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# Need for Greater Attention to Joint Damage in Rhupus Patients: Results from an Ultrasound Study

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** The aim of this study was to evaluate the prevalence of inflammation and bone destruction of hand joints in rhupus patients through ultrasound examination.





**Material/Methods:** Ten rhupus patients and 33 systemic lupus erythematosus (SLE) patients with hand arthropathy were recruited in this single-center study, and the clinical features and ultrasound manifestations of these patients were analyzed.

**Results:** We discovered that rhupus patients were older ( $47.31 \pm 4.35$  years vs.  $38.58 \pm 2.50$  years,  $P=0.040$ ), had longer duration of disease (median 72 months vs. median 12 months,  $P=0.040$ ), had a higher positive rate (70% vs. 10.71%,  $P<0.001$ ), and had higher titers of anti-CCP antibody ( $42.633 \pm 14.520$  vs.  $2.121 \pm 0.970$ ,  $P<0.001$ ) than SLE patients with arthropathy. More importantly, the prevalence rates of synovial hyperplasia (90% vs. 42.42%,  $P=0.008$ ), synovitis (90% vs. 18.18%,  $P<0.001$ ), synovial hyperplasia (70% vs. 10.71%,  $P<0.001$ ), and bone destruction (70% vs. 6.06%,  $P<0.001$ ) were higher in rhupus patients than in SLE patients with arthropathy.

**Conclusions:** Rhupus patients are more prone to develop synovitis, synovial hyperplasia, and bone destruction. Therefore, more attention should be paid to protection of the joints in rhupus patients.

**MeSH Keywords:** **Joint Diseases • Lupus Erythematosus, Systemic • Ultrasonography, Doppler**

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## Background

Rhus syndrome is characterized by both rheumatoid arthritis (RA)-specific arthritis and systemic lupus erythematosus (SLE)-specific antibodies such as anti-dsDNA antibodies and anti-cyclic citrullinated peptide (anti-CCP) antibodies [1]. The concept of "rhus" was proposed by Schur in 1971 [2]. Patients who fulfill both RA and SLE clinical classification criteria are diagnosed with rhus in clinical practice. There is no widely accepted classification standard or diagnosis criteria for rhus [3,4]. Due to differences in classification criteria, the prevalence of rhus in SLE patients ranges from 0.09% to 9.7% [4,5]. Two reports recently observed that the prevalence of rhus was about 1.5% [3,6]. Unfortunately, there is currently no effective strategy to treat rhus syndrome, most of which are based on clinical experience or literature reviews.

Most clinical reports focused on describing the disease characteristics of rhus [3,4] and its pathogenesis [7]. There were also several studies on joint symptoms and bone destruction in SLE patients [8–10]. However, the inflammation and bone destruction of the joints of rhus patients were rarely described.

Therefore, we aimed to assess the prevalence rates of inflammation and bone destruction of the wrist and hand joints in rhus patients as determined by ultrasonography, compared with SLE patients with wrist or hand joint arthropathy.

## Material and Methods

This was a single-center, retrospective study. All patients included in this study visited the First Affiliated Hospital of Guangzhou University of Chinese Medicine from Jan 1, 2015 to May 31, 2019. There were 1231 patients who fulfilled the RA classification, 571 patients fulfilled the SLE classification, and 35 patients fulfilled both RA and SLE classifications. Only 10 of the 35 patients underwent the hand ultrasound test (2 male and 8 female patients, respectively), and these patients were assigned to the rhus group. In 536 SLE patients (excluding 35 rhus patients), 215 had hand joint pain or joint swelling. Thirty-three of the 215 SLE patients underwent the hand ultrasound test (7 male and 26 female patients), and these patients were assigned to the SLE with arthropathy group. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. ZYCEK [2018] 175) and was conducted in accordance with the World Medical Association Declaration of Helsinki (2000). All patients provided signed informed consent.

Inclusion criteria for the rhus with joint arthropathy group were: (1) simultaneously fulfilling the American College of Rheumatology/European League Against Rheumatism

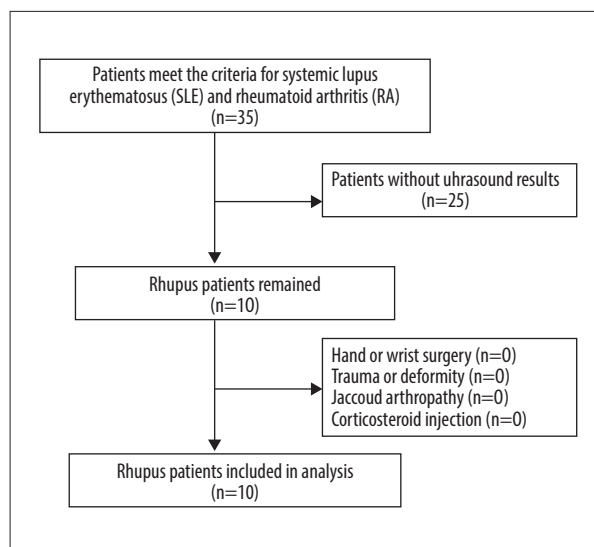


Figure 1. Enrollment of rhus patients.

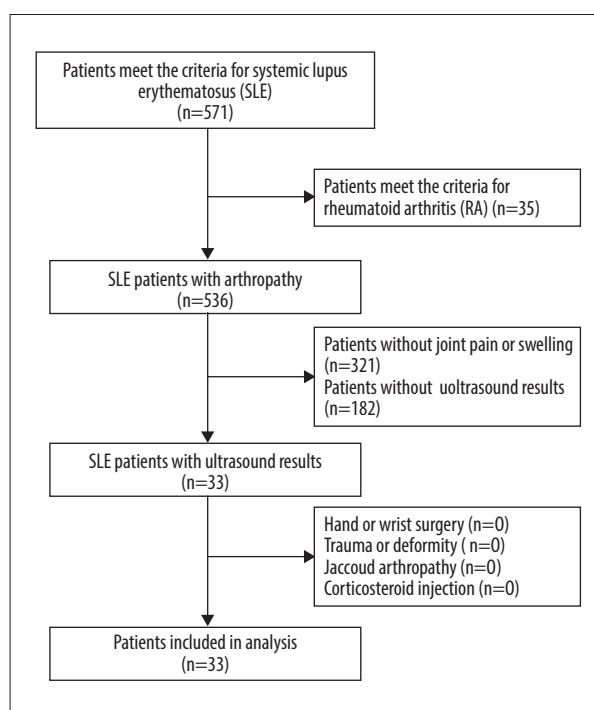


Figure 2. Enrollment of SLE patients with arthropathy.

(ACR/EULAR) 2010 Rheumatoid Arthritis Classification criteria [11] and American College of Rheumatology (ACR) Classification criteria revised for SLE in 2012 [12], and (2) having hand joint pain and/or swelling.

Inclusion criteria for the SLE with arthropathy group were: (1) fulfilling the ACR Classification criteria revised for SLE in 2012 [12], and (2) having hand joint pain and/or swelling. Exclusion criteria for both groups were: history of hand or wrist surgery, trauma, deformity, osteoarthritis, Jaccoud

arthropathy, or corticosteroid injection within the last 6 months before ultrasound study. The enrollment processes are shown in Figures 1 and 2.

## Data collection

### Baseline characteristics and medication use

We collected baseline data on: age (years), onset age (years), sex (male or female), duration of disease (months), and extra-articular manifestations of rhus (cutaneous involvement, Raynaud syndrome, renal involvement, serositis, neuropsychiatric involvement, cytopenia, lung involvement, interstitial lung disease, and pulmonary artery pressure). Medications used were prednisone, methotrexate (MTX), hydroxychloroquine (HCQ), leflunomide (LEF), biologics such as Adalimumab, Etanercept, and *Tripterygium hypoglaucom* hutch (THH, a Chinese herb widely used in treating SLE and RA), mycophenolate mofetil (MMF), and cyclosporine (CsA).

### Laboratory indicators and testing methods

We performed the following tests: blood cell counting and classification, anti-nuclear antibody (ANA), double-stranded DNA (dsDNA), anti-extractable nuclear antibody (anti-ENA), lupus anticoagulant (LAC), anticardiolipin antibody (ACA), C reactive protein (CRP), erythrocyte sedimentation rate (ESR), complementary 3 (C3), complementary 4 (C4), RF (rheumatoid factor), and anti-citrullinated protein antibody (anti-CCP).

ANA was measured by indirect immunofluorescence method, with a normal reference value of negative. dsDNA was measured by enzyme-linked immunosorbent assay (ELISA) method, with a normal reference value of negative. Anti-ENA antibodies were measured by immunoblotting method, with a normal reference value of each antibody of negative. LAC was measured by silica clotting time method, with a normal reference value of 31–44 s. ACA was measured by ELISA method, with a normal reference value of negative. CRP was detected by the nephelometry method with a normal reference value of 0–8 mg/L. ESR was measured by the Westergren method, with a normal reference value of 0–15 mm/h. C3 was measured by scatter turbidimetry method, with a normal reference value of 0.79–1.52 g/L. C4 was measured by scatter turbidimetry method, with a normal reference value of 0.16–0.38 g/L. Anti-CCP was measured by microparticle enzyme-linked immunoassay (MEIA) method, with a normal reference value of 0–5 IU/ml. RF was measured by immunoturbidimetry and latex agglutination, with a normal reference value of negative.

### Ultrasound test

All the recruited patients were tested by high-frequency ultrasound method on both hands, including proximal

interphalangeal (PIP), metacarpophalangeal (MCP), and wrist joints using the HITACHI EZU-MT29-S1 device (Hitachi Medical Corporation, Tokyo, Japan). A rheumatologist blinded to the diagnosis of rhus performed the ultrasonography examinations. Communication between doctors and patients was allowed during the ultrasound test.

The consensus US definition of OMERACT [13] was used for the pathologic changes of ultrasound test in hand joints of patients. Synovial hypertrophy is an abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible. Synovitis is hypoechoic or anechoic thickened tissue with or without fluid. Bone erosion is a visible intra-articular discontinuity of bone surfaces that is visible in 2 perpendicular planes.

## Statistical analysis

Our analysis was performed using Graphpad Prism 7.0 statistical software (La Jolla, CA, USA). Categorical variables are expressed as numbers (percentage), and continuous variables are expressed as mean±standard deviation (SD) or median [interquartile range, IQR]. Chi-square and Fisher's exact test were used to compare qualitative differences between joint groups, while Wilcoxon's test or Mann-Whitney U test was performed to compare parametric variables. All statistical analyses were 2-sided and  $P<0.05$  was considered to be statistically significant.

## Results

### Clinical characteristics of rhus and SLE with joint arthropathy

Overall, 10 rhus and 33 SLE patients with hand arthropathy were included in this study. The mean age of the rhus patients was slightly older than in the SLE patients with joint arthropathy ( $47.31\pm 4.35$  years old vs.  $38.58\pm 2.50$  years old,  $P=0.040$ ). The median disease duration of rhus patients was also slightly longer than in the SLE patients with joint arthropathy (median 72 months vs. median 12 months,  $P=0.040$ ). The 2 groups showed no significant differences in sex (male: female, 2: 8 vs. 7: 26,  $p=0.934$ ) or onset age ( $41.53\pm 4.68$  vs.  $35.58\pm 2.48$ ,  $P=0.083$ ). The extra-articular manifestations of rhus were cytopenia (80%), lung involvement (60%), pulmonary artery pressure (44.44%), interstitial lung disease (40%), cutaneous involvement (10%), renal involvement (10%), and serositis (10%). There were no significant differences ( $p<0.05$ ) between the 2 groups in prevalence of cutaneous involvement, Raynaud syndrome, renal involvement, serositis, neuropsychiatric involvement, cytopenia, lung involvement, interstitial lung disease (ILD), or pulmonary artery pressure (PAH) (Table 1).

**Table 1.** Clinical characteristics of rhus patients and SLE with arthropathy patients.

Clinical manifestations	Rhus	SLE with arthropathy	P value
Age, years, mean±S.D	47.31±4.35	38.58±2.50	0.040*
Gender, male: female	2: 8	7: 26	0.934
Duration of disease, months, median(IQR)	72 (4–192)	12 (1–240)	0.040*
Onset age, years, mean±S.D	41.53±4.68	35.58±2.48	0.083
Cutaneous involvement, n (%)	1/10 (10.00%)	13/33 (39.39%)	0.082
Raynaud Syndrome, n (%)	1/10 (0.00%)	13/33 (39.39%)	0.082
Renal involvement, n (%)	1/10 (10.00%)	12/33 (36.36%)	0.112
Serositis, n (%)	1/10 (10.00%)	5/33 (15.15%)	0.680
Neuropsychiatric involvement, n (%)	0/6 (0.00%)	2/13 (15.38%)	0.310
Cytopenia, n (%)	8/10 (80.00%)	28/33 (84.85%)	0.716
Lung involvement, n (%)	6/10 (60.00%)	12/33 (36.36%)	0.184
ILD, n (%)	4/10 (40.00%)	9/33 (27.27%)	0.443
PAH, n (%)	4/9 (44.44%)	4/28 (14.29%)	0.056

\*  $P < 0.05$ ; SLE – systemic lupus erythematosus; S.D – standard deviation; IQR – interquartile range; ILD – interstitial lung disease; PAH – pulmonary artery pressure. Categorical variables are expressed as number (percentage); continuous variables are expressed as mean±standard deviation (S.D) or median [interquartile range].

### Laboratory characteristics of rhus

All the rhus patients had positive ANA and dsDNA antibody. The rhus patients had lower positive prevalence of total anti-ENA antibodies (70% vs. 96.97%,  $p = 0.011$ ). However, in further analysis, there were no significant differences in the positive rate of anti-Sm, anti-SSA, anti-SSB, anti-Ro52, anti-rRNP, anti-AnuA, anti-AHA, anti-CenpB, or anti-Scl70 antibodies between the 2 groups. There were also no significant differences in the positive incidence of LAC and ACA between the 2 groups.

In the rhus patient group, the levels of CRP (36.471±10.232 mg/L vs. 14.243±2.639 mg/L,  $P = 0.004$ ) and C3 (0.811±0.110 g/L vs. 0.559±0.047 g/L,  $P = 0.020$ ) were significantly higher than in the SLE with arthropathy group. However, there were no significant differences in the levels of ESR and C4 between the 2 groups. Both the positive prevalence (70% vs. 10.71%,  $P < 0.001$ ) and titer of anti-CCP (42.633±14.520 IU/ml vs. 2.121±0.970 IU/ml,  $P = 0.045$ ) in the rhus patient group were higher than in the SLE with arthropathy group.

The titer of RF in rhus patients was higher than in the SLE patients (798.212±653.235 IU/ml vs. 60.624±18.873 IU/ml,  $P = 0.045$ ), but there was no significant difference in the positive prevalence of RF (80% vs. 48.48%,  $P = 0.079$ ) between the 2 groups (Table 2).

### Treatment of rhus with medication

A lower proportion of patients were treated with prednisone in the rhus patient group (50% vs. 93.9%,  $p = 0.001$ ). Prednisone and HCQ were the most frequently used medications in SLE patients with arthropathy (93.97% and 90.1%, respectively). The most frequently used medications in treating rhus patients were MTX (60%) and THH (60%), then prednisone (50%) and HCQ (40%). A few rhus patients were treated with biologics (20%) (Figure 3, Table 3).

### Ultrasound findings in rhus patients

The prevalence rates of synovial hyperplasia, synovitis, and bone erosion in rhus patients were 90%, 90% and 70%, respectively, which were higher than in SLE patients (42.42%, 18.18%, and 6.06%, respectively) (all  $P < 0.05$ ).

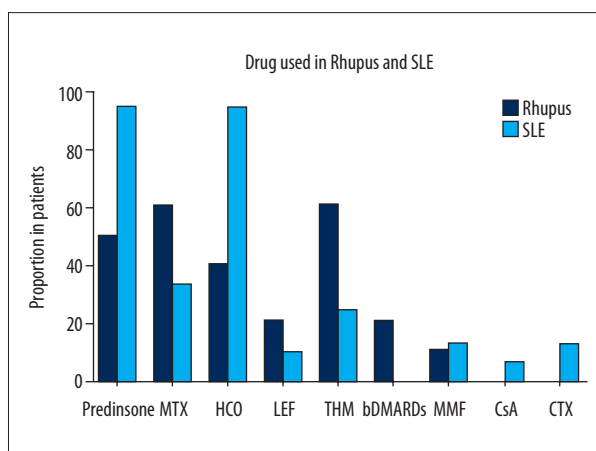
After further analysis, the number of affected joints (regardless of PIP, MCP, or wrist joints) with synovial hyperplasia, synovitis, and bone erosion was much higher in rhus patients than in SLE patients with arthropathy.

In further analysis, we assessed the ultrasound results in various joints. We found there were more PIP, MCP, and wrist joints affected by synovial hyperplasia in rhus patients than in SLE patients, and the same results were found in PIP, MCP, and wrist joints affected by synovitis and bone erosion (Table 4, Figure 4).

**Table 2.** Laboratory manifestations of rhus patients and SLE with arthropathy patients.

Laboratory manifestations	Rhus	SLE with arthropathy	P value
ANA, n (%)	10/10 (100.00%)	33/33 (100.00%)	0.641
ds-DNA, n (%)	10/10 (100.00%)	32/33 (96.97%)	0.578
Anti-ENA antibody, n (%)	7/10 (70.00%)	32/33 (96.97%)	0.011*
Anti-Sm, n (%)	1/10 (10.00%)	9/33 (27.30%)	0.258
Anti-SSA, n (%)	7/10 (70.00%)	21/33 (63.63%)	0.712
Anti-SSB, n (%)	2/10 (20.00%)	8/33 (24.24%)	0.781
Anti-Ro52, n (%)	2/10 (20.00%)	14/33 (42.42%)	0.199
Anti-nRNP, n (%)	1/10 (10.00%)	15/33 (45.50%)	0.042*
Anti-rRNP, n (%)	0/10 (0.00%)	7/33 (21.21%)	0.111
Anti-AnuA, n (%)	5/10 (50.00%)	18/33 (54.55%)	0.801
Anti-AHA, n (%)	2/10 (20.00%)	15/33 (45.50%)	0.149
Anti-CenpB, n (%)	0/10 (0.00%)	1/33 (3.00%)	0.578
Anti-Scl70, n (%)	0/10 (0.00%)	1/33 (3.00%)	0.578
LAC, n (%)	0/5 (0.00%)	9/28 (32.14%)	0.137
ACA, n (%)	1/6 (16.67%)	1/27 (3.70%)	0.216
CRP, mean (SD), mg/L	36.471±10.232	14.243±2.639	0.004*
ESR, mean (SD),mm/h	66±14.72	44.13±4.709	0.068
C3, g/L, mean±SD	0.811±0.110	0.559±0.047	0.020*
C4, g/L, mean±SD	0.139±0.012	0.118±0.013	0.363
RF, n (%)	8/10 (80.00%)	16/33 (48.48%)	0.079
Anti-CCP, n (%)	7/10 (70.00%)	3/28 (10.71%)	<0.001**
RF, IU/ml, mean±SD	798.212±653.235	60.624±18.873	0.045*
Anti-CCP, IU/ml, mean±SD	42.633±14.520	2.121±0.970	<0.001**

LAC – lupus anticoagulant; ACA – anti-cardiolipin antibody; CRP – C reactive protein; ESR – erythrocyte sedimentation rate; RF – rheumatoid factor; anti-CCP – anti-cyclic citrullinated peptide antibody. \* P<0.05; \*\* P<0.001.



**Figure 3.** Proportion of patients in the 2 groups who received steroids, MTX, HCO, LEF, THM, bDMARDs, MMF, CsA, and CTX.

## Discussion

Compared to SLE patients with arthropathy, the rhus patients were slightly older and had a longer disease duration. Similar to our study, Mu et al. [14] found that rhus patients were significantly older than patients with SLE, and the average age of rhus patients was about 45 years old.

RA-like arthritis is an obvious feature of rhus patients [15]. Our results agree with those of Tani et al. [4], showing that

**Table 3.** Prednisone, DMARDs, and biologics used in rhus patients and SLE with arthropathy patients.

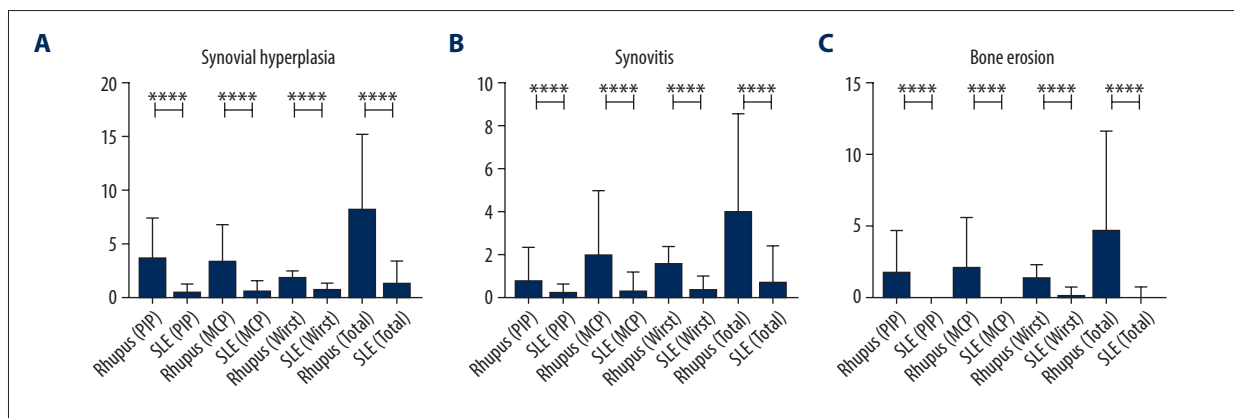
Medication use	Rhus	SLE with arthropathy	P value
Prednisone, n (%)	5/10 (50.00%)	31/33 (93.90%)	0.001*
Biological drugs used, n (%)	2/10 (20.00%)	0/33 (0.00%)	0.009*
MTX, n (%)	6/10 (60.00%)	12/33 (36.40%)	0.275
HCQ, n (%)	4/10 (40.00%)	30/33 (90.10%)	0.002*
LEF, n (%)	2/10 (20.00%)	2/33 (6.00%)	0.226
THH, n (%)	6/10 (60.00%)	8/33 (24.24%)	0.055
MMF, n (%)	1/10 (10.00%)	4/33 (12.12%)	>0.999
CsA, n (%)	0/10 (0.00%)	2/33 (6.00%)	>0.999
CTX, n (%)	0/10 (0.00%)	4/33 (12.12%)	0.558

MTX – methatrexate; HCQ – hydroxychloroquine; LEF – leflunomide; THH – tripterygium hypoglucum hutch; MMF – mycophenolate mofetil; CsA – cyclosporine A; CTX – cyclophosphamide. \* P<0.05.

**Table 4.** Ultrasound results of rhus patients and SLE with arthropathy patients.

Ultrasound result	Rhus	SLE with arthropathy	P value
Synovial hyperplasia, n (%)	9/10 (90.00%)	14/33 (42.42%)	0.008*
Synovitis, n (%)	9/10 (90.00%)	6/33 (18.18%)	<0.001**
Bone erosion, n (%)	7/10 (70.00%)	2/33 (6.06%)	<0.001**

\* P<0.05; \*\* P<0.001.



**Figure 4.** The number of affected hand joints in the 2 groups assessed by ultrasound testing, showing that rhus patients had more affected joints (including PIP, MCP, and wrist) than SLE patients. (A) Synovial hyperplasia. (B) Synovitis. (C) Bone erosion.

the prevalence rates of synovial hyperplasia, synovitis, and bone erosion in hand joints (including PIP, MCP, and wrist joints) in rhus patients were much higher, and there were many more joints affected with synovial hyperplasia, synovitis, and bone erosion in rhus patients than in SLE patients. According to the ultrasound results, the affected joints in rhus patients had characteristics of RA, which can cause disability and lower the quality of life of rhus patients. Unlike

previous research, we found that extra-articular manifestations of rhus patient were not significantly different from those of SLE patients with arthropathy.

Some studies showed that major SLE characteristics of rhus patients were skin involvement, blood involvement, and serositis involvement [16]. However, the prevalence of skin involvement, serositis involvement, and kidney involvement was

lower in our study, which may be due to ethnic differences in the various study cohorts. We also found that kidney involvement and nerve involvement were less common, and our findings agree with previous studies [4,5].

Patients with rhus had higher concentrations of CRP than in SLE patients with arthropathy, and other studies have reached the same conclusion [3,4]. Patients with rhus syndrome have been reported to have ANA, dsDNA, RF, and anti-CCP antibodies [16]. In the present study, the positive rates of anti-CCP and titer of anti-CCP were significantly higher in rhus patients than in the SLE with arthropathy group, which agrees with some previous studies [17,18]. Anti-CCP antibodies have been shown to play an essential diagnostic role in patients with rhus symptom and may increase the risk of erosive arthritis in RS patients [19].

In our study, the most frequently used medications in treating rhus patients were MTX, THH, prednisone, and HCQ. Corticosteroids and DMARDs are often used to prevent erosive arthritis in rhus patients [16]. A few studies observed the effect of biologics on rhus. A recent study demonstrated that TNFi was effective and safe in treating rhus, with a follow-up period of 112 months [20]. A pilot study found that

Rituximab was a potential option in treating refractory rhus [21]. Abatacept was also effective in treating MTX-failed rhus patients [22]. In that study, 2 in 10 patients were treated with Etanercept-Yisaipu, which is an Etanercept biomimic. Unfortunately, they were not followed-up. Clinical researchers recommend caution in use of biologics [23], although a few studies showed that biologics were effective in treating rhus patients with joint arthropathy. Unfortunately, only 10 rhus patients were included in the present study. In addition, this was a retrospective, cross-sectional, single-center study. Further longitudinal follow-up and multi-center studies are warranted.

## Conclusions

In conclusion, rhus is a systemic syndrome that combines the characteristics of RA and SLE. Rheumatologists should pay much more attention to protecting the joints of these patients.

## Conflict of interests

None.

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