ISSN 1756-1841 VOLUME 24 NUMBER 12 2021

International Journal of Rheumatic Diseases

Official journal of the Asia Pacific League of Associations for Rheumatology (APLAR)

WILEY

International Journal of Rheumatic Diseases

APL.JEB.May21

WILEY

For submission instructions, subscription and all other information visit http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1756-185X

View this journal online at wileyonlinelibrary.com/journal/apl

International Journal of Rheumatic Diseases

Volume 24 | Number 12 | December 2021

Contents

Received: 20 October 2021 | Revised: 25 October 2021 | Accepted: 27 October 2021

DOI: 10.1111/1756-185X.14237

International Journal of Rheumatic Diseases WILEY

EDITORIAL

Is a fat thumb another sign of psoriatic arthritis?

Which arthritis is it?

It's psoriatic arthritis!

Whether it is teaching on arthritis or in your day-to-day practice and you are pondering as to which arthritis it is, it reminds me of the Christmas pantomime, except the response will be "It's psoriatic arthritis!" For psoriatic arthritis (PsA) is one of the truly great rheumatology mimics, with presentations resembling gout, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis.[1,2] If a patient has an inflammatory arthritis in an exam, I teach my students they have at least 1 answer, as it could be PsA. The presence of psoriasis or psoriatic nail change, or a family history of psoriasis is a major clue, particularly in the presence of one of the Moll and Wright classical patterns.[1] The CASPAR classification criteria for PsA[3] when applied to patients with musculoskeletal inflammation performs well for diagnosis. But mimics work both ways and psoriasis is common, and therefore commonly co-exists with its dupe arthritis.

In this issue of the *Journal* Mathew and colleagues from Vellore, India use low-field magnetic resonance imaging (MRI) of the thumb interphalangeal joint (IPJ) to interrogate clinical swelling as a proposed "distinct" and diagnostic entity in PsA.[4] Danda et al originally proposed this in 2000 after noting disproportionate swelling of the thumb IPJ of patients with psoriasis. They subsequently examined over 4000 patients with various arthropathies noting thumb IPJ swelling in 29% of psoriatic arthropathy patients compared to 0.28% of non-PsA spondyloarthropathy, 0.18% of degenerative arthropathy and 0.24% of rheumatoid arthritis patients.[5] The thumb IPJ swelling was distinct from dactylitis and periostitis, and while not sensitive was very specific (99.7%) for PsA. Involvement of the thumb IPJ is well recognized by clinicians and is commonly documented in illustrations or images on the subject of PsA, see Figure 1 from the *Lancet* series. However, the Vellore group have taken their observation and investigated its diagnostic utility in a reproduction cohort inclusive of imaging.

Their MRI study was a retrospective analysis of subjects undergoing MRI hand for any reason, with attendant bias. In this smaller cohort 36% of the PsA subjects had clinically detectable thumb IPJ swelling and a much larger 11% of the rheumatoid arthritis subjects which will impact on the high specificity originally reported. Among the 62 psoriasis patients not fulfilling CASPAR criteria but still warranting an MRI of the hand, clinical IPJ swelling was present in 6%, and extra data as to the place of careful thumb IPJ examination as a diagnostic clue in this group would have been informative.

I don't understand why a particular joint is affected by a systemic inflammatory process and not its nearby neighbor. Mathew et al reflects on the proximity of the nail enthesis organ to the thumb IPJ and considers the IPJ analogous to the distal interphalangeal (DIP) joint of other digits and 1 of the classical patterns of PsA. While microtrauma secondary to mechanical stress may occur at the thumb IPJ, and the Nordic study of psoriatic arthritis mutilans noted thumb IPJ involvement as the most common upper limb site, but it was also most commonly in the left thumb and therefore presumably more often the non-dominant hand and less prone to stress than the dominant (although this was not reported).[6] The original paper by Danda et al had few DIP joint arthritis patients, but noted none of them had thumb IPJ swelling which might be expected if it was a combination of proximity to the nail enthesis organ and microtrauma.

The Outcome Measures in Rheumatology (OMERACT) PsA MRI scoring system definitions of synovitis, tenosynovitis, and bone marrow edema were adapted for the thumb IPJ, and Mathew et al give due consideration to the limitations of low-field imaging without contrast enhancement and imaging planes that accommodate fingers rather than thumbs. Their preliminary results suggest that tenosynovitis rather than synovitis underpins the distinct clinical finding of IPJ swelling in PsA. The presence of any of the 3 MRI detectable changes

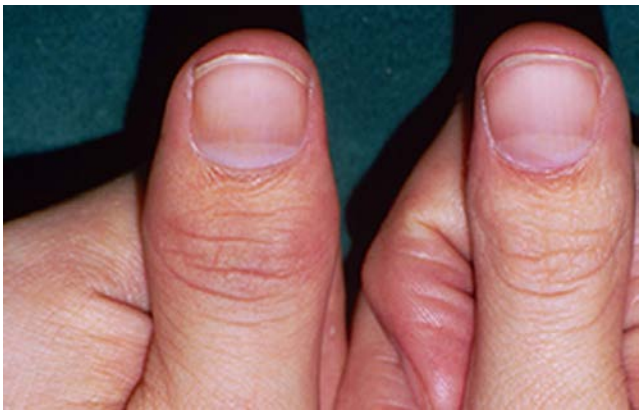


FIGURE 1 Psoriatic arthritis thumb interphalangeal joint swelling ?Danda's sign. Reproduced with permission from Psoriatic arthritis series. *Lancet* vol 391 (10136), 2 June 2018, www.thelancet.com/series/psoriatic-arthritis. Copyright Elsevier 2018

largely mirrored the clinical assessment undertaken, suggesting that clinically detectable findings rather than subclinical disease was being detected by their imaging. High-field MRI with contrast is designed to be sensitive and detect subclinical change. A study using these techniques in early RA reported thumb IPJ tenosynovitis in 38% of patients,[7] which is much higher than the 4% found by Mathew et al. The degree to which this was clinical or subclinical cannot be determined, but highlights the impact of technical differences across studies of different populations.

The authors have found prominent thumb IPJ swelling to be more prevalent in PsA than other inflammatory arthropathies that may be part of the differential diagnosis. Their 3.2 risk ratio of MRI global inflammation at the thumb IPJ in PsA comparative to undifferentiated inflammatory arthritis is a starting point, as this may be a more serious confounder than rheumatoid arthritis. As to whether "Danda's sign" is unique or distinct enough to be highly indicative of PsA requires analysis of other clinical cohorts, preferably with concomitant high-quality imaging to provide a clinicopathologic correlate.

Kevin Pile

Department of Medicine, Campbelltown Hospital, Western Sydney University, Sydney, New South Wales, Australia

Correspondence
Kevin Pile, Department of Medicine, Campbelltown Hospital, Western Sydney University, Sydney, New South Wales 2560, Australia.
Email: kevin.pile@health.nsw.gov.au

ORCID
Kevin Pile https://orcid.org/0000-0003-3815-7698

REFERENCES

1. Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum*. 1973;3:55-78.
2. Veale D, Rogers S, Fitzgerald O. Classification of clinical subsets in psoriatic arthritis. *Br J Rheumatol*. 1994;33:133-138.
3. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54:2665-2673.
4. Mathew AJ, Ganapati A, Panwar J, Koshy V, Desai A, Danda D. Magnetic resonance imaging evidence of inflammation at interphalangeal joint of thumb. *Int J Rheum Dis*. 2021;24:1467-1472.
5. Danda D, Cherian AM, Jayaseelan L. Disproportionate swelling of interphalangeal joint of thumb: is it unique to psoriatic arthropathy? *J Ind Rheum Assoc*. 2000;8:1-4.
6. Gudbjornsson B, Ejstrup L, Gran JT, et al. Psoriatic arthritis mutilans (PAM) in the Nordic countries: demographics and disease status. The Nordic PAM study. *Scand J Rheumatol*. 2013;42:373-378.
7. Mo YQ, Yang ZH, Wang JW, et al. The value of MRI examination on bilateral hands including proximal interphalangeal joints for disease assessment in patients with early rheumatoid arthritis: a cross-sectional cohort study. *Arthritis Res Ther*. 2019;21:279-291.

Received: 18 March 2021 | Revised: 7 August 2021 | Accepted: 9 August 2021

DOI: 10.1111/1756-185X.14206

REVIEW

International Journal of Rheumatic Diseases | WILEY

Prevalence and risk factors of systemic sclerosis-associated interstitial lung disease in East Asia: A systematic review and meta-analysis

Meihua Qiu[1] | Xueyuan Nian[2] | Lingling Pang[1] | Pengfei Yu[1] | Shenchun Zou[1]

[1]Department of Respiratory and Critical Care Medicine, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, Yantai, China

[2]Department of Gastroenterology, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, Yantai, China

Correspondence
Pengfei Yu and Shenchun Zou, Department of Respiratory and Critical Care Medicine, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, 20 Yuhuangding East Road, Yantai, Shandong 264200, China.
Email: huxi901013@163.com (P.Y); ytyhdpccm@163.com (S.Z)

Funding information
the Science and Technology Program of Yantai City, Grant/Award Number: 2020YD024

Abstract

Objective: Interstitial lung disease (ILD) is a common and potentially life-threatening complication for individuals with systemic sclerosis (SSc). The purpose of this study was to complete a systematic review and meta-analysis on prevalence and risk factors of SSc-ILD in East Asia.

Methods: Medline, EMBASE, and Cochrane Library were searched up to January 22, 2021. The Reporting of Observational Studies in Epidemiology (STROBE) statement was applied to access the methodological quality of the eligible studies. Study characteristics and magnitude of effect sizes were extracted. Then, we calculated the pooled prevalence, weighted mean differences (WMDs), pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs), and performed subgroup analysis, sensitivity analysis, and publication bias with Egger's test.

Results: Twenty-seven of 1584 articles were eligible and a total of 5250 patients with SSc were selected in the meta-analysis. The pooled prevalence of SSc-ILD in East Asia was 56% (95% CI 49%-63%). The SSc-ILD prevalence was higher in China (72%) than in Japan (46%) and Korea (51%). Longer disease duration (WMD = 1.97, 95% CI 0.55-3.38), diffuse SSc (OR = 2.84, 95% CI 1.91-4.21), positive anti-topoisomerase I antibody (ATA) (OR = 4.92, 95% CI 2.74-8.84), positive anti-centromere body antibody (ACA) (OR = 0.14, 95% CI 0.08-0.25), positive anti-U3 ribonucleoprotein (RNP) antibody (OR = 0.17, 95% CI 0.04-0.66), and higher erythrocyte sedimentation rate (ESR) (WMD = 6.62, 95% CI 1.19-12.05) were associated with SSc-ILD in East Asia.

Conclusion: Through this systematic review and meta-analysis, we found that ILD occurs in up to approximately 56% of patients with SSc in East Asia. Longer disease duration, diffuse SSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and higher ESR were risk factors for SSc-ILD.

KEYWORDS

interstitial lung disease, meta-analysis, prevalence, risk factor, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue, characterized by microvascular damage, immune dysfunction, and fibrosis of multiple organs.[1] It is a rare disease, with an estimated global prevalence of 3-24 per 100 000.[2] SSc is generally classified into two categories based on the extent of skin sclerosis: limited cutaneous SSc (lSSc) and diffuse cutaneous SSc (dSSc).[3] The causes of death in individuals with SSc have dramatically changed over the past 30 years.[4,5] Interstitial lung disease (ILD) is currently the leading causes of death in patients with SSc, but reported prevalence of ILD in patients with SSc ranges from 25% to 90%, depending on the subtype of SSc and the criteria used to define ILD in different countries.[6] SSc-associated interstitial lung disease (SSc-ILD) has a heterogeneous clinical presentation and disease course, and providing a prognosis for SSc-ILD is challenging. High-resolution computed tomography (HRCT) is a high-sensitivity diagnostic method useful for early detection of ILD complications in patients with SSc, commonly finding nonspecific interstitial pneumonitis and usual interstitial pneumonitis. Furthermore, the risk factors in patients with SSc-ILD remain controversial. To address these issues, this systematic review and meta-analysis was performed to identify the prevalence and potential risk factors for SSc-ILD in East Asia.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines throughout this review.[7] We searched Medline, EMBASE, and Cochrane databases, the Cochrane Library (the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials [CENTRAL]) through to January 22, 2021. Databases were searched and data were abstracted by two authors working independently. We used medical subject headings (MeSH) terms, EMBASE subject headings (EMTREE), and text words related to study population to finish the search. The search terms used in Medline were: ((((systemic sclerosis[MeSH Terms]) AND (systemic sclerosis[Title/Abstract])) OR ((scleroderma[MeSH Terms]) AND (scleroderma[Title/Abstract]))) AND ((((interstitial lung disease[MeSH Terms]) OR (diffuse parenchymal lung disease)) OR (interstitial pneumonia)) OR (interstitial pneumonitis))) AND ((incidence[Title/Abstract] OR prevalence[Title/Abstract] OR epidemiology[Title/Abstract]) OR (risk factor[Title/Abstract] OR predictor[Title/Abstract] OR relate[Title/Abstract] OR associate[Title/Abstract] OR correlation[Title/Abstract])). The search terms used in EMBASE were (('systemic sclerosis'/exp OR 'systemic sclerosis') AND 'systemic sclerosis':ab,ti) AND (('interstitial lung disease'/exp OR 'interstitial lung disease') OR ('diffuse parenchymal lung disease'/exp OR 'diffuse parenchymal lung disease') OR ('interstitial pneumonia'/exp OR 'interstitial pneumonia')) AND ((incidence OR prevalence OR epidemiology OR 'risk factor' OR predictor OR relate OR associate OR correlation). mp. (mp = title, abstract)). The search terms used in CENTRAL were (systemic sclerosis) [Title/Abstract/keyword] AND ((interstitial lung disease) or (interstitial pneumonia)).

The reference lists of eligible studies and relevant review articles were also hand-searched to find additional reports.

2.2 | Eligibility criteria

Two authors independently evaluated each study for eligibility, sequentially reviewing the title, abstract, and full text of each publication. The inclusion criteria were: (a) studies on SSc patients with ILD—variable criteria were used for the diagnosis of ILD, including findings on CT and/or HRCT; HRCT and pulmonary function tests; and a combination of clinical presentation, pulmonary function tests, and HRCT findings; (b) studies reporting or providing data for calculating the SSc-ILD prevalence, and/or investigating risk factors for SSc-ILD; (c) observational studies; (d) the sample size of study more than 30; and (e) the area of study belongs to East Asia. The exclusion criteria were: (a) case reports, editorials, letters, reviews articles, and conference proceedings; (b) irrelevant to study topic; and (c) duplicated publications. If SSc patients were overlapping between two studies, the study with the largest samples size was prioritized in the analysis. Any uncertainties or disagreements between two authors were resolved by discussions and consensus.

2.3 | Data extraction and study quality assessment

Two authors independently extracted data from included articles based on a predefined data extraction form. Extracted data included first author's name, year of publication, study location, study design, number of SSc patients, number of ILD patients, demographic features of participants, SSc-ILD prevalence, classification criteria of SSc, the diagnostic method of ILD, risk factors for SSc-ILD. The methodological quality of study was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, with a checklist of 22 terms.[8] Studies were of high quality if scores were 17 or more. Two investigators assessed the quality of the studies through consultations to reach consensus.

2.4 | Statistical analysis

All statistical analyses were performed using STATA software (version 13; StataCorp, College Station, TX, USA). The prevalence of SSc-ILD was log-transformed according to the Shapiro-Wilk test. Risk factors of ILD in SSc patients in more than one of the selected studies were quantified by weighed mean differences (WMDs) with 95% confidence intervals (CIs) for continuous variables and pooled odd ratios (ORs) with 95% CIs for categorical variables. The results from the fixed-effect model were presented only when there was no heterogeneity between studies; otherwise, the results from the

random-effects model were presented. Heterogeneity between studies was assessed using I^2 statistics and statistical significance was considered with a P value of less than 0.05.[9] Forest plots were used to display the results from the individual studies and the pooled estimates. We also performed subgroup analysis stratified by region, study quality, publication year, and SSc criteria to investigate heterogeneity. Sensitivity analysis was conducted by sequentially omitting individual studies. The potential for publication bias was evaluated by Egger test if five or more studies were available for meta-analysis.[10] If combining data were deemed inappropriate, the results were reported qualitatively (because of the small number of studies or substantial clinical or methodological diversity). P values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Search strategy

A total of 1584 reports were identified through Medline, EMBASE, and Cochrane Central Register of Controlled Trials. After excluding 163 duplicates, 803 reports of ineligible types (consisting of 633 conference proceedings, 149 review articles or case reports, and 21 editorials or letters) and 560 irrelevant articles, the remaining 58 reports were screened as full texts. Out of these, 31 reports were excluded for no data on prevalence of SSc-ILD in 11 articles and no data on risk factors of SSc-ILD in 20 articles. Finally, 27 articles were eligible for this meta-analysis and review (Figure 1).[11-36]

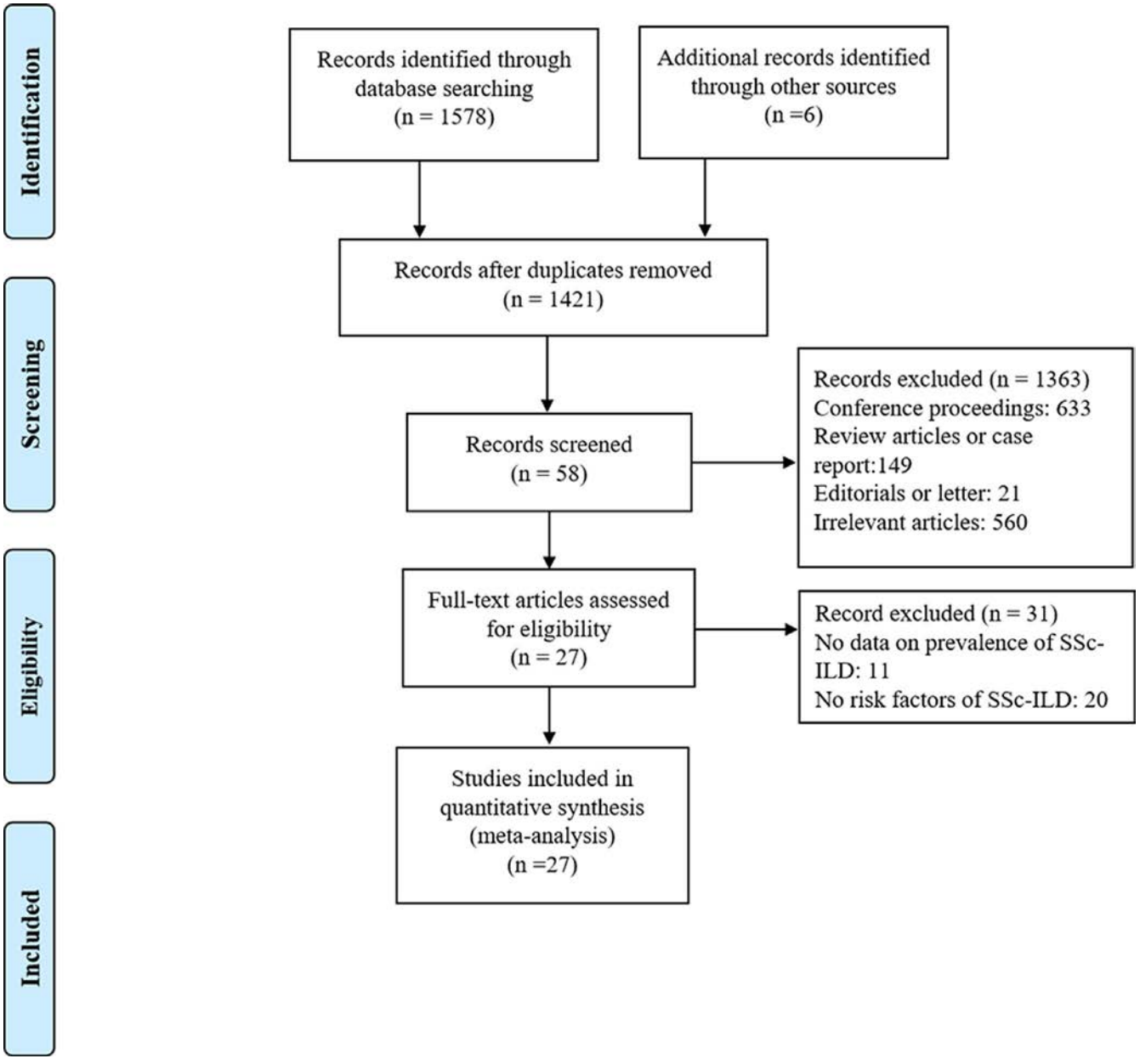


FIGURE 1 The Study flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the studies for the prevalence of SSc-ILD

Study	Design	Country	No. of SSc patients	Age, y	Female (%)	No. with ILD	SSc Classification criteria	ILD diagnosis methods	STROBE checklist
Kim 2010	Cohort study	Korean	230	43.7 ± 14	89.1	134	1980 ACR criteria	Chest radiography or HRCT	17/22
Won-Moon 2018	Cohort study	Korean	751	48.9 ± 13.3	86.7	396	1980 ACR criteria	Chest radiography or HRCT	19/22
Jung 2018	Cross-sectional study	Korean	108	50.1 ± 13.5	92.2	43	1980 ACR criteria	HRCT	16/22
Ooi 2003	Cross-sectional study	China	45	48.5 ± 13.4	88.9	39	1980 ACR criteria	HRCT	15/22
Mok 2008	Cross-sectional study	China	43	47.7 ± 13.0	88.4	37	1980 ACR criteria	HRCT	14/22
Wang 2013	Cross-sectional study	China	419	NA	83.1	327	1980 ACR criteria or have at least three out of five CREST features	HRCT	17/22
Hu 2018	Cohort study	China	448	42.8 ± 12.1	90.4	382	2013 ACR/EULAR criteria	HRCT	18/22
Li 2018	Cohort study	China	201	41.6 ± 13.5	91	148	1980 ACR criteria	Chest X-ray and/or CT	19/22
Liu 2019	Cross-sectional study	China	320	48.2 ± 12.92	86.6	202	2013 ACR/EULAR criteria	HRCT	15/22
Zhang 2020	Cross-sectional study	China	169	58 ± 14.7	68.6	92	2013 ACR/EULAR criteria	Pulmonary function tests and HRCT scans	19/22
Zheng 2020	Cross-sectional study	China	31	51 ± 13	87	21	2013 ACR/EULAR criteria	Chest radiography or HRCT	20/22
Zhou 2020	Cross-sectional study	China	204	52.8 ± 12.9	77.9	129	1980 ACR criteria or 2013 ACR/EULAR criteria	HRCT and pulmonary function	18/22
Ji 2018	Cross-sectional study	China	71	52.59 ± 12.77	91.5	45	1980 ACR criteria or 2013 ACR/EULAR criteria	HRCT	17/22
Kuwana 1994	Cohort study	Japan	275	41.7	88.7	151	1980 ACR criteria	Chest radiograph	15/22
Sato 2000	Cross-sectional study	Japan	45	50	88.9	12	1980 ACR criteria	Chest radiogram and HRCT	15/22
Hamaguchi 2007	Cohort study	Japan	203	46 ± 15	85	89	1980 ACR criteria	Chest radiogram and HRCT	19/22
Ashida 2007	Cohort study	Japan	350	52	72	117	1980 ACR criteria	Chest radiogram and HRCT	15/22
Hashimoto 2011	Cohort study	Japan	405	47 ± 0.7	92.8	204	1980 ACR criteria	Chest radiographs or by computed tomography	19/22

(Continues)

TABLE 1 (Continued)

Study	Design	Country	No. of SSc patients	Age, y	Female (%)	No. with ILD	SSc Classification criteria	ILD diagnosis methods	STROBE checklist
Odani 2012	Cohort study	Japan	149	51 ± 13.6/41 ± 12	85.9	81	1980 ACR criteria	HRCT	19/22
Komura 2008	Cross-sectional study	Japan	63	55	85.7	27	1980 ACR criteria	Chest radiogram and HRCT	15/22
Tomiyama 2016	Cohort study	Japan	139	49.1 ± 15.1	81.3	66	2013 ACR/EULAR criteria	HRCT	17/22
Kawashiri 2018	Cohort study	Japan	60	64 (57-69)	93.3	24	2013 ACR/EULAR criteria	HRCT	17/22
Taniguchi 2018	Cross-sectional study	Japan	56	59 (51.5-69)	92.9	33	2013 ACR/EULAR criteria	HRCT	17/22
Aozasa 2020	Cohort study	Japan	43	57 (45-71)	88.4	22	2013 ACR/EULAR criteria	NA	15/22
Matsuda 2020	Cohort study	Japan	198	55.4 ± 15.5	89.4	87	2013 ACR/EULAR criteria	HRCT	20/22
Kubo 2020	Cross-sectional study	Japan	79	61.4 ± 18.4	88.6	37	1980 ACR criteria or 2013 ACR/EULAR criteria	CT	16/22
Sekiguchi 2020	Cohort study	Japan	145	63.1 ± 1	83.4	61	2013 ACR/EULAR criteria	Clinical symptoms, physical examination findings and HRCT findings	17/22

Abbreviations: ACR, American College of Rheumatology; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; EULAR, European league against rheumatism; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

3.2 | Study characteristics

The characteristics of the included study are shown in Table 1. The 27 studies included 14 retrospective cohort studies and 13 cross-sectional studies. The studies were from three different countries (Japan, Korea, and China). The majority of studies took place in Japan (n = 14),[24-37] followed by China (n = 10),[14-23] and Korea (n = 3).[11-13] Fourteen studies only used the 1980 American College of Rheumatology (ACR) diagnosis of SSc[38] and 10 studies only used the 2013 ACR/European League Against Rheumatism (EULAR) diagnosis criteria of SSc.[39] Three studies used the 1980 ACR or 2013 ACR/EULAR diagnosis criteria.[22,35] In one study, SSc patients either met the 1980 ACR criteria or had at least three out of five CREST features (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) with sclerodactyly being mandatory.[17] The methodological quality of each included study was assessed by the STROBE criteria. Sixteen studies were generally of good quality with a score of at least 17.

3.3 | Meta-analysis of SSc-ILD prevalence

There was a total of 5250 individuals with SSc in the included studies, with 3007 SSc-ILD patients. The prevalence of SSc-ILD ranged from 26.7% to 86%. The pooled SSc-ILD prevalence was 56% (95% CI 49-63) (Figure 2), which was stable in the sensitivity analysis (Figure 3).[11-37] Heterogeneity across studies was high (I^2 = 96.1%). There were significant differences in the prevalence of SSc-ILD for subgroups stratified by region, study quality, SSc classification criteria, and publication year (Table 2). The SSc-ILD prevalence was higher in China (72%) than in Japan (46%) and Korea (51%). There was a higher SSc-ILD prevalence in studies with STROBE checklist score of at least 17 than in those with a STROBE checklist score below 17. Further, SSc-ILD prevalence was higher in studies using two criteria than in those only using 1980 ACR criteria and only using 2013 ACR/EULAR criteria. Furthermore, SSc-ILD prevalence was lower in studies published before 2013 than in those published

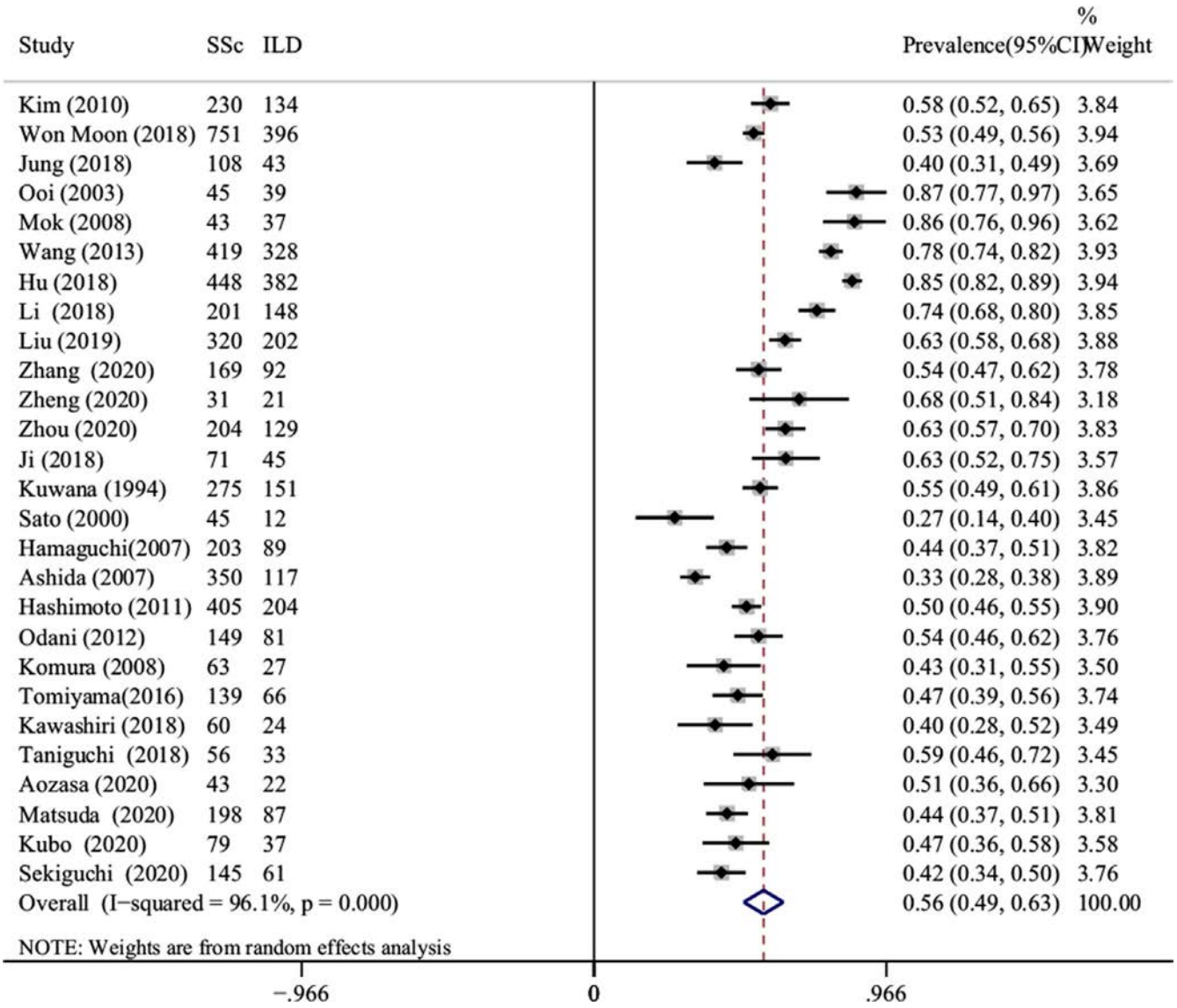


FIGURE 2 Forrest plots of SSc-ILD prevalence. SSc-ILD, systemic sclerosis-associated interstitial lung disease [Colour figure can be viewed at wileyonlinelibrary.com]

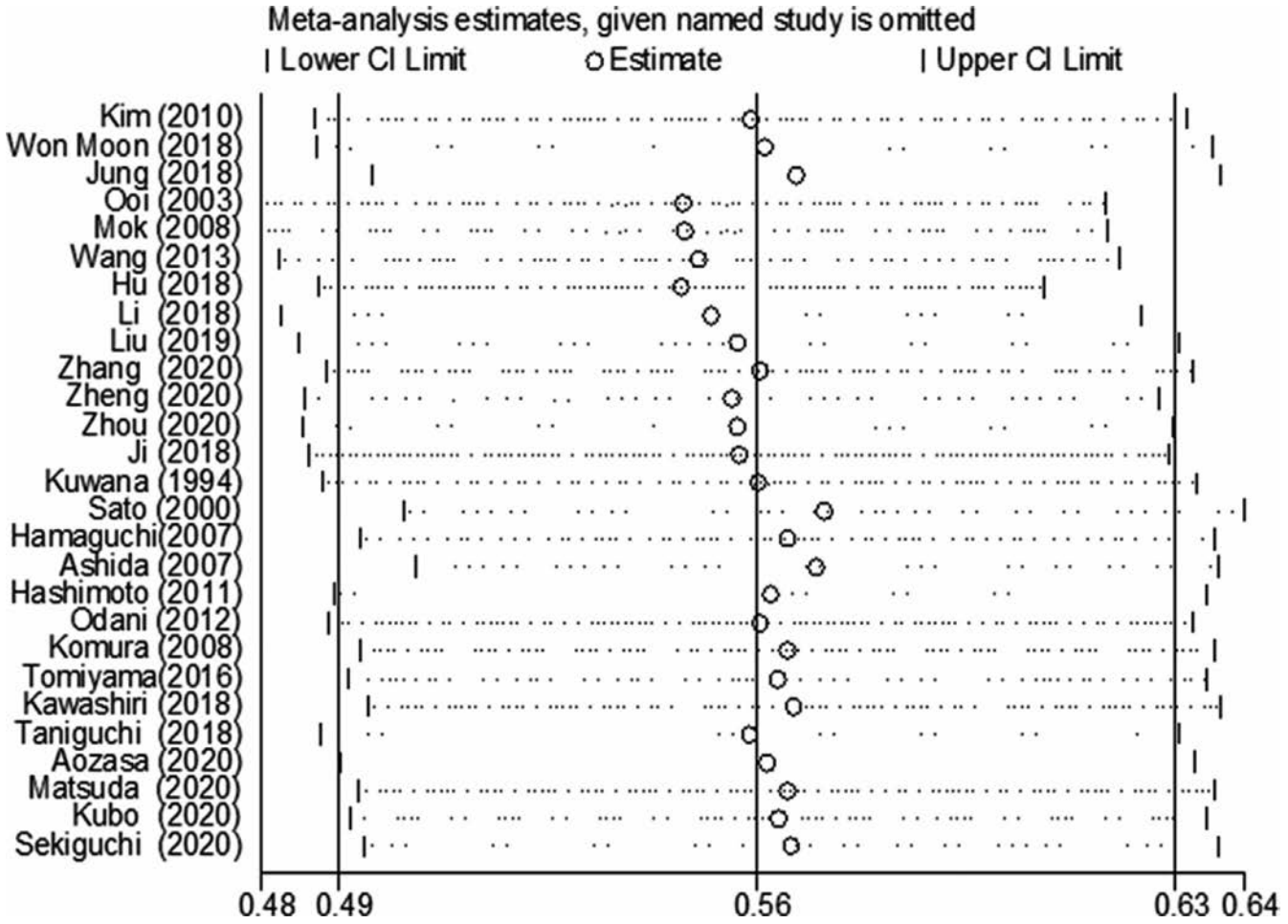


FIGURE 3 Sensitivity analysis of SSc-ILD prevalence. SSc-ILD, systemic sclerosis-associated interstitial lung disease

during 2013-2020. There was no publication bias among the 27 studies by the Egger test ($t = -1.84$, $P = 0.08$) (Figure S1A).

3.4 | Meta-analysis of risk factors for SSc-ILD

We evaluated the potential risk factors for SSc-ILD in 10 studies with 1795 SSc patients in East Asia.[12,17,20,21,23,24,30,31,37,40] The following 15 risk factors appearing in more than one study were selected in the meta-analysis: disease duration, dSSc, anti-topoisomerase I antibody (ATA), anti-centromere body antibody (ACA), anti-U3 ribonucleoprotein (RNP) antibody, digital ulcer, age, male sex, antinuclear antibody (ANA), anti-U1 RNP antibody, anti-Th/To antibody, Raynaud phenomenon, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-ribonucleic acid polymerases (RNAP). SSc-ILD patients had a longer disease duration than SSc patients without ILD (WMD = 1.97, 95% CI 0.55-3.38).[12,21,23] Diffuse SSc (OR = 2.84, 95% CI 1.91-4.21),[12,20,21,23,30] positive ATA (OR = 4.92, 95% CI 2.74-8.84),[12,17,20,21,23,24,30,31,37,40] positive ACA (OR = 0.14, 95% CI 0.08-0.25),[12,17,20,21,23,24,30,31,37] positive anti-U3 RNP antibody (OR = 0.17, 95% CI 0.04-0.66),[23,37] and higher ESR (WMD = 6.62, 95% CI 1.19-12.05)[12,21,23] were associated with ILD in SSc patients (Figure 4A-F). There was no publication bias among studies about dSSc by Egger test ($t = 0.29$, $P = 0.79$), about ATA by Egger test ($t = 1.39$, $P = 0.20$), or about ACA by Egger test ($t = 1.45$, $P = 0.19$) (Figure S1B-D). However, age (WMD = 3.39, 95% CI −1.54 to 8.31),[12,20,21,23,30] male sex (OR = 1.31, 95% CI 0.83-2.06),[12,20,21,23,30] Raynaud phenomenon (OR = 0.68, 95% CI 0.30-1.54),[12,21,23,30] digital ulcer (OR = 1.79, 95% CI 1.00-3.20),[12,29] CRP (WMD = 0.98, 95% CI 0.00-1.95),[12,23] positive ANA (OR = 1.6, 95% CI 0.62-4.17),[12,20,21] positive anti-U1 RNP antibody (OR = 0.98, 95% CI 0.69-1.40),[17,21,23,24,30,31,37] positive anti-Th/To antibody (OR = 0.35, 95% CI 0.09-1.31),[23,37] and positive anti-RNAP (OR = 0.49, 95% CI 0.23-1.03)[17,23,31,37] were not associated with ILD in SSc patients (Figure S2A-I). There was no publication bias in the studies about age by the Egger's test ($t = -0.43$, $P = 0.70$), about male sex by the Egger's test ($t = 1.55$, $P = 0.33$), and about anti-U1 RNP by the Egger's test ($t = 1.35$, $P = 0.24$) (Figure S3A-C).

4 | DISCUSSION

To our knowledge, this is the first meta-analysis of the prevalence and risk factors in SSc patients in East Asia. We showed that the pooled SSc-ILD prevalence was 56% (95% CI 49%-63%). Moreover, we identified six risk factors associated with SSc-ILD: longer disease duration, dSSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and

TABLE 2 Subgroup analysis for the prevalence of SSc-ILD

Subgroups	No. studies	ILD/total patients	I^2 (%)	*P* value	Prevalence (%)	95% CI
Overall prevalence	27	3007/5250	96.1	<0.05	56	49-63
Region						
Korea	3	573/1089	80.8	<0.05	51	43-59
China	10	1424/1951	92.2	<0.05	72	65-79
Japan	14	1011/2210	77	<0.05	46	41-50
STROBE checklist						
Score ≥17	17	2374/3819	96.3	<0.05	58	50-65
Score <17	10	633/1342	95.1	<0.05	53	41-65
Classification criteria						
1980 ACR criteria	13	1478/2868	94.7	<0.05	54	46-52
2013ACR/EULAR criteria	10	990/1609	96.7	<0.05	55	43-68
1980 ACR or other[a]	4	539/773	92.2	<0.05	64	50-77
Publication year						
Before 2013	10	891/1808	94.7	<0.05	54	44-64
2013-2020	17	2116/3442	95.9	<0.05	56	49-63

Abbreviations: ACR, American College of Rheumatology; CI, confidence intervals; EULAR, European league against rheumatism; ILD, interstitial lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

[a]Other criteria: have at least out of five CREST features or the 2013 ACR/EULAR criteria; CREST: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.

higher ESR. The knowledge of risk factors for ILD, which are composed of clinical information that is easily accessible in daily clinical practice, will be of great help in the management of individuals with SSc.

Interstitial lung disease was a common complication in SSc patients. In our meta-analysis, the SSc-ILD prevalence was 56% in East Asia. However, the SSc-ILD prevalence remains controversial, which is probably due to the discrepancies in study region, SSc classification criteria, and publication year. The SSc-ILD prevalence was stable in sensitivity analysis, suggesting that the conclusion is robust. There was great variation in reported prevalence estimates in this meta-analysis. A significantly higher SS-ILD prevalence was reported in China than in Japan and Korea. The same phenomenon occurs outside East Asia; African Americans are more likely to develop SSc than Caucasians and experience worse pulmonary disease and greater morbidity.[40] A previous study found that African American ethnicity was associated with worse lung function in SSc patients.[40] It is not clear what contributes to the differences, but lineages, ethnicities, and genetic factors may have important impacts.[41]

In our meta-analysis, we confirmed that longer disease duration, dSSc subtype, and higher ESR were risk factors for ILD in SSc patients. In the UK, individuals with dSSc have a high incidence of ILD, renal crisis, and gastrointestinal involvement whereas individuals with lSSc frequently develop pulmonary hypertension.[42] As previously demonstrated, clinically significant ILD was twice as common among dSSc patients as among lSSc patients.[43] As expected, the presence of dSSc in East Asia was associated with ILD in our meta-analysis. Several previous studies have described variables that predict clinically significant pulmonary fibrosis development, including greater age at onset.[42] However, we reported no difference in age between SSc-ILD and non-ILD patients (WMD = 3.39, 95% CI −1.54 to 8.31); SSc-ILD patients had longer disease duration and higher ESR than the SSc patients without ILD in our study. A potential explanation for age difference was a geographical difference or an introduced bias. Moreover, we speculated that SSc patients with longer disease duration were more likely to have ILD. Disease in SSc-ILD patients tends to be more severe and there is higher disease activity with higher ESR than in SSc patients.

The significance of autoantibodies in SSc remains unclear, although a variety of autoantibodies are not just markers of disease, but also have a role in pathogenesis.[44] The presence of ANA is most frequently a representative feature of the immunological abnormalities in SSc patients, and more than 90% of SSc patients are positive for ANA. The common serum ANAs in SSc patients include anti-ATA (anti-topo I, formerly termed anti-Scl-70), ACA, anti-U1 RNP antibody, anti-RNAP antibody, anti-Th/To antibody, and anti-U3 RNP antibody. This meta-analysis showed that positive ATA, negative ACA, and negative anti-U3 RNP were risk factors for ILD in SSc patients. It has been demonstrated that ATA themselves display anti-fibroblast antibody activity by reacting with determinants at the fibroblast surface. Anti-fibroblast antibodies induce a pro-inflammatory phenotype in fibroblasts and are strongly correlated with ATA and pulmonary fibrosis in patients with SSc.[45] ACA are the most frequently seen autoantibodies in SSc patients and their presence is highly specific in distinguishing SSc

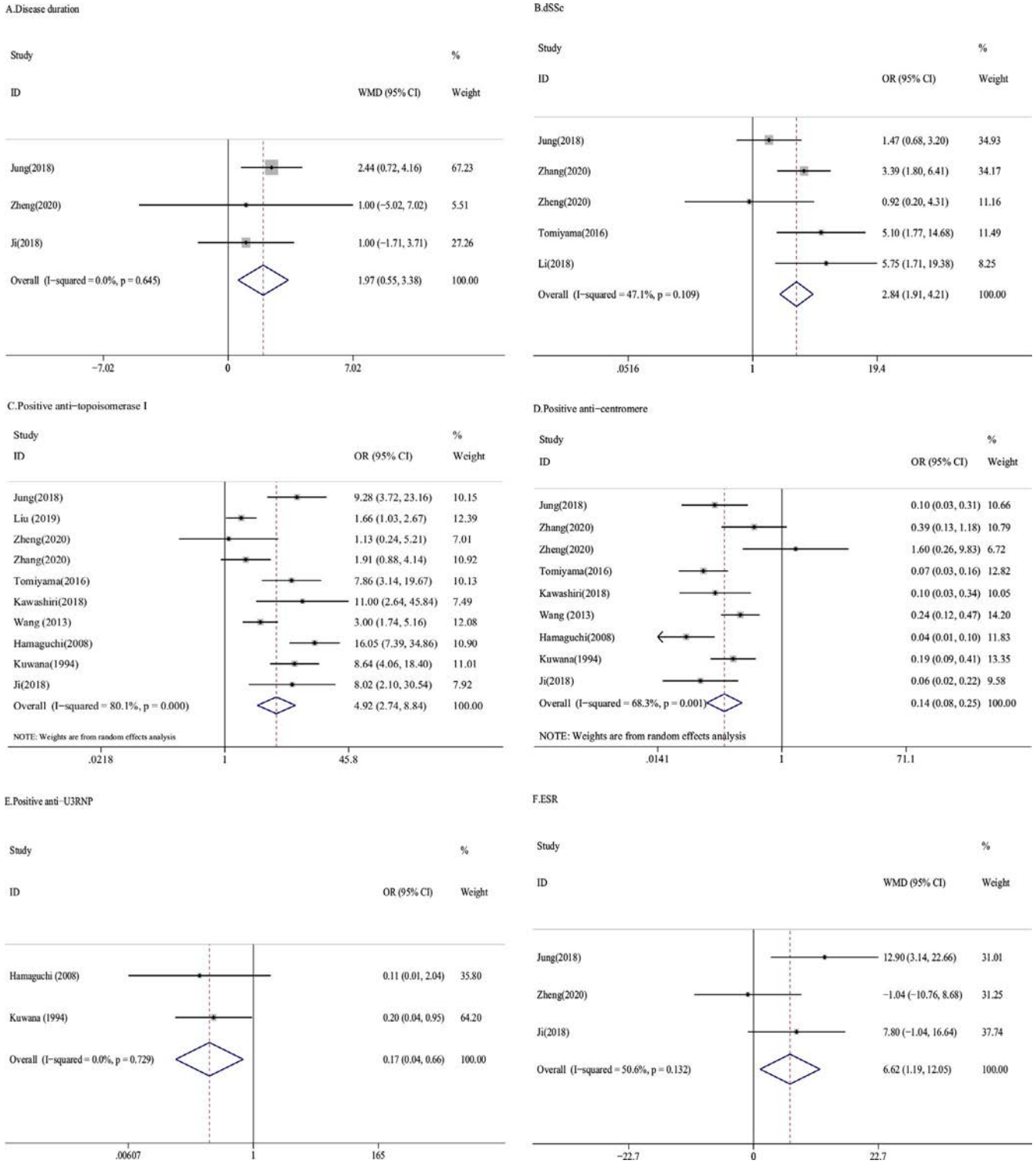


FIGURE 4 Forrest plots of risk factors of SSc-ILD. (A) Pooled WMDs for correlation of disease duration with SSc-ILD; (B) pooled ORs for correlation of dSSc with SSc-ILD; (C) pooled ORs for correlation of positive ATA with SSc-ILD; (D) pooled ORs for correlation of positive ACA with SSc-ILD; (E) pooled ORs for correlation of positive anti-U3 RNP antibody with SSc-ILD; (F) pooled WMDs for correlation of ESR with SSc-ILD. Abbreviations: ACA, anti-centromere antibody; ATA, anti-topoisomerase I antibody; dSSc, diffuse systemic sclerosis; ESR, erythrocyte sedimentation rate; ORs, odd ratios; SSc-ILD, systemic sclerosis-associated interstitial lung disease; U3 RNP, anti-U3 ribonucleoprotein; WMDs, weighted mean differences [Colour figure can be viewed at wileyonlinelibrary.com]

patients from healthy individuals or study participants with other connective tissue diseases. ACA positivity is strongly associated with the occurrence of lSSc and has been described as conferring relative protection from SSc-associated pulmonary fibrosis.[37,46,47] Some studies have even reported that ATA-positive patients have a considerably higher incidence of digital ulcers compared with

ACA-positive participants.[46,47] Anti-U3 RNP antibody is frequently detected in patients with dSSc with a low frequency of pulmonary involvement,[48] whereas anti-U1 RNP antibody is generally found in overlap syndrome, especially mixed connective tissue disease, and is associated with isolated pulmonary arterial hypertension and arthritis.[49] Anti-Th/To antibody is associated with lSSc and a low frequency of severe internal organ involvement.[50] Anti-RNAP antibody is often detected in patients with dSSc and is associated with a high frequency of renal disease.[51] Likewise, we showed that anti-U1 RNP antibody, anti-Th/To antibody, and anti-RNAP antibody are not associated with SSc-ILD in this meta-analysis.

Our study has several limitations. First, as no eligible studies were found for North Korea and Mongolia, the pooled result may be not totally representative of the prevalence of SSc-ILD in East Asia. Second, the study design, methodology quality, sample size, study population, and ILD diagnostic methods might result in significant heterogeneities of SSc-ILD prevalence in the identified studies. A random model was used in calculating the pooled SSc-ILD prevalence, and the sensitivity analysis confirmed that the result was stable. Third, all studies were observational studies, which makes it difficult to determine the causal relationship of risk factors.

5 | CONCLUSION

In conclusion, this meta-analysis showed that ILD occurs in up to 56% of patients with SSc in East Asia. Longer disease duration, dSSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and higher ESR were risk factors for ILD in SSc patients. However, the data should be interpreted cautiously because of the methodological differences and the limitations inherent in observational studies.

ACKNOWLEDGEMENTS

We really appreciate the efforts of all the researchers whose articles were included in this study.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHORS CONTRIBUTIONS

MHQ, SCZ, and PFY designed the study. MHQ and XYN conducted the literature search and data extraction. MHQ, XYN, and LLP conducted the meta-analysis. MHQ and XYN interpreted the data and wrote the draft of the manuscript. SCZ and PFY critically revised the manuscript. All authors approved submission of the final version of the manuscript. MHQ and XYN contributed equally to this work and are co-first authors. PFY and SCZ contributed equally to this work and are co-correspondence authors.

ORCID

Meihua Qiu https://orcid.org/0000-0001-6803-5582

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685-1699.
2. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. *Autoimmun Rev*. 2010;9(5):A311-318.
3. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15(2):202-205.
4. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med*. 2005;118(1):2-10.
5. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007;66(7):940-944.
6. White B. Interstitial lung disease in scleroderma. *Rheum Dis Clin N Am*. 2003;29(2):371-390.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, w264.
8. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelin es for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
9. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systemati c Reviews of Interventions. *Cochrane database syst rev*. 2019;10:Ed000142.
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
11. Kim J, Park SK, Moon KW, et al. The prognostic factors of systemic sclerosis for survival among Koreans. *Clin Rheumatol*. 2010;29(3):297-302.
12. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. *Arch Rheumatol*. 2018;33(3):322-327. https://doi.org/10.5606/ArchRheumatol.2018.6630
13. Moon KW, Lee SS, Lee YJ, et al. Clinical and laboratory characteristics and mortality in Korean patients with systemic sclerosis: A nationwide multicenter retrospective cohort study. *J Rheumatol*. 2018;45(9):1281-1288. https://doi.org/10.3899/jrheum.171443
14. Ooi GC, Mok MY, Tsang KW, et al. Interstitial lung disease in systemic sclerosis. *Acta Radiol* (Stockholm, Sweden: 1987). 2003;44(3):258-264.
15. Mok MY, Fung PCW, Ooi C, et al. Serum nitric oxide metabolites and disease activity in patients with systemic sclerosis. *Clin Rheumatol*. 2008;27(3):315-322. https://doi.org/10.1007/s10067-007-0708-9
16. Low AH, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with system ic sclerosis. *J Rheumatol*. 2009;36(4):787-793.
17. Wang J, Assassi S, Guo G, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. *Clin Rheumatol*. 2013;32(5):617-621.
18. Hu S, Hou Y, Wang Q, Li M, Xu D, Zeng X. Prognostic profile of systemic sclerosis: Analysis of the clinical EUSTAR cohort in China. *Arthritis Res Ther*. 2018;20(1):235. https://doi.org/10.1186/s13075-018-1735-4
19. Li X, Qian YQ, Liu N, et al. Survival rate, causes of death, and risk factors in systemic sclerosis: a large cohort study. *Clin Rheumatol*. 2018;37(11):3051-3056. https://doi.org/10.1007/s10067-018-4291-z
20. Zhang M, Zhang L, Linning E, et al. Increased levels of HE4 (WFDC2) in systemic sclerosis: a novel biomarker reflecting interstitial lung disease severity? *Ther Adv Chronic Dis*. 2020;11:1-11. https://doi.org/10.1177/2040622320956420

21. Zheng JN, Li Y, Yan YM, Yu Y, Shao WQ, Wang Q. Increased serum calpain activity is associated with HMGB1 levels in systemic sclerosis. *Arthritis Res Ther*. 2020;22(1):110. https://doi.org/10.1186/s13075-020-02195-y
22. Zhou M, Jiang L, Nie L, et al. Myopathy is a risk factor for poor prognosis of patients with systemic sclerosis: A retrospective cohort study. *Medicine*. 2020;99(33):e21734. https://doi.org/10.1097/MD.0000000000021734
23. Ji LL, Wang H, Zhang XH, Zhang ZL. Correlation between nailfold capillaroscopic findings and presence of interstitial lung disease in systemic sclerosis patients. *J Peking Univ Health Sci*. 2018;50(3):501-506. http://xuebao.bjmu.edu.cn/EN/Y2018/V50/I3/501
24. Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Arthritis Rheum*. 1994;37(1):75-83.
25. Sato S, Nagaoka T, Hasegawa M, Nishijima C, Takehara K. Elevated serum KL-6 levels in patients with systemic sclerosis: Association with the severity of pulmonary fibrosis. *Dermatology (Basel, Switzerland)*. 2000;200(3):196-201. https://doi.org/10.1159/000018382
26. Ashida R, Ihn H, Mimura Y, et al. Clinical features of scleroderma patients with contracture of phalanges. *Clin Rheumatol*. 2007;26(8):1275-1277. https://doi.org/10.1007/s10067-006-0490-0
27. Komura K, Fujimoto M, Hasegawa M, et al. Increased serum interleukin 23 in patients with systemic sclerosis. *J Rheumatol*. 2008;35(1):120-125.
28. Hashimoto A, Tejima S, Tono T, et al. Predictors of survival and causes of death in Japanese patients with systemic sclerosis. *J Rheumatol*. 2011;38(9):1931-1939.
29. Odani T, Yasuda S, Ota Y, et al. Up-regulated expression of HLA-DRB5 transcripts and high frequency of the HLA-DRB5*01:05 allele in scleroderma patients with interstitial lung disease. *Rheumatology*. 2012;51(10):1765-1774. https://doi.org/10.1093/rheumatology/kes149
30. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku J Exp Med*. 2016;239(4):279-305. https://doi.org/10.1620/tjem.239.297
31. Kawashiri SY, Nishino A, Igawa T, et al. Prediction of organ involvement in systemic sclerosis by serum biomarkers and peripheral endothelial function. *Clin Exp Rheumatol*. 2018;36 Suppl 113(4);102-108.
32. Taniguchi T, Miyagawa T, Toyama S, et al. CXCL13 produced by macrophages due to Fli1 deficiency may contribute to the development of tissue fibrosis, vasculopathy and immune activation in systemic sclerosis. *Exp Dermatol*. 2018;27(9):1030-1037. https://doi.org/10.1111/exd.13724
33. Matsuda KM, Yoshizaki A, Kuzumi A, et al. Skin thickness score as a surrogate marker of organ involvements in systemic sclerosis: A retrospective observational study. *Arthritis Res Ther*. 2019;21(1):129. https://doi.org/10.1186/s13075-019-1919-6
34. Aozasa N, Hatano M, Saigusa R, et al. Clinical significance of endothelial vasodilatory function evaluated by EndoPAT in patients with systemic sclerosis. *J Dermatol*. 2020;47(6):609-614. https://doi.org/10.1111/1346-8138.15334
35. Kubo S, Siebuhr AS, Bay-Jensen AC, et al. Correlation between serological biomarkers of extracellular matrix turnover and lung fibrosis and pulmonary artery hypertension in patients with systemic sclerosis. *Int J Rheum Dis*. 2020;23(4):532-539. https://doi.org/10.1111/1756-185X.13804
36. Sekiguchi A, Inoue Y, Yamazaki S, et al. Prevalence and clinical characteristics of earlobe crease in systemic sclerosis: Possible association with vascular dysfunction. *J Dermatol*. 2020;47(8):870-875. https://doi.org/10.1111/1346-8138.15400
37. Hamaguchi Y, Hasegawa M, Fujimoto M, et al. The clinical relevance of serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Br J Dermatol*. 2008;158(3):487-495. https://doi.org/10.1111/j.1365-2133.2007.08392.x
38. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scl eroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committ ee. *Arthritis Rheum*. 1980;23(5):581-590.
39. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European lea gue against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72(11):1747-1755.
40. Greidinger EL, Flaherty KT, White B, Rosen A, Wigley FM, Wise RA. African-American race and antibodies to topoisomerase I are associated with increased severity of scl eroderma lung disease. *Chest*. 1998;114(3):801-807.
41. Ramos PS, Silver RM, Feghali-Bostwick CA. Genetics of systemic sclerosis: recent advances. *Curr Opin Rheumatol*. 2015;27(6):521-529.
42. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol*. 2014;66(6):1625-1635.
43. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ dis ease: a retrospective cohort study. *QJM*. 2010;103(2):109-115.
44. Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. *Nat Rev Rheumatol*. 2010;6(2):112-116.
45. Hénault J, Tremblay M, Clément I, Raymond Y, Senécal J-L. Direct binding of anti-DNA topoisomerase I autoantibodies to the cell surface of fibroblasts in patie nts with systemic sclerosis. *Arthritis Rheum*. 2004;50(10):3265-3274.
46. Walker UA, Tyndall A, Czirjak L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scler oderma Trials And Research group database. *Ann Rheum Dis*. 2007;66(6):754-763.
47. Hachulla E, Carpentier P, Gressin V, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. *Rheumatology* (Oxford). 2009;48(3):304-308.
48. Okano Y, Steen VD, Medsger TA. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. *Arthritis Rheum*. 1992;35(1):95-100.
49. Jacobsen S, Halberg P, Ullman S, et al. Clinical features and serum antinuclear antibodies in 230 Danish patients with systemic sclerosis. *Br J Rheumatol*. 1998;37(1):39-45.
50. Kuwana M, Kimura K, Hirakata M, Kawakami Y, Ikeda Y. Differences in autoantibody response to Th/To between systemic sclerosis and other autoimmune disease s. *Ann Rheum Dis*. 2002;61(9):842-846.
51. Okano Y, Steen VD, Medsger TA. Autoantibody reactive with RNA polymerase III in systemic sclerosis. *Ann Intern Med*. 1993;119(10):1005-1013.

SUPPORTING INFORMATION

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

How to cite this article: Qiu M, Nian X, Pang L, Yu P, Zou S. Prevalence and risk factors of systemic sclerosis-associated interstitial lung disease in East Asia: A systematic review and meta-analysis. *Int J Rheum Dis*. 2021;24:1449–1459. https://doi.org/10.1111/1756-185X.14206

Received: 12 May 2021 | Accepted: 25 August 2021

DOI: 10.1111/1756-185X.14213

International Journal of Rheumatic Diseases

WILEY

INVITED REVIEW

Myeloperoxidase and associated lung disease: Review of the latest developments

Hannah Hu[1,2] | Karuna Keat[1,3]

[1]Department of Immunology, Campbelltown Hospital, Sydney, New South Wales, Australia

[2]University of New South Wales, Sydney, New South Wales, Australia

[3]Western Sydney University, Sydney, New South Wales, Australia

Correspondence
Hannah Hu, Department of Immunology, Campbelltown Hospital, Therry Road, Campbelltown, NSW 2560, Australia.
Email: hannah.hu@unsw.edu.au

Abstract

Myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibodies (ANCA) are often detected in association with a variety of lung pathologies, the most common being interstitial lung disease (ILD). A growing cohort of patients are being diagnosed with MPO-ANCA in the context of ILD without ANCA-associated vasculitis. Clinically and radiologically, there is little to differentiate this cohort from MPO-ANCA-negative ILD patients; however, the pathophysiology is likely different and different treatments are likely required. We present here a brief summary of the proposed pathophysiology of MPO-ANCA-positive ILD, and a more detailed review of the latest evidence on management, including monitoring for development of ANCA-associated vasculitis, immunosuppression, anti-fibrotics, and novel agents that have yet to be trialled in human experiments.

KEYWORDS

anti-neutrophil cytoplasmic antibodies, fibrotic lung disease, interstitial lung disease, myeloperoxidase antibody, vasculitis

1 | INTRODUCTION

Anti-neutrophil cytoplasmic antibodies (ANCA) are auto-antibodies directed against antigens in the cytoplasmic granules of neutrophils and lysosomes of monocytes.[1] The most clinically relevant two antigens have been those directed against proteinase 3 and myeloperoxidase (MPO). These antibodies are found in pauci-immune necrotizing vasculitis of the small blood vessels, with the clinically relevant syndromes being: eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA).[2]

ANCA are also found in patients without clinical vasculitis syndromes. The association of MPO with lung disease can therefore be divided into two groups: associated with clinical vasculitis syndrome (ANCA-associated vasculitis involving interstitial lung disease [AAV-ILD]) or in isolated lung disease (with the diagnosis of vasculitis based on the American College of Rheumatology criteria and the Chapel Hill Consensus Conference definitions).[2]

The manifestations of pulmonary involvement in AAV has been well covered in numerous reviews[3-7] so we will only summarize what has been described previously, and we will mainly focus on lung disease in the context of MPO-ANCA positivity only, without clinical vasculitis.

2 | AAV AND LUNG INVOLVEMENT

Anti-MPO antibodies are the main ANCA subtype associated with ILD in vasculitis syndromes, present in about 46%-71% of cases.[5] They are more commonly found in patients with EGPA and MPA, but are also seen in GPA, though to a lesser extent.

Declarations: Both authors contributed equally to the conception, literature review, synthesis and review of this paper.

GPA is characterized by relatively acute onset of dyspnea, hemoptysis, and cough, due to inflammation of the lower airways.[8] It has heterogeneous pulmonary manifestations on lung computed tomography (CT), with bilateral cavitating and non-cavitating lung nodules being the most common, often increasing in frequency as the disease progresses, followed in frequency by pulmonary consolidation, segmental bronchial wall thickening, bronchial stenosis, and ground-glass opacities (often due to alveolar hemorrhage).[9-11] As necrosis becomes associated with the granulomatous inflammation, organizing pneumonia can also develop, seen on CT as bilateral irregular consolidation.[12] The nodular lesions are often associated with vessels, and affect predominantly the subpleural regions.[8] The typical histopathology is necrosis, and focal and lumen-eccentric inflammation of arterioles, venules, and capillaries.[8] Granulomatous inflammation is key, with the inflammatory infiltrate primarily neutrophils, as well as lymphocytes, plasma cells, macrophages, giant cells, and eosinophils.

EGPA is characterized by an association with peripheral and tissue eosinophilia. The most common pulmonary manifestation is asthma, followed by eosinophilic pneumonia and hypereosinophilic bronchiolitis.[13] EGPA often presents with transient, bilateral, pulmonary infiltrates, mostly peripheral, responsive to corticosteroids, and therefore often presenting without abnormalities by the time imaging is performed.[14] Peripherally distributed ground-glass opacities are also commonly seen. Associated hypereosinophilic bronchiolitis is seen on CT as bronchiectasis, centrilobular nodules, and bronchial wall thickening.[15] Histopathology demonstrates granulomatous necrotizing inflammation of the small arteries, similar to GPA, but with a much more eosinophil-rich inflammatory infiltrate.[13]

MPA is characterized by necrotizing inflammation of blood vessels, predominantly of the pulmonary and renal small-sized vessels; unlike EGPA, however, there are no granulomas.[2,16] The most common pulmonary manifestation is diffuse alveolar hemorrhage, on a spectrum ranging from chronic and asymptomatic to hemoptysis.[17] Diffuse alveolar hemorrhage is a clinical syndrome of hemoptysis, diffuse alveolar infiltrates, and a drop in hematocrit level. GPA and MPA comprise the majority of etiology of causes of diffuse alveolar hemorrhage, comprising 45% of cases.[18,19] Biopsy findings may not show a characteristic infiltrate, but diffuse alveolar hemorrhage can be identified based on bronchoalveolar lavage showing erythrocytes and siderophages.[20] Lung imaging of MPA is often non-specific, with alveolar hemorrhage either not seen, or presenting as ground-glass opacities, seen as patchy or diffuse bilateral opacifications and consolidation, ranging from peri-hilar or mid-lower zones.[18,20,21]

Treatment for MPO-positive AAV-ILD is predominantly the standard therapy for systemic vasculitis, including systemic corticosteroids, cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine and, to a lesser extent, methotrexate (due to its side effect of pulmonary fibrosis).[22] However, good evidence for these treatments is lacking, and the prognosis of AAV-ILD is not improved with immunosuppression.[23,24] There are no comparative studies looking at efficacy of anti-fibrosing agents in AAV-ILD, though there are small reports of improvement in survival predominantly for those with a usual interstitial pneumonia (UIP) pattern.[25]

3 | MPO-ANCA AND LUNG DISEASE

MPO-ANCA in ILD without vasculitis has been increasingly described.[3,4,26-34] Non-AAV ANCA-associated lung diseases are predominantly of the fibrotic lung disease type, particularly UIP followed by nonspecific interstitial pneumonia, but have also been described in cryptogenic organizing pneumonia, or unclassifiable idiopathic pneumonia.[5,7,33] ANCA have been found in up to 10% of those with a diagnosis of idiopathic pulmonary fibrosis (IPF), and up to 10% of ANCA-negative IPF patients sero-convert during follow up.[29,35]

The ILD seen in MPO-ANCA mostly have a UIP pattern on CT with a radiological appearance of bilateral, patchy, honeycombing, ground-glass opacity and consolidation.[27] Histopathology is generally non-specific, and cannot differentiate between ANCA-positive and ANCA-negative lung disease.[36] Usual pathology findings include interstitial inflammation, plasma cell infiltration, lymphoid follicles with germinal centers, cysts, and cellular bronchiolitis.[3,27,36] There should not be evidence of vasculitis (as this would indicate AAV-ILD).

MPO antibodies are more frequently described in association with ILD than anti-proteinase 3 antibodies, 46%-71% of cases for the former compared with 0%-29% for the latter.[28,30,37,38]

Studies looking at the clinical difference between ANCA-positive and ANCA-negative pulmonary fibrosis patients identified little difference in symptoms, lung function tests, CT findings, and bronchoalveolar lavage findings.[30,39] There are inconsistent reports of differences such as higher percentage of neutrophils in bronchoalveolar lavage fluid, increased attenuation around honeycombing and cysts,[27] more ground-glass opacities as well as more moderate or severe honeycombing,[31,32] and possibly a preponderance of lower lobe ground-glass changes.[33] A recent study identified more incidence of MPO-ANCA positivity in IPF in women than men (47% vs 23%),[31] but this has not been reported elsewhere (of uncertain significance contributing to this difference was its North American patient population vs Japanese cohorts in the other studies).

Despite seemingly having the same phenotype, the relevance of identification of MPO-ANCA is for its potentially significant clinical implications. MPO-ANCA can pre-date AAV by up to 5 years (range from 5 to120 months), and ILD can pre-date diagnosis of an ANCA vasculitis by up to 14 years,[40] so ongoing clinical vigilance is required if there is a suspicion.[4,41] A recent study[42] retrospectively performed autoimmune antibody testing on a cohort of patients diagnosed with ILD, and MPO-ANCA was identified in 2.5% of patients, suggesting a small population of patients who may be missed if ANCA testing is not performed. Between 4% and 39% of patients with pulmonary fibrosis have ANCA positivity (predominantly MPO), and 7%-40% with MPO positivity will develop AAV during follow up.[30,31,33,43,44]

However, caution needs to be shown in over-interpreting the significance of MPO positivity, due to a high incidence of positivity in patients without AAV, being up to 39.5%[45] in patients with inflammatory conditions. Background rates of ANCA positivity in the general population with low pre-testing clinical suspicion are as high as 5.1%.[46] The high rate of MPO positivity may lead to an over-attribution of its significance and clinical meaning when found in the context of lung disease. False-positive MPO are most commonly found in association with gastrointestinal disorders, infections, malignancy, and other connective tissue disorders. Almost 10% have no clinical finding at all, and other auto-antibodies were found in association in 76%, suggesting a polyclonal response to non-vasculitis inflammatory triggers.[45] Non-AAV MPO is more often found in association with other autoimmune conditions than non-AAV proteinase 3, for which infection is the most common association.[47,48]

3.1 | Pathophysiology

There are multiple postulated causes of ILD in MPO-ANCA-positive patients. It is thought that ILD can directly induce MPO-ANCA production.[3] Bronchoalveolar lavage of IPF patients has identified neutrophilia. In the context of inflammation, auto-antibodies can be generated against the intracytoplasmic granules of these neutrophils, including MPO.[23,49] Additionally, activated neutrophils may contribute to the induction of fibrosis through the process of NETosis-neutrophilic death through extrusion of cellular contents via the formation of neutrophilic extracellular traps (NETs).[50] NET components can exacerbate the inflammatory response through mediating complement activation, acting as danger-associated molecular patterns and activate inflammasomes.[49]

Another hypothesis is that MPO-ANCA develops first, and has anti-oxidative and pro-fibrotic activity causing progressive lung fibrosis.[51,52] Injection of neutrophil lysosomal extract containing MPO into the pulmonary arterial vasculature of MPO-sensitized rats triggered development of patchy inflammatory cell infiltrates associated with granuloma formation, vasculitis, and hemorrhage.[53]

Smoking appears to be a significant risk factor, with ANCA-positive ILD patients more likely to be smokers and/or to smoke more heavily.[29,38] Cigarette smoke may induce expression of MPO on epithelial cells and through its pro-inflammatory effects, induce neutrophilic infiltration into the lung tissue.[54]

It has also been postulated that lung fibrosis in MPO-ANCA ILD is due to repeated episodes of subclinical alveolar microhemorrhage secondary to capillaritis, based on histological findings of leukocytoclastic capillaritis and siderophages with fibroblast foci.[55,56] Fibrosis forms due to abnormal repair processes or persistent inflammation.[57] However, this theory is contradicted by comparison with other vasculitic lung pathologies such as anti-glomerular basement membrane antibody disease, which is characterized by auto-antibodies directed against renal glomeruli and alveolar capillary basement membranes causing alveolar hemorrhage.[58] Interstitial lung disease has not been reported to be a manifestation associated with this condition.[59] There are two possible explanations for this; a case report of repeated lung biopsies on a patient with vasculitis initially demonstrated alveolar capillaritis, but subsequently only interstitial fibrosis without features of vasculitis.[60] It is possible that lung biopsy during active inflammation is required to identify clinical vasculitis rather than isolated fibrosis. Additionally, anti-glomerular basement membrane disease usually presents with rapidly progressive respiratory symptoms[59,61] and is not associated with chronic, subclinical inflammation, thereby not causing sufficient impaired healing to trigger development of lung fibrosis.

3.2 | Prognosis

Median survival for MPO-ANCA ILD (with and without systemic vasculitis) has been reported to be from 62 to 132 months,[27,33,43,62] without significant difference compared with survival of MPO-negative IPF patients.[30] Factors associated with poorer survival include honeycomb lesions in lower lobes (bilaterally) on high-resolution CT,[63] and UIP pattern on imaging.[23]

3.3 | Treatment

3.3.1 | Anti-fibrotic agents

It has been reported that higher titers of ANCA may predict more severe lung disease, and possible association with MPA[30] but no further studies have been performed. In the absence of a vasculitic syndrome, the detection of an MPO-ANCA should not prevent treatment of IPF according to usual guidelines, such as with anti-fibrotic agents.[64] The main side effects of pirfenidone and nintedanib are gastrointestinal upset including diarrhea, rash and abnormalities of liver function tests in a small proportion of patients.[65,66] Both agents have also been shown to have anti-inflammatory effects, and may be of benefit in ILD due to an inflammatory cause.[67,68] A recently completed Phase 2 randomized controlled trial examining the use of pirfenidone in patients with unclassifiable progressive fibrotic lung disease (ANCA status not described) demonstrated reduced mean forced vital capacity reduction over 24 months compared with placebo, but ultimately there were no differences in progression-free survival.[69] There is better evidence for nintedanib in treatment of progressive fibrosing ILD other than IPF, with demonstration of reduction in rate of ILD progression (measured by forced vital capacity decline).[70] They are both relatively well-tolerated agents and could be considered in the treatment of non-AAV MPO-ANCA ILD.[25] Preliminary evidence has shown a trend toward less forced vital capacity decline over 12 weeks with a combination of both agents compared with patients on nintedanib alone; the combination, at

least over this short follow-up period appeared to be well tolerated with adverse events similar to those for treatment with either agent alone without an increase in frequency of liver function test abnormalities.[71,72] A Phase 2 study examining the safety and efficacy of pirfenidone in pulmonary fibrosis with MPO positivity (NCT03385668) that recruited 7 (of an expected 15) participants was completed in July 2020; results were expected in February 2021, however at last update (May 2021), results are still pending.[73]

3.3.2 | Immunosuppression

The evidence for immunosuppression is variable in this small cohort of non-AAV MPO-ANCA ILD patients. Biopsies of non-AAV MPO-ANCA-positive patients with UIP have more inflammation than MPO-ANCA-negative patients with UIP,[74] suggesting that immunosuppression may be beneficial.

Immunosuppression in small cohorts has been shown to be effective in improving clinical parameters, but no data on long-term progression-free survival have been described,[27] and response rates were not stratified by pattern on lung imaging or histopathology findings. Of note, however, no ANCA-positive ILD patients on immunosuppression have developed systemic vasculitis while immunosuppressed.[27,29,44]

In a cohort of MPO-ANCA patients that included those with AAV, patients with a nonspecific interstitial pneumonia pattern appear to respond to immunosuppression; however, UIP pattern patients appeared to follow the disease trajectory of IPF.[3,7] Based on this, clinicians from the Mayo Clinic have suggested treating nonspecific interstitial pneumonia pattern patients with immunosuppression, but for those with a UIP pattern without associated systemic vasculitis, to avoid immunosuppressive therapy and take a watch-and-wait approach, similar to the usual treatment paradigms for IPF.[7] This finding was not seen in other studies.[23,24] Of note, in the Mayo Clinic cohort, the classification of patients based on ILD subtype was based on radiology,[7] but Baqir et al[33] have demonstrated that though radiology may not identify UIP pattern, histopathology on biopsy subsequently demonstrated predominant UIP pattern in a non-AAV MPO-ANCA ILD cohort. Corticosteroids have been shown to be mildly effective, but the difference was not significant and made no difference to mortality.[23]

Caution is advised in consideration of immunosuppression for non-AAV MPO-ILD patients as the PANTHER-IPF study showed that IPF patients given prednisone, azathioprine, and *N*-acetylcysteine had increased mortality compared with those given placebo.[75] Poorer outcomes in association with immunosuppression therapy have also been seen in a more recent study.[23]

Despite the variable evidence, although the exact pathophysiology of non-AAV MPO-ANCA ILD is uncertain, it is likely there is a combination of both autoimmune inflammation and fibrosis, so a combination of therapies targeting dual pathologies is likely to be effective.

4 | NOVEL THERAPEUTIC AGENTS

4.1 | Janus kinase inhibitors

Other new avenues of therapy to be explored and studied come from the discovery of monogenic forms of fibrotic lung disease associated with ANCA positivity. Gain-of-function mutations in the *TMEM17* gene, which encodes the stimulator of interferon gene (STING) causes STING-associated vasculopathy with onset in infancy.[76] These mutations lead to increased interferon signaling and related cytokine secretion in monocytes leading to a clinical syndrome of systemic inflammation, peripheral vasculitis with skin manifestations, and ILD.[77] Antibody positivity is common and broad, including ANCA.[76] The use of Janus kinase (JAK) inhibitors—tofacitinib, ruxolitinib, and baracitinib—has been shown to be effective.[76,78-80] Reducing the transferability of these findings is the strong interferon signature of this interferonopathy condition; a finding not reported in non-AAV MPO-ANCA ILD. There are, however, increasing numbers of case reports of medium- and large-vessel vasculitis that is refractory to traditional immunosuppression responding to tofacitinib.[81,82] Tofacitinib has been shown to reduce the inflammatory and pro-fibrotic effects of idiopathic inflammatory myopathy-associated ILD-derived T cells in vitro.[83] It has been used effectively in refractory rapidly progressive ILD associated with anti-melanoma differentiation-associated 5 antibody-positive dermatomyositis.[84,85] There are safety signals emerging, particularly of viral infections, which would need to be evaluated carefully.[86] High-quality, randomized controlled studies are necessary, though the small numbers of patients may make recruitment difficult for sufficiently powered studies.

4.2 | Peptidylarginine deiminase inhibitors

New therapies are in development to prevent NET formation and the resultant MPO-ANCA production. NETs are composed of a web of extracellular DNA and antimicrobial proteins (including MPO). In the process of the decondensation of DNA, histones are citrullinated by peptidylarginine deiminase 4 (PAD4). Mouse studies of C1-amidine, a pan-PAD inhibitor, have shown effective reduction in citrullination of DNA, and subsequent significantly lower MPO-ANCA titers.[87] As MPO-ANCA has been postulated to be directly pathogenic in the induction of lung fibrosis, and may have implications in triggering development of AAV, blockade of excessive NET formation and development of MPO-ANCA may ameliorate the disease process. These are early days for targets of this disease process and more research is needed.

4.3 | Adelmidrol

Adelmidrol is a ethanolamide derivate. They are a group of proteins expressed in mammals that have a range of physiological functions,

including inflammation and cryoprotection.[88] Adelmidrol is a synthetic analogue of *N*-palmitoyethanolamine, an *N*-acylethanolamine that is being increasingly investigated for its anti-inflammatory and anti-oxidant activities.[89] *N*-Palmitoyethanolamine stabilizes mitochondrial function, and inhibits mast cell degranulation and anandamide degradation through modulation of interleukin-6. In mouse studies, adelmidrol has been shown to modulate the inflammatory pathways implicated in pulmonary fibrosis and improve the histopathological score as well as mortality rates.[90]

4.4 | MPO inhibitors

As MPO has been implicated as a possible cause of lung pathology via direct induction of inflammation and fibrosis or via excessive generation of its reactive oxidant by-products, there are currently many agents and pathways under investigation to block the function of MPO.[91] These include agents to limit MPO substrate availability, non-selective MPO inhibition, and selective, irreversible MPO inhibitors, with a recent summary providing a comprehensive overview.[91]

5 | CONCLUSIONS

In summary, MPO-ANCA-positive lung disease can be an individual entity, or be the initial presentation of a systemic vasculitis. Presently, there do not appear to be clinical, radiological, or serological signatures to identify the trajectory of antibody positivity in non-AAV ILD patients. In non-AAV MPO-ANCA ILD, there is conflicting evidence for whether there are significant clinical or treatment outcome differences in comparison with MPO-negative ILD or IPF, though the preponderance of evidence suggests that there are more similarities than differences. Immunosuppression does not appear to change lung-related mortality, but there is evidence to show that it may slow decline in lung function. Furthermore, immunosuppression appears to prevent the development of systemic vasculitis in the third of patients who do progress to systemic disease. However, caution should be shown in the consideration of immunosuppression due to the increased mortality associated with use in IPF, from which non-AAV MPO-ANCA ILD can be indistinguishable. Of tolerable side effect profile and with likely improvements in lung function decline are the anti-fibrotic agents pirfenidone and nintedanib, which could be considered as therapy. We eagerly await the results of the PIRFENIVAS study. Perhaps a new approach would be a combination of immunosuppression with anti-fibrotic agents.[92] More exciting treatments on the horizon are the JAK inhibitors, of which tofacitinib is being increasingly used in proven medium- to large-vessel vasculitis. Its transferability to treatment of non-AAV MPO-positive lung diseases remains to be seen.

Clinical trials in the treatment of non-IPF, non-connective tissue related ANCA-positive fibrotic lung diseases are required, particularly looking at the safety and efficacy of immunosuppression and anti-fibrotics. Stratifying by type of ILD may be necessary, i.e. differentiating between those with UIP and nonspecific interstitial pneumonia radiological or histopathological patterns.

ETHICAL APPROVAL, CONSENT TO PARTICIPATE, CONSENT FOR PUBLICATION

Not applicable.

ORCID

Hannah Hu https://orcid.org/0000-0002-5006-5828

REFERENCES

1. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. *Lancet*. 2006;368(9533):404-418.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheumatism*. 2013;65(1):1-11.
3. Alba MA, Flores-Suárez LF, Henderson AG, et al. Interstital lung disease in ANCA vasculitis. *Autoimmun Rev*. 2017;16(7):722-729.
4. Comarmond C, Crestani B, Tazi A, et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. *Medicine*. 2014;93(24):340-349.
5. Sebastiani M, Manfredi A, Vacchi C, et al. Epidemiology and management of interstitial lung disease in ANCA-associated vasculitis. *Clin Exp Rheumatol*. 2020;38(Suppl 124(2)):221-231.
6. Yamada H. ANCA: associated lung fibrosis. *Semin Respir Crit Care Med*. 2011;32(03):322-327.
7. Thompson GE, Specks U. Update on the management of respiratory manifestations of the antineutrophil cytoplasmic antibodies-associated vasculitides. *Clin Chest Med*. 2019;40(3):573-582.
8. Frankel SK, Cosgrove GP, Fischer A, Meehan RT, Brown KK. Update in the diagnosis and management of pulmonary vasculitis. *Chest*. 2006;129(2):452-465.
9. Thickett DR, Richter AG, Nathani N, Perkins GD, Harper L. Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. *Rheumatology*. 2006;45(3):261-268.
10. Ananthakrishnan L, Sharma N, Kanne JP. Wegener's granulomatosis in the chest: high-resolution CT findings. *Am J Roentgenol*. 2009;192(3):676-682.
11. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992;116(6):488.
12. Seo JB, Im JG, Chung JW, et al. Pulmonary vasculitis: the spectrum of radiological findings. *Br J Radiology*. 2000;73(875):1224-1231.
13. Cottin V, Bel E, Bottero P, et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). *Eur Respir J*. 2016;48(5):1429-1441.
14. Choi YH, Im J-G, Han BK, Kim J-H, Lee KY, Myoung NH. Thoracic manifestation of churg-strauss syndrome radiologic and clinical findings. *Chest*. 2000;117(1):117-124.
15. Cordier J-F, Cottin V, Khouatra C, et al. Hypereosinophilic obliterative bronchiolitis: a distinct, unrecognised syndrome. *Eur Respir J*. 2012;41(5):1126-1134.
16. Karras A. Microscopic polyangiitis: new insights into pathogenesis, clinical features and therapy. *Semin Resp Crit Care*. 2018;39(04):459-464.
17. Villiger PM, Guillevin L. Microscopic polyangiitis: clinical presentation. *Autoimmun Rev*. 2010;9(12):812-819.
18. Feragalli B, Mantini C, Sperandeo M, et al. The lung in systemic vasculitis: radiological patterns and differential diagnosis. *Br J Radiology*. 2016;89(1061):20150992.

19. Travis WD, Colby TV, Lombard C, Carpenter HA. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. *Am J Surg Pathology*. 1990;14(12):1112-1125.
20. Nasser M, Cottin V. Alveolar hemorrhage in vasculitis (primary and secondary). *Semin Resp Crit Care*. 2018;39(04):482-493.
21. Suzuki A, Sakamoto S, Kurosaki A, et al. Chest high-resolution CT findings of microscopic polyangiitis: a Japanese first nationwide prospective cohort study. *Am J Roentgenol*. 2019;213(1):104-114.
22. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016;75(9):1583.
23. Maillet T, Goletto T, Beltramo G, et al. Usual interstitial pneumonia in ANCA-associated vasculitis: a poor prognostic factor. *J Autoimmun*. 2020;106:102338.
24. Watanabe T, Minezawa T, Hasegawa M, et al. Prognosis of pulmonary fibrosis presenting with a usual interstitial pneumonia pattern on computed tomography in patients with myeloperoxidase antineutrophil cytoplasmic antibody-related nephritis: a retrospective single-center study. *Bmc Pulm Med*. 2019;19(1):194.
25. Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. *European Respir Rev*. 2019;28(153):190022.
26. Kishore N, Gupta N, Dhar A, Abrari A, Rath P. Interstitial lung disease with usual interstitial pneumonia pattern preceding the presentation of ANCA-associated vasculitis by 4 years: coincidence or correlation? *Breathe*. 2018;14(3):e105-e110.
27. Hosoda C, Baba T, Hagiwara E, et al. Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis. *Respirology*. 2016;21(5):920-926.
28. Katsumata Y, Kawaguchi Y, Yamanaka H. Interstitial Lung Disease with ANCA-associated Vasculitis. *Clin Med Insights Circulatory Respir Pulm Med*. 2015;9(Suppl 1):51-56.
29. Ando M, Miyazaki E, Ishii T, et al. Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. *Resp Med*. 2013;107(4):608-615.
30. Nozu T, Kondo M, Suzuki K, Tamaoki J, Nagai A. A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. *Respiration*. 2009;77(4):407-415.
31. Suarez-Cuartin G, Molina-Molina M. Clinical implications of ANCA positivity in idiopathic pulmonary fibrosis patients. *Breathe*. 2020;16(1):190321.
32. Liu GY, Ventura IB, Achtar-Zadeh N, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in North American patients with idiopathic pulmonary fibrosis. *Chest*. 2019;156(4):715-723.
33. Baqir M, Yi EY, Colby TV, Cox CW, Ryu JH, Specks U. Radiologic and pathologic characteristics of myeloperoxidase-antineutrophil cytoplasmic antibody-associated interstitial lung disease: a retrospective analysis. *Sarcoidosis Vasc Diffuse Lung Dis Official J Wasog*. 2020;36(3):195-201.
34. Hervier B, Pagnoux C, Agard C, et al. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. *Ann Rheum Dis*. 2009;68(3):404.
35. Hozumi H, Enomoto N, Oyama Y, et al. Clinical implication of proteinase-3-antineutrophil cytoplasmic antibody in patients with idiopathic interstitial pneumonias. *Lung*. 2016;194(2):235-242.
36. Gaudin PB, Askin FB, Falk RJ, Jennette JC. The pathologic spectrum of pulmonary lesions in patients with anti-neutrophil cytoplasmic autoantibodies specific for anti-proteinase 3 and anti-myeloperoxidase. *Am J Clin Pathol*. 1995;104(1):7-16.
37. Hirayama K, Kobayashi M, Usui J, et al. Pulmonary involvements of anti-neutrophil cytoplasmic autoantibody-associated renal vasculitis in Japan. *Nephrol Dial Transpl*. 2015;30(suppl_1):i83-i93.
38. Foulon G, Delaval P, Valeyre D, et al. ANCA-associated lung fibrosis: analysis of 17 patients. *Resp Med*. 2008;102(10):1392-1398.
39. Lee JS, Kim EJ, Lynch KL, et al. Prevalence and clinical significance of circulating autoantibodies in idiopathic pulmonary fibrosis. *Resp Med*. 2013;107(2):249-255.
40. Wurmann P, Sabugo F, Elgueta F, et al. Interstitial lung disease and microscopic polyangiitis in chilean patients. *Sarcoidosis Vasc Diffuse Lung Dis*. 2020;37(1):37-42.
41. Olson SW, Arbogast CB, Baker TP, et al. Asymptomatic autoantibodies associate with future anti-glomerular basement membrane disease. *J Am Soc Nephrol*. 2011;22(10):1946-1952.
42. Stevenson BR, Thompson GA, Watson MC, et al. Autoantibodies in interstitial lung diseases. *Pathology*. 2019;51(5):518-523.
43. Tzelepis GE, Kokosi M, Tzioufas A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. *Eur Respir J*. 2009;36(1):116-121.
44. Kagiyama N, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. *Bmj Open Respir Res*. 2015;2(1):e000058.
45. Antonelou M, Ortega LP, Harvey J, Salama AD. Anti-myeloperoxidase antibody positivity in patients without primary systemic vasculitis. *Clin Exp Rheumatol*. 2019;37(Suppl 117(2)):86-89.
46. Deshpande P, Lucas M, Brunt S, Lucas A, Hollingsworth P, Bundell C. Low level autoantibodies can be frequently detected in the general Australian population. *Pathology*. 2016;48(5):483-490.
47. Houben E, Bax WA, van Dam B, et al. Diagnosing ANCA-associated vasculitis in ANCA positive patients. *Medicine*. 2016;95(40):e5096.
48. Kakoullis L, Parperis K, Papachristodoulou E, Panos G. Infection-induced myeloperoxidase specific antineutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis: a systematic review. *Clin Immunol*. 2020;220:108595.
49. Fousert E, Toes R, Desai J. Neutrophil Extracellular Traps (NETs) take the central stage in driving autoimmune responses. *Cells*. 2020;9(4):915.
50. Frangou E, Vassilopoulos D, Boletis J, Boumpas DT. An emerging role of neutrophils and NETosis in chronic inflammation and fibrosis in systemic lupus erythematosus (SLE) and ANCA-associated vasculitides (AAV): implications for the pathogenesis and treatment. *Autoimmun Rev*. 2019;18(8):751-760.
51. Foucher P, Heeringa P, Petersen AH, et al. Antimyeloperoxidase-associated lung disease. *Am J Resp Crit Care*. 1999;160(3):987-994.
52. Guilpain P, Chereau C, Goulvestre C, et al. The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis. *Eur Respir J*. 2010;37(6):1503-1513.
53. Heeringa P, Foucher P, Klok PA, et al. Systemic injection of products of activated neutrophils and H2O2 in myeloperoxidase-immunized rats leads to necrotizing vasculitis in the lungs and gut. *Am J Pathology*. 1997;151(1):131-140.
54. Churg A, Zay K, Shay S, et al. Acute cigarette smoke-induced connective tissue breakdown requires both neutrophils and macrophage metalloelastase in mice. *Am J Resp Cell Mol*. 2002;27(3):368-374.
55. Birnbaum J, Danoff S, Askin FB, Stone JH. Microscopic polyangiitis presenting as a "pulmonary-muscle" syndrome: Is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? *Arthritis Rheumatism*. 2007;56(6):2065-2071.
56. Schnabel A, Reuter M, Csernok E, Richter C, Gross W. Subclinical alveolar bleeding in pulmonary vasculitides: correlation with indices of disease activity. *Eur Respir J*. 1999;14(1):118-124.
57. de Chambrun MP, Nunes H, Brochériou I, Hertig A. Idiopathic lung fibrosis and anti myeloperoxidase glomerulonephritis: the tree that hides the forest. *Bmc Pulm Med*. 2015;15(1):130.
58. Borza D-B, Hudson BG. Molecular characterization of the target antigens of anti-glomerular basement membrane antibody disease. *Springer Semin Immun*. 2003;24(4):345-361.

59. Ball JA, Young JKR. Pulmonary manifestations of Goodpasture's syndrome: antiglomerular basement membrane disease and related disorders. *Clin Chest Med*. 1998;19(4):777-791.
60. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. *Am J Pathology*. 1989;135(5):921-930.
61. Hellmark T, Segelmark M. Diagnosis and classification of Goodpasture's disease (anti-GBM). *J Autoimmun*. 2014;48:108-112.
62. Arulkumaran N, Periselneris N, Gaskin G, et al. Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. *Rheumatology*. 2011;50(11):2035-2043.
63. Matsuda S, Kotani T, Suzuka T, et al. Evaluation of poor prognostic factors of respiratory related death in microscopic polyangiitis complicated by interstitial lung disease. *Sci Rep*. 2021;11(1):1490.
64. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline. *Am J Resp Crit Care*. 2015;192(2):e3-19.
65. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083-2092.
66. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082.
67. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J Pharmacol Exp Ther*. 2014;349(2):209-220.
68. Iyer SN, Hyde DM, Giri SN. Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. *Inflammation*. 2000;24(5):477-491.
69. Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2020;8(2):147-157.
70. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. 2020;8(5):453-460.
71. Vancheri C, Kreuter M, Richeldi L, et al. Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. *Am J Resp Crit Care*. 2018;197(3):356-363.
72. Flaherty KR, Fell CD, Huggins JT, et al. Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis. *Eur Respir J*. 2018;52(2):1800230.
73. National Institutes of Health Clinical Center Pilot study of pirfenidone in pulmonary fibrosis with anti-myeloperoxydase antibodies (PIRFENIVAS) [Internet]. Last updated: 2021 May 3rd. [cited 2021 Sep 6]. Available from: https://clinicaltrials.gov/ct2/show/NCT03385668
74. Chino H, Hagiwara E, Kitamura H, et al. Myeloperoxidase anti-neutrophil cytoplasmic antibody-positive interstitial pneumonia associated with granulomatosis with polyangiitis diagnosed by surgical lung biopsy. *Respiration*. 2016;92(5):348-355.
75. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-Acetylcysteine for pulmonary fibrosis. *New Engl J Medicine*. 2012;366(21):1968-1977.
76. Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med*. 2014;371(6):507-518.
77. Picard C, Thouvenin G, Kannengiesser C, et al. Severe pulmonary fibrosis as the first manifestation of interferonopathy (TMEM173 Mutation). *Chest*. 2016;150(3):e65-71.
78. Seo J, Kang J-A, Suh DI, et al. Tofacitinib relieves symptoms of stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy caused by 2 de novo variants in TMEM173. *J Allergy Clin Immun*. 2017;139(4):1396-1399.e12.
79. Frémond M-L, Rodero MP, Jeremiah N, et al. Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immun*. 2016;138(6):1752-1755.
80. Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. 2018;128(7):3041-3052.
81. Zhang H, Watanabe R, Berry GJ, Tian L, Goronzy JJ, Weyand CM. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. *Circulation*. 2018;137(18):1934-1948.
82. Yamamura Y, Matsumoto Y, Asano Y, et al. Refractory Takayasu arteritis responding to the oral janus kinase inhibitor, tofacitinib. *Rheumatol Adv Pract*. 2019;4(1):rkz050.
83. Wang K, Zhao J, Chen Z, et al. CD4+CXCR4+ T cells as a novel prognostic biomarker in patients with idiopathic inflammatory myopathy-associated interstitial lung disease. *Rheumatology*. 2018;58(3):511-521.
84. Chen Z, Wang X, Ye S. Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. *N Engl J Med*. 2019;381(3):291-293.
85. Kurasawa K, Arai S, Namiki Y, et al. Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. *Rheumatology*. 2018;57(12):2114-2119.
86. You H, Xu D, Zhao J, et al. JAK inhibitors: prospects in connective tissue diseases. *Clin Rev Allerg Immu*. 2020;59(3):334-351.
87. Kusunoki Y, Nakazawa D, Shida H, et al. Peptidylarginine deiminase inhibitor suppresses neutrophil extracellular trap formation and MPO-ANCA production. *Front Immunol*. 2016;7:227.
88. Schmid HHO, Berdyshev EV. Cannabinoid receptor-inactive N -acylethanolamines and other fatty acid amides: metabolism and function. *Prostaglandins Leukot Essent Fat Acids Plefa*. 2002;66(2–3):363-376.
89. Paola RD, Impellizzeri D, Fusco R, et al. Ultramicronized palmitoylethanolamide (PEA-um®) in the treatment of idiopathic pulmonary fibrosis. *Pharmacol Res*. 2016;111:405-412.
90. Fusco R, Cordaro M, Genovese T, et al. Adelmidrol: a new promising antioxidant and anti-inflammatory therapeutic tool in pulmonary fibrosis. *Antioxidants*. 2020;9(7):601.
91. Davies MJ, Hawkins CL. The role of myeloperoxidase in biomolecule modification, chronic inflammation, and disease. *Antioxid Redox Sign*. 2020;32(13):957-981.
92. Morisset J, Lee JS. New trajectories in the treatment of interstitial lung disease: treat the disease or treat the underlying pattern? *Curr Opin Pulm Med*. 2019;25(5):442-449.

How to cite this article: Hu H, Keat K. Myeloperoxidase and associated lung disease: Review of the latest developments. *Int J Rheum Dis*. 2021;24:1460–1466. https://doi.org/10.1111/1756-185X.14213

Received: 10 December 2020 | Revised: 13 May 2021 | Accepted: 23 May 2021

DOI: 10.1111/1756-185X.14156

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

Magnetic Resonance Imaging evidence of Inflammation at Interphalangeal joint of Thumb — A distinct entity in psoriatic arthritis

Ashish J Mathew[1] | Arvind Ganapati[1] | Jyoti Panwar[2] | Varghese Koshy[1,3] | Anu Desai[4] | Debashish Danda[1]

[1]Department of Clinical Immunology & Rheumatology, Christian Medical College, Vellore, India

[2]Department of Radiology, Christian Medical College, Vellore, India

[3]Department of Rheumatology and Clinical Immunology, Command Hospital (Central Command), Lucknow, India

[4]Department of Inflammation and Ageing, University of Birmingham, Birmingham, UK

Correspondence
Debashish Danda, Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore 632 004, India.
Email: debashish.danda@cmcvellore.ac.in and debashisdandacmc@hotmail.com

Funding information
Asia Pacific League of Associations for Rheumatology (APLAR) research grant 2015.

Abstract

Background: This study aimed to compare inflammation at the interphalangeal (IP) joint of thumb in patients with psoriatic arthritis (PsA), rheumatoid arthritis (RA), undifferentiated inflammatory arthritis (UIA), and in psoriasis patients without clinical arthritis (PsO) using low-field magnetic resonance imaging (MRI).

Methods: Age-matched and disease duration-matched patients with inflammatory arthritis (RA, PsA, and UIA) and psoriasis patients without clinical arthritis (PsO), who had undergone MRI of hands were included in this study. The presence or absence of MRI inflammatory lesions including synovitis, tenosynovitis, and bone marrow edema was assessed by three independent readers. Agreement between the readers was assessed using the intraclass correlation coefficient. Risk ratio of MRI global inflammation around thumb IP joints among patients with PsA was compared with the other groups.

Results: Clinical parameters and MRI inflammation were studied in 161 patients (42 PsA, 28 RA, 29 UIA, and 62 PsO). Global MRI inflammation at the IP joint of the thumb was observed in 33.3% of PsA patients compared with 14.3% in RA, and 10.3% in UIA. Subclinical MRI inflammation was observed in 8.1% of patients with PsO. The risk ratios of MRI global inflammation at the IP joint of the thumb in PsA patients were 2.3 (95% confidence interval [CI] 0.86-6.36) and 3.2 (95% CI 1.02-10.21) compared with RA and UIA patients, respectively.

Conclusion: Global MRI inflammation around the IP joint of the thumb is significantly more common in patients with PsA as compared to individuals with UIA.

KEYWORDS

inflammation, magnetic resonance imaging, psoriatic arthritis, interphalangeal joint of thumb

1 | INTRODUCTION

Symmetric, inflammatory polyarthritis is a common presentation in patients with psoriatic arthritis (PsA), which can at times be difficult to differentiate from other forms of polyarthritis like rheumatoid arthritis (RA).[1] Magnetic resonance imaging (MRI) has been shown to be sensitive in diagnosing and monitoring patients with PsA, and is being increasingly used. Over the past two decades there has been a renewed interest in imaging of patients with

PsA, mostly to detect early disease, and to use the window of opportunity for aggressive therapy, so reducing long-term structural damage.[2,3] A wide array of targeted therapies being discovered for treatment of PsA warrants the need for sensitive tools to objectively monitor outcome. The Outcome Measures in Rheumatology (OMERACT) PsA MRI scoring system (PsAMRIS) has been validated to estimate inflammation in and around the small joints of the hand in patients with PsA. The inflammatory pathologies, as defined by PsAMRIS, include synovitis, flexor tenosynovitis, periarticular inflammation, and bone marrow edema. The joints in the thumb, however, have not been included in the PsAMRIS.[4,5]

The potential role of micro-trauma in the pathogenesis of PsA is well recognized.[6,7] Recent high-definition MRI studies have emphasized the role of a "deep Koebner phenomenon" initiating inflammation and thickening of flexor tendon pulleys leading to tenosynovitis and dactylitis, which are recognized as pathognomonic features of PsA.[8,9] The joints in the thumb are among the most used joints in the body, and consequently are subjected to microtrauma more often compared to other small joints of the hand. Moreover, unlike in other digits, the thumb has only one interphalangeal (IP) joint, which is subjected to microtrauma on a regular basis. A disproportionate swelling at the IP joint of the thumb was proposed to have high diagnostic significance for PsA in a previous study.[10] In another small cohort, non-contrast 0.2T extremity MRI was found to differentiate between patients with PsA and RA, based on synovitis and tenosynovitis at the IP joint of the thumb in PsA.[11]

The aim of the present study, therefore, was to evaluate low-field MRI-defined inflammation around the IP joint of the thumb in patients with PsA, RA, and undifferentiated inflammatory arthritis (UIA), and in psoriasis patients without clinical arthritis (PsO).

Key points

1. Disproportionate swelling at the interphalangeal joint of thumb is a specific clinical feature of psoriatic arthritis
2. MRI inflammation at the interphalangeal joint of thumb may aid in differentiating patients with psoriatic arthritis from those with rheumatoid arthritis and undifferentiated inflammatory arthritis
3. This finding needs to be validated using a high-field MRI with dedicated coil and gadolinium enhancement.

2 | MATERIALS AND METHODS

Our study patients included adults with diagnoses of (a) PsA (fulfilling classification criteria for psoriatic arthritis—CASPAR); (b) RA (fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria); (c) UIA (seronegative inflammatory polyarthritis, not fulfilling the RA or any other connective tissue disease criteria); and (d) psoriasis (diagnosed by a dermatologist) without clinical arthritis from general rheumatology and combined psoriatic clinic of our tertiary care teaching hospital, who had undergone routine MRI of their hands for any indication between July 23, 2014 and July 22, 2017.[12,13] We had retrospectively retrieved prospectively documented demographic data and clinical details from the hospital Electronic medical record. The protocol of this study was approved by the Christian Medical College Vellore Institutional Research Review Board (Ref. 10926; October 25, 2017) before data retrieval.

2.1 | Magnetic resonance imaging

Non-contrast MRI of the most affected hand (PsA, RA, and UIA) or dominant hand (psoriasis) was performed in the Department of Clinical Immunology and Rheumatology using a low-field extremity MRI (0.2T C-scan, Esaote, Genova, Italy). All MRI scans were performed using a standardized protocol, and included three dimensional-gradient echo (3D-GE) coronal [Repetition time (TR) 50 ms, Time to Echo (TE) 16 ms, slice thickness 1.1 mm, Matrix 192 × 176, number of acquisition 1, flip angle 65 degrees], short-tau inversion recovery (STIR) coronal [TR 1060 ms, TE 18 ms, inversion time 75 ms, slice thickness 3.5 mm, Matrix 192 × 128], turbo spin echo (TSE) T2-transverse [TR 4160 ms, TE 80 ms, slice thickness 3.5 mm, Matrix 192 × 148] and STIR transverse [TR 2280 ms, TE 18 ms, inversion time 75 ms, slice thickness 3.5 mm, Matrix 192 × 148] sequences. The included MRI scans were scored at the level of the IP joint of the thumb for the presence or absence of inflammatory variables (synovitis, tenosynovitis, and bone marrow edema) following definitions adapted from the OMERACT PsAMRIS. "MRI global inflammation" was defined as the presence of any of these MRI pathologies in a patient. Images were read centrally by three independent readers (AJM, JP, AG), anonymized to demographic and clinical details.

2.2 | Statistical analysis

Demographic, clinical, and MRI data were entered and analyzed using SPSS software v.21 (IBM, Armonk, NY, USA). Continuous variables are depicted as mean ± standard deviation or median with range (based on the normality of data distribution) and categorical variables are given as frequencies with percentages. There was no data imputation. MRI global inflammation in RA and UIA patients was compared with that in PsA patients (reference group) using Fisher exact tests. Significance was assumed at a level of 5%. Inter-reader reliability for MRI inflammatory lesions was calculated using intra-class correlation coefficient (ICC) by two-way mixed effects model, with single measure for absolute agreement.[14]

3 | RESULTS

3.1 | Study population

Following a screening of all MRIs to be reported, data of 161 patients (42 PsA, 28 RA, 29 UIA, and 62 PsO) were included. The mean age of

TABLE 1 Demographic and clinical characteristics of patients in different groups

Parameters	PsA	RA	UIA	PsO
Number of patients	42	28	29	62
Age (years), mean ± SD	42.08 ± 11.90	48.39 ± 10.92	46.4 ± 12.45	40.9 ± 13.3
Female:Male	14:28	25:3	22:7	14:48
Total duration of illness (months), median (range)	29.14 (6-126)	31.5 (2-340)	33 (1-194)	72 (1-240)
TJC, median (range)	9.5/68 (0-40)	11/28 (0-28)	6/28 (0-27)	0/68
SJC, median (range)	8.5/66 (0-22)	8/28 (0 - 22)	5/28 (0 - 22)	4/66
CRP, median (range)	22.67(5.4-59.4)	11 (1.06-58.8)	8.2 (0.2-51.4)	2.47 (0.16-53.4)

Abbreviations: CRP, C-reactive protein; PsA, psoriatic arthritis; PsO, psoriasis without fulfilling CASPAR criteria; RA, rheumatoid arthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; UIA, undifferentiated inflammatory arthritis.

all patients with inflammatory arthropathies was 45.7 ± 10.9 years, and it was 40.9 ± 13.3 years in psoriasis patients without arthritis. These two groups comprised of 38 (38.3%) and 48 (77.4%) men, respectively. Table 1 describes the demographic, clinical, and laboratory details of all patients included in the study, divided into different subgroups.

3.2 | Inter-reader reliability

Thirty-three images in the RA + UIA group and 22 images in the PsA group were randomly scored by two independent readers who were blinded to the clinical features and diagnosis. The ICC as the measure of inter rater reliability between the readers for all MRI inflammatory pathologies was moderate (0.61-0.79).

3.3 | Thumb IP joint swelling on clinical examination

In the PsA group 15/42 (36%) had swelling at the IP joint on physical examination, compared with 3/28 (11%) and 1/29 (3%) in the RA and UIA groups, respectively. In the PsO group this finding was present in 4/62 (6%) of patients (Figure 1).

3.4 | MRI inflammation in different groups

MRI inflammation around the IP joint of the thumb was noted in 33.3% of PsA patients, compared with 14.3% ($P = 0.06$) and 10.3% ($P = 0.02$) in the RA and UIA groups, respectively (Figure 2). In the PsO group, 8.1% of patients had MRI global inflammation at the IP joint of the thumb. Tenosynovitis was the predominant inflammatory variable in PsA (19%) and PsO (4.8%) groups, as compared with 3.6% ($P = 0.05$) and 3.4% ($P = 0.05$) in RA and UIA, respectively. MRI synovitis at the IP joint, though proportionately larger in PsA, did not differ significantly between the groups (Table 2). The risk of global MRI inflammation around the IP joint of thumb in PsA patients was twice as high compared to RA patients, and 3.2 times compared to UIA patients (Table 3).

4 | DISCUSSION

This cross-sectional study included random individuals with PsA, RA, and UIA recruited from rheumatology clinics; comparison of MRI inflammation at or around the IP joint of the thumb using a low-field magnet demonstrated overall higher involvement in the PsA patients compared with the other two subsets of arthritis patients.

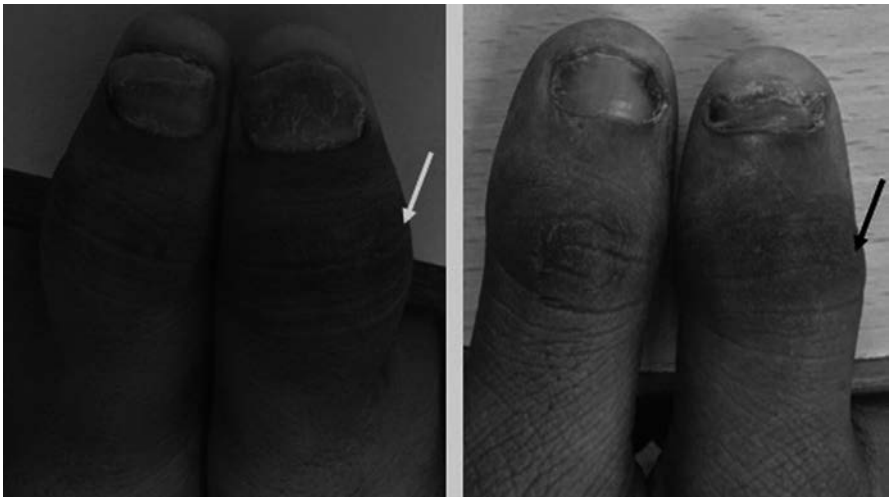


FIGURE 1 Clinical pictures of swelling at the interphalangeal joint of the right thumb in patients with psoriatic arthritis

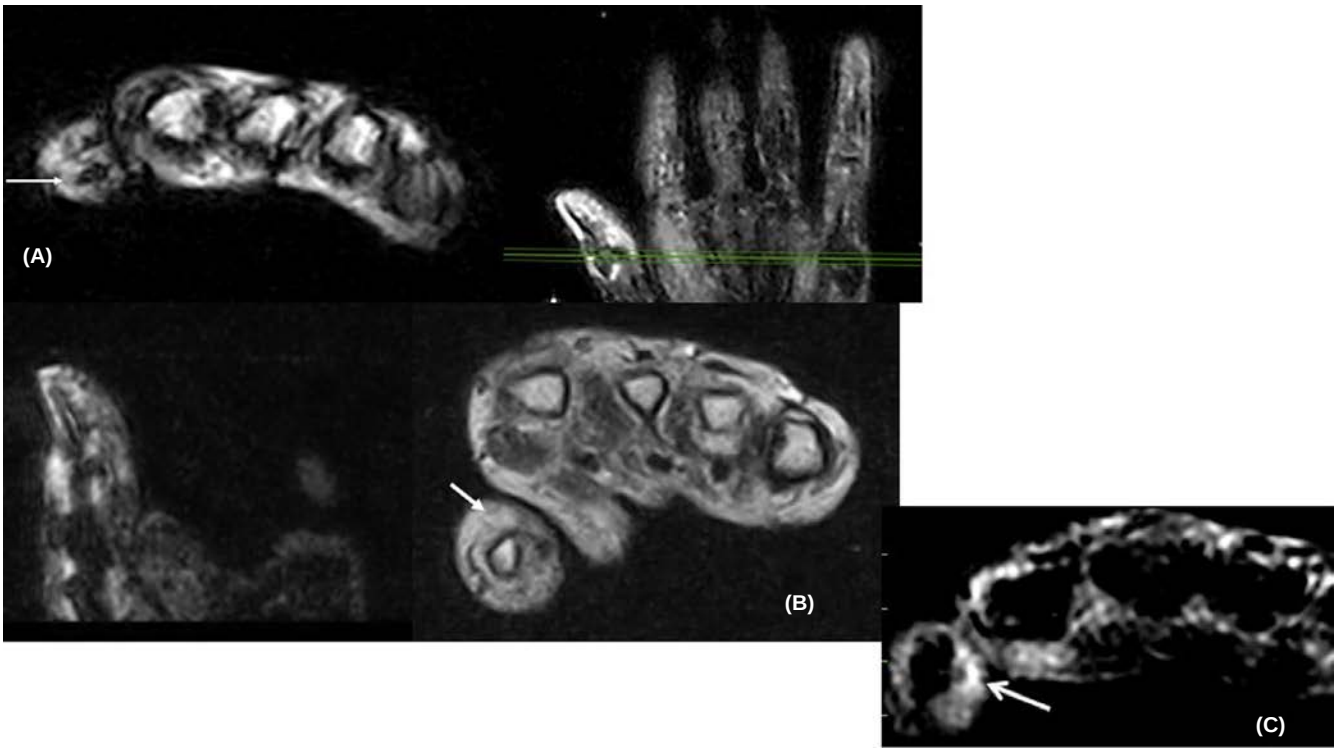


FIGURE 2 A,B, Extremity magnetic resonaonce imaging (MRI) of hand in STIR coronal and axial sequences, with arrows pointing to synovitis at the interphalangeal (IP) joint of the thumb. C, Extremity MRI of hand in STIR axial sequence with arrow pointing to tenosynovitis at the IP joint of thumb

TABLE 2 Comparison of MRI pathologies and global MRI inflammation between the groups

Diagnosis	Clinical swelling at thumb IP joint n (%)	MRI synovitis* n (%)	MRI tenosynovitis** n (%)	Global MRI inflammation*** n (%)
PsA (N = 42)	15 (35.7)	6 (14.3)	8 (19)	14 (33.3)
RA (N = 28)	3 (10.7)	3 (10.7)	1 (3.6)	4 (14.3)
UIA (N = 29)	1 (3.4)	2 (6.9)	1 (3.4)	3 (10.3)
PsO (N = 62)	4 (6.4)	2 (3.2)	3 (4.8)	5 (8.1)

Abbreviations: IP, interphalangeal; MRI, magnetic resonance imaging; PsA, psoriatic arthritis; PsO, psoriasis without fulfilling CASPAR criteria; RA, rheumatoid arthritis; UIA, undifferentiated inflammatory arthritis.

*P values: PsA vs RA, $P = 0.48$; PsA vs UIA, $P = 0.28$; **P values: PsA vs RA, $P = 0.05$; PsA vs UIA, $P = 0.05$; ***P values: PsA vs RA, $P = 0.06$; PsA vs UIA, $P = 0.02$.

TABLE 3 Risk ratio of global MRI inflammation in RA and UIA compared with PsA patients

	Group 1		Group 2				
Diagnosis	MRI Inf+	MRI Inf−	MRI Inf+	MRI Inf−	Risk ratio	95% CI	*P* value
PsA vs RA	14	28	4	24	2.33	0.86-6.36	0.09
PsA vs UIA	14	28	3	26	3.22	1.02-10.21	**0.04**
RA vs UIA	4	24	3	26	1.2	0.29-4.95	0.79

Abbreviations: MRI Inf, global MRI inflammation; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UIA, undifferentiated inflammatory arthritis.

Group 1 – reference disease group; Group 2 – group that is being compared.

Bold value was because that particular *P* value was significant as it was less than 0.05.

Involvement of the thumb in psoriatic arthritis is not well described in the literature. Our findings agree with the clinical observation of disproportionate involvement of IP joints of the thumb observed in 28.7% of PsA patients described earlier by Danda et al. That study also had demonstrated a positive predictive value of 84% for disproportional swelling at the IP joint of the thumb for a diagnosis of PsA.[10] In an epidemiological study on psoriatic patients with arthritis mutilans in the Scandinavian countries, the IP joint of the thumb was the most commonly involved joint in the hand.[15] Base of the thumb is also a common site to be involved in hand osteoarthritis. Kroon et al. have demonstrated that structural lesions have stronger association with thumb base pain in hand osteoarthritis as compared to synovitis.[16] Yet another study has highlighted the importance of enlargement of thumb sesamoids assisting the diagnosis of PsA in comparison with patients of RA and osteoarthritis.[17]

The PsAMRIS has not included the thumb because of its involvement in other forms of arthritis like osteoarthritis. Identifying MRI pathologies in the thumb tendons can be challenging because of the presence of both abductors and adductors, in addition to flexors and extensors. Difference in the planes of fingers and thumb also pose major challenges with specificity of scoring.

The plausible biological explanations for this finding at the IP joint of the thumb need to be studied further. The thumb has only one IP joint, unlike proximal and distal IPs in other fingers. The IP thumb joint, because of its close proximity to the nail enthesis organ, could anatomically behave more like a distal IP joint of the other fingers and this may explain its predilection for inflammation in PsA patients. Tan et al, using high-resolution MRIs and histology of the distal IP joints of patients with PsA or OA and in normal joints, have demonstrated the extended nature of the enthesis organ associated with the distal IP joint in PsA patients; and, thereby, explained the diffuse inflammation around the distal IP joints in PsA.[18] The IP joint of thumb, especially on the dominant hand, is a site of high mechanical stress, being one of the most used joints. Repeated use of the joint can lead to microtrauma, eventually triggering a "deep Koebner phenomenon". Our present study has, therefore, validated a bedside clinical observation that can be used for early diagnosis of PsA and for differential diagnosis, especially among seronegative patients with inflammatory polyarthritis involving small joints of the hands including seronegative/early RA and UIA.

The findings of this study should be interpreted while acknowledging certain technical limitations. First, the low field magnet used and lack of contrast enhancement are known to decrease sensitivity and specificity, and consequently increase false-positive rates.[19] Second, the thumb and fingers are not in the same plane while imaging, and no dedicated surface coils were used for viewing the thumb joints. This could again affect the sensitivity of observations of lesions. Third, the retrospective nature and convenient sampling of patients in this study could lead to some bias. However, similar findings were demonstrated in both the PsA group and some of the patients of psoriasis without arthritis, and the findings were significant in PsA compared with the other groups under similar constraints; thereby, some of these limitations were overcome.

This research question, nevertheless, warrants further validation in a prospective study using dedicated, high-resolution coils, high magnetic fields and contrast enhancing imaging; an ultrasound comparator arm may add additional strength.

In conclusion, MRI global inflammation at and around the IP joint of the thumb was noted to be significantly more common in patients with PsA with a risk ratio of 3.2 in comparison with that in UIA; further validation studies are warranted for wider generalizability.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. E Rasu for helping with the MRI acquisition. Part of this study was funded by the Asia Pacific League of Associations for Rheumatology (APLAR) research grant 2015.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Ashish J Mathew https://orcid.org/0000-0002-2061-2042
Anu Desai https://orcid.org/0000-0002-9525-3435
Debashish Danda https://orcid.org/0000-0002-2121-0942

REFERENCES

1. Gladman DD. Clinical features and diagnostic considerations in psoriatic arthritis. *Rheum Dis Clin North Am*. 2015;41:569–579.
2. Østergaard M, Eder L, Christiansen SN, Kaeley GS. Imaging in the diagnosis and management of peripheral psoriatic arthritis – the clinical utility of magnetic resonance imaging and ultrasonography. *Best Pract Res Clin Rheumatol*. 2016;30:624–637.
3. Mathew AJ, Coates LC, Danda D, Conaghan PG. Psoriatic arthritis: lessons from imaging studies and implications for therapy. *Expert Rev Clin Immunol*. 2017;13:133–142.
4. Østergaard M, McQueen F, Wiell C, et al. The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): definitions of key pathologies, suggested MRI sequences, and preliminary scoring system for PsA hands. *J Rheumatol*. 2009;36:1816–1824.
5. Glinatsi D, Bird P, Gandjbakhch F, et al. Validation of the OMERACT psoriatic arthritis magnetic resonance imaging score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. *J Rheumatol*. 2015;42:2473–2479.
6. Eder L, Law T, Chandran V, et al. Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis. *Arthritis Care Res (Hoboken)*. 2011;63:1091–1097.
7. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin S. The early phase of psoriatic arthritis. *Ann Rheum Dis*. 2011;70(Suppl 1):i71–i76.
8. Tan AL, Fukuba E, Halliday NA, Tanner SF, Emery P, McGonagle D. High-resolution MRI assessment of dactylitis in psoriatic arthritis shows flexor tendon pulley and sheath-related enthesitis. *Ann Rheum Dis*. 2015;74:185–189.
9. Tinazzi I, McGonagle D, Aydin SZ, Chessa D, Marchetta A, Macchioni P. 'Deep Koebner' phenomenon of the flexor tendon-associated accessory pulleys as a novel factor in tenosynovitis and dactyltis in psoriatic arthritis. *Ann Rheum Dis*. 2018;77:922–925.
10. Danda D, Cherian AM, Jayaseelan L. Disproportionate swelling of interphalangeal joint of thumb: Is it unique to psoriatic arthropathy? *J Indian Rheumatol Assoc*. 2000;8:1–4.
11. Mathew AJ, Panwar J, Francis I, Koshy V, Danda D. Office extremity magnetic resonance imaging can differentiate psoriatic and rheumatoid arthritis without contrast enhancement. *Ann Rheum Dis*. 2015;74:1246.

12. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. and the CASPAR Study Group. Classification criteria for psoriatic arthritis. Development of new criteria from a large international study. *Arthritis Rheum*. 2006;54:2665–2673.
13. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria. An American College of Rheumatology/European League Against Rheumatism collaborative initiatve. *Arthritis Rheum*. 2010;9:2569–2581.
14. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15:153–163.
15. Gudbjornsson B, Ejstrup L, Gran JT, et al. Psoriatic arthritis mutilans (PAM) in the Nordic countries: demographics and disease status. The Nordic PAM study. *Scand J Rheumatol*. 2013;42:373–378.
16. Kroon FPB, van Beest S, Ermurat S, et al. In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis. *Osteoarthritis Cartilage*. 2018;26:1196–1202.
17. Whitehouse RW, Aslam R, Bukhari M, Groves C, Cassar-Pullicino V. The sesamoid index in psoriatic arthropathy. *Skeletal Radiol*. 2005;34:217–220.
18. Tan AL, Benjamin M, Toumi H, et al. The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis – a high-resolution MRI and histological study. *Rheumatology (Oxford)*. 2007;46:253–256.
19. Bird P, Ejbjerg B, Lassere M, et al. A multireader reliability study comparing conventional high-field magnetic resonance imaging with extremity low-field MRI in rheumatoid arthritis. *J Rheumatol*. 2007;34:854–856.

How to cite this article: Mathew AJ, Ganapati A, Panwar J, Koshy V, Desai A, Danda D. Magnetic Resonance Imaging evidence of Inflammation at Interphalangeal joint of Thumb. *Int J Rheum Dis*. 2021;24:1467–1472. https://doi.org/10.1111/1756-185X.14156

Received: 28 January 2021 | Revised: 15 June 2021 | Accepted: 18 June 2021

DOI: 10.1111/1756-185X.14169

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Acceptance and image quality of high-resolution peripheral quantitative computed tomography of the metacarpophalangeal joints in rheumatoid arthritis

Rasmus Klose-Jensen[1,2] | Kresten Krarup Keller[1] | Bente Langdahl[3,2] | Ellen-Margrethe Hauge[1,2]

[1]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[3]Department of Endocrinology and Internal Medicine, Aarhus University, Aarhus, Denmark

Correspondence
Rasmus Klose-Jensen, Department of Rheumatology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 45, 8200 Aarhus N, Denmark.
Email: raujen@rm.dk

Funding information
The study has been financially supported by Aarhus University, The Danish Rheumatism Association, Novo Nordic Foundation and AP Møller Fonden. The funding sources did not have any role in the collection, analysis and interpretation of data.

Abstract

Objective: High-resolution peripheral quantitative computed tomography (HR-pQCT) requires longer immobilization time than conventional radiography, which challenges patient acceptance and image quality. Therefore, the aim was to investigate the acceptance of HR-pQCT in patients with rheumatoid arthritis (RA), and secondly the effect of an inflatable hand immobilization device on motion artefacts of the metacarpophalangeal (MCP) joints.

Methods: Fifty patients with established RA and a median (interquartile range) age of 64.3 (55.0-71.2) years had their MCP joints scanned by HR-pQCT with the hand positioned with and without an inflatable immobilization device followed by a full radiographic examination and a questionnaire on the imaging experience. The comparability of the erosion measures was investigated with and without the immobilization device using Bland-Altman plot and intrareader repeatability by intraclass correlation coefficient. The motion artefacts were graded for each acquisition, and intrareader repeatability was investigated by Cohen's kappa coefficient.

Results: Forty percent of the patients preferred HR-pQCT imaging, only 6% preferred conventional X-ray. Seventy-four percent reported it was not difficult to keep their fingers steady during the scan. Sixty percent of the patients reported the immobilization device helped keep their fingers steady. However, as motion artefacts were sparse, no clinically relevant difference was observed concerning the effect of the immobilization device on readability. The intrareader repeatability and comparability for the erosion measures were excellent.

Conclusion: The high patient acceptance adds to the feasibility of HR-pQCT imaging of MCP joints in RA. The inflatable immobilization device did not reduce motion-induced image degradation.

KEYWORDS

erosions, HR-pQCT (high-resolution peripheral quantitative computed tomography), motion artefact, patient-reported experience measures, rheumatoid arthritis

1 | INTRODUCTION

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a promising imaging modality for monitoring rheumatoid arthritis (RA).[1,2] However, HR-pQCT imaging time for the metacarpophalangeal (MCP) joints alone yields an acquisition time of 9 minutes, far longer than the current gold-standard conventional X-ray. Immobilizing the hand during the acquisition might discomfort the patients, resulting in poor acceptance and adherence. Presently, the patient acceptance of HR-pQCT imaging has not been investigated.

HR-pQCT uses the same principles as traditional CT, which has an inherent contrast between bone and soft tissue; this makes it ideal for the detection of bone damage *in vivo*.[3] Furthermore, the HR-pQCT scanner has a very low radiation dose of roughly 0.025 mSv for the wrist and MCP joints.[4] However, the long imaging time may induce motion-induced image degradation. A previous study has shown that HR-pQCT imaging of the radius had to be repeated for 67% of patients due to motion artefacts.[5] The acquisition time for the radius is only 3 minutes. Therefore, the 9 minutes acquisition time for the MCP joints might exacerbate the motion artefacts. However, motion-induced image degradation and the number of repeated acquisitions are rarely reported for the MCP joints.[6-9] One study has reported 5.7% of MCP, and proximal interphalangeal joints had to be excluded from erosion analysis due to motion-induced image degradation.[8]

Movements of the fingers and hand occur from neuro-muscular activation in the forearm and hand or from the arm and upper body and may be related to joint pain or uncomfortable positioning. Therefore, measures to reduce motion-induced image degradation of the MCP joint during imaging should focus on both muscle relaxation and blocking of movements.

The objective of this study was 2-fold. First, to investigate the acceptance of HR-pQCT in patients with RA, and evaluate whether replacing conventional X-ray with HR-pQCT imaging in clinical practice would negatively influence the patient experience. Second, to investigate the comparability and repeatability of visual grading of motion artefacts and erosion measures of the 2nd and 3rd MCP joints with the hand positioned with and without an inflatable immobilization device. The use of an immobilization device during image acquisition will apply compression on the digits, restricting their movements, and is thus hypothesized to reduce motion-induced image degradation.

2 | METHODS

2.1 | Study design and population

Patients with RA, according to the American College of Rheumatology / European League Against Rheumatism (2010) classification criteria,[10] were recruited from the outpatient clinic at the Department of Rheumatology, Aarhus University Hospital. Inclusion criteria were the ability to give consent, age ≥18 years and disease duration ≥5 years. Exclusion criteria were fracture or luxation of the MCP joints in both hands, evidence of active malignant disease, hypocalcemia, impaired renal function (estimated glomerular filtration rate <35 mL/min), untreated hypo- or hyperthyroidism or pregnancy.

A full medical history was obtained, and a clinical examination was performed for all individuals. Specifically, demographic and clinical data were obtained, including age, gender, disease duration, number of tender and swollen joints, C-reactive protein, as well as anti-citrullinated protein antibodies and immunoglobulin M rheumatoid factor.

2.2 | Conventional radiography

All patients had their hands, wrists and feet examined with radiographs using the standard dorsopalmar projection. The image was generated at a focus distance of 100-115 cm, 50-55 kV and 2-12 mAs. If radiographs had been performed within the last 3 months or were scheduled in the 3 months following inclusion, this was recorded as the baseline. The radiographs were evaluated with the Sharp/van der Heijde method.[11]

2.3 | HR-pQCT acquisition procedure

An image acquisition protocol endorsed by the Study grouP for xtrEme-Computed Tomography in Rheumatoid Arthritis (SPECTRA) was used.[12] The 2nd and 3rd MCP joint was imaged using first-generation XtremeCT (Scanco Medical AG, Wangen-Brüttiselen, Switzerland). A 2.7-cm long volume of interest was scanned with a spatial resolution of 82 μm^3, an X-ray tube voltage of 59.4 kVp, a current of 900 μA, and an integration time of 100 ms The scan was performed within a region of 80 slices (6.56 mm) distal and 250 slices (20.5 mm) proximal to the distal end of the 3rd metacarpal head. The dominant hand was scanned except in cases with prior fracture or luxation in the MCP joints.

The patients were scanned twice with the hand positioned with and without an inflatable immobilization device.[13] Splint without the inflatable immobilization device: the hand and forearm were positioned parallel to the long axis of a rigid splint and strapped down to the rigid splint at the MCP joints and the distal and proximal part of the forearm. The splint-supported hand and forearm were then positioned within a cylindrical holder manufactured by Scanco Medical AG. The cylindrical holder was placed inside the HR-pQCT unit for scan acquisition (Figure 1A,B). Splint with the inflatable immobilization device: the hand was immobilized using a rigid splint as described above. However, an inflatable immobilization device (Multipad Bendy, Pearltec AG, Zurich, Switzerland) was then positioned over the fingers and inflated to immobilize the fingers (Figure 1C,D).

Twenty-five patients were scanned first without the inflatable immobilization device and subsequently with the inflatable immobilization device. The other 25 patients were scanned first with the inflatable immobilization device and subsequently without the

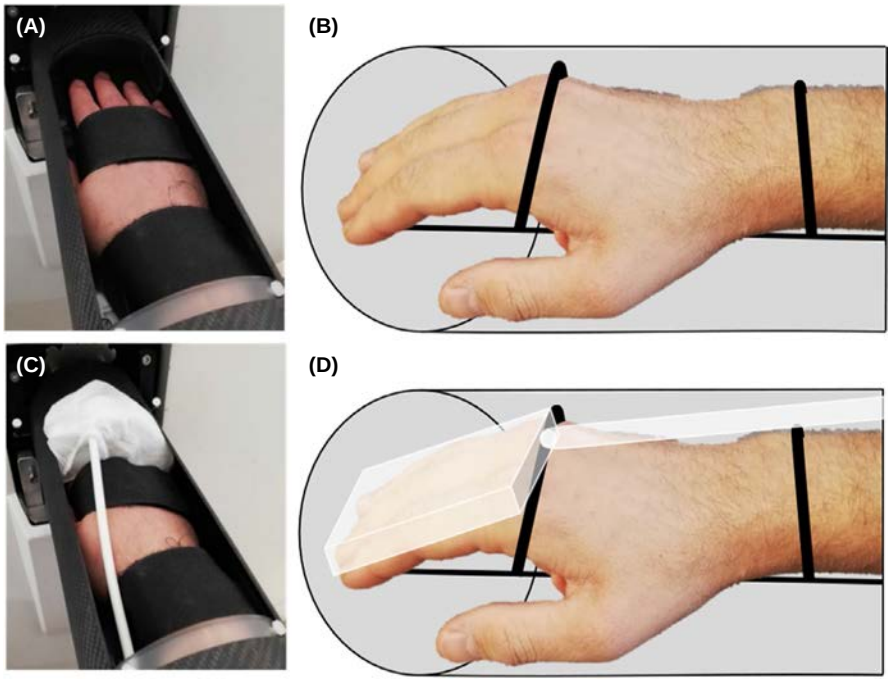


FIGURE 1 Hand positioning. A, Without the inflatable immobilization device (acquisition A). The hand is placed in a rigid splint with straps to immobilize the fingers. B, Schematic illustration of the hand placed in the rigid splint. C, With the inflatable immobilization device (acquisition B). The splinted hand is placed in the rigid splint, and the inflatable immobilization device is inflated around the hand. D, Schematic illustration of the hand placed in the rigid splint, with the inflatable immobilization device

inflatable immobilization device in order to minimize bias. Each image was anonymized before analysis in random order using Osirix software (Version 9.0.1; Pixmeo, Bernex, Switzerland) and a 27-inch cinema screen iMac.

2.4 | Patient-reported experience measure

A questionnaire was developed, in conjunction with RA patients at our department, to investigate the patient-reported experience measure.[14] The questionnaire investigated the acceptance of HR-pQCT imaging, with and without the inflatable immobilization device (Table 1). The patients were asked to fill out the questionnaire after the conventional radiographs and both HR-pQCT acquisitions.[15]

2.5 | Visual grading of motion artefacts for HR-pQCT images

For each anonymized acquisition, the motion-induced image degradation was graded for the distal, middle, and proximal 110-slices stack of the 330-slices stack. The grading of motion-induced image degradation was based on a grading scale proposed by the scanner manufacturer for the 110-slices stack of radius and tibia acquisitions, where the presence and extent of horizontal streaking, disruption of cortical contiguity and trabecular smearing is used for grading.[16] Five different grades were defined from grade 1 (no visible motion artefacts) to grade 5 (severe motion artefacts). A visual grade ≤3 is adequate for the reproducibility of standard morphological parameters such as bone mineral density and microstructure in the radius.[17]

2.6 | HR-pQCT erosion measures

The metacarpal head and proximal phalanx of the 2nd and 3rd MCP joints were assessed for erosions by a single trained reader (RKJ). Erosions were defined according to the SPECTRA collaboration: (a) a definite break in the cortical bone; (b) the cortical break must extend over at least 2 consecutive slices; (c) the cortical break must be detectable in 2 perpendicular planes; (d) the cortical interruption must have a loss of underlying trabecular bone; and (e) the cortical interruption must be nonlinear in shape to differentiate from vascular channels penetrating the cortices.[18] For all erosions, the maximum width, depth and length were measured. Width and depth were measured in the axial plane. The length was measured in the coronal plane for erosions located in either the radial or ulnar quadrant. Conversely, the length was measured in the sagittal plane for erosions located in the palmar or dorsal quadrant.

2.7 | Intrareader repeatability

Ten images from the acquisitions without the inflatable immobilization device and 10 images from the acquisition with the inflatable immobilization device were chosen at random and re-evaluated by a single trained reader (RKJ) 1 week later to determine intrareader repeatability of the visual grading for motion artefacts and the erosion measures.

2.8 | Ethical considerations

The Ethics Committee of Medical Research in Central Denmark Region (J. no. 1-10-72-437-17) and The Danish Data Protection

TABLE 1 The patient-reported procedure experience according to the high-resolution peripheral quantitative computed tomography (HR-pQCT) imaging and the inflatable immobilization device

	Strongly disagree n (%)		Disagree n (%)		Neither agree nor disagree n (%)		Agree n (%)		Strongly agree n (%)	
	A	B	A	B	A	B	A	B	A	B
I felt well informed about the radiation risk.				1 (2)	1 (2)	1 (2)	6 (12)	7 (14)	18 (36)	16 (32)
I had the opportunity to ask questions before the imaging.							5 (10)	6 (12)	20 (40)	19 (38)
I felt well informed about how the imaging would proceed.							5 (10)	6 (12)	20 (40)	19 (38)
I felt that I could stop the imaging at any time.						1 (2)	3 (6)	6 (12)	22 (44)	18 (36)
The imaging time was acceptable.						1 (2)	6 (12)	8 (16)	19 (38)	16 (32)
I sat in an acceptable position during the imaging.							7 (14)	9 (18)	18 (36)	16 (32)
It was challenging to keep my arm at rest.	14 (28)	7 (14)	8 (16)	9 (18)		4 (8)	3 (6)	2 (4)		3 (6)
I did not experience significant pain during the imaging.		1 (2)					7 (14)	5 (10)	18 (36)	19 (38)
It was challenging to keep my fingers at rest during the imaging.	15 (30)	5 (10)	7 (14)	10 (20)		3 (6)	3 (6)	4 (8)		3 (6)
If asked, would you be examined by this type of imaging again?						1 (2)	5 (10)	6 (12)	20 (40)	18 (36)
I would prefer to be examined with HR-pQCT imaging rather than ordinary X-ray in the future.	1 (2)	1 (2)		1 (2)	12 (24)	15 (30)	4 (8)	3 (6)	8 (16)	5 (10)
Imaging with the inflatable cushion helped me keep my fingers at rest.	1 (2)		1 (2)	1 (2)	6 (12)	11 (22)	7 (14)	7 (14)	10 (20)	6 (12)
Imaging with the inflatable cushion was more comfortable.		1 (2)	4 (8)	4 (8)	7 (14)	13 (26)	6 (12)	3 (6)	8 (16)	4 (8)

Note: A: Patients scanned first without the inflatable immobilization device and subsequently, with the inflatable immobilization device (n = 25). B: Scanned first with the inflatable immobilization device and subsequently without the inflatable immobilization device in order to minimize bias (n = 25).

Agency (J.nr: 2012-58-006) approved the study. Written informed consent was obtained from the patients.

2.9 | Statistics

Data were analyzed using STATA 12 (StataCorp LP, College Station, TX, USA). Normal distribution of the data was investigated with Q-Q plots and histograms. Normally distributed data were presented as arithmetic mean (95% CI) and statistical significance tested using Student's *t* test. Non-normally distributed data were presented as median (25th to 75th percentile), and statistical significance was tested using the Mann-Whitney *U* test.

The number of erosions and the average maximum width, depth, and length of the erosions were measured, and the statistical significance was investigated between acquisitions with and without

the inflatable immobilization device. The measures of erosion were compared between the acquisitions with and without the inflatable immobilization device using Bland-Altman plots.[19] The intrareader repeatability of maximum width, depth, length, and the number of erosions was investigated by the intraclass correlation coefficient (ICC) for both of the acquisitions with the hand positioned with and without the inflatable immobilization device. For visual grading of motion artefacts, the intrareader repeatability was investigated with Cohen's kappa coefficient (κ) for every 110 slices of the 330-slice image stacks.

Correlation between the patient-reported experience and either disease duration, age, body mass index, gender, Sharp/van der Heijde score, erosion number and size were investigated using Spearman's rank correlation coefficient to identify whether disease severity influenced the patients' experience of having their hand imaged by HR-pQCT. The results were considered significant at $P < .05$.

3 | RESULTS

3.1 | Patient characteristics

Patients demographics and clinical characteristics are shown in Table 2.

3.2 | Patient-reported experience measure

The patient-reported experience is presented in Table 1. Forty-nine of the 50 (98%) patients reported that the HR-pQCT imaging time was acceptable. None of the patients found the imaging time unacceptable or reported they would not want to be examined with the HR-pQCT on another occasion. Twenty of the 50 (40%) patients reported they would rather be examined with the HR-pQCT compared to conventional X-ray, compared to only 3 of the 50 (6%) patients who preferred to be examined with conventional X-ray (Table 1).

Thirty of the 50 (60%) patients agreed or strongly agreed with the statement "Imaging with the inflatable cushion helped me keep my fingers still", while only 3 of the 50 (6%) patients disagreed or strongly disagreed. Twenty-one of the 50 (42%) patients agreed or strongly agreed with the statement "Imaging with the inflatable cushion was more comfortable", while only 9 of the 50 (18%) patients disagreed or strongly disagreed (Table 1). A single patient experienced pain during the imaging. The pain was caused by the patient's forearm having a larger diameter than the cast, which resulted in uncomfortable pressure; this was not related to the inflatable immobilization device.

The majority of patients who were imaged first with the inflatable immobilization device answered that they disagreed with the statement "It was challenging to keep my arm at rest", while the majority of patients who were imaged first without the inflatable immobilization device answered that they strongly disagreed with the statement ($P = .014$). We observed the same for question 9 "It was challenging to keep my fingers at rest during the imaging" ($P < .001$). We found no significant correlation between the patient-reported experiences and Sharp/van der Heijde, the number of swollen and tender joints, Health Assessment Questionnaire, disease duration or activity score.

3.3 | Comparability

The overall visual grading for motion artefacts was low; none of the patients had repeat scans. The highest visual grade was 3 in the proximal and middle part of the 330-slices stack, while 1 patient had grade 4 in the distal part of the 330-slices stack. The median (interquartile range) visual grade was 1 (1-1) in the proximal, middle and distal parts of the 330-slices stack; this was seen in

TABLE 2 Clinical characteristics of the participants

Age, y, median [IQR]	64.3 [55.0-71.2]
Female, n (%)	36 (72)
BMI, geometric mean (95% CI)	25.4 (24.0-26.9)
Disease duration, y, geometric mean (95% CI)	15.3 (12.9-18.2)
Serum CRP, mg/L, median [IQR]	2.0 [1.0-5.8]
HAQ, median [IQR]	0.25 [0-0.75]
Visual analog scale pain, median [IQR]	18.5 [5.0-30.0]
SDAI, median [IQR]	5.4 [2.5-11.1]
RF positive, n (%)	28 (56)
ACPA positive, n (%)	35 (70)
ACPA and RF positive, n (%)	26 (52)
Charlson comorbidity index, median [IQR]	1.0 [1.0-1.0]
Sharp/van der Heijde Score, geometric mean (95% CI)	19.2 (13.4-27.4)

Abbreviations: ACPA, anti-citrullinated protein antibody; BMI, body mass index; CRP, C-reactive protein; HAQ, Health Assessment Questionnaire; IQR, interquartile range; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

both acquisitions. However, the calculated average visual grading for motion artefacts was significantly higher with the inflatable immobilization device compared to the acquisitions without the inflatable immobilization device (1 [1-1.33] vs 1 [1-1], $P = .038$). We did not observe significant differences in the erosion measures between the 2 methods of standardized positioning of the hand (Table 3). The Bland-Altman plots for the erosion measure are shown in Figure 2.

3.4 | Repeatability

Intrareader agreement for visual grading of motion artefacts was investigated for every 110 slices of the 330-slice stacks in both acquisitions with and without the inflatable hand immobilization (Table 3). All discrepancies were within 1 grade level.

The ICC for the average width, depth, and length of erosions was excellent in both acquisitions (>0.90). There was no sizable difference in ICC between the acquisitions without the inflatable immobilization device and acquisitions with the inflatable immobilization device with regard to the number and average width, depth, or length of erosions (Table 3).

4 | DISCUSSION

This is the first study investigating the patient-reported experience of HR-pQCT imaging in patients with inflammatory arthritis. The study indicates that patients with established RA have high acceptance of HR-pQCT imaging, independent of the erosive damage, disease duration, or disease activity score. The repeatability and comparability of visual grading of motion artefacts and erosion measures were excellent for both of the acquisitions with and without the inflatable immobilization device.

4.1 | Patient-reported experiences

Measures of patient-reported outcomes are becoming more and more common when assessing treatment outcomes in patients with all kinds of disorders. However, patient-reported experiences are rarely considered, even though improving patients' experiences has been shown to increase outcome scores.[14] In the present study, the patient-reported experiences with HR-pQCT imaging were generally encouraging. Only a few patients would rather undergo conventional X-ray imaging. This indicates that the HR-pQCT imaging modality has high acceptance and will likely have high patient adherence in clinical practice. The majority of patients experienced that the inflatable immobilization device helped them keep their hand at rest. However, this was not apparent in the visual grading for motion artefacts. We did not observe any correlation of the patient-reported experiences with RA severity; this shows that the modality should be acceptable for the majority, if not all patients.

All patients reported they sat in an acceptable position during HR-pQCT scanning; this was indeed positive compared to imaging modalities such as magnetic resonance imaging (MRI). Imaging of the hand with MRI usually requires prone positioning with the arm of interest over the subject's head. This places the anatomy of interest in the best location for imaging but can be uncomfortable and difficult to maintain for long periods of time, which predisposes motion artefacts.[20]

4.2 | Visual grading of motion artefacts

Motion-induced image degradation has been observed to impair reproducibility in longitudinal studies.[5] Motion artefacts are common both for the tibia and radius where the scan quality is inadequate in a substantial number of cases, especially the radius has shown to be susceptible to motion-induced image degradation.[21] Immobilization of the radius and tibia are achieved with standard casts provided by the manufacturer. However, no standardized cast or holders for positioning of the MCP joints exist. Therefore, positioning devices for the MCP joints are custom-made with the hand in a fully pronated position.[6,13] The standard for positioning of the MCP joints by the SPECTRA collaboration are the following: the MCP joints should be positioned with 0° to 15° of flexion, consistent with current clinical, radiographic imaging positioning of the MCP joints.[12] However, to obtain reliable measurements of volumetric joint space width, the recommendations are to acquire imaging of the MCP joints <10° of flexion.[22] In the present study, the visual grading for motion artefacts was low for acquisitions both with or without the inflatable immobilization device; this was evident as no reacquisition was needed, and the median grade in all parts of the 330-slices stack was one. This indicates that the inflatable immobilization device does not yield either better or worse imaging. Feehan et al. found a high degree of motion-induced image degradation in 220-slices stack of the metacarpal heads (visual grading of motion artefacts >3) was detected in 2 out of 12 healthy participants.[6] A previous study by Barnabe et al. found, in a group of 15 subjects, that 15.7% of the joints imaged had to be excluded from joint space width and periarticular microstructure analysis due to poor image quality. Still, only 5.7% of the joints had to be excluded from erosion analysis.[8] However, they investigated 220-slices stack of the 1st to 5th MCP and the 2nd to 5th proximal interphalangeal joints (PIP) and not only the 2nd and 3rd MCP joints, which we investigated in the present study. Imaging of both the MCP and PIP joints must be obtained by multiple acquisitions. Therefore, increasing the number of acquisitions also increases the risk of an acquisition having motion-induced image degradation. However, it appears that motion artefacts in HR-pQCT imaging of the MCP joints are less of a problem compared to the radius shown in other studies.[5] The imaging time for the MCP joints is 3 times longer than the radius. Therefore, we expected that motion artefact would be a greater problem for the MCP joints. However, for imaging of the patient's wrist, the hand is positioned around a handle. It may be hard not to alternate the force

TABLE 3 Visual grading of motion artefacts and the number, width, depth and length of erosions. Intrareader repeatability of visual grading of motion artefacts and the number, width, depth and length of erosions

	Without the inflatable immobilization device	With the inflatable immobilization device	*P* value
Visual grading of motion artefacts	1 [1-1]	1 [1-1.33]	.038
Cohen's kappa coefficient, κ	0.85 (0.66-1.00)	0.78 (0.55-0.91)	
Erosions, n	4 [0-10]	3 [0-9]	.749
ICC (95% CI)	0.99 (0.94-1.00)	0.98 (0.91-1.00)	
Average maximum width, mm	2.04 [1.37-2.20]	1.87 [1.68-2.49]	.422
ICC (95% CI)	0.98 (0.92-0.99)	0.99 (0.95-1.00)	
Average maximum depth, mm	1.69 [1.37-2.13]	1.91 [1.49-2.34]	.673
ICC (95% CI)	0.98 (0.92-0.99)	0.97 (0.89-0.99)	
Average maximum length, mm	2.44 [1.74-3.19]	2.26 [1.81-3.18]	.845
ICC (95% CI)	0.93 (0.75-0.98)	0.98 (0.94-1.00)	

Note: Data presented as median [IQR], statistical significance was tested using the Mann-Whitney *U* test. Cohen's kappa coefficient and intraclass correlation coefficients (ICC) are presented as mean (95% confidence intervals).

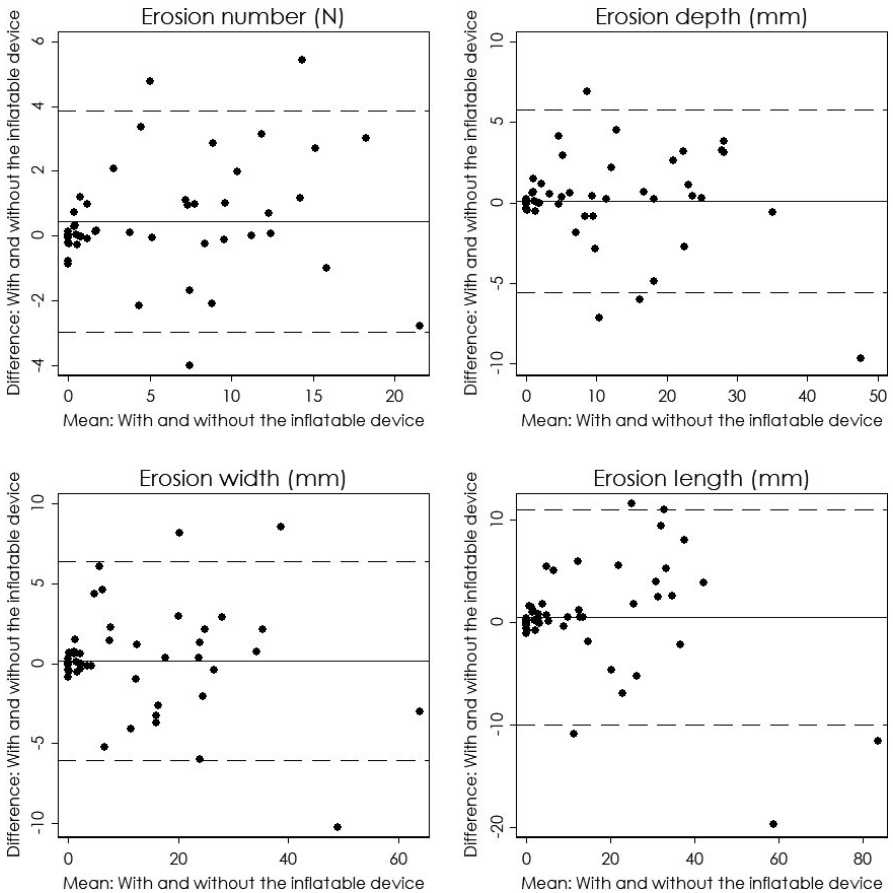


FIGURE 2 Bland-Altman plots for assessing agreement between acquisitions with and without the inflatable immobilization device, Erosion number (A), depth (B), width (C) and length (D). For each plot: on the x-axis, the mean of the acquisitions with and without the inflatable immobilization device; on the *y*-axis, the difference between the acquisitions with and without the inflatable immobilization device; the central line shows the mean difference between the 2 measurements; the dotted lines represent the limits of agreements, which correspond to 1.96 *SD* of the mean difference between the 2 measurements

of the hand's grip during the scan. The variations in the patient's grip will result in motion-induced image degradation as the variation in the force of the handgrip results in movement of the wrist. For MRI of the hand, motion-induced image degradation has not been thoroughly investigated, but motion artefacts are a known predicament. In order to reduce the motion-induced artefacts, the common advice is to reassure the patient, using sequences with shorter acquisition time, using an appropriate coil, performing the scan under sedation, using soft pads between the inner surface of the coil and the patient's skin, and the use of immobilizing devices like straps.[23]

4.3 | Comparability

We did not see any clinically relevant difference in the visual grading for motion artefacts between the acquisitions with or without the inflatable immobilization device, neither did we observe a significant difference in any of the erosion measures. Hence, further immobilization does not appear to be the most prudent way to ensure images without disruptive motion artefacts. The scan time has improved for the 2nd-generation HR-pQCT scanner. Although it was not used in the present study, it could be expected that a shorter scan time would reduce the risk for motion artefacts. Using the 1st-generation HR-pQCT scanner, the most pragmatic advice for reducing motion artefacts are proper patient instruction.

4.4 | Repeatability

The repeatability for visual grading for motion artefacts and number, width, depth and length of erosions of the 2nd and 3rd MCP joints were all high. We observed no discernible difference in the intrareader repeatability between the acquisitions with or without the inflatable immobilization device.

4.5 | Limitations

There are several limitations to this study. First, we evaluated whether the total number of erosions per patient corresponded between the 2 manners of acquisition but did not consider correspondence of erosions in the exact same location. This might have led to an overestimation of repeatability. Second, the study only included patients with established RA. These patients often have more chronic damage to the joints and less active inflammation (Figure 3) compared to newly diagnosed RA patients. Whether pain is a trigger for motion during imaging has not been established. However, whether pain is a trigger for motion during imaging has not been investigated. Third, only intrareader repeatability was investigated as all image analysis was carried out by one reader. The Inter-reader repeatability is generally higher in comparison with intrareader repeatability.[24] Finally, only one operator with extensive experience with HR-pQCT imaging scanned all the patients. As such, the results might vary between other imaging facilities with operators less familiar with or trained in HR-pQCT image acquisition.

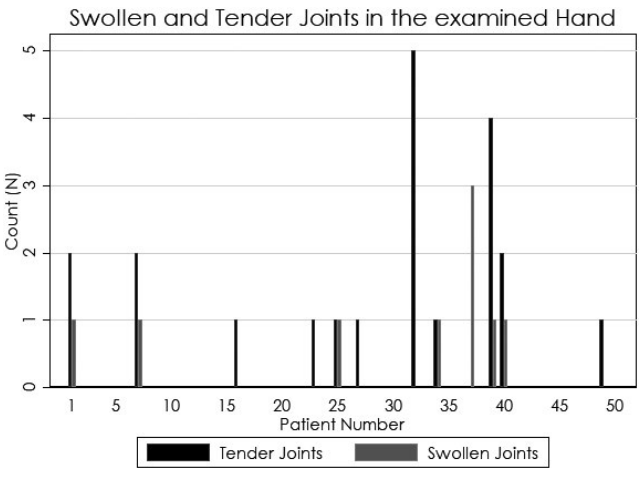


FIGURE 3 The number of swollen and tender joints in the imaged hand of the individual patient at baseline. This includes wrist, the 1st to 5th metacarpophalangeal joints, the 2nd to 5th proximal interphalangeal joints and the thumb interphalangeal joint

5 | CONCLUSION

The high acceptance shown by the patient-reported experience measures adds to the feasibility of the HR-pQCT imaging of the MCP joints in patients with RA, as more patients prefer HR-pQCT over conventional radiographs. The inflatable immobilization device did not improve the overall image quality as the visual grading of motion-induced image degradation was low with both acquisitions.

ACKNOWLEDGEMENTS

The authors are grateful for the excellent assistance in recruiting and scheduling the patients by Mia Marie Remmer, Lone Thomasen and Else Sloth Rousing.

CONFLICT OF INTEREST

Ellen-Margrethe Hauge reports personal fees from MSD, personal fees from Pfizer, personal fees from UCB, personal fees from Sobi, grants from Roche, grants from Novartis outside the submitted work. Bente Langdahl reports personal fees from Eli Lilly, Amgen, UCB, Gilead, and Gideon-Richter and grants from Novo Nordisk and Amgen outside the submitted work. Rasmus Klose-Jensen and Kresten Krarup Keller have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Study conception and design: Rasmus Klose-Jensen, Kresten Krarup Keller, and Ellen-Margrethe Hauge. Image acquisitions: Rasmus Klose-Jensen. Image analysis: Rasmus Klose-Jensen. Analysis and interpretation of data: Rasmus Klose-Jensen, Kresten Krarup Keller, Bente Langdahl and Ellen-Margrethe Hauge.

ORCID

Rasmus Klose-Jensen https://orcid.org/0000-0002-3318-4251

REFERENCES

1. Shimizu T, Choi HJ, Heilmeier U, et al. Assessment of 3-month changes in bone microstructure under anti-TNFα therapy in patients with rheumatoid arthritis using high-resolution peripheral quantitative computed tomography (HR-pQCT). *Arthritis Res Ther.* 2017;19:222. https://doi.org/10.1186/s13075-017-1430-x

2. Yue J, Griffith JF, Xiao F, et al. Repair of bone erosion in rheumatoid arthritis by denosumab: a high-resolution peripheral quantitative computed tomography study. *Arthritis Care Res (Hoboken)*. 2017;69:1156-1163. https://doi.org/10.1002/acr.23133
3. Østergaard M, Boesen M. Imaging in rheumatoid arthritis: the role of magnetic resonance imaging and computed tomography. *Radiol Med*. 2019;124:1128-1141. https://doi.org/10.1007/s11547-019-01014-y
4. Lee CH, Srikhum W, Burghardt AJ, et al. Correlation of structural abnormalities of the wrist and metacarpophalangeal joints evaluated by high-resolution peripheral quantitative computed tomography, 3 Tesla magnetic resonance imaging and conventional radiographs in rheumatoid arthritis. *Int J Rheum Dis*. 2015;18:628-639. https://doi.org/10.1111/1756-185X.12495
5. Pialat J, Burghardt AJ, Sode M, Link TM, Majumdar S. Visual grading of motion induced image degradation in high resolution peripheral computed tomography: Impact of image quality on measures of bone density and micro-architecture. *Bone*. 2012;50(1):111-118. https://doi.org/10.1016/j.bone.2011.10.003
6. Feehan L, Buie H, Li L, McKay H. A customized protocol to assess bone quality in the metacarpal head, metacarpal shaft and distal radius: a high resolution peripheral quantitative computed tomography precision study. *BMC Musculoskelet Disord*. 2013;14:367. https://doi.org/10.1186/1471-2474-14-367
7. Keller K, Thomsen J, Stengaard-Pedersen K, et al. Local bone loss in patients with anti-citrullinated peptide antibody and arthralgia, evaluated with high-resolution peripheral quantitative computed tomography. *Scand J Rheumatol*. 2018;47(2):110-116. https://doi.org/10.1080/03009742.2017.1333629
8. Barnabe C, Szabo E, Martin L, et al. Quantification of small joint space width, periarticular bone microstructure and erosions using high-resolution peripheral quantitative computed tomography in rheumatoid arthritis. *Clin Exp Rheumatol*. 2013;31:243-250. https://doi.org/10.1016/j.bone.2010.05.034
9. Klose-Jensen R, Tse JJ, Keller KK, et al. High-resolution peripheral quantitative computed tomography for bone evaluation in inflammatory rheumatic disease. *Front Med*. 2020;7:337. https://doi.org/10.3389/FMED.2020.00337
10. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69(9):1580-1588. https://doi.org/10.1136/ard.2010.138461
11. Van Der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol*. 2000;26:743-745.
12. Barnabe C, Feehan L. High-resolution peripheral quantitative computed tomography imaging protocol for metacarpophalangeal joints in inflammatory arthritis: the SPECTRA collaboration. *J Rheumatol*. 2012;39(7):1494-1495. https://doi.org/10.3899/jrheum.120218
13. Barnabe C, Buie H, Kan M, et al. Reproducible metacarpal joint space width measurements using 3D analysis of images acquired with high-resolution peripheral quantitative computed tomography. *Med Eng Phys*. 2013;35(10):1540-1544. https://doi.org/10.1016/j.medengphy.2013.04.003
14. Kingsley C, Patel S. Patient-reported outcome measures and patient-reported experience measures. *BJA Educ*. 2017;17:137-144. https://doi.org/10.1093/bjaed/mkw060
15. Boers M, Beaton DE, Shea BJ, et al. OMERACT filter 2.1: Elaboration of the conceptual framework for outcome measurement in health intervention studies. *J Rheumatol*. 2019;46(8):1021-1027. https://doi.org/10.3899/jrheum.181096
16. Sode M, Burghardt AJ, Pialat J-B, Link TM, Majumdar S. Quantitative characterization of subject motion in HR-pQCT images of the distal radius and tibia. *Bone*. 2011;48(6):1291-1297. https://doi.org/10.1016/j.bone.2011.03.755
17. Pauchard Y, Liphardt AM, Macdonald HM, Hanley DA, Boyd SK. Quality control for bone quality parameters affected by subject motion in high-resolution peripheral quantitative computed tomography. *Bone*. 2012;50(6):1304-1310. https://doi.org/10.1016/j.bone.2012.03.003
18. Barnabe C, Toepfer D, Marotte H, et al. Definition for rheumatoid arthritis erosions imaged with high resolution peripheral quantitative computed tomography and interreader reliability for detection and measurement. *J Rheumatol*. 2016;43(10):1935-1940. https://doi.org/10.3899/jrheum.160648
19. Martin Bland J, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;327:307-310. https://doi.org/10.1016/S0140-6736(86)90837-8
20. Johnson D, Stevens KJ, Riley G, Shapiro L, Yoshioka H, Gold GE. Approach to MR imaging of the elbow and wrist. *Magn Reson Imaging Clin N Am*. 2015;23(3):355-366. https://doi.org/10.1016/j.mric.2015.04.008
21. MacNeil JA, Boyd SK. Improved reproducibility of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys*. 2008;30(6):792-799. https://doi.org/10.1016/j.medengphy.2007.11.003
22. Tom S, Frayne M, Manske SL, et al. Determining metacarpophalangeal flexion angle tolerance for reliable volumetric joint space measurements by high-resolution peripheral quantitative computed tomography. *J Rheumatol*. 2016;43:1941-1944. https://doi.org/10.3899/jrheum.160649
23. Singh DR, Chin MSM, Peh WCG. Artifacts in musculoskeletal MR imaging. *Semin Musculoskelet Radiol*. 2014;18:12-22. https://doi.org/10.1055/s-0034-1365831
24. Salaffi F, Carotti M. Interobserver variation in quantitative analysis of hand radiographs in rheumatoid arthritis: comparison of 3 different reading procedures. *J Rheumatol*. 1997;24:2055-2056.

How to cite this article: Klose-Jensen R, Keller KK, Langdahl B, Hauge E-M. Acceptance and image quality of high-resolution peripheral quantitative computed tomography of the metacarpophalangeal joints in rheumatoid arthritis. *Int J Rheum Dis*. 2021;24:1473–1481. https://doi.org/10.1111/1756-185X.14169

Received: 10 July 2021 | Revised: 26 September 2021 | Accepted: 3 October 2021

DOI: 10.1111/1756-185X.14227

International Journal of Rheumatic Diseases WILEY

ORIGINAL ARTICLE

Asymptomatic myocardial dysfunction was revealed by feature tracking cardiac magnetic resonance imaging in patients with primary Sjögren's syndrome

Isamu Yokoe[1] | Hitomi Kobayashi[1] | Atsuma Nishiwaki[1] | Yosuke Nagasawa[1] | Noboru Kitamura[1] | Masaki Haraoka[2] | Yasuyuki Kobayashi[2] | Masami Takei[1] | Hideki Nakamura[1]

[1]Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

[2]Department of Medical Information and Communication Technology Research, Graduate School of Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Correspondence
Hitomi Kobayashi, Division of Hematology and Rheumatology, Department of Medicine Nihon University School of Medicine 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
Email: pero1995@gmail.com

Abstract

Aim: To evaluate subclinical left ventricular (LV) regional dysfunction in patients with primary Sjögren's syndrome (pSS) using feature tracking cardiac magnetic resonance (FT-CMR) imaging and to identify pSS characteristics independently associated with LV regional dysfunction.

Method: Fifty patients with pSS and 20 controls without cardiovascular disease underwent non-contrast CMR imaging. Labial gland biopsy was performed in 42 patients (84%). Disease activity was assessed using the European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI). LV global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) were measured using FT-CMR.

Results: No significant differences in cardiovascular risk factors were found between the pSS group and controls. The pSS group had significantly lower GLS ($P = .015$) and GCS ($P = .008$) than the control group. Multiple linear regression analysis indicated that GCS was significantly associated with Raynaud's phenomenon ($P = .015$), focus score ≥2 ($P = .032$), and total ESSDAI score ≥8 ($P = .029$).

Conclusion: FT-CMR can reveal subclinical LV regional dysfunction in patients with pSS without cardiovascular disease. Furthermore, patients with pSS and Raynaud's phenomenon, a focus score ≥2, or an ESSDAI score ≥8 were considered to be at high risk for myocardial dysfunction.

KEYWORDS

European League Against Rheumatism Sjögren's syndrome disease activity index, feature tracking cardiac magnetic resonance imaging, focus score, global longitudinal strain, left ventricular regional function, primary Sjögren's syndrome, Raynaud's phenomenon

1 | INTRODUCTION

Primary Sjögren's syndrome (pSS) is a rheumatic disease characterized by chronic inflammation of the exocrine glands, but chronic inflammation can also be present in multiple other organs. Furthermore, patients with pSS share several clinical and pathophysiological characteristics with those with rheumatoid arthritis (RA) and systematic lupus erythematosus (SLE). Recently, many studies have reported increased cardiovascular disease (CVD) morbidity and premature mortality in patients with rheumatic diseases, such as SLE and RA.[1,2] In addition, a meta-analysis of CVD showed that pSS was associated with increased cardiovascular morbidity, and a previous study reported that chronic inflammation in patients with pSS, as with patients with other immune-mediated inflammatory diseases, may increase the risk of CVD. However, the interaction between the disease-related features of pSS and myocardial regional dysfunction remains unclear.[3,4]

Cardiac magnetic resonance (CMR) imaging has been used to identify early left ventricular (LV) structural and functional changes that precede the development of overt heart failure. With the recent advances in CMR, T1/T2 mapping has emerged as a method of quantifying myocardial tissue properties. While these approaches can quantify myocardial tissue, their imaging capabilities are limited.

On the other hand, feature tracking CMR (FT-CMR) imaging is a non-invasive approach that does not require contrast, which can be used to obtain a quantitative functional evaluation of the myocardium and the direct measurement of myocardial strain from two-dimensional cine MRI. Myocardial strain analysis quantifies the stretch and contraction of regional myocardium in 3 directions: circumferential strain (CS), longitudinal strain (LS), and radial strain (RS). It has attracted attention as an index that can quantitatively evaluate wall motion abnormalities in more detail than the LV ejection fraction. Moreover, FT-CMR imaging can be performed in patients with renal dysfunction, allergic reactions, or asthma as it does not require contrast.

Compared to tagging MRI, FT-CMR can be easily measured from cine MRI without the need for additional examinations, and has high inter-observer reproducibility.[5] Although echocardiography is superior in terms of convenience and cost, FT-CMR has the advantages of objectivity and reproducibility because it does not depend on the skill of the surgeon or the body size of the subject. Especially in RA patients, it is often difficult to obtain images because they may not be able to posture sufficiently due to joint deformity or limited range of motion.

Recently, several reports have indicated that global LS (GLS) and global CS (GCS) on FT-CMR are highly correlated with speckle tracking echocardiography findings as well as the ejection fraction on CMR.[6-8] The overall average strain is called global strain, whereas global strain in the long-axis direction is referred to as GLS, which has received increasing recognition as an index of overall ventricular contractility. In a large general population study, GLS was reported to be a predictor of mortality associated with CVD,[9] while GCS was shown to be a predictor of future heart failure in the Multi-Ethnic Study of Atherosclerosis.[10]

This functional index shows early lowering and is thus a promising predictor of cardiovascular events, including heart failure, myocardial infarction, and cardiovascular death. We demonstrated that subclinical LV dysfunction is prominent in RA patients without cardiac symptoms using FT-CMR imaging. Moreover, biologic treatment may be associated with better LV function, possibly due to the reduction in disease activity.[11]

Patients with pSS who have LV regional dysfunction may not exhibit any clinical cardiac symptoms for clinical or pathophysiological features shared with RA; thus, asymptomatic cardiac complications might be missed.[12]

Therefore, we hypothesized that patients with pSS without cardiac symptoms would have LV regional dysfunction. To test this, we measured GLS, GCS, and global RS (GRS) using FT-CMR to evaluate LV regional function in patients with pSS. Furthermore, we evaluated pSS characteristics associated with LV regional function.

2 | MATERIALS AND METHODS

2.1 | Study population

This cross-sectional study included women with pSS recruited at our hospital between January 2014 and April 2017. We enrolled only women because the prevalence of pSS is much higher in women than in men and to avoid the potential confounding effect of gender in this study. Patients with secondary SS were excluded from this study as we would have been unable to rule out the myocardial effects of complications such as RA and SLE.

All patients met the 2002 revised American-European Consensus Group classification criteria or the 2012 American College of Rheumatology classification criteria.[13,14] Additionally, 20 healthy age-matched women were recruited as a control group.

The exclusion criteria included prior cardiovascular events (heart failure, angina, myocardial infarction, and arrhythmia) or procedures. Additionally, current or past smokers as well as patients with a history of diabetes mellitus (glycated hemoglobin (HbA1c: National Glycohemoglobin Standardization Program) > 6.1%), hypertension (>140/90 mm Hg), dyslipidemia (low-density lipoprotein [LDL] cholesterol >3.6 mmol/L by the Friedwald equation, high-density lipoprotein [HDL] cholesterol <1.0 mmol/L, triglycerides [TG] > 1.7 mmol/L), renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2), liver insufficiency, and a known cancer or lymphoma were excluded. Furthermore, patients with contraindications to MRI scanning (eg, cardiac pacemaker user or claustrophobia) were excluded.

This study was approved by the local ethics committee of Nihon University Itabashi Hospital, Japan (research number: RK-160112-07). All procedures performed in this study involving human participants, including informed consent which was obtained from all patients, were in accordance with the 1975 Declaration of Helsinki (as revised in Brazil 2013).

2.1.1 | Clinical assessments and pathological examination of Sjögren's syndrome

Disease activity in all patients with pSS was evaluated using the European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI).[15] All patients were clinically evaluated by the same observer for disease activity measures. They received corticosteroids and/or immunosuppressants, as decided by the treating rheumatologist. The presence or absence of Raynaud's phenomenon (RP) was determined based on the 2014 classification criteria.[16] Regarding the histological evaluation of the labial gland biopsy, salivary gland focus scores (FS) were defined as the mean number of lymphocytic foci containing ≥50 infiltrating lymphocytes per 4 mm^2 of periductal or perivascular tissue detected by hematoxylin and eosin staining.[17] Additionally, lymphocytic foci had to exist in close proximity to the normal acinar cells. Histopathological analyses were performed by experienced pathologists and rheumatologists.

2.2 | Laboratory assessment

Fasting samples of serum and plasma were centrifuged and stored at −80°C. All assays were performed in our institute using our internal quality control procedures. Patients underwent measurement of total cholesterol, TG, HDL cholesterol, LDL cholesterol, and fasting blood glucose concentration to assess the traditional atherosclerotic disease risk factors at the time of visit. We used typical blood test parameters required for pSS diagnosis (eg, rheumatoid factor, anti-Ro [SS-A] antibodies, and anti-La [SS-B] antibodies). We measured anti-Ro (SS-A) and anti-La (SS-B) antibodies using a commercial enzyme-linked immunosorbent assay kit based on purified antigens (Orgentec). Furthermore, we separately measured anti-Ro52 and anti-Ro60 antibodies, subtypes of anti-Ro (SS-A) antibodies, using BioPlex 2200 ANA Screen (Bio-Rad Laboratories).

2.3 | MRI acquisition and analysis

All patients and controls underwent non-contrast-enhanced CMR imaging with steady-state free-precession cine MRI on a 3.0T MRI scanner (Achieva; Philips Healthcare, Best, Netherlands) within a week after a clinical examination. Cine MRI is commonly used in LV regional functional analysis with CMR. Fifteen-second breath-holding cine images (slice thickness, 8-10 mm) ranging from the base to the apex of the heart were acquired in the following orientations: single long-axis view and contiguous short-axis slices covering the entire LV. The cine MRI were used to measure the following variables: LV function; ejection fraction (EF), end-systolic volume, end-diastolic volume, cardiac output and LV hypertrophy; LV mass (LVM), and LV mass index. In strain analysis, the LV 4- and 2-chamber views were used to measure LS and diastolic rates, whereas the mid LV short-axis view was used to measure CS, RS, and diastolic strain rates. A software application, MR-Wall Motion Tracking (Canon Medical Systems Corporation), was used for the analysis of myocardial strain from cine MRI. This software program enables semi-automatic imaging of the left and right ventricular walls and papillary muscles in electrocardiogram-gated cardiac cine MRI to obtain a quantitative analysis based on contours and myocardial tissue voxel motion. The percentage change (%) in the distance between 2 points of the myocardium during the phase from the resting state (end diastolic) to the state of contraction was calculated. Global strain was assessed by averaging the peak systolic values using the 16-segment model of the American Heart Association Classification.[18] GLS, GCS, and GRS were used as indices of the LV regional function. A radiologist blinded to clinical information viewed and analyzed images.

2.4 | Statistical analyses

All continuous variables were considered non-normally distributed as the sample size was small. Continuous variables are expressed as medians and interquartile ranges and were compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts and proportions and were compared using Fisher's exact test. We searched for independent pSS characteristics associated with LV regional dysfunction detected by CMR. In a linear regression analysis to identify independent pSS characteristics (ie, explanatory variables) with GCS as the dependent variable, we first selected several pSS characteristics with reference to multivariable correlations between GCS and pSS characteristics using Spearman's rank correlation coefficient. Additionally, after consideration of clinical significance, pSS characteristics for multivariable analysis were confirmed. In the multivariable analysis model, variables identified as significant in univariate linear regression analysis ($P < .05$) were fed using the forced entry method. All statistical analyses were performed using JMP® 14.0 software (SAS Institute Inc.). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of participants

Fifty women with pSS (median age, 55 years; interquartile range, 47-60.3 years) and 20 healthy female controls (median age, 54.5 years; interquartile range, 50-57.5 years) were included in this study. Baseline characteristics were similar between the RA and control groups (Table 1).

The median duration of the illness was 36 months (Table 2). Most patients with pSS presented with dry mouth and eye symptoms, but only 22% were diagnosed with RP. Regarding autoantibodies, 46 (92%) of the 50 patients with pSS were anti-Ro (SS-A) antibody-positive (anti-Ro52 antibodies were observed in 20 of 26 patients [77%]; anti-Ro60 antibodies were observed in 23 of 26 patients [88%]), whereas 19 (38%) were anti-La (SS-B) antibody-positive. Few patients with pSS were prescribed oral steroids (average dose 4.6 mg/d) and/or immunosuppressants (ie, mizoribine or tacrolimus).

TABLE 1 Baseline characteristics of controls and patients with pSS

	Patients with pSS (n = 50)	Controls (n = 20)	*P* value
Demographic factors			
Age, y*	55 (47-60.3)	54.5 (50-57.5)	.81
Male, n (%) **	0 (0)	0 (0)	1
Cardiovascular risk factors			
Systolic blood pressure, mm Hg*	120 (110-132.3)	122.5 (118.3-125)	.78
Diastolic blood pressure, mm Hg*	70 (64.8-77.3)	70 (66.8-78.0)	.98
Total cholesterol, mg/dL*	178.5 (160.8-209)	175 (161.3-186)	.81
LDL cholesterol, mg/dL*	100 (91.8-117.3)	88 (84-95.5)	.30
HDL cholesterol, mg/dL*	56 (44.8-67.3)	59 (53-71)	.65
Triglycerides, mg/dL*	99.5 (77-131)	116 (104.8-142.5)	.13
Diabetes, n (%) **	0 (0)	0 (0)	1
Smoking status			
Current smoker, n (%) **	0 (0)	0 (0)	1
Baseline CMR data			
LV ejection fraction, %*	61.3 (58-68)	62 (59-66.5)	.51
End-systolic volume, mL*	33.4 (25.5-40.4)	31.5 (28-36.5)	.23
End-diastolic volume, mL*	88.25 (74.8-101.2)	95.3 (84.2-107.6)	.12
Cardiac output, L/min*	3.8 (3.08-4.43)	4.2 (3.7-4.8)	.36
LV mass, g*	59.5 (48-76)	68 (55-90)	.082
LV mass index, g/m^{2}*	44.9 (37.1-57.1)	52.6 (41.8-56)	.092
GLS, %*	-16.0 (−18.0 to −13.0)	-18.2 (−19.6 to −16.2)	.015
GCS, %*	-17.6 (−20.4 to −16.2)	-19.7 (−23.0 to −18.4)	.008
GRS, %*	78.9 (61.5-88.6)	83.6 (68.0-100)	.11
Peak diastolic GLS rate, S^{-1}*	0.94 (0.82-1.2)	1.25 (0.95-1.75)	.01
Peak diastolic GCS rate, S^{-1}*	0.89 (0.75-1.07)	1.12 (0.94-1.37)	<.001
Peak diastolic GRS rate, S^{-1}*	4.29 (3.55-5.16)	4.57 (4.13-5.93)	.21

Median (interquartile range) depicted unless otherwise indicated. *Wilcoxon rank-sum test, **Fisher's exact test

Abbreviations: CMR, cardiac magnetic resonance; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; pSS, primary Sjögren's syndrome.

3.2 | Salivary gland focus score

Forty-two patients (84%) underwent labial gland biopsy. The majority had 0 ≤ salivary gland FS <3, but only 17% reported 3 ≤ salivary gland FS <6. There were no patients with salivary gland FS ≥6.

3.3 | ESSDAI

The median total ESSDAI score was 4 (interquartile range, 0-8). Most patients (52%) had a low ESSDAI, while only 7 (34%) were classified as having high disease activity based on the ESSDAI. Many patients displayed glandular, articular, hematological, or biological findings, but only a few patients exhibited renal, muscular, or peripheral nervous system involvement, and no patients demonstrated central nervous system involvement. In any case, none of the patients had high disease activity in any of the 12 domains.

3.4 | Comparison of regional function between patients with pSS and controls

The median GLS was 12% lower in the pSS group than in the control group (−16.0% vs −18.2%, $P = .015$; Figure 1A). Likewise, the median GCS was 11% lower in the pSS group than in the control group (−17.6% vs −19.7%, $P = .008$; Figure 1B). There was no significant difference in GRS between the pSS and control groups (78.9% vs 83.6%, $P = .11$). Diastolic GLS and GCS rates were significantly lower in the pSS group than in the control group ($P = .01$ and <0.001, respectively); however,

TABLE 2 Characteristics of patients with pSS

	Patients with pSS (n = 50)
pSS status	
Disease duration, mo	36 (12-107)
Dry mouth symptoms, n (%)	47 (94)
Dry eye symptoms, n (%)	39 (78)
Salivary gland scintigraphy, n (%)	36 (72)
Schirmer (n = 41) <5 mm/5 min, n (%)	28 (68)
Ocular staining score ≥3 or van Bijsterveld score ≥4 (n = 41), n (%)	26 (63)
Raynaud's phenomenon, n (%)	11 (22)
Anti-Ro (SS-A) ≥30 index, n (%)	46 (92)
Anti-La (SS-B) ≥25 index, n (%)	19 (38)
RF, IU/mL	21.2 (7.4-50.6)
ANA titer ≥1:320, n (%)	20 (40)
IgG, mg/dL	1876 (1418-2233)
C3 <86 mg/dL or C4 <16 mg/dL or CH50 <30 U/mL, n (%)	5 (10)
C-reactive protein ≥0.3 mg/dL, n (%)	5 (10)
ESR, mm/h	33.3 (19.6-45.4)
WBC, /μL	4550 (3750-5450)
Labial gland biopsy (salivary gland FS)	
Salivary gland FS (n = 42)	1 (1-2)
Salivary gland FS (n = 42) ≥0, <1, n (%)	5 (12)
Salivary gland FS (n = 42) ≥1, <2, n (%)	18 (43)
Salivary gland FS (n = 42) ≥2, <3, n (%)	12 (29)
Salivary gland FS (n = 42) ≥3, <4, n (%)	2 (5)
Salivary gland FS (n = 42) ≥4, <5, n (%)	2 (5)
Salivary gland FS (n = 42) ≥5, <6, n (%)	3 (7)
ESSDAI	
Total ESSDAI score	4 (0-8)
Constitutional domain, n (%)	7 (14)
Lymphadenopathy domain, n (%)	7 (14)
Glandular domain, n (%)	14 (28)
Articular domain, n (%)	10 (20)
Cutaneous domain, n (%)	5 (10)
Pulmonary domain, n (%)	8 (16)
Renal domain, n (%)	1 (2)
Muscular domain, n (%)	1 (2)
PNS domain, n (%)	2 (4)
CNS domain, n (%)	0 (0)
Hematological domain, n (%)	11 (22)
Biological domain, n (%)	18 (36)
Current treatment	
Prednisolone use, n (%)	6 (12)
Mizoribine use, n (%)	10 (20)
Tacrolimus use, n (%)	1 (2)

Median (interquartile range) depicted unless otherwise indicated

Abbreviations: pSS, primary Sjögren's syndrome; RF, rheumatoid factor; ANA, antinuclear antibody; IgG, immunoglobulin G; C3, complement 3; C4, complement 4; CH50, 50% hemolytic complement activity; ESR, erythrocyte sedimentation rate; WBC, white blood cell; FS, focus score; ESSDAI, European League Against Rheumatism Sjögren's syndrome disease activity index; PNS, peripheral nervous system; CNS, central nervous system

there was no significant difference in the GRS rate between the pSS and control groups ($P = .21$).

3.5 | Association of GLS and GRS with pSS characteristics

GLS and GRS were not associated with any classical CVD risk factors or pSS characteristics (data not shown).

3.6 | Association of GCS with pSS characteristics

GLS was significantly associated with some pSS characteristics, but not with CVD risk factors. In bivariate analysis, factors significantly associated with GCS were RP, a salivary gland FS ≥2, a total ESSDAI score ≥8, and the presence of the ESSDAI constitutional domain ($P = .011$, .013, .019, and .046, respectively; Figure 2). Anti-Ro (SS-A) and anti-La (SS-B) antibodies were not associated with GCS, GLS, or GRS.

3.7 | Multivariable analysis

We performed multiple linear regression analysis to identify pSS characteristics with GCS as the objective variable (Table 3). After consideration of clinical significance, RP, salivary gland FS ≥2, total ESSDAI score ≥8, and the presence of ESSDAI constitutional domain were selected as factors for multivariable analysis. Variables identified as significant in univariate linear regression analysis were used in the multivariable analysis model using the forced entry method.

After adjustment, multiple linear regression analysis identified RP, a salivary gland FS ≥2, and a total ESSDAI score ≥8 as independent pSS characteristics. The R^2 associated with these 3 variables was 0.32.

3.8 | Global circumferential strain prediction by linear regression

Predicted GCS values were examined using the salivary gland FS (≥2:1, <2:0). An equation was obtained by univariate linear regression analysis of GCS and salivary gland FS (Figure 3). From this equation, GCS is 2.6 units higher for every unit rise in salivary gland FS. Evaluation of the prediction accuracy identified the mean absolute error and root mean square error as indicators. In this study, the mean absolute error and root mean square error of the regression model were 2.37 and 2.93, respectively.

4 | DISCUSSION

This study has several noteworthy findings. First, it showed that GLS and GCS were significantly lower in patients with pSS without cardiac

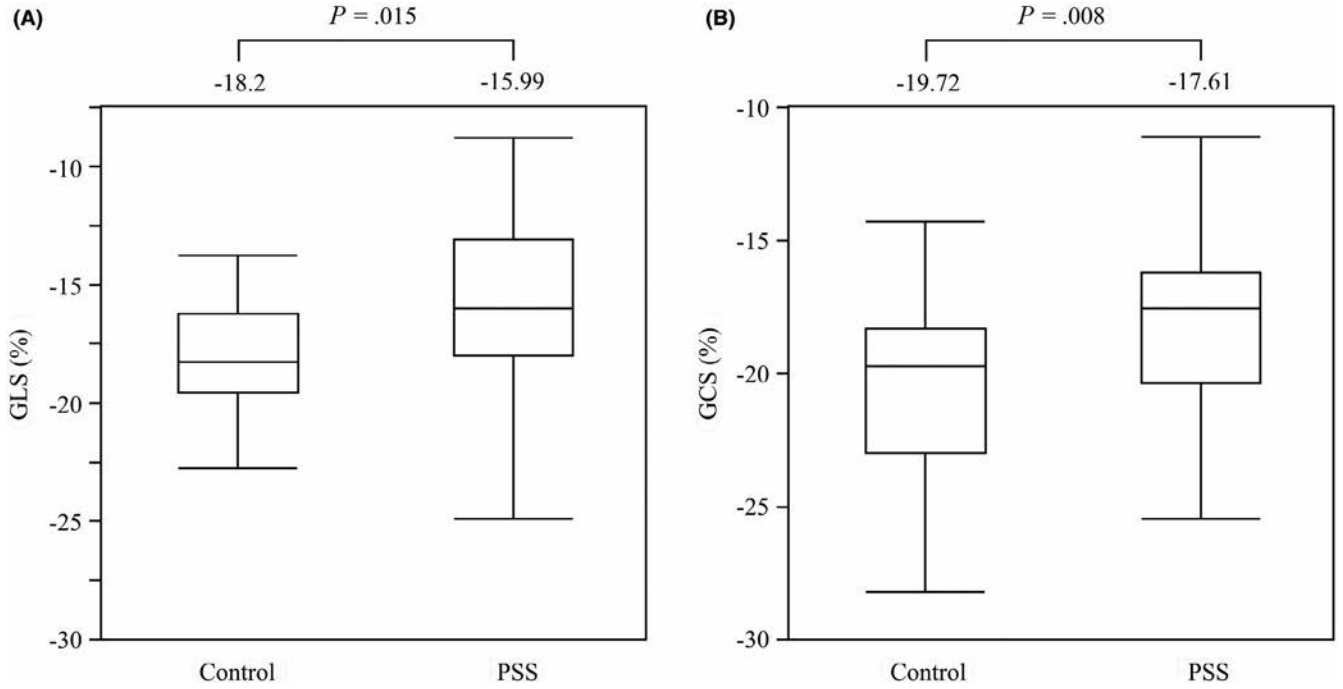


FIGURE 1 Comparison of regional function between the pSS and control groups. Group comparisons were performed using Wilcoxon rank-sum test. (A) Control and pSS: the median GLS was significantly lower in patients with pSS than in controls ($P = .015$). (B) Control and pSS: the median GCS was significantly lower in patients with pSS than in controls ($P = .008$). PSS, primary Sjögren's syndrome; GLS, global longitudinal strain; GCS, global circumferential strain

symptoms. Second, RP, a salivary gland FS ≥2, and a total ESSDAI score ≥8 were independent pSS characteristics significantly associated with lower GCS by multivariable analysis after adjustment.

The decrease in GLS and GCS was found to be associated with the amount of fibrosis and qualitative abnormality in the endocardium and middle myocardium, respectively.[19] In fact, previous studies showed lower GLS (ie, more positive) to be associated with structural heart disease, myocardial infarction, hypertensive heart disease, and stroke.[20,21]

On the other hand, in our prior study, GCS was significantly lower in patients with RA than in the control group, suggesting an impairment in the middle myocardium.[11] Furthermore, we reported that myocardial abnormalities, as detected by CMR imaging, were frequent in patients with RA without CVD, and LGE in the middle layer was observed in more than half of patients.[22] Moreover, diastolic GLS and diastolic GCS rates were significantly lower in the pSS group than in the control group in the longitudinal and circumferential directions as was the case of strain. This may indicate an increased risk of transition to heart failure with preserved EF (HFpEF). Previous studies investigating pressure-volume relationships, myocardial wall stress, and diastolic strain rate suggested that the main cause of HFpEF was increased diastolic myocardial stiffness and delayed myocardial relaxation.[23,24] We should consider that even if patients with pSS without CVD risk factors have normal EF, they may have potential LV regional dysfunction, as in this study. Namely, the results of this study suggest that cardiac complications are considered extraglandular complications of the pSS.

This study identified several GCS-related characteristics for pSS. Specifically, multivariable analysis after adjustment with GCS as the objective variable determined salivary gland FS ≥2, RP, and total ESSDAI score ≥8 as independent pSS characteristics. These characteristics may provide hints about the pathogenesis of LV regional dysfunction in patients with pSS.

Salivary gland FS indicates the degree of infiltration of inflammatory cells (ie, lymphocytes) into salivary glands, and in a broad sense, it can be an indicator of inflammatory changes. Additionally, lymphocytic infiltration into, and the destruction of, exocrine glands leads to the chronic activation of lymphocytes and lymphocytic infiltration into other organs; in fact, Watanabe et al histologically demonstrated cardiac inflammatory cell infiltration in patients with pSS.[25,26] Although we have not histologically demonstrated lymphocytic infiltration into the myocardium of individual patients, the results of this study suggested that the stronger the extent of lymphocytic infiltration into the small salivary glands, the higher the possibility of LV regional dysfunction, and lymphocyte infiltration may have occurred in the myocardium as well.

Similarly, a total ESSDAI score ≥8 was an independent pSS characteristic that was significantly associated with lower GCS. ESSDAI domains do not include those related to the levels of cardiac symptoms, RP, or salivary gland FS.[14] However, a report has indicated that patients with pSS who have CVD may have increased disease activity, in particular in the pulmonary and central nervous system

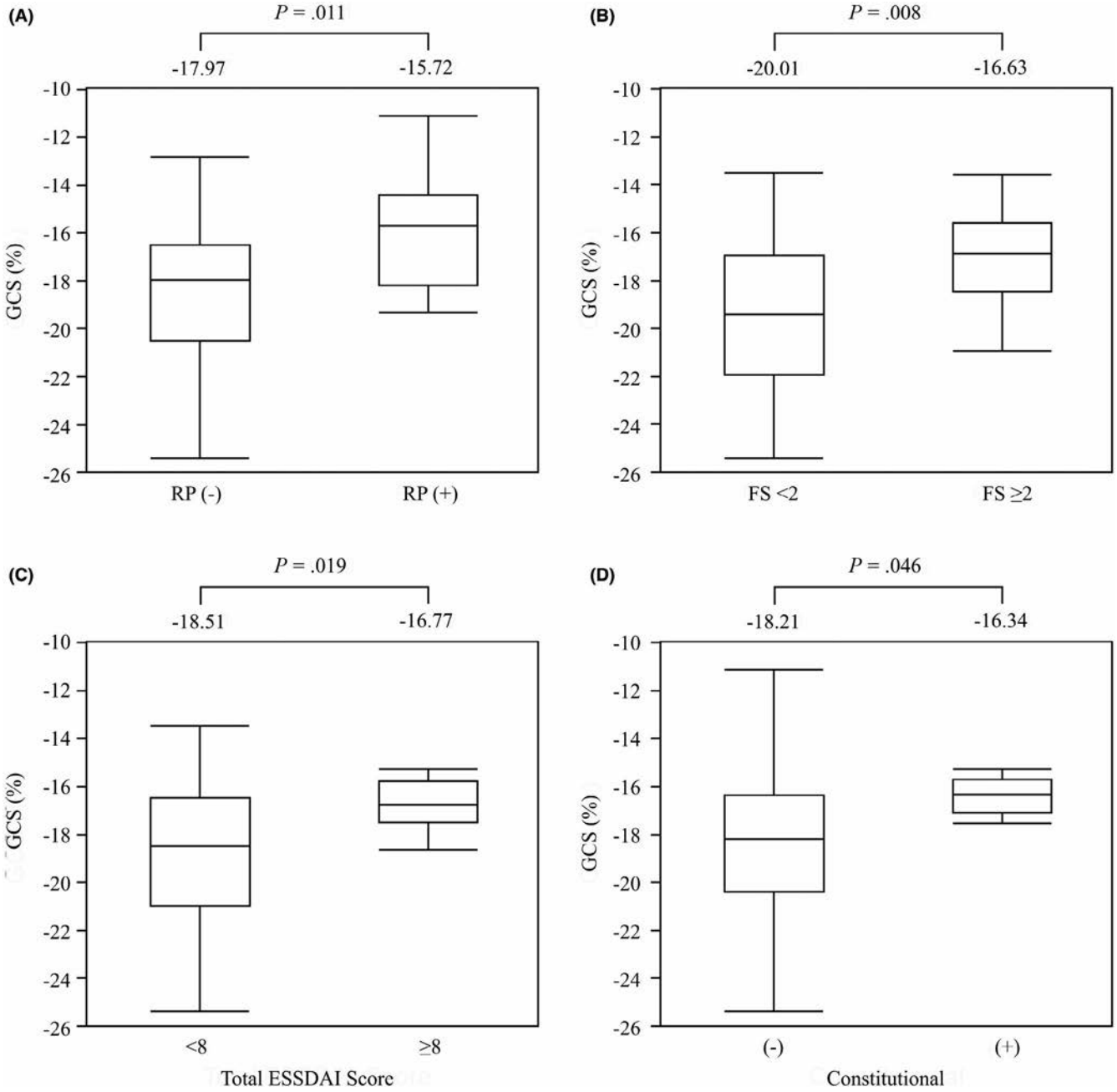


FIGURE 2 Global circumferential strain vs pSS status. Group comparisons were performed using the Wilcoxon rank-sum test. (A) RP: the median GCS was significantly lower in patients with pSS with RP than in those without RP ($P = .011$). (B) Salivary gland FS (n = 42) ≥2: the median GCS was significantly lower in patients with pSS with salivary gland FS ≥2 than in those with salivary gland FS <2 ($P = .013$). (C) Total ESSDAI score ≥8: the median GCS was significantly lower in patients with total ESSDAI score ≥8 than in those with total ESSDAI score <8 ($P = .019$). (D) Constitutional symptoms: the median GCS was significantly lower in patients with constitutional symptoms than in those without any constitutional symptoms ($P = .046$). pSS, primary Sjögren's syndrome; GCS, global circumferential strain; RP, Raynaud's phenomenon; FS, focus score; ESSDAI, European League Against Rheumatism Sjögren's syndrome disease activity index

domains, and more frequently increased use of corticosteroids and immunosuppressants.[27]

In addition, RP was independently associated with lower GCS. In rheumatic diseases, the main cause of cardiac complications in patients with systemic sclerosis, as with those who have RP, is reported to be vasospasm of small blood vessels.[28] In our previous study on patients with systemic sclerosis, we also reported findings suggestive of the existence of a pathophysiological mechanism common to cardiac complications, as detected by CMR and RP.[29] We speculated that chronic vasospasm would contribute to angiopathy, promoting the progression of myocardial injury.

This study has some limitations. First, this study had a cross-sectional design; therefore, no follow-up was performed. Second, this study did not evaluate patients with pSS with CVD risk factors

TABLE 3 Linear regression analysis with global circumferential strain as the dependent variable

	Crude models		Multivariable model	
Variable	**B**	***P***	**β**	***P***
Diagnosed Raynaud's phenomenon, n (%)*	0.365	.009	0.340	.015
Salivary gland FS ≥2, n (%)*	0.404	.008	0.296	.032
Total ESSDAI score ≥8, n (%)*	0.346	.014	0.271	.029
Presence of constitutional symptoms, n (%)*	0.224	.117		
Adjusted R^2**			0.318	

Abbreviations: FS, focus score; ESSDAI, European League Against Rheumatism Sjögren's syndrome disease activity index.

*β coefficients represent the average change in the outcome (global circumferential strain) for those with the characteristic vs those without.

**R^2 is the percentage of the total variability in the outcome explained by the aggregate of the predictors in the model.

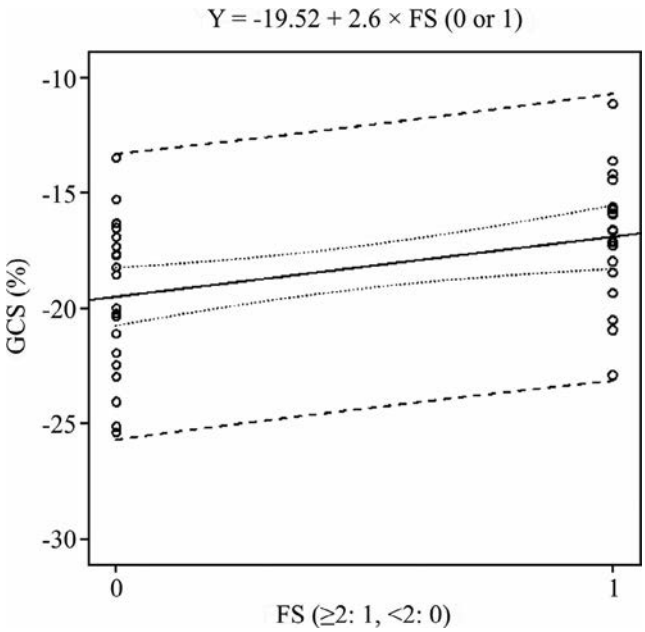


FIGURE 3 GCS prediction by linear regression. Predicted GCS values were examined using salivary gland FS (≥2:1, <2:0). Dotted line: 95% confidence interval (predicted interval) of the mean. Dashed line: 95% confidence interval (predicted interval) of the data. Y = −19.52 + 2.6 × salivary gland FS (1 or 0) was obtained by simple linear regression analysis of GCS and salivary gland FS. From this equation, GCS is 2.6 units higher for every unit rise in salivary gland FS. GCS, global circumferential strain; FS, focus score

using FT-CMR. We also did not enroll male patients or patients with secondary SS as we would have been unable to rule out the myocardial effects of complications such as RA and SLE. Third, we did not use methods to completely exclude potential atherosclerosis, such as carotid ultrasound and cardiac catheterization. Fourth, we did not perform a histological examination of the LV regional dysfunction. Fifth, we did not perform T1/T2 mapping. T1/T2 mapping is a method of quantifying tissue properties while FT is used to quantify LV regional function, and both have different purposes. Accordingly, some studies have reported that T1/T2 mapping and FT are complementary and that their combined use leads to improved lesion detection.[30,31] We also plan to combine these 2 methods in future studies.

In conclusion, our findings suggest that subclinical LV regional dysfunction is prominent in patients with pSS without cardiac symptoms. Furthermore, the pathogenesis of pSS was thought to play an important role in the development of LV regional dysfunction. The clinical impact of our findings is that they suggest that LV dysfunction could be considered an extraglandular complication of pSS.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to all members and staff of the Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan. We would also like to express our sincere gratitude to Dr Jon T. Giles (Division of Rheumatology, Columbia University, College of Physicians and Surgeons, New York, USA) for the helpful discussion and comments on the manuscript.

CONFLICT OF INTEREST

All authors attest they have no financial conflicts of interest pertaining to this investigation.

ORCID

Isamu Yokoe https://orcid.org/0000-0002-2676-5357
Hitomi Kobayashi https://orcid.org/0000-0002-0282-7074
Atsuma Nishiwaki https://orcid.org/0000-0003-2517-7235
Yosuke Nagasawa https://orcid.org/0000-0003-3416-1649
Noboru Kitamura https://orcid.org/0000-0002-8454-988X
Masaki Haraoka https://orcid.org/0000-0002-5843-2645
Yasuyuki Kobayashi https://orcid.org/0000-0001-6058-8166
Masami Takei https://orcid.org/0000-0002-5791-3359
Hideki Nakamura https://orcid.org/0000-0002-5837-6348

REFERENCES

1. Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus*. 2016;25:727-734.

2. Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003;107:1303-1307.
3. Beltai A, Barnetche T, Daien C, et al. Cardiovascular morbidity and mortality in primary Sjögren's syndrome: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2020;72:131-139.
4. Wu XF, Huang JY, Chiou JY, Chen HH, Wei JC, Dong LL. Increased risk of coronary heart disease among patients with primary Sjögren's syndrome: a nationwide population-based cohort study. *Sci Rep*. 2018;8:2209.
5. Schuster A, Morton G, Hussain ST, et al. The intra-observer reproducibility of cardiovascular magnetic resonance myocardial feature tracking strain assessment is independent of field strength. *Eur J Radiol*. 2013;82:296-301.
6. Obokata M, Nagata Y, Wu VC, et al. Direct comparison of cardiac magnetic resonance feature tracking and 2D/3D echocardiography speckle tracking for evaluation of global left ventricular strain. *Eur Heart J Cardiovasc Imaging*. 2016;17:525-532.
7. Aurich M, Keller M, Greiner S, et al. Left ventricular mechanics assessed by two-dimensional echocardiography and cardiac magnetic resonance imaging: comparison of high-resolution speckle tracking and feature tracking. *Eur Heart J Cardiovasc Imaging*. 2016;17:1370-1378.
8. Onishi T, Saha SK, Delgado-Montero A, et al. Global longitudinal strain and global circumferential strain by speckle-tracking echocardiography and feature-tracking cardiac magnetic resonance imaging: comparison with left ventricular ejection fraction. *J Am Soc Echocardiogr*. 2015;28:587-596.
9. Biering-Sørensen T, Biering-Sørensen SR, Olsen FJ, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the Copenhagen City heart study. *Circ Cardiovasc Imaging*. 2017;10:e005521.
10. Choi EY, Rosen BD, Fernandes VR, et al. Prognostic value of myocardial circumferential strain for incident heart failure and cardiovascular events in asymptomatic individuals: the multi-ethnic study of atherosclerosis. *Eur Heart J*. 2013;34:2354-2361.
11. Yokoe I, Kobayashi H, Kobayashi Y, et al. Impact of biological treatment on left ventricular dysfunction determined by global circumferential, longitudinal and radial strain values using cardiac magnetic resonance imaging in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2020;23:1363-1371.
12. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum*. 1994;37:481-494.
13. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. *Ann Rheum Dis*. 2002;61:554-558.
14. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's international collaborative clinical alliance cohort. *Arthritis Care Res (Hoboken)*. 2012;64:475-487.
15. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis*. 2010;69:1103-1109.
16. Maverakis E, Patel F, Kronenberg DG, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. *J Autoimmun*. 2014;48–49:60-65.
17. Greenspan JS, Danniels TE, Talan N, Sylvester RA. The histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg Oral Med Oral Pathol*. 1974;37:217-229.
18. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the American heart association. *Circulation*. 2002;105:539-542.
19. Ishizu T, Seo Y, Kameda Y, et al. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. *Hypertension*. 2014;63:500-506.
20. Koshizuka R, Ishizu T, Kameda Y, Kawamura R, Seo Y, Aonuma K. Longitudinal strain impairment as a marker of the progression of heart failure with preserved ejection fraction in a rat model. *J Am Soc Echocardiogr*. 2013;26:316-323.
21. Choi JO, Cho SW, Song YB, et al. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. *Eur J Echocardiogr*. 2009;10:695-701.
22. Kobayashi Y, Giles JT, Hirano M, et al. Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. *Arthritis Res Ther*. 2010;12:R171.
23. Smith SP, Secomb TW, Hong BD, Moulton MJ. Time-dependent regional myocardial strains in patients with heart failure with a preserved ejection fraction. *Biomed Res Int*. 2016;2016:8957307.
24. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953-1959.
25. Voulgarelis M, Tzioufas AG. Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome. *Nat Rev Rheumatol*. 2010;6:529-537.
26. Watanabe T, Takahashi Y, Hirabayashi K, Tomaru U, Machida M. Acute fulminant myocarditis in a patient with primary Sjögren's syndrome. *Scand J Rheumatol*. 2019;48:164-165.
27. Bartoloni E, Baldini C, Schillaci G, et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med*. 2015;278:185-192.
28. Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia in systemic sclerosis. *Lancet*. 1989;2:475-479.
29. Kobayashi H, Yokoe I, Hirano M, et al. Cardiac magnetic resonance imaging with pharmacological stress perfusion and delayed enhancement in asymptomatic patients with systemic sclerosis. *J Rheumatol*. 2009;36:106-112.
30. Guglielmo M, Fusini L, Muscogiuri G, et al. T1 mapping and cardiac magnetic resonance feature tracking in mitral valve prolapse. *Eur Radiol*. 2021;31:1100-1109.
31. Gastl M, Lachmann V, Christidi A, et al. Cardiac magnetic resonance T2 mapping and feature tracking in athlete's heart and HCM. *Eur Radiol*. 2021;31:2768-2777.

How to cite this article: Yokoe I, Kobayashi H, Nishiwaki A, et al. Asymptomatic myocardial dysfunction was revealed by feature tracking cardiac magnetic resonance imaging in patients with primary Sjögren's syndrome. *Int J Rheum Dis*. 2021;24:1482–1490. https://doi.org/10.1111/1756-185X.14227

Received: 20 April 2021 | Revised: 30 August 2021 | Accepted: 27 September 2021

DOI: 10.1111/1756-185X.14229

International Journal of Rheumatic Diseases WILEY

ORIGINAL ARTICLE

Trajectory mapping of primary Sjögren's syndrome via transcriptome learning demonstrates limitations of peripheral blood sequencing

Bing Zhong[1] | Yaqiong Wang[2] | Qinghua Zou[1] | Chen Xuemeng[1] | Can Qian[1] | Chengshun Chen[1] | Jie Xiong[3] | Zihan Zheng[4] | Liyun Zou[1,5] | Jingyi Li[1,4]

[1]Department of Rheumatology, Southwest Hospital, Army Medical University, Chongqing, China

[2]Department of Stomatology, Southwest Hospital, Army Medical University, Chongqing, China

[3]Department of Ophthalmology, Southwest Hospital, Army Medical University, Chongqing, China

[4]Chongqing International Institute for Immunology, Chongqing, China

[5]Department of Immunology, Army Medical University, Chongqing, China

Correspondence
Jingyi Li, Department of Rheumatology and Immunology, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing 630030, China.
Email: lijingyi_tmmu@foxmail.com

Funding information
This work was supported in part by a grant from the Chongqing Science and Health Union as Medical Research Project 2020MSXM046 to BZ and National Natural Science Foundation of China 81971546 to LZ

Abstract

Primary Sjögren's syndrome (pSS) is a complex autoimmune disease characterized by aberrant immune cell action against secretory glands throughout the body. A number of studies have previously identified unique characteristics in the circulating expression profile of white blood cells of pSS patients. However, the molecular progression pattern of pSS is unclear. Through a systematic analysis of pSS transcriptome information, we found that pSS transcriptomes display broad heterogeneity, but cannot be distinguished from the broad range of possible profiles of healthy controls. Instead, only sample learning using a subset of pre-identified signature genes could achieve partial separation through a trajectory governed by interferon activity. Interestingly, this trajectory is correlated with a decrease in dendritic cell counts. Our study thus highlights a major limitation to the utility of broad blood transcriptome analysis in the context of pSS, while also identifying several factors that influence the divergence between patient samples.

KEYWORDS

Sjögren's syndrome, trajectory mapping

1 | INTRODUCTION

Primary Sjögren's syndrome (pSS) is a complex autoimmune disease characterized by excessive dryness at sensitive mucosal membranes often associated with immune cell infiltration into secretory glands.[1,2] Many patients with pSS also experience chronic fatigue, and a portion of patients may develop systemic manifestations, as a result of antibody-mediated involvement in other organ systems.[3-5] pSS progression and drug response is understood to involve participation from both antigen-presenting cells that mediate innate responses, as well as adaptive responses from T and B lymphocytes in the form of directed cell killing and antibody secretion.[6] On a transcriptome level, a number of molecular pathways have been demonstrated to be involved in this progression process, particularly those related to interferon activity.[7,8] However, it is unclear if other biological processes may also be critically involved, and the extent to which autoreactive responses in pSS may differ from healthy immune responses to pathogen insult is also under investigation.

In recent years, improvements in transcriptome profiling have made it increasingly possible to carefully characterize the expression

profiles of complex clinical samples. New methods for data analysis have also been developed to help uncover more biological and clinical insights from these large-scale genomic data. When coupled together, these advances have created the potential for biomarker identification across a wide range of pathophysiological conditions. In the context of autoimmune diseases, a large number of transcriptome profiling studies have already been conducted to identify expression signatures associated with disease status, drug response, and other clinical phenotypes. However, the extent to which transcriptome profiling may help inform the current understanding of pSS progression is incompletely understood. Some previous studies have attempted to apply commonly used clustering approaches to identify differentially expressed genes between pSS patients and healthy controls.[9-11] While these approaches have been able to identify some putative hub genes to associate with disease status,[12,13] such analyses rely on a premise that pSS is a generally homogenous disease with relatively strong shared signature of disease. However, the wide observed variation in clinical phenotypes between pSS patients suggests otherwise. As such, alternative analysis approaches that embrace transcriptome heterogeneity may yield additional insights.

One novel approach has been to utilize newer dimension reduction and clustering algorithms (such as t-distributed stochastic neighbor embedding and Uniform Manifold Approximation and Projection [UMAP]) to distinguish unique groups within a larger pool of samples. These algorithms tend to emphasize the larger transcriptome differences to help uncover defining characteristics for each group. At the same time, trajectory inference algorithms have also been developed to resolve the finer differences between individual samples, and are designed to learn the most likely order in which changes in gene expression occur. Because a large pool of samples can be presumed to encompass individual variation in temporal progression along a given process, trajectory inference of a cluster(s) of cells sampled at a single point in time can be used to infer possible past and future states for an intermediate cell by learning the drivers of temporal variation. Trajectory inference is now commonly used on single-cell sequencing data to understand the order and mechanisms by which early progenitors develop into mature effectors. However, more broadly, trajectory inference may be used to predict possible progression patterns in the absence of true longitudinal sampling, and this extension may have significant utility for large-cohort translational studies. In this manuscript, we set out to apply a trajectory inference approach to characterize the transcriptome progression pattern of pSS by treating each patient transcriptome as an individual point for consideration. We then apply trajectory-based analysis to identify key pathways and molecules that contribute to disease progression.

2 | METHODS

2.1 | Data compilation

To find transcriptome data on patients with pSS, we searched the National Center for Biotechnology Information GEO database for "sjogren syndrome" and manually reviewed each of the results returned. Three large (n > 50) transcriptome studies were recovered that investigated the peripheral blood profiles of patients with SS. GSE66795 utilized microarrays to profile the expression of 160 samples from the UK pSS registry (UKPSSR) cohort.[14] GSE140161 utilized microarrays to profile the expression of 351 samples from the Assessment of Systemic Signs and Evolution in Sjögren's Syndrome (ASSESS) cohort.[15] GSE51092 utilized microarrays to profile 222 samples in work contributed by the Sjögren's Genetics Network (SGENE).[16] An additional RNA sequencing dataset containing 114 samples of salivary gland transcriptomes from pSS and controls was also analyzed.[17]

2.2 | Dimension reduction and trajectory inference

Taking the expression matrix and associated metadata collected above, we loaded the files into R for management using the Seurat package.[18] Data were log-normalized and scaled, and highly variable genes (HVGs) were identified using the vst algorithm in Seurat. Initial dimension reduction into a 2-D manifold was achieved using UMAP,[19] as implemented through the uwot package in R. Processed data was subsequently transferred into the monocle suite in R for trajectory alignment using the DDRTree algorithm.[20]

2.3 | Pathway inference

In order to identify the pathways contributing to the progression of pSS transcriptomes, we used the TIPS workflow[21] in R with recommended settings. Using the Reactome pathway knowledgebase[22] as our reference, we assessed the relative contribution of all pathways with at least 20 genes detected in each dataset through a process of iterated trajectory mapping. Associated visualizations of pathway temporal order and gene correlation were also computed via the shiny app.

2.4 | Deconvolution and drug-gene network analysis

Immune cell type deconvolution was performed using the Xcell package in R,[23] with cell types passing the recommended detection threshold being retained for analysis. Drug-gene network analysis was performed using interaction information provided by DSigDB.[24] The gene correlation network was constructed using tidygraph in the tidyverse environment[25] in R.

3 | RESULTS

3.1 | Manifold learning of pSS transcriptome signatures in peripheral blood

In order to learn the trajectory of transcriptome changes in the peripheral blood of pSS patients, we first used a number of distinct

manifold learning algorithms on the UKPSSR cohort. Much to our surprise, we discovered that dimension reduction using standard approaches of considering the full transcriptome, or otherwise the portion of genes displaying high variation (HVGs), were unable to clearly delineate differences between pSS and healthy control samples (Figure 1A,B). This lack of stratification was algorithm-independent, indicating that it was not influenced by potential biases in any one approach (Figure S1). Rather, this result demonstrates that on a holistic level, the peripheral transcriptome profiles of patients with pSS are not completely unique.

Since these canonical unsupervised stratification approaches fail to identify clear transcriptome differences, we then attempted to use a supervised approach to learn a manifold using only a small subset of genes previously reported to be differentially expressed in pSS patients (SS signature). Through this approach, we could observe significant isolation of healthy control (HC) samples from pSS samples (Figure 1C,D). However, we observed that a substantial number of pSS samples were still indistinguishable from HC nonetheless. Furthermore, when we examined the resulting manifold for patient-reported fatigue, we observed that it was also unable to reflect differences in fatigue (Figure 1E). Indeed, focused differential analysis of the dataset based on fatigue classification found few differentially expressed genes (DEGs) between different fatigue levels, and manifold learning based on significant DEGs was unable to stratify clearly (Figure S2). On the other hand, unsupervised clustering of the manifold learned according to the reported SS signature was able to identify 3 clusters that did have significant amounts of DEGs between themselves (Figure 1F).

3.2 | Trajectory mapping of UKPSSR cohort

In order to understand the biological processes that were driving transcriptome progression from HC and the 2 pSS clusters, we then performed trajectory mapping using DDRTree. When we applied the SS signature list as the basis for trajectory mapping, we observed that pseudotime ordering was unable to clearly separate samples based on fatigue levels (Figure 2B), but readily distinguished between the 3 clusters uncovered from the UMAP manifold and could consequently place HC samples at the start point of the trajectory (Figure 2C). In contrast, when we applied canonical HVGs for trajectory analysis, we observed no separation between HC

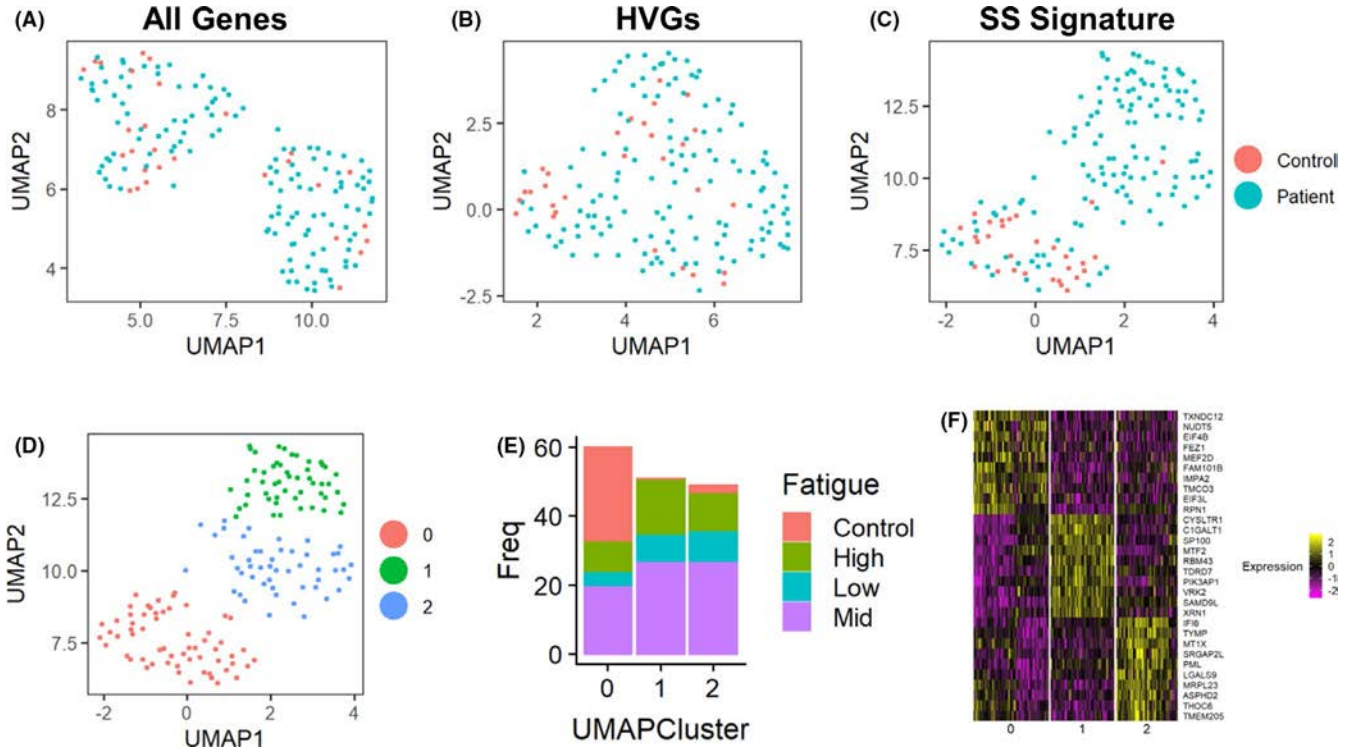


FIGURE 1 Cluster ordering of UK primary Sjögren's syndrome (pSS) registry (UKPSSR) cohort data. (A) Uniform Manifold Approximation and Projection (UMAP) dimension reduction of peripheral blood transcriptomes using all expressed genes shows no apparent stratification between control and pSS patient samples, although 2 dominant clusters of expression states are found. (B) UMAP dimension reduction of peripheral blood transcriptomes using the portion of genes showing high expression variation (HVGs) shows no apparent stratification between control and pSS patient samples. (C) UMAP dimension reduction of peripheral blood transcriptomes using only genes previously reported to be associated with pSS shows stratification between a large portion of control and pSS patient samples. However, we note that the lower third of the UMAP space still shows interspersed control and pSS samples. (D) Clustering of the UMAP space learned from application of the SS signature yields 3 clusters of similar size. (E) Bar graph visualization of the fatigue status of each patient sample from the clusters identified in (D). Notably, samples from patients with low and medium fatigue levels are found in all 3 clusters. (F) Heatmap of the top representative marker genes for each cluster identified in (D)

and pSS samples (Figure S3). We then performed a holistic analysis of pathway contributions to this overall trajectory using the TIPS method. Interestingly, we observed that only 8 pathways from the Reactome knowledgebase (2263 total) showed significant contribution (Figure 2D, Table S1). These included a number of pathways associated with interferon response and activity, as anticipated (Figure 2E). However, we also identified previously unreported pathways involving complement cascade and nicotinate metabolism. Progression ordering of these pathways demonstrated that they all underwent activation at essentially the same point along the trajectory (Figure 2F). Of note, pathway progression was largely driven by relatively linear changes in gene expression, and no rapid-activation events were observed (Figure 2G). Taken together, these results confirm that an interferon-driven progression may be involved in pSS, and that other unrelated pathways may also show concurrent changes in expression.

3.3 | Trajectory mapping of ASSESS cohort

To validate the conclusions drawn above, we further analyzed another large dataset of peripheral blood transcriptome of pSS patients taken from the ASSESS cohort. As before, we observed that conventional approaches toward manifold learning were unable to meaningfully separate antibody-positive patients from antibody-negative controls (Figure 3A,B). However, supervised learning using the SS signature was able to achieve partial stratification in both the UMAP (Figure 3C) and trajectory manifolds (Figure 3D-F). Interestingly, we also observed no significant stratification between patients who were positive for anti-Ro vs anti-La antibodies, suggesting that the type of antigen involved did not have a strong influence on the overall transcriptome.

Through TIPS analysis, we observed a strong recapitulation of the interferon signature observed in the UKPSSR cohort (Figure 3G, Table S2). However, we could not identify a statistically significant association of the complement cascade and nicotinate metabolism pathways. Collectively, this validation analysis further demonstrates that peripheral pSS transcriptomes are highly similar to HC, with some differences driven by interferon signaling.

3.4 | Trajectory mapping of SGEN cohort

To further validate these results, we also considered the microarray data from the SGEN cohort. Consistent with the previous analysis, dimension reduction based on HVGs and the full transcriptome was unable to separate out cases from controls (Figure S4A-B). However, reduction based on the SS signature list was able to achieve partial stratification in both UMAP and DDRTree (Figure S4C-E). However, unfortunately, this dataset featured a relatively smaller number of unique probes, and did not provide information on a large enough number of genes to enable accurate pathway inference. As such, we did not apply this dataset in our further analysis.

3.5 | Changes in cell composition over trajectory progression

While the analyses above explored the peripheral transcriptome of pSS on a general level, it is also well appreciated that the transcriptome is contributed by a range of distinct immune cell types with their own functional characteristics. In order to explore the influence of this heterogeneity on the manifolds learned, we then performed deconvolution analysis to track relative changes between cell populations. Interestingly, only a relatively small number of cell types appeared to display significant associations with trajectory progression along the SS signature manifold. In both the UKPSSR and ASSESS cohorts, we found that conventional dendritic cell (cDC) populations declined with trajectory advancement (Figure 4A,B). Consistent with this analysis, inspection of key dendritic cell markers revealed that the cDC markers *FCER1A* and *CD1C* indeed declined over the course of the trajectory in both cohorts (Figure 4C,D). cDCs are understood to play critical roles in antigen processing and presentation to T cells. However, interestingly, the decline of cDC percentages did not appear to be associated with a decline in genes associated with antigen presentation, or T cell co-stimulation. Taken together, these results suggest that while cDCs decline in number under the influence of interferon activity, the key functions of these cells is not similarly affected.

To investigate the potential of these changes contributing to alterations in the infiltrating immune cell populations within the secretory glands of pSS patients, we then repeated this deconvolution analysis on a dataset of parotid and labial transcriptomes of pSS patients and healthy controls. From UMAP reduction using HVGs, we observed that labial and parotid specimens were substantially distinct from each other, and that a portion of pSS patients had highly unique transcriptome profiles (Figure S5A). These unique pSS profiles were characterized by the presence of large amounts of CD45+ immune cells (Figure S5C). Interestingly, we observed that activated DCs and cDCs were highly enriched in both parotid and labial glands of pSS patients with high immune cell infiltration, while plasma cells were limited to the labial glands with high infiltration (Figure S5D). Weaker signatures of monocytes and M1 macrophages could also be seen in these patients. These results thus suggest that several of the immune cell populations found to be associated with trajectory progression in the peripheral blood of pSS patients may also be found among the infiltrating immune cells in patient secretory glands. Further studies may clarify if peripheral counts of these cells may have direct correlations with their presence in salivary infiltrates.

3.6 | Identification of putative therapeutic targets over trajectory progression

In order to explore the translational potential of our manifold learning analysis, we further mined drug-gene interaction databases to explore the possibility that some of the genes contributing to trajectory progression may be viable targets for therapeutic intervention.

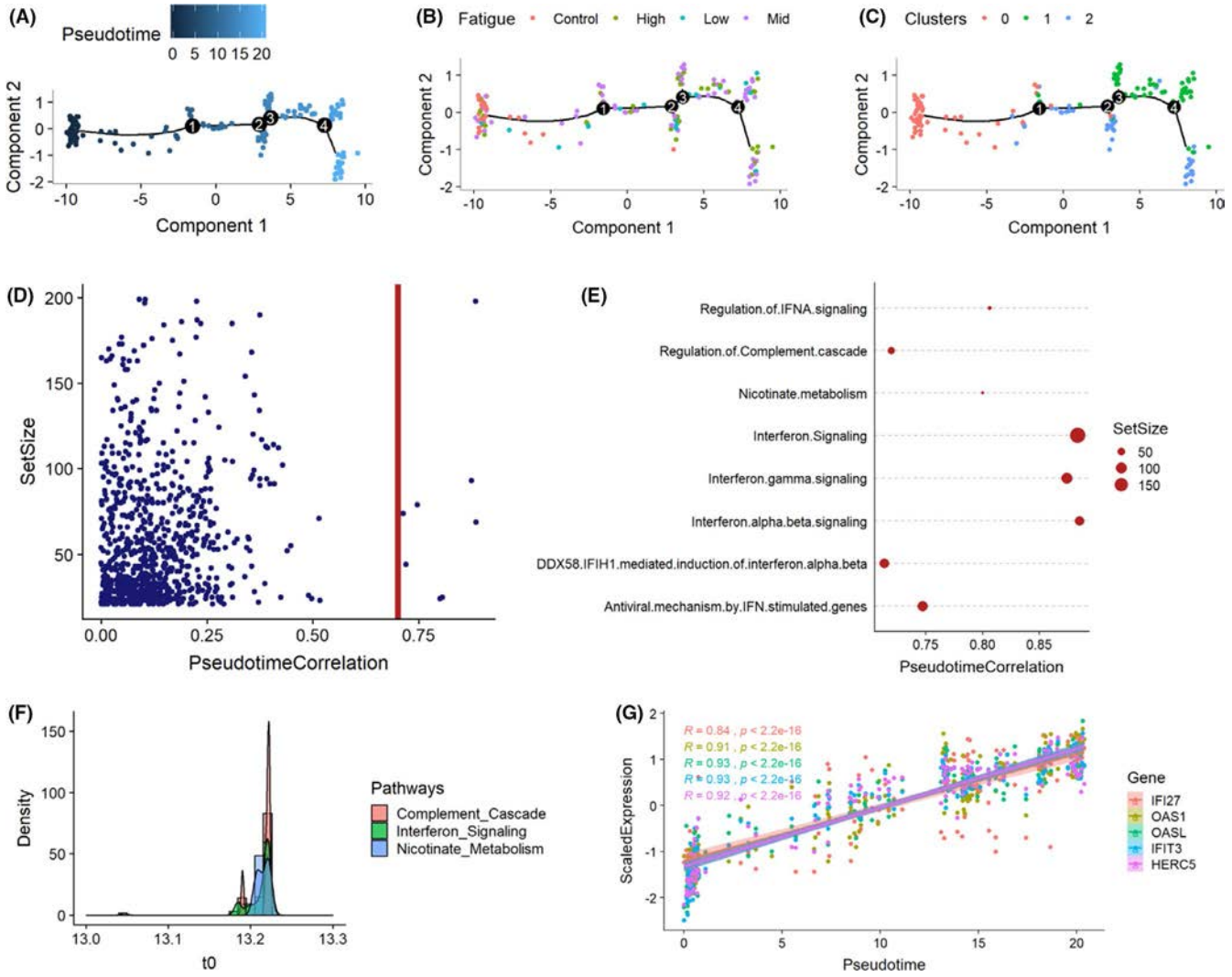


FIGURE 2 Trajectory mapping of UK primary Sjögren's syndrome (pSS) registry (UKPSSR) cohort data identifies interferon (IFN) signature. (A) Pseudotime assignment onto the DDRTree mapping of the UKPSSR data per the SS signature gene set yields a relatively linear trajectory with only minor bifurcations. (B) Overlay of patient fatigue characteristics on the DDRTree mapping also shows no apparent correlation in this learning approach. (C) Overlay of the cluster assignments recovered (as in Figure 1D) shows that each cluster falls into a distinct timeframe along the pseudotime progression trajectory. (D) Scatterplot of the pseudotime correlation (absolute Pearson's *R*) for all Reactome pathways analyzed relative to the size of the pathway (number of genes). A clear delineation can be seen, wherein 8 pathways have the highest absolute enrichment. (E) Dotplot of the 8 pathways with highest contributory significance from (D). (F) Temporal alignment of the pathways along the pseudotime trajectory shows that all of the pathways essentially change concurrently. (G) Scatterplot profile of the top 5 genes from the IFN-signaling pathway with pseudotime correlation demonstrates that each gene undergoes a linear increase in expression over the course of trajectory progression

Through merged consideration of both cohorts, we identified a subset of 148 genes corresponding to a pool of 49 currently Food and Drug Administration-approved drugs as possible candidates (Figure 5A,B). We further filtered this list using the criteria that these genes must show significant overexpression in pSS patients compared to HC (Figure 5C), as the vast majority of these drugs are known to inhibit the function of their cognate gene. Through network clustering and visualization of these possible targets in both cohorts, we observed a shared identification of 2 independent networks (Figure 5D,E). The smaller hub, containing PSMA5 and PSMB5 in both cohorts, indicates an association between the trajectory and proteasome function and highlighted a number of proteasome inhibitors such as bortezomib. We could also identify a larger and more complex network, containing hub genes such as Janus-activated kinase 2 (JAK2), signal transducer and activator of transcription 1 (STAT1), and TNF Superfamily Member 10 (TNFSF10) and which highlighted JAK inhibitors such as tofacitnib, as well as an array of kinase inhibitors typically used for chemotherapy. A full list of the therapeutic agents and their cognate targets is included as Table S3. Overall, this analysis demonstrates that 2 independent interaction networks may play a role in interferon-driven pSS progression and include possible targets for intervention.

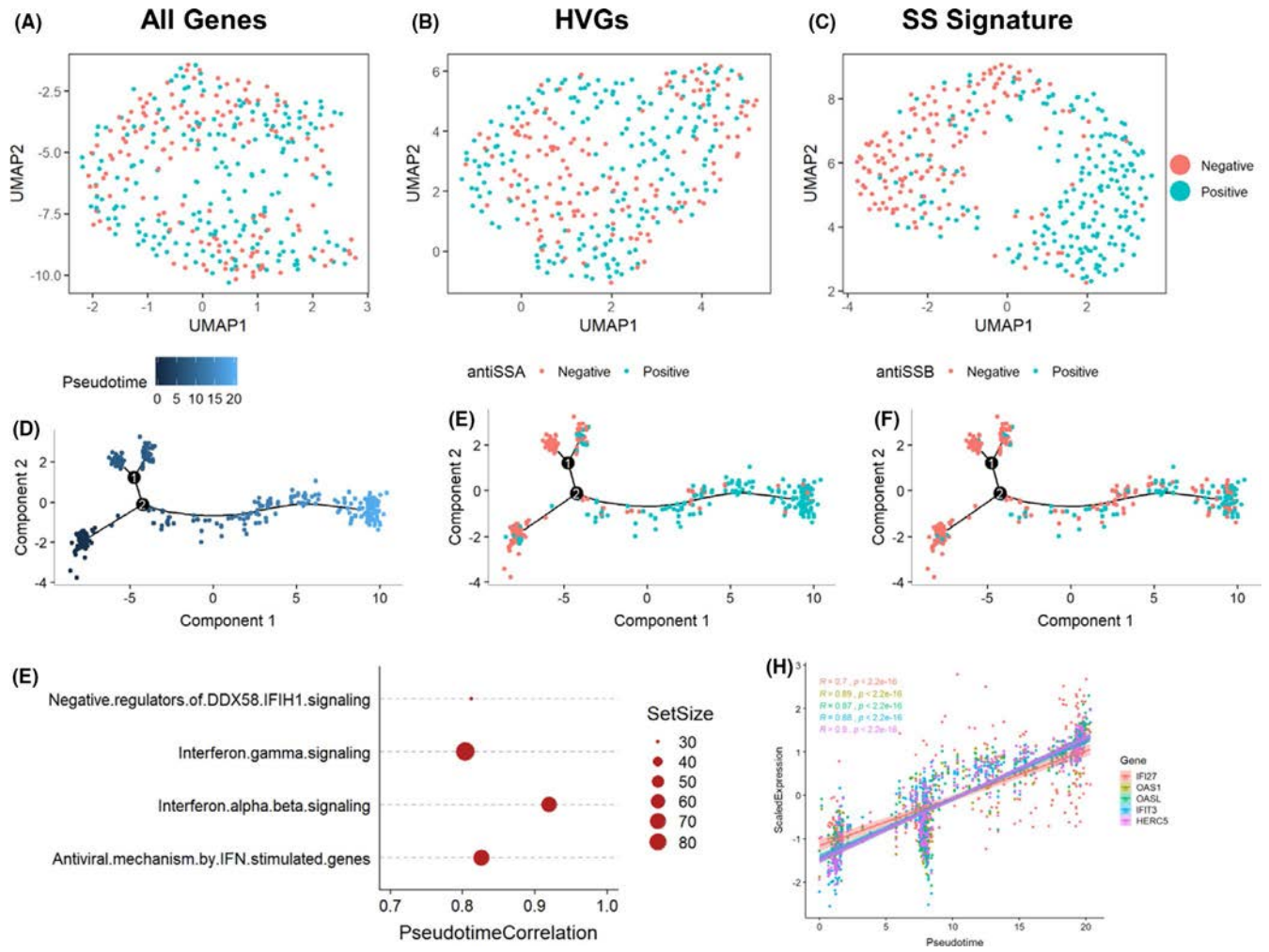


FIGURE 3 Trajectory mapping of ASSESS cohort. (A) Uniform Manifold Approximation and Projection (UMAP) dimension reduction of peripheral blood transcriptomes using all expressed genes shows no apparent stratification between control (antibody-negative) and primary Sjögren's syndrome (pSS) (antibody-positive) patient samples, although 2 dominant clusters of expression states are found. (B) UMAP dimension reduction of peripheral blood transcriptomes using the portion of genes showing high expression variation (HVGs) shows no apparent stratification between control and pSS patient samples. (C) UMAP dimension reduction of peripheral blood transcriptomes using only genes previously reported to be associated with pSS shows stratification between a large portion of control and pSS patient samples. (D) Pseudotime assignment onto the DDRTree mapping per the SS signature gene set yields a relatively linear trajectory with one intermediate bifurcation. (E, F) Antibody-negative patients span the early portion of the trajectory, while antibody-positive patients span the later portions. (G) Pathway inference of the dataset only recovers 4 pathways to contribute to pseudotime progression, all of which are intimately associated with interferon (IFN) signaling. (H) Scatterplot of the IFN-signaling associated genes identified in the UK pSS registry (UKPSSR) cohort demonstrates that these genes are also highly significantly associated with pseudotime progression in the ASSESS cohort

4 | DISCUSSION

Current therapeutic options for pSS patients are generally limited to topical therapies to provide symptomatic relief for dryness, and the off-label applications of common glucocorticoids and other disease-modifying anti-rheumatic drugs (DMARDs) approved for similar autoimmune diseases. However, none of these treatments have been demonstrated to have clear and sustained efficacy in clinical trials. Furthermore, many of these treatments are relatively non-specific, and current clinical recommendations are unable to suggest anything more effective. Through our trajectory-driven analysis, we identify 2 novel avenues for potential therapy, via proteasome inhibition or JAK/STAT inhibition.

The proteasome complex plays a key role in a range of immune cell activities, particularly antigen processing and antibody secretion. While proteasome inhibitors are typically applied in clinical practice to treat multiple myeloma, some case reports and translational studies have indicated successful treatment of autoimmune disorders via proteasome inhibition.[26,27] Interestingly, the proteasome inhibitor bortezomib has been reported to ameliorate fatigue and allow steroid tapering in a single case of refractory pSS; it is unclear if these benefits would extend to a larger-scale clinical

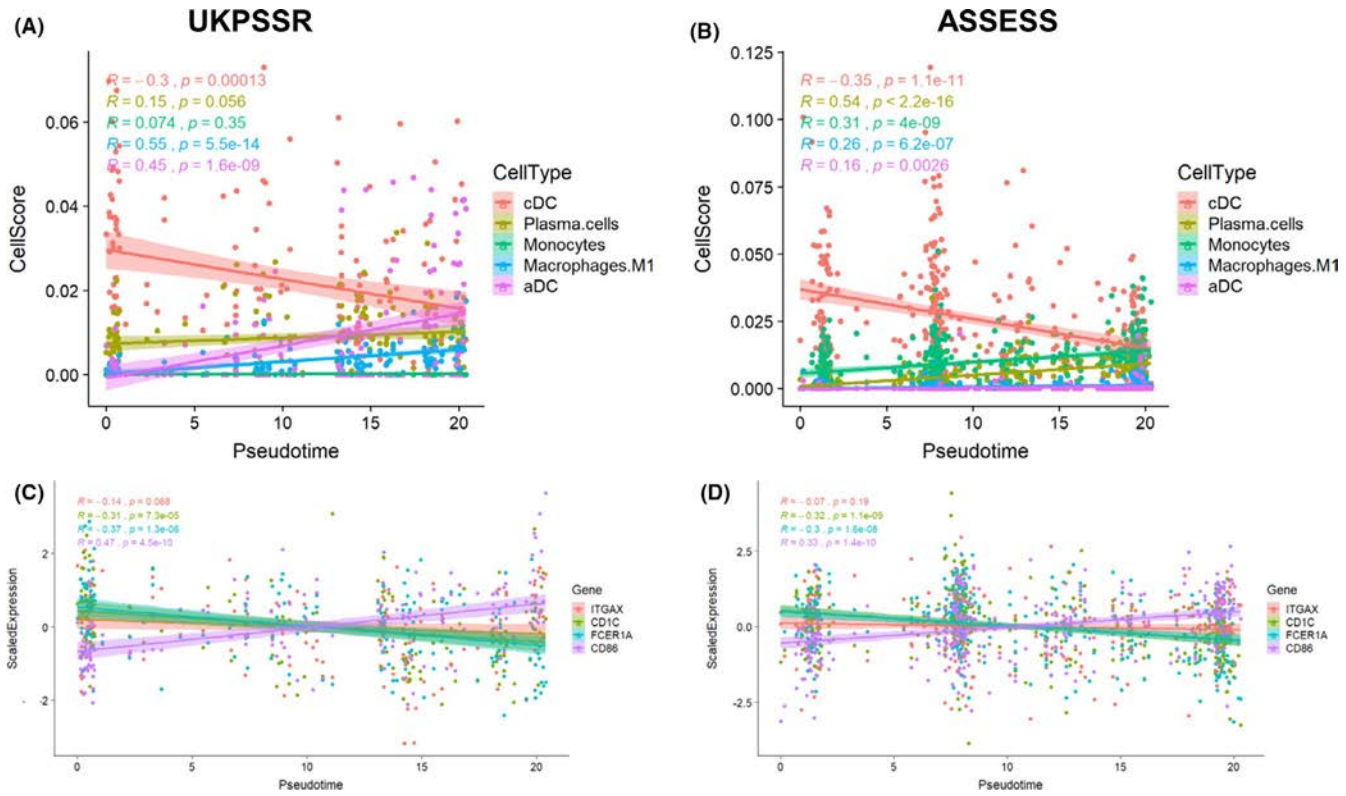


FIGURE 4 Changes in cell composition over trajectory progression. (A) Scatterplot of changes in predicted cell scoring (from XCell) over the course of pseudotime progression in the UK primary Sjögren's syndrome (pSS) registry (UKPSSR) cohort. A noticeable decline in conventional dendritic cells (cDCs) can be prominently observed, while M1 macrophages and activated DCs increase. (B) Scatterplot of changes in predicted cell scoring (from XCell) over the course of pseudotime progression in the ASSESS cohort. A noticeable decline in cDC can be prominently observed as in (A), but changes in M1 macrophages and activated DC are not pronounced. (C, D) Human cDCs are understood to have prominent expression of the surface molecules CD1C and FCER1A, both of which decline in expression over the course of pseudotime progression in both cohorts. Interestingly, no significant change is seen in the broader DC marker CD11c (ITGAX), suggesting the possibility of DC status conversion, as opposed to outright DC depletion

evaluation.[28] However, since proteasome inhibition would likely be beneficial in suppressing plasma cell antibody secretion at a minimum, irrespective of additional impact on antigen presentation, we believe that this approach holds promise for patients refractory to other treatment options.

The JAK/STAT pathway is a common signaling pathway involved in driving immune cell behavior across a wide range of populations. Although the precise molecular mechanisms explaining its therapeutic efficacy are still not fully understood, a number of large clinical trials have demonstrated its efficacy as a DMARD in the context of rheumatoid arthritis and other autoimmune diseases.[29] Per our understanding, a number of translational studies are currently underway to examine the efficacy of JAK inhibition in patients with pSS.[30,31] Extrapolating from our analysis results, we hypothesize that inhibiting the JAK-centered network may be effective in causing direct reduction in the expression of the surface molecule TRAIL (encoded by TNFSF10), and interrupt interferon-driven pSS progression. However, this strategy may be much less effective in patients with peripheral transcriptomes lacking interferon signatures.

More generally, our analyses discovered a reduction in cDC proportion over the course of interferon-driven pSS progression. Through examination of the literature, we found that this phenotype is supported by studies on animal models and in small clinical cohorts.[32-34] However, this phenotype is also quite perplexing, given that interferon signaling is generally understood to play a positive role in promoting DC maturation in both physiological and pathological settings. As histological examinations of affected salivary glands in pSS patients have shown DC infiltration, one possible explanation for the DC decrease may be that the matured DCs migrated into these sites of active inflammation. However, single-cell analysis of the chemokine response of these DC populations would be required to demonstrate this phenomenon.

At the same time, we believe that the negative result found through our analysis (in the form of failed direct delineation between HC and pSS transcriptomes) also raises an important warning for the future direction of large-cohort studies of pSS. This failure is particularly surprising given that application of unsupervised learning methods is generally effective in the context of other autoimmune diseases such as lupus and rheumatoid arthritis at separating cases from controls. We are unsure of the cause for this divergence. However, we believe that these results clearly demonstrate that although transcriptome profiling is becoming increasingly accessible and economical, general sequencing of the heterogeneous circulating immune cell populations may not always be an ideal investigative

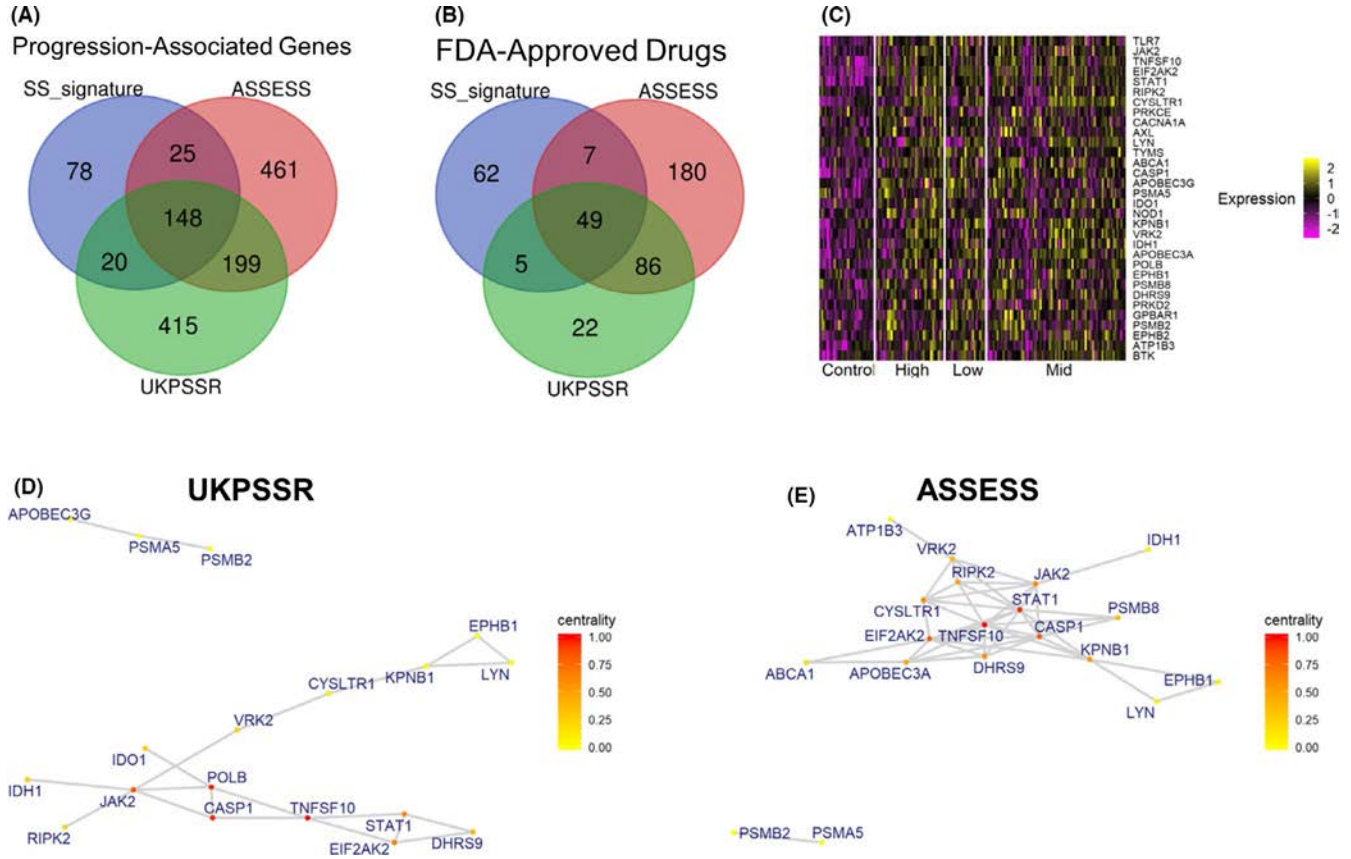


FIGURE 5 Significantly correlated genes include possible therapeutic targets. (A) Venn diagram of all genes associated with pseudotime progression in the ASSESS and UK primary Sjögren's syndrome (pSS) registry (UKPSSR) cohorts. Notably, while the trajectories for both cohorts were constructed using the SS signature list, learning based on the 2 cohorts yielded a substantial pool of genes (199) that were shared in both cohorts, but not seen in the original SS signature list. (B) Annotation of these genes based on known gene-drug interactions of Food and Drug Administration-approved drugs. Notably, these include a number of druggable candidates (86) not recoverable from direct analysis on the SS signature list. (C) Heatmap of the expression of several of the top druggable candidates identified as a result of the synthesis of both cohorts, following the exclusion of genes which had higher expression in control samples compared to pSS samples. (D) Network co-expression analysis of the genes in (C) identifies 2 primary networks in both datasets. One network is driven primarily by the PSMA5-PSMB2 pair of proteasome components. The other, larger, network, is driven by hub genes of Janus-activated kinase 2 (JAK2), signal transducer and activator of transcription 1 (STAT1) signaling, and the costimulatory molecule TRAIL (TNF Superfamily Member 10 [TNFSF10]), known to be involved in regulation of lymphocyte cell death. (E) Network co-expression analysis of the genes in (C) using data from the ASSESS cohort identifies 2 primary networks as in (D), with higher connectivity in the JAK/STAT module than in the UKPSSR cohort data

strategy. In the context of pSS, generic sequencing is not helpful for explaining some of the key clinical characteristics of the disease (such as patient fatigue level or antibody presence). This type of approach is also unlikely to identify strong signatures that reflect clinical intervention, as pSS transcriptomes are insufficiently unique. Rather, more targeted and/or longitudinal profiling of select populations may be required to unlock new knowledge regarding the mechanistic underpinnings of these clinical phenotypes. Longitudinal profiling of affected tissues, such as salivary glands, may also reveal a more accurate understanding of pSS progression.

In conclusion, from applying our manifold learning approach to analyzing the peripheral blood transcriptomes of patients with pSS, we identified a number of contributing characteristics and potential drug targets in interferon-driven pSS development, as well as a major limitation to applying transcriptome analysis in this context. Further validation work on DC function and JAK/STAT signaling may help identify new avenues for treatment in pSS patients with high levels of interferon activity. However, broad transcriptome profiling of patient peripheral blood is likely insufficient for personalizing patient treatment or otherwise identifying unique biomarkers of pSS.

ORCID

Zihan Zheng https://orcid.org/0000-0003-1486-9586

REFERENCES

1. Fox RI. Sjögren's syndrome. *Lancet*. 2005;366(9482):321-331. https://doi.org/10.1016/S0140-6736(05)66990-5
2. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X. Primary Sjogren syndrome. *BMJ*. 2012;14(344):e3821. https://doi.org/10.1136/bmj.e3821
3. Chai J, Logigian EL. Neurological manifestations of primary Sjogren's syndrome. *Curr Opin Neurol*. 2010;23(5):509-513. https://doi.org/10.1097/WCO.0b013e32833de6ab

4. Popov Y, Salomon-Escoto K. Gastrointestinal and hepatic disease in Sjogren syndrome. *Rheum Dis Clin North Am*. 2018;44(1):143-151. https://doi.org/10.1016/j.rdc.2017.09.010
5. François H, Mariette X. Renal involvement in primary Sjogren syndrome. *Nat Rev Nephrol*. 2016;12(2):82-93. https://doi.org/10.1038/nrneph.2015.174
6. Youinou P, Saraux A, Pers JO. B-lymphocytes govern the pathogenesis of Sjogren's syndrome. *Curr Pharm Biotechnol*. 2012;13(10):2071-2077. https://doi.org/10.2174/138920112802273100
7. Marketos N, Cinoku I, Rapti A, Mavragani CP. Type I interferon signature in Sjogren's syndrome: pathophysiological and clinical implications. *Clin Exp Rheumatol*. 2019;37 Suppl 118(3);185-191.
8. Lee J, Lee J, Kwok SK, et al. JAK-1 inhibition suppresses interferon-induced BAFF production in human salivary gland: potential therapeutic strategy for primary Sjogren's syndrome. *Arthritis Rheumatol*. 2018;70(12):2057-2066. https://doi.org/10.1002/art.40589
9. Horvath S, Nazmul-Hossain AN, Pollard RP, et al. Systems analysis of primary Sjögren's syndrome pathogenesis in salivary glands identifies shared pathways in human and a mouse model. *Arthritis Res Ther*. 2012;14(6):R238. https://doi.org/10.1186/ar4081
10. Peck AB, Nguyen CQ. Transcriptome analysis of the interferon-signature defining the autoimmune process of Sjogren's syndrome. *Scand J Immunol*. 2012;76(3):237-245. https://doi.org/10.1111/j.1365-3083.2012.02749.x
11. James K, Al-Ali S, Tarn J, et al. A transcriptional signature of fatigue derived from patients with primary Sjogren's syndrome. *PLoS One*. 2015;10(12):e0143970. https://doi.org/10.1371/journal.pone.0143970
12. Tasaki S, Suzuki K, Nishikawa A, et al. Multiomic disease signatures converge to cytotoxic CD8 T cells in primary Sjogren's syndrome. *Ann Rheum Dis*. 2017;76(8):1458-1466. https://doi.org/10.1136/annrheumdis-2016-210788
13. Luo J, Liao X, Zhang L, et al. Transcriptome sequencing reveals potential roles of ICOS in primary Sjögren's syndrome. *Front Cell Dev Biol*. 2020;8:592490. https://doi.org/10.3389/fcell.2020.592490
14. Tarn JR, Howard-Tripps N, Ng WF, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. *Lancet Rheumatol*. 2019;1(2):e85-e94.
15. Gottenberg JE, Seror R, Miceli-Richard C, et al. Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjogren's syndrome. Data at enrollment in the prospective ASSESS cohort. *PLoS One*. 2013;8(5):e59868. https://doi.org/10.1371/journal.pone.0059868
16. Lessard CJ, Li H, Adrianto I, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome. *Nat Genet*. 2013;45(11):1284-1292. https://doi.org/10.1038/ng.2792
17. Verstappen GM, Gao L, Pringle S, et al. The transcriptome of paired major and minor salivary gland tissue in patients with primary Sjögren's syndrome. *Front Immunol*. 2021;6(12):681941. https://doi.org/10.3389/fimmu.2021.681941
18. Butler A, Hoffman P, Smibert P, Papalexi E, Satija R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nat Biotechnol*. 2018;36(5):411-420. https://doi.org/10.1038/nbt.4096
19. Becht E, McInnes L, Healy J, et al. Dimensionality reduction for visualizing single-cell data using UMAP. *Nat Biotechnol*. 2019;37(1):38-44. https://doi.org/10.1038/nbt.4314
20. Qiu X, Mao Q, Tang Y, et al. Reversed graph embedding resolves complex single-cell trajectories. *Nat Methods*. 2017;14(10):979-982. https://doi.org/10.1038/nmeth.4402
21. Zheng Z, Xin Q, Ni Q, et al. TIPS: trajectory inference of pathway significance through pseudotime comparison for functional assessment of single-cell RNAseq data. *Brief Bioinform*. 2021;22(5):bbab124. https://doi.org/10.1093/bib/bbab124
22. Jassal B, Matthews L, Viteri G, et al. The reactome pathway knowledgebase. *Nucleic Acids Res*. 2020;48(D1):D498-D503. https://doi.org/10.1093/nar/gkz1031
23. Aran D. Cell-type enrichment analysis of bulk transcriptomes using xCell. *Methods Mol Biol*. 2020;2120:263-276. https://doi.org/10.1007/978-1-0716-0327-7_19
24. Yoo M, Shin J, Kim J, et al. DSigDB: drug signatures database for gene set analysis. *Bioinformatics*. 2015;31(18):3069-3071. https://doi.org/10.1093/bioinformatics/btv313
25. Wickham H. tidyverse: easily install and load the 'Tidyverse'. R package version. 2017;1(2):1. https://CRAN.R-project.org/package=tidyverse
26. Xiao F, Lin X, Tian J, et al. Proteasome inhibition suppresses Th17 cell generation and ameliorates autoimmune development in experimental Sjogren's syndrome. *Cell Mol Immunol*. 2017;14(11):924-934. https://doi.org/10.1038/cmi.2017.8
27. Verbrugge SE, Scheper RJ, Lems WF, de Gruijl TD, Jansen G. Proteasome inhibitors as experimental therapeutics of autoimmune diseases. *Arthritis Res Ther*. 2015;17(1):17. https://doi.org/10.1186/s13075-015-0529-1
28. Jakez-Ocampo J, Atisha-Fregoso Y, Llorente L. Refractory primary Sjogren syndrome successfully treated with bortezomib. *J Clin Rheumatol*. 2015;21(1):31-32. https://doi.org/10.1097/RHU.0000000000000210
29. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):495-507. https://doi.org/10.1056/NEJMoa1109071
30. Barrera MJ, Aguilera S, Castro I, et al. Tofacitinib counteracts IL-6 overexpression induced by deficient autophagy: implications in Sjogren's syndrome. *Rheumatology*. 2021;60(4):1951-1962. https://doi.org/10.1093/rheumatology/keaa670
31. Aota K, Yamanoi T, Kani K, Ono S, Momota Y, Azuma M. Inhibition of JAK-STAT signaling by baricitinib reduces interferon-gamma-induced CXCL10 production in human salivary gland ductal cells. *Inflammation*. 2021;44(1):206-216. https://doi.org/10.1007/s10753-020-01322-w
32. Zhao J, Kubo S, Nakayamada S, et al. Association of plasmacytoid dendritic cells with B cell infiltration in minor salivary glands in patients with Sjogren's syndrome. *Mod Rheumatol*. 2016;26(5):716-724. https://doi.org/10.3109/14397595.2015.1129694
33. Gottenberg JE, Cagnard N, Lucchesi C, et al. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjogren's syndrome. *Proc Natl Acad Sci USA*. 2006;103(8):2770-2775. https://doi.org/10.1073/pnas.0510837103
34. Konno A, Takada K, Saegusa J, Takiguchi M. Presence of B7–2+ dendritic cells and expression of Th1 cytokines in the early development of sialodacryoadenitis in the IqI/Jic mouse model of primary Sjorgren's syndrome. *Autoimmunity*. 2003;36(4):247-254. https://doi.org/10.1080/0891693031000141077

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Zhong B, Wang Y, Zou Q, et al. Trajectory mapping of primary Sjögren's syndrome via transcriptome learning demonstrates limitations of peripheral blood sequencing. *Int J Rheum Dis*. 2021;24:1491–1499. https://doi.org/10.1111/1756-185X.14229

Received: 8 July 2021 | Revised: 24 September 2021 | Accepted: 3 October 2021

DOI: 10.1111/1756-185X.14228

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Comparison of renal remission and relapse-free rate in initial- and delayed-onset lupus nephritis

Eiji Suzuki[1,2] | Makiko Yashiro-Furuya[2] | Jumpei Temmoku[2] | Yuya Fujita[2] | Naoki Matsuoka[2] | Momoko Hazama[3] | Tomoyuki Asano[2] | Shuzo Sato[2] | Hiroko Kobayashi[2] | Hiroshi Watanabe[2] | Takashi Kanno[1] | Kiyoshi Migita[2]

[1]Department of Rheumatology, Ohta-Nishinouchi Hospital, Fukushima, Japan

[2]Department of Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan

[3]Ohga Clinic, Fukushima, Japan

Correspondence
Eiji Suzuki, Department of Rheumatology, Ohta-Nishinouchi Hospital, 2-5-20, Nishinouchi, Koriyama-shi, Fukushima 963-8558, Japan.
Email: azsuzuki@ohta-hp.or.jp

Abstract

Introduction: Lupus nephritis (LN) is a major manifestation of systemic lupus erythematosus (SLE) which contributes to significant morbidity and mortality. It is unclear whether the timing of LN onset influences renal outcome. This study aimed to investigate differences in clinical features—particularly the relapse-free rate—in remission duration from induction therapies for LN and the onset timing of LN after the development of SLE.

Methods: We enrolled 66 LN patients from January 2004 to March 2020. We collected the following: demographic data, laboratory data, renal histology data, and LN induction therapy data. Renal remission and relapse-free rates were calculated for each group.

Results: Patients were first divided into early remission group (achieved renal remission in <12 months [n = 44]) and others (n = 22). There were no significant differences in clinical data, treatments, and relapse-free rate of LN. Patients were then divided into initial-onset LN (<12 months after development of SLE [n = 49]) and delayed-onset LN (≥12 months after development of SLE [n = 17]). Kaplan–Meier analysis showed that the relapse-free rate was significantly higher in all patients with initial-onset LN than those with delayed-onset LN ($P = .0094$).

Conclusion: The relapse-free rate was significantly higher in the initial-onset LN group than the delayed-onset LN group of patients with LN of various histopathological backgrounds. These data suggest that delayed-onset LN is a risk factor for the relapse of LN.

KEYWORDS

immunosuppressive agents, lupus nephritis, prednisolone, recurrence, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a loss of self-tolerance and formation of nuclear autoantigens and immune complexes, resulting in inflammation of multiple organs.[1] Lupus nephritis (LN) is a major manifestation of SLE that contributes to significant morbidity and mortality.[2] Patients with LN have higher mortality rates than SLE patients without LN.[3] From 2012 to 2013, clinical guidelines for LN were reported from the American College of Rheumatology (ACR),[4] Kidney Disease Improving Global Outcome,[5] joint European League Against Rheumatism (EULAR), European Renal Association (ERA), European Dialysis and Transplant Association (EDTA),[6] and Asian Lupus Nephritis Network.[7] EULAR updated the management recommendation for SLE in 2019.[8] Those clinical guidelines recommend performing a renal biopsy in order to obtain renal histology unless strongly contraindicated. Also, treatment should be based on the type of LN, as classified by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria.[9,10] Additionally, in induction therapies for classes III or IV LN, the use of mycophenolate mofetil (MMF) or intravenous cyclophosphamide (IVCY), along with glucocorticoids, was recommended based on various clinical trials including the Aspreva Lupus Management Study.[11] Further, it has been reported that renal response after 6 months of treatment with IVCY can predict long-term renal outcomes based on data obtained in the Euro-Lupus Nephritis Trial.[12] Reports also suggest that, in Japan, achieving early renal remission of classes III or IV LN using glucocorticoids with immunosuppressants might predict good outcomes, such as reduced organ damage and a low incidence of disease flare.[13,14]

On the other hand, some patients develop SLE and LN simultaneously, while others develop LN after an SLE diagnosis without renal involvement. According to several reports, the number of SLE patients who developed LN later was fewer compared to those who were diagnosed with LN simultaneously or within a few years.[15-18] It is unclear whether the timing of the onset of LN influences renal outcome. Reports from Ugolini-Lopes et al[19] and Dlifino et al[20] showed that no major differences were noted when disease profile or treatment outcome of early- and late-onset LN were compared. On the other hand, several reports from Japan showed that SLE patients with early-onset LN had better renal outcomes when compared to those with late delayed-onset LN.[18,21,22] Because the results were different, it is unclear how the timing of LN onset affects its pathophysiology. Although a renal biopsy is recommended for diagnosing and treating LN, it is difficult to achieve in patients at risk of bleeding, in poor general condition, or who refuse it. In clinical settings, it is often difficult to treat and predict the prognosis of patients with LN who have not been histologically diagnosed.

This study investigated SLE patients with LN at Ohta-Nishinouchi Hospital and Fukushima Medical University Hospital to assess if there were differences in clinical, serologic profile, treatments, and relapse-free rate of 2 groups of patients. One group involved duration of remission of LN from induction therapies (<6 months and ≥6 months), and the other involved onset timing of LN after SLE development (<12 months after SLE development or ≥12 months).

2 | METHODS

2.1 | Patients

Medical records of LN patients at Ohta-Nishinouchi Hospital and Fukushima Medical University Hospital who suffered from the disease for 1 or more years—from January 2004 to March 2020—were reviewed. SLE was diagnosed according to the ACR classification criteria of SLE,[23] while LN was diagnosed according to pathological findings obtained from renal biopsy. In lieu of renal biopsy, diagnosis of LN was made using the criteria of renal disorder aspect of the ACR classification criteria of SLE.[23] The study population consisted of 66 patients (55 female and 11 male). Complete renal response (CR) and partial renal response (PR) were defined on the basis of EULAR/ERA-EDTA recommendations for LN,[6] with CR defined as a urine protein/creatinine ratio (UPCR) <50 mg/mmol and normal or near-normal (within 10% of normal glomerular filtration rate [GFR] if previously abnormal) renal function, and PR defined as a ≥ 50% reduction in proteinuria and normal or near-normal GFR. As previously described by Hanaoka et al, 0.5 g/g creatinine was considered equivalent to UPCR 50 mg/mmol.[14] This study defined renal remission as PR including CR if achieved. Renal relapse was defined as loss of CR or PR status after achieving CR or PR. We divided patients into 2 groups based on time of renal remission and time of LN development from SLE onset.

2.2 | Data collection

Patients' baseline characteristics were collected at the time of diagnosis with SLE and LN. Demographic data included age at onset of SLE and LN, gender, disease duration of SLE and LN, time lag between onset of SLE and LN, observation period of the patients, patient scores on the SLE disease activity index 2000 (SLEDAI-2K),[24] one of the disease activity scoring systems for SLE, at the time of diagnosis with LN, and comorbidities of anti-phospholipid syndrome (APS). Laboratory data collected at the onset of LN included total protein, albumin, serum creatinine, estimated GFR (eGFR), complement 3 (C3), complement 4 (C4), UPCR, and positivity of anti-double-strand-DNA (anti-ds-DNA) antibodies. Anti-ds-DNA antibodies were measured by radioimmunoassay, enzyme-linked immunosorbent assay, or fluorescent enzyme immunoassay methods. Obtained renal tissues were diagnosed with LN according to the World Health Organization criteria or ISN/RPS classification of LN if renal biopsy was performed. Data on induction therapy of LN were also collected from medical records.

2.3 | Statistical analysis

Continuous values are shown as median and interquartile range (IQR). A nonparametric Mann–Whitney *U* test was used for intergroup comparisons of multiple variables. Fisher's exact test was used to investigate a possible association between each variable. Kaplan–Meier method was used to calculate the rate of remission and relapse-free rate, while a log-rank test was used to assess differences between the 2 groups. GraphPad Prism 5 software (GraphPad Software, San Diego, CA) was used to perform all of the statistical analyses. The significance level was set at $P < .05$.

2.4 | Ethics approval and consent to participate

The study was approved by the Ethics Committee of Fukushima Medical University (No. 30155).

3 | RESULTS

3.1 | Patient characteristics

The demographic and disease-related features of the enrolled 66 patients are as follows (Table 1). The majority of the patients were female (83.3%). The median age at onset of LN was 31.0 years (IQR 25.0-44.0 years), the disease duration of SLE was 81.5 months (IQR 37.3-143.0 months), observation period of the patients was 56.0 months (IQR 30.0-122.3), and SLEDAI-2K score at the time of onset of LN was 10.0 (IQR 10.0-18.0). Renal biopsy was performed on 45 (68.2%) patients. Thirty-eight (57.6%) patients were treated with intravenous methyl-prednisolone (mPSL) pulse therapy, 17 (25.6%) with IVCY, 8 (12.1%) with tacrolimus (TAC), 9 (13.6%) with MMF, and 3 (4.5%) with TAC plus MMF for induction therapy. Sixty-five patients (98.5%) achieved renal remission during the study period.

3.2 | Comparison of LN patients according to time of renal remission

Enrolled SLE patients were initially divided into 2 groups based on the time of renal remission. Since the Euro-Lupus Nephritis Trial results showed that early response to therapy at 6 months was the best predictor of good long-term renal outcomes,[12] we categorized the patients as follows. Patients who achieved renal remission in <6 months were defined as early remission, and others (ie, patients who achieved renal remission at ≥6 months and those who did not achieve remission) were defined as late remission. The demographic, disease-related features, renal histopathology, and induction therapies were summarized in each group and compared (Table 2): 44 patients (66.7%) achieved early remission, while 22 (33.3%) achieved late remission. There were no significant differences between the 2 groups regarding disease-related features at baseline. No significant difference was observed in terms of the observation period between the 2 groups, and 1 patient in the late remission group did not achieve partial remission during the observation period. There were no significant differences regarding kidney histopathology of LN, although 14 patients of early remission and 7 patients of late remission did not have renal biopsies conducted for various reasons. In induction therapies for LN, more patients were treated with mPSL pulse therapy in the early remission group, but there was no significant difference. A Kaplan–Meier analysis showed that the relapse-free rate after induction therapies was not significantly different between the early and late remission groups ($P = .1202$, log-rank test) (Figure 1A). Regarding medication of induction therapies, there were no significant differences in the relapse-free rate in the 2 groups treated with only PSL including mPSL pulse therapy (early remission 13/19 [68.4%] vs late remission 1/1 [100%]), and treated with PSL (including mPSL pulse therapy) plus immunosuppressants including IVCY, TAC, MMF, and TAC plus MMF (early remission: n = 22, late remission: n = 14, $P = .1429$, log-rank test) (Figure 1B).

3.3 | Comparison of LN patients according to timing of LN development from SLE onset

Enrolled SLE patients were then divided into another 2 groups based on timing of LN development from SLE onset. Jacobsen et al[16] and Seligman et al[17] demonstrated that renal manifestation in most SLE patients was observed within a year, and therefore, we divided the patients as follows. Patients who were diagnosed with SLE and LN simultaneously, or LN within <12 months of diagnosis with SLE, were defined as initial-onset LN, and others (ie, patients who were diagnosed with LN after ≥12 months of diagnosis with SLE, and who had already achieved remission of SLE before being diagnosed with LN) were defined as delayed-onset LN (Table 3). There were 49 patients (74.2%) with initial-onset LN, and 17 (25.8%) with delayed-onset LN. Median duration from onset of SLE to onset of LN in delayed-onset LN patients was 41.0 months. No significant difference in observation period was observed between the 2 groups, and 1 patient in the initial-onset LN group did not achieve partial remission during the observation period. Of the disease-related features at baseline, higher serum albumin levels ($P = .0086$) and higher serum C3 levels ($P = .0477$) were significantly related to delayed-onset LN, and significantly higher SLEDAI-2K scores at the time of onset of LN ($P = .0069$) were also observed in the delayed-onset LN group. There were no significant differences regarding histopathology of the LN kidney, although 17 patients of initial-onset LN and 4 patients of delayed-onset LN did not have renal biopsies for various reasons. With respect to induction therapies for LN, more patients were treated with mPSL pulse therapy in initial-onset LN compared with delayed-onset LN ($P = .0461$). Among 49 patients, 48 (98.0%) in initial-onset LN, and 17 of 17 (100%) patients in delayed-onset LN groups achieved renal remission during the observation period. Kaplan–Meier

TABLE 1 Baseline characteristics of patients

Characteristics		Overall (n = 66)
Female, n (%)		55 (83.3)
Age at onset of LN, y, median [IQR]		31.0 [25.0-44.0]
Disease duration of LN, mo, median [IQR]		81.5 [37.3-143.0]
Observation period, mo, median [IQR]		56.0 [30.0-122.3]
SLEDAI-2K score at the onset of LN, median [IQR]		15.0 [10.0-18.0]
Total protein, mg/dL, median [IQR]		6.7 [5.9-7.6]
Albumin, mg/dL, median [IQR]		3.2 [2.5-3.7]
Creatinine, mg/dL, median [IQR]		0.70 [0.59-0.93]
eGFR, mL/min, median [IQR]		79.3 [59.5-93.9] (n = 61)
C3, mg/dL, median [IQR]		42.0 [29.1-70.5] (n = 65)
C4, mg/dL, median [IQR]		5.0 [3.2-11.0] (n = 65)
Urine protein, g/g creatinine, median [IQR]		1.34 [0.61-3.12] (n = 56)
Anti-dsDNA antibody, n (%)		52 (78.8)
Antiphospholipid antibody syndrome, n (%)		5 (7.6)
Renal histopathology of lupus nephritis	II	4
	III	8
	IV	11
	V	10
	II +V	1
	III +V	6
	IV +V	5
	N/A	21
Induction therapy	Intravenous mPSL pulse (%)	38 (57.6)
	CYC (%)	17 (25.8)
	TAC (%)	8 (12.1)
	MMF (%)	9 (13.6)
	MMF +TAC (%)	3 (4.5)

Abbreviations: C3, complement 3; C4, complement 4; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LN, lupus nephritis; MMF, mycophenolate mofetil; mPSL, methylprednisolone; N/A, not available; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; TAC, tacrolimus.

analysis showed that the renal remission rate was not significantly different between initial-onset LN and delayed-onset LN (data not shown). We then analyzed the relapse-free rate of initial-onset LN and delayed-onset LN after induction of LN. Thirty-eight of the 48 patients (79.2%) in initial-onset LN, and 9 of 17 patients (52.9%) in delayed-onset LN did not experience renal relapse during the observation period. Kaplan–Meier analysis showed that the relapse-free rate was significantly higher in patients of initial-onset LN when compared to those of delayed-onset LN ($P = .0094$, log-rank test) (Figure 2A). Regarding medication for induction therapies, there was no significant difference in the relapse-free rate in the 2 groups treated with only PSL including mPSL pulse therapy (initial-onset LN 13/18 [72.2%] vs delayed-onset LN 1/2 [50%]). Also, the relapse-free rates of initial-onset LN patients treated with PSL (including mPSL pulse therapy) plus immunosuppressants—including IVCY, TAC, MMF, and TAC plus MMF—tended to be higher when compared to those of delayed-onset LN patients (initial-onset LN: n = 25, delayed-onset LN: n = 11, $P = .0588$, log-rank test) (Figure 2B).

4 | DISCUSSION

This study demonstrated that the relapse-free rate of LN in delayed-onset LN patients was significantly low when compared to that of initial-onset LN patients. We also showed that delayed-onset LN patients who were administered immunosuppressants experienced more relapses of LN when compared to initial-onset LN patients who were administered immunosuppressants. We could not show those differences in the study of time of remission (early remission and late remission) in our patients.

In delayed-onset LN patients, serum albumin and C3 were significantly high when compared to initial-onset LN patients. However, there was no difference regarding the distribution of renal

TABLE 2 Comparison of the characteristics of LN patients with early remission and late remission (including non-remission)

Characteristics		Early remission (n = 44)	Late remission (n = 22)	*P* value*
Female, n (%)		38 (86.3)	17 (77.3)	.4849
Age at onset of LN, y, median [IQR]		30.0 [24.3-43.8]	28.5 [23.0-44.3]	.8917
Disease duration of LN, mo, median [IQR]		91.0 [35.8-152.8]	66.5 [37.3-133.5]	.6732
Observation period, mo, median [IQR]		75.0 [27.8-136.5]	52.5 [31.5-100.5]	.5050
SLEDAI-2K score at the onset of LN, median [IQR]		15.0 [10.3-18.0]	15.5 [9.8-18.3]	.9077
Total protein, mg/dL, median [IQR]		6.7 [5.9-7.8]	6.8 [6.0-7.1]	.6732
Albumin, mg/dL, median [IQR]		3.0 [2.5-3.6]	3.2 [2.6-3.7]	.4454
Creatinine, mg/dL, median [IQR]		0.70 [0.59-0.88]	0.77 [0.62-1.02]	.1257
eGFR, mL/min, median [IQR]		83.5 [64.7-99.9] (n = 40)	70.8 [51.5-91.8] (n = 21)	.0835
C3, mg/dL, median [IQR]		42.6 [28.0-63.0] (n = 43)	38.7 [30.9-73.3]	.8842
C4, mg/dL, median [IQR]		5.0 [3.0-13.0] (n = 43)	5.0 [3.6-8.6]	.8241
Urine protein, g/g creatinine, median [IQR]		1.28 [0.57-2.82] (n = 37)	1.40 [0.90-3.68] (n = 19)	.5738
Anti-dsDNA antibody, n (%)		35 (79.5)	17 (77.3)	1.0000
Antiphospholipid antibody syndrome, n (%)		3 (6.8)	2 (9.1)	1.0000
Renal histopathology of lupus nephritis	II	3	1	1.0000
	III	6	2	1.0000
	IV	5	6	.1594
	V	8	2	.4755
	II +V	0	1	.3333
	III +V	5	1	.6549
	IV +V	3	2	1.0000
	N/A	14	7	1.0000
Induction therapy	Intravenous mPSL pulse (%)	29 (65.9)	9 (40.9)	.0674
	CYC (%)	11 (25.0)	6 (27.3)	1.0000
	TAC (%)	5 (11.4)	3 (13.6)	1.0000
	MMF (%)	6 (13.6)	3 (13.6)	1.0000
	MMF +TAC (%)	0 (0)	3 (13.6)	N/A

Abbreviations: C3, complement 3; C4, complement 4; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LN, lupus nephritis; MMF, mycophenolate mofetil; mPSL, methylprednisolone; N/A, not available; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; TAC, tacrolimus.

**P* values were determined using nonparametric Mann–Whitney *U* test or Fisher's exact test.

histopathology in patients who underwent renal biopsy. In addition, there was no difference in induction therapies between initial-onset LN and delayed-onset LN, except that patients who were prescribed steroid pulse therapy were significantly higher in the initial-onset LN group. Delayed-onset LN patients had immunosuppressive treatments for SLE before LN development. In our LN patients, there were no delayed-onset LN patients who developed neuropsychiatric SLE before development of LN. With the exception of only a few delayed-onset LN patients who received immunosuppressants, most delayed-onset LN patients were administered a low to moderate amount of glucocorticoid for mild to moderate symptoms—such as arthritis and rash—before development of LN. Therefore, although the nature of nephritis is possibly associated with poor immune complex activity in delayed-onset LN, it was considered that the reason serum albumin and C3 levels were high in delayed-onset LN patients was that the immune complex activity of SLE improved following prior treatments, as suggested by the lower SLEDAI-2K score in the delayed-onset LN patients. It was also considered that delayed-onset LN patients were being watched closer, therefore, their proteinuria was caught earlier than the initial-onset LN patients. Therefore, urinary loss of protein and increased complement consumption might have been going on for weeks or months before initial-onset LN patients present for clinical care and are diagnosed with LN which would result in the reduction of serum albumin and C3. However, although laboratory data of delayed-onset LN patients tended to be better than those of initial-onset LN patients because of preceding treatments, the relapse-free rate was lower in delayed-onset LN patients when compared to initial-onset LN patients. Also, compared to initial-onset LN patients, delayed-onset LN patients had more relapses of LN, even with the addition of immunosuppressants. Patients included in this study were selected based on the guidelines for the treatment of LN;[4-6] therefore, the available treatment options widely

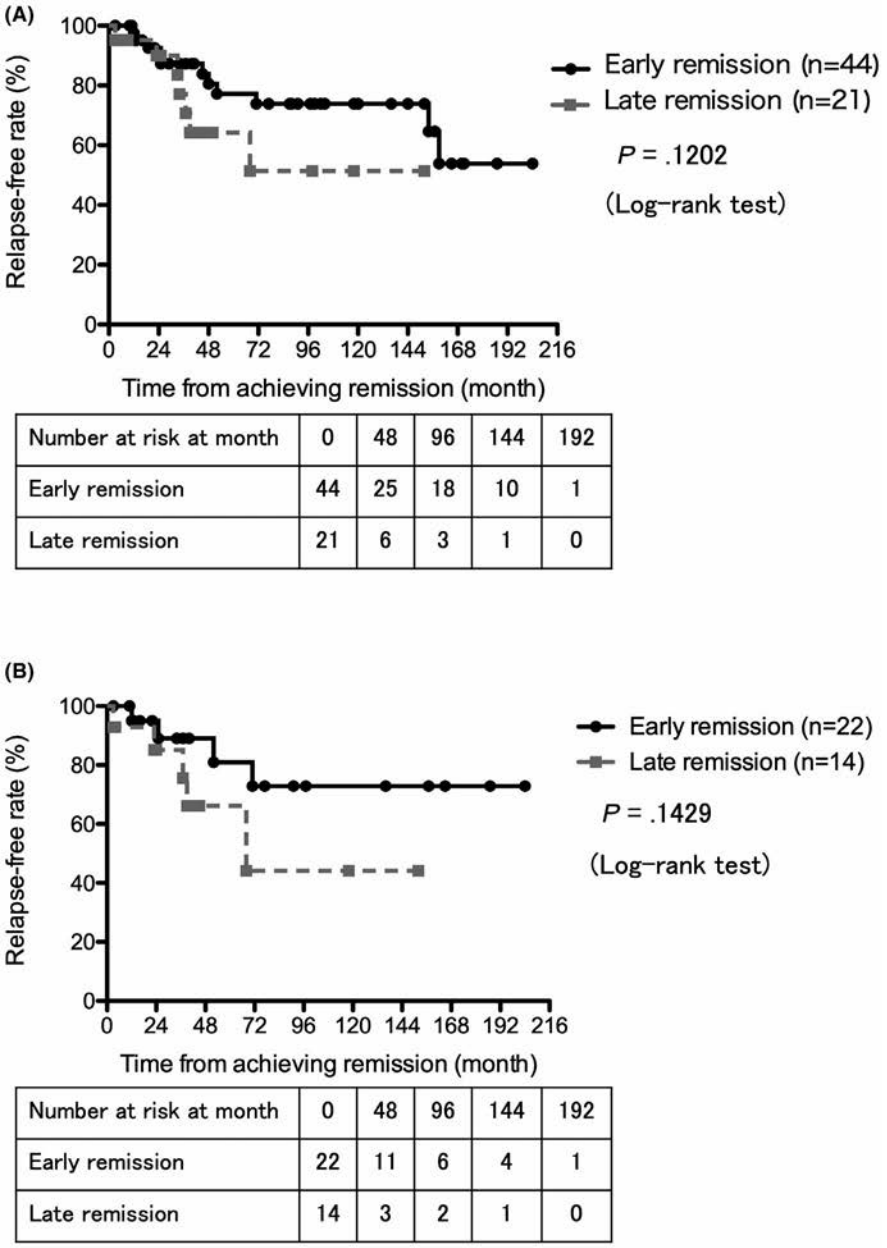


FIGURE 1 The relapse-free rate from achieving renal remission between early and late remission patients of lupus nephritis. A: There is no significant difference in the relapse-free rate between early (n = 44) and late (n = 21) remission patients of lupus nephritis (log-rank test, *P* =.1202). B: There is no significant difference in the relapse-free rate between early (n = 22) and late (n = 14) remission patients of lupus nephritis treated with prednisolone plus immunosuppressants (log-rank test, *P* =.1429)

varied. In terms of induction therapies for LN, although more patients in the initial-onset than those in the delayed-onset LN groups were treated with mPSL pulse therapy, no significant difference was observed regarding the use of immunosuppressants between the 2 groups. Maintenance treatment for LN varied from case to case and included immunosuppressants, such as azathioprine, cyclosporine, TAC, mizoribine, and MMF. It was difficult to discuss the differences between different types of immunosuppressants because of the small number of cases that were administered each drug. In the present study, we were unable to describe the relationship between the use of immunosuppressants for maintenance treatment and the difference in relapse-free rate between the initial- and delayed-onset LN groups. Nakano et al reported a lower relapse-free rate in the delayed-onset LN group, but no difference was observed between the 2 groups in terms of the maintenance medications used;[18] thus, this report may be informative. Ichinose et al previously reported that the early-onset LN group was characterized by higher levels of anti-dsDNA antibodies and hypocomplementemia with higher serological activity, and a lower index of chronicity compared to the late-onset group.[22] Park et al reported that glomerular sclerosis in the chronicity index was an independent predictor of complete remission after start of therapy in LN patients.[25] In addition, it was difficult to calculate and compare the chronicity index due to the different historical backgrounds and organized evaluators. Comparing renal histological findings to the extent possible, in the initial-onset LN group, 10 and 6 cases of global glomerulosclerosis and fibrous crescents, respectively, were observed among the 24 patients in the no-recurrence group, whereas 3 and 1 cases of global glomerulosclerosis and fibrous crescents were observed among the 6 patients in the recurrence group. Conversely, in the delayed-onset LN group, 2

TABLE 3 Comparison of the characteristics of patients with initial-onset LN and delayed-onset LN

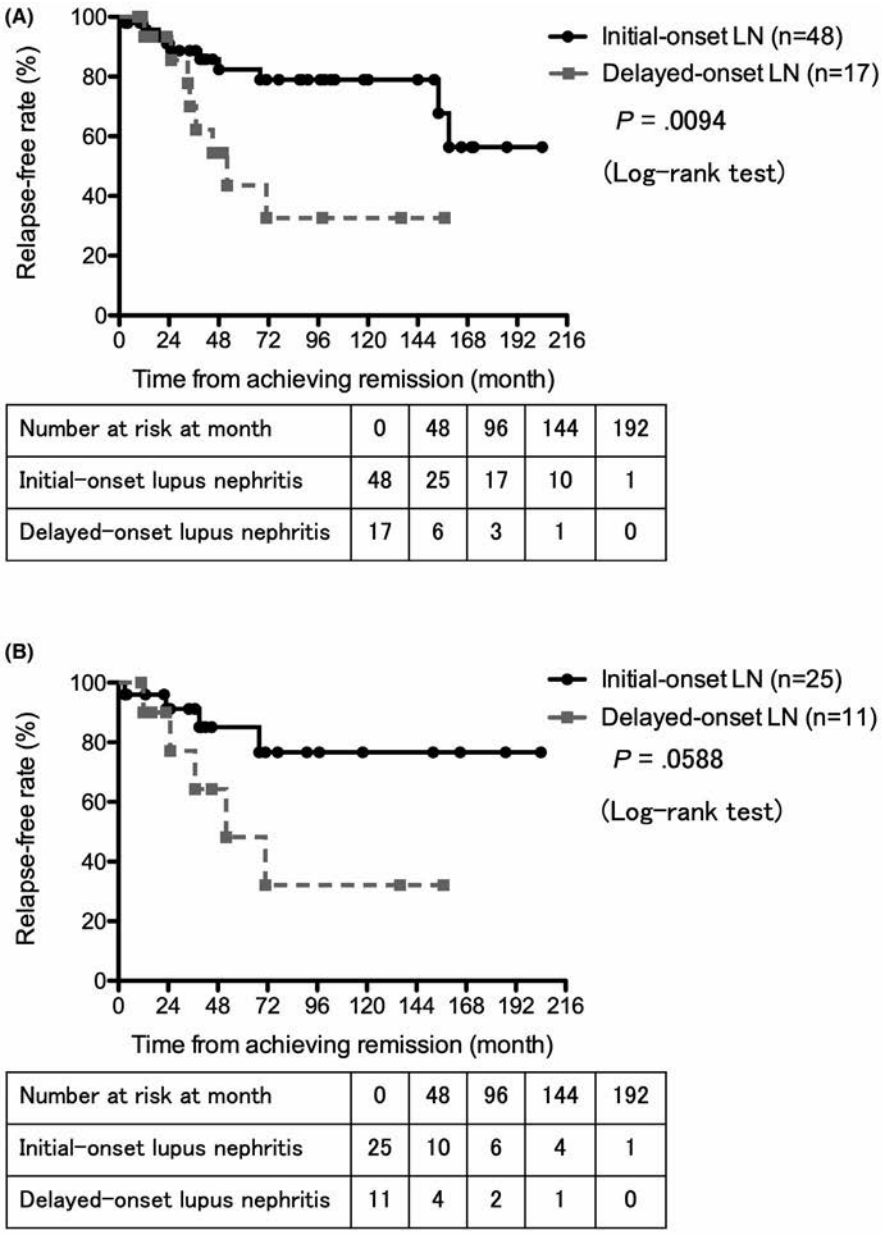
Characteristics		Initial-onset LN (n = 49)	Delayed-onset LN (n = 17)	*P* value†
Female, n (%)		41 (83.7)	14 (82.4)	1.0000
Age at onset of LN, y, median [IQR]		30.0 [24.5-44.5]	33.0 [27.5-40.5]	.3826
Disease duration of LN, mo, median [IQR]		90.0 [38.0-151.5]	67.0 [32.0-138.0]	.8834
Duration between onset of SLE and onset of LN, mo, median [IQR]			41.0 [26.0-106.5]	
Observation period, mo, median [IQR]		74.0 [33.0-126.5]	46.0 [27.5-80.5]	.2588
SLEDAI-2K score at onset of LN, median [IQR]		16.0 [13.0-19.0]	10.0 [8/0-16.5]	.00069*
Total protein, mg/dL, median [IQR]		6.7 [5.9-7.8]	6.7 [6.0-7.0]	.8487
Albumin, mg/dL, median [IQR]		3.0 [2.4-3.5]	3.7 [3.0-3.9]	.0086*
Creatinine, mg/dL, median [IQR]		0.71 [0.59-0.97]	0.67 [0.63-0.74]	.5377
eGFR, mL/min, median [IQR]		78.6 [55.2-93.1] (n = 44)	83.0 [66.8-98.7]	.4545
C3, mg/dL, median [IQR]		38.0 [27.5-63.0]	54.6 [37.5-76.0] (n = 16)	.0477*
C4, mg/dL, median [IQR]		5.0 [3.0-12.3]	6.6 [3.7-9.9] (n = 16)	.6417
Urine protein, g/g creatinine, median [IQR]		1.28 [0.57-2.97] (n = 41)	1.78 [0.7.0-3.64] (n = 15)	.5476
Anti-dsDNA antibody, n (%)		37 (75.5)	15 (88.2)	.3272
Antiphospholipid antibody syndrome, n (%)		4 (8.2)	1 (5.9)	1.0000
Renal histopathology of lupus nephritis	II	3	1	1.0000
	III	7	1	.6689
	IV	8	3	1.0000
	V	7	3	.7093
	II +V	1	0	1.0000
	III +V	3	3	.1722
	IV +V	3	2	.5970
	N/A	17	4	.5485
Induction therapy	Intravenous mPSL pulse (%)	32 (65.3)	6 (35.3)	.0461*
	CYC (%)	14 (28.6)	3 (17.6)	.5247
	TAC (%)	4 (8.2)	4 (23.5)	.1889
	MMF (%)	6 (12.2)	3 (17.6)	.6844
	MMF +TAC (%)	2 (4.1)	1 (5.9)	1.0000

Abbreviations: C3, complement 3; C4, complement 4; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LN, lupus nephritis; MMF, mycophenolate mofetil; mPSL, methylprednisolone; N/A, not available; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; TAC: tacrolimus.

†*P* values were determined using nonparametric Mann–Whitney *U* test or Fisher's exact test.

*indicates $P < .05$.

and 1 cases of global glomerulosclerosis and fibrous crescents were observed among the 6 patients in the no-recurrence group, whereas 3 cases of global glomerulosclerosis and fibrous crescents each were observed among the 7 patients in the recurrence group although the comparison was based only on the presence or absence of findings without considering differences in degree. In this study, we could not show the differences in chronicity findings between the initial- and delayed-onset LN groups. Nakano et al stated that the relatively worse long-term renal outcome in delayed-onset LN was primarily because of failure to achieve sustained remission in these patients, and delayed-onset LN might be a potential predictor of poorer treatment outcomes.[18] Some reports state that a poor renal response to initial treatment and renal flares were strongly associated with future renal damages.[26-28] It was thought that delayed-onset LN patients were difficult to treat because they had already received immunosuppressive treatments for SLE before development of LN. As previously reported, one reason why delayed-onset LN was hard to treat was that kidneys of delayed-onset LN patients had more chronic damaged lesions compared to kidneys of initial-onset LN patients. Therefore, delayed-onset LN patients are considered to have a poor response to immunosuppressive therapies because immunosuppressive therapies are usually effective against active lesions of the kidneys, and not chronic damaged lesions. Medicines used before development of LN also might have influenced chronic damage of kidneys. It was also considered that some patients needed aggressive immunosuppressive treatments for extended periods



Number at risk at month	0	48	96	144	192
Initial-onset lupus nephritis	48	25	17	10	1
Delayed-onset lupus nephritis	17	6	3	1	0

Number at risk at month	0	48	96	144	192
Initial-onset lupus nephritis	25	10	6	4	1
Delayed-onset lupus nephritis	11	4	2	1	0

FIGURE 2 The relapse-free rate from achieving renal remission between patients of initial- and delayed-onset lupus nephritis (LN). A: There is a significant difference in the relapse-free rate between patients of initial- (n = 48) and delayed-onset LN (n = 17) (log-rank test, *P* =.0094). B: The relapse-free rate of patients of initial-onset LN (n = 25) treated with prednisolone plus immunosuppressants was higher when compared to patients of delayed-onset LN (n = 11) (*P* = .0588, log-rank test)

because of active immune reaction since LN had newly developed despite prior treatment for SLE. The kidneys are among the main target organs of SLE. Jakes et al reported that renal involvement of SLE was observed in Asians, 21%–65% at diagnosis and 40%–82% over time.[29] LN is an important factor that influences mortality in SLE.[3] It was suggested that SLE patients without renal manifestation at disease onset should pay more attention to renal function and urinalysis in order to monitor development of LN. Since LN patients in this study were heterogeneous, this result was considered more useful in SLE patients.

On the other hand, we could not show any difference in relapse-free rate between early and late remission patients as previously reported.[14] One reason might be that renal histological background was varied in this study. Also, more LN patients of early remission had achieved remission by treatment with only PSL when compared to patients of late remission. It was suggested that LN patients of early remission might have included more patients with mild nephritis, and patients with early diagnosis and treatment with plasticity in renal lesions. However, patients of early remission who were treated with only PSL tended to experience recurrence of LN later. We were reminded of the importance of performing histological examination by renal biopsy as much as possible, and treating by adding immunosuppressants according to the algorithms of treatment of LN.

Despite the above, some study limitations were noted. First, renal biopsy was not performed in about 1/3 of the patients for reasons, such as high risk of bleeding complicated by APS, poor general condition, and refusal of examination. In clinical practice, because a number of LN patients had not undergone histological diagnosis of LN, it was relevant to include these patients. Second, due to the retrospective nature of the study, heterogeneity in LN patients could not be fully excluded, which has been reported as a limitation with retrospective observational studies on LN.[21,22,30] Owing to the long

study duration, the treatment regimen for LN varied based on time, and because many physicians treated patients in this study, treatment regimens were subtly different for each treating physician. Additionally, because we did not store serum samples from patients, we could not measure several biomarkers that are useful for determining the pathophysiology of LN. Third, the sample size was relatively small, especially the number of patients in late remission and delayed-onset LN. Fourth, the histological diagnosis of the kidney did not follow the ISN/RPS classification for LN; therefore, some patients were diagnosed based on the World Health Organization's classification. Finally, it was difficult to define patients with delayed-onset LN, and we defined such patients as those who were diagnosed with LN at ≥12 months after SLE diagnosis and who had already achieved remission of SLE before being diagnosed with LN. Although Jacobsen et al[16] and Seligman et al[17] reported that renal manifestation in most patients with SLE was observed within a year; several studies[15,19,22] have defined delayed-onset LN based on a time gap of 5 years between SLE diagnosis and LN development. Therefore, it could not be ruled out that the patients with delayed-onset LN in this study might have included several patients with initial-onset LN. Further, because the development of LN can sometimes be silent, that is, without an initial manifestation of proteinuria and hematuria, the inclusion of initial-onset LN patients in the delayed-onset LN group could not be ruled out. Therefore, we must focus on and interpret the results of similar studies reported from various countries, and it is necessary to conduct a prospective large-scale, multicenter international collaborative study to verify the findings described here.

In conclusion, our study demonstrated that the relapse-free rate was significantly higher in the initial-onset LN group when compared to the delayed-onset LN group of LN patients of various histopathological backgrounds. These data suggest that delayed-onset LN is a risk factor for relapse of LN. Therefore, it is important that SLE patients who are not complicated by LN also be carefully monitored regarding renal function and urinalysis. When LN develops, a renal biopsy should be conducted and immunosuppressive therapies commenced as soon as possible.

ACKNOWLEDGEMENTS

We would like to thank Enago (www.enago.jp) for the English language review.

CONFLICT OF INTEREST

The authors of this work have nothing to disclose.

AUTHOR CONTRIBUTIONS

Conceptualization, ES, MYF, JT, YF, NM, MH, TA, SS, TK, KM; methodology, ES, MYF, and KM; validation, ES, and KM; formal analysis, ES, MYF, and KM; investigation, ES, MYF, JT, YF, NM, MH, TA, SS, and KM; resources, ES, HK, HW, and KM; data curation, ES; writing—original draft preparation, ES, and KM; writing—review and editing, ES, TK, and KM; visualization, KM; supervision, HK, HW, KM; project administration, KM; funding acquisition, KM All authors have read and agreed to the published version of the manuscript.

ORCID

Eiji Suzuki https://orcid.org/0000-0001-9042-4947

REFERENCES

1. Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet*. 2019;393:2332-2343.
2. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2017;365:2110-2121.
3. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol*. 2017;12:825-835.
4. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64:797-808.
5. Chapter 12: Lupus nephritis. *Kidney Int Suppl*. 2011;2:221-232.
6. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association- European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. *Ann Rheum Dis*. 2012;71:1771-1782.
7. Mok CC, Yap DY, Navarra SV, et al. Overview of lupus nephritis management guidelines and perspective from Asia. *Int J Rheum Dis*. 2013;16:625-636.
8. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78:736-745.
9. Weening JJ, D'Agait VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revised. *Kidney Int*. 2004;65:521-530.
10. Weening JJ, D'Agait VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revised. *J Am Soc Nephrol*. 2004;15:241-250.
11. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009;20:1103-1112.
12. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term follow up of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum*. 2004;50:3934-3940.
13. Hanaoka H, Kaneko Y, Kuwana M, Takeuchi T. Early achievement of complete renal response predicts good long-term renal outcome and low systemic damage in newly diagnosed lupus nephritis class III or IV. *Mod Rheumatol*. 2015;25:714-718.
14. Hanaoka H, Yamada H, Kiyokawa T, et al. Lack of partial renal response by 12 weeks after induction therapy predicts poor renal response and systemic damage accrual in lupus nephritis class III or IV. *Arthritis Res Ther*. 2017;19:4.
15. Varela DC, Quintana G, Somers EC, et al. Delayed lupus nephritis. *Ann Rheum Dis*. 2008;67:1044-1046.
16. Jacobsen S, Petersen J, Ullman S, et al. A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets. *Clin Rheumatol*. 1998;17:468-477.
17. Seligman VA, Lum RF, Olson JL, Li H, Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. *Am J Med*. 2002;112:726-729.
18. Ugolini-Lopes MR, Santos LPS, Stagnaro C, Seguro LPC, Mosca M, Bonfá E. Late-onset biopsy-proven lupus nephritis without other associated autoimmune disease: severity and long-term outcome. *Lupus*. 2019;28:123-128.
19. Delfino J, Dos Santos TAFG, Skare TL. Comparison of lupus patients with early and late onset nephritis: a study in 71 patients from a single referral center. *Adv Rheumatol*. 2020;60:5.

20. Takahashi Y, Mizoue T, Suzuki A, et al. Time of initial appearance of renal symptoms in the course of systemic lupus erythematosus as a prognostic factor for lupus nephritis. *Mod Rheumatol*. 2009;19:293-301.
21. Nakano M, Kubo K, Shirota Y, et al. Delayed lupus nephritis in the course of systemic lupus erythematosus is associated with poorer treatment response: a multicentre retrospective cohort study in Japan. *Lupus*. 2019;28:1062-1073.
22. Ichinose K, Kitamura M, Sato S, et al. Comparison of complete renal response and mortality in early- and late-onset lupus nephritis: a multicenter retrospective study of Japanese cohort. *Arthritis Res Ther*. 2020;22:175.
23. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.
24. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002;29:288-291.
25. Park DJ, Choi SE, Xu H, et al. Chronicity index, especially glomerular sclerosis, is the most powerful predictor of renal response following immunosuppressive treatment in patients with lupus nephritis. *Int J Rheum Dis*. 2018;21:458-467.
26. Mok CC, Ying KY, Tang S, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum*. 2004;50:2559-2568.
27. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ. Collaborative Study Group Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol*. 2008;3:46-53.
28. Moon SJ, Kwok SK, Ju JH, et al. Predictors of chronic kidney disease in Korean patients with lupus nephritis. *J Rheumatol*. 2011;38:2588-2597.
29. Jakes RW, Bae SC, Louthrenoo W, Mok CC, Navarra SV, Kwon N. Systemic review of the epidemiology of systemic lupus erythematosus in the Asian-Pacific region: prevalence, incidence, clinical features, and morality. *Arthritis Care Res*. 2012;64:159-168.
30. Faurschou M, Dreyer L, Kamper A, Starklint H, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. *Arthritis Care Res*. 2010;62:873-880.

How to cite this article: Suzuki E, Yashiro-Furuya M, Temmoku J, et al. Comparison of renal remission and relapse-free rate in initial- and delayed-onset lupus nephritis. *Int J Rheum Dis*. 2021;24:1500–1509. https://doi.org/10.1111/1756-185X.14228

Received: 21 June 2021 | Revised: 13 October 2021 | Accepted: 14 October 2021

DOI: 10.1111/1756-185X.14230

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Thrombotic risk assessment in patients with systemic lupus erythematosus: Validation of the adjusted-Global Antiphospholipid Syndrome Score (aGAPSS) in Thai patients

Wanitcha Chanloung | **Nuntana Kasitanon** | **Ramjai Wichainun** | **Worawit Louthrenoo**

Faculty of Medicine, Division of Rheumatology, Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand

Correspondence
Nuntana Kasitanon, Faculty of Medicine, Division of Rheumatology, Department of Internal Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
Email: nkasitan@gmail.com

Funding information
This work was supported by the Division of Rheumatology and Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract

Background: The adjusted-Global Antiphospholipid Syndrome Score (aGAPSS) has been validated and used to predict antiphospholipid antibodies (aPL) related to vascular thrombosis (VT).

Objective: To validate aGAPSS for predicted aPL-related VT and pregnancy complications (PC) in Thai systemic lupus erythematosus (SLE) patients.

Methods: A cross-sectional study was performed among Thai SLE patients with clinical manifestations; history of VT and PC, cardiovascular risk factors, and aPL profiles were collected. The aGAPSS was calculated from the sum of the risk factors (hyperlipidemia = 3.0, arterial hypertension = 1.0, anti-cardiolipin antibody = 5.0, anti-b2 glycoprotein I antibody = 4.0, and lupus anticoagulant = 4.0).

Results: Of 132 SLE patients, 12 (9.1%) had VT and 5 (4.1%) had PC. When comparing the aGAPSS (median; interquartile range [IQR]) of patients with events (VT and/or PC) (6.5; IQR 3.3-9.0), VT (8.0; IQR 4.0-9.0), arterial thrombosis (3.5; IQR 1.0-5.8), and PC (9.0; IQR 8.0-11.5), and the aGAPSS of patients without an event (3.0; IQR 0-4.0), aGAPSS of patients with events was significantly higher, except in patients with arterial thrombosis. An aGAPSS of 4.5 or more was associated with risk of aPL-related VT (sensitivity 71.4%, specificity 76.7%), and an aGAPSS of 6.0 or more was associated with risk of aPL-PC (sensitivity 100%, specificity 84.0%).

Conclusion: The aGAPSS could predict the risk of aPL-PC and aPL-related VT in Thai SLE patients.

KEYWORDS

adjusted-Global Antiphospholipid Syndrome Score, antiphospholipid syndrome, systemic lupus erythematosus, thrombosis

1 | INTRODUCTION

Antiphospholipid syndrome (APS) is defined by the occurrence of (often multiple) venous and arterial thromboses and recurrent fetal losses. In the laboratory, it is defined by the presence of antiphospholipid antibodies (aPL).[1] The risk of thrombosis among healthy individuals who are incidentally found to have aPL is likely to be low (1% per year).[2] In previous studies, the prevalence of positive anti-cardiolipin antibodies (aCL) in individuals with systemic lupus erythematosus (SLE) has ranged between 14.3% and 55.4%

[3-6] and the lupus anticoagulant (LA) was found in 17.5%-27.5% of patients.[4-7] Between 20% and 40% of these SLE patients developed APS-related adverse events.[3,8] Along with thrombotic complications in SLE, APS is a major risk factor for irreversible organ damage.[8-10]

Several tools have been used to predict thrombotic events in patients with aPL. Initially, Otomo et al[11] developed the accurate, though expensive, aPL-based antiphospholipid score to diagnose APS and predict vascular thrombosis. More recently, the Global APS score (GAPSS) has been used to predict vascular events in SLE patients by assessing risk factors for thrombosis, pregnancy loss, and conventional cardiovascular disease as well as antiphospholipid (aCL, LA, anti-b2 glycoprotein-I [anti-b2GPI], anti-phosphatidylserine/prothrombin [aPS/PT]) antibodies.[12] An adjusted GAPSS (aGAPSS) that excludes aPS/PT has been shown to accurately stratify patients for predicting aPL-related vascular thrombosis (aPL-VT) and aPL-related pregnancy complications (aPL-PC) in primary APS patients.[13-15]

The current study aimed to validate aGAPSS in predicting aPL-VT and aPL-PC and to find the prevalence of vascular thrombosis and pregnancy complications in Thai SLE patients.

2 | PATIENTS AND METHODS

2.1 | Patients

All 139 SLE patients seen at the Division of Rheumatology, Chiang Mai University, Thailand between January 2018 and December 2019 participated in the study. These patients fulfilled the 1997 American College of Rheumatology Criteria for Classification of SLE,[16] were older than 15 years of age, and had disease onset less than 1 year before entry to the lupus cohort. The study and control groups comprised SLE patients with or without vascular and/or pregnancy complications, respectively. After participants had provided consent, 10 mL blood samples were collected to determine fasting blood sugar, lipid, and aPL profiles (aCL, anti-b2GPI, and LA). Clinical manifestations, cardiovascular risk factors, and medical history were assessed on the same day.

This study was approved by the Thai national research committee the Ethics Committee of the Faculty of Medicine, Chiang Mai University (CMU; no. 051/2018) in accordance with the 1964 Helsinki Declaration and its later amendments.

2.2 | Assessment of cardiovascular risk factors

Enrolled patients underwent a physical examination, blood pressure determination, and blood collection for hyperlipidemia, hypertension, oral contraceptive use, and diabetes. These factors were assessed according to the National Institute for Health and Care Excellence (NICE) Guidelines.[17] Blood pressure was measured using an appropriate size cuff sphygmomanometer. Hypertension was defined as systolic blood pressure values of ≥140 mm Hg and/or diastolic blood pressure values of ≥90 mm Hg on at least two occasions or use of oral antihypertensive medications.[18] Untreated total serum and low-density lipoprotein cholesterol levels were determined and interpreted according to current dyslipidemia cut-off values[19] or also the use of hypolipidemia medications.

2.3 | Autoantibody detection

For this study, each aPL profile (aCL, anti-b2GPI, and LA) test result was dichotomized as positive/ negative. The aCL (IgM/IgG) and anti-b2GPI (IgM/IgG) were detected by enzyme-linked immunosorbent assay (EUROIMMUN®). Solid-phase assay cut-off values were based on the manufacturer's procedures.[20] Cut-off values of 12 GPL/mL (anti-cardiolipin IgG) and 12 MPL/mL (anti-cardiolipin IgM) were used for aCL and IgG/IgM, respectively, and 20 U/mL was used for b2GPI. LA was detected according to the International Society on Thrombosis and Hemostasis subcommittee on LA/aPL standardization.[20]

2.4 | Adjusted-Global Antiphospholipid Syndrome Score calculation

The aGAPSS was calculated as the sum of points for the corresponding risk factors ranging from 0 to 17: (ie 3 points for hyperlipidemia, 1 for arterial hypertension, 5 for aCL, 4 for anti-b2GPI, and 4 for LA).[21]

2.5 | Outcome measures

Arterial thrombotic complications comprised stroke, myocardial infarction, and artery occlusion, as confirmed by clinical features, laboratory findings (electrocardiogram or cardiac enzymes), or imaging studies (computed tomography scanning, magnetic resonance imaging, or conventional angiography). Deep vein thrombosis and pulmonary thrombosis were defined as venous thrombosis and were confirmed by CT scanning, angiography, or scintigraphy. Pregnancy complications were defined according to the revised Sapporo criteria for APS.[11,22]

2.6 | Statistical analysis

Categorical data were assessed using the chi-squared test and Fisher's exact test. Continuous data were presented as means (standard deviation [SD]) and compared using Student's *t* test or non-parametric Mann-Whitney *U* test depending on the distribution. A two-sided *P*-value less than 0.05 was considered statistically significant. Multivariate analysis was used to examine the relationship between multiple cardiovascular risk factors and laboratory parameters on the occurrence of vascular thrombosis or pregnancy complications. Results were expressed as odds ratios (ORs) with 95% confidence interval (95% CI). Sensitivity and specificity of aGAPSS was calculated

using the receiver operating characteristic (ROC) curve. All statistical analyses were performed using SPSS statistical software version 25.0.

3 | RESULTS

3.1 | Demographics and characteristics

One hundred and thirty-two (121 females) of the 139 patients from the CMU lupus cohort were included in the study (mean age 39.7 ± 13.3 years); seven patients were excluded because of incomplete aPL profiles. Baseline characteristics are summarized in Table 1. Clinical and laboratory parameters (complete blood count, renal and liver functions), as well as the type of treatment were evenly distributed across groups. Although the prevalence of aCL IgM was similar in both groups, aCL IgG and LA levels were significantly higher in patients with vascular thrombosis and/ or pregnancy complications. In addition, anti-b2GPI IgG- or IgM-positive tests occurred exclusively in patients without vascular thrombosis/ pregnancy complications.

3.2 | Prevalence of antiphospholipid antibody, vascular thrombosis, and/or pregnancy complications

Of 132 patients, 42 (31.8%) patients had at least one positive aPL (aCL IgM/IgG, LA, anti-b2GPI IgM/IgG). Positive aCL, LA, and anti-b2GPI were detected in 16 (12.1%), 28 (21.2%), and 18 (13.6%) patients, respectively. Sixteen of the 132 patients (12.1%) had a history of at least one vascular thrombosis and/ or pregnancy complication—12 patients (9.1%) had vascular thrombosis and five patients (4.1%) had pregnancy complications (one miscarriage, four fetal deaths). One of five patients with pregnancy complications had venous thrombosis. Table 1 summarizes aPL in patients with vascular thrombosis and/or pregnancy complications.

3.3 | Risk factors associated with vascular thrombosis and/or pregnancy complications

Proportions of conventional cardiovascular risk factors and aPL in patients with vascular thrombotic and/ or pregnancy complications are summarized in Table 2. When aPL-related complications were compared, 10 of 42 (23.8%) aPL-positive patients had a history of at least one vascular thrombosis and/or pregnancy complication whereas six of 90 patients (6.7%) without aPL had a history of at least one vascular thrombosis (Table 2). The prevalence risk ratio of aPL-related complications in patients with aPL was 3.6 (95% CI 1.4-9.2) when compared with patients without aPL. Approximately one of six aPL-positive patients developed vascular and/ or pregnancy complications (ie the number needed to harm = 5.8).

Multivariate modeling results are summarized in Tables 3 and 4. Among the laboratory parameters, LA and aCL were significantly associated with an increased risk of vascular thrombosis and/ or pregnancy complications (OR 9.1; 95% CI 2.9-28.1 and OR 4.3; 95% CI 1.3-14.8, respectively).

In a subgroup analysis, only LA was associated with an increased risk of vascular thrombosis (OR 5.4; 95% CI 1.6-18.8). For pregnancy complications, both LA and aCL increased the risk of events (OR 22.5; 95% CI 2.4-214.5 and OR 16.17; 95% CI 2.38-109.73, respectively). No statistically significant differences were observed when comparing individual conventional cardiovascular risk factors (contraceptive drug use, diabetes, arterial hypertension, dyslipidemia, and obesity).

3.4 | Adjusted-GAPSS in vascular thrombosis and/ or pregnancy complications

Patients with vascular thrombosis and/ or pregnancy complications had significantly higher aGAPSS scores when compared with the control group (median 6.5; IQR 3.3-9.0 vs median 3.0; IQR 0-4.0, $P = 0.002$) (Figure 1). Similarly, in a subgroup analysis, significantly higher median aGAPSS values were observed in patients with venous thrombosis (8.0; IQR 4.0-9.0 vs 3.0; IQR 0-4.0, $P = 0.010$) and those with pregnancy complications (9.0; IQR 8.0-11.5 vs. 3.0; IQR 0-4.0, $P = 0.001$) than controls. However, no statistically significant difference in median aGAPSS values was found by arterial thrombosis status (3.5; IQR 1.0-5.8 vs 3.0; IQR 0-4.0, $P = 0.472$).

The ROC curve indicated that a cut-off value of aGAPSS of 3.5 or more had the best diagnostic accuracy for the detection of aPL-VT and/ or aPL-PC (OR 3.3; 95% CI 1.0-10.9) compared with an aGAPSS less than 3.5 (Figure 2).

In a subgroup analysis, the cut-off value of aGAPSS of 3.5 or more had the best diagnostic accuracy for the detection of aPL-VT (OR 2.2; 95% CI 0.6-7.7). The sensitivity for the detection of aPL-VT was 66.7% and specificity was 52.6%. If we used an aGAPSS cut-off of 5.0 or more, as recommended in a previous study for aPL-VT,[13] the sensitivity decreased to 50.0%, with a specificity of 76.7%. However, the cut-off value of an aGAPSS of 4.5 or more was strongly associated with a higher risk of venous thrombosis with the OR of the best risk accuracy of 8.2 (95 CI 1.5-44.9), with a sensitivity and specificity of 71.4% and 76.7%, respectively. Among aPL-PC, the cut-off value of aGAPSS of 6.0 or more was strongly associated with a higher risk of pregnancy complications with sensitivity and specificity of 100% and 84.0%, respectively.

4 | DISCUSSION

In this study, the prevalence of aPL in Thai SLE patients was 32.8%, which is comparable to that found in previous studies.[3-5,8,9,12,23,24] In Europe, the prevalence of aCL, LA, and anti-b2GPI in SLE patients ranged from 21.0% to 55.4%, 18.0% to 27.5%, and 20.0% to 22.7%, respectively,[4,5,25] whereas this study found the prevalence of aCL, LA, and anti-b2GPI to be 12.1%, 21.2%, and 13.6%, respectively.

TABLE 1 Baseline characteristics between SLE patients with and without vascular thrombotic and/ or pregnancy complications

Characteristics	Vascular thrombosis/ pregnancy complications N = 16 (%)	No vascular thrombosis/ pregnancy complications N = 116 (%)	*P* value
Age (y)	38.9 ± 12.6	39.8 ± 13.4	0.805
Sex: female	15.0 (93.8)	106.0 (91.4)	0.748
Prevalence of pregnancy	9 (59.3)	55 (47.4)	0.598
BMI (kg/m^2)	23.9 ± 4.6	23.1 ± 3.8	0.455
BMI in obesity[b] (kg/m^2)	29.1 ± 3.6	27.9 ± 2.3	0.322
Mean ± SD (range) disease duration (mo)	101.9 ± 40.2	94.0 ± 54.0	0.560
Modified SLEDAI score[a]	1.1 ± 1.8	1.8 ± 2.6	0.158
Clinical manifestation at diagnosis			
Malar rash	7 (43.8)	48 (41.4)	0.857
Discoid rash	6 (35.7)	38 (32.8)	0.706
Photosensitivity	3 (18.8)	16 (13.8)	0.596
Oral ulcer	5 (31.3)	33 (28.4)	0.817
Arthritis	6 (37.5)	58 (50.0)	0.348
Serositis			
Pleuritis	3 (18.8)	21 (18.1)	0.950
Pericarditis	1 (6.3)	8 (6.9)	0.923
Renal disorder			
Urine +3 proteinuria or >500 mg/d	10 (62.5)	76 (65.5)	0.812
Cellular cast	0	1 (0.9)	0.709
Neurologic disorder			
Seizure	1 (6.3)	12 (10.3)	0.606
Psychosis	1 (6.3)	4 (3.4)	0.582
Hematologic disorder			
Hemolytic anemia	5 (31.3)	40 (34.5)	0.789
Leukopenia (white blood cells <4000/ mm^3)	9 (56.3)	61 (52.6)	0.783
Lymphopenia (lymphocytes <1500/ mm^3)	0	13 (11.2)	0.158
Thrombocytopenia (platelets <100 000/mm^3)	0	15 (12.9)	0.127
Immunologic disorder			
Anti-dsDNA antibody	13 (81.3)	87 (75.0)	0.584
Anti-Sm antibody	1 (6.3)	10 (8.6)	0.748
Anticardiolipin IgM	1 (6.3)	2 (1.7)	0.225
Anticardiolipin IgG	4 (25.0)	9 (7.8)	0.030
Lupus anticoagulant	9 (56.3)	17 (14.7)	0.001
Anti-b2 glycoprotein I antibody IgM	0	17 (14.7)	0.101
Anti-b2 glycoprotein I antibody IgG	0	3 (2.6)	0.515
Anti-b2 glycoprotein I antibody IgG and IgM	0	2 (1.7)	1.000
Anticardiolipin and lupus anticoagulant	4 (25.0)	5 (4.3)	0.013
Anticardiolipin and anti-b2 glycoprotein I antibodies	0 (0)	5 (4.3)	1.00
Lupus anticoagulant and Anti-b2 glycoprotein I antibody	0 (0)	6 (5.2)	1.00
Triple positive aPL	0 (0)	3 (2.6)	1.00

(Continues)

TABLE 1 (Continued)

Characteristics	Vascular thrombosis/ pregnancy complications N = 16 (%)	No vascular thrombosis/ pregnancy complications N = 116 (%)	*P* value
Positive ANA	16 (100.0)	115 (99.1)	0.709
Prevalence of pregnancy	9 (59.3)	55 (47.4)	0.598
Pregnancy complication	5 (31.3)[c]	0 (0)	<0.001
Vascular thrombosis	12 (75.0)	0 (0)	<0.001
Arterial thrombosis	6[d]		
Venous thrombosis	7[e]		
Both arterial and venous thrombosis	1[f]		
Risk factors			
Oral contraceptive drug /DMPA used	2 (12.5%)	11 (9.5%)	0.704
Diabetes	1 (6.3%)	4 (3.4%)	0.582
Hypertension	11 (68.8%)	51 (44.0%)	0.063
Dyslipidemia	7 (43.8%)	47 (40.5%)	0.805
Drug			
Hydroxychloroquine	5 (31.3%)	41 (35.3%)	0.747
Corticosteroid	15 (93.8%)	105 (90.5%)	0.673
Immunosuppressive drugs	8 (50.0%)	66 (56.9%)	0.602
Antihypertensive drugs	10 (62.5%)	48 (41.4%)	0.111
Dyslipidemia drugs (statin)	4 (25.0%)	28 (24.1%)	0.940

Abbreviations: aCL, anti-cardiolipin antibody; ANA, antinuclear antibodies; anti-b2GPI, anti-b2 glycoprotein; aPL, antiphospholipid antibodies; BMI, body mass index; CI, confidence interval; DMPA, depot medroxyprogesterone acetate; LA, lupus anti-coagulant; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

[a]At study entry.

[b]Obesity = BMI >25 kg/m^2.

[c]LA positive in two patients, LA and aCL positive in two patients and aCL positive in one patient.

[d]LA positive in two patients and aPL negative in other four patients.

[e]LA positive in two patients, aCL positive in one patient, LA and aCL positive in two patients.

[f]LA positive.

TABLE 2 Proportions of risk factors in patients with and without vascular thrombotic and/ or pregnancy complications

		With complications				
	No events (N = 116)	Any events (N = 16)	Any vascular thrombosis (N = 12)[a]	Arterial thrombosis (N = 6)	Venous thrombosis (N = 7)	Pregnancy complications (N = 5)**
Female	106 (91.4%)	15 (93.8%)	11 (91.7%)	6 (100%)	6 (85.7%)	5 (100%)
Age ± SD (y)	39.8 ± 13.4	38.9 ± 12.6	36.8 ± 12.7	34.7 ± 11.4	36.6 ± 14.6	42.8 ± 11.6
Hypertension	51 (44.0%)	11 (68.8%)	7 (58.3%)	3 (50.0%)	4 (57.1%)	5 (100%)
Dyslipidemia	47 (40.5%)	7 (43.8%)	4 (33.3%)	2 (33.3%)	2 (28.6%)	4 (80.0%)
Diabetes	4 (3.4%)	1 (6.3%)	0	0	0	1 (20.0%)
LA	18 (15.5%)	10 (62.5%)	6 (50.0%)	2 (33.3%)	5 (71.4%)	4 (80.0%)
aCL IgM/IgG	11 (9.5%)	5 (31.3%)	3 (25.0%)	0	3 (42.9%)	3 (60.0%)
Anti-b2GPI IgM/IgG	18 (15.5%)	0	0	0	0	0

Abbreviations: aCL, anti-cardiolipin antibody; anti-b2GPI, anti-b2. glycoprotein I, IgM/IgG IgM and/ or IgG; LA, lupus anti-coagulant; SD, standard deviation.

[a]One had both arterial and venous thrombosis.

**One had both venous thrombosis and pregnancy complication.

TABLE 3 Associated risk factors in all patients with vascular thrombosis or pregnancy complications

Variable	Odds ratio	95% CI	*P* value[a]
Conventional risk factor			
Contraceptive drug	1.4	0.3-6.8	0.705
Diabetic	1.9	0.2-17.8	0.588
Hypertension	2.8	0.9-8.6	0.071
Dyslipidemia	0.9	0.3-2.5	0.805
Obesity	1.1	0.3-3.3	0.930
LA	9.1	2.9-28.1	<0.001
aCL IgM/IgG	4.3	1.3-14.8	0.019
Anti-b2GPI IgM/IgG	–	–	0.998

Abbreviations: aCL, anti-cardiolipin antibody; anti-b2GPI, anti-b2 glycoprotein; CI, confidence interval; LA, lupus anti-coagulant.
[a]From multivariate logistic regression analysis.

common in Caucasians than in African Americans.[31] However, in the same ethnicity and same country, there was relatively high variability of prevalence of anti-b2GPI positivity within the same ethnicity and country. For example, in two UK studies, the prevalence of anti-b2GPI antibodies in SLE patients ranged from 5%[24] to 20.8%.[4] Another source of variability for anti-b2GPI detection can occur with enzyme-linked immunosorbent immunoassay.[32] Lastly, as our study was cross-sectional, the timing of blood draws occurred more than 3 months after a thrombotic event. One study showed that only 25% of SLE patients were persistently positive for anti-b2GPI antibodies across blood draw 3 months apart.[31] Also, in our study, no patient with aPL complications had triple aPL positivity despite it being a risk factor.[33]

Our results indicate that the best cut-off values of aGAPSS as an independent prognosticator for vascular thrombosis and/ or pregnancy complication, venous thrombosis, and pregnancy complications

TABLE 4 Associated risk factors in subgroup analysis

	Vascular thrombosis				Pregnancy complication			
	Yes (N = 12)[b]	No (N = 116)	*P* value	OR[a] (95% CI)	Yes (N = 5)	No (N = 106)	*P* value	OR[a] (95% CI)
LA	6 (50.0%)	18 (15.5%)	0.007	5.4 (1.6-18.8)	4 (80.0%)	16 (15.1%)	0.007	22.5 (2.4-214.5)
aCL IgM/IgG	3 (25.0%)	11 (9.5%)	0.117	3.2 (0.7-13.5)	3 (60.0%)	9 (8.5%)	0.004	16.2 (2.4-109.7)
Anti-b2GPI IgM/IgG	0	18 (15.5%)	–	–	0	15 (14.2%)	–	–

Abbreviations: aCL, anti-cardiolipin antibody; anti-b2GPI, anti-b2 glycoprotein I; CI, confidence interval; LA, lupus anti-coagulant; OR, odds ratio.
[a]From multivariate logistic regression analysis.
[b]One had both arterial and venous thrombosis.

The prevalence of vascular thrombosis and/ or pregnancy complications in Thai SLE patients with positive aPL in this study was 23.8%, which is comparable to those previous reports (20.0%-40.0%).[3,8,9,23] Consistent with previous studies indicating that aPL increases the risk of vascular thrombosis and pregnancy complications,[26-28] this study provides evidence that SLE patients with aPL also have an increased risk of aPL-related complications. The prevalence risk ratio of aPL-related complications in patients with aPL was 3.6 when compared with controls.

We also found that LA and aCL were independent risk factors in both vascular thrombosis and pregnancy complications, with LA being the most highly associated risk factor.

The prevalence of anti-b2GPI antibody IgM/IgG in SLE patients in this study (13.6%) was lower than the prevalence found in previous studies (20.0%-22.7%).[4,5,25] In addition, none of the SLE patients with aPL-related complications were positive for anti-b2GPI IgM/ IgG. This finding contradicted other studies that indicate strong associations between anti-b2GPI and vascular thrombosis.[29,30] This difference may be due to the small number of SLE patients in our study, which may not represent the entire Thai population. In addition, ethnicity may affect the prevalence of anti-b2GPI antibody. For example, in a US study that stratified SLE patients by race, being positive for anti-b2GPI antibodies was more

are 3.5 or more, 4.5 or more, and 6.0 or more, respectively. These values differ from the previously validated aGAPSS where a cut-off of 5.0 or more was associated with vascular thrombosis (arterial and venous thrombosis)[13] and 6.7 or more was found in patients with pregnancy complications.[34] However, the low prevalence of anti-b2GPI antibody in this study can explain these differences.

In this study, high sensitivity and specificity were found for aGAPSS cut-offs of 4.5 or more for venous thrombosis and 6 or more for pregnancy complications, which were consistent with previous studies. However, because of the small numbers of positive aPL patients with arterial thrombosis, this study cannot evaluate aGAPSS cut-off values for arterial thrombosis.

At present, aGAPSS is being applied, evaluated, and validated in primary APS patients with various specific thrombotic events such as cardiovascular disease,[35] acute myocardial infarction in young APS patients (up to 50 years),[15] and in recurrent thrombosis. This study extended the evaluation of aGAPSS to predict vascular thrombosis and/ or pregnancy complications in Thai SLE patients. The results indicate that SLE patients with venous thrombosis and pregnancy complications had significantly higher aGAPSS values.

Sciascia et al,[4] found significant risk associations between hyperlipidemia, hypertension, and thrombotic phenotypes in primary APS

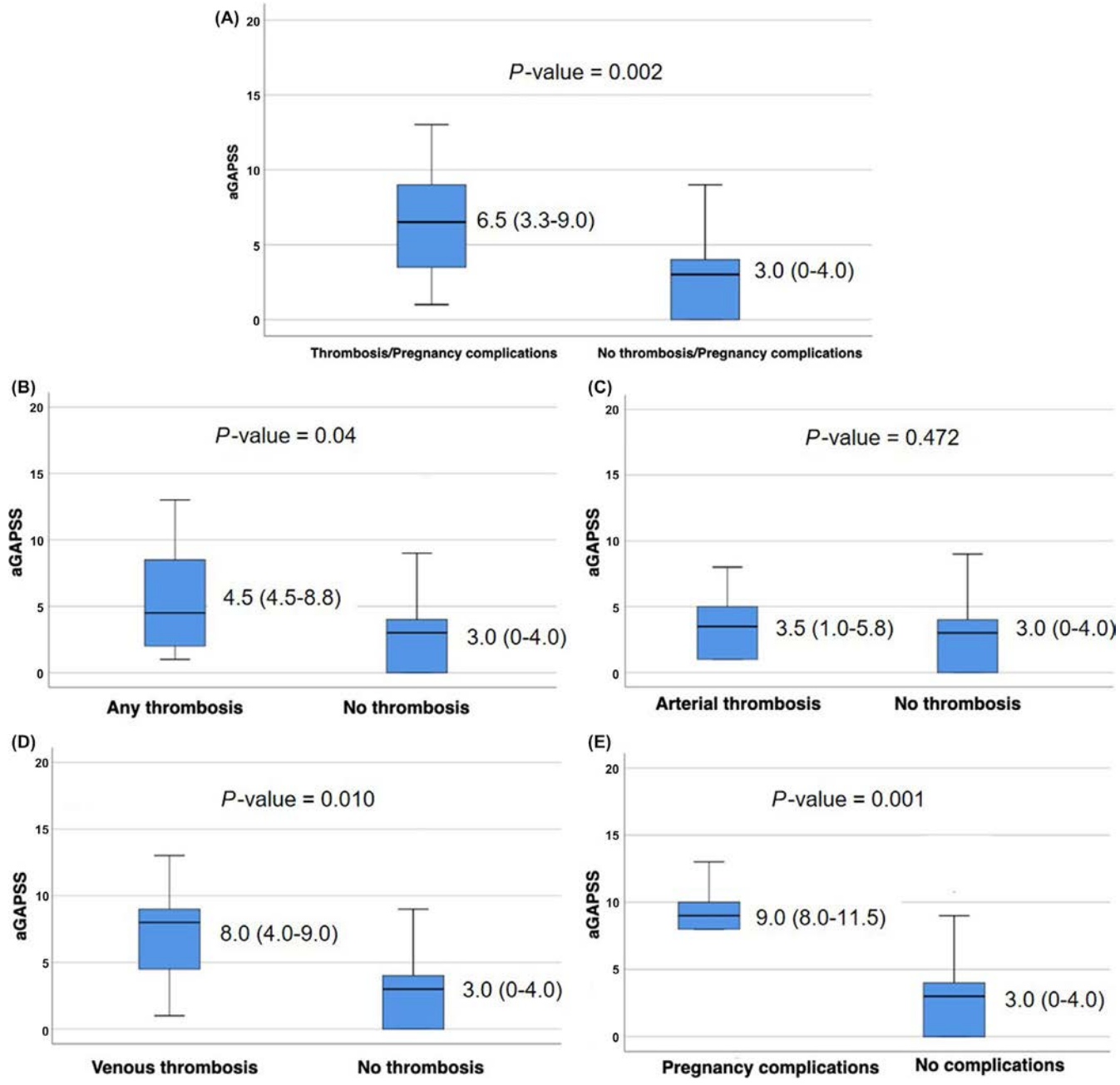


FIGURE 1 Distribution of aGAPSS shown as box plots, where each box represents the 25th-75th centile: lines inside the box represent the median, and the whiskers represent the 95% CI, between patients with and without vascular thrombosis or pregnancy complication (A), patients with and without vascular thrombosis (B), patients with and without arterial thrombosis (C), patients with and without venous thrombosis (D), and patients with and without pregnancy complication (E)

patients. However, classical thrombotic risk factors such as hyperlipidemia, arterial hypertension, obesity, diabetes, and smoking habits did not increase the risk of thrombotic events in SLE patients. These results support a previous study in SLE patients where traditional thrombotic risk factors alone could not explain the excess risk of premature cardiovascular disease among SLE patients.[36]

Our study had several limitations. First, with a cross-sectional design and follow-up duration of 2 years, the risk of vascular thrombosis and/ or pregnancy complications in patients who recently entered the cohort was not assessed. However, the mean observation period for patients included in the analyses was 95.0 (SD 52.5) months. A study strength was that all SLE patients were diagnosed and treated by the same group of physicians from the inception of disease less than 1 year before participating in the cohort. Therefore, complete medical information for vascular thrombosis and pregnancy complication events was available for review.

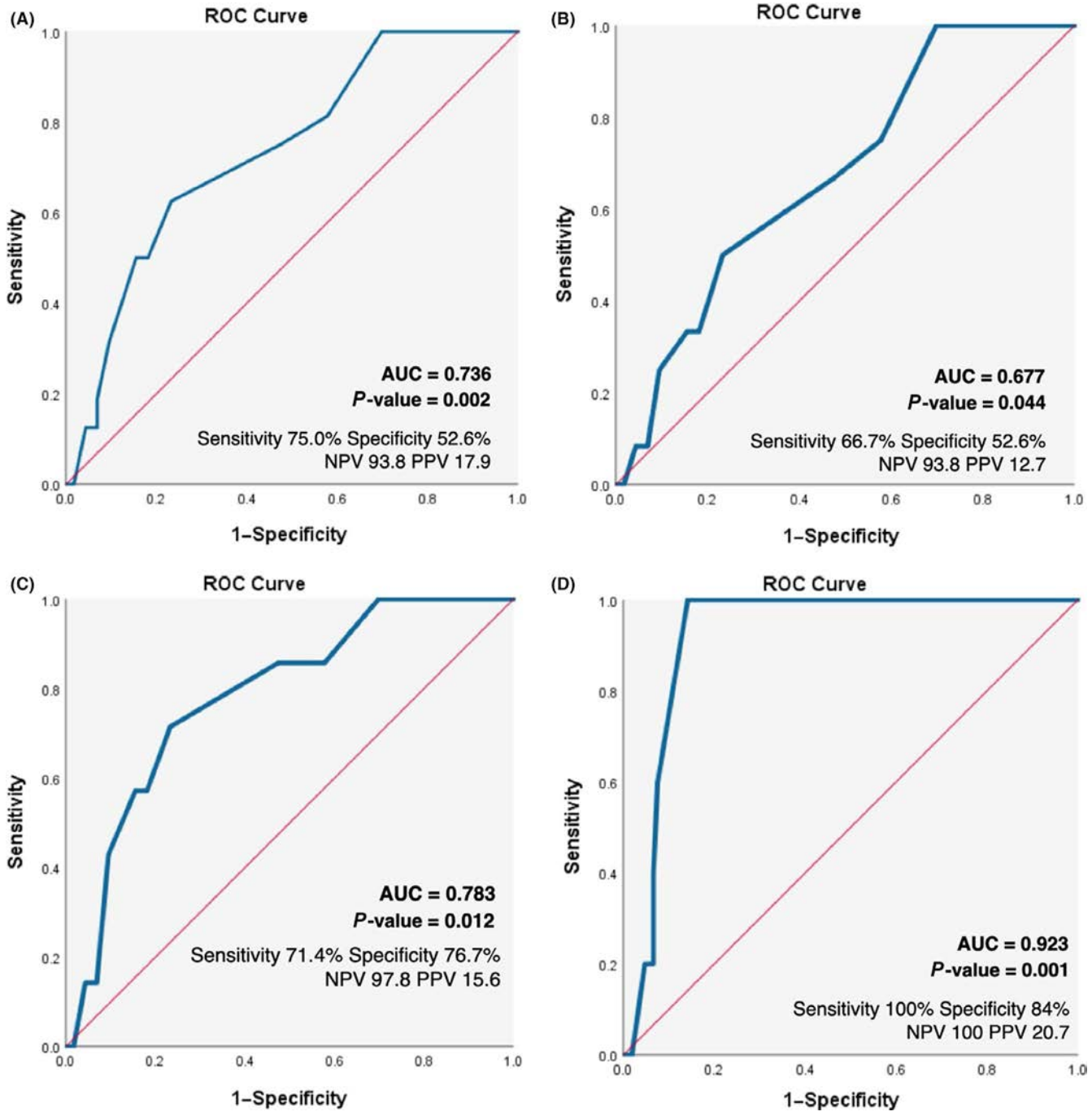


FIGURE 2 The receiver operating characteristic (ROC) curve of aGAPSS, aGAPSS ≥3.5 associated with a higher risk of anti-phospholipid (aPL) -related vascular thrombosis or pregnancy complication (PC) (A), aGAPSS ≥3.5 associated with a higher risk of aPL-related vascular thrombosis (B), aGAPSS ≥4.5 associated with a higher risk of aPL-related venous thrombosis (C), and aGAPSS ≥6.0 associated with aPL-related PC (D). AUC area under the curve, NPV negative predictive value, PPV positive predictive value

5 | CONCLUSION

This study found that SLE patients with vascular thrombosis and/ or pregnancy complications had significantly higher aGAPSS than those without. It demonstrated that aGAPSS could predict the risk of aPL-related conditions, in Thai patients with SLE. This study confirms the validation of aGAPSS score in Thai SLE patients. However, more studies with a larger sample size and longer follow up are needed to confirm these findings.

ACKNOWLEDGEMENTS

The authors thank Dr. Antika Wongthanee for statistical assistance and Dr. Elizabeth Matovinovic for manuscript editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University.

ORCID

Nuntana Kasitanon https://orcid.org/0000-0002-1150-6424
Worawit Louthrenoo https://orcid.org/0000-0003-3105-6122

REFERENCES

1. Gomez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. *J Autoimmun*. 2014;48–49:20-25.
2. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA*. 2006;295:1050-1057.
3. Wanachiwanawin W, Piankijagum A. A preliminary study on the frequencies and clinical significance of positive anti-cardiolipin antibody in patients with systemic lupus erythematous and autoimmune cytopenias. *Thai J Hemato Transfusion Med*. 1992;165-171.
4. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the global anti-phospholipid syndrome score. *Rheumatology*. 2013;52:1397-1403.
5. Marchetti T, Ribi C, Perneger T, et al. Prevalence, persistence and clinical correlations of classic and novel antiphospholipid antibodies in systemic lupus erythematosus. *Rheumatology*. 2018;57:1350-1357.
6. Parkpian V, Verasertniyom O, Vanichapuntu M, et al. Specificity and sensitivity of anti-beta2-glycoprotein I as compared with anticardiolipin antibody and lupus anticoagulant in Thai systemic lupus erythematosus patients with clinical features of antiphospholipid syndrome. *Clin Rheumatol*. 2007;26:1663-1670.
7. Intragumtornchai T, Akkawat B, Mahasandana S, Watananukul P, Deesomchok U. Lupus anticoagulant in Thai systemic lupus erythematosus patients. *Southeast Asian J Trop Med Public Health*. 1993;24(Suppl 1):241-245.
8. Oku K, Amengual O, Yasuda S, Atsumi T. How to identify high-risk APS patients: clinical utility and predictive values of validated scores. *Curr Rheumatol Rep*. 2017;19:51.
9. Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. *Arch Intern Med*. 2004;164:77-82.
10. Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. *Arthritis Rheum*. 2005;52:2774-2782.
11. Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum*. 2012;64:504-512.
12. Sciascia S, Cuadrado MJ, Sanna G, et al. Thrombotic risk assessment in systemic lupus erythematosus: validation of the global antiphospholipid syndrome score in a prospective cohort. *Arthritis Care Res*. 2014;66:1915-1920.
13. Fernandez Mosteirin N, Saez Comet L, Salvador Osuna C, Calvo Villas JM, Velilla MJ. Independent validation of the adjusted GAPSS: role of thrombotic risk assessment in the real-life setting. *Lupus*. 2017;26:1328-1332.
14. Zuo Y, Li C, Karp DR, Li ZG. Clinical and epidemiological correlates of the adjusted global anti-phospholipid syndrome score in a large cohort of Chinese APS patients. *Arthritis Rheumatol*. 2015;67(suppl 10).https://acrabstracts.org/abstract/clinical-and-epidemiological-correlates-of-the-adjusted-global-anti-phospholipid-syndrome-score-in-a-large-cohort-of-chinese-aps-patients/. Accessed October 27, 2021.
15. Radin M, Schreiber K, Costanzo P, et al. The adjusted global antiphospholipid syndrome score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction. *Int J Cardiol*. 2017;240:72-77.
16. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.
17. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation*. 2008;117:743-753.
18. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of cardiology (ESC) and the European society of hypertension (ESH). *Eur Heart J*. 2018;39:3021-3104.
19. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European society of cardiology (ESC) and European atherosclerosis society (EAS). *Eur Heart J*. 2019;41:111-188.
20. Devreese KM, Pierangeli SS, de Laat B, et al. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:792-795.
21. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. The global anti-phospholipid syndrome score in primary APS. *Rheumatology*. 2015;54:134-138.
22. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306.
23. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum*. 2009;61:29-36.
24. Pericleous C, D'Souza A, McDonnell T, et al. Antiphospholipid antibody levels in early systemic lupus erythematosus: are they associated with subsequent mortality and vascular events? *Rheumatology*. 2020;59:146-152.
25. Sebastiani GD, Galeazzi M, Tincani A, et al. Anticardiolipin and anti-beta2GPI antibodies in a large series of European patients with systemic lupus erythematosus. Prevalence and clinical associations. European concerted action on the immunogenetics of SLE. *Scand J Rheumatol*. 1999;28:344-351.
26. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res*. 2013;65:1869-1873.
27. Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol*. 2009;8:998-1005.
28. Martinez-Zamora MA, Peralta S, Creus M, et al. Risk of thromboembolic events after recurrent spontaneous abortion in antiphospholipid syndrome: a case-control study. *Ann Rheum Dis*. 2012;71:61-66.
29. Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The antiphospholipid syndrome in patients with systemic lupus erythematosus. *J Autoimmun*. 2017;76:10-20.
30. Schreiber K, Sciascia S, de Groot PG, et al. Antiphospholipid syndrome. *Nat Rev Dis Primers*. 2018;4:18005.

31. Danowski A, Kickler TS, Petri M. Anti-beta2-glycoprotein I: prevalence, clinical correlations, and importance of persistent positivity in patients with antiphospholipid syndrome and systemic lupus erythematosus. *J Rheumatol*. 2006;33:1775-1779.
32. Reber G, Boehlen F, de Moerloose P. Technical aspects in laboratory testing for antiphospholipid antibodies: is standardization an impossible dream? *Semin Thromb Hemost*. 2008;34:340-346.
33. Khamashta M, Taraborelli M, Sciascia S, Tincani A. Antiphospholipid syndrome. *Best Pract Res Clin Rheumatol*. 2016;30:133-148.
34. Sciascia S, Radin M, Sanna G, Cecchi I, Roccatello D, Bertolaccini ML. Clinical utility of the global anti-phospholipid syndrome score for risk stratification: a pooled analysis. *Rheumatology*. 2018;57:661-665.
35. Di Minno MND, Scalera A, Tufano A, et al. The association of adjusted global antiphospholipid syndrome Score (aGAPSS) with cardiovascular disease in subjects with antiphospholipid antibodies. *Atherosclerosis*. 2018;278:60-65.
36. Sinicato NA, da Silva Cardoso PA, Appenzeller S. Risk factors in cardiovascular disease in systemic lupus erythematosus. *Curr Cardiol Rev*. 2013;9:15-19.

How to cite this article: Chanloung W, Kasitanon N, Wichainun R, Louthrenoo W. Thrombotic risk assessment in patients with systemic lupus erythematosus: Validation of the adjusted-Global Antiphospholipid Syndrome Score (aGAPSS) in Thai patients. *Int J Rheum Dis*. 2021;24:1510–1519. https://doi.org/10.1111/1756-185X.14230

Received: 2 July 2021 | Revised: 28 September 2021 | Accepted: 17 October 2021

DOI: 10.1111/1756-185X.14231

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Pain catastrophizing hinders Disease Activity Score 28 – erythrocyte sedimentation rate remission of rheumatoid arthritis in patients with normal C-reactive protein levels

Tamami Yoshida[1] | Motomu Hashimoto[2] | Go Horiguchi[3] | Kosaku Murakami[4,5] | Koichi Murata[6,7] | Kohei Nishitani[6,7] | Ryu Watanabe[2] | Wataru Yamamoto[8] | Masao Tanaka[6] | Akio Morinobu[4] | Hiromu Ito[6,7] | Shuichi Matsuda[7] | Ritei Uehara[1]

[1]Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

[2]Department of Clinical Immunology, Graduate School of Medicine, Osaka City University, Osaka, Japan

[3]The Clinical and Translational Research Center, Kyoto Prefectural University of Medicine, Kyoto, Japan

[4]Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[5]The Center for Cancer Immunotherapy and Immunobiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[6]Department of Advanced Medicine for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[7]Department of Orthopedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[8]Department of Health Information Management, Kurashiki Sweet Hospital, Kurashiki, Japan

Correspondence
Tamami Yoshida, Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan.
Email: imamat01@koto.kpu-m.ac.jp

Funding information
This work was supported by JSPS KAKENHI (grant numbers 18H06346 and 19K21429). The Department of Advanced Medicine for Rheumatic Diseases is supported by Nagahama City, Shiga, Japan; Toyooka City, Hyogo, Japan; and 5 pharmaceutical companies (Mitsubishi Tanabe Pharma Corp., Chugai Pharmaceutical Co. Ltd., UCB Japan Co. Ltd., Asahi Kasei Pharma Corp., and AYUMI Pharmaceutical Co.). This study was also supported by a grant from Daiichi Sankyo Co., Ltd. The above-mentioned pharmaceutical companies were not involved in the study design, data collection and analysis, manuscript writing, and manuscript submission.

Abstract

Aim: This study aimed to assess the relationship between pain catastrophizing and achievement of 28-joint Disease Activity Score-defined remission of rheumatoid arthritis (RA), considering the presence or absence of systemic inflammation, and to evaluate associated factors for pain catastrophizing.

Method: This cross-sectional study included 421 RA outpatients. The relationship between pain catastrophizing and remission was analyzed by adjusting several confounding factors. Univariable and multivariable analyses were performed to determine the relationship between pain catastrophizing and RA-related factors, comorbidities, and lifestyle habits.

Results: The prevalence of pain catastrophizing was 26%. Pain catastrophizing was negatively associated with remission (odds ratio 0.62, 95% confidence interval 0.38-1.00, $P = .048$). A multinomial logistic analysis showed that the presence of pain catastrophizing was an independent factor that was negatively correlated with the achievement of remission in the absence of systemic inflammation (odds ratio 0.51, 95% confidence interval 0.28-0.93, $P = .029$). Factors associated with elevated ratings on the Pain Catastrophizing Scale were a history of falls within the past year, a Health Assessment Questionnaire score >0.5, and smoking habit. Further, patients' subjective symptoms, including patient global assessment minus evaluator global assessment values ≥20 and high tender joint count minus swollen joint counts, were associated with elevated pain catastrophizing.

Conclusion: Pain catastrophizing is a major obstacle to achieving remission in RA patients with normal C-reactive protein levels. Advanced physical disability, smoking habit, and history of falls were associated with pain catastrophizing, in addition to patients' subjective symptoms.

KEYWORDS
clinical remission, nociplastic pain, pain catastrophizing, rheumatoid arthritis, systemic inflammation

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition, characterized by pain and joint deformity, leading to a reduced quality of life.[1,2] The primary goal of RA treatment is to prevent the inflammatory process. The standard treatment for achieving remission is pharmacological therapy utilizing the treat-to-target strategy under the tight control of disease activity.[3] However, remission is difficult to achieve in the presence of poor prognostic factors, such as a positive anti-citrullinated peptide antibody (ACPA) result and/or intractable pathology.[3,4] In addition, difficulty in evaluating the patient global assessment (PGA), which is included as part of the remission criteria, may result in an overestimation of disease activity and further hinder achieving remission. PGA is affected by RA-related factors, such as joint structural damage, non-RA factors (ie, demographic and social characteristics), and disease activity.[5] In particular, pain is a main determinant in PGA, accounting for 75.6% of the score.[6] Non-inflammatory factors, such as nociplastic pain,[7,8] which is thought to be caused by central sensitization, and patient quality of life, should not be evaluated in PGA, which is meant to assess disease activity with inflammation.

Pain can traumatize patients; it can induce an abnormal psychological state of morbid anxiety or fear and a type of maladaptive cognitive response to pain called pain catastrophizing.[9,10] Pain catastrophizing causes nociplastic pain and contributes to the distortion in pain perception in patients with RA.[11] A previous report found pain catastrophizing in 22% of RA patients using biological disease-modifying antirheumatic drugs (bDMARDs), and a positive correlation was observed between pain catastrophizing and the visual analog scale (VAS) score for pain.[12] Moreover, several reports suggest that pain catastrophizing adversely affects clinical remission.[11,13]

However, the relationship between pain catastrophizing and non-remission, categorized by the presence or absence of systemic inflammation, has not yet been elucidated. Inflammatory pain also instinctively causes anxiety and fear. Anti-inflammatory pharmacotherapy, and not psychotherapy, is the first priority for patients who face inflammatory pain; consequently, it is important to first determine if patients are experiencing acute inflammation, and then, for patients without inflammation, to consider the availability of a psychological or cognitive approach. The prevalence of refractory pain due to nociplastic causes merits further investigation.

This study aimed to evaluate the relationship between pain catastrophizing, the state of systemic inflammation, and achievement of remission, and to clarify the characteristics of patients with pain catastrophizing. We hypothesized the following: (1) even with controlled inflammatory activity, the presence of pain catastrophizing will result in a high PGA score, leading to an overestimation of disease activity; and (2) in patients suffering from pain catastrophizing, there is a discrepancy between the patients' and physicians' evaluations. To test these hypotheses, we evaluated the presence of pain catastrophizing in patients without systemic inflammation who were not in remission, as well as the variables related to the discrepancy between the patient's subjective outcomes and objective indices of RA, comorbidities, and lifestyle habits. The association of these variables with pain catastrophizing was analyzed to clarify the clinical findings for the patients with pain catastrophizing.

2 | MATERIALS AND METHODS

2.1 | Procedure and participants

We conducted a cross-sectional study of RA patients who participated in the Kyoto University Rheumatoid Arthritis Management Alliance cohort (KURAMA cohort study).[14,15] The cohort was founded in May 2011 on the principle of appropriate control and improved prognosis for RA patients at the Center for Rheumatic Diseases in Kyoto University Hospital and included 507 RA outpatients who visited the hospital between May 1 and October 31, 2018, and who fulfilled the 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification.[16] Of the 507 participants, we excluded participants who had missing data, including onset age, 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR), and serological C-reactive protein (CRP) level. The remaining 421 participants were subjected to the analysis. All study procedures were in accordance with the Declaration of Helsinki and were approved by the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R-0357) and the Kyoto Prefectural University of Medicine (ERB-E-397). In all cases, patient consent was obtained prior to sample and data collection.

2.2 | Evaluation of pain catastrophizing and RA-related factors

Pain catastrophizing is described by 3 psychological factors: ruminating about pain, magnification of pain symptoms, and feeling helpless about pain.[9] A validated questionnaire known as the Pain Catastrophizing Scale (PCS) is available for the quantitative measurement of pain catastrophizing.[17] The total score can range from 0 to 52; scores ≥30 indicate pain catastrophizing.

We assessed the disease activity of RA using the DAS28-ESR.[18] Physical disability and the severity of joint destruction were assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI)[19] and Steinbrocker stages, respectively. Serological data, including rheumatoid factor, ACPA, CRP, and ESR, were also evaluated.

In addition, we reviewed the use of therapeutic agents, including methotrexate, prednisolone (PSL), bDMARDs (tumor necrosis factor inhibitors, interleukin-6 receptor inhibitors, and cytotoxic T-lymphocyte antigen 4-immunoglobulin), nonsteroidal anti-inflammatory drugs (NSAIDs), opioids (tramadol), and pregabalin. The targeted synthetic DMARDs (tsDMARDs) used in the cohort were tofacitinib and baricitinib. We grouped tsDMARDs and bDMARDs as molecular targeted drugs. Based on a previous report, we defined difficult-to-treat RA by a DAS28-ESR score >3.2 and the use of ≥2 types of molecular targeted drugs.[4]

2.3 | Phenotype with a combination of remission and systemic inflammatory status

We defined the absence of systemic inflammation by a CRP value ≤0.2 mg/dL. We divided patients into 4 groups based on the combination of the remission status, defined by DAS28-ESR (remission <2.6), and the CRP status as follows: Group 1, remission and normal CRP level; Group 2, remission and CRP >0.2 mg/dL; Group 3, non-remission and normal CRP; and Group 4, non-remission and CRP >0.2 mg/dL.

2.4 | Comorbidities and lifestyle habits

Sociodemographic factors, lifestyle variables, and the presence of comorbidities were analyzed to determine the clinical characteristics of patients with pain catastrophizing. Each patient's age, gender, smoking habit, frequency of alcohol intake, exercise and sports habit, collagen tissue disease, extra-articular lesions, respiratory disease, psychiatric treatment (detailed disease names were not collected), and history of herpes zoster infection, cancer, falls within the past year, or surgery within the past year were assessed using a questionnaire and routine clinical examinations. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

2.5 | Assessment of discrepancy between the evaluator global assessment (EGA) and PGA

The EGA and PGA were represented by VAS values of 0-100 mm. EGA, PGA, swollen joint count (SJC), and tender joint count (TJC) were measured to verify the DAS28-ESR variables. We used the PGA and TJC as patient-subjective evaluation variables, and EGA and SJC as evaluator-objective evaluation variables. To express the discrepancy between the objective and subjective evaluations, we created variables for "EGA minus PGA" and "SJC minus TJC."

2.6 | Statistical analysis

Variables with a normal distribution are expressed as the mean ± SD, and those with a non-normal distribution are expressed as the median and range. Categorical variables are expressed as numbers (%). Comparisons between the pain catastrophizing and non-pain catastrophizing groups were performed using *t* tests for normally distributed continuous variables, the Mann-Whitney *U* test for non-normally distributed continuous variables, and Fisher's exact test for categorical variables.

The relationship between clinical remission and pain catastrophizing was evaluated by calculating the odds ratios (OR) and their corresponding 95% confidence intervals (CI) using logistic regression analysis. The relationship between pain catastrophizing and phenotype (Groups 1, 2, 3, and 4) with a combination of remission and systemic inflammatory status was evaluated using an a priori Steel's comparison test with Group 1 as the reference. Next, we constructed adjusted models to test the association between the phenotypes of 3 groups (Groups 1, 3, and 4) and their characteristics, including RA-related variables and pain catastrophizing. We used a multinomial logistic regression model that allowed simultaneous estimation of the probability of different outcomes. Separate ORs and 95% CIs were calculated for the 3 groups, comparing each with the reference group, to clarify the groups in which pain catastrophizing are strongly involved.

Univariable regression analysis was performed to evaluate the association between pain catastrophizing and RA-related factors, comorbidities, and lifestyle habits. Multivariable regression analysis was performed using variables selected with forward-backward, stepwise variable selection ($P < .2$) on all variables in the univariable analysis to identify independent and significantly associated factors for pain catastrophizing. We planned to eliminate multicollinearity, indicated by a variance inflation factor >5. All reported *P* values were 2-sided, and a *P* value <.05 was considered significant. All statistical analyses were performed using JMP version 14.0.0 (SAS Institute Inc., Cary NC, USA), except for the Jonckheere-Terpstra trend test, which was assessed using SAS version 9.4 (SAS Institute Inc.).

TABLE 1 Comparison of demographic and clinical features of patients with rheumatoid arthritis between pain catastrophizing statuses

	Overall	Pain catastrophizing	Non-pain catastrophizing	
	N = 421[a]	n = 110 (26.1%)[b]	n = 311 (73.9%)[b]	*P* value
Gender, female, n (%)	359 (85.3)	100 (90.9)	259 (83.3)	.060
Age, y, mean (SD)	65.2 (12.0)	65.0 (11.9)	65.8 (12.3)	.584
Body mass index	22.0 83.6)	21.9 (3.9)	22.0 83.4)	.888
Onset age, y, mean (SD)	50.8 (14.9)	51.8 (14.2)	50.5 (15.1)	.409
Disease duration, y, median (range)	10 (1-60)	9.5 (2-57)	10.0 (1-60)	.806
Pain catastrophizing score, mean (SD)	20.8 (13.1)	37.7 (5.8)	14.9 (9.2)	<.001
Pain VAS, 0-100 mm, median (range)	14 (0-96)	26 (0-96)	11 (0-90)	<.001
PGA,VAS 0-100 mm, median (range)	14 (0-99)	25 (0-99)	13 (0-91)	<.001
EGA, VAS 0-100, median (range)	6 (0-85)	9 (0-85)	5 (0-77)	.047
PGA minus EGA, mean (SD)	13.5 (20.5)	19.4 (24.2)	11.4 (18.6)	<.001
History of psychiatric treatment, n (%)	55 (13.1)	16 (14.5)	39 (12.5)	.622
Steinbrocker stages 3 and 4, n (%)	203 (48.2)	54 (49.1)	149 (47.9)	.912
Tender joint count, 0-28, median (range)	0 (0-17)	0 (0-17)	0 (0-13)	.002
Swollen joint count, 0-28, median (range)	0 (0-14)	0 (0-14)	0 (0-9)	.313
ACPA, U/mL, median (range)	76.5 (0.5-6190)	61.0 (0.5-3200)	87.1 (0.5-6190)	.309
CRP, mg/dL, median (range)	0.1 (0.1-7.5)	0.1 (0.1-5.9)	0.1 (0.1-7.5)	.719
ESR, median (range)	15 (3-120)	15.5 (4-78)	15.0 (1.7-120)	.732
HAQ score, 0-3, median (range)	0.25 (0-3)	0.50 (0-2.9)	0.25 (0-3)	.001
DAS28-ESR, mean (SD)	2.6 (1.0)	2.9 (1.1)	2.6 (1.0)	.003
DAS28-ESR remission, n (%)	234 (56)	51 (46.4)	183 (58.8)	.026
Methotrexate use, n (%)	303 (72.0)	74 (67.3)	229 (73.6)	.218
Prednisolone use, n (%)	93 (22.1)	93 (22.1)	66 (21.2)	.504
Dose, mg/d, median (range)	0 (0-20)	0 (0-10)	0 (0-20)	.547
Biological DMARD use, n (%)	202 (48.8)	53 (48.2)	148 (47.9)	1.000
Targeted synthetic DMARD use, n (%)	5 (1.2)	1 (0.9)	4 (1.3)	1.000
NSAID use, n (%)	168 (39.9)	45 (40.9)	123 (39.6)	.821
Opioid use, n (%)	46 (10.9)	16 (14.6)	30 (9.7)	.159
Pregabalin use, n (%)	14 (3.3)	4 (3.6)	10 (3.2)	.766

Abbreviations: ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; DMARD, disease-modifying antirheumatic drug; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; PGA, patient global assessment; SD, standard deviation; VAS, visual analog scale.

[a]Excluding body mass index (n = 419) and ACPA (n = 400).

[b]Excluding body mass index and ACPA. Pain catastrophizing vs non-pain catastrophizing: n = 109 (26.0%) vs n = 310 (74.0%) in rheumatoid factor, n = 105 (26.3%) vs n = 295 (73.7%) for ACPA.

3 | RESULTS

3.1 | Patient demographics

Patient characteristics are shown in Table 1. In general, patients were older adults with a relatively long disease duration (mean age, 65.2 ± 12.0 years; median disease duration, 10 years); only 3 patients (0.7%) had a disease duration of ≤24 months. Approximately half of the patients were receiving bDMARDs or tsDMARDs. A total of 234 patients (56%) achieved clinical remission (DAS28-ESR score <2.6). Sixteen patients (3.8%) were difficult to treat. One patient had fibromyalgia.

3.2 | Pain catastrophizing was associated with patient-reported outcomes

We compared patients with and without pain catastrophizing (Table 1). Among 421 patients, 26.1% were pain catastrophizers. The proportion of DAS28-ESR remission in the pain catastrophizing

group was significantly lower than that in the non-pain catastrophizing group (46.4% vs 58.8%, $P < .026$).

The disease duration, onset age, BMI, SJC, percentage of patients with an advanced Steinbrocker stage, percentage of patients using medications, including PSL and bDMARDs; and serum ACPA, CRP, and ESR levels were not significantly different between the 2 groups. There was no significant difference between the 2 groups with respect to the use of pain medications, including NSAIDs, opioids, and pregabalin, and the proportion of patients with a history of psychiatric treatment.

PGA, TJC, and HAQ scores were significantly higher in the pain catastrophizing group than in the non-pain catastrophizing group ($P < .001$, $P = .002$, and $P = .001$, respectively). Although the pain catastrophizing group had a slightly higher EGA value than the non-pain catastrophizing group ($P = .047$), the median EGA values of each group were ≤10 mm. However, PGA minus EGA values were higher in the pain catastrophizing group than in the non-pain catastrophizing group ($P < .001$). These variables, which showed a significant difference from the binary variables of pain catastrophizing, tended to significantly increase as the PCS score increased (Table S1).

3.3 | Pain catastrophizing was associated with non-remission in RA patients when CRP levels were normal

Table 2 shows that pain catastrophizing was negatively associated with remission (OR: 0.62, 95% CI: 0.38-1.00, $P = .048$). To clarify whether pain catastrophizing was associated with non-remission without systemic inflammation, we analyzed whether Groups 3 or 4 had variables that were different from those of Group 1 using multiple comparison tests (Table 3). Age, disease duration, and the HAQ score were higher in the non-remission groups (Groups 3 and 4) than in Group 1 (all $P < .01$). An advanced Steinbrocker stage and the use of pain medications were more prevalent in Groups 3 and 4 than in Group 1. ACPA levels were higher in Group 4 than in Group 1 ($P = .0152$). PGA minus EGA was significantly higher in Group 3 than in Group 1 ($P = .0026$).

Table 4 shows the adjusted multinomial logistic regression models comparing characteristics for Groups 1, 3, and 4 with each reference group, excluding 21 (5%) of 421 participants who had missing data for ACPA as covariates. Group 3 participants were more likely to suffer from pain catastrophizing than Group 1 participants (41 Group 1 participants [20.3%] vs 36 Group 3 participants [34.3%] had pain catastrophizing); the presence of pain catastrophizing was independently associated with a difference between Group 1 and Group 3 (OR 0.51, 95% CI 0.28-0.93). Group 4 participants were more likely to have a higher ACPA level; 43 Group 1 participants (23.0%) were in the top quartile of ACPA level vs 31 Group 4 participants (39.2%) (OR 0.41, 95% CI 0.17-0.96), and 31 Group 4 participants (39.2%) were in the top quartile of ACPA level vs 20 Group 3 participants (19.2%) (OR 2.81, 95% CI 1.13-7.25).

3.4 | Clinical and lifestyle characteristics predicting pain catastrophizing in RA patients

We set the cutoff value of PGA minus EGA to be 20 mm based on the average value of PGA minus EGA in patients with pain catastrophizing (average value, 19.4; Table 1). Table 5 presents the results of the univariable and multivariable analyses for the association of several independent variables with pain catastrophizing. In the univariable analysis, a high HAQ score, TJC, or TJC minus SJC value; a PGA

TABLE 2 Analysis of clinical features including pain catastrophizing associated with DAS28-ESR remission

N = 421	Univariable		Multivariable	
DAS28-ESR remission (n = 234)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.00 (1.00-1.00)	.190	0.96 (0.94-0.98)	<.001
Gender, male	0.97 (0.66-1.42)	.884	1.99 (1.05-3.79)	.033
Disease duration	1.00 (0.99-1.00)	.477	1.00 (0.98-1.03)	.819
bDMARD use	1.35 (0.92-1.98)	.130	1.39 (0.89-2.16)	.100
Methotrexate, mg per week	1.04 (1.01-1.07)	.004	1.00 (0.95-1.05)	.894
Prednisolone, mg per day	0.92 (0.84-1.00)	.051	0.89 (0.81-0.98)	.013
Steinbrocker stage 3 or 4 vs 1 or 2	0.31 (0.21-0.46)	<.001	0.35 (0.21-0.59)	<.001
Pain catastrophizing score ≥30	0.60 (0.39-0.94)	.024	0.62 (0.38-1.00)	.048

Note: Covariates are all the above variables. DAS28-ESR remission, <2.6.

Abbreviations: bDMARD, biological disease-modifying antirheumatic drugs; CI, confidence interval; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; OR, odds ratio.

TABLE 3 Patient demographics stratified by phenotype of combined DAS remission and inflammatory status

	Remission in DAS28-ESR		Non-remission in DAS28-ESR	
	CRP ≤0.2 mg/dL	CRP >0.2 mg/dL	CRP ≤0.2 mg/dL	CRP >0.2 mg/dL
	n = 202 (48.0%)	n = 33 (7.8%)	n = 105 (25.0%)	n = 81 (19.2%)
	Group 1	Group 2	Group 3	Group 4
Age, y	62.3 ± 12.0	63.9 ± 11.8	68.8 ± 9.7†††	68.5 ± 11.8††
Body mass index	21.9 ± 2.9	23.1 ± 3.0	21.8 ± 3.7	22.1 ± 4.8
Disease duration, y	11.8 ± 10.7	12.7 ± 9.7	15.9 ± 12.0†	16.8 ± 11.9††
CRP, mg/dL	0.11 ± 0.06	0.82 ± 1.51†††	0.12 ± 0.04	1.25 ± 1.17†††
ACPA, U/mL	243 ± 398	178 ± 249	270 ± 531	483 ± 874*
Tender joint count, 0-28	0.13 ± 0.44	0.12 ± 0.42	1.59 ± 2.31†††	1.79 ± 2.54†††
Swollen joint count, 0-28	0.15 ± 0.49	0.12 ± 0.33	1.17 ± 1.61†††	1.84 ± 2.59†††
HAQ score	0.3 ± 0.6	0.3 ± 0.4	0.8 ± 0.7†††	0.9 ± 0.9†††
PGA, VAS 0-100 mm	13.1 ± 14.9	10.5 ± 11.0	37.0 ± 25.4†††	35.9 ± 25.0†††
EGA, VAS 0-100 mm	4.0 ± 5.9	5.1 ± 7.0	15.3 ± 12.0†††	19.0 ± 15.2†††
Pain, VAS 0-100 mm	14.3 ± 18.9	11.3 ± 16.9	34.0 ± 26.1†††	36.0 ± 27.7†††
PGA minus EGA	9.2 ± 14.0	5.4 ± 12.1	21.8 ± 25.9**	16.9 ± 24.5
Pain catastrophizing score	18.8 ± 12.5	21.6 ± 13.3	23.5 ± 14.2*	22.1 ± 12.6
Pain catastrophizing score‡ ≥30, n (%)	41 (20.3%)	10 (30.3%)	36 (34.3%)	23 (28.4%)
Steinbrocker stages 3 and 4§, n (%)	72 (35.6%)	11 (33.3%)	63 (60.0%)	57 (70.4%)
NSAID use$^{\|\|}$, n (%)	95 (47.0%)	13 (39.4%)	62 (59.1%)	48 (59.3%)
bDMARD or tsDMARD use¶, n (%)	110 (54.5%)	11 (33.3%)	53 (50.5%)	33 (40.7%)
Prednisolone use¶¶, n (%)	23 (11.4%)	10 (36.3%)	33 (31.4%)	27 (33.3%)
Methotrexate use¶¶¶, n (%)	151 (74.8%)	27 (81.8%)	71 (67.6%)	54 (66.7%)

Note: n = 421, excluding body mass index (n = 419) and ACPA (n = 400). Data are expressed as mean ± SD or as number (%). *$P < .05$, **$P < .01$ in Steel's multiple comparison test using "Group 1" as the control group. $^{\dagger}P < .01$, $^{\dagger\dagger}P < .001$, $^{\dagger\dagger\dagger}P < .0001$ in Steel's multiple comparison test with "Group 1" as the control group. $^{\ddagger}P = .053$, $^{\S}P = .0001$, $^{\|\|}P = .048$, $^{\P}P = .047$, $^{\P\P}P < .0001$, and $^{\P\P\P}P = .214$ in Chi-square test among all groups.

Abbreviations: ACPA, anti-citrullinated peptide antibody; bDMARD, biological disease-modifying antirheumatic drugs; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; PGA, patient global assessment; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs; VAS, visual analog scale.

minus EGA value ≥20 mm; and history of respiratory disease, herpes zoster infection, and falls were positively associated with pain catastrophizing. Exercise and sports habits were negatively associated with pain catastrophizing. In the multivariable analysis, a high HAQ score, a PGA minus EGA value ≥20 mm, a high TJC minus SJC value, a history of falls, and current smoking were positively associated with the PCS score ($P = .0001$, $P = .002$, $P = .001$, $P = .034$, and $P = .017$, respectively). Female gender was positively associated and age was negatively associated with the PCS score, although no interventions could modify these results in general.

4 | DISCUSSION

Our study revealed 3 major findings. First, we showed that pain catastrophizing is a major obstacle to achieving remission of RA in patients with normal CRP levels. Second, the overestimation of RA disease activity due to elevated PGA was more likely in the presence of pain catastrophizing, which was especially observed in patients with normal CRP levels. Third, we found that falls and smoking were associated with increased PCS scores and are therefore risk factors for pain catastrophizing.

TABLE 4 Multivariate adjusted association between phenotype of DAS remission combined with inflammatory status and characteristics

	Group 1 vs Group 4 (ref)		Group 1 vs Group 3 (ref)		Group 4 vs Group 3 (ref)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y	0.96 (0.93-0.98)	.002*	0.95 (0.93-0.97)	<.0001*	0.99 (0.96-1.02)	.571
Disease duration, y	1.01 (0.98-1.04)	.642	1.01 (0.98-1.04)	.658	1.00 (0.97-1.03)	.960
Gender						
Female	1 (ref)	.262	1 (ref)	.343	1 (ref)	.766
Male	1.74 (0.69-4.89)		1.49 (0.67-3.49)		0.85 (0.29-2.35)	
bDMARD or tsDMARD						
No current use	1 (ref)	.031*	1 (ref)	.640	1 (ref)	.097
Current use	1.93 (1.07-3.52)		1.14 (0.67-1.94)		0.59 (0.31-1.09)	
Prednisolone						
No current use	1 (ref)	.001*	1 (ref)	.001*	1 (ref)	.935
Current use	0.30 (0.14-0.61)		0.31 (0.16-0.59)		1.03 (0.53-2.00)	
Steinbrocker stages						
1 or 2	1 (ref)	.002*	1 (ref)	.028*	1 (ref)	.278
3 or 4	0.30 (0.14-0.63)		0.47 (0.24-0.92)		1.56 (0.70-3.48)	
ACPA						
Negative, <4.5, U/mL	1 (ref)		1 (ref)		1 (ref)	
Positive, 4.5 to less than 13.5	0.94 (0.29-3.33)	.926	2.16 (0.70-7.66)	.200	2.29 (0.55-9.85)	.252
Strong positive, 13.5 to less than 329	0.68 (0.29-1.53)	.355	0.64 (0.32-1.25)	.196	0.95 (0.40-2.28)	.902
Top quartile, ≥329: third quartile	0.41 (0.17-0.96)	.043*	1.16 (0.52-2.58)	.715	2.81 (1.13-7.25)	.029*
Pain catastrophizing						
Negative, scale <30	1 (ref)	.142	1 (ref)	.029*	1 (ref)	.628
Positive, scale ≥30	0.61 (0.31-1.19)		0.51 (0.28-0.93)		0.85 (0.44-1.64)	

Note: *$P < .005$. Group 1: DAS28-ESR remission (<2.6) and CRP ≤0.2 mg/dL, Group 3: non-remission and CRP ≤0.2 mg/dL, Group 4: non-remission and CRP >0.2 mg/dL. The model used was adjusted for age, disease duration, gender, pharmacotherapy (DMARD and prednisolone), Steinbrocker stages status, ACPA status, and pain catastrophizing status. The results are based on n = 400 participants with complete data for all covariates (21 [5%] of 421 had missing data of ACPA and were excluded).

Abbreviations: ACPA, anti-citrullinated peptide antibody; bDMARD, biological disease-modifying antirheumatic drugs; CI, confidence interval; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs.

The presence of pain catastrophizing was associated with all patient-reported outcomes (PROs), including pain VAS, PGA, TJS, and HAQ; however, the inflammatory indexes, including CRP levels, ACPA positivity, and SJC, were not influenced by the presence of pain catastrophizing. The difference in EGA, an objective index, was significant between the pain catastrophizing and non-pain catastrophizing groups. However, there was a correlation between the presence of pain catastrophizing and TJC, which may have affected the physician's evaluation. Therefore, we should pay attention to the discrepancy between PGA and EGA. Notably, the discrepancy between PGA and EGA (PGA minus EGA) was larger in the group with pain catastrophizing, indicating that patients with pain catastrophizing estimate their disease condition more severely than those without it.

This study demonstrated that pain catastrophizing was negatively correlated with the composite score of disease activity, making it difficult to achieve remission. Although only 48.8% of our study population used bDMARDs, the results of the relationship between pain catastrophizing and remission were similar to those previously reported in a population of RA patients using only bDMARDs.[20] In addition, by detecting the proportion of patients who did not reach remission due to pain catastrophizing, we hypothesized that the presence of pain catastrophizing would result in an increased PGA score and overestimation of disease activity, even under controlled systemic inflammation. Table 3 clearly shows that Group 3 (non-remission despite normal CRP level) had the highest PCS score, highest PGA score, and highest discrepancy between PGA and EGA (PGA minus EGA) among the groups. Moreover, a multinomial logistic analysis comparing the characteristics of Group 1 and Group 3 (Table 4) revealed that the presence of pain catastrophizing was an independent factor that was negatively correlated with the achievement of remission in Group 3. This result suggests that some patients are unable to achieve remission due to an overestimation of PGA caused by the psychological or cognitive impact of pain catastrophizing. Further, among the groups, the mean ACPA value, an indicator of poor prognosis in RA,[3] was the

TABLE 5 Univariable and multivariable regression analyses for independent variables associated with the Pain Catastrophizing Scale score

		Univariable				Multivariable			
				95% CI				95% CI	
	Applicable number (n = 421[a])	Estimates	*P* value	Lower	Upper	Estimates	*P* value	Lower	Upper
Gender, female vs male	359	1.77	.0501	−0.001	3.54	1.85	.039	0.090	3.61
Age, 10 y		−0.63	.243	−1.68	0.43	−1.69	.002	−2.75	−0.64
Body mass index, 1 unit		−0.04	.827	−0.39	0.31				
RA disease characteristics									
Disease duration, 1 y		0.03	.547	−0.08	0.14				
Stage 3 or 4, vs stage 1 or 2	203	1.07	.096	−0.19	2.32				
HAQ score >0.5, vs HAQ score ≤0.5	140	4.00	<.0001	2.72	5.28	2.81	.0001	1.37	4.25
PGA − EGA ≥20 mm VAS, vs <20 mm	122	3.23	<.0001	1.97	4.67	2.22	.002	0.81	3.63
SJC in 28 joints		0.02	.951	−0.68	0.72				
TJC in 28 joints		0.81	.0007	0.35	1.28				
TJC minus SJC in 28 joints		1.48	<.0001	0.75	0.84	1.15	.001	0.45	1.84
ACPA, 10 U/mL		−0.01	.402	−0.03	0.01				
ESR, 1 mm/h		−0.01	.726	−0.09	0.06				
CRP, 1 mg/mL		0.83	.295	−0.73	2.39				
RA therapeutics									
Prednisolone use	93	1.44	.062	−0.07	2.95	0.97	.186	−0.47	2.41
MTD[b] use (current)	206	0.11	.859	−1.15	1.37				
Difficult-to-treat[c] group	16	1.03	.540	−2.26	4.32				
Comorbidities									
Collagen tissue disease	20	2.21	.141	−0.74	5.16				
Extra-articular lesion	68	1.56	.072	−0.14	3.27				
Respiratory disease	124	1.74	.013	0.37	3.11	1.01	.139	−0.33	2.34
History of psychiatric treatment	55	1.61	.090	−0.25	3.47				
History of herpes zoster infection	6	7.78	.004	2.52	13.03	4.04	.113	−0.96	9.09
History of cancer	10	0.75	.722	−3.38	4.88				
Fall history within the past y	55	2.85	.003	1.01	4.70	1.89	.034	0.15	3.63
Surgery within the past y	30	−0.15	.907	−2.59	2.30				
Lifestyle habits									
Current smoking	28	1.39	.280	−1.13	3.91	3.02	.017	0.54	5.51
Daily alcohol intake	57	−0.86	.359	−2.70	0.98				
Exercise and sports habits	85	−2.01	.012	−3.56	-0.45				

Abbreviations: ACPA, anti-citrullinated peptide antibody; CI, confidence interval; CRP, C-reactive protein; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MTD, molecular targeted drug; PGA, patient global assessment; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale.

[a]n = 421, excluding body mass index (n = 419) and ACPA (n = 400).

[b]MTD: biological and/or targeted synthetic disease-modifying antirheumatic drug.

[c]Difficult-to-treat was defined as Disease Activity Score 28-Erythrocyte Sedimentation Rate >3.2 and MTD ≥2 types used.

highest in Group 4, and a significant difference from Group 1 emerged only in Group 4 in the multiple comparison test and multinomial logistic analysis. In addition, multinomial logistic analysis (Table 4) showed a difference in the proportion of ACPA in the top quartile between Groups 3 and 4, which was an independent factor that determined the group. Therefore, it is reasonable to assume that there are differences

in the refractory proportion between Groups 3 and 4, even though both were assessed by DAS28 as non-remission. Hence, approximately 34% of patients with normal CRP levels but no DAS28 remission, the proportion of patients with pain catastrophizing in Group 3 (Table 3), may be subjected to disease activity overestimation due to pain catastrophizing and an elevated PGA. However, we did not find any signs of overtreatment in our data (Table 3); hence, it seems as if rheumatologists are well aware of the discordance of the PGA and inflammation and have accordingly adjusted their treatment decisions.

Pain catastrophizing is difficult to diagnose in an outpatient rheumatology clinic; however, proper management of psychological problems, including pain catastrophizing, is important. In addition, few studies have attempted to clarify the clinical characteristics of patients with pain catastrophizing. Our multivariable analysis results indicate that the PCS score is significantly associated with discrepancies in the evaluations between patients and rheumatologists, especially when the PGA is ≥20 mm more than EGA. These results may be a useful clinical finding for physicians to detect pain catastrophizing. Smoking was also associated with pain catastrophizing in the multivariable analysis. Univariable analysis showed an association between respiratory disease and pain catastrophizing, given that 21% of the patients who were smokers had respiratory complications, including chronic obstructive pulmonary disease (data not shown), suggesting that this disease was associated with pain catastrophizing. Therefore, it is necessary to support smoking cessation. Cognitive behavioral therapy is known to have an effect on both pain catastrophizing and smoking cessation and may be a helpful strategy in the future.[21-23] Similarly, the HAQ score and a history of falls were also associated with PCS. There is a possibility that the level of physical activity gradually decreased as a result of the fear-avoidance model of pain catastrophizing, which causes disuse disorder and/or falls by maintaining excessive rest to avoid pain.[24] Conversely, the patient may exhibit pain catastrophizing because of pain after a fall. A more detailed analysis based on longitudinal data is necessary to investigate this process.

We acknowledge that the present study has limitations. This is a cross-sectional study without longitudinal data, and our results do not imply causation. In addition, these results are obtained from a single institution and cannot be extrapolated to general clinical practice. However, it is possible to refer to our results, considering that the treatment was provided based on a treat-to-target strategy according to the guidelines of the ACR, the EULAR, and the Japan College of Rheumatology. Next, we used DAS28-ESR and the CRP level as indicators for grouping in terms of remission and systemic inflammation, but we need to consider the limitations of these variables. Patients whose main symptoms involve the foot, such as symptoms in the toe joints, may have underestimated disease activities, and patients taking interleukin-6 inhibitors may be more likely to have normal CRP levels. Therefore, we will need more careful observation of pain catastrophizing and nociplastic pain in applicable patients. Finally, our study used only a history of herpes zoster infection as a variable of neuropathic pain in the multivariable analysis because we were unable to identify the pain as neuropathic pain despite rigid checking. A previous study reported that 3.0% and 11.0% of RA patients likely have neuropathic pain and possible neuropathic pain, respectively, depending on the proportion with complications such as diabetes, spinal diseases, and herpes zoster infection.[25] Nevertheless, as there was no relationship between treatment with pregabalin, which is often prescribed for neuropathic pain, and the presence of pain catastrophizing, the association or overlap of neuropathic pain with pain catastrophizing may be negligible. However, comprehensive assessments, considering the possibility of neuropathic pain, should be performed.

In conclusion, pain catastrophizing is a major obstacle to achieving clinical remission in RA patients, especially in patients with normal CRP levels. Advanced physical disability, smoking habit, and a history of falls were associated with pain catastrophizing. This study reveals the potential risk of overestimation of disease activity caused by the presence of pain catastrophizing and may help identify patients suffering from nociplastic pain.

ACKNOWLEDGEMENTS

We thank Nobuo Uetsuki for teaching the concept of pain relief.

CONFLICT OF INTEREST

Motomu Hashimoto, Koichi Murata, Masao Tanaka, Kohei Nishitani, Ryu Watanabe, and Hiromu Ito belong to the Department of Advanced Medicine for Rheumatic Diseases, which is financially supported by Nagahama City, Shiga, Japan; Toyooka City, Hyogo, Japan; and 5 pharmaceutical companies (Mitsubishi Tanabe, Chugai, UCB Japan, AYUMI, and Asahi Kasei). The KURAMA cohort study is supported by a grant from Daiichi Sankyo Co., Ltd. Motomu Hashimoto received a research grant and/or speaker fee from Mitsubishi Tanabe Pharma Corp.; Bristol-Myers Squibb; Eisai Co., Ltd.; and Eli Lilly and Company. Kosaku Murakami received speaking fees and/or consulting fees from Eisai Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Pfizer Inc; Bristol-Myers Squibb; Mitsubishi Tanabe Pharma Corp.; UCB Japan Co., Ltd.; Daiichi Sankyo Co., Ltd.; and Astellas Pharma Inc. Koichi Murata received a speaking fee and/or consulting fee from Eisai Co., Ltd. and Astellas Pharma Inc. Kohei Nishitani received a research grant from Asahi Kasei Pharma. Ryu Watanabe received a speaking fee from Mitsubishi Tanabe Pharma Co; Pfizer Inc; Sanofi SA; AbbVie GK; Asahi Kasei Pharma; Eisai Co., Ltd.; Eli Lilly and Company; Bristol-Myers Squibb; and Janssen Pharmaceutical KK. Masao Tanaka received research grants and/or speaker fees from AbbVie GK; Asahi Kasei Pharma; Astellas Pharma Inc; AYUMI Pharmaceutical Co.; Chugai Pharmaceutical Co., Ltd.; Eisai Co., Ltd.; Eli Lilly Japan KK; Janssen Pharmaceutical KK; Mitsubishi Tanabe Pharma Co.; Novartis Pharma KK; Pfizer Inc; Taisyo Pharma., Ltd.; and UCB Japan Co., Ltd. Akio Morinobu received research grants and/or speaker fees from AbbVie; Asahi Kasei Pharma; Chugai Pharmaceutical; Ono Pharmaceutical; Eli Lilly; AbbVie; Ono Pharmaceutical; Pfizer; Astellas Pharmaceutical; and Chugai Pharmaceutical. Hiromu Ito received research grants from Bristol-Myers Squibb; Eisai Co., Ltd.; Taisyo Pharma; and Mochida. Tamami Yoshida, Go Horiguchi, Wataru Yamamoto, Ritei Uehara, and Shuichi Matsuda declare no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Tamami Yoshida, Motomu Hashimoto. Methodology: Tamami Yoshida, Motomu Hashimoto. Formal analysis and interpretation of the data: Tamami Yoshida, Motomu Hashimoto, Go Horiguchi. Data management: Wataru Yamamoto. Writing - original initial draft preparation: Tamami Yoshida. Resources and writing - review and editing: Tamami Yoshida, Motomu Hashimoto, Kosaku Murakami, Masao Tanaka, Koichi Mutara, Nishitani Kohei, and Hiromu Ito. Funding acquisition: Tamami Yoshida. Supervision: Ritei Uehara, Akio Morinobu, and Shuichi Matsuda.

DATA AVAILABILITY STATEMENT

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

ORCID

Tamami Yoshida https://orcid.org/0000-0002-4571-1362
Koichi Murata https://orcid.org/0000-0002-7896-3937
Ryu Watanabe https://orcid.org/0000-0002-1089-5296
Hiromu Ito https://orcid.org/0000-0002-1827-382X

REFERENCES

1. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. *Rheumatology*. 2000;39:122-132.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023-2038.
3. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76:960-977.
4. de Hair MJH, Jacobs JWG, Schoneveld JLM, van Laar JM. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology*. 2018;57:1135-1144.
5. Nikiphorou E, Radner H, Chatzidionysiou K, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther*. 2016;18:251.
6. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum*. 2012;64:2814-2823.
7. Aydede M, Shriver A. Recently introduced definition of "nociplastic pain" by the International Association for the Study of Pain needs better formulation. *Pain*. 2018;159:1176-1177.
8. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet*. 2021;397:2098-2110.
9. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain*. 2001;17:52-64.
10. Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain catastrophizing and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. *Clin J Pain*. 2019;35:279-293.
11. Edwards RR, Cahalan C, Calahan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. *Nat Rev Rheumatol*. 2011;7:216-224.
12. Penhoat M, Saraux A, Le Goff B, Augereau P, Maugars Y, Berthelot JM. High pain catastrophizing scores in one-fourth of patients on biotherapy for spondylarthritis or rheumatoid arthritis. *Joint Bone Spine*. 2014;81:235-239.
13. Edwards RR, Bingham CO, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Rheum*. 2006;55:325-332.
14. Minamino H, Katsushima M, Yoshida T, et al. Increased circulating adiponectin is an independent disease activity marker in patients with rheumatoid arthritis: a cross-sectional study using the KURAMA database. *PLoS One*. 2020;15:e0229998.
15. Murata K, Ito H, Hashimoto M, et al. Elderly onset of early rheumatoid arthritis is a risk factor for bone erosions, refractory to treatment: KURAMA cohort. *Int J Rheum Dis*. 2019;22:1084-1093.
16. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581.
17. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Asess*. 1995;7:524-532.
18. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis*. 2009;68:954-960.
19. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol*. 2003;30:167-178.
20. Hammer HB, Uhlig T, Kvien TK, Lampa J. Pain catastrophizing, subjective outcomes, and inflammatory assessments including ultrasound: results from a longitudinal study of rheumatoid arthritis patients. *Arthritis Care Res*. 2018;70:703-712.
21. Seminowicz DA, Shpaner M, Keaser ML, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain*. 2013;14:1573-1584.
22. Fanshawe TR, Halliwell W, Lindson N, Aveyard P, Livingstone-Banks J, Hartmann-Boyce J. Tobacco cessation interventions for young people. *Cochrane Database Syst Rev*. 2017;11:CD003289.
23. Thorn BE, Pence LB, Ward LC, et al. A randomized clinical trial of targeted cognitive behavioral treatment to reduce catastrophizing in chronic headache sufferers. *J Pain*. 2007;8:938-949.
24. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85:317-332.
25. Ito S, Kobayashi D, Murasawa A, Narita I, Nakazono K. An analysis of the neuropathic pain components in rheumatoid arthritis patients. *Intern Med*. 2018;57:479-485.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Yoshida T, Hashimoto M, Horiguchi G, et al. Pain catastrophizing hinders Disease Activity Score 28 – erythrocyte sedimentation rate remission of rheumatoid arthritis in patients with normal C-reactive protein levels. *Int J Rheum Dis*. 2021;24:1520–1529. https://doi.org/10.1111/1756-185X.14231

Received: 26 May 2021 | Revised: 22 September 2021 | Accepted: 26 September 2021

DOI: 10.1111/1756-185X.14235

International Journal of Rheumatic Diseases WILEY

ORIGINAL ARTICLE

Upadacitinib in patients from China, Brazil, and South Korea with rheumatoid arthritis and an inadequate response to conventional therapy

Xiaofeng Zeng[1,2] | Dongbao Zhao[3] | Sebastiao C. Radominski[4] | Mauro Keiserman[5] | Chang K. Lee[6] | Sebastian Meerwein[7] | Jeffrey Enejosa[8] | Yunxia Sui[8] | Mohamed-Eslam F. Mohamed[8] | Won Park[9]

[1]Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, Beijing, China

[2]Key Laboratory of Rheumatology & Clinical Immunology, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Beijing, China

[3]Department of Rheumatology and Immunology, Shanghai Changhai Hospital, Shanghai, China

[4]Department of Rheumatology, Universidade Federal do Paraná, Curitiba, Brazil

[5]Department of Rheumatology, Pontifical Catholic University, Porto Alegre, Brazil

[6]Rheumatology, Asan Medical Center, Seoul, South Korea

[7]Immunology, AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

[8]Immunology, AbbVie Inc., Chicago, Illinois, USA

[9]Rheumatology, School of Medicine, Inha University, Incheon, South Korea

Correspondence
Xiaofeng Zeng, Director and Professor, Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, Peking Union Medical College, No. 1 Shuaifuyuan, Eastern District, Beijing 100730, China.
Email: xiaofeng.zeng@cstar.org.cn

Funding information
AbbVie

Abstract

Aim: This study assessed the efficacy and safety of upadacitinib (UPA), in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), in Chinese, Brazilian, and South Korean patients with active rheumatoid arthritis (RA) and an inadequate response (IR) to csDMARDs.

Methods: Patients on stable csDMARDs were randomized (1:1) to once-daily UPA 15 mg or matching placebo (PBO) for a 12-week, double-blind period. The primary endpoint was the proportion of patients achieving ≥20% improvement in American College of Rheumatology criteria (ACR20) at week 12.

Results: In total, 338 patients were randomized and treated, of whom 310 (91.7%) completed the double-blind phase. The study met the primary endpoint of ACR20 at week 12 for UPA 15 mg vs PBO (71.6% vs 31.4%, $P < .001$), with a treatment difference observed as early as week 1. All ranked and other key secondary endpoints, including more stringent responses such as ACR50, ACR70 (≥50%/70% improvement in ACR criteria), and Disease Activity Score in 28 joints using C-reactive protein <2.6, were met for UPA 15 mg vs PBO. The incidence of serious infections (2.4% vs 0.6%) and herpes zoster (HZ: 1.8% vs 0.6%) was higher with UPA 15 mg vs PBO. There was one case of venous thromboembolism reported in the UPA group.

Conclusion: UPA 15 mg in combination with csDMARDs demonstrated clinical and functional improvement and an acceptable safety profile over 12 weeks among patients from China, Brazil, and South Korea who had moderately to severely active RA and an IR to csDMARDs.

KEYWORDS

autoinflammatory conditions, biologic therapies, immunosuppressants, inflammation, rheumatoid arthritis

This trial was registered with ClinicalTrials.gov, identifier: NCT02955212.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that, if left untreated or inadequately treated, could lead to progressive functional impairment, significant disability, reduced quality of life, and increased mortality.[1,2] Methotrexate (MTX; a conventional synthetic disease-modifying antirheumatic drug [csDMARD]) is generally the recommended first-line therapy in the treatment of RA, with addition of other csDMARDs, biologic DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs) in patients with an inadequate response (IR) after 3 months.[3-5]

There remains a large unmet medical need in the treatment of RA despite major progress over the last 30 years and development of therapies such as anti-tumor necrosis factor, anti-interleukin-6, CTLA4-Ig, and anti-CD20 agents, among others.[6-9] The percentage of patients with RA who reach and maintain a status of low disease activity (LDA) or clinical remission (CR) remains unsatisfactory and, over time, many patients discontinue treatment due to adverse events (AEs) or loss of efficacy.[10,11] To address this, novel therapies are required to complement the available RA armamentarium.[10-12]

The Janus kinase (JAK) family of signaling molecules (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) mediates intracellular signaling downstream of multiple cytokines and growth factors.[13] JAK pathway activation initiates the expression of survival factors and other molecules that facilitate leukocyte cell trafficking and proliferation, and thereby contributes to the pathogenesis of inflammatory and autoimmune disorders including RA.[13,14] Inhibition of JAK signaling is an established approach for the treatment of RA,[14-17] and JAK inhibitors form the tsDMARD class of treatments.[5] Upadacitinib (UPA) is a JAK inhibitor engineered to have greater selectivity for JAK1 over JAK2, JAK3, and TYK2, and is approved by the United States Food and Drug Administration, the European Medicines Agency, the Pharmaceuticals and Medical Devices Agency, and several other regulatory agencies (including in South Korea and Brazil) for the treatment of patients with moderately to severely active RA and an IR to MTX.[18-21] UPA has a favorable benefit–risk profile based on several global phase III trials in a variety of patient populations.[22-26]

The objective of this study was to assess the efficacy and safety of UPA 15 mg in combination with csDMARDs over 12 weeks in patients from China, Brazil, and South Korea who had moderately to severely active RA and an IR to csDMARDs.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

This is a phase III, multicenter study that includes 2 periods. This report describes the results from period 1, which was the 12-week, randomized, double-blind, placebo (PBO)-controlled period of the study conducted at 37 sites in China, Brazil, and South Korea. Period 2 is the open-label, 52-week extension in patients who completed period 1 and which is ongoing and therefore not discussed in this report (Figure S1).

Eligible patients were adults (≥18 years) who had moderately to severely active RA and an RA diagnosis of ≥3 months duration, and who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA.[27] Active disease was defined as ≥6 swollen joints (based on a swollen joint count of 66 joints [SJC66]) and ≥6 tender joints (based on a tender joint count of 68 joints [TJC68]) at screening and baseline visits, and a high-sensitivity C-reactive protein (CRP) concentration of ≥3 mg/L at screening. Patients had been receiving csDMARD therapy for ≥3 months and had been on a stable dose for ≥4 weeks prior to the first dose of study drug. Patients had a prior IR to ≥1 csDMARD (MTX, sulfasalazine, or leflunomide). Patients who had an IR to hydroxychloroquine and/or chloroquine were only included if they had also failed MTX, sulfasalazine, or leflunomide treatment. Prior exposure to ≤1 bDMARD for RA was allowed in up to 20% of patients if they had limited exposure (<3 months) or did not tolerate the bDMARD, and patients had to have discontinued bDMARD therapy prior to the first dose of study drug and gone through an appropriate washout period. Exclusion criteria included prior exposure to any JAK inhibitor, IR to bDMARD therapy, history of any arthritis with onset prior to age 17, or current diagnosis of inflammatory joint disease other than RA. Clinical tests at screening included chest X-ray, electrocardiogram, tuberculin purified protein derivative skin test, hepatitis testing, and a serum pregnancy test. Patients with a history of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix were excluded from participating in the trial. All possible malignancies were identified using the search criteria "malignancies" Standard MedDRA Queries (SMQ) (narrow). Preferred terms which represent confirmed malignancies were subsequently identified based on a narrower "malignant tumors" SMQ.

The study was conducted according to the International Conference on Harmonization of Technical Regulations for Pharmaceuticals for Human Use guidelines, applicable regulations, and the Declaration of Helsinki. All study-related documents were approved by independent ethics committees and institutional review boards. All patients provided written informed consent.

2.2 | Randomization and masking

Patients who met the eligibility criteria were randomized 1:1 to receive either a once-daily extended-release formulation of UPA 15 mg or matching PBO, administered orally for 12 weeks, along with background csDMARD treatment. Randomization was stratified by country; patients from China were expected to comprise up to 80% of the total study population. Patients were randomized using an interactive response technology with a randomization schedule generated by the Data and Statistical Sciences Department of the study sponsor. Patients, investigators, and the sponsor were masked to this allocation. UPA 15 mg

extended-release tablets and PBO tablets were identical in appearance in order to maintain blinding.

2.3 | Outcomes

The primary endpoint was the proportion of patients achieving ≥20% improvement in ACR criteria (ACR20 response) at week 12. Ranked key secondary endpoints at week 12 were change from baseline in Disease Activity Score in 28 joints using CRP (DAS28-CRP), Health Assessment Questionnaire-Disability Index (HAQ-DI), and Short-Form 36-item Health Survey (SF-36), and the proportion of patients achieving LDA based on DAS28-CR) ≤3.2, CR based on DAS28-CRP <2.6, and LDA based on Clinical Disease Activity Index (CDAI) ≤10 (see Table S1). Other key secondary endpoints were the proportion of patients achieving an ACR50/70 response (≥50%/70% improvement in ACR criteria) at week 12 and an ACR20 response at week 1 (see Table S1). Additional endpoints included change from baseline in pain using a visual analog scale, remission based on CDAI ≤2.8, and Boolean remission (defined as SJC [based on 28 joints] ≤1, TJC [based on 28 joints] ≤1, CRP ≤1 mg/dL, and patient's global assessment of disease activity ≤10 mm [range: 0-100 mm]). Blood samples for pharmacokinetic analysis were obtained throughout the study. AEs, physical examinations, laboratory assessments, electrocardiograms, and vital signs data were assessed throughout the study.

2.4 | Statistical analysis

A sample size of 322 was planned to provide ≥90% power for a 21.7% difference in ACR20 response rate at week 12 (assuming a PBO ACR20 response rate of 36.7%), at a 2-sided significance level of 0.05 and accounting for a 10% dropout rate. This sample size was also planned to provide ≥90% power for most of the key secondary endpoints, including change from baseline in DAS28-CRP, ACR50 response rate, LDA and CR based on DAS28-CRP, and SF-36 Physical Component Summary (PCS), at a 2-sided significance level of 0.05 and accounting for a 10% dropout rate.

All efficacy analyses were carried out using the Full Analysis Set (FAS), which included all randomized patients who received ≥1 dose of study drug. For binary endpoints, frequencies and percentages were reported for each treatment group and comparison between UPA 15 mg and PBO was conducted using the Cochran–Mantel–Haenszel test adjusting for the stratification factor (country). Non-responder imputation was used to handle missing data for binary endpoints. Patients who discontinued the study drug prematurely were considered as non-responders for all subsequent visits after discontinuation, and patients with missing values at a specific visit were considered as non-responders for that visit. For the continuous endpoints of change from baseline in DAS28-CRP and HAQ-DI, missing data were handled by multiple imputation (MI) and statistical inference was conducted using analysis of covariance (ANCOVA), with treatment group as the fixed factor and the corresponding baseline value and country as covariates. For other continuous endpoints, statistical inference was conducted using the mixed-model repeated measures (MMRM) method, which included the fixed effects of treatment, visit, treatment by visit interaction, and country, and the fixed covariate of baseline value in the model, using an unstructured variance–covariance matrix. From both the ANCOVA (coupled with MI) and MMRM analyses, the least squares (LS) mean and 95% confidence interval (CI) were reported for each treatment group, and LS mean treatment differences and associated 95% CI and *P* values were reported comparing UPA 15 mg with PBO. A sequential testing method was used to control the overall type I error rate of primary and ranked key secondary endpoints.

Safety analyses were carried out using the Safety Analysis Set, which included all patients who received ≥1 dose of study drug. Patients with treatment-emergent AEs (TEAEs) were tabulated by preferred term as in the Medical Dictionary for Regulatory Activities, system organ class, severity, and relationship to study drug as assessed by the investigator.

This trial was registered with ClinicalTrials.gov, identifier: NCT02955212.

3 | RESULTS

3.1 | Patients

Between January 3, 2018 and August 14, 2019, 338 patients from 37 sites in China, Brazil, and South Korea were randomized to UPA 15 mg (n = 169) or PBO (n = 169). Discontinuation rates through week 12 were similar in the UPA 15 mg and PBO groups, although discontinuation due to AEs was more common in the UPA 15 mg group and patient withdrawal of consent was more common in the PBO group (Figure 1). All 338 patients were included in the FAS.

At baseline, demographics and disease characteristics were generally well balanced across the UPA and PBO groups; 228 (67.5%), 58 (17.2%), and 52 (15.4%) patients were enrolled in China, South Korea, and Brazil, respectively. Patients from each country were split evenly between UPA 15 mg and PBO. Most patients were female (81.1%) with a mean age of 51.7 years in both the UPA 15 mg and PBO groups. Patients had a mean (SD) disease duration of 7.2 (7.2) and 7.5 (7.6) years in the UPA 15 mg and PBO groups, respectively. All patients were on background csDMARDs for at least 3 months, and at least 4 weeks on stable doses prior to the first dose of study drug. Subjects had to have failed (lack of efficacy) at least 1 of the following: MTX, sulfasalazine, or leflunomide. Subjects with IR to hydroxychloroquine and/or chloroquine could only be included if they had also failed (lack of efficacy or intolerability) MTX, sulfasalazine, or leflunomide. Up to week 24, the background csDMARD dose had to be kept stable and could be decreased only for safety reasons. The majority of patients received either MTX alone or MTX in combination with another csDMARD, and most patients also received stable treatment with

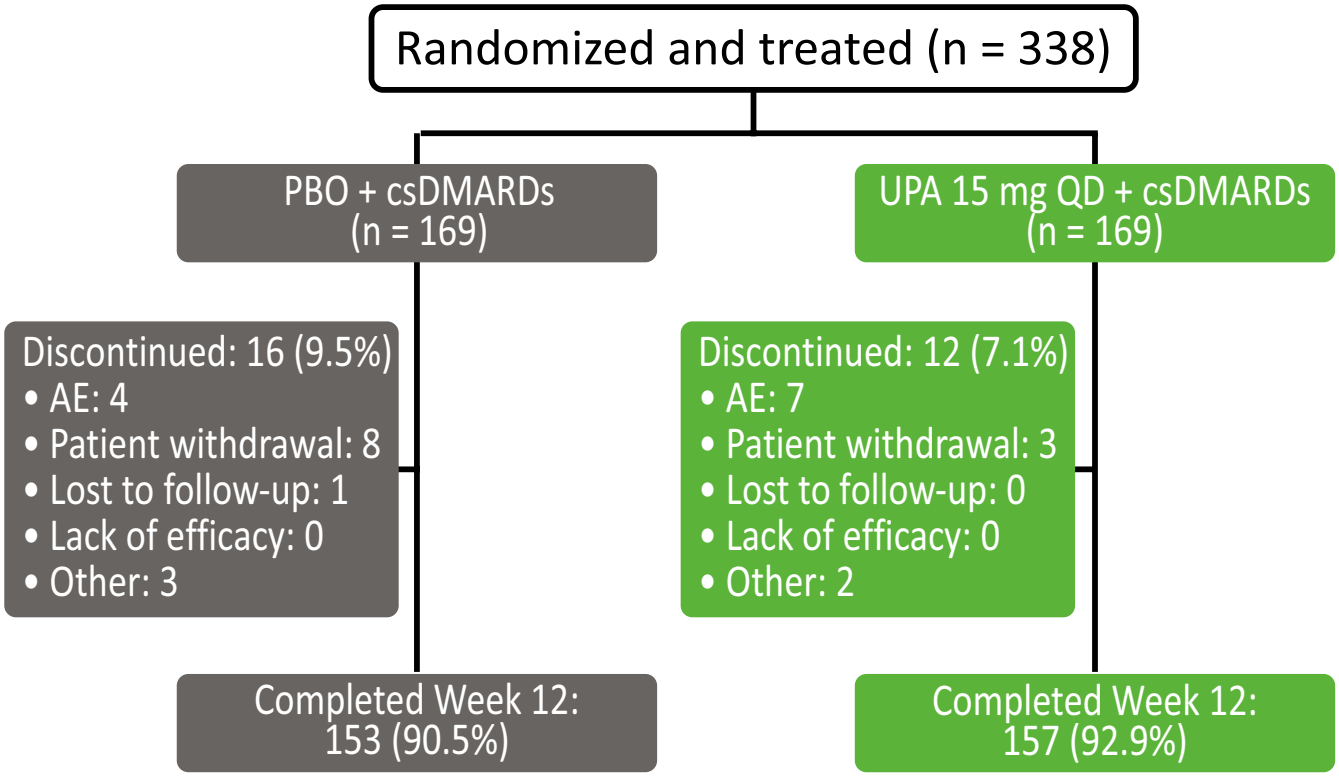


FIGURE 1 Patient disposition. AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drug; PBO, placebo; QD, once daily; UPA, upadacitinib

low-dose oral glucocorticoids (Table 1). The concomitant csDMARDs the patients were receiving are detailed in Table S2.

3.2 | Efficacy

At week 12, ACR20 (primary endpoint) was achieved by a significantly greater proportion of patients receiving UPA 15 mg vs PBO (71.6% [95% CI 64.8-78.4] vs 31.4% [95% CI 24.4-38.4], $P < .001$) (Figure 2). ACR50 and ACR70 responses were also achieved by greater proportions of patients receiving UPA 15 mg (40.8% and 21.3%) vs PBO (8.3% and 3.6%) at week 12 (nominal $P < .001$ for both comparisons) (Figure 2). Onset of action with UPA 15 mg was rapid, with 25.4% vs 5.9% of patients achieving ACR20 at week 1 with UPA 15 mg vs PBO, respectively (nominal $P < .001$) (Figure 2). A breakdown of the ACR20 placebo response and the ACR20 UPA 15 mg response by country is shown in Table 2, where South Korea had lower responses compared with China and Brazil. A breakdown of the ACR components is shown in Table S3, and demonstrates that greater improvements are seen with UPA 15 mg vs PBO in all components of the ACR response. In the UPA 15 mg group, ACR20 at week 12 was achieved by numerically greater proportions of patients receiving concomitant MTX and another csDMARD (78.1%) compared with MTX alone (72.2%) or a csDMARD other than MTX (68.4%). ACR20 response rates at week 12 by concomitant csDMARD at baseline are shown in Table S4. The differences in ACR20 response rates at week 12 between the treatment groups are as follows: for those on MTX only, 37%; for those on MTX and another csDMARD, 46.4%; and for those on a csDMARD other than MTX, 42.1%.

At week 12, all ranked secondary endpoints were met. Patients receiving UPA 15 mg showed significantly greater improvements from baseline vs PBO in DAS28-CRP, HAQ-DI, and SF-36 PCS (Figure 3). LDA, as defined by DAS28-CRP ≤3.2 and CDAI ≤10, was achieved by a significantly greater proportion of patients receiving UPA 15 mg compared with PBO at week 12 (Figure 4). CR, as defined by DAS28-CRP <2.6, was also achieved by a significantly greater proportion of patients receiving UPA 15 mg compared with PBO at week 12 (Figure 4). Patients receiving UPA 15 mg also achieved greater response rates for more stringent measures of efficacy compared with PBO at week 12, including CDAI ≤2.8 and Boolean remission (Figure 4). In addition, at all visits from week 1 onward, improvements from baseline in all ACR components were greater (nominal $P < .01$) in the UPA 15 mg group compared with the PBO group, including improvements in patients' assessments of pain (Figure 3).

3.3 | Safety

Through week 12, rates of TEAEs were numerically higher in the UPA 15 mg group compared with the PBO group (Table 3). The most frequently reported TEAEs (≥2% of patients in any treatment group) through week 12 were upper respiratory tract infection (UPA 15 mg: 9.5%, PBO: 6.5%) and increased alanine aminotransferase (UPA

TABLE 1 Baseline demographics and disease characteristics

Characteristic, mean (SD)[a]	PBO +csDMARDs (n = 169)	UPA 15 mg QD +csDMARDs (n = 169)
Female, n (%)	139 (82.2)	135 (79.9)
Age, y	51.7 (11.4)	51.7 (10.6)
RA duration since diagnosis, y	7.5 (7.6)	7.2 (7.2)
Country, n (%)		
China	114 (67.5)	114 (67.5)
Brazil	26 (15.4)	26 (15.4)
South Korea	29 (17.2)	29 (17.2)
RF+ and/or anti-CCP+, n (%)	152 (89.9)	159 (94.1)
TJC68	23.0 (14.5)	21.5 (14.8)
SJC66	11.9 (6.0)	11.9 (6.9)
DAS28-CRP[b]	5.6 (0.9)	5.6 (1.0)
CDAI[c]	35.9 (11.2)	35.2 (12.4)
HAQ-DI[b]	1.4 (0.7)	1.3 (0.7)
SF-36 PCS[b]	34.2 (7.6)	34.5 (7.7)
Pain VAS[d]	63.8 (20.6)	66.8 (20.6)
CRP, mg/L	20.2 (25.2)	20.0 (21.5)
Prior bDMARD exposure, n (%)	3 (1.8)	5 (3.0)
csDMARD use at baseline		
MTX alone, n (%)	71 (42.0)	79 (47.0)
MTX and other csDMARD, n (%)	41 (24.3)	32 (19.0)
csDMARD other than MTX, n (%)	57 (33.7)	57 (33.9)
MTX dose[e], mg/wk	13.0 (3.5)	12.9 (4.3)
Oral glucocorticoid use, n (%)	112 (66.3)	108 (63.9)
Mean glucocorticoid dose, mg/d[f]	6.1 (2.6)	5.5 (2.3)

Abbreviations: Anti-CCP+, anti-cyclic citrullinated peptide positive; bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, Disease Activity Score in 28 joints using CRP; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; PBO, placebo; PCS, Physical Component Summary; QD, once daily; RA, rheumatoid arthritis; RF+, rheumatoid factor positive; SF-36, Short-Form 36-item Health Survey; SJC66, swollen joint count of 66 joints; TJC68, tender joint count of 68 joints; UPA, upadacitinib; VAS, visual analog scale.

[a]Unless otherwise stated.

[b]PBO: n = 166, UPA: n = 166.

[c]PBO: n = 166, UPA: n = 163.

[d]PBO: n = 166, UPA: n = 165.

[e]PBO: n = 112, UPA: n = 111.

[f]PBO: n = 112, UPA: n = 108.

15 mg: 5.3%, PBO: 1.2%). The percentage of TEAEs leading to discontinuation of study drug through week 12 was numerically higher in the UPA 15 mg group compared with the PBO group (Table 3).

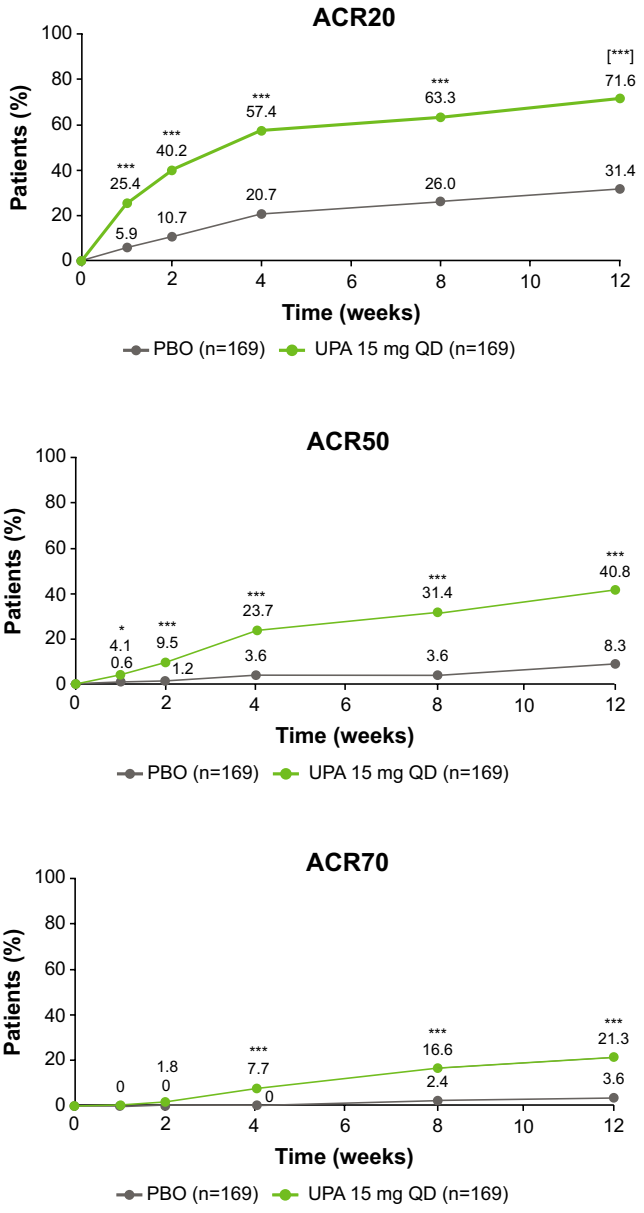


FIGURE 2 Proportion of patients achieving ACR responses over time (NRI). *Nominal $P < .05$ vs PBO; ***nominal $P < .001$ vs PBO (not adjusted for multiplicity); [***]$P < .001$ vs PBO (adjusted for multiplicity). ACR, American College of Rheumatology; ACR20/50/70, ≥20%/50%/70% improvement in ACR criteria; NRI, non-responder imputation; PBO, placebo; QD, once daily; UPA, upadacitinib [Colour figure can be viewed at wileyonlinelibrary.com]

The percentage of patients with serious AEs (SAEs) through week 12 was also numerically higher in the UPA 15 mg group compared with the PBO group (Table 3). Individual SAEs were reported in no more than 1 patient in either treatment group, except for pneumonia (3 cases in the UPA 15 mg group) and tendon rupture (2 cases in the UPA 15 mg group). SAEs leading to discontinuation of study drug were reported in 5 patients in the UPA 15 mg group (HZ, pneumonia, tendon rupture, worsening RA, and angioedema) and 2 patients in the PBO group (drug-induced liver injury and pneumonia). For all but 1 patient (tendon rupture), the event resolved following

discontinuation of the study drug and appropriate treatment. There were no patient deaths during the study.

Through week 12, the frequency of AEs of special interest (AESIs) in the UPA 15 mg group was generally similar compared with the PBO group, with the exception of serious infection, HZ, hepatic disorder, neutropenia, and creatine phosphokinase (CPK) elevation, which were reported in a higher percentage of patients in the UPA 15 mg group (Table 3). There were 5 serious infections (4 in the UPA 15 mg group and 1 in the PBO group) and HZ was reported in 4 patients (3 in the UPA 15 mg group and 1 in the PBO group); 1 patient in the UPA 15 mg group had a serious HZ event that led to discontinuation of study drug. Treatment-emergent opportunistic infections were reported in 2 patients in the UPA 15 mg group (non-serious cytomegalovirus infection and a non-serious oral candidiasis). Treatment-emergent malignancy was reported in 1 Korean patient in the UPA 15 mg group who was diagnosed with breast cancer on the day of randomization. This event led to discontinuation but was not considered by the investigator to have a reasonable possibility of being related to the study drug, but rather related to age (46 years) and/or environmental factors (former smoker and drinker). Pulmonary embolism and deep vein thrombosis (DVT) (both adjudicated by an external adjudication committee to be a venous thromboembolism [VTE]) were both reported in 1 patient in the UPA 15 mg group who had several risk factors for VTE, including obesity, a history of DVT, and use of estrogen preparations. There were no cases of active/latent tuberculosis, gastrointestinal perforation, renal dysfunction, treatment-emergent NMSC, or adjudicated major adverse cardiovascular event in either treatment group through week 12.

Laboratory measures were assessed at baseline and at each study visit. The frequency of laboratory abnormalities was generally similar in both treatment groups, except for neutropenia and CPK elevation, which were reported in a higher percentage of patients in the UPA 15 mg group. No patients with CPK elevation had symptoms of muscle pain or rhabdomyolysis, or discontinued the study drug due

TABLE 2 Breakdown in ACR20 PBO response and ACR20 UPA 15 mg QD response for the 3 countries at week 12

	Responder, n (%)	
	PBO	UPA 15 mg QD
China, n = 114	36 (31.6)	82 (71.9)
South Korea, n = 29	7 (24.1)	19 (65.6)
Brazil, n = 26	10 (38.5)	20 (76.9)

Abbreviations: ACR20, ≥20% improvement in American College of Rheumatology criteria; PBO, placebo; QD, once daily; UPA, upadacitinib.

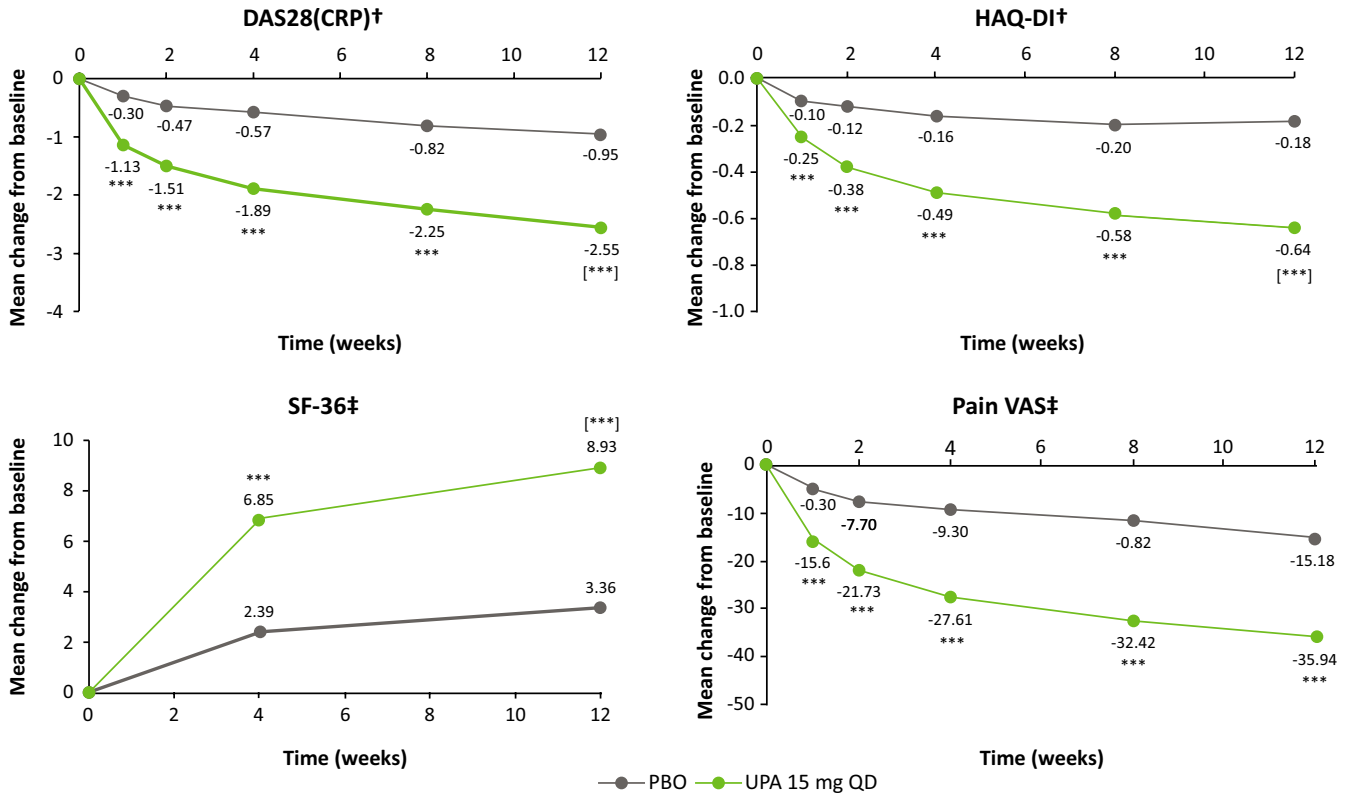


FIGURE 3 Mean change from baseline in DAS28-CRP, HAQ-DI, SF-36 PCS, and pain VAS over time. ***Nominal $P < .001$ vs PBO (not adjusted for multiplicity); [***]$P < .001$ vs PBO (adjusted for multiplicity). †Analysis of covariance coupled with multiple imputation. ‡Mixed-model repeated measures. DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; PBO, placebo; PCS, Physical Component Summary; QD, once daily; SF-36, Short-Form 36-item Health Survey; UPA, upadacitinib; VAS, visual analog scale

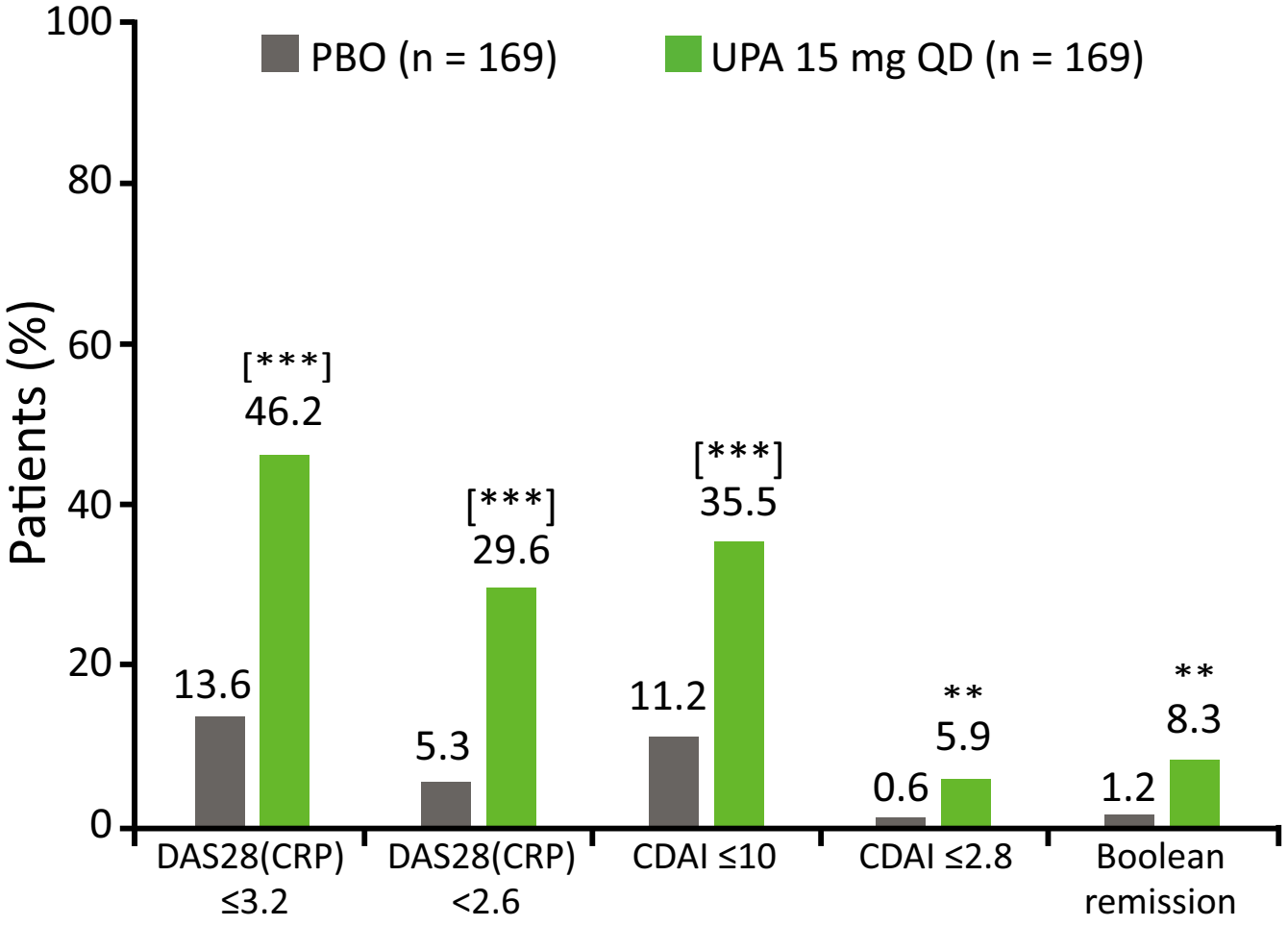


FIGURE 4 Proportion of patients achieving DAS28-CRP ≤3.2/<2.6, CDAI ≤10/≤2.8, and Boolean remission at week 12 (NRI). **Nominal $P < .01$ vs PBO (not adjusted for multiplicity); [***]$P < .001$ vs PBO (adjusted for multiplicity). Boolean remission was defined as SJC (based on 28 joints) ≤1, TJC (based on 28 joints) ≤1, CRP ≤1 mg/dL, and patient's global assessment of disease activity ≤10 mm (range: 0-100 mm). CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score in 28 joints using CRP; NRI, non-responder imputation; PBO, placebo; QD, once daily; SJC, swollen joint count; TJC, tender joint count; UPA, upadacitinib

to the elevation of CPK. Through week 12, hematology variables (hemoglobin, hematocrit, lymphocytes, neutrophils, and platelets) were generally within the normal range at baseline and at all visits for both treatment groups. Grade 3 and Grade 4 decreases in hematology values were generally infrequent and similar in both treatment groups. Grade 3 decreases in lymphocytes, from baseline through week 12, occurred frequently during the study, but were comparable between UPA 15 mg (16 patients [9.6%]) and PBO (17 patients [10.2%]) groups (Table S5). One patient in the PBO group experienced an event of drug-induced liver injury and met Hy's law criteria. The patient was taking isoniazid as a prophylactic treatment for latent tuberculosis identified at screening, and the event resolved on day 45 after both isoniazid and study drug (PBO) were permanently discontinued.

3.4 | Pharmacokinetics

Within 24 hours of dosing, UPA mean plasma concentrations ranged from 58.7 ng/mL (around the peak time) to 6.1 ng/mL (close to the trough time) in patients in the UPA 15 mg group. These concentrations were consistent with the predicted concentrations based on prior pharmacokinetic evaluations of UPA.[28,29]

4 | DISCUSSION

This study was the first to assess the efficacy and safety of UPA 15 mg in combination with csDMARDs in patients from China, Brazil, and South Korea with moderately to severely active RA and an IR to csDMARDs. The primary endpoint was met in this study, with a significantly greater proportion of patients who received UPA 15 mg achieving an ACR20 response at week 12 compared with those receiving PBO. All ranked key secondary endpoints (change from baseline in DAS28-CRP, HAQ-DI, SF-36 PCS, LDA based on DAS28-CRP, CR based on DAS28-CRP, and LDA based on CDAI) showed a similar, clinically meaningful, and statistically significant improvement in patients receiving UPA 15 mg compared with patients receiving PBO. The efficacy results of this study were comparable with those of the

TABLE 3 Treatment-emergent AEs through week 12

Event, n (%)	PBO+ csDMARDs (n = 169)	UPA 15 mg QD +csDMARDs (n = 169)
Any AE	83 (49.1)	104 (61.5)
Any SAE[b]	5 (3.0)	12 (7.1)
Any AE leading to discontinuation of study drug	5 (3.0)	8 (4.7)
Deaths[c]	0	0
AESI		
Serious infection[d]	1 (0.6)	4 (2.4)
Opportunistic infection	0	2 (1.2)
Latent/active tuberculosis	0	0
HZ	1 (0.6)	3 (1.8)
Hepatic disorder	12 (7.1)[a]	16 (9.5)
Gastrointestinal perforation	0	0
Renal dysfunction	0	0
Any malignancy, excluding NMSC	0	1 (0.6)
NMSC	0	0
MACE, adjudicated[e]	0	0
VTE, adjudicated[f]	0	1 (0.6)
Anemia	4 (2.4)	5 (3.0)
Neutropenia	0	5 (3.0)[b]
Lymphopenia	2 (1.2)	1 (0.6)
CPK elevation	1 (0.6)	3 (1.8)[c]

Abbreviations: AE, adverse event; AESI, AE of special interest; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; HZ, herpes zoster; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; QD, once daily; SAE, serious AE; UPA, upadacitinib; VTE, venous thromboembolism.

[a]SAEs were reported in no more than 1 patient in any treatment group, with the exception of pneumonia and tendon rupture.

[b]Including non-treatment-emergent deaths.

[c]Includes 4 cases of pneumonia (UPA: 3, PBO: 1). Also includes 1 case of HZ infection in the UPA group (also counted under HZ); the patient subsequently discontinued treatment.

[d]Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

[e]Including DVT and pulmonary embolism; VTE observed in a patient with a history of DVT.

[f]One patient on PBO experienced an event of drug-induced liver injury and met Hy's law criteria.

[g]Only Grade 1 or 2 decreases in neutrophil levels.

[h]Grade 3 increases in CPK observed in 2 patients; neither had rhabdomyolysis.

SELECT-NEXT study, which assessed the efficacy and safety of UPA in a global population of patients with RA and an IR to csDMARDs.[22] In this study, similar to SELECT-NEXT and SELECT-COMPARE, all patients were on background csDMARDs for at least 3 months, and at least 4 weeks on stable doses prior to the first dose of study drug. In line with SELECT-NEXT and SELECT-COMPARE no changes in background treatment of concomitant csDMARDs were allowed during the double-blind period of the study.

Treatment targets of LDA and CR are recommended by treat-to-target guidelines[4,5] and, in this study, more than one-third of patients who received UPA 15 mg met LDA criteria as defined by DAS28-CRP ≤3.2 and CDAI ≤10 after 12 weeks. Treatment with UPA 15 mg also improved the proportion of patients achieving stringent response criteria such as DAS28-CRP <2.6, CDAI ≤2.8, and Boolean remission. RA has diverse detrimental effects on patients' physical and mental well-being,[30,31] and LDA and remission are associated with improvements in health-related quality of life and physical function.[32] In this study, improvements in physical function, as shown by patient-reported outcomes including HAQ-DI and SF-36 PCS, were significantly greater in patients receiving UPA 15 mg compared with patients receiving PBO. The safety profile of this study is generally comparable with that of global studies, with no new safety signals observed in the Chinese, Brazilian, and South Korean population.[22,23]

UPA 15 mg was generally well tolerated, although the proportion of patients with TEAEs, SAEs, and TEAEs leading to discontinuation

of study drug was numerically higher in patients receiving UPA 15 mg compared with patients receiving PBO. The frequency of AESIs experienced by patients receiving UPA 15 mg through week 12 was generally similar compared with patients receiving PBO, except for serious infection, HZ, hepatic disorder, neutropenia, and CPK elevation, which were reported in a higher proportion of patients receiving UPA 15 mg. These events have also been reported in global phase III trials of UPA.[22,24,26]

This study has some limitations. The majority of patients were Chinese, so conclusions for patients from Brazil and South Korea may be limited. Structural damage was not assessed, therefore it was not possible to evaluate radiographic inhibition in response to UPA, as has been demonstrated in global studies.[23,26] Also, 12 weeks is a short period of time for safety analysis; the ongoing 52-week open-label extension will provide a more comprehensive report on safety.

In summary, UPA 15 mg in combination with csDMARDs demonstrated clinical and functional improvement and an acceptable safety profile among patients from China, Brazil, and South Korea who had moderately to severely active RA and an IR to csDMARDs. The benefit–risk profile of UPA 15 mg, based on efficacy and safety, was favorable in this patient population and was comparable with other studies in the UPA global phase III program.[22-26]

ACKNOWLEDGMENTS

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Laura Chalmers, PhD, of 2 the Nth (Cheshire, UK), and was funded by AbbVie.

CONFLICT OF INTEREST

SM is an employee of AbbVie Deutschland GmbH & Co. KG, and JE, M-EM, and YS are employees of AbbVie Inc and may own stock or stock options. The other authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. XZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: CKL, SM, JE, YS, M-EM; acquisition of the data: XZ, DZ, SR, MK, CKL, WP; analysis and interpretation of the data: XZ, DZ, SR, MK, CKL, SM, JE, YS, M-EM, WP.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and triallevel data (analysis datasets), as well as other information (eg protocols and Clinical Study Reports), provided the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

REFERENCES

1. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med*. 2008;121(10 Suppl 1):S9-14.
2. Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford)*. 2007;46(2):350-357.
3. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. *Lancet*. 2017;389(10086):2338-2348.
4. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-699.
6. Geiler J, Buch M, McDermott MF. Anti-TNF treatment in rheumatoid arthritis. *Curr Pharm Des*. 2011;17(29):3141-3154.
7. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum*. 2008;58(10):2968-2980.
8. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. *Ann Rheum Dis*. 2009;68(2):216-221.
9. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med*. 2003;349(20):1907-1915.
10. Burmester GR, Feist E, Dörner T. Emerging cell and cytokine targets in rheumatoid arthritis. *Nat Rev Rheumatol*. 2014;10(2):77-88.
11. Emery P. Why is there persistent disease despite biologic therapy? Importance of early intervention. *Arthritis Res Ther*. 2014;16(3):115.
12. Meier FM, McInnes IB. Small-molecule therapeutics in rheumatoid arthritis: scientific rationale, efficacy and safety. *Best Pract Res Clin Rheumatol*. 2014;28(4):605-624.
13. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med*. 2015;66:311-328.
14. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs*. 2017;77(5):521-546.
15. Cheung TT, McInnes IB. Future therapeutic targets in rheumatoid arthritis? *Semin Immunopathol*. 2017;39(4):487-500.
16. Iwata S, Tanaka Y. Progress in understanding the safety and efficacy of Janus kinase inhibitors for treatment of rheumatoid arthritis. *Expert Rev Clin Immunol*. 2016;12(10):1047-1057.

17. Vaddi K, Luchi M. JAK inhibition for the treatment of rheumatoid arthritis: a new era in oral DMARD therapy. *Expert Opin Investig Drugs*. 2012;21(7):961-973.
18. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol*. 2018;2:23.
19. PharmaShots. AbbVie's Rinvoq (upadacitinib) receives ANVISA's approval for rheumatoid arthritis. 2020. Available from: https://pharmashotscom/27015/abbvies-rinvoq-upadacitinib-receives-anvisas-approval-for-rheumatoid-arthritis/. Accessed February 8, 2021
20. Korea Biomedical Review. Rinvoq joins competition among JAK inhibitors. 2020. Available from: https://wwwkoreabiomedcom/news/articleViewhtml?idxno=8429#:~:text=SNS%20%EA%B8%B0%EC%82%AC%EB%B3%B4%EB%82%B4%EA%B8%B0&text=AbbVie%20Korea%20has%20obtained%20approval,Janus%20kinase%20(JAK)%20inhibitors. Accessed February 8, 2021.
21. Tanaka Y. A review of upadacitinib in rheumatoid arthritis. *Mod Rheumatol*. 2020;30(5):779-787.
22. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391(10139):2503-2512.
23. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind. Randomized controlled trial. *Arthritis Rheumatol*. 2019;71(11):1788-1800.
24. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391(10139):2513-2524.
25. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393(10188):2303-2311.
26. van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naïve patients with moderately to severely active rheumatoid arthritis (SELECT-EARLY): a randomized, double-blind, active-comparator, multi-center, multi-country trial. *Arthritis Rheumatol*. 2020;72(10):1607-1620.
27. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581.
28. Klünder B, Mittapalli RK, Mohamed MF, Friedel A, Noertersheuser P, Othman AA. Population pharmacokinetics of upadacitinib using the immediate-release and extended-release formulations in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I-III clinical trials. *Clin Pharmacokinet*. 2019;58(8):1045-1058.
29. Klünder B, Mohamed MF, Othman AA. Population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I and II clinical trials. *Clin Pharmacokinet*. 2018;57(8):977-988.
30. Kojima M, Kojima T, Ishiguro N, et al. Psychosocial factors, disease status, and quality of life in patients with rheumatoid arthritis. *J Psychosom Res*. 2009;67(5):425-431.
31. Matcham F, Scott IC, Rayner L, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2014;44(2):123-130.
32. Ishiguro N, Dougados M, Cai Z, et al. Relationship between disease activity and patient-reported outcomes in rheumatoid arthritis: Post hoc analyses of overall and Japanese results from two phase 3 clinical trials. *Mod Rheumatol*. 2018;28(6):950-959.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Zeng X, Zhao D, Radominski SC, et al. Upadacitinib in patients from China, Brazil, and South Korea with rheumatoid arthritis and an inadequate response to conventional therapy. *Int J Rheum Dis*. 2021;24:1530–1539. https://doi.org/10.1111/1756-185X.14235

Received: 25 August 2021 | Accepted: 28 August 2021

DOI: 10.1111/1756-185X.14215

International Journal of Rheumatic Diseases WILEY

COCHRANE CORNER

Which interventions are effective for cutaneous disease in systemic lupus erythematosus? A Cochrane Review summary with commentary

Alessandro de Sire

Physical and Rehabilitative Medicine Unit, Department of Medical and Surgical Sciences, University of Catanzaro, Catanzaro, Italy

Correspondence
Alessandro de Sire, Associate Professor of Physical and Rehabilitative Medicine, Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy.
Email: alessandro.desire@unicz.it

Keywords: chloroquine, Cochrane Review summary, hydroxychloroquine, lupus erythematosus, systemic, rheumatic diseases, skin

Cochrane Rehabilitation

http://rehabilitation.cochrane.org

The aim of this commentary is to discuss the published Cochrane Review "Interventions for cutaneous disease in systemic lupus erythematosus"[1] by Hannon CW, McCourt C, Lima HC, Chen S, Bennett C,[a] under the direct supervision of the Cochrane Skin Group. This Cochrane Corner is produced in agreement with *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

1 | BACKGROUND

Lupus erythematosus is an autoimmune disease, affecting multiple organ systems (ie brain, heart, kidneys, lungs, joints, liver, blood, eyes, and skin), with a high morbidity and mortality.[2] Many clinical variants are grouped under the name "lupus erythematosus".[3] Frequent variants are systemic lupus erythematosus (SLE), diagnosed through standard criteria,[4] as established by the American College of Rheumatology (ACR)[5] or by the Systemic Lupus International Collaborating Clinics (SLICC),[6] and cutaneous lupus erythematosus (CLE), characterized by skin symptoms.[1] Of the estimated 7.5 million people with SLE in the world, 70% are believed to have at least one skin symptom at some point in their disease.[7] It has been shown that skin is second only to joints as the most affected organ system in patients with SLE.[8] It has been shown that quality of life is significantly impaired in patients with CLE.[9] A wide variety of interventions are available for cutaneous disease in SLE, including pharmacological agents and complementary and alternative therapies, as well as other interventions.

2 | INTERVENTIONS FOR CUTANEOUS DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS

(Hannon CW, McCourt C, Lima HC, Chen S, Bennett C, 2021)[1]

2.1 | What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to assess the effects of interventions for cutaneous disease in SLE.

2.2 | What was studied in the Cochrane Review?

The population addressed in this review were patients diagnosed with CLE and who at the same time meet full ACR criteria for SLE, as well as patients with child-onset lupus who meet ACR (or other)

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2021, Issue 3, Art. No.:CD007478. DOI: 10.1002/14651858.CD007478.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.

The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

criteria and have at least 1 skin symptom. The interventions studied were: interventions compared to placebo; trials between different interventions; interventions versus no treatment trials; multi-arm trials including those with factorial designs; trials with different doses of the same intervention; cross-over studies, and trials of split-body-part design with multiple interventions for each participant. The outcomes studied were: (a) complete clinical response, defined as the percentage of participants with SLE with complete resolution of cutaneous disease based on the Gilliam classification (lupus-specific or lupus-non-specific); (b) partial clinical response, defined as the percentage of participants with SLE with at least 50% improvement in cutaneous disease; (c) reduction in the number of SLE participants with clinical flares in cutaneous disease; (d) increase in time-to-flare in cutaneous disease in SLE participants; (e) relapse rate in cutaneous disease when medications are stopped or reduced; (f) skin-specific measures of SLE disease activity (Cutaneous Lupus Disease Area and Severity Index [CLASI], integument domain of the Systemic Lupus Activity Measurement [SLAM], mucocutaneous domains of the British Isles Lupus Assessment Group [BILAG], the Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] and the SLE Responder Index [SRI]); (g) Dermatology Quality-of-Life Measures (DLQI) in SLE patients. Authors measured outcomes from the start of treatment in the short term (less than 12 months) and over the long term (12 months or greater).

2.3 | What was the search methodology and search date of the Cochrane Review?

The review authors searched for studies that had been published up to June 27, 2019 on MEDLINE, Embase, CENTRAL, Cochrane Library, Wiley Interscience Online Library, LILACS, ClinicalTrials.gov, and International Standard Randomized Controlled Trials Number (ISRCTN) Registry.

2.4 | What are the main results of the Cochrane Review?

The review included 61 randomized controlled trials (RCTs) comprising a total of 11 232 participants, who ranged in age from younger than 18 years to 80 years. The mean or median age for study participants was between 10-20 years in 1 study, between 20 and 30 years in 3 studies, between 30 and 40 years in 20 studies, and between 40 and 50 years in 21 studies. However, some RCTs did not report mean or median age of the participants. The RCTs included in the Cochrane Review defined 3 categories of patients based on severity of CLE in SLE: mild (3 studies), moderate (13 studies), and severe (8 studies). A total of 43 pharmacological interventions were identified (20 different classes of interventions) for cutaneous disease in SLE: 1 antibiotic, 2 antimalarials, 4 biologic therapies, 1 oral calcineurin inhibitor, 1 topical calcineurin inhibitor, 2 oral calcium channel blockers, 1 cover-up make-up, 1 cereblon inhibitor, 2 chemotherapy agents, 2 systemic corticosteroids, 1 topical steroid, 2 hormonal therapies, 5 immunomodulatory agents, 1 oral Janus-activated kinase (JAK) inhibitor, 1 topical JAK inhibitor, 1 light therapy, 1 leukotriene synthesis inhibitor, 10 monoclonal antibiotics, 3 oral supplements, and 2 traditional Chinese medicines. However, the treatment duration for the different studies was very heterogeneous, ranging from 1 week to 24 months (ie 1 week, 3 weeks, 1 month, 6 weeks, 9 weeks, 2 months, 3 months, 4 months, 4 and one-half months, 6 months, 9 months, 10 months, 12 months, 18 months, and 24 months).

The review shows the following.

- *Complete clinical response*Studies comparing oral hydroxychloroquine against placebo did not report complete clinical response.

Chloroquine may increase complete clinical response at 12 months follow-up compared with placebo (absence of skin lesions) (risk ratio [RR] 1.57, 95% confidence interval [CI] 0.95-2.61; 1 study, 24 participants; low-quality evidence).

There may be little to no difference between methotrexate and chloroquine in complete clinical response (skin rash resolution) at 6 months follow-up (RR 1.13, 95% CI 0.84-1.50; 1 study, 25 participants; low-quality evidence).

Methotrexate may be superior to placebo regarding complete clinical response (absence of malar/discoid rash) at 6 months follow-up (RR 3.57, 95% CI 1.63-7.84; 1 study, 41 participants; low-quality evidence).

At 12 months follow-up, there may be little to no difference between azathioprine and cyclosporin in complete clinical response (malar rash resolution) (RR 0.83, 95% CI 0.46-1.52; 1 study, 89 participants; low-quality evidence).

- *Partial clinical response*Partial clinical response was reported for only 1 key comparison: hydroxychloroquine may increase partial clinical response at 12 months compared to placebo, but the 95% CI indicates that hydroxychloroquine may make no difference or may decrease response (RR 7.00, 95% CI 0.41-120.16; 20 pregnant participants, 1 trial; low-quality evidence).
- *Clinical flares*Clinical flares were reported for only 2 key comparisons. At 6 months follow-up, hydroxychloroquine is probably superior to placebo for reducing clinical flares (RR 0.49, 95% CI 0.28-0.89; 1 study, 47 participants; moderate-quality evidence). At 12 months follow-up, there may be no difference between methotrexate and placebo, but the 95% CI indicates there may be more or fewer flares with methotrexate (RR 0.77, 95% CI 0.32-1.83; 1 study, 86 participants; moderate-quality evidence).
- *Adverse events*Data for adverse events were limited and were inconsistently reported, but hydroxychloroquine, chloroquine, and methotrexate have well-documented adverse effects including gastrointestinal symptoms, liver problems, and retinopathy for hydroxychloroquine and chloroquine, and teratogenicity during pregnancy for methotrexate.

2.5 | What did the authors conclude?

The authors concluded that evidence supported the commonly used treatment hydroxychloroquine, and there is also evidence supporting

chloroquine and methotrexate for treating cutaneous disease in SLE. Evidence is limited due to the small number of studies reporting key outcomes. Evidence for most key outcomes was of low or moderate quality, meaning findings should be interpreted with caution. Head-to-head intervention trials designed to detect differences in efficacy between treatments for specific CLE subtypes are needed. Thirteen further trials are awaiting classification and have not yet been incorporated into this review; they may alter the review conclusions.

3 | WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN RHEUMATOLOGY?

Clinicians should use caution in translating the findings of this review into clinical practice.[1] Available evidence consists mainly of small RCTs for many of the interventions, resulting in imprecision and considerable uncertainty. In this systematic review[1] there is only limited-quality evidence; authors were unable to draw firm conclusions regarding the effects of interventions for cutaneous disease in SLE. The included studies assessed a range of interventions, and there were a few opportunities to combine results in meta-analyses.

It was not possible to compare the statistical consistency or inconsistency of most results at this time due to the small number of studies, with only 1 study found for most interventions. Comparisons between studies were difficult to conduct due to differences in the timing of outcome assessments, clinical heterogeneity in skin outcomes reported (types of primary vs secondary outcomes), differences in the clinical populations studied (eg differences in disease severity and burden, possible recalcitrant disease), and differences among clinical cutaneous subgroups noted in each study (lupus-specific vs lupus-nonspecific).

Key interventions with potential benefit compared with placebo derived from low- to moderate-quality quantitative evidence were methotrexate, dehydroepiandrosterone (DHEA), and chloroquine (complete clinical clearance), and hydroxychloroquine (clinical flare).

Of note, this review did not explore the best treatment for CLE in patients without sufficient systemic symptoms to make a diagnosis of SLE.[10]

Furthermore, it should be noticed that patients affected by SLE might be of rehabilitative interest, considering that disease duration and organ damage could be considered as indicators of low physical capacity.[9] Thus, it is important to address these aspects to increase physical capacity in the management of subjects with SLE.

The systematic review[1] summarized in the present Cochrane Corner highlighted that most RCTs for SLE patients did not report skin-specific outcomes. Researchers are encouraged to collect and report skin-specific outcomes given the importance of such information to patients and clinicians. Studies have shown that skin disease is more important to participants than internal organ damage.[7]

Taken together, evidence supports the use of hydroxychloroquine, chloroquine, and methotrexate for the treatment of cutaneous disease in SLE. However, there are still 13 trials awaiting classification that have not yet been incorporated into the systematic review.[1] When incorporated, these trials may potentially alter future conclusions.

ACKNOWLEDGEMENTS

The author thanks Cochrane Rehabilitation and Cochrane Skin Group for reviewing the contents of the Cochrane Corner.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. Hannon CW, McCourt C, Lima HC, Chen S, Bennett C. Interventions for cutaneous disease in systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2021;3(3):CD007478. https://doi.org/10.1002/14651858.CD007478.pub2
2. Wallace D, Hahn B. *Dubois' Lupus Erythematosus*, 7th edn. Lippincott Williams Wilkins; 2007.
3. Yazdany J, Dall'Era M. Definition and Classification of Lupus and Lupus Related Disorders. Chapter 2. In: Wallace D, Hahn BH, eds. *Dubois' Lupus Erythematosus. Ninth edition*. Amsterdam, Netherlands: Elsevier Inc, 2019:15-22.
4. Feldman CH, Costenbader KH. Epidemiology and classification of systemic lupus erythematosus. Chapter 133. In: Hochberg MC, Gravallese EM, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH eds. *Rheumatology. Seventh edition*. Elsevier, 2019:1091-1095.
5. Tan EM, Cohen AS, Fries JF, et al. The 1982 Revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25(11):1271-1277.
6. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(8):2677-2686.
7. Tebbe B, Orfanos CE. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. *Lupus*. 1997;6(2):96-104.
8. Vitali C, Doria A, Tincani A, et al. International survey on the management of patients with SLE. I. General data on the participating centers and the results of a questionnaire regarding mucocutaneous involvement. *Clin Exp Rheumatol*. 1996;14(Suppl 16):S17-S22.
9. Castellano-Rioja E, Giménez-Espert MDC, Soto-Rubio A. Lupus erythematosus quality of life questionnaire (LEQoL): development and psychometric properties. *Int J Environ Res Public Health*. 2020;17(22):8642.
10. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745.

Received: 28 September 2021 | Accepted: 18 October 2021

DOI: 10.1111/1756-185X.14234

International Journal of Rheumatic Diseases WILEY

CORRESPONDENCE

Scientific critique on the effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial

Dear Editor,

We read with great interest the article by Yakut et al,[1] which focused on comparing the effects of a supervised exercise program and a home-based exercise program in people with systemic sclerosis (SSc). The study concludes that both exercise programs can improve functional capacity and health status in people with SSc. Nevertheless, we remain sceptical about the validity of this study's conclusions, because of the number of important limitations that this study has.

First, the study is based on an incomplete literature review. Namely, the authors mention that there is "limited evidence of the effectiveness and safety of exercise in people with SSc", and that there is "no study that has examined the effects of supervised exercise on aerobic and resistance training". This is incorrect, as at least our group has published three, open-access papers,[2-4] dated between 2018 and 2020, which establish the feasibility and safety of a supervised exercise program consisting of aerobic and resistance training in people with SSc, papers that also hint at elements of effectiveness as well.

Second, the study's aim remains generic, exploring the effects of exercise through multiple baseline assessments, rather than focusing on the SSc-specific pathology and the pragmatic needs of people with this clinical condition.

Third, the study design itself presents several limitations. (a) The age range is limited to between 35 and 65 years, therefore excluding a significant number of age groups of people with SSc; this raises ethical as well as applicability questions for the current results. (b) The applicability and reliability of the results is challenged further by the absence of a control group. (c) The article notes that the exercise intervention was created based on relevant literature and exercise programs that have been implemented in people with rheumatic and respiratory diseases. However, the included references are not related to any exercise interventions or recommendations of people with rheumatic diseases. We are surprised that your reviewers failed to notice such an important omission. (d) The training intensity, and concomitantly the training dose, both in resistance and aerobic training seems arbitrary with a large deviation of a 30% (eg, 50%-80% of one-repetition maximum; 1RM) and 45% (eg, 40%-85% of heart rate reserve), respectively. This challenges the consistency and replicability of the final outcomes. For example, an individual who would perform a resistance exercise at 50% of 1RM would rest for 2 minutes, questioning the aim, effectiveness, and progression of this resistance protocol, supporting this concern on the basic training principles of resistance training.[5] (e) Another concern is in relation to the assessment of progression to greater resistance levels, which was assessed by the individual's ability to perform 12 or more repetitions. Common good practice suggests that in order to track progression based on the repetition there should be a stable resting period and intensity.[5] This did not happen in this study, as the implemented resistance protocol (50%-80% of 1RM) suggests.

Fourthly, the selection of 20 minutes walking on the treadmill and 10 minutes on the cycle ergometer, totalling 30 minutes of aerobic exercise, has not been substantiated based on physiological responses, disease pathology, and previous literature. The prescribed intensity of 40%-85% indicates that some participants were exercised above the anaerobic threshold (AT) and others were below the AT.[6] Different exercise intensities are associated not only with a shift in blood lactate responses but also with changes in ventilation, oxygen uptake kinetics, and catecholamine responses. For example, constant-intensity exercise within the AT is characterized by a continuous increase in ventilation and V_{O_2}, progressive acidosis, and metabolite accumulation, whereas constant-intensity exercise equal to or below the AT is associated with a physiological steady state. Apparently, the physiological responses varied widely between participants, questioning the applicability and replicability of the current results in this clinical condition.

Finally, the current study concludes that the supervised exercise training is superior to a home-based exercise programme; nevertheless, these two exercise programmes cannot be balanced (eg, intensity, modality) and therefore are not comparable.

To summarize, the current study: (a) has not included recent literature, (b) lacks a clear rationale of specific outcomes, (c) excludes important (for this condition) age groups, (d) does not have a control group, (e) lacks a specific, training dose that could be replicated, and (f) implements exercise programmes that are not comparable concerning the effects of exercise in people with SSc. Therefore, although we encourage future research clinical trials exploring the effects of exercise in people with SSc, aiming to improve their

health-related quality of life, we would like to express our concerns on the conclusions, applicability, and replicability of the current study's results.

Alexandros Mitropoulos
Markos Klonizakis

Lifestyle, Exercise and Nutrition Improvement (LENI) Research Group, Department of Nursing and Midwifery, College of Health Wellbeing and Life Science, Sheffield Hallam University, Sheffield, UK

Correspondence
Alexandros Mitropoulos, Lifestyle, Exercise and Nutrition Improvement (LENI) Research Group, Department of Nursing and Midwifery, College of Health Wellbeing and Life Science, Sheffield Hallam University, Sheffield, UK.
Email: alexandros.mitropoulos@shu.ac.uk

ORCID

Alexandros Mitropoulos https://orcid.org/0000-0002-9453-0808

REFERENCES

1. Yakut H, Özalevli S, Aktan R, Özgen Alpaydın A, Merih Birlik A, Can G. Effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial. *Int J Rheumatic Dis*. 2021;24(9):1200-1212.
2. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. Exploring the feasibility of an exercise programme including aerobic and resistance training in people with limited cutaneous systemic sclerosis. *Clin Rheumatol*. 2020;39(6):1889-1898.
3. Mitropoulos A, Gumber A, Akil M, Klonizakis M. Exploring the microcirculatory effects of an exercise programme including aerobic and resistance training in people with limited cutaneous systemic sclerosis. *Microvasc Res*. 2019;125:103887.
4. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. The effects of upper and lower limb exercise on the microvascular reactivity in limited cutaneous systemic sclerosis patients. *Arthritis Res Ther*. 2018;20(1):112.
5. Fleck SJ, Kraemer WJ. Resistance training: Basic principles (part 1 of 4). *Phys Sportsmed*. 1988;16(3):160-171.
6. Mann T, Lamberts RP, Lambert MI. Methods of prescribing relative exercise intensity: Physiological and practical considerations. *Sports Med*. 2013;43(7):613-625.

Received: 20 October 2021 | Accepted: 20 October 2021

DOI: 10.1111/1756-185X.14233

International Journal of Rheumatic Diseases WILEY

CORRESPONDENCE

Response to "Scientific critique on the effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial"

Dear Editor,

We thank Mitropoulos et al for their interest and commentary on our research.

While they advise the statement "(that there is) no study that have examined the effects of supervised exercise on aerobic and resistance training" is incorrect based on their publications – that is not what we wrote. They have overlooked "breathing exercises" and changed the meaning of our sentence which read "However, there has been no studies investigating the role of a supervised exercise program consisting of breathing exercises, aerobic and resistance training in SSc."[1] One of the strengths of our study was the use of a supervised exercise program that included breathing exercises as well as aerobic and resistance exercises to investigate the impact of these on pulmonary functions and respiratory muscle strength. A 2019 systematic review that included Mitropoulos et al's studies[2,3] concluded that, "the evidence on the effect and safety of exercise therapy in SSc is scanty."[4] This was the basis of the statement "However, the strength of evidence regarding the efficacy of exercise intervention in the rehabilitation of SSc is restricted" based on the literature in our study. As seen, the sentence in our article has been supported by the literature. We also suggest that 3 studies is insufficient to establish a treatment evidence base and that scientific studies are still needed in this area.

SSc is a multisystem disease with multidimensional impact on a person's physical and mental health, and their interaction with family and society, and our aims reflected this. The results of our study demonstrated the effect of supervised and home-based exercise programs on the disease-related symptoms, pulmonary function, respiratory-peripheral muscle strength, functional capacity and health-related life quality with both objective and subjective outcomes. In doing so our study focuses "on the SSc-specific pathology and the pragmatic needs of people with this clinical condition."

Our age range of 35-65 years reflects the onset of the SSc disease occurring between the ages of 30-50 with an incidence that generally increases in the 5th decade, and is similar to the age range used by other authors.[5] Our study also used evaluations in which age could be a confounding factor such as pulmonary function tests and functional capacity. Thus, we think that these current results do not create ethical and applicability problems.

We did not think it ethical to include a 3rd control group that did not receive any rehabilitation-type intervention and addressed this in our discussion of study limitations and implications for future research.

Mitropoulos et al question the literature on which our exercise intervention was based. The reference on exercise intervention or advice for people with rheumatic diseases was reference 11;[6] however, we neglected to cite this article again in this section.

The training intensity used in our study follows the American College of Sports Medicine (ACSM)'s exercise prescription guide.[7] In the stated guideline, 40%-89% heart rate reserve for aerobic exercises is specified as moderate to vigorous/(submaximal) intensity and 50%-84% one repetition maximum for resistance training is specified as moderate to vigorous/(submaximal) intensity.[7] For this reason, the intensity range of the exercise programs in our study was not "arbitrary" as the correspondent stated. Our study included patients of varied age, with and without lung involvement, and for this reason exercise intensity was kept in a wide range. The most basic principle of exercise is that the exercise prescription should be prepared specifically for the individual. For example, given that the heart rate reserve of a 35-year-old patient and 65-year-old patient will not be the same, the exercise intensities given are applicable and explainable. The same applies for patients with and without lung involvement, such as pulmonary arterial hypertension (PAH) or interstitial lung disease (ILD).

In the exercise prescription guide, 2-3 minutes rest intervals are indicated as effective for achieving desired increases in muscle strength and hypertrophy. In addition, it is recommended to increase the intensity from mild to moderate or moderate to high intensity according to the initial physical fitness and comorbidity status of the individuals. For strength gain, it is recommended to do 8-12 repetitions per set without creating fatigue. It is recommended to increase the intensity of the exercise when the patients can perform 12 or more repetitions without fatigue.[7] In line with the recommendations of the guidelines, we prepared the resistant training program considering the initial physical fitness status of the patients and the presence of comorbidities such as PAH and ILD. In addition, there were stable rest intervals in our study. However, the progression was achieved by increasing the intensity of exercise.

de Oliveira et al in their review state that patients with SSc without pulmonary involvement can do at least moderate-intensity aerobic exercises and benefit from it, and should be as physically active as the general population. They also stated that patients with mild pulmonary involvement should be physically active by doing moderate-intensity exercises and participate in moderate weight resistance exercises.[6] The ACSM's exercise prescription recommends 30-60 minutes of purposeful moderate exercise or 20-60 minutes of vigorous exercise or a combination of moderate and vigorous exercise for aerobic exercise.[7] Based on the recommendations of both articles, we applied aerobic exercises consisting of bicycle ergometer and treadmill for approximately 30 minutes in our study. As the patients adjusted, we increased the exercise intensity according to the heart rate reserve.

In our critique of our study, we noted that cardiopulmonary exercise test was not undertaken and that this limited the demonstration of the effects of exercise on the cellular level in patients with SSc. Future research and inclusion of such methodology may clarify whether the suggested observations of Mitropoulos et al are replicated with this exercise program.

Finally, a PubMed search of "supervised exercise program versus home-based exercise program" identifies approximately 140 publications. To the best of our knowledge, our study is the first to comprehensively compare a supervised exercise program and a home-based exercise program in SSc, although this type of study has been done extensively in many different patient groups such as ankylosing spondylitis, intermittent claudication, subacromial impingement syndrome, heart failure, chronic obstructive pulmonary disease and knee arthroplasty. In our study, we revealed the effect of both exercise programs on functional capacity, pulmonary function, diffusion capacity, respiratory muscle strength, dyspnea severity, peripheral muscle strength, health-related quality of life and fatigue level. In our results, we stated that both supervised and home-based exercise programs are beneficial, overall resulting in improved functional capacity, respiratory muscle strength, knee extension muscle strength, disease-specific and general health-related quality of life and fatigue level. We also stated that in addition to these effects, a supervised exercise program provides significant improvements in respiratory functions, dyspnea severity and hand grip strength. In addition, as the most important outcome, we suggested that both exercise programs should be added to the routine treatment in SSc in order to maintain functional independence. We did not claim that the content of both exercise programs is balanced. However, this does not preclude their comparison. In many countries, clinical environments and conditions in which supervised exercise programs can be implemented are insufficient. In addition, patient and system-related problems such as dislike for group-based classes, demands for returning to work, lack of exercise programs, transportation, poor motivation and lack of time are among the situations that make it difficult to implement supervised exercise programs. Therefore, it is important to know the effect and applicability of home-based exercises at this point. Thus, our study is of great importance as it shows that home-based exercises are safe and effective alternative interventions for SSc patients who cannot access supervised or hospital-based exercise programs. Therefore, we think that the aim and results of our study were not well understood by the correspondent. As a result, we would like to reiterate a sentence from our article: "In this context, the results obtained from our study can guide studies that include supervised and home exercise programs in SSc patients to create a standard physiotherapy program. However, there is a need for more RCTs (randomized controlled trials) including exercise interventions."

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Hazal Yakut[1]
Sevgi Özalevli[2]

[1]*Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Eskişehir Osmangazi University, Eskişehir, Turkey*
[2]*School of Physical Therapy and Rehabilitation, Dokuz Eylul University, Izmir, Turkey*

Correspondence
Hazal Yakut, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Eskişehir Osmangazi University, 26040 Odunpazarı/Eskişehir, Turkey.
Email: fzthazalyakut@outlook.com

ORCID

Hazal Yakut https://orcid.org/0000-0003-4918-9249

REFERENCES

1. Yakut H, Özalevli S, Aktan R, Özgen Alpaydın A, Merih Birlik A, Can G. Effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial. *Int J Rheum Dis*. 2021;24(9):1200-1212.
2. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. Investigating the effectiveness and feasibility of exercise on microvascular reactivity and quality of life in systemic sclerosis patients: study protocol for a feasibility study. *Trials*. 2018;19:647.
3. Mitropoulos A, Gumber A, Akil M, Klonizakis M. Exploring the microcirculatory effects of an exercise programme including aerobic and resistance training in people with limited cutaneous systemic sclerosis. *Microvascular Res*. 2019;125:103887.
4. Liem SIE, Vliet Vlieland TPM, Schoones JW, de Vries-Bouwstra JK. The effect and safety of exercise therapy in patients with systemic sclerosis: a systematic review. *Rheumatol Adv Pract*. 2019;3(2):rkz044.
5. Oliveira NC, dos Santos Sabbag LM, de Sá Pinto AL, Borges CL, Lima FR. Aerobic exercise is safe and effective in systemic sclerosis. *Int J Sports Med*. 2009;30(10):728-732.
6. de Oliveira NC, Portes LA, Pettersson H, Alexanderson H, Boström C. Aerobic and resistance exercise in systemic sclerosis: State of the art. *Musculoskelet Care*. 2017;15(4):316-323.
7. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334-1359.

DOI: 10.1111/1756-185X.14192

International Journal of Rheumatic Diseases WILEY

Your help is needed in the fight against COVID-19: Please contribute to the COVID-19 Global rheumatology alliance registry

The COVID-19 Global Rheumatology Alliance is a global collaboration of rheumatologists, scientists, patients and organisations all committed to addressing the issues in rheumatology created by the COVID-19 global pandemic. To date the alliance has published important data on the effect of COVID-19 infection on outcomes and the effect of rheumatic medications on COVID-19 outcomes.

We currently have 3520 cases from all over the world but we still need to collect many more cases and we need cases from all around the world including the Asia-Pacific region. We are hoping for more cases from the Asia-Pacific region because this is currently under-represented in the registry.

To contribute we ask that you provide details of the case, rheumatic diagnosis details, treatments, and the outcome of the case.

You can join the mailing list for the COVID-19 Global Rheumatology Alliance by signing up on our webpage (top right hand corner)

For more information please visit our website at www.rheum-covid.org, if you have questions or issues and would like to know more information please email rheum.covid@gmail.com.