual bias.

4.2 | Effectiveness of IIT: SSc-Associated PAH

The second key finding was that IIT was effective in improving pulmonary hemodynamics in some patients with SSc-PAH. Previous reports have suggested that IIT was ineffective for SSc-PAH, leading to its exclusion from the ESC/ERS guidelines [4, 9]. However, these studies incorporated a limited sample size, and recent case reports indicate that IIT can improve pulmonary hemodynamics in patients with SSc-PAH [21, 22]. Additionally, a larger study showed that immunosuppressive therapy with rituximab, which targets B cells, enhances exercise capacity in these patients [23].

In this study, IIT improved pulmonary hemodynamics in patients with SSc-PAH more effectively than previously reported [9]. Two primary factors may explain this discrepancy. First, our cohort included a higher proportion of patients with overlapping CTDs other than SSc. Previous studies have shown that SSc-PAH patients with lupus tend to respond better to IIT [22, 24]. Second, the IIT-SSc-PAH group exhibited significantly greater reductions in mPAP and PVR during the acute pulmonary vasoreactivity test compared to the non-IIT-SSc-PAH group. Previous studies have reported a lower positive response rate in SSc-PAH than in idiopathic PAH, with decreased vasoreactivity being correlated with disease progression [25–28]. Importantly, the analysis demonstrated a positive correlation between reductions in PVR and mPAP during the acute vasoreactivity test, and subsequent improvements in mPAP following IIT. This suggests that patients with SSc-PAH with better hemodynamic responses may exhibit less severe vascular remodeling, making them more likely to benefit from IIT. Although previous studies did not report data on overlap with other CTDs or the results of the acute vasoreactivity test [9]. Our findings suggest that some SSc-PAH patients may retain pulmonary vasoreactivity. This potential selection bias might have contributed to the favorable outcomes observed in our study. These findings indicate that a subset of patients with SSc-PAH may respond favorably to IIT, although further research with larger cohorts is needed to confirm these outcomes owing to the small sample size.

4.3 | Limitations

The present study has several limitations. First, this was a retrospective cohort study conducted at a single center. Owing to these characteristics, the differences in the patient characteristics between the groups and the presence of

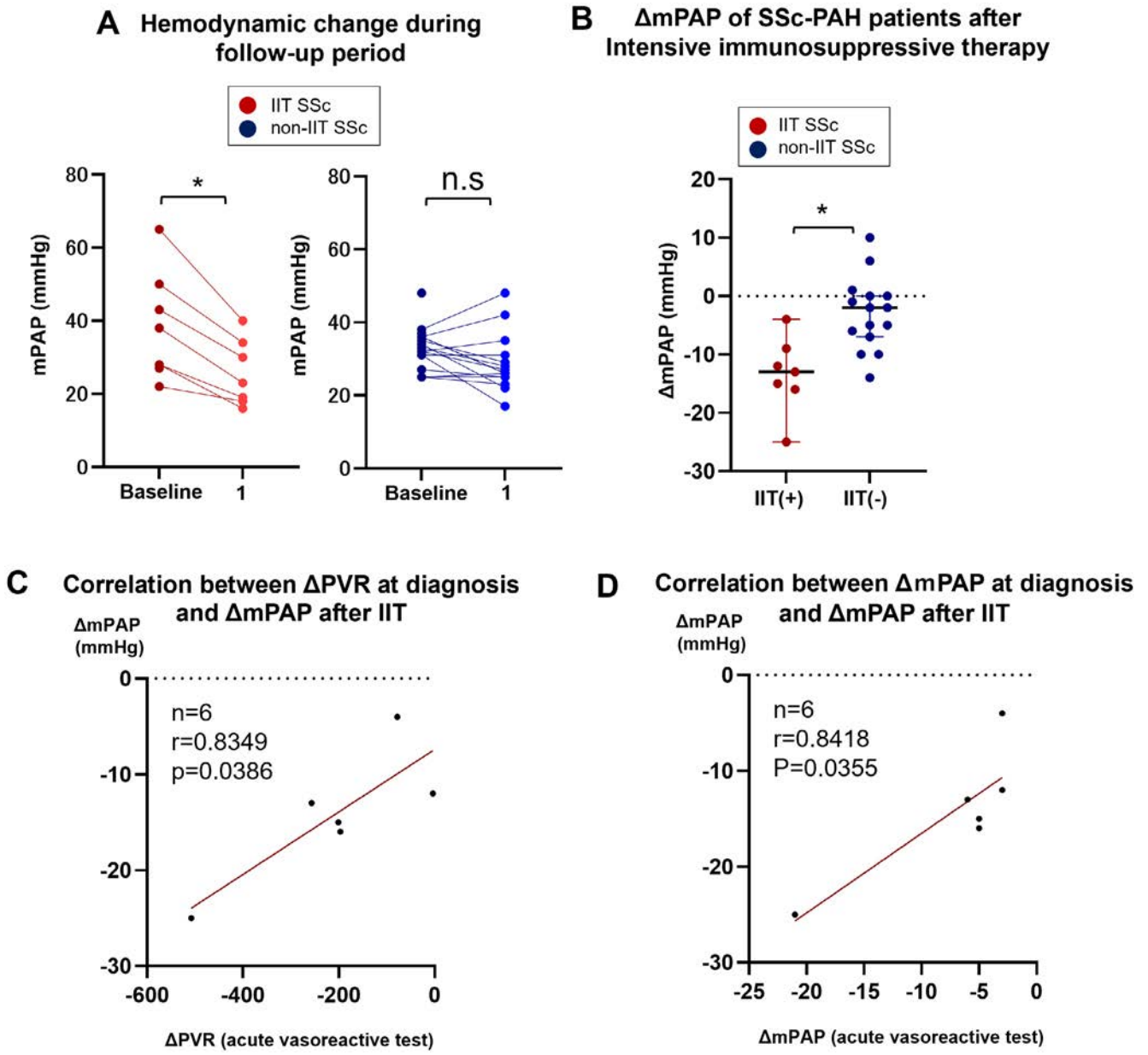


FIGURE 4 | Effects of IIT on pulmonary hemodynamics in patients with systemic sclerosis. (A) Effect of intensive immunosuppressive therapy (IIT) on pulmonary hemodynamics in patients with pulmonary arterial hypertension associated with systemic sclerosis. The red bars represent the IIT group, while the blue bars represent the non-IIT group. (B) Change in the mean pulmonary artery pressure (ΔmPAP) in patients with systemic sclerosis 1 year after intensive immunosuppressive therapy (IIT group) and no IIT (non-IIT group). (C) Correlation between the decrease in pulmonary vascular resistance (PVR) during the acute vasoreactive test at diagnosis and the improvement in the mPAP after IIT in the IIT-SSc-PAH group. (D) Correlation between the decrease in the mPAP during the acute vasoreactive test at diagnosis and the improvement in the mPAP after IIT in the IIT-SSc-PAH group. The results are presented as the mean ± SEM. Statistical comparisons were performed using paired *t*-tests, two-tailed Student's *t*-tests, or Welch's *t*-tests as appropriate. The significance levels are indicated as follows: $*p < 0.05$, $**p < 0.01$.

multiple confounding factors might have influenced the results. Therefore, the findings regarding the effectiveness of IIT need to be validated in a larger, multicenter study. Second, the treatment of patients with CTD-PAH was individualized rather than randomized, based on pulmonary hemodynamics and comorbidities. Third, the use of IIT was determined at the physicians' discretion, and the baseline characteristics of the two groups differed considerably. These differences may have introduced residual confounding, and thus the possibility of selection bias influencing the results cannot be excluded. Fourth, isolating the effect of IIT was challenging, as patients with CTD-PAH received pulmonary vasodilators in conjunction with IIT. Finally, although IIT appeared effective in reducing PH-related death, the small number of events may have resulted in an overestimation of the effect. Therefore, further studies with larger sample sizes are warranted to confirm these findings.

5 | Conclusions

These findings suggest that IIT may lead to sustained improvements in pulmonary hemodynamics and better long-term

outcomes in patients with CTD-PAH, including potential benefits in patients with SSc-PAH.

Author Contributions

K.Y., N.Y., and S.Y. contributed to the conceptualization of the study. T.S., S.Y., Y.Y., N.C., K.K., H.S., N.K., K.N., S.T., and T.I. supervised the study and performed data acquisition. S.M. performed statistical analysis. All authors read and approved the final manuscript. K.Y. takes responsibility for the content of the manuscript, including the data and analyses.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** apl70431-sup-0001-AppendixS1.docx.

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LETTER TO THE EDITOR

Mendelian Randomization Suggests a Bidirectional Causal Relationship Between Sjögren's Syndrome and Interstitial Lung Disease

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Dear Editor,

Sjögren's syndrome (SS) is an autoimmune disorder characterized by the infiltration of lymphocytes into the exocrine glands [1]. Salivary gland and lacrimal gland injuries are the main manifestations of SS, but SS can also present with systemic involvement. Interstitial lung disease (ILD) is the most common pulmonary involvement, occurring in 10%–27% of SS patients [2]. ILDs are a group of diffuse lung diseases that primarily affect the interstitial tissue and alveolar space of the lungs, leading to the loss of alveolar–capillary functional units. They are characterized mainly by dyspnea, cough, and reduced exercise tolerance and can eventually progress to respiratory failure and death [3]. Observational studies have suggested that late onset, older age, Raynaud's phenomenon, and esophageal involvement are predictive parameters of ILD in SS patients [4–6]. The combination of ILD seriously affects the quality of life of SS patients and greatly increases mortality [7]. Although existing studies have suggested an association between SS and ILD, drawing causal inferences from observational epidemiology can be challenging owing to potential reverse causation and confounders. Therefore, it is imperative to conduct further in-depth research into the causal relationship between SS and ILD.

Mendelian randomization (MR) is a valuable tool for investigating causal relationships between a risk factor and a health outcome through human genetics. MR uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to test for causal effects of exposure on specific outcomes, which can minimize confounding and reverse causation because genetic variants are randomly assigned during conception. The availability of pooled statistics from large, publicly available genome-wide association studies (GWASs) helped us find disease-associated genetic variants to provide statistical power and accuracy. With this in mind, we conducted a bidirectional two-sample Mendelian Randomization (MR) analysis to explore the causal relationship between SS and ILD. Figure 1 shows a prime description of the bidirectional MR design.

Four MR methods were used in this study, including inverse variance weighting, MR–Egger regression, the weighted median, and the weighted mode. The MR Steiger test also verified the correct direction of causality between exposure and outcome. All analyses were based on publicly available GWAS summary statistics. Summary statistics for both SS and ILD can be found in the FinnGen studies, R11 release (http://www.finng

Y. Zhang and Q. Wang are the co-first authors of this paper.

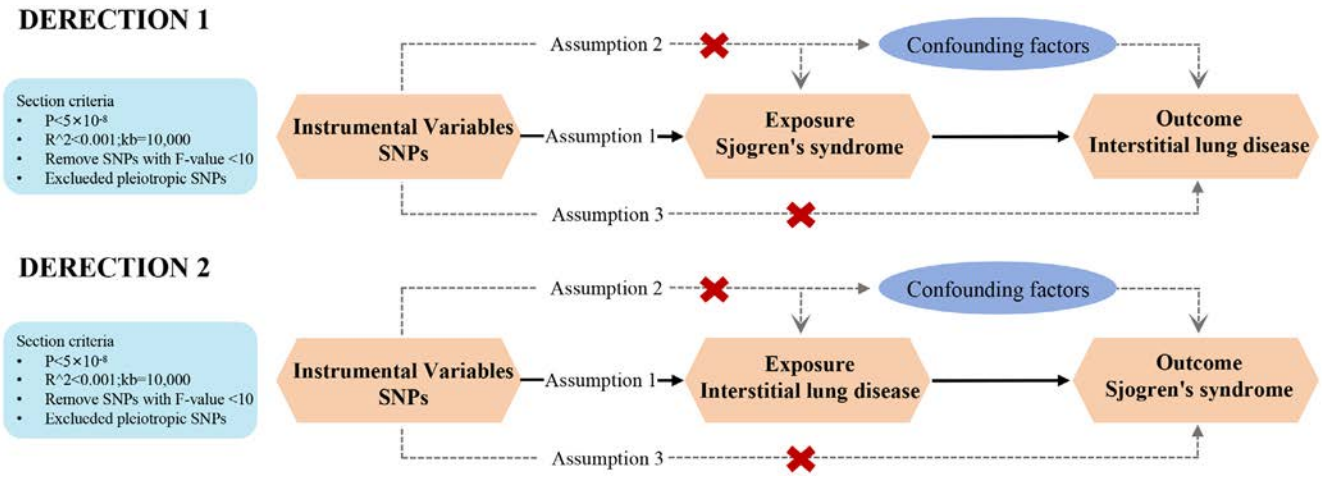

FIGURE 1 | Schematic representation of the bidirectional MR study of the associations of the SS with the ILD. Assumption 1, the selected genetic variances are robustly associated with exposure. Assumption 2, the selected genetic variances are not associated with confounders. Assumption 3, the selected genetic variances are strongly related to the outcome only through exposure.

en.fi/en/). The SS dataset comprises 2981 cases and 439424 controls and uses the phenocode "M13_SJOGREN", which contains 21 306 553 SNPs. The ILD dataset consists of 5097 cases and 448 636 controls, which are identified by the phenocode "ILD_ENDPOINTS", including a total of 21 306 794 SNPs. All participants are from European ancestry.

The causal effect of SS on ILD was explored first. By setting a correlation threshold with the exposure and performing linkage disequilibrium removal, 8 SNPs were identified as genetic instrumental variables for SS (Table S1). MR analysis revealed that genetically predicted SS was associated with an increased risk of ILD (IVW: OR = 1.14, 95% CI = 1.08–1.21, $p = 3.341e-06$). Subsequently, to investigate potential reverse causation, we analyzed the causal effect of ILD on SS. After excluding SNPs with pleiotropic effects, 12 SNPs were identified as robust IVs for ILD (Table S2). MR analysis indicated that genetically predicted ILD was also associated with an increased risk of SS (IVW: OR = 1.13, 95% CI = 1.04–1.22; $p = 0.002$; Table 1). Similarly, the MR–Egger method, the weighted median approach, and the weighted mode approach yielded similar results (Table 1). Additionally, no significant heterogeneity or horizontal pleiotropy was detected. The Steiger test was performed for all the SNPs, and each included SNP was in the "TRUE" direction. These results support the reliability of the results (Table 1). To the best of our knowledge, this is the first study utilizing bidirectional MR analysis to investigate the causal relationships between SS and ILD. The results indicate that the presence of SS may increase the risk of ILD by 14%. Surprisingly, we discovered that the presence of ILD could increase the risk of SS by 13%.

ILD represents the most prevalent type of pulmonary involvement in SS. This study initially confirmed the causal connection from the SS to the ILD. The immune imbalance of SS seemingly elevates the incidence of ILD. Clinical studies have revealed that the presence of anti-SSA is a potential predisposing factor for ILD in SS. Anti-Ro/SSA antibodies are detected in up to 70% of patients with SS [1], which is a potential predisposing factor for ILD in SS [8]. The identification of anti-SSA antibodies in the bronchoalveolar lavage fluid (BALF) of SS-ILD patients [9] implies that autoimmune reactions also occur in the lungs of SS patients. Additionally, anti-Ro52 antibodies, which are common in 70%–90% of SS patients, have been demonstrated to be associated with a higher incidence of ILD [10] and may suggest a poorer prognosis and lower survival [11]. Therefore, regular pulmonary function tests and HRCT in SS patients are necessary to detect early ILD.

At present, the pathogenesis of SS-ILD is not fully understood and may be driven by immune disorders caused by genetic, environmental, hormonal, and infection factors [12]. In SS, the active autoimmune response prompts the activation of glandular epithelial cells, which in turn leads to the activation of B and T lymphocytes [13], ultimately leading to damage to target organs [12, 14]. In the salivary glands, the release of autoantigens triggers the activation of toll-like receptors (TLRs). The activation of TLRs leads to the production of type I interferons (IFNs) and interleukin-12 (IL-12), and increased levels of type I interferons induce the release of B cell activators (BAFFs), promoting B cell activation and autoantibody production [15]. Autoantibodies bind to antigens to form immune complexes that stimulate plasmacytoid dendritic cells (pDCs), leading to further release of type I interferons [16]. Together, type I interferon and IL-12 activate natural killer (NK) cells and Th1 cells, increase interferon-γ (IFN-γ) production, and mediate epithelial cell activation, apoptosis, inflammation, and tissue damage [14]. In addition, epithelial cells also produce T cell homeostatic cytokines, such as IL-7, upon stimulation by TLRs, thereby activating CD4+ T cells (Th1 and Th17 cells) to release proinflammatory cytokines, such as IFN-γ, IL-6, and IL-17, which ultimately promote the epithelial inflammatory response and tissue damage [17, 18]. CD4+ T cells also promote B cell recruitment and interact in tissues to form germinal centers and cause tissue damage, and similar features have been observed in lung tissue of patients with SS [12, 19]. Epithelial cells present in the airway or lung parenchyma are targeted in SS. The immune response may extend from the salivary glands to the epithelial cells of the lung [12], causing similar pathophysiological changes, including lymphocyte infiltration in the lung, ultimately mediating the development of fibrosis [20].

TABLE 1 | The results of the MR study, heterogeneity, pleiotropy analysis, and Steiger test.

								Heterogeneity				Horizontal pleiotropy				
								MR-Egger		IVW		MR-Egger		MR-PRESSO	Steiger test	
Exposure	Out-come	Method	SNP (N)	*β*	SE	*p*	OR (95% CI)	*Q*	*Q_pval*	*Q*	*Q_pval*	Intercept	*p*	*p*	Direction	*p*
SS	ILD	IVW	8	0.132	0.028	3.341e-06	1.14 (1.08–1.21)	3.082	0.798	3.118	0.874	−0.004	0.856	0.905	TRUE	5.433e-73
		MR-Egger	8	0.142	0.061	0.060	1.15 (1.02–1.30)									
		Weighted edian	8	0.130	0.036	2.984e-04	1.14 (1.06–1.22)									
		Weighted mode	8	0.130	0.041	0.016	1.14 (1.05–1.23)									
ILD	SS	IVW	12	0.120	0.039	0.002	1.13 (1.04–1.22)	8.123	0.617	10.817	0.459	−0.033	0.132	0.523	TRUE	1.032e-124
		MR-Egger	12	0.206	0.066	0.011	1.23 (1.08–1.40)									
		Weighted edian	12	0.146	0.049	0.003	1.16 (1.05–1.27)									
		Weighted mode	12	0.151	0.051	0.013	1.16 (1.05–1.29)									

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; OR, odds ratio; SS, Sjögren's syndrome.

In contrast, our study is the first to suggest a causal effect of ILD on SS at the genetic level. Clinically, ILD-associated dry cough or shortness of breath after activity can be the first symptom of SS, but clinicians generally believe that ILD occurs as a result of latent SS. In 2015, "interstitial pneumonia with autoimmune" features (IPAF) was proposed and used to describe individuals with both ILD and combinations of other clinical, serologic, and/or pulmonary morphologic features which putatively stem from an underlying systemic autoimmune condition, but do not meet current rheumatologic criteria for a characterized connective tissue disease [21]. A retrospective cohort study from the US [22] revealed that 16% of patients with IPAF developed autoimmune rheumatic disease (ARD) within a median follow-up of 5.2 years, including two cases of rheumatoid arthritis, three cases of systemic sclerosis, one case of polymyositis, and two cases of ANCA-associated vasculitis. After adjusting for age, sex, smoking status, and the use of immunosuppressive therapy, patients with IPAF were 14 times more likely to develop ARD than patients without IPAF. Similarly, a Mendelian randomization study confirmed a causal effect of idiopathic pulmonary fibrosis on rheumatoid arthritis [23]. Unfortunately, no studies have reported the epidemiological characteristics of the progression to SS in idiopathic ILD patients, and no relevant studies have been conducted to elucidate the mechanism of its occurrence. Screening for antinuclear antibody profiles should be included in follow-up plans for ILD patients to facilitate early identification of those who may progress to ARD. In particular, attention should be given to tracking the specific clinical manifestations and serological abnormalities associated with SS to carry out active treatment as soon as possible. Moreover, further mechanistic studies are worthy of researching in the future, such as investigating whether shared pathways could serve as therapeutic targets for both conditions, which will be conducive to the development of clinical drugs.

Nevertheless, the majority of the samples in the GWAS database were of European ancestry, so the results need to be validated in non-European populations. Second, owing to the scarcity of valid SNPs as IVs in the existing GWAS data, the causal relationships between SS and each specific subtype of ILD remain undetermined, necessitating further research in the future.

Our findings suggest a potential causal relationship between SS and ILD. The significant causal effect of ILD on SS suggests that pathomechanisms involved in the development of ILD may promote SS. However, research on the relationship and pathogenesis of these two conditions is still limited. Elucidating the causal relationship between these two diseases will help to expand the current research.

Author Contributions

J.L. and Q.-W.T. contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by C.-X.L., J.-Q.C., J.-H.L., and X.-Y.Z. The first draft of the manuscript was co-authored by Y.Z. and Q.W. as co-first authors. All authors critically reviewed the manuscript and approved the final version for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in FinnGen studies at http://www.finngen.fi/en/. These data were derived from the following resources available in the public domain: - M13_SJOGREN, https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_M13_SJOGREN.gz—ILD_ENDPOINTS, https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_ILD_ENDPOINTS.gz.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Detailed information on the instrumental variables used in the MR analyses (causal effects of SS on ILD). **Table S2:** Detailed information on the instrumental variables used in the MR analyses (causal effects of ILD on SS).

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REVIEW

Dysregulation of Different Modes of Programmed Cell Death in Rheumatoid Arthritis Fibroblast-Like Synoviocyte

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by chronic synovitis and skeletal joint deformities, often accompanied by systemic symptoms. Over the past few decades, various susceptibility factors for RA have been revealed, and numerous therapeutic drugs have been developed, including analgesics, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biological agents (bDMARDs). Despite the availability of multiple treatment options, the therapeutic outcomes for some patients remain suboptimal due to the complex pathogenesis of RA. As a key pathological mechanism, programmed cell death (PCD) in RA has received extensive attention. Dysregulation of PCD in RA impacts the progression of the disease. This article systematically reviews the roles of various cell death modalities, including apoptosis, necroptosis, ferroptosis, pyroptosis, and autophagy in the pathophysiology of RA, aiming to provide a theoretical basis and direction for the discovery of new therapeutic targets and drug development.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic inflammation of the joint synovium and destruction of joint structures. Clinically, it presents with symmetric pain, stiffness, and swelling in one or more joints, which may eventually lead to joint destruction, functional impairment, and even disability [1]. The pathological features of RA include proliferation of synovial cells, neovascularization, inflammatory cell infiltration, and destruction of cartilage and bone tissues [2]. The main drugs currently used to treat RA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) [3, 4]. However, these drugs only alleviate symptoms or slow disease progression, are costly, and have numerous adverse effects. Consequently, developing new therapeutic strategies has become a priority [5, 6].

Therefore, a thorough exploration of the specific roles and regulatory mechanisms of these cell death modalities in RA can not only enhance our understanding of the pathogenesis of RA but also provide important clues for the development of new therapeutic strategies. This article aims to systematically review the dysregulation of key programmed cell death (PCD) modalities in RA, including apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy. It analyzes their interactions and effects on the survival of synovial fibroblasts (FLS), while also evaluating the potential of novel therapeutic strategies targeting PCD pathways. Furthermore, it proposes future research directions to provide a theoretical basis for precision treatment of RA.

2 | The Role of FLS in RA

FLS play a crucial role in both the healthy and diseased states of joint synovium. In normal joints, FLS contribute to joint health by synthesizing synovial fluid and regulating the composition of the extracellular matrix, providing lubrication and nutrition to the joint cartilage [7, 8]. However, during the progression of RA, the behavior of FLS changes significantly; the resistance of FLS cells to cell death leads to excessive proliferation of synovial cells, causing pathological hyperplasia of the joint synovium and further joint destruction [9]. Concurrently, the excessive secretion of pro-inflammatory cytokines, angiogenic factors, and matrix metalloproteinases (MMPs) by FLS can contribute to tissue infiltration and destruction, further triggering RA progression [10]. FLS also secrete various chemokines to recruit macrophages, T cells, and B cells to the joints, enhancing the inflammatory response and indirectly damaging bones and joints. Moreover, FLS can inhibit the apoptosis of T cells and B cells, prolonging the inflammatory response and intensifying damage to bones and joints [11].

In summary, dysfunction, especially resistance to apoptosis of FLS, can lead to abnormal synovial proliferation, inflammatory cell infiltration, cartilage and bone erosion, joint destruction, and deformities, ultimately resulting in RA progression.

3 | FLS Apoptotic Dysregulation

One of the key mechanisms involved in the pathogenesis of RA is the dysregulated apoptosis, leading to abnormal proliferation and decreased apoptosis of FLS [12]. Apoptosis is a fundamental mechanism for organism development, tissue remodeling, and immune regulation. However, in the RA environment, FLS exhibit a significant imbalance in apoptosis [10]. Specifically, FLS regulate Bcl-2 family proteins, inhibit Caspase activity, inactivate p53 function, and activate anti-apoptotic signaling pathways (such as PI3K/Akt, MAPK, NF-κB), thereby constructing a complex anti-apoptotic network [13]. In addition, the endoplasmic reticulum stress (ERS) tolerance mechanism also provides FLS with a survival advantage in the harsh microenvironment, further exacerbating their resistance to apoptosis [14]. The following sections will discuss the molecular mechanisms related to apoptosis imbalance in FLS during RA progression (Figure 1).

3.1 | The Role of p53

In RA, p53, a crucial tumor suppressor and transcription factor, plays a significant role in regulating apoptosis [15]. Under normal conditions, p53 activates pro-apoptotic factors in response to DNA damage and cellular stress, triggering the apoptotic process. However, in RA, p53 is frequently inactivated or mutated, leading to apoptosis resistance in FLS. In the RA microenvironment, inflammatory cytokines such as TNF-α and IL-6 inhibit p53 activity, further enhancing FLS resistance to apoptosis signals [16].

The downstream signaling of p53 is also disrupted in RA. For example, p53-induced pro-apoptotic genes such as Bax, PUMA, and Noxa show reduced expression in RA FLS, which diminishes

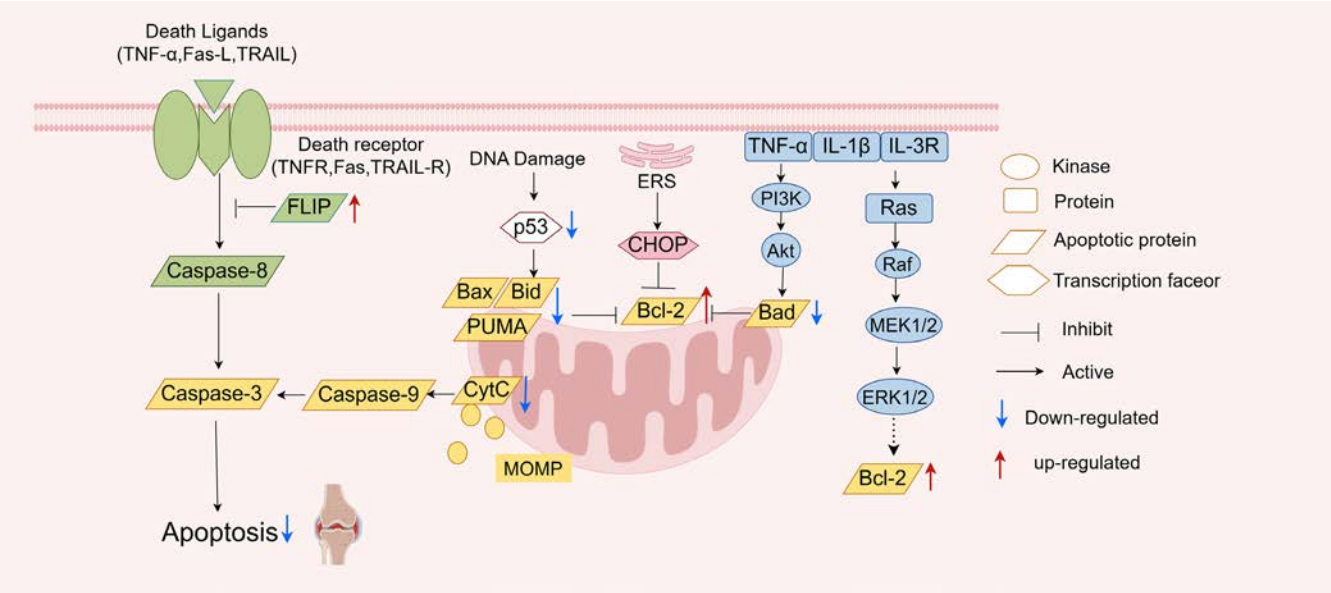

FIGURE 1 | Coordinated anti-apoptotic network in RA FLS and cross-pathway interfaces. In RA FLS, a complex anti-apoptotic network operates through cross-pathway interactions: PI3K/Akt signaling upregulates Bcl-2/Bcl-xL expression and phosphorylates pro-apoptotic proteins (eg., Bad), stabilizing mitochondrial outer membrane integrity and suppressing caspase cascades (eg., caspase-9 → caspase-3). p53 promotes mitochondrial apoptosis by transcriptionally activating Bax/PUMA/Noxa while repressing SLC7A11, depleting GSH and weakening GPX4 activity. This dual role links apoptosis to ferroptosis via lipid peroxidation. Caspase-8 serves as a master switch: its activation triggers caspase-3/7-mediated apoptosis, while its inhibition permits RIPK1/RIPK3-MLKL-driven necroptosis. Caspase-8 and caspase-3 can also process gasdermins, influencing transitions between pyroptosis and apoptosis. ERS (eg., PERK/IRE1α/ATF6) and NF-κB/PI3K-Akt signaling converge to enhance survival programs, lower apoptotic sensitivity, and modulate pyroptosis/ferroptosis thresholds. This coordinated network highlights the interplay among survival signals, mitochondrial integrity, and cell death regulation, explaining the abnormal survival and proliferation of RA FLS under pathological conditions. The main figure was drawn by Figdraw.

the sensitivity of cells to apoptotic signals [17]. Moreover, p53 is involved in autophagy regulation, which enhances FLS survival and further contributes to their abnormal proliferation and apoptosis resistance in RA [18]. p53 also plays a role in ferroptosis regulation, promoting lipid peroxidation and FLS death by inhibiting SLC7A11 expression [19]. However, certain p53 mutations (eg., p53^3KR) and the p53-p21-DPP4 axis may counteract ferroptosis by maintaining glutathione (GSH) homeostasis, forming a complex survival network [20].

In summary, the functional loss and mutations of p53 in RA not only disrupt the apoptosis signaling pathway but also enhance FLS survival and proliferation through mechanisms like autophagy and ferroptosis regulation. These changes contribute to the pathogenesis of joint inflammation and destruction in RA, highlighting p53 as a potential therapeutic target for reversing FLS apoptosis resistance.

3.2 | ERS Regulation of RA Apoptosis

ERS plays a critical role in RA. When cells encounter stimuli (such as protein misfolding or Ca^{2+} imbalance), ERS is regulated through the unfolded protein response (UPR), activating sensors like IRE1α, PERK, and ATF6α to restore cellular homeostasis [14]. In early stages, UPR helps the cell adapt to stress, but prolonged stress leads to pro-apoptotic signaling. In RA, synovial tissue shows high expression of key ERS proteins (BiP, XBP1s, PERK), indicating a close relationship between ERS, inflammation, and oxidative stress. The mechanisms underlying ERS-related apoptosis resistance may involve abnormal regulation of CHOP/Bcl-2 imbalance, disrupted calcium signaling (eg., calpain activation), and interference of pro-apoptotic UPR branches by the inflammatory microenvironment [21]. Targeting ERS pathways may represent a new strategy to overcome FLS apoptosis resistance [22].

In summary, FLS resist apoptosis through multiple mechanisms, which play an important role in the pathogenesis of RA. In-depth study of these mechanisms will help reveal the pathophysiology of RA and provide potential targets for the development of new therapeutic strategies.

4 | The Dysregulation of Other PCDs in FLS

PCD is a controlled death process involving complex signaling cascades, coordinated by a series of specific effector molecules, ensuring precise execution of cell death [23]. Besides, apoptosis plays a significant role in RA; current researchers indicate PCD, such as necroptosis, pyroptosis, ferroptosis, NETosis, autophagy, and cuproptosis may exacerbate inflammatory responses [24]. These complex forms of cell death collectively contribute to the pathology of RA. Targeting PCD may offer potential therapeutic avenues for RA, warranting further research and development. Next, we will delve into specific cell death modalities and their roles in RA to better understand how these death mechanisms influence disease progression and treatment strategies (a summary of key inhibitors is presented in Table 1).

4.1 | Necroptosis

Necroptosis is mainly initiated by members of the tumor necrosis factor receptor (TNFR) and Toll-like receptor (TLR) families, interferon, intracellular RNA and DNA sensors, and other mediators [25–27]. Subsequently, the protein kinase RIPK1 (receptor-interacting protein kinase 1) and RIPK3 interact with the receptor protein, which transduces death signals and further recruits and phosphorylates MLKL (mixed lineage kinase domain-like protein), forming a specific signaling complex known as the "necrosome," a process essential for necroptosis [28].

In RA, necroptosis promotes joint inflammation. Studies have shown that plasma levels of RIPK1 and MLKL are higher in RA patients than in healthy individuals, with these levels positively correlating with the severity of RA, suggesting that RIPK1 and MLKL may serve as novel biomarkers for RA [29]. Additionally, it has been reported that the absence of IFN-γ enhances the expression of RIPK1, RIPK3, and MLKL in collagen-induced arthritis (CIA) mice, increases the number of Th17 cells, and promotes the release of IL-17 and TNF-α, thus exacerbating inflammation and joint damage in RA [30]. Necroptosis also drives chondrocyte death and aggravates cartilage degeneration and inflammation.

Studies have found that small molecule inhibitors targeting RIPK1 hold potential as therapeutic strategies for RA. For example, KW2449, by inhibiting RIPK1-dependent necroptosis, was used in adjuvant arthritis (AA) rat cartilage; expression levels of RIPK1, RIPK3, and P-MLKL mediated by ASIC-1a were elevated, correlating with necroptosis [31]. The RIPK1 inhibitor Necrostatin-1 can alleviate joint damage and inflammation. Moreover, RIPK3 inhibitors (such as GSK'872 and AZ-628) and MLKL inhibitors (such as NSA and GW806742X) have shown clear potential in suppressing cartilage degeneration and inflammation. Future studies should focus on optimizing inhibitor specificity, exploring multi-target combination strategies, and validating their long-term safety and efficacy in humans.

4.2 | Pyroptosis

Pyroptosis is a pro-inflammatory form of PCD that morphologically differs from apoptosis and necrosis. The main features include cell swelling, nuclear condensation, and the formation of bubble-like large vesicles on the cell membrane, ultimately leading to membrane rupture [32–34]. Pyroptosis is triggered by inflammasome activation, which is designed to defend against harmful pathogens and maintain internal homeostasis. Meanwhile, excessive activation of the NLRP3 inflammasome can lead to the release of inflammatory mediators, potentially resulting in inflammatory responses and tissue damage [35–37].

Studies have shown that pyroptosis is observed in FLS of RA patients. High levels of GSDMD (a key molecule in pyroptosis), and NLRP3, caspase-1, IL-18, IL-6, and IL-1β (key molecules in inflammasome), were detected in their serum and synovial tissues [38, 39]. These findings suggest that pyroptosis is involved not only in the pathogenesis of RA but also that its incidence may be positively correlated with RA activity. Therefore, inhibiting core

TABLE 1 | Dysregulated programmed cell death pathways in rheumatoid arthritis.

PCD pathway	Key features	Role in RA	The therapeutic targets and inhibitors
Necroptosis	Programmed cell death mediated by RIPK1, RIPK3, and MLKL involves cell swelling, membrane rupture, and the release of DAMPs and inflammatory factors	TNF-α activates necroptosis in RA FLS, leading to upregulation of RIPK3 expression, which drives the release of inflammatory factors (IL-1β, IL-6) and exacerbates arthritis inflammation and synovial hyperplasia	Targets: RIPK1, RIPK3, MLKL; Inhibitors: RIPK1 inhibitors (KW2449, Necrostatin-1), RIPK3 inhibitors (GSK'872, AZ-628, etc.), MLKL inhibitors (NSA, GW806742X)
Pyroptosis	Activation of inflammasomes (such as NLRP3) induces the activation of caspase-1/11, which cleaves GSDMD to form membrane pores, leading to cell swelling and the release of IL-1β/IL-18	In RA synovial tissue, abnormal activation of NLRP3 inflammasomes releases IL-1β and IL-18, mediating pyroptosis of FLS and immune cells, exacerbating joint inflammation and cartilage destruction	Targets: NLRP3, GSDMD, Caspase-1; Inhibitors: NLRP3 inhibitors (MCC950, CY-09), GSDMD inhibitors (Disulfiram, LDC7559)
Ferroptosis	Lipid peroxidation is driven by iron ions and GPX4 inhibition, characterized by mitochondrial shrinkage, increased membrane density, and loss of cristae	In RA, oxidative stress and iron overload promote ferroptosis, aggravating RA synovial inflammation and joint damage. High expression of SLC7A11 in FLS confers resistance to ferroptosis, enhancing invasiveness	Targets: GPX4, SLC7A11; Direct inhibitors: Icariin; Indirect regulation: Coenzyme Q10, Resveratrol, Quercetin, Curcumin, and other natural antioxidants
NETosis	NETs (Neutrophil Extracellular Traps) are mediated by DNA, histones, and proteases (such as MPO, NE)	NETs accumulate in RA synovial tissue, releasing pro-inflammatory factors that exacerbate RA autoimmune responses, promoting synovitis and cartilage degradation	Targets: PAD4, MPO; Inhibitors: PAD4 inhibitors (Cl-amidine), DNase I, NOX inhibitors (DPI)
Autophagy	Damaged organelles and proteins are cleared via the autophagosome-lysosome pathway to maintain homeostasis. Overactivation of this process can lead to cell death. Core molecules include LC3, Beclin-1, and mTOR pathway regulation	In RA synovial tissue, autophagy-related protein expression is upregulated, promoting FLS survival and invasiveness. Autophagy deficiency leads to mitochondrial damage, promoting necroptosis, apoptosis, and oxidative stress	Targets: mTOR, Beclin-1, ATG5, LC3; Inhibitors: Autophagy activators (Rapamycin), Autophagy inhibitors (Chloroquine), PI3K inhibitors (3-MA)
Cuprotosis	Copper ion accumulation causes mitochondrial damage through FDX1-mediated inhibition of mitochondrial respiratory chain complex IV, leading to oxidative stress	In RA, serum copper levels are elevated and correlated with disease activity. FLS exhibit copper death inhibition due to glutamine consumption, exacerbating abnormal cell proliferation and resistance to apoptosis	Targets: Positive regulators of copper death (FDX1, DLAT) and negative regulators (MTF1, GLS); Inhibitors: Copper chelators (such as Penicillamine)

Note: The table summarizes key features, pathogenic roles in RA synovium, and potential therapeutic targets/inhibitors for six PCD modalities: necroptosis, pyroptosis, ferroptosis, NETosis, autophagy-related death, and cuproptosis.
Abbreviations: DAMPs, damage-associated molecular patterns; FLS, fibroblast-like synoviocytes; IL, interleukin; NETs, neutrophil extracellular traps.

molecules of pyroptosis may become a key strategy to prevent the progression of RA.

Currently, several inhibitors have been developed to regulate NLRP3 inflammasomes and GSDMD. MCC950, a specific NLRP3 inhibitor, directly interacts with the NACHT domain of NLRP3, blocking ASC oligomerization and significantly suppressing synovitis and cartilage erosion. CY-09, by interacting with the Walker A motif of NLRP3, prevents ATP binding and activation of NLRP3 [40]. Additionally, GSDMD, a downstream effector protein of the NLRP3 inflammasome, has led to new hope for RA treatment with small molecule inhibitors such as disulfiram and LDC7559. In traditional Chinese medicine research, Baihu Guizhi Decoction (BHGZD) inhibits NLRP3 inflammasome activation and pyroptosis; quercetin targets CASP1 and regulates pyroptosis, effectively alleviating the immune-inflammatory imbalance in RA [41, 42]. Moreover, Salicylalazine (SAZ) can exert significant anti-arthritic effects by regulating the TLR4/NLRP3/GSDMD signaling axis-mediated pyroptosis cascade. Inhibition of ASIC1a function significantly reduces pyroptosis in RA FLS [43]. Notably, Pentraxin 3 (PTX3) has emerged as a novel biomarker for RA diagnosis. After binding to complement C1q, PTX3 can induce monocytic pyroptosis, releasing large amounts of IL-1β, IL-6, and other inflammatory factors, creating an "inflammatory cytokine storm" that exacerbates joint destruction [44].

4.3 | Ferroptosis

Ferroptosis is an iron-dependent and lipid peroxidation-driven form of PCD characterized by excessive iron accumulation, increased iron-dependent ROS, and lipid peroxidation, leading to membrane rupture, release of contents, and necrosis-like cell death [45, 46]. Ferroptosis releases inflammatory cytokines such as IL-1β, TNF-α, and IL-6, triggering an inflammatory response.

Studies have shown higher iron content and increased levels of ROS and lipid peroxidation in the serum and synovial fluid of RA patients, with abnormal antioxidant systems [47, 48]. ROS levels are positively correlated with RA disease severity scores and are one of the key factors in disease progression [49]. Elevated lipid ROS levels, which are regulated by GPX4, can inhibit ferroptosis. Notably, ROS continuously stimulate TNF-α production by activating the NF-κB pathway, forming a positive feedback loop of ROS/TNF-α [50]. The increased iron intake accelerates the vicious cycle of inflammation and hemorrhage, leading to synovial hyperplasia and invasion of joint cartilage.

Recent studies indicate that glycine drives ferroptosis in RA FLS by methylating the S-adenosylmethionine (SAM)-related GPX4 promoter and enhancing this effect [51]. This discovery provides crucial clues for the molecular mechanisms of ferroptosis in RA and the development of new therapeutic strategies. Moreover, the bioactive peptide G1dP3 promotes ferroptosis in RA FLS through the p53/SLC7A11 axis, demonstrating its therapeutic potential in RA. Similarly, drugs like sulfasalazine regulate ferroptosis by inhibiting the Xc- system and the expression of GSH and GPX4. On the other hand, it also induces ferroptosis by increasing iron ion levels and generating excessive lipid ROS [52]. Natural antioxidants also play a role in ferroptosis regulation. For example, Icariin inhibits ferroptosis in synovial cells through activation of the Xc-/GPX4 axis and exerts a protective effect [53].

4.4 | Netotic Cell Death

Netotic cell death is characterized by the release of extracellular net-like DNA-protein structures known as neutrophil extracellular traps (NETs) [54]. NETs consist of DNA, histones, neutrophil-specific alarm proteins, myeloperoxidase (MPO), neutrophil elastase (NE), and cathepsin G, and their function is to eliminate harmful pathogens [55]. Neutrophils, under various signaling stimuli, generate NETs, which ultimately lead to cell death and the release of NETs. This process is referred to as NETosis.

NETosis serves as an inflammation-driving factor in RA [56]. In RA patients, activated neutrophils in the synovial fluid significantly increase, participating in the synergistic effects of immune complexes and the complement system, leading to excessive NETosis, the release of inflammatory mediators, and causing inflammation and joint destruction [57]. The spontaneous increase in neutrophil populations is associated with ROS production, MPO expression, and PAD4-mediated citrullination, and NETosis derivatives are closely correlated with the severity of RA [57].

Therefore, targeting NETosis has been considered a new therapeutic strategy in RA treatment. Suppressing key molecules of NETosis, such as PAD enzyme inhibitors to inhibit PAD2/PAD4 activity, reduces histone citrullination and NET formation [58, 59]. Furthermore, small molecule inhibitors like Cl-amidine have been validated in animal models for their anti-inflammatory effects, and NOX inhibitors such as diphenyl iodonium (DPI) and protease inhibitors help reduce NET release and tissue damage factors [60].

Regarding natural compounds and traditional drugs, studies have shown that emodin, by inhibiting autophagy and NETosis, alleviates RA symptoms in the AA model [61]. Other potential drugs, such as hydroxychloroquine and MTX, may indirectly influence NETosis by regulating immune cell functions. Furthermore, anti-TNF-α and anti-IL-6R treatments can reduce NET formation and alleviate inflammation. Notably, NETosis-derived markers such as serum MPO-DNA complexes and calprotectin levels are positively correlated with anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF) titers, and disease severity, and could serve as biomarkers for RA diagnosis and therapeutic efficacy evaluation [62]. In conclusion, excessive NETosis promotes RA progression by facilitating immune complex formation and the release of inflammatory mediators. Targeting NETosis can effectively alleviate inflammation, reduce NET formation, and slow the pathological progression of RA.

4.5 | Autophagy

Autophagy is a non-apoptotic form of PCD that primarily removes damaged organelles and waste proteins via the

autophagosome-lysosome pathway, maintaining cellular homeostasis [63, 64]. However, it can sometimes have adverse effects by disrupting the balance between life and death by selectively degrading proteins associated with other types of PCD [65].

In RA, autophagy exhibits complex roles. Analysis of synovial tissue from RA patients shows increased expression of autophagy-related proteins (such as Beclin1, ATG5, LC3), which are positively correlated with inflammatory markers and autoantibody levels [66]. Autophagy is closely related to the development of RA, and autophagy inhibition has become a new therapeutic strategy for improving RA.

Regulating the autophagy process has become a new direction in RA treatment. For example, triptolide can block the CaMKKβ-AMPK-mTOR pathway and inhibit FLS autophagy, while tomorutin extract can downregulate LC3B protein, upregulate caspase-3, and correct the abnormal expression of ULK-1, thus alleviating synovial inflammation and bone erosion [67, 68]. Additionally, intervention in the AKT/PI3K signaling axis, such as with dexamethasone, astragalus polysaccharides, and hesperidin/5-methoxyflavone, targets AKT signaling to inhibit autophagy in synovial cells. Moreover, autophagy inhibitors like 3-MA/chloroquine can directly inhibit autophagosome formation and reduce the levels of inflammatory factors [69].

4.6 | Cuproptosis

Cuproptosis is a novel form of cell death triggered by copper ion overload, independent of apoptosis, necroptosis, pyroptosis, and ferroptosis. Copper, as an essential trace element, is a cofactor for several enzymes, such as cytochrome oxidase (complex IV of the respiratory chain) and superoxide dismutase (SOD), playing a crucial role in maintaining normal cellular functions. However, excessive copper can lead to toxicity, triggering the cuproptosis mechanism [70].

In cuproptosis, copper overload primarily induces cell death through FDX1/DLAT-mediated mitochondrial dysfunction [71]. The specific mechanism involves ferredoxin 1 (FDX1), a core regulator of cuproptosis, whose activity is directly modulated by excessive copper ions [72]. FDX1 reduces Cu^{2+} to Cu^{+}, enhancing the reactivity of copper ions. Activated FDX1 further catalyzes excessive modification of mitochondrial lipoylated proteins, such as DLAT. As a key component of the pyruvate dehydrogenase (PDH) complex, abnormal lipoylation of DLAT leads to protein aggregation and disrupts mitochondrial protein homeostasis. Lipoylation modification of DLAT induces protein aggregation, impairs the function of iron–sulfur cluster proteins (Fe-S proteins), and causes inactivation of the tricarboxylic acid (TCA) cycle and respiratory chain complexes. Ultimately, this results in the collapse of mitochondrial membrane potential and accumulation of reactive oxygen species (ROS), triggering cuproptosis.

Studies have shown that copper levels in the serum of RA patients are significantly elevated and closely related to disease activity. Specifically, in patients with active RA, copper levels are positively correlated with erythrocyte sedimentation rate (ESR) and negatively correlated with hemoglobin levels [73]. Additionally, the overall levels of glucose and glutamine in RA FLS are reduced, indicating enhanced consumption, suggesting that glutamine plays a critical role in FLS proliferation [12].

Mechanistically, glutamine fuels the TCA cycle via GLS-mediated conversion to glutamate and α-ketoglutarate (α-KG) [74]. Adequate TCA flux maintains mitochondrial lipoylation dynamics of pivotal E2 components such as DLAT, which is required for FDX1-dependent cuproptosis execution [75]. Under glutamine depletion, reduced α-KG supply diminishes TCA flux, lessens DLAT lipoylation substrates, and attenuates copper-induced aggregation of lipoylated proteins, thereby elevating the death threshold and suppressing cuproptosis. In RA-FLS, which display glutamine addiction to sustain proliferation and invasion, nutrient competition and metabolic reprogramming under inflammatory stress can paradoxically blunt cuproptosis and favor synovial hyperplasia [76]. Functionally, restoring anaplerosis (eg., α-KG supplementation or GLS modulation) or leveraging copper ionophores under controlled metabolic support may re-sensitize RA FLS to cuproptosis and restrain pannus overgrowth.

Currently, therapeutic strategies targeting cuproptosis in RA involve regulating copper homeostasis by intervening with drugs (such as D-penicillamine and other copper chelators) to modulate copper absorption, distribution, and excretion, restoring copper homeostasis [77]. Alternatively, targeting copper ion transporters to develop synovial-targeted copper ion carriers (eg., coupling FLS-specific antibodies) can help reduce inflammation [78]. Furthermore, targeting cuproptosis-related genes, including positive regulators of cuproptosis (such as FDX1, DLAT) and negative regulators (such as MTF1, GLS), by developing gene therapy or small molecule inhibitors, could potentially modulate copper death sensitivity and improve RA symptoms [70]. Combination therapies, using copper homeostasis regulators together with traditional anti-rheumatic drugs (such as DMARDs and biologics), may enhance efficacy and reduce side effects [78].

5 | Interactions Between Cell Death Pathways

The signaling pathways involved in apoptosis, necroptosis, pyroptosis, ferroptosis, NETosis, and autophagy are distinct, yet there are tight interconnections and regulatory mechanisms that form a “crosstalk” network, collectively contributing to the decision-making process in regulating cell fate. Therefore, exploring the interplay and synergy of these cell death pathways is crucial for understanding disease progression and developing new therapeutic strategies.

5.1 | Interaction Between Autophagy and Apoptosis

In RA, there is a significant negative correlation between autophagy and apoptosis; inducing autophagy may lead to self-protective apoptosis resistance in RA cells. Studies show that autophagy markers (Beclin-1, LC3B) are significantly upregulated in synovial tissues of RA patients, while apoptosis levels

are notably reduced, suggesting a negative correlation between the two. Inhibition of autophagy can reverse the anti-apoptotic phenotype of FLS, promoting their death [79]. Studies found that resveratrol inhibits autophagy by downregulating Beclin-1 and LC3A/B, promoting mitochondrial-dependent apoptosis and alleviating AA [80]. PADI4 gene silencing inhibits autophagy and induces FLS apoptosis, indicating the potential value of epigenetic regulation [81].

Autophagy counteracts apoptosis in RA through multiple mechanisms. TNF-α enhances autophagic activity by activating the PI3K/AKT/mTOR pathway, inhibiting FLS apoptosis, and forming an "inflammation-autophagy-survival" vicious cycle. FLS enhance resistance to MTX by increasing the expression of HMGB1 and Beclin-1, inducing autophagosome formation [82]. TNF-α, IL-1β, or LPS can stimulate the upregulation of protein tyrosine phosphatase non-receptor type 2 (PTPN2), which promotes FLS survival by inhibiting apoptosis and enhancing autophagy [83]. Upregulating DNM1L inhibits apoptosis and activates NF-κB inflammatory signaling by increasing LC3B expression and ROS levels [84].

The interaction between autophagy and apoptosis in RA is complex and diverse; a deeper understanding of the interaction between autophagy and apoptosis could provide new targets and strategies for clinical treatment.

5.2 | Interaction Between Necroptosis and Autophagy

In RA, the abnormal regulation of necroptosis and autophagy directly participates in the occurrence and progression of the disease. Studies have found that upregulated LC3B and Beclin-1 significantly inhibit RIPK1/RIPK3 activation and promote the abnormal survival and invasive ability of RA FLS [85]. Inflammatory factors such as TNF-α activate necroptotic pathways in FLS, leading to cell death and the release of inflammatory mediators, further exacerbating joint inflammation [86]. Notably, TNF-α also activates NF-κB signaling, which enhances autophagic activity and inhibits caspase-8 function, forming an "autophagy-necroptosis resistance" vicious cycle.

On the other hand, autophagic dysfunction may lead to the accumulation of damaged organelles and misfolded proteins, further promoting necroptosis. This dynamic imbalance is especially evident in clinical treatments: studies on MTX resistance suggest that FLS accelerate MTX degradation via upregulated autophagy, simultaneously reducing the release of necroptosis-related factor HMGB1, leading to drug failure [87]. In contrast, commonly used biologics, such as anti-TNF-α therapy, may indirectly suppress necroptosis pathways by excessively enhancing autophagic activity, weakening the inflammation-clearing effects.

Therefore, the regulatory mechanisms between necroptosis and autophagy are very complex. Animal experiments provide important evidence: in a CIA mouse model, co-administration of autophagy inhibitors (eg., chloroquine, as described in 4.5) and necroptosis inducers (TSQ) significantly reduced joint destruction [88]. Clinical sample analysis also showed that the autophagy marker LC3B co-expressed with the necroptosis inhibitor cFLIP in RA synovial tissue, further suggesting the close interaction between the two pathways [66]. Future research should further explore the key regulatory factors of these pathways to provide new therapeutic approaches for RA.

5.3 | Interaction Between Apoptosis and Necroptosis

Furthermore, during the progression of RA, there is an interrelationship between apoptosis and necroptosis. Studies suggest that SMAC mimetics (SMs) inhibit the anti-apoptotic effects of SMAC by competing with CIAP1/2 proteins, thereby enhancing TNF-α release and activating RIPK1, RIPK3, and MLKL in pro-inflammatory M1 macrophages, thereby inducing apoptosis and necroptosis [89].

Additionally, compared to traditional TNF-α inhibitors like etanercept, geldanamycin regulates cell death balance through a dual mechanism: on one hand, it inhibits RIPK1 kinase activity and NF-κB inflammatory pathways, blocking TNF-α-induced necroptotic signals; on the other hand, it enhances caspase-8 activation, promoting apoptosis in RA synovial cells. In a CIA mouse model, this drug significantly reduced synovial hyperplasia and improved arthritis phenotypes, showing better clinical potential than etanercept [90].

5.4 | Interaction Between Apoptosis and Pyroptosis

The process of cell death is typically initiated by mitochondrial release of apoptotic factors. When cells are subjected to TNF and oxidative stress, mitochondria release a series of pro-apoptotic factors, ultimately leading to apoptosis. However, in certain cases, especially when caspase-8 activity is inhibited, cells may switch to necroptosis. The presence of GSDME protein has been found to promote the shift from apoptosis to pyroptosis, further increasing the diversity of cell death pathways. Moreover, lactoferrin and GSDMD participate in inducing NETosis to digest pathogens, highlighting the interaction between pyroptosis and NETosis pathways [91].

Additionally, inflammasomes are related to pyroptosis, and there is a complex interaction between apoptosis and pyroptosis [25]. Caspase-8 plays a key regulatory role in cell death pathways as a central regulatory node in the cysteine-aspartic protease family. The caspase family coordinates the dynamic balance between apoptosis execution and necroptosis inhibition through a complex protein–protein interaction network [92]. The following sections will elaborate on its dual function in regulating cell death.

5.5 | Interaction Between Apoptosis and Ferroptosis

The presence of GSDME protein can promote the transition from apoptosis to pyroptosis. Similarly, there is a potential conversion between apoptosis and ferroptosis. Iron accumulation regulates osteoblast apoptosis through the XIST/miR-758-3p/caspase-3 axis;

ROS play a key role in ferroptosis-induced osteoblast necroptosis, and the RIPK1/RIPK3/MLKL pathway is the core mechanism of iron overload-induced necroptosis in vitro [28, 93, 94].

5.6 | Interaction Between Ferroptosis and Pyroptosis

Moreover, ferroptosis, mediated by iron ions, has a certain connection with pyroptosis. Studies have shown that in iron-treated MC3T3-E1 osteoblasts, the accumulation of iron increases ROS production and activates caspase-3, which further cleaves GSDME protein, causing the transition from TNF-α-induced apoptosis to pyroptosis. The GPX4 and GSDMD signals play important roles in triggering ferroptosis and pyroptosis, respectively, which may lead to excessive ferroptosis and pyroptosis in bone cells in RA, causing abnormal bone cell function or death [95]. The interaction between GPX4 and GSDMD signals provides new research directions and potential targets for RA treatment.

5.7 | Caspase-8 Acts as a Molecular Hub for Cell Death Modalities

As a core regulator, caspase-8 coordinates different modes of cell death through the following mechanisms. In apoptosis, upon death receptor activation, FADD-mediated caspase-8 activation triggers the downstream caspase-3/7 cascade, executing the classical apoptotic program [96]. Additionally, when caspase-8 activity is inhibited (eg., by viral infection or pharmacological intervention), RIPK1/RIPK3 oligomerizes to form the necrosome, activating MLKL-mediated membrane rupture and potentially shifting the cell toward necroptosis [97].

Caspase-8 can directly induce pyroptosis by cleaving GSDMD or indirectly promote NLRP3 inflammasome activation via the RIPK3-MLKL axis, leading to the release of pro-inflammatory factors such as IL-1β and triggering pyroptosis [98]. In the regulation of both apoptosis and pyroptosis, caspase-8 plays a critical role. Upon activation, it cleaves the Pannexin-1 channel via caspase-3, inducing potassium efflux and activating the NLRP3 inflammasome. If caspase-8 remains active, it further activates caspase-3 to induce apoptosis; if its activity is inhibited, the cell shifts toward caspase-1 activation and pyroptosis [99].

Furthermore, caspase-3/8 can directly act on GSDMD family proteins to regulate pyroptosis, while delayed GSDMD pore formation may cause a transition from pyroptosis to apoptosis [100].

The PCD pathways form a dynamic interactive network centered on caspase-8. The balance among these pathways is regulated by microenvironmental signals and metabolic states. Deciphering these mechanisms provides new insights for developing targeted therapeutic strategies.

6 | Clinical Implications and Translational Perspectives

As reviewed in this article, the dysregulation of multiple PCD pathways in RA FLS extends beyond elucidating pathogenic mechanisms, offering substantial translational potential for refining RA management.

These insights provide promising avenues for novel therapeutic development. Key molecular nodes within specific PCD pathways—such as RIPK1/RIPK3/MLKL in necroptosis, NLRP3/GSDMD in pyroptosis, GPX4/xCT in ferroptosis, PAD4 in NETosis, and copper homeostasis regulators—represent compelling targets for next-generation therapies. Understanding the mechanisms underlying apoptosis resistance (eg., p53 inactivation, endoplasmic reticulum stress tolerance, survival pathway activation) and PCD crosstalk informs strategies to overcome drug resistance and enables the design of precision combination therapies. Nevertheless, robust clinical evidence remains limited at present; these therapeutic prospects are largely extrapolated from preclinical/basic studies and require further validation.

Secondly, PCD dysregulation serves as a rich source for biomarker discovery and validation. Molecules associated with specific PCD modes—such as soluble RIPK1/MLKL, PTX3, GSDMD-N-terminal fragments, NETosis derivatives (MPO–DNA complexes, calprotectin), indices of iron metabolism (ferritin, transferrin saturation), copper and copper-binding proteins (ceruloplasmin), and lipid peroxidation products (MDA, 4-HNE)—detected in serum or synovial fluid hold promise for improving RA diagnosis, stratifying disease subtypes, assessing disease activity, predicting responses to targeted therapies, and monitoring treatment efficacy and prognosis. At present, there are no broadly validated, reliable panels for routine clinical use; most signals derive from exploratory cohorts and will need prospective, standardized studies.

Building on the above biomarker and pipeline landscape, current and emerging interventions can be reinterpreted through the lens of PCD modulation, informing rational combinations and patient endotyping. For instance, the efficacy of sulfasalazine may be partially attributable to modulation of ferroptosis susceptibility, while biologics (anti-TNFα, anti-IL-6R) likely exert effects partly by normalizing dysregulated PCD in FLS (eg., suppressing necroptosis/pyroptosis). The anti-RA actions of natural compounds (eg., triptolide, icariin, resveratrol, quercetin) are increasingly linked to their regulation of multiple PCD pathways, providing a mechanistic basis for their use or derivative development. While challenges remain regarding target specificity, pathway complexity, and prospective biomarker validation, strategically targeting dysregulated PCD pathways and deploying associated biomarkers offers substantial promise for advancing personalized and more effective therapeutic strategies in RA.

7 | Conclusions and Future Directions

RA is a complex multifactorial disease involving intricate interactions between various immune cells and cell death pathways. The pathological process of RA includes not only the excessive proliferation of synovial cells and the infiltration of inflammatory cells but also the activation of various forms of PCD. These forms of PCD include apoptosis, pyroptosis, necroptosis, and ferroptosis, which are not isolated events but interconnected and regulated processes that collectively drive the pathogenesis of RA.

Although significant progress has been made in RA treatment, a comprehensive understanding of its complex pathological mechanisms remains to be achieved. Future research should explore the specific roles of different PCD pathways in RA and their interconnections, especially how they collectively regulate inflammatory responses and immune balance. Moreover, developing targeted therapies for emerging drug targets will be an important direction in RA treatment research. By integrating studies on these cell death pathways, new strategies for the diagnosis, treatment, and prevention of RA can be developed.

Author Contributions

Xiaorong Zhi: conceptualization, methodology, writing – original draft, visualization. **Hong Zhu:** conceptualization, writing – review and editing. **Xiaoyan Sun:** writing – review and editing. **Zhaoxia Wang:** writing – review and editing. **Lin Wang:** conceptualization, writing – original draft, writing – review and editing, supervision, management, and coordination responsibility for the research activity planning and execution. **Guanhua Song:** conceptualization, methodology, writing – original draft, writing – review and editing, supervision, management, and coordination responsibility for the research activity planning and execution.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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