ISSN 1756-1841 VOLUME 24 NUMBER 2 2021

International Journal of Rheumatic Diseases

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

WILEY

International Journal of Rheumatic Diseases

Production Editor

Aishwarya Radhakrishnan (APL@wiley.com)

Editorial Assistant

Lalitha Pari (IJRD.EO@wiley.com)

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

International Journal of Rheumatic Diseases

Volume 24 | Number 2 | February 2021

Contents

Received: 25 October 2020 | Accepted: 28 October 2020

DOI: 10.1111/1756-185X.14029

International Journal of Rheumatic Diseases

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EDITORIAL

Fibromyalgia and psoriatic arthritis: Partners together

Fibromyalgia is a common condition characterized by widespread pain and tenderness, associated with elevated levels of sleep disturbance, fatigue, cognitive dysfunction and background emotional distress.[1] Prevalence rates vary according to classification criteria and range between 2% and 8% in different communities.[1] These rates increase significantly in the context of chronic illness, particularly rheumatic diseases, with the symptoms of fibromyalgia often merging with those of the underlying disease. This creates a higher symptom burden and diminished quality of life for the patient. It also greatly increases difficulties for the clinician in the assessment of response to treatment of both the rheumatic disease and the fibromyalgia.

In this issue of the *Journal* 2 studies address this matter in patients with psoriatic arthritis (PsA), a condition which affects up to 1% of the population.[2-4]

Alsawy et al identified fibromyalgia, using the 2016 modification of the 2010/11 American College of Rheumatology (ACR) criteria,[5] in 38.3% of 60 patients with PsA attending an outpatient department.[2] More PsA fibromyalgia patients were female, and more had symmetrical polyarthritis than those without fibromyalgia. There was no difference between the groups in objective measures of disease activity, such as C-reactive protein, swollen joint count and dactylitis count. However, in the fibromyalgia group there were significant increases in scores that incorporated measurements of pain and tenderness compared to those without fibromyalgia. This included standard instruments to assess PsA "disease activity", including the psoriasis area severity index (PASI), the disease activity in psoriatic arthritis (DAPSA) index, the composite psoriatic disease index (CPDAI), tender joint count, Leeds enthesitis index, and Bath ankylosing spondylitis disease activity scores. Fibromyalgia patients also had higher fatigue and lower quality of life scores. The fibromyalgia severity scale and the fibromyalgia impact questionnaire (FIQ) each correlated with many of the disease assessment and quality of life measures.

Ulutatar et al, using the same criteria,[5] identified fibromyalgia in 64% of 50 consecutively assessed patients with PsA, also more common in females.[3] Those with fibromyalgia had significantly higher enthesopathy scores, FIQ scores, poorer sleep quality, greater fatigue, and lower quality of life. There was a moderate association between FIQ and Disease Activity Score of 28 joints (DAS28), and both enthesopathy scores, and DAS28 contributed to FIQ scores. Thus, measurements assessing fibromyalgia characteristics overlapped with those designed to assess inflammatory-related disease activity. The problem is that "disease activity" instruments incorporate measures that are common to both conditions, particularly pain and tenderness.

Both these studies add to the knowledge of the interaction between fibromyalgia and PsA. Other studies have shown fibromyalgia prevalence rates between 17% and 53.3% in different sub-types of PsA, more common in females, with variation attributed to diagnostic criteria.[6-9] These studies also highlight the disconnect between subjective patient-reported symptoms and objective measures of disease activity, with higher scores in fibromyalgia PsA patients compared to those with PsA alone. In short, PsA patients with fibromyalgia report higher levels of pain, tenderness, fatigue, and cognitive dysfunction and lower quality of life.[6,10]

This may result in a number of outcomes. Enthesitis assessed by tenderness will be overestimated in PsA patients with fibromyalgia.[11] The evaluation of synovitis and dactylitis in PsA, using standard clinical examination techniques, are also subject to the influence of the background allodynia that characterizes fibromyalgia.[12] As a consequence, PsA treatment protocols may be influenced by the presence of the symptoms of fibromyalgia.[10] Patients may be inappropriately treated with disease-modifying drugs when in fact they need pain modulatory drugs and lifestyle advise. As these studies indicate, as FIQ scores increase so do the clinical and functional outcomes worsen.[3]

In each of the above studies the diagnosis of fibromyalgia has been defined as either present of absent. However, fibromyalgia symptoms actually exist on a spectrum and many patients have sub-criteria symptoms that will influence their self-report of pain, fatigue, sleep and cognition.[5] These symptoms contribute to low quality of life and demand attention.

The FIQ captures fibromyalgia-related clinical items relating to everyday function and overall impact, and rates the severity of typical symptoms such as pain, energy, sleep quality, and mood,[13] with memory, tenderness, balance and environmental sensitivity added in the latest iteration.[14] The FIQ thus provides a spectrum of responses that range from mild to severe. Higher scores clearly represent more significant impact and associate with worse function. The FIQ taps into central processes that relate to emotions, distress and non-inflammatory PsA symptoms. The continuous scale derived from the widespread pain index and the symptom severity score of the 2010/2011 ACR criteria,[15] modified in 2016,[5] variously termed polysymptomatic distress scale or central sensitivity score,[16]

also does this. This score acts as both a clinical biomarker to identify central sensitization and also a tool that will predict outcomes to interventions, such as is seen in osteoarthritis (OA)[17] and rheumatoid arthritis (RA).[18] The use of these validated instruments in addition to current PsA assessment tools[19] will aid the clinician in assessing the relative contribution of inflammatory disease activity, joint or soft tissue damage, and fibromyalgia symptoms to the patient's overall quality of life.

Fibromyalgia commonly associates with other inflammatory rheumatic diseases, being identified in around 20%-30% of patients with RA, spondyloarthropathy, systemic lupus erythematosus, and Sjögren's disease.[20-23] It is also similarly associated with a range of other rheumatological, neurological, gastrointestinal, infectious, endocrinological, and other internal diseases.[24,25] It is present in 20%-65% of patients with various other chronic pain conditions and there are increased rates of fibromyalgia in mental health disorders.[24,25] Furthermore, as the number of comorbidities increase so will the rate of fibromyalgia increase.[25]

In each of these diseases/conditions the patient's fibromyalgia-related symptoms may also lead to increased investigations, modification of otherwise effective medication, or increased use of glucocorticoid medication. All of these responses may incur higher cost and morbidity, and yet still not treat the key symptoms affecting the overall quality of life of the patient.

Fibromyalgia has been traditionally considered as a comorbidity when it is present in conjunction with another disease or condition.[24] Another way to look at this association would be to consider fibromyalgia as part of the primary disease or condition, as it is part of the patient's response to a variety of life factors that include the effects of the disease/condition on the patient as a whole. Fibromyalgia is the clinical expression of stress-related neurobiological responses that lead to increased reactivity in a number of sensory neural systems, particularly those in the musculoskeletal system.[26] These systems are variably inbuilt into every person. The mechanism that results in the clinical phenotype labeled as fibromyalgia is present in all of us. Some of us are resilient with few related symptoms, some are more reactive due to genetic factors modifying neural responses, and some become more sensitive after early-life neural sensitization. Others, and perhaps the majority, are responding to the burden of having a chronic illness. This includes the symptoms of the disease, the effect on general health, the need for tests, drugs, and treatments, the disability, loss of quality of life, and modification of social and work roles, among others, as exemplified by PsA.[27] Psychological response to each of these issues can also feed back into the sensitization process.

In order to optimize management and achieve better outcomes, fibromyalgia, as a clinically defined phenotype reflecting activation of inbuilt stress-related neural algorithms,[28] needs to be identified in PsA, as it does in any chronic illness.

Geoffrey Owen Littlejohn

Monash University and Monash Health Rheumatology, Melbourne, Vic., Australia

Correspondence
Geoffrey Owen Littlejohn, Monash Medical Centre, Suite H, Private Consulting Rooms, 246 Clayton Road, Clayton, Vic., Australia.
Email: geoff.littlejohn@monash.edu

ORCID
Geoffrey Owen Littlejohn https://orcid.org/0000-0002-7896-055X

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Received: 29 November 2020 | Revised: 1 December 2020 | Accepted: 7 December 2020

DOI: 10.1111/1756-185X.14048

International Journal of Rheumatic Diseases

WILEY

EDITORIAL

Emerging COVID-19 vaccines: A rheumatology perspective

The coronavirus disease 2019 (COVID-19) pandemic gripped the world unexpectedly and little was known about the virus or its effects on various cohorts of patients. In the first wave, rheumatology patients on immunosuppressive agents were asked to shield or self-isolate because they were deemed highly clinically vulnerable. As evidence emerged, it became apparent that most of our patients were not adversely affected with their disease management and so it gradually returned to normal.[1] Nevertheless, in light of the second wave much uncertainty remains. In this regard, the COVID-19 vaccine is eagerly anticipated to be one of the solutions to the pandemic. Emergence of several potential vaccines has been the topic of discussion in recent weeks. In this Editorial we explore the emerging vaccines and the perception, anxieties, and concerns around them from a rheumatology perspective.

COVID-19 vaccines are being developed by various pharmaceutical companies but there are three that seem to be the most promising. Pfizer/BioNTechs COVID-19 vaccine is an RNA vaccine, which is reported to be 95% effective against COVID-19 and is currently in phase 3 of its trials with over 43 000 participants; 41% of global and 45% of US participants are between 56 and 85 years, and 42% of the overall study population have a diverse ethnic background including Asian, Black, Hispanic, and Native American. Most participants have received a second dose as part of a two-dose regimen, but the details of this regimen have not been released.[2] Moderna, has also developed an RNA-based vaccine, which is up to 94.5% effective when given over two doses on days 1 and 29.[3] The clinical trial cohort includes over 30 000 participants including 7000 over 65 years of age and 5000 participants under 65 years of age with high-risk chronic diseases. AstraZeneca has produced a slightly different COVID-19 vaccine consisting of a viral vector, which is 90% effective when using one of its vaccination regimens consisting of giving a half dose initially then a full dose 1 month later. The trial population is slightly smaller than the others with over 23 000 participants and it is being conducted in the UK, Brazil and South Africa. The cohort consists of participants who are healthy and have medically stable chronic diseases.[4] At the time of writing this editorial (November 2020), the results of the phase 3 trials of these three vaccines are yet to be published and peer-reviewed, therefore available data so far are limited to press-releases.

Efficacy and safety of these emerging vaccines in the rheumatology population are unknown. It is unclear in the trials which chronic disease patient groups were included or if they were on immunosuppressive therapy. Published phase 1/2 trial data included healthy patients between the ages of 18 and 55 years, patient demographics for phase 3 trials have not been released. However, as none of these vaccines are live attenuated it is assumed that they are safe to be taken by patients on immunosuppressive treatment. The main resistance we envisage with some of the rheumatology patients in taking the vaccine is likely to be their perception rather than scientific reasoning. The RNA vaccine is the first of its kind and understandably we are all apprehensive, as little is known about the long-term side effects of this novel vaccine. So far, none of the three pharmaceutical companies has reported any serious short-term adverse effects. The most common side effects have been fatigue and headache, similar to the influenza vaccine.[2,3]

The relationship between vaccination uptake and perception is complex. The measles, mumps, and rubella (MMR) controversy in 1998 demonstrates how MMR vaccine uptake fell in subsequent years and the efforts of health authorities to rebuild public trust. Knowledge is power, and educating parents on the correct information was key after the MMR controversy. Milward describes certain features that affect public perception of health messages, which include the relevance of information to everyday life, its relation to other perceived risks, and the extent to which the source of information is trusted.[5] Information sourced from informal sources on the internet, social media, and print media will have a potential negative impact. Rheumatology patients are eager to have more information regarding the COVID-19 vaccine so that they can make an informed decision about their long-term disease management. Reflecting on times when vaccines have been introduced or publicized, we can appreciate how the distribution of data regarding their safety and use is imperative to enable rational patient decisions. There are other factors that influence patients' health decisions on a personal level, which include cultural norms, and religious, educational, and philosophical views, which can all influence attitudes to vaccinations.[6] Many patients also rely on the advice and opinion of their healthcare professional and so disseminating accurate information is vital.

The concept of vaccination is based on herd immunity where most people in a population have immunity against an infection either directly by previous infection or indirectly via a vaccine to reduce the risk of transmission to those who lack immunity.[7] The proportion of people that need to be vaccinated to achieve herd immunity depends on the infection, for example for measles it is 95%, for polio it is 80%.[8] Nevertheless, it is usually most of the population that needs to be vaccinated to protect those who cannot be

vaccinated. The level to achieve herd immunity against COVID-19 is unknown, but until it is achieved patients must strictly adhere to the advice from the Government to protect themselves and the community. Indeed, one of our main concerns is that rheumatology patients may become complacent after taking the vaccine. Although the full efficacy of the vaccine will only be determined with mass vaccination, it does not necessarily confer complete immunity. It is imperative that we stress to our rheumatology patients that they should continue to take protective measures.

Lockdown, social distancing, and increased hand washing have gone some way in reducing the incidence of the virus below a reproduction rate of 1, but this will not be enough to eliminate the virus. History has demonstrated recurrent epidemic cycles with other contagious infections such as measles, mumps, and smallpox in the pre-vaccine period.[9] It is unknown whether the COVID-19 immunization program will achieve disease elimination or eradication. Elimination is the absence of sustained endemic community transmission in a geographical area and eradication is the reduction of cases to zero globally. Another factor contributing to eradication vs elimination is how long a patient will retain immunogenicity to COVID-19 after the vaccine. There have been a handful of patients globally who seem to have been re-infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after recovering from their first infection and having a negative swab. Gouseff et al highlight 11 patients who had a second episode of COVID-19.[10] The patients are of a variety of ages and some have no co-morbidities, one patient was on rituximab as chemotherapy but there does not seem to be any consistent clinical characteristics. Zhang et al describe two patients who had reduced IgG anti-SARS-CoV-2 antibody before the second re-infection and subsequent increase in titers in the second re-infection, and one patient had reactivity of IgM anti-SARS-CoV-2 antibody [11] . This demonstrates that patients who did not mount a strong response from the first infection are perhaps at increased risk of a second SARS-CoV-2 infection. However, as all the proposed COVID-19 vaccines are two dose regimens the second dose will hopefully cover those patients who did not produce a strong immune response with the first dose.

A concern among clinicians is whether immunosuppressed patients will mount a sufficient immune response to the vaccine. The current vaccines being produced use "next-generation platforms",[12] there are no RNA vaccines currently licensed and the only viral vector vaccine approved is the vesicular stomatitis virus (VSV) -based Ebola vaccine. In the VSV-Ebola vaccine trial a smaller proportion of human immunodeficiency virus (HIV)-positive patients developed an antibody response compared with HIV-negative patients.[13] However, there are few data from practical use because the vaccine was used for "compassionate use", so only a small number of patients who were considered to be high risk were given the vaccine in sub-Saharan Africa. In terms of adverse effects, the main side effects were flu-like symptoms in the first 4 days following vaccination, which is like live virus vaccines. The influenza vaccine is an annual inactivated vaccine recommended to certain groups of vulnerable people including those who are immunocompromised. In the rheumatology population it seems the vaccine mounts a good immune response and reduces the risk of respiratory morbidity and mortality.[14] Apart from live vaccines, all other vaccines are currently safe to use in the rheumatology population and it seems that they mount a sufficient response to provide immunity. This creates an optimistic outlook for the new COVID-19 vaccine and its anticipated therapeutic effect.

The need for revaccination is yet to be determined. The genome of the current SARS-CoV-2 virus strongly resembles its predecessor SARS-CoV, with novel glycosylation sites secondary to antigenic divergence. Therefore, although a vaccine now may confer protection against the current SARS-CoV-2 strain, it begs the question if the vaccine will be effective against evolving genomics in the coming years. There is yet the possibility that because of antigenic drift, further modifications in the vaccine maybe necessary to protect against novel coronaviruses.[15]

The COVID-19 vaccine brings hope to what has seemed quite a bleak and uncertain year. Vaccines provide a long-term solution to the pandemic; however, before we recommend these vaccines to our rheumatology patients, we must have adequate information about their efficacy and safety in the immunosuppressed population. Patients are both eager and anxious to receive the COVID-19 vaccine. Therefore, as healthcare professionals we need to be armed with the correct information before counseling our patients.

KEYWORDS

coronavirus disease 2019, rheumatology, safety, vaccine

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

Swetha Byravan[1]
Armin Fardanesh[2]
Hasan Tahir[2,4]
Arumugam Moorthy[1,3]

[1]*University Hospitals of Leicester NHS Trust, Leicester, UK*
[2]*Royal Free London NHS Foundation Trust, London, UK*
[3]*College of Life Sciences, University of Leicester, Leicester, UK*
[4]*Division of Medicine, University College London, London, UK*

Correspondence
Arumugam Moorthy, University Hospitals of Leicester NHS Trust, Leicester, UK.
Email: arumugam.moorthy@uhl-tr.nhs.uk

ORCID

Swetha Byravan https://orcid.org/0000-0001-7684-7708
Armin Fardanesh https://orcid.org/0000-0003-1076-4592
Hasan Tahir https://orcid.org/0000-0002-2148-736X
Arumugam Moorthy https://orcid.org/0000-0001-5903-1125

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Received: 29 June 2020 | Revised: 19 September 2020 | Accepted: 14 October 2020

DOI: 10.1111/1756-185X.14017

REVIEW

International Journal of Rheumatic Diseases | WILEY

Association of *MBL2* gene polymorphisms and systemic lupus erythematosus susceptibility: A meta-analysis

Zhi-Chao Yuan[1] | Wang-Dong Xu[1] | You-Yu Lan[1] | Jia-Min Wang[1] | Qian Wu[1] | Jie Zhou[1] | An-Fang Huang[2]

[1]Department of Evidence-Based Medicine, School of Public Health, Southwest Medical University, Luzhou, China

[2]Department of Rheumatology and Immunology, Affiliated Hospital of Southwest Medical University, Luzhou, China

Correspondence
Wang-Dong Xu, Department of Evidence-Based Medicine, School of Public Health, Southwest Medical University, 1 Xianglin Road, Luzhou, Sichuan 646 000, China.
Email: loutch123@163.com

An-Fang Huang, Department of Rheumatology and Immunology, Affiliated Hospital of Southwest Medical University, 25 Taiping Road, Luzhou, Sichuan 646000, China.
Email: loutch211@163.com

Funding information
This work was supported by grants from the National Natural Science Foundation of China (81701606), Sichuan Provincial Science and Technology Program (2019YJ0540).

Abstract

Objectives: Mannose binding lectin (MBL) gene single nucleotide polymorphisms have been associated with systemic lupus erythematosus (SLE) risk with inconsistent results. This study aimed to explore whether *MBL2* A\B, A\C, A\D, A\O, L\H and Y\X polymorphisms affected SLE susceptibility.

Methods: A meta-analysis was performed on 20 studies, containing allelic contrast, additive, dominant and recessive models. Odds ratio (OR) was calculated to reflect the effect of association.

Results: A total of 64 pooled comparisons were conducted, including 7194 SLE patients and 7401 healthy controls. The meta-analysis inducted a significant association between allele B and SLE (OR = 0.766, 95% CI = 0.681-0.862, $P < .001$). The genotype BB in the additive model and AB + BB in the recessive model both reduced the risk of SLE (OR = 0.611, 95% CI = 0.422-0.882, $P = .009$; OR = 0.806, 95% CI = 0.688-0.944, $P = .008$). Regarding A\O polymorphisms, results revealed statistical differences in allelic contrast, additive model and recessive models (OR = 0.826, 95% CI = 0.732-0.931, $P = .002$; OR = 0.737, 95% CI = 0.557-0.977, $P = .034$ and OR = 0.793, 95% CI = 0.683-0.921, $P = .002$, respectively). As for L\H, meta-analysis revealed that allele H and genotype HH both decreased SLE susceptibility in allelic contrast and dominant models (OR = 1.463, 95% CI = 1.097-2.007, $P = .018$; OR = 1.383, 95% CI = 1.124-1.701, $P = .002$). Stratification by ethnicity indicated that allele H related to SLE in European populations (OR = 0.736, 95% CI = 0.617-0.879, $P = .001$), and the recessive model correlated with SLE in Asians (OR = 0.808, 95% CI = 0.667-0.979, $P = .03$).

Conclusion: The present study suggests that A\B and A\O polymorphisms were associated with SLE susceptibility, and the allele H may be a protective factor in SLE.

KEYWORDS

mannose binding lectin, meta-analysis, polymorphism, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with high heterogeneity. It is characterized by immunoglobulin G (IgG) auto-antibody production and immune complex formation and deposition, which causes a complex spectrum of clinical and immunologic manifestations. The etiology of SLE is still elusive, which may relate to environmental conditions, hormone levels and genetic factors. A higher concordance rate in monozygotic twins than dizygotic twins and the high sibling recurrence risk ratio indicate there is a strong genetic component in SLE.[1]

Mannose binding lectin (MBL) is an acute-phase protein secreted in the liver. It is composed of 3 identical polypeptides.[2] It is involved in host defense and innate immunity. The polymer form of MBL makes it functionally similar to complement C1q, which participates in complement activation and opsonization of antigens. Studies indicated that low levels of MBL are associated with SLE by down-regulating complement-mediated clearance of immune complexes and macrophages-mediated uptake of apoptotic cells.[3,4] *MBL2* gene is located at chromosome 10 (10q11.2-21) in humans and encodes MBL encompassing 4 exons and 3 introns. Polymorphisms of *MBL2* gene emerged as a candidate for SLE susceptibility because of regulation for MBL secretion. There are 3 functional single nucleotide polymorphisms (SNPs) on the exon 1 at codons 52 (allele C: rs5030737), 54 (allele B: rs1800450) and 57 (allele D: rs1800451), respectively (B, C, D were collectively designated as O allele, whereas A is the common non-mutated allele). In addition, SNP rs11003125 (H/L) at position −550 and rs7096206 (Y/X) at position −221 on the promoter region of the *MBL2* gene were identified. These polymorphic variants, both at the promoter region and the coding region of *MBL2* gene, are associated with MBL deficiency, leading to increased degradation of mutated protein.[5,6] Recently, studies have discussed correlation between these polymorphic variants and SLE susceptibility,[7-9] where the results were not consistent.[10-12] This discrepancy correlates with low statistical power for small sample size and the select bias for racial and ethnic differences. Meta-analysis is a statistical method which increases the sample size by combining relevant literature and thereby reduces the probability of false-positive or false-negative associations due to random errors. In this meta-analysis, we explored whether the *MBL2* gene polymorphisms affect SLE susceptibility.

2 | MATERIALS AND METHODS

2.1 | Identification of eligible studies and data extraction

In November 2019, a comprehensive and detailed literature search was performed in PubMed Medline, Embase, Cochrane Library, Web of Science and Chinese National Knowledge Infrastructure (CNKI) to identify articles. The key words were as follows: "systemic lupus erythematosus", "SLE", "mannose binding lectin", "MBL", "polymorphism". References of available articles were also investigated to seek additional eligible papers. The inclusion criteria were as follows. (a) The study type was case-control or cohort study. (b) The study assessed association between *MBL2* gene polymorphisms and SLE risk. (c) The paper could provide the number of individual alleles or genotypes in cases and controls to calculate odds ratio (OR) and 95% confidence interval (95% CI). (d) The language was limited to English. All the patients included in these studies met the American College of Rheumatology 1997 revised criteria for SLE.[13] The exclusion criteria were as follows. (a) The study was a pedigree research. (b) The articles contained overlapping data. The quality of the original studies was assessed by Newcastle-Ottawa Scale which included 3 parts (selection, comparability, exposure). Each of these parts had questions with options and could gain 1 or 2 points (stars/*) if the criteria were achieved. In the assessment, the studies were segregated into three different grades dependent on the corresponding point score. To be specific, 1-3 points represent low quality, 4-6 points were defined as intermediated quality, and 7-9 points were regarded as high quality (Table S1).

Data were extracted from all qualified literature by two independent investigators with standard protocol and inconsistency was resolved by a third investigator. The following items were extracted from recruited articles: first author, publication year, ethnicity, sample size, allele and genotype number in cases and controls. We finally screened out 20 studies on the association between *MBL2* polymorphisms and susceptibility for SLE (Figure 1). There were 6 gene variants (A\B, A\C, A\D, L\H and Y\X) which were identified and underwent meta-analysis.

2.2 | Meta-analysis methods

The strength of associations between *MBL2* polymorphisms (A\O, A\B\, A\C, A\D, L\H, Y\X) and SLE risk was evaluated by OR with the corresponding 95% CI for allelic contrast (A vs O, A vs B, A vs C, A vs D, L vs H and Y vs X), additive model (AA vs OO, AA vs BB, AA vs

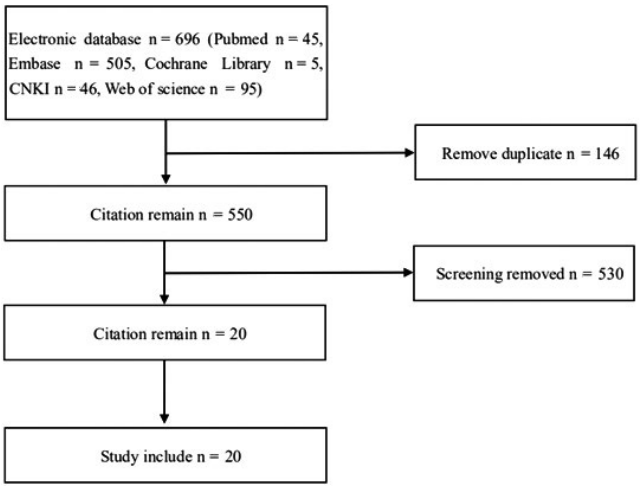

FIGURE 1 Flowchart of the study selection. In total 696 studied were found in electronic databases in the first step of bibliography retrieval. Finally, 20 study were included in the meta-analysis

CC, AA vs DD, LL vs HH and YY vs XX), dominant model (AA + AO vs OO, AA + AB vs BB, AA + AC vs CC, AA + AD vs DD, LL + LH vs HH and YY + YX vs XX) and recessive model (AA vs AO + OO, AA vs AB + BB, AA vs AC + CC, AA vs AD + DD, LL vs LH + HH and YY vs YX + XX). The statistical significance of OR was determined by the Z test. Heterogeneity between studies was assessed by the *P* value from Cochran's Q statistic and the I^2 test.[14,15] Based on the heterogeneity, we executed the meta-analysis in a fixed/random effects model. If $P < .1$ or $I^2 > 50\%$, the random effects model was adopted, otherwise, the fixed effects model was used. Further, Hardy-Weinberg equilibrium (HWE) of genotypes in each of the studies was separately estimated by Chi-squared test. The subgroup analysis was adopted in different ethnic populations when each subgroup included more than 3 studies to present the virtual SLE risk in a certain race. We simultaneously performed a sensitivity analysis when the *P* values of HWE were lower than .05 to estimate the influence of individual studies on the summary effect.

2.3 | Evaluation of publication bias

Publication bias was detected via funnel plots and Egger's test.[16] The statistical process was performed by Stata 11.0 statistical software (StataCorp). When the funnel plots showed dissymmetry or the *P* value was lower than .05, it indicated that publication bias may exist. As for the possible publication bias, trim and fill method was adopted to evaluate the influence to the results.

3 | RESULTS

3.1 | Eligible studies in the present meta-analysis

The main characteristics of selected studies are summarized in Table 1. There were 20 qualified studies on association between *MBL2* polymorphisms and SLE risk finally recruited. A\B variant related to 15 independent studies (including 7 Asian, 6 European and 2 African studies), with total 2012 SLE patients and 1993 healthy controls. A\C and A\D variants both included 7 studies with 937 and 935 SLE patients, respectively. As regard to A\O variant, 10 studies met the inclusion criteria, consisting of 1470 patients and 1503 controls, including 6 European studies. For L\H variant, we recruited 8 relevant articles containing 999 patients and 1047 controls, and 4 studies belonged to European studies. Y\X variant referred to 8 original studies with in total 1771 SLE patients and 1029 healthy controls.

3.2 | Association of *MBL2* gene polymorphisms with SLE

Meta-analysis discussed the association between *MBL2* polymorphisms and SLE susceptibility for the 6 variants (A\B, A\C, A\D, A\O, L\H and Y\X). For A\B polymorphism, results indicated a significant association between allele B and SLE (OR = 0.766, 95% CI = 0.681-0.862, $P < .001$, Figure 2). In the additive model (AA vs BB) and recessive model (AA vs AB + BB), we observed increased risk for the patients carrying genotypes of BB and AB + BB (OR = 0.611, 95% CI = 0.422-0.882, $P = .009$; OR = 0.806, 95% CI = 0.688-0.944, $P = .008$). However, we did not find any statistic association among the A\C polymorphisms. As for A\D variant, we observed that patients carrying genotype AD and DD had remarkably higher SLE risk in comparison with those with genotype AA (OR = 0.131, 95% CI = 0.072-0.241, $P = .001$). Allele O was the collective term for allele B, C and D. To explore the comprehensive effects of allele B, C and D on SLE, we analyzed association between A\O and SLE. Results showed statistic differences in the allelic contrast, additive model and recessive model (OR = 0.826, 95% CI = 0.732-0.931, $P = .002$, Figure S1; OR = 0.737, 95% CI = 0.557-0.977, $P = .034$ and OR = 0.793, 95% CI = 0.683-0.921, $P = .002$, respectively). Moreover, we analyzed the relationship between allele H and SLE. Meta-analysis revealed that allele H and genotype HH both decreased SLE susceptibility in allelic contrast and recessive model (OR = 1.463, 95% CI = 1.097-2.007, $P = .018$, Figure S2; OR = 1.383, 95% CI = 1.124-1.701, $P = .002$). Finally, we analyzed the association between Y\X and SLE. As with the A\C variant, we did not find any statistic difference when we merged the original results (Table 2).

3.3 | Subgroup analysis

Considering the effect of ethnicity, we performed a stratified analysis of A\B, A\D, A\O, H\L and Y\X. The subgroup analysis for A\C was not performed since most of the original data for genotype CC was inadequate in European populations. For the A\B variant, we observed statistical differences between allele A and B in European populations as well as between genotype AA and AA + AB in Asian populations (OR = 0.748, 95% CI = 0.628-0.891, $P = .001$, Figure S3; OR = 0.808, 95% CI = 0.667-0.979, $P = .03$, Figure S4). However, we did not find any statistical association between A\B variant genotypes and SLE risk in European descent. Interestingly, after dividing the subjects into European populations by ethnicity, we observed a conspicuous association between genotype AD + DD and SLE (OR = 0.116, 95% CI = 0.054-0.250, $P = .001$). Moreover, we found that allele O and genotype AO + OO linked to susceptibility of SLE in allelic contrast and recessive model (OR = 0.870, 95% CI = 0.758-0.998, $P = .047$; OR = 0.841 95% CI = 0.709-0.998, $P = .047$). With regard to H\L variant of European populations, the polymorphisms were comparable both in allelic contrast, additive model, dominant model and recessive model. Similarly, we did not observe any statistical significant in the Y\X variant of European populations (Table 2).

3.4 | Sensitivity analysis

We conducted a sensitivity analysis for A\B, A\C and A\D polymorphisms due to one study that was not compliant with HWE. The results

TABLE 1 Characteristics of studies included in the meta-analysis

Author	Years	Ethnicity	Numbers		Case			Control			HWE
			Case	Control	WW	WM	MM	WW	WM	MM	*P* value
MBL2-A\B											
Negi et al[26]	2017	Indian	300	460	239	55	6	374	69	17	.015
Hristova et al[10]	2014	Bulgarian	45	78	34	11	0	57	20	1	.835
Panda et al[28]	2012	Indian	108	105	74	9	25	85	15	5	.130
El-Sherif[7]	2010	Egyptian	46	17	24	10	12	12	3	2	.509
Tsai et al[30]	2009	Chinese	150	100	99	48	3	61	37	2	.629
Piao-1 et al[11]	2007	Caucasian	93	108	64	26	3	80	24	4	.649
Piao-2 et al[11]	2007	African	9	4	8	0	1	4	0	0	1.000
Takahashi et al[31]	2005	Japanese	147	160	84	54	9	101	57	2	.262
Lee-1 et al[29]	2005	European American	96	96	77	15	4	77	18	1	.999
Lee-2 et al[29]	2005	German	285	200	199	78	8	151	44	5	.900
Huang et al[32]	2002	Chinese	41	111	30	10	1	92	18	1	.999
Tsutsumi et al[24]	2001	Japanese	157	129	97	50	10	88	39	2	.669
Horiuchi et al[33]	2000	Japanese	95	105	53	41	1	66	29	10	.312
Jakab et al[12]	2007	Hungarian	315	182	-	-	-	-	-	-	-
Villarreal et al[23]	2001	Spanish	125	138	-	-	-	-	-	-	-
MBL2-A\C											
Negi et al[26]	2017	Indian	300	460	289	4	7	445	9	6	.004
Lee-1 et al[29]	2005	European American	96	96	95	1	0	90	6	0	1.000
Lee-2 et al[29]	2005	German	285	200	270	15	0	187	13	0	1.000
Piao-1 et al[11]	2007	Caucasian	69	87	64	5	0	80	4	3	.083
Piao-2 et al[11]	2007	African	17	5	8	7	2	4	1	0	1.000
Hristova et al[10]	2014	Bulgarian	45	78	45	0	0	78	0	0	1.000
Villarreal et al[23]	2001	Spanish	125	138	-	-	-	-	-	-	-
MBL2-A\D											
Negi et al[26]	2017	Indian	300	460	280	18	2	414	41	5	.004
Lee-1 et al[29]	2005	European American	96	96	85	10	1	89	6	1	.584
Lee-2 et al[29]	2005	German	285	200	253	32	0	175	25	0	.581
Piao-1 et al[11]	2007	Caucasian	76	96	64	9	3	80	11	5	.086
Piao-2 et al[11]	2007	African	8	6	8	0	0	4	2	0	1.000
Hristova et al[10]	2014	Bulgarian	45	78	36	9	0	66	10	2	.696
Villarreal et al[23]	2001	Spanish	125	138	-	-	-	-	-	-	-
MBL2-A\O											
Pradhan et al[25]	2015	Indian	100	100	39	37	24	49	35	16	.295
Sandrin-Garcia et al[9]	2011	Brazilian	134	101	60	61	13	65	28	8	.511
Monticielo-1 et al[35]	2010	European descent	249	244	129	95	25	150	81	13	.953
Monticielo-2 et al[35]	2010	African descent	78	101	45	29	4	58	38	5	.947
Jakab et al[12]	2007	Hungarian	315	182	181	105	29	105	60	17	.416
Piao-1 et al[11]	2007	Caucasian	111	130	64	42	5	80	39	11	.420
Piao-2 et al[11]	2007	African	18	7	8	7	3	4	3	0	.725
Lee et al[29]	2005	German	285	200	163	103	19	122	64	14	.685

(Continues)

TABLE 1 (Continued)

Author	Years	Ethnicity	Numbers		Case			Control			HWE
			Case	Control	WW	WM	MM	WW	WM	MM	*P* value
García-Laorden et al[36]	2003	Spanish	89	188	45	39	5	100	75	13	.977
Garred et al[21]	1999	Danish	91	250	54	30	7	157	86	7	.679
MBL2-L\H											
Hristova et al[10]	2014	Bulgarian	45	78	6	26	13	15	37	26	.970
Panda et al[28]	2012	Indian	108	105	78	28	2	70	27	8	.325
Sandrin-Garcia et al[9]	2011	Brazilian	134	101	62	53	19	43	45	13	.972
Glesse-1 et al[8]	2011	European descent	244	248	101	107	36	81	138	29	.178
Glesse-2 et al[8]	2011	African descent	100	77	69	24	7	32	38	7	.766
Jönsen et al[27]	2003	Sweden	143	200	81	43	19	106	66	28	.105
Pradhan et al[25]	2015	Indian	100	100	-	-	-	-	-	-	-
Villarreal et al[23]	2001	Spanish	125	138	-	-	-	-	-	-	-
MBL2-Y\X											
Sandrin-Garcia et al[9]	2011	Brazilian	134	101	110	21	3	74	22	5	.597
Panda et al[28]	2012	Indian	108	105	64	19	25	56	32	17	.107
Glesse-1 et al[8]	2011	European descent	244	248	162	72	10	164	75	9	.998
Glesse-2 et al[8]	2011	African descent	100	77	64	30	6	55	22	0	.325
Hristova et al[10]	2014	Bulgarian	45	78	26	19	0	54	23	1	.805
Jakab et al[12]	2007	Hungarian	315	182	201	92	22	102	68	12	.998
Villarreal et al[23]	2001	Spanish	125	138	-	-	-	-	-	-	-
Pradhan et al[25]	2015	Indian	100	100	-	-	-	-	-	-	-

Abbreviations: HWE, Hardy-Weinberg equilibrium; M, mutational allele; W, wild allele.

are summarized in Table 3. The sensitivity analysis revealed that the differences were still statistically significant for A\B variant under allelic contrast, additive model and recessive model (OR = 0.736, 95% CI = 0.648-0.836, $P < .001$; OR = 0.483, 95% CI = 0.318-0.734, $P = .001$; OR = 0.782, 95% CI = 0.656-0.932, $P = .006$). Moreover, we found significant difference between AA + AB and BB (OR = 0.508, 95% CI = 0.337-0.767, $P = .006$). Subgroup analysis showed that statistical difference existed in the recessive model for Asian populations (OR = 0.776, 95% CI = 0.619-0.973, $P = .028$). As regards A\C and A\D variants, our merged results did not change before or after sensitivity analysis.

3.5 | Evaluation of publication bias

There were publication biases in the dominant model of L\H polymorphisms in overall populations and recessive model of A\D polymorphisms in European populations ($t = 4.37$, $P = .012$; $t = -8.45$, $P = .014$, Table 2). We adopted the trim and fill method to investigate the effect of publication biases on the results. For L/H variant, corrected results indicated that the *P* value did not changed too much after adjustment (from .413 to .623). Furthermore, the fail-safe number of missing studies that would change the *P* value was 8 (Figure 3). Thus, the publication bias did not affect the results of L/H polymorphism in the present analysis. The publication bias of CC genotype failed to be calculated as the number of CC genotype was almost 0 in our selected original study. On the other hand, we could not adjust the publication bias in the European recessive model of A\D polymorphism. Consequently, the association between genotypes AD + DD and SLE should be interpreted with caution.

4 | DISCUSSION

Systemic lupus erythematosus is an inflammatory autoimmune disease involving multiple organs damage, with unclear etiology. Under the same environmental exposure, individual susceptibility was different. Heritability has received attention in the field of rheumatology. In the past decade, genome-wide association studies (GWAS) identified a number of loci related to autoimmune diseases, by which more than 40 loci were associated with SLE risk.[17] According to the GWAS data, 3 major cellular pathways (lymphocyte signaling, interferon signaling pathway, the clearance of immune complex and other waste) may be involved in the pathogenesis of SLE.[18]

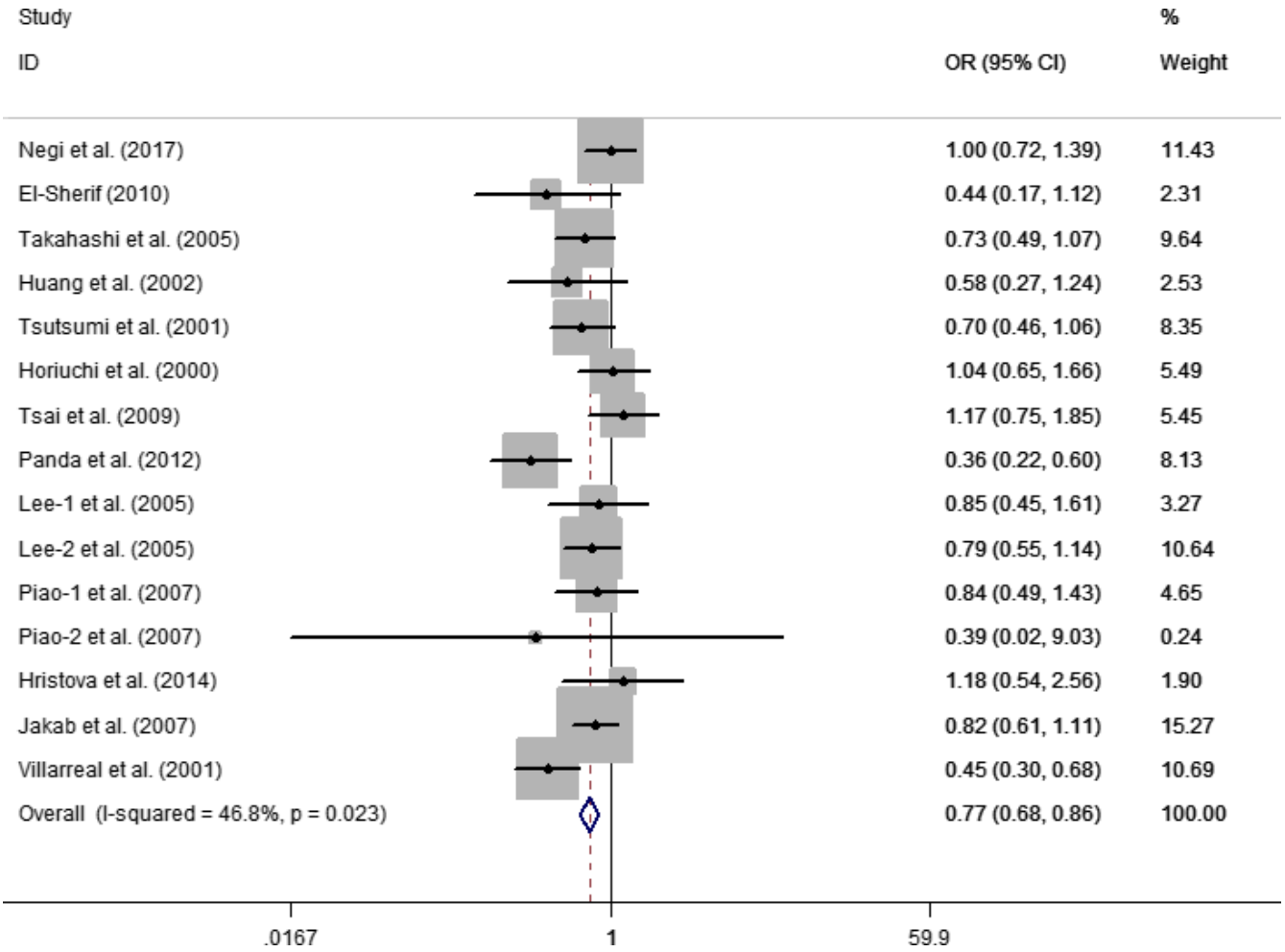

FIGURE 2 The forest plot of allele A vs B. Pooled data for the association between allele A vs B of mannose binding lectin (MBL) 2 gene polymorphism and systemic lupus erythematosus (SLE). Authors of Lee-1 and Lee-2 represent the same study but include the results from European American (Lee-1), German (Lee-2). Authors of Piao-1 and Piao-2 represent the same study but include the results from Caucasian (Piao-1), African (Piao-2) [Colour figure can be viewed at wileyonlinelibrary.com]

Consequently, this information has expanded our understanding that genetic factors represent a part of the complex mechanism in SLE etiopathogenesis.

Mannose binding lectin is a member of the collectins in the C-type lectin superfamily with lectin domains and collagenous regions. It is an acute-phase protein that is increasingly secreted in response to inflammation. MBL activates the lectin pathway of complement on account of its homologous structure as C1q. It is known that the complement system plays significant roles in cell lysis, cell phagocytosis, immune regulation, inflammatory mediation, and clearance of immune complexes. MBL interacting with MBL-associated serine proteases (MASPs) takes part in host defense and innate immunity. The MBL-MASPS mediates C3 convertase generation through the lectin pathway to active membrane attack complex, further opsonizing mannose-rich microorganisms and activating macrophages and the complement cascade. A previous study showed that the incidence of MBL deficiency in SLE patients was 2-3 times higher than in healthy controls.[19] Low levels of MBL are associated with SLE. MBL binds to immune complexes and cell debris. Consequently, MBL may be consumed to clear these debris in SLE patients. On the other hand, anti-MBL may be another reason for declined MBL levels in SLE patients, where anti-MBL was detected in SLE patients and associated with decreased serum MBL concentration activity. However, the exact mechanisms need to be clarified in the future.

Considering the role of genetic factors in SLE, numerous studies on *MBL2* polymorphisms have been discussed.[20] Allele B, which is located at exon 1 with a G to A substitution, alters an aspartic acid to a glycine at the protein level.[21] Allele C variant leads to a change from arginine to cysteine and allele D results in glycine to glutamic acid.[6,22] Allele O variant showed a collective effect of alleles B, C, D. These substitutions in the amino acid sequences led to a decline in MBL expression. To date, results of association between *MBL2* polymorphisms and SLE are inconsistent. Several studies reported that allele B was a risk factor for SLE. In a Spanish study, the authors found that the frequencies of allele B were 2.2 times higher in SLE patients.[23] Frequencies of genotypes AB and BB were significantly different between Japanese SLE patients and healthy controls.[24] In

TABLE 2 Meta-analysis of *MBL2* gene polymorphisms in systemic lupus erythematosus

Polymorphism	Comparisons	Population	Sample size		No. of studies	Test of association				Test of heterogeneity			Publication bias	
			Case	Control		Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*t*	*P*
MBL2-A\B	A vs B	Overall	2012	1993	15	F	0.766 (0.681-0.862)	4.41	.001	26.33	.023	46.8	−0.80	.439
		Asian	998	1170	7	R	0.771 (0.581-1.023)	1.80	.072	16.48	.011	63.6	−1.11	.318
		European	959	802	6	F	0.748 (0.628-0.891)	3.25	.001	7.94	.160	37.0	0.47	.665
	AA vs BB	Overall	1165	1300	13	R	0.611 (0.422-0.882)	2.63	.009	23.72	.022	49.4	0.12	.907
		Asian	731	906	6	R	0.594 (0.202-1.745)	0.95	.343	21.34	.002	71.9	0.14	.893
		European	389	376	4	F	0.746 (0.348-1.680)	0.67	.503	1.45	.694	0.0	−0.13	.910
	AA + AB vs BB	Overall	1572	1673	13	R	0.629 (0.323-1.225)	1.36	.173	25.44	.013	52.8	0.16	.874
		Asian	998	1170	6	R	0.619 (0.204-1.877)	0.85	.397	22.95	.001	73.9	0.20	.847
		European	519	482	4	F	0.804 (0.367-1.759)	0.55	.584	1.61	.658	0.0	−0.22	.844
	AA vs AB + BB	Overall	1572	1673	13	F	0.806 (0.688-0.944)	2.67	.008	7.81	.800	0.0	−0.85	.416
		Asian	998	1170	6	F	0.808 (0.667-0.979)	2.17	.030	5.77	.450	0.1	−1.43	.211
		European	519	482	4	F	0.832 (0.624-1.109)	1.26	.209	1.09	.780	0.0	2.85	.104
MBL2-A\C	A vs C	Overall	937	1064	7	R	0.874 (0.474-1.610)	0.43	.666	13.87	.016	63.9	1.47	.215
	AA vs CC	Overall	780	893	6	F	0.798 (0.321-1.981)	0.49	.626	2.26	.323	11.4	0.61	.651
	AA + AC vs CC	Overall	812	926	6	F	0.831 (0.334-2.070)	0.40	.692	2.20	.332	9.2	0.86	.547
	AA vs AC + CC	Overall	812	926	6	F	1.133 (0.713-1.801)	0.53	.596	4.71	.318	15.2	0.12	.911
MBL2-A\D	A vs D	Overall	935	1074	7	F	1.077 (0.821-1.413)	0.53	.593	8.61	.197	30.3	−0.38	.719
		European	627	608	5	F	0.889 (0.639-1.237)	0.70	.485	4.03	.403	0.6	−2.67	.076
	AA vs DD	Overall	732	841	6	F	1.522 (0.585-3.959)	0.86	.390	0.30	.961	0.0	0.31	.784
		European	442	418	4	F	1.438 (0.443-4.666)	0.61	.545	0.26	.876	0.0	0.35	.786
	AA + AD vs DD	Overall	810	936	6	F	1.531 (0.589-3.976)	0.87	.382	0.31	.958	0.0	0.47	.682
		European	502	470	4	F	1.477 (0.457-4.773)	0.65	.515	0.29	.863	0.0	0.44	.738
	AA vs AD + DD	Overall	810	841	6	F	0.131 (0.072-0.241)	6.57	.001	4.74	.315	15.6	−2.67	.076
		European	502	418	4	F	0.116 (0.054-0.250)	5.51	.001	4.98	.173	39.7	−8.45	.014

(Continues)

TABLE 2 (Continued)

Polymorphism	Comparisons	Population	Sample size		No. of studies	Test of association				Test of heterogeneity			Publication bias	
			Case	Control		Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*t*	*P*
MBL2-A\O	A vs O	Overall	1470	1503	8	F	0.826 (0.732-0.931)	3.12	.002	9.79	.368	8.1	−0.58	.576
		European	1140	1194	6	F	0.870 (0.758-0.998)	1.99	.047	4.53	.475	0.1	0.60	.584
	AA vs OO	Overall	992	994	8	F	0.737 (0.557-0.977)	2.12	.034	9.91	.358	9.2	−0.16	.874
		European	726	789	6	F	0.811 (0.581-1.130)	1.24	.215	8.10	.151	38.3	0.18	.865
	AA + AO vs OO	Overall	1470	1503	8	F	0.806 (0.613-1.060)	1.54	.122	9.52	.391	5.4	−0.10	.923
		European	1140	1194	6	F	0.863 (0.624-1.195)	0.89	.375	8.27	.142	39.5	0.20	.854
	AA vs AO + OO	Overall	1470	1503	8	F	0.793 (0.683-0.921)	3.03	.002	8.29	.505	0.1	−0.51	.625
		European	1140	1194	6	F	0.841 (0.709-0.998)	1.99	.047	2.32	.803	0.1	0.52	.633
MBL2-L\H	L vs H	Overall	999	1047	7	R	1.463 (1.097-2.007)	2.36	.018	37.25	.001	81.2	0.50	.633
		European	691	765	5	R	1.363 (0.857-2.167)	1.31	.191	33.89	.001	88.2	0.12	.911
	LL vs HH	Overall	493	453	5	F	1.176 (0.846-1.636)	0.96	.335	4.75	.447	0.1	1.80	.147
		European	337	341	4	F	1.014 (0.708-1.451)	0.27	.966	0.27	.966	0.1	−1.56	.259
	LL + LH vs HH	Overall	774	809	5	F	1.032 (0.764-1.394)	5.02	.413	5.02	.413	0.4	4.37	.012
		European	566	627	4	F	0.930 (0.674-1.285)	0.44	.662	1.19	.756	0.1	1.58	.256
	LL vs LH + HH	Overall	774	809	5	F	1.383 (1.124-1.701)	3.07	.002	9.96	.076	49.8	−0.25	.814
		European	566	627	4	F	1.235 (0.972-1.567)	2.43	.087	2.43	.487	0.1	−3.88	.060
MBL2-Y\X	Y vs X	Overall	1171	1029	8	F	1.090 (0.947-1.271)	1.24	.215	10.34	.170	32.3	−0.75	.482
		European	729	646	4	F	1.087 (0.898-1.315)	0.85	.394	2.69	.441	0.0	−1.04	.407
	YY vs XX	Overall	663	549	6	F	0.890 (0.591-1.341)	0.56	.577	4.78	.444	0.0	−0.29	.787
		European	421	342	3	F	1.010 (0.571-1.787)	0.04	.972	0.15	.928	0.0	0.44	.733
	YY + YX vs XX	Overall	946	791	6	F	0.797 (0.534-1.191)	1.11	.269	4.96	.421	0.0	−0.01	.991
		European	604	508	3	F	0.938 (0.535-1.642)	0.23	.822	0.16	.921	0.0	1.89	.309
	YY vs YX + XX	Overall	946	791	6	F	1.123 (0.919-1.374)	1.13	.258	7.71	.173	35.1	−0.91	.413
		European	604	508	3	F	1.102 (0.859-1.413)	0.76	.445	3.97	.138	49.6	−1.41	.392

Abbreviations: CI, confidence interval; F, fixed effects mode; MBL, mannose binding lectin; OR, odds ratio; R, random effects model; SLE, systemic lupus erythematosus.

TABLE 3 Meta-analysis of the *MBL2* polymorphism and systemic lupus erythematosus by sensitivity analysis

Polymorphism	Comparisons	Population	Sample size		No. of studies	Test of association				Test of heterogeneity			Publication bias	
			Case	Control		Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*t*	*P*
MBL2-A/B	A vs B	Overall	1712	1533	13	F	0.736 (0.648-0.836)	4.73	.001	23.42	.037	44.5	−0.51	.616
		Asian	698	710	6	R	0.727 (0.523-1.011)	1.89	.058	14.12	.015	64.6	−0.61	.574
	AA vs BB	Overall	920	909	9	F	0.483 (0.318-0.734)	3.41	.001	17.24	.101	36.2	1.18	.266
		Asian	486	515	6	R	0.454 (0.148-1.387)	1.39	.166	13.32	.021	62.4	1.51	.206
	AA + AB vs BB	Overall	1272	1213	9	F	0.508 (0.337-0.767)	3.23	.001	18.92	.063	41.8	1.18	.265
		Asian	698	710	6	R	0.477 (0.148-1.537)	1.24	.215	14.74	.012	66.1	1.59	.187
	AA vs AB + BB	Overall	1272	1213	9	F	0.782 (0.656-0.932)	2.74	.006	7.45	.683	0.0	−0.64	.541
		Asian	698	710	6	F	0.776 (0.619-0.973)	2.20	.028	5.30	.380	5.7	−1.14	.319
MBL2-A/C	A vs C	Overall	637	603	6	R	0.958 (0.412-2.231)	0.10	.921	13.72	.008	70.9	1.28	.290
	AA vs CC	Overall	484	442	5	F	1.830 (0.319-10.484)	0.68	.498	1.45	.228	31.1	-	-
	AA + AC vs CC	Overall	512	466	5	F	2.216 (0.371-13.233)	0.87	.383	1.10	.294	9.3	-	-
	AA vs AC + CC	Overall	512	466	5	F	1.286 (0.728-2.272)	0.87	.387	4.27	.234	29.7	−0.05	.967
MBL2-A/D	A vs D	Overall	635	614	6	F	0.922 (0.665-1.277)	0.49	.623	5.84	.322	14.4	0.15	.888
	AA vs DD	Overall	450	422	5	F	1.438 (0.443-4.666)	0.61	.545	0.26	.876	0.0	0.35	.786
	AA + AD vs DD	Overall	510	476	5	F	1.477 (0.457-4.773)	0.65	.515	0.29	.863	0.0	0.44	.738
	AA vs AD + DD	Overall	510	422	5	F	0.116 (0.054-0.250)	5.51	.001	4.98	.173	39.7	−8.45	.014

Abbreviations: 95% CI, 95% confidence interval; F, fixed effects model; MBL, mannose binding lectin; OR, odds ratio; R, random effects model.

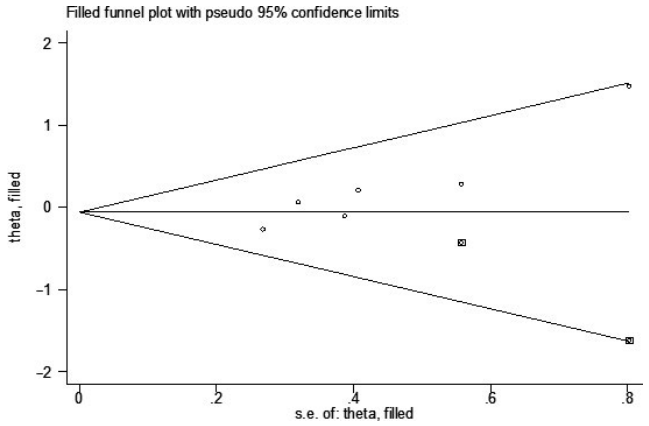

FIGURE 3 The funnel plot of genotype LL + LH vs HH by means of trim and fill method. Egger's funnel plot of genotypes LL + LH vs HH under the dominant model was symmetrical after adjustment with trim and fill method

contrast, another Japanese study did not find any association between allele B variant and SLE susceptibility. Regarding allele C, as well as allele D, all 7 selected original studies in our analysis indicated a comparable difference between SLE patients and healthy controls.[11,23,25,26] However, 5 of 7 eligible articles showed statistical differences under the recessive model (AA vs.AD + DD).[10,11,25,26] Moreover, allele H was recognized to play a protective role in SLE in Bulgarian and Spanish studies,[10,23] although other studies related to allele H and SLE did not find statistical associations.[8,9,25,27,28] Similar to the meta-analysis published in 2005,[29] our pooled study indicated that the patients carrying allele B had increased risk of SLE. But alleles C and D are both comparable between SLE patients and healthy controls. Allele L was considered as a potential protective factor in SLE. Furthermore, several new findings were noted in the present meta-analysis. In comparison to the 2005 published meta-analysis, subgroup analysis detected differences between allele A and B in European populations, and genotypes AA and AB + BB in Asian populations.[7,28,30-33] Under the additive model, genotype BB was associated with SLE. These above findings suggest that allele B is possibly involved in SLE and genotype BB may be a risk factor. In addition, our present meta-analysis pooled seven independent studies to explore the association between allele C and SLE, and we did not observe any association in overall and European populations. Further analysis under genotype models (additive model, dominant model and recessive model), the present study also did not find any statistical difference. Thus, more studies are needed to demonstrate the authentic association between A\C variant and SLE. On the other hand, we found a new statistical difference under AA vs AD + DD model compared with the 2005 meta-analysis. It indicated that allele D was possibly a recessive mutation. Allele L mutation was located at position −550 on the promoter region. In comparison to the 2005 meta-analysis, the present study added three new original studies to integrate the effect of L/H variant in SLE. Besides a consistent result of allele L, we further found a significant difference under the recessive model. Until now, the studies about gene polymorphism mainly focus on exons, but the mechanism of intron promoter region is limited. Introns possibly regulate messenger RNA translation by blocking gene linear expression and alternative splicing. Larger-scale studies are needed in the future to clarify the mechanism between allele H variant and SLE risk. As for A\O variant, we added two new studies into our current meta-analysis compared to our study published in 2011.[34] Two new statistical differences were observed in the additive model and recessive models. Moreover, subgroup analysis for European descent[11,35-37] indicated statistical significance in allelic contrast and recessive model. We argue that alterations of these results may be attributed to the increased number of studies. The added studies expand over half the scale of sample size which increased statistic power (from 654 to 999 patients).

There are some limitations in our present meta-analysis. First, heterogeneity could exist between included studies due to differences in study design, test conditions, and outcome indicators. Second, the number of our eligible studies is relatively small. The limited articles may restrict the statistic power to evaluate the association between *MBL2* polymorphisms and SLE susceptibility. Third, there were publication biases in the dominant model of L\H polymorphism in overall populations and recessive model of A\D polymorphism in European populations. After adjustment with trim and fill method, we found that the publication bias in L\H had little effect on our result. However, the publication bias in A\D cannot be corrected. Thus, the association between genotypes AD + DD and SLE should be cautiously interpreted. Fourth, since the number of genotype CC was 0 in the most received studies, the publication biases were not able to be calculated in additive and dominant models.

In summary, our present study indicated that A\B and A\O polymorphisms were associated with SLE susceptibility, and the allele H may be a protective factor in SLE.

CONFLICT OF INTEREST

There are no competing interests.

ORCID

Wang-Dong Xu https://orcid.org/0000-0001-8276-1249
An-Fang Huang https://orcid.org/0000-0002-3860-8383

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SUPPORTING INFORMATION

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

How to cite this article: Yuan Z-C, Xu W-D, Lan Y-Y, et al. Association of *MBL2* gene polymorphisms and systemic lupus erythematosus susceptibility: A meta-analysis. *Int J Rheum Dis*. 2021;24:147–158. https://doi.org/10.1111/1756-185X.14017

Received: 13 August 2020 | Revised: 1 October 2020 | Accepted: 15 October 2020

DOI: 10.1111/1756-185X.14021

REVIEW

International Journal of Rheumatic Diseases | WILEY

Role of exosome in autoimmunity, with a particular emphasis on rheumatoid arthritis

Alireza Hejrati[1] | Bahare Hasani[2,3] | Mozhgan Esmaili[2,3] | Davood Bashash[4] | Naeimeh Tavakolinia[5] | Parisa Zafari[2,3]

[1]Department of Internal Medicine, Hazrate-Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran

[2]Department of Immunology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[3]Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

[4]Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[5]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Parisa Zafari, Department of Immunology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
Emails: pzafari.70@gmail.com; p.zafari@mazums.ac.ir

Funding information
Mazandaran University of Medical Sciences.

Abstract

Cell-derived exosomes are identified as carriers of lipids, proteins, and genetic materials that participate in cell-cell signal communication, biological process, and cell signaling. Also, their involvement has been reported in a vast array of disorders and inflammatory conditions such as autoimmune diseases. Rheumatoid arthritis (RA), a common cause of joint disorder, is an inflammation-based disease in which the precise understanding of its pathogenesis needs to be further investigated. Also, there is only a palliative care approach for the alleviation of RA symptoms. This paper discusses the recent advances in the biology of exosomes in autoimmune disorders especially in RA, and also provides a new line of research for arthritis therapy using exosomes.

KEYWORDS

autoimmunity, exosome, rheumatoid arthritis, rheumatologic disorders

1 | INTRODUCTION

The immune cells patrol all areas of the body and establish an immune system, capable of recognizing and responding to the foreign substances. Autoimmunity develops when adaptive immune responses to autoantigens are initiated, leading to dysregulated immune homeostasis.[1] Autoimmune diseases are among the heterogeneous group of poorly understood disorders leading to morbidity and mortality of approximately 5% of the world population.[2] These diseases include a diverse array of systemic and organ-specific disorders. The presumed pathogenesis of most of them is based on the observations taken from animal model studies so there is still much to be learned about their underlying mechanisms.[3] Rheumatoid arthritis (RA) as a systemic autoimmune disease with primary involvement of synovial joints and then, other organs such as the cardiovascular or respiratory systems.[4,5] Exosomes are membrane-bound extracellular vehicles (EVs) with diameters ranging from 30 to 100 nm that are produced in the endosomal compartment of most eukaryotic cells.[6] First, endocytic vesicles form through endocytosis at lipid raft regions of the plasma membrane. These early endosomes, in cooperation with the Golgi complex, become late endosomes. The limiting membrane of late endosomes has invaginated into the lumen to form intraluminal vesicles (ILVs). Late endosomes with the accumulation of ILVs are also called multivesicular body (MVBs).[7,8] Finally, MVBs can be transferred to the lysosome for degradation or fuse with the plasma membrane to release their exosomes and all other content, into the extracellular space (Figure 1).[9] Exosomes should be

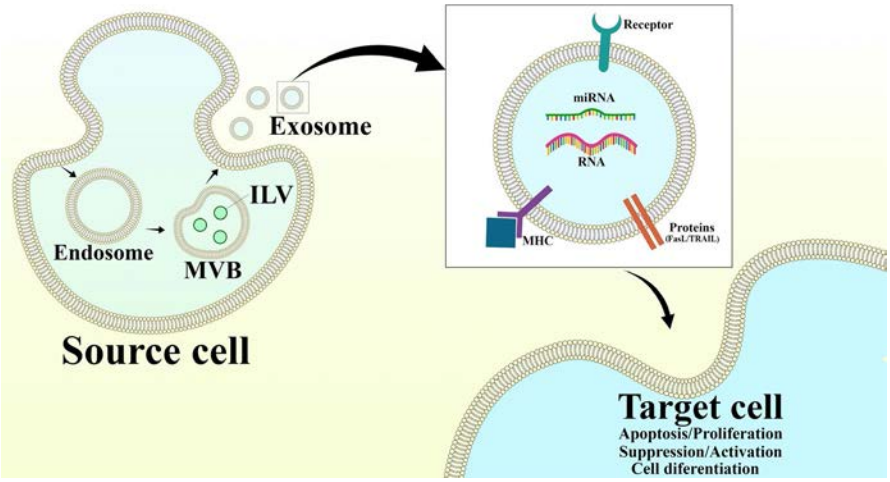

FIGURE 1 Exosome biogenesis. Exosome biogenesis starts with fusion of multivesicular bodies (MVBs) with the plasma membrane following the endocytosis into early endosome. Majority of the endosomes mature to MVB or late endosome. Their cargo such as RNA, protein receptors, protein ligands is packaged into intraluminal vesicles (ILVs) within MVBs. Then, MVBs fuse with plasma membrane, resulting in ILVs release to extracellular spaces as exosomes and can effect targets cell and participate in various intracellular processes based on their cargos

uptaken by recipient cells to exert their effects, which resemble their parent cells. These nanoscale particles carry molecular genetic materials and proteins which may mediate information transfer between cells.[10] A rapidly expanding body of evidence now indicates that exosomes are involved in many cell processes such as cell signaling, angiogenesis, and inflammation, as well as in the pathological and physiological conditions of autoimmune diseases. Moreover, intrinsic characteristics of exosomes such as biocompatibility and stability make them a therapeutic target to be manipulated.[11] Although exosome research is in its infancy, clear data exist to demonstrate it can have promising future prospects. In this review, we endeavor to summarize the current knowledge of the exosome biogenesis, secretion, and mechanism of action in the immune system. Finally, we highlight the likely role of the exosome in RA disorder which provides us a promising new approach to identify therapeutic strategies.

2 | IMMUNE CELL-DERIVED EXOSOMES

The immunosuppressive effects of exosomes should also not be ignored as they create a favorable microenvironment for cancer development, metastasis, and progression.[12] It has been shown in different studies that tumor cells as well as immune cells secrete immunologically active exosomes called tumor-derived exosomes (TEX) which affect intercellular communication, antigen presentation, activation of immune cells, and immune surveillance, likely blunting specific T cell immunity and skewing innate immune cells toward a pro-tumorigenic phenotype.[13] Exosomes were shown to be independent producers of adenosine by surface expression of CD73 and CD39 and to induce differentiation of CD4 + T cells to CD39 + regulatory T cells (Tregs), potentiating immune suppression in the tumor microenvironment (TME).[14-16] They can also modulate angiogenesis to elevate the malignant degree of tumor cells. They also carry immunosuppressive factors affecting the antitumor activities of immune cells. TEX can inhibit immune cell proliferation, induce apoptosis of activated CD8 + effector T cells (Teffs), suppress natural killer cell activity, interfere with monocyte differentiation, and promote Treg as well as myeloid-derived suppressor cells (MDSC) expansion.[17] Exosomes of TME may also contribute to the development of drug resistance in cancer therapy.[12,13,18] A wide array of cells including B cells, T cells, macrophage, adipocyte, dendritic cells (DC), endothelial cells, and epithelial cells can secrete exosomes.[19,20] In the following sections, we discuss immune cells-derived exosomes.

2.1 | B cell-derived exosomes

B cell-derived exosomes carry on major histocompatibility complex (MHC)I, MHCII, CD45RA, and other adhesion and costimulatory molecules. They also express different types of antigens that can lead to different immune responses.[21] Exosomes from human and murine B cell lines express MHCII specific antigen and Lamp1 and CD63 which can induce MHCII-restricted T cell response.[22,23] B cell-derived exosomes from patients with birch pollen allergy express MHCII and costimulatory molecules like CD86, tetraspanins protein like CD81, and CD19 which can present allergen peptides and induce T cells proliferation and TH2 like production of cytokines such as interleukin (IL)13 and IL5.[24]

2.2 | T cell-derived exosomes

Peripheral blood T cell activation induced by anti-CD28 and anti-CD3 promotes the production of exosomes that contain T cell receptor (TCR), CD63, CD2, integrin (LFA1), MHC class 1, MHC class 2

TABLE 1 The involvement of various exosomal cargos in autoimmune disorders

Autoimmune disease	Origin of exosome	Exosomal cargo	Biological activity	Ref
Type 1 diabetes mellitus (T1DM)	Pancreatic β-cell	GAD65, IA-2 and insulin/pro-insulin	Taken by dendritic cell, activating CD4 + T cells, breaking the tolerance.	82
	T lymphocyte	miR-142-3p, miR-142-5p, and miR-155	Immune cell recruitment by triggering apoptosis and the expression of genes involved in chemokine signaling, including CCL2, CCL7, and CXCL10, exclusively in β cells.	83
	Macrophage	CD63 and Alix	Inhibition of inflammation by reducing the secretion of TNF-α and IL-6, accelerating re-epithelization and angiogenesis, and improving wound healing.	84
	Adipose tissue-derived mesenchymal stem cell	-	Increase of TGF-β, IL-4, and IL-10 production, decrease in IL-17 and IFN-γ secretion, inducing regulatory T cells	85
	Human urine-derived stem cells	Growth factor, TGF-β1, angiogenin and bone morphogenetic protein-7	Preventing kidney injury from diabetes by inhibiting podocyte apoptosis and promoting vascular regeneration and cell survival.	86
Rheumatoid arthritis (RA)	Synovial fibroblast	Membrane-bound TNF-α	Taken up by anti-CD3-activated T cells, activating AKT and NF-κB and rendering these activated T cells resistant to apoptosis.	47
	Synovial fluid	Citrullinated proteins	Induction and dissemination of citrullinated proteins, specific recognition of these proteins and breaking the tolerance.	45
	MSC	miR-150-5p	Reducing joint destruction by inhibiting synoviocyte hyperplasia and angiogenesis.	87
	Serum	TLR3	Markedly increased in patients with active RA, may reflect the inflammatory condition of fibroblast-like synoviocytes.	48
Systemic lupus erythematosus (SLE)	Plasma	miRNAs	Inducing plasmacytoid DC (pDCs) activation and secretion of IFN-α by exosome-delivered microRNAs and TLR7 endogenous ligands.	88
	Serum	AChE, CD63, and CD81	Inducing a higher production of IFN-α, TNF-α, IL-1β, and IL-6 in PBMC.	89
	Urine	miR-29c	Correlated with the degree of renal chronicity.	90
Multiple sclerosis (MS)	Plasma	let-7i	Suppressing induction of Treg cells by targeting IGF1R and TGFBR1.	91
	DC	Myelin	Inducing oligodendrocytes to increase myelination.	92
	Oligodendrocyte	PLP	Retarding myelin formation during CNS development.	93

(Continues)

TABLE 1 (Continued)

Autoimmune disease	Origin of exosome	Exosomal cargo	Biological activity	Ref
Experimental autoimmune myasthenia gravis (EAMG)	DC	TSG101	Elevating the expression of Aire, which further induces Foxp3$^+$ nTreg formation in the thymus.	29
	DC	microRNA-146a	Mitigating levels of CD80 and CD86, switching Th1/Th17 differentiation to Th2/Treg both in serum and spleen.	31
Hashimoto thyroiditis	Serum	TPO, HSP60, and MHC-II	Presenting antigens to DCs and bind TLR2/3, causing DCs activation via the NF-κB signaling pathway, leading to an imbalance in CD4 + T lymphocytes differentiation, and contributing to starting Hashimoto thyroiditis.	94
Graves' disease (GD)	human thyroid follicular epithelial cell line (NTHY-ori 3-1) and thyroid carcinoma cell lines (8305C, 8505C, and FTC-133)	Thyrotropin receptor (TSHR)	Sequestering autoantibodies, ameliorating autoantibody-mediated activation of thyroid function.	95
	Serum	Small RNAs	Stimulating mRNA expression of IL-1β and TNF-α in PBMC.	96
Psoriasis	Keratinocyte	CD9, CD63, CD81, HSP70, and GM130	Activating neutrophils and increasing skin inflammation.	97
	Serum	Interleukin-17A	Participating in moderate-to-severe psoriasis, through IL-17A-secretion.	98
Sjögren's syndrome (SS)	Salivary gland epithelial cells	Ro/SSA, La/SSB, Sm RNPs, epithelial-specific cytokeratins	Exposing autoantigens to the immune system leading to autoimmunity.	99
	EBV-infected B cell	EBV-miR-BART13-3p	Targeting Store-Operated Ca(2+) Entry (SOCE) pathway via STIM1, leading to loss of SOCE and Ca(2+)-dependent activation of NFAT, which is essential for salivary glands function.	100
Systemic sclerosis (SSc)	Serum	miRNAs	Inducing a profibrotic phenotype in target normal fibroblasts in vitro, extend the fibrotic SSc process to non-affected tissues.	101
Experimental autoimmune uveitis (EUA)	MSC	CD63, CD9 and CD81	Inhibiting the migration of inflammatory cells to the eye.	102
Autoimmune hepatitis	MSC	miR-223	Inhibiting liver injury by regulation of NLRP3 and caspase-1.	103
Alopecia Areata (AA)	MDSC	MDSC markers, cytokines, and chemokine receptors	Enhancing Treg, reducing T helper proliferation, suppressing cytotoxic activity, slight increase in lymphocyte apoptosis, and partial hair regrowth.	38

Abbreviations: AChE, acetylcholinesterase; CCL, CC chemokine ligands; CNS, central nervous system; CXCL, chemokine (C-X-C motif) ligand 1; EBV, Epstein-Barr virus; GAD65, glutamic acid decarboxylase enzyme; IA-2, Islet antigen-2; MDSC, myeloid-derived suppressor cells; MSC, mesenchymal stem cells; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor κB; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PBMC, peripheral blood mononuclear cell; PLP, proteolipid protein.

and chemokine receptor 4 (CXCR4).[25] Stimulated CD3 + T cells can secrete exosomes that with IL2 can induce proliferation in autologous resting CD3 + T cells.[26]

Exosomes from activated ovalbumin (OVA)-specific $CD4^+$ T cells contain Lamp1, LFA1, TCR, CD4, CD25, and Fas ligand protein. EXOOVA can be taken up by antigen-specific DCs via the interaction of MHCII/TCR and CD54/LFA1. This interaction mediates the suppression of T cell response in the antigen-specific pathways by inducing DC apoptosis via FAS/ FAS ligand interaction exosomes secreted by Treg cells which inhibit cytotoxic T lymphocytes (CTLs) proliferation.[27,28] This inhibition effect was associated with the reduction of interferon (IFN)-γ expression and perforin production in them and improvement of liver allograft survival.[29]

2.3 | DC-derived exosomes

The proteomic analysis (proteomics) of DC-derived exosomes has shown that they contain different types of immune-related proteins (such as MHC class I, MHC class II, CD86), apoptosis-related proteins (such as ALIX, galectin 3, thioredoxin peroxidase), cytoskeleton-related proteins (such as cofilin, profilin1), and intracellular membrane transport and signaling factors (such as rab7, rab11, rap1B, several annexins, and syntenin). Therefore DC-derived exosomes contain different molecular compositions and play a crucial role in the immune response.[30] Thus they are used for therapeutic goals. Exosomes derived from microRNA (miRNA)-146a-overexpressing DCs contain low levels of CD80 and CD86 which can suppress myasthenia gravis (MG) progression and change the profile of Th1/Th2 to Th2/Treg in spleen and serum. These effects of exosomes rely on being antigen-specific and dose-dependent.[31] Exosomes from genetically modified BM-DC expressing Fas ligand can induce antigen-specific immune suppression via the class II-dependent pathway; in a murine model of delayed-type hypersensitivity, it has been shown that it can improve the treatment of collagen-induced arthritis and has anti-inflammatory effects.[32]

2.4 | Macrophage-derived exosomes

Some data have shown that lipopolysaccharide (LPS)-stimulated macrophages induce the production of exosomes to contain a higher level of 3 murine homologs for human miRNA (miR146a, miR146b, and miR21-3p). These miRNAs can inhibit the initiation of immune responses and the production of pro-inflammatory cytokines.[33,34] Exosomes from LPS stimulated RAW264.7 cells (murine macrophage cell lines) can inhibit the production of pro-inflammatory enzymes and cytokines. Also, they can improve wound healing via their anti-inflammatory effects in diabetic rat models by inducing endothelial cell 2 proliferation and migration to enhance angiogenesis and re-epithelialization.[34] M1 macrophage produces pro-inflammatory exosomes after myocardial infarction (MI) which carry on a different kind of pro-inflammatory miRNAs like miR155. MiR155 affects its target genes like RAC1, p21-activated kinase 2, situin1, and adenosine monophosphate-activated protein kinase α subunit (AMPKα2); it is transferred to endothelial cells and inhibits angiogenesis, therefore, it can enhance MI injury.[35]

2.5 | MDSC-derived exosomes

MDSCs can inhibit immune response in malignancies via their proteins and soluble mediator productions. MDSC-derived exosomes from Balb/c mice with 4T1 mammary carcinoma carry on histones, enzymes active in energy metabolism, proteasome subunits, and pro-inflammatory mediators such as S100A9 and S100A8. This study suggests that exosomes from MDSCs lead to M2 macrophage formation; also, they can affect MDSCs migration via their S100A8 and S100A9.[36] Exosomes derived from granulocytic MDSCs (G-MDSCs) reduce the leukocyte infiltration, mean arthritis index, and joint destruction. The miR-29a-3p and miR-93-5p contained in these exosomes were verified to inhibit Th1 and Th17 cell differentiation by targeting T-bet and STAT3 expression, respectively.[37] MDSC exosomes (MDSC-Exo) can suppress Th cell proliferation and cytotoxic activity in the naïve and autoimmune Alopecia Areata (AA) mouse T cells. Also, treatment of AA mice with MDSC-Exo upregulates IL-10, FoxP3, and Arginase1 mRNA level expression and reduces IFN-ϒ, IL-1β, and IL-6 expression.[38]

3 | ROLE OF EXOSOMES IN RA

It has been reported that exosomes derived from different cells participate in the initiation and progression of a diverse array of autoimmune diseases (Table 1). Exosomes, depending on their cargo, have immunomodulatory or immunostimulatory effects; however, their precise physiological and pathological functions have yet to be explored.

In the context of RA, exosomes carry on a variety of functional molecules including proteins, lipids, and non-coding RNAs (microRNA and lncRNA), thus its function depends on them.[39] miRNA17 was upregulated in the exosomes purified from RA patients' plasma which can suppress Treg induction by inhibiting the expression of transforming growth factor-beta receptor II (TGFBR II) in RA patients.[40] With TNF-α stimulation, 4 miRNA (miR-155-5p, miR-146a-5p, miR-323a-5p, mir-1307-3p) were detected to be upregulated in the exosomes derived from the MH7A (RA synovial fibroblast cell line).[36] Studies have shown the role of these miRNAs in the pathogenesis of RA. MiR-155-5p expression was increased in the synovial membrane and macrophages of RA patients and it could downregulate SHIP1 protein level as the inhibitory protein of inflammation.[41] MiR146a-5p was upregulated in synovial fibroblasts, synovial tissues, and peripheral blood mononuclear cells in RA patients. MiR146a expression was found to be upregulated in the CD4 + T cells of RA patients; miR-146a overexpression suppresses the Jurkat T cell apoptosis by effect on FAS associated factor 1 (FAF1).[42,43]

MiR323-3p was predicted to target CD6, which is an extracellular receptor on T lymphocyte that can attenuate T cell activation signaling.[36] MiR1307-3p was predicted to suppress the expression of protein-encoding gene N-myc downstream-regulated gene 2 (NDRG2) which inhibits osteoclast differentiation.[36,44] Exosomes are also able to carry citrullinated proteins. Citrullinated proteins such as fibrinogen and citrullinated SPα associated with an anti-citrullinated antibody has been detected in synovial exosome from synovial fluid in patients with RA.[45] Anti-citrullinated antibodies and citrullinated proteins are powerful predictors of the progression of inflammatory arthritis. These antibodies were detected in the collagen-induced arthritis (CIA) mice models. A monoclonal antibody specific to citrullinated fibrinogen enhanced arthritis and induction of tolerance with citrullinated peptide protected from inflammatory injury in the CIA model.[46] Exosomes from RA synovial fibroblast contain a membrane form of TNF-α which affects activated T cells when bound to its receptor on these cells. Also, they trigger the activation of AKT and nuclear factor kappa B (NF-κB) pathway and apoptosis inhibition in these T cells. Inhibiting this pathway by adding soluble TNFRI can break this resistance.[47]

Serum exosomes in RA patients have more TLR3 proteins than healthy controls and osteoarthritis patients.[48] TLR3 recognizes double-stranded RNA, that activation of the receptor induces the activation of the NF-κB pathway and the production of type I interferons (IFNs).[49] TLR3 and TLR4 were elevated in the synovial tissue from patients with early RA.[50] TLR3 was upregulated in macrophages from pristane-induced arthritis (PIA), a rat model for the beginning of RA.[51] Further, exosome can be used as a diagnostic marker for RA disease activity. The expression level of Hotair, a kind of lncRNA leading to the migration of active macrophages, was higher in the exosome from RA patients' blood samples than the control group (non-RA group) with high C-reactive protein levels. Therefore this study has suggested that the Hotair could be used as a diagnostic marker for RA.[52] Serum and exosomal concentration of serum amyloid A were higher in patients with higher disease activity; conversely, the exosomal concentration of LYVE1 was lower in patients with higher disease activity. These new markers have the potential to be the diagnostic markers of disease activity.[53] The role of different exosomal cargos in RA disease is shown in Table 2.

4 | ROLE OF EXOSOMES IN THE TREATMENT OF RA

Although there are some biological therapies for RA which target inflammatory factors such as TNF-α, these proteins and antibodies are mostly palliative and cannot reverse the symptoms of the disease. Also, the "gene therapy strategy" showed some promising initial results; however, its outcomes are still under investigation.[54,55] Recent studies have revealed that exosomes could be used as drug delivery vehicles due to their unique features. Exosomes encapsulate the drugs, carry them into lesion areas by their ability to pass through a biological membrane, such as synovial membranes.[56] Also, the encapsulation increases the half-life of the drug in the blood; exosomal curcumin has shown longer half-life in the blood compared to free curcumin.[57] In the context of inflammatory disorders and RA, exosome has the potential to be used in the therapeutic industry as both a drug delivery vehicle as well as the exosome content per se. Biologic drugs such as anti-TNF-α or other anti-inflammatory therapies could be encapsulated into exosomes to reach target cells

TABLE 2 Role of different exosomal cargos in rheumatoid arthritis (RA)

Origin of exosome	Exosomal cargo	Role	References
Plasma of RA patient	miRNA17	Decreasing TGFβRII on $CD4^+$ T cell Inhibiting Treg induction	40
MH7A (RA synovial fibroblast cell line)	miR-155-5p	Inhibiting SHIP1 protein expression, an inhibitor of inflammation	36,104
	miR-146a-5p	Inhibit Jurkat T cell apoptosis	36,43
	miR-323a-5p	Predicting to inhibit CD6 expression on T cells	36
	miR-1307-3p	Suppressing the expression of NDGRT2 protein	36,44
Synovial fluid	Citrullinated protein (fibrinogen and citrullinated SPα)	Presenting autoantigen	45
Synovial fibroblast cells	Membrane form of TNF-α	Activating AKT and NFkappaβ Inhibiting T cells apoptosis	47
Serum exosome of RA patient	TLR3	Related with the beginning of RA in PIA RAT model	48,51
	Hotair	Increased in exosomes of RA patients	52
	Amyloid a	Increased in serum and exosomes of RA patients with high activity	53
	LYVE1	Decreased in the exosome of RA patients with high activity	53

Abbreviations: Hotair, HOX transcript antisense RNA; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; PIA, pristane-induced arthritis; SHIP1, SH-2 containing inositol 5' polyphosphatase 1; TLR, Toll-like receptor.

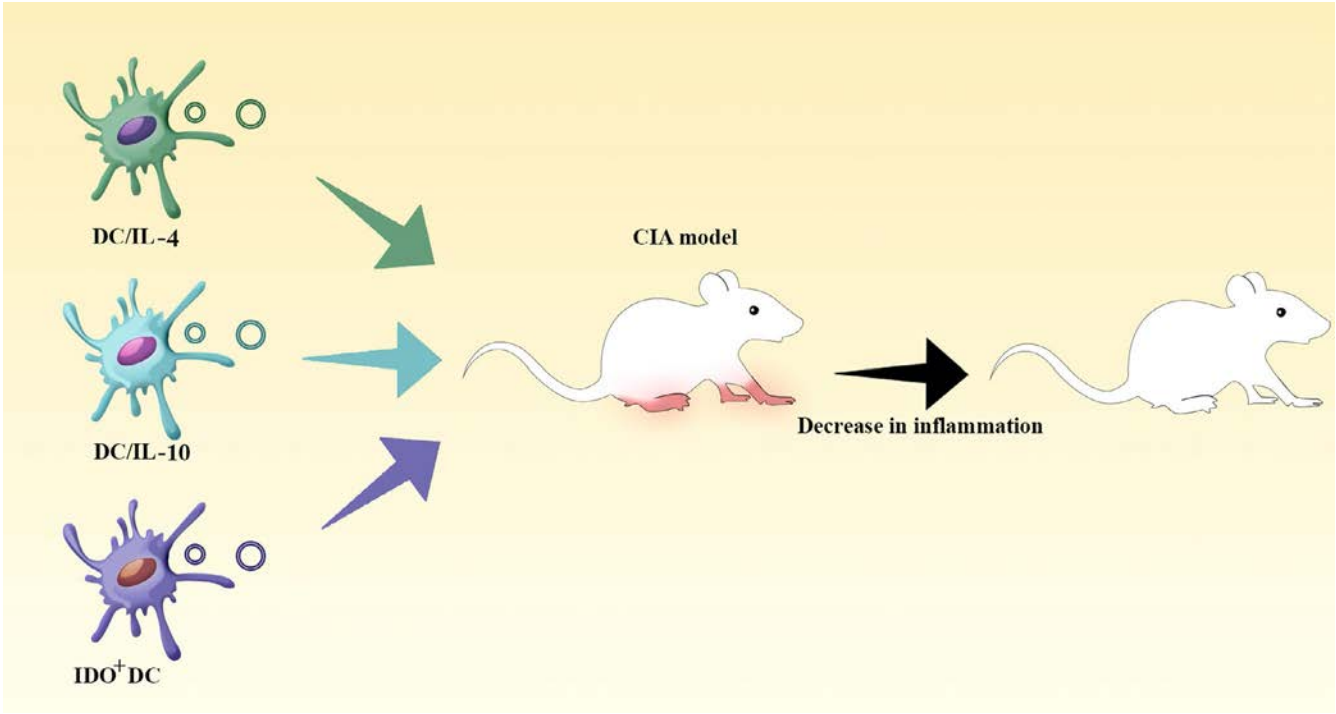

FIGURE 2 Dendritic cell (DC)-derived exosomes in the management of collagen-induced arthritis (CIA). Exosomes derived from immunosuppressive DC such as DCs genetically engineered to express interleukin (IL)-4, DCs treated with recombinant murine IL-10 (rmIL-10), and DCs expressing the tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO) showed a potent potential to decrease inflammation in CIA animal model

without being affected by enzymatic degradation. Anti-inflammatory and immunosuppressive properties of exosomes have been identified in inflammatory bowel disease (IBD) and CIA.[58,59] Herein, we review the current studies on the application of biologically derived exosomes and engineered exosomes in the alleviation of RA disease or the CIA model.

4.1 | Biologically derived exosome

The anti-inflammatory function of immune cell-derived exosomes such as exosomes derived from MSCs and neutrophils has been detected in some studies. MSC-derived exosomes suppress autoreactive T cells and induce anti-inflammatory cytokines production such as IL-10 and TGF-β.[60] Moreover, the neutrophil that is a double-edged sword in RA pathogenesis releases inflammatory factors acting as autoantigens.[61] On the other hand, it has been shown that exosomes derived from neutrophils are also involved in cartilage protection.[62]

In addition to cell-derived exosomes, biological fluid exosomes may also have the potential to treat the RA disease. It has been reported that exosomes can be derived from various sources of the body fluid including placenta,[63] serum,[64] bronchoalveolar fluid,[65] breast milk and colostrum,[66] and plasma.[67] The isolated exosomes from the plasma of antigen-immunized mice showed repressed DTH response in an antigen-specific manner that was dependent on MHC class II + exosomes.[67] Also, the result of a human clinical study indicated that local injection of exosomes derived from physiochemically conditioned autologous patient serum reduces joint pain and decreases blood inflammatory markers in refractory RA disease.[68,69]

4.2 | Engineered exosomes

Currently, considerable attention is being focused on engineering exosomes because of the possibility of exosome customizing. A vast variety of cells can be the source of exosomes that create a heterogeneous population, so this issue can be circumvented by modification of them and provide more homogenous types.[70] Engineered exosomes namely iExosomes have been designed for the delivery of functional agents such as therapeutic agents and vaccines but most of them are under investigation in cancer therapy because of the high number of exosomes in malignant effusions.[70] Genetically engineered exosomes are a popular therapy among the modified exosomes and recently, exosomes derived from immunosuppressive DCs including DCs genetically engineered to express IL-4, DCs treated with the recombinant murine IL-10 (rmIL-10), and DCs expressing the tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO) have been found to confer potent immunosuppressive effect for the treatment of murine CIA and reduction of diseases severity[59,71,72] (Figure 2). In addition, MSC-derived exosomes loaded with miR-320a can inhibit the migration, activation, and invasion of RA-fibroblast-like synoviocytes (FLS) in vitro as well as alleviate the arthritis score and bone damage in the CIA model in vivo.[73] Human

studies of exosome therapy in RA are in their infancy and additional studies are warranted to determine their pros and cons in the clinic.

5 | CONCLUDING REMARKS

Exosomes can be considered as "nanoshuttles" that mediate cell-cell communication. They carry various molecules including DNAs, RNAs, lipids, and proteins resulting in pleiotropic effects on target cells.[74] In RA patients, there are exosomes with both stimulatory and inhibitory functions that participate in the inflammatory process and perpetuation of the disease. Also, some of them can be considered as reliable biomarkers for the evaluation of RA disease activity or even as diagnostic biomarkers. However, the use of exosomes as biomarkers is not without its challenges. Despite the fast growth in exosome research, isolation and purification techniques are still poorly developed and standardized. Various techniques have been introduced for exosome purification and these methods all impact the yield, diversity, and functions of EVs recovered. Additionally, because the exosome populations expressed from single cells are heterogeneous; the content concentrations are expected to exist in a range and not at a set standard.[75-78]

Exosome isolation from raw biological fluids is challenging as some components of biological fluids such as lipoprotein, chylomicrons, and microvesicles have size overlaps with exosomes.[79,80] Isolation from conditioned cell culture media is less complicated; however, other types of EVs are often co-isolated due to their size overlap and lack of specific biomarkers. Furthermore, cells produce similar sets of proteins and miRNAs while exosomes also express similar protein and RNA profiles. Furthermore, exosome circulation in the body originates from a variety of different cell types and as such, unless they contain exceedingly distinct cargos, it would be challenging to determine their tissue of origin. However, there are few unique cell-specific proteins.[81] So, developing efficient and reliable isolation methods is urgent to further advance this field.

To date, there is a general lack of compiled data to be able to diagnose diseases based on exosomes alone, and, considering practical clinical limitations, there are currently no technologies for the detection and analysis of exosomes that are convenient in terms of the specificity, time spent to analyze a sample, sample throughput, quality control, inter-lab variability, and accuracy of the results. Prior to the implementation of any diagnostic practice, a complete database of the exosomal profiles seen in diseases should be compiled to prevent misdiagnosis due to similar cargo contents, and technologies must be developed for a clinical setting.

The improvements in the methods of exosome isolation and purifications are needed in order to study the cargo contents and functions, which would shed light on the biogenesis in return. Once such limitations are overcome, new biomarkers can be identified for exosome characterization and use them in diagnostic applications. Moreover, with more information on exosome biogenesis and functions, there would be significant opportunities to manipulate their composition, properties, and cell interactions to further advance their therapeutic application. Nonetheless, recent advances in using exosomes as biomarkers for disease detection and as natural drug/gene delivery systems have been stimulating. The potential of using exosomes as a therapeutic platform is clearly demonstrated.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Student Research Committee of Mazandaran University of Medical Science, Sari, Iran for financially supporting this research [Grant Number: IR.MAZUMS.REC.1399.704]

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

PZ and AH contributed to the idea design and literature search. BH, ME and DB wrote parts of the manuscript. PZ contributed to designing the figures. NT contributed to language editing.

ETHICAL APPROVAL

Ethical approval is not applicable.

INFORMED CONSENT

Informed consent not applicable.

ORCID

Parisa Zafari https://orcid.org/0000-0002-7826-1185

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How to cite this article: Hejrati A, Hasani B, Esmaili M, Bashash D, Tavakolinia N, Zafari P. Role of exosome in autoimmunity, with a particular emphasis on rheumatoid arthritis. *Int J Rheum Dis*. 2021;24:159–169. https://doi.org/10.1111/1756-185X.14021

Received: 17 August 2020 | Revised: 28 September 2020 | Accepted: 26 October 2020

DOI: 10.1111/1756-185X.14035

REVIEW

International Journal of Rheumatic Diseases | WILEY

Therapeutic exercises and rehabilitation in axial spondyloarthropathy: Balancing benefits with unique challenges in the Asia-Pacific countries

Parthajit Das[1] | Rathindranath Haldar[2] | Sham Santhanam[3] | Vinod Ravindran[4]

[1]Apollo Gleneagles Hospital & Vivekananda Institute of Medical Science, Kolkata, India

[2]Department of Physical Medicine and Rehabilitation, Institute of Post Graduate Medical Education and Research, Kolkata, India

[3]Gleneagles Global Health City, Chennai, India

[4]Centre for Rheumatology at Calicut, Kozhikode, India

Correspondence
Parthajit Das, Vivekananda Institute of Medical Science, 99, Sarat Bose Rd, Hazra, Kalighat, Kolkata, West Bengal 700026, India.
Email: parthajit.das21@gmail.com

Abstract

The burden of axial spondyloarthropathy (axSpA) in the Asia-Pacific region is substantial. The management of axSpA has been revolutionized with the advent of biological therapy where the disease activity, functional disability and negative psychological affect can be mitigated to a great extent. On the other hand, exercise remains an essential component of the treatment of axSpA at all stages, which is often discounted or underused. This is compounded by a gap in demand and supply between increasing number patients with axSpA and paucity of trained specialists and rehabilitation personnel in the Asia-Pacific countries. The acceptability and uptake of therapeutic exercise is strikingly poor in this region because of multiple factors such as lack of awareness among health professionals and the general population, poor healthcare infrastructure, lack of resources and limited accessibility to rehabilitation services. Health authorities and professional bodies in these countries need to work in tandem to expand healthcare facilities, encourage training opportunities and promote safe and effective exercise interventions which is accessible to the general population and individuals with axSpA. Adequate patient education, optimum control of disease activity and strict adherence to therapeutic exercise is essential to predict the best clinical outcome. In this narrative review we have appraised the impact of therapeutic exercise in this era of biological therapies in axSpA and have explored the challenges of rehabilitation services in the Asia-Pacific countries. Overall, the available quality of evidence is mixed, acknowledging the beneficial role of exercise and optimum usage and protocols pertaining to axSpA specific exercises and therefore further research is warranted.

KEYWORDS

ankylosing spondylitis, axial spondyloarthropathy, exercise, physiotherapy, rehabilitation

1 | INTRODUCTION

Spondyloarthropathies (SpA) is a group of autoimmune chronic inflammatory diseases that mainly affects the axial skeleton (axSpA), with possible manifestation of arthritis, enthesitis, dactylitis and/or extra-articular features such as psoriasis, inflammatory bowel disease and anterior uveitis. The hallmark feature of this disease is inflammatory back pain which arises due to sacroiliac joint synovitis, enthesitis throughout the spine, and/or involvement of peripheral entheseal structures.[1] The Assessment of SpondyloArthritis

International Society (ASAS) has validated the classification criterion of axSpA that includes radiographic sacroiliitis (radiographic axSpA or ankylosing spondylitis) and non-radiographic sacroiliitis (non-radiographic axSpA).[2] The prevalence of spondyloarthropathy in the Asia-Pacific countries has been estimated to range from 0.01% to 0.49%.[3] Affected individuals are usually young and in the productive age group. Therefore SpA has the potential of having a negative societal impact as a result of physical disability, loss of productivity, poor quality of life and increased healthcare expenditure. Patients with axSpA from the Asia-Pacific region have demonstrated higher prevalence of anxiety, depression and poorer quality of life as compared with healthy controls and people with rheumatoid arthritis (RA).[4,5]

By and large, patients with axSpA had been managed with the use of on-demand nonsteroidal anti-inflammatory drugs (NSAIDs) and therapeutic exercises. However, the management of axSpA was revolutionized with the advent of biological therapies where control of spinal and joint inflammation, induction of remission or low disease activity, improvement in functional status can be successfully achieved to a considerable extent. Therefore, concerns regarding the role of exercise therapy in the management of axSpA in this present scenario are justified. In this context, organizations such as the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have provided recommendations to include physical therapy (PT) intervention in the management of axSpA.[6,7] The Asia-Pacific League of Associations of Rheumatology (APLAR) and Taiwan Rheumatology Association (TRA) have also emphasized the inclusion of PT interventions in the management of axSpA.[8,9]

In addition to its specific benefits in axSPA, it is widely acknowledged that regular exercise has a multifold beneficial effect not only on people with coronary artery disease, cerebrovascular disease, and diabetes but also individuals with rheumatic disease.[10,11]

However, in order to optimize the benefit of PT interventions for patients with SpA, one has to take into account the diverse healthcare systems and rehabilitation networks which prevail across countries in the Asia-Pacific region, driven by unique demographics, epidemiological transitions, region-specific socioeconomic developments, political and cultural environments.[12] Because of wide variability in the organization of and access to PT interventions, it is desirable that regional needs are specifically addressed, for example by recommendations such as from the TRA.[9]

Unmet rehabilitation needs may impair function, restrict participation, increase dependency and decrease quality of life. Individuals with axSpA are often unable to perceive the beneficial impact of institutional or community-based rehabilitation in these countries because of lack of awareness, limitations of structured healthcare infrastructure, poor accessibility and suboptimal exercise prescription by healthcare or rehabilitation professionals.[13] In this narrative review we have appraised the positive impact of various PT interventions in axSpA and have explored the challenges to the provision of high-quality rehabilitation services in the Asia-Pacific countries.

Key messages

- Therapeutic exercise has a beneficial role in the management of axSpA.
- Adequate patient education, optimum control of disease activity and strict adherence to therapeutic exercise is essential to predict the best clinical outcome.
- More research is warranted on the optimal dosage and protocol of AS specific exercise prescription.
- Strengthening the rehabilitation network in Asia-Pacific countries is essential to provide institutional or community-based rehabilitation care and optimize its acceptability.
- Due to wide variations in the provision and access to physiotherapy and rehabilitation services in countries from the Asia-Pacific region, the need for locally applicable recommendations appear justified.

2 | SEARCH STRATEGY

Our literature search covered the Medline, Embase, Scopus, Web of Science and Google Scholar databases and included articles published in English between January 2000 to June 2020, but did not intend to ignore any high-quality relevant earlier literature. The key words used were Exercise, Exercise Program, Physiotherapy, Rehabilitation, Ankylosing Spondylitis, Spondyloarthropathy, South East Asia, Asian and Asia-Pacific Countries. In addition we manually searched national rheumatology societies, the *Indian Journal of Rheumatology* (India) and *Modern Rheumatology* (Japan). We included the studies where at least one of the comparative groups received a PT intervention and demonstrated significant clinical outcomes. Overall, we observed a paucity of research data investigating the impact of therapeutic exercise on individuals with axSpA in the Asia-Pacific countries. We have followed the guidelines for writing narrative reviews.[14]

3 | RATIONALE FOR EXERCISE THERAPY AND REHABILITATION IN axSpA

In order to understand the rationale of therapeutic exercise in axSpA it would be useful to understand the types of exercise. According to the American College of Sports Medicine (ACSM) recommendations, exercises in general are classified into 4 core categories.[15]

1. Muscle strengthening or resistance exercises are aimed to increase force of muscle contraction (eg, lifting weights, squats).
2. Aerobic exercises are designed to improve cardiorespiratory endurance (eg, walking, running, swimming, cycling, and aerobic dance).

3. Flexibility or stretching exercises tend to improve joint and muscle flexibility (eg, hamstring stretch, gastrocnemius stretch etc).
4. Neuromotor skills training to improve balance and coordination (eg, wobble board).

A mixed exercise program including more than one aforementioned core exercise categories are often advocated in order to improve stiffness, function and quality of life.[16] In addition, mind–body exercise programs are designed to integrate psychological well-being into PT interventions such as Tai Chi and Yoga.

The main biomechanical pathology in patients with axSpA are restricted spinal (forward craning of the neck, high dorsal kyphosis, obliteration of lumber lordosis) and peripheral joint mobility, limited chest expansion and compromised aerobic capacity. To address this, AS specific exercises encompass a group of exercises including: (a) range of motion exercises (ROM) aimed to improve mobility of axial (flexion, extension, lateral flexion and rotation) and peripheral joints; (b) muscle strengthening exercises involving antigravity muscles or "core stability" exercises; (c) stretching of specific muscle groups; and (d) cardiorespiratory fitness.[17]

Rehabilitation, on the other hand is the combined use of medical, educational, social, vocational measures for training and retaining the individual to the highest possible level of functional ability in individuals suffering from axSpA. This can be achieved through judicious use of various modalities such as:

1. home care programs (splinting, recreational activity)
2. provision of assistive devices (orthotics) and joint protection techniques designed to increase mobility and function (mobility devices, splints, braces, prismatic spectacles, long-handled grabber and shoe horn etc)
3. thermotherapies (cryotherapy, hot pack, wax bath etc)
4. electrical therapies: short wave diathermy, ultrasound therapy, interferential therapy (IFT), transcutaneous electrical stimulation (TENS)
5. hydrotherapy (individual or group exercise sessions in swimming pools, or bath tubs)
6. spa or balneotherapy.

4 | IMPACT OF EXERCISE AND REHABILITATION ON axSpA

Previous well-designed exercise programs have demonstrated multidimensional beneficial impact on people with rheumatic diseases such as RA. However, the effect of PT interventions on axSpA has shown incongruous results. ACR, EULAR and APLAR guidelines have reassured the safety profile of therapeutic exercises without any progression of joint damage or flare of disease activity.[6,7,9] De Jong et al[18] reported that long-term high-intensity exercise programs are safe without any progressive damage of large or small joints of hand and feet in RA. However, it is prudent that additional vigilance should be practiced when handling people with ankylosed or osteoporotic spine and/or with joint replacements. High impact sport/activities such as football, martial arts, rugby, long distance road running and golf should be avoided in patients with active axSpA due to the risk of disease exacerbation or injury.

Continued supervision, assessment and monitoring of PT interventions remain an essential component of the therapeutic strategy in axSpA. The ASAS/Outcome Measures in Rheumatology (OMERACT) group has recommended specific tools to assess and monitor physical function (Bath Ankylosing Spondylitis Functional Index [BASFI]), pain (visual analog scale [VAS]), global assessment of disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), spinal mobility (Bath Ankylosing Spondylitis Metrology Index [BASMI]), fatigue (VAS) and quality of life (ASAS Health Index and AS quality of life [ASQoL]) questionnaire).[19]

The impact of PT interventions on the individuals with axSpA has been assessed in various studies (summarized in Table 1). We have discussed these studies individually and have appraised their overall quality of evidence as per guidelines by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group.[20] The majority of studies (including randomized controlled trials [RCTs]) were of short duration ranging from 3 weeks to 3 years which could influence their correct interpretation. Where available we have also mentioned the quality of evidence appraising the impact of PT interventions on health and functional status in patients with axSpA based on the available literature as summarized in the ACR/SPARTAN/SAA (Spodyloarthritis Research and Treatment Network/ Spondylitis Association of America).[7] The APLAR recommendations have observed "Very low" grade of evidence but have conditionally recommended PT and exercise in patients with axSpA.[8]

4.1 | Effect of patient education on exercise in axSpA

In patients with chronic ailments such as diabetes, rheumatic diseases, and bronchial asthma, appropriate patient education remains an integral component of the non-pharmacological therapeutic strategies to enhance knowledge, coping skills, self-efficacy, treatment adherence and disease control.[21] Educational needs may vary depending on their disease stage, physical and psychological state, social and educational background. Kraag et al[22] have found that a combination of supervised therapeutic exercise program with adequate patient education and disease information resulted in improved functional status at 4 months, which persisted thereafter with minimal intervention. Rodriguez-Lozano et al[23] reported that patients receiving educational intervention with unsupervised physical exercise program at home performed more regular exercise and achieved significant improvement of pain, functional status and quality of life when compared to controls. Healthcare professionals should be prepared to deliver customized patient education to meet patients' specific needs and priorities.

TABLE 1 Studies appraising the effect of exercise on axSpA

Author, y, reference	Type of study	No. of participants	Duration of study	Interventions	Result	GRADE of evidence
Effect of patient education on exercise in axSpA						
Kraig G et al 1990[22]	RCT	53	4 mo	Combination of patient education, home physiotherapy and individualized therapeutic exercise Control – no treatment	Improvement in fingertip-to-floor distance and in function than control. Improved adherence to exercise in intervention group.	Low
Rodriguez-Lozano et al 2013[23]	RCT	756	6 mo	Education intervention (2-h session regarding the disease and a non-supervised home-based physical activity)	Mean difference between control and educational groups for BASDAI ($P = .005$), and for BASFI ($P = .002$).Improved adherence to exercise in intervention group	
Effect of exercise on cardiorespiratory health						
Sveaas et al 2014[27]	RCT	28	12 wk	Endurance and strength exercise	Significant effect upon arterial stiffness augmentation index, pulse wave velocity (m/s), VO_2 peak (mL/kg/min), and trunk fat, BASDAI and BASFI.	Low
Niedermann et al 2013[28]	RCT	106	12 wk	Cardiovascular and flexibility training program	Lower level of peripheral pain ($P = .01$). Higher fitness level in the training group vs. control group.No effect on BASDAI	
Durmus et al 2009[29]	RCT	56	12 wk	Global posture re-education (GPR) exercise method	The GPR method demonstrated greater improvements in specific forced vital capacity, forced expiratory volume in 1 s, and peak expiratory flow parameters compared to conventional exercise	
Sveaas et al 2018[30]	RCT	28	12 wk	Cardiorespiratory and strength exercises	Promising effects of cardiorespiratory and strength exercises on emotional distress ($P < .01$), fatigue ($P = .02$), and ability to do a full day's work ($P = .02$)	
Effect of exercise on bone mineral density (BMI)						
De Jong et al 2004[32]	RCT	300	2 y	High-intensity weight-bearing exercise program	The change in hip BMD was positively associated with changes in both muscle strength (multivariate odds ratio [OR] 1.75, 95% CI 1.07-2.86) and aerobic fitness (OR 1.79, 95% CI 1.10-2.90)	Very low
Effect of exercise on function, mood and quality of life in axSpA						
Hilberdink et al 2019[34]	Observational	118	3 y	Cardiorespiratory and strengthening exercise	Majority of the patients were satisfied with the group exercises.	Moderate (Function-active AS) Low (Function-stable AS) Very low Mood and quality of life

(Continues)

TABLE 1 (Continued)

Author, y, reference	Type of study	No. of participants	Duration of study	Interventions	Result	GRADE of evidence
Effect of home-based exercise programs (HEP) vs. supervised group exercise programs (GEP) on axSpA						
Liang et al 2015[37]	Meta-analysis	1098	NA	Home-based exercise	Home-based exercise interventions significantly reduced the BASFI ($P = .001$), BASDAI ($P = .04$), depression ($P = .001$)	Moderate
Analay et al 2003[35]	RCT	51	3 mo	Intensive group exercise under the supervision of a physiotherapist and a HEP.	GEP was more effective than HEP.	
Cagliyan et al 2007[38]	RCT	46	6 mo	Group 1- performed instructed exercises at home for 6 mo.Group 2- did same exercises at the hospital for 2 h weekly under the observation of a physiotherapist for 3 mo	HEP had significant improvement in rest and during activity pain ($P < .005$). Functional improvement was better in the supervised exercise group within 3 mo.	
Karapolat et al 2008[39]	Non-RCT	41	6 wk	Compared the impact of GEP and a HEP	No statistically significant differences were concluded between the 2 exercise groups ($P > .05$)	
Helliwel et al 1996[40]	RCT	44	6 mo		Significant differences between HEP and supervised GEP; VAS ($P = .001$) and cervical rotation ($P = .03$).No significant differences were found at 6 mo	
Effect of exercise on nr-axSpA vs radiographic axSpA						
Levitova et al 2016[41]	RCT	46	3 mo	Outpatient group physiotherapy for 60 min twice a wk and a daily HEP	Significant improvement in ASDAS-CRP in the nr-axSpA subgroup ($P < .05$) and in the BASMI in both, the nr-axSpA and the AS subgroups ($P < .0001$ and $P < .0001$, respectively)	Moderate(Active AS) Low(Stable AS) Low (non-radiographic axSpA)
Escalas et al 2016[42]	Observational cohort	708	6 mo	Supervised physiotherapy	No statistically significant effect upon BASFI and ASAS20 in early spondyloarthropathy.	
Pecourneau et al 2018[43]	Meta-analysis	331	NA	HEP, swimming, Pilates training, supervised exercises	Statistically significant improvement of BASDAI and BASFI in r-axSpA and nr-axSpA patients, and the impact was largest wherein aerobic and strengthening exercise programs predominate over stretching and breathing exercises	
Viitanen et al 2001[44]	RCT	25	3 y	Intensive 3-wk inpatient exercise program in nr-axSpA patients	Small but significant improvements in BASDAI, and stiffness-VAS but no improvements in BASFI and HAQ scores after 3 mo.These changes were lost during 3 y follow up.	
Effect of exercise monotherapy vs combination therapy with therapeutic agents						
Yigit et al 2013[45]	Prospective	42	10 wk	HEP + TNF inhibitors therapy	Significant Improvement in BASDAI, BASMI, BASFI, fatigue, quality of life	Low
Liang et al 2015[46]	Meta-analysis	221	NA	Exercise combined with TNF inhibitors	Intervention with exercises TNF inhibitors therapy significantly reduced the BASMI scores (MD, −0.99; 95% CI, −1.61 to −0.38) and BASDAI scores (MD, −0.58; 95% CI, −1.10 to −0.06)	

(Continues)

TABLE 1 (Continued)

Author, y, reference	Type of study	No. of participants	Duration of study	Interventions	Result	GRADE of evidence
Effect of various physical therapy modalities on axSpA						
Gemignani et al 1991[47]	RCT	20	3 wk	Transcutaneous electrical nerve stimulation	Significant short-term differences ($P < .025$) in pain and stiffness, no statistically significant improvement in lumbar mobility.	Very low
Falagas et al 2009[48]	Meta-analysis	1720		Balneotherapy	Balneotherapy did result in statistically significant improvement in pain	
Lee et al 2008[49]	RCT	40	8 wk	Tai Chi for RA program; plus home practice; Tai Chi video; telephoned by researchers × 2/wk	BASDAI and flexibility both improved significantly compared to control group ($P < .05$)	
Karapolat et al 2009[50]	RCT	45	6 wk	Group 1- swimmingGroup 2 -walkingGroup 3 – conventional exercise (CE)	Swimming, walking in addition to CE had beneficial effects on the quality of life and pulmonary functions	
Altan et al 2012[51]	RCT	55	24 wk	Pilates with trainer, × 3/wk	BASFI showed significant improvement at wk 12 ($P = .031$) and wk 24 ($P = .007$)	

Abbreviations: ASAS 20 score; Assessment in SpondyloArthritis International Society 20 score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; GPR, Global Posture Re-education; HAQ, Health Assessment Questionnaire; VAS-QoL, visual analog scale quality of life; RCT, randomized controlled trial.

4.1.1 | Assessment of evidence

We found "Low" grade quality of evidence to suggest positive impact of patient education on spinal mobility, function and quality of life. Further research is warranted to explore the impact of long-term disease-specific qualitative and quantitative patient education on exercise and axSpA.

4.2 | Effect of exercise on cardiorespiratory health

Chronic inflammation has been recognized as a cardiovascular (CV) risk factor and is associated with accelerated atherosclerosis and higher incidence of coronary artery disease.[24] Franklin et al[25] reported an inverse association between aerobic fitness and CV mortality in people with comorbidities such as coronary artery diseases, obesity, hypertension and diabetes mellitus. A systematic review and meta-analysis of observational studies has demonstrated significantly higher risk of coronary artery disease (41%) among patients with axSpA.[26] Sveaas et al[27] observed that high-intensity cardiorespiratory and strengthening exercise have improved disease activity and reduced CV risk in axSpA. However, Niederman et al[28] reported that although inclusion of aerobic training to flexibility exercises improved cardiorespiratory fitness (as assessed by sub-maximal bicycle test), no significant positive impact on CV risk factors (cholesterol and triglyceride levels). Cardiorespiratory exercises have a positive impact on fatigue, mood, function and general well-being. Durmus et al[29] demonstrated a significant improvement in 6 minutes walk distance but insignificant improvement in pulmonary function tests in the exercise group when compared to controls. Sveaas et al[30] reported that high-intensity cardiorespiratory and strength exercises had a promising impact on fatigue, emotional distress and functional status in patients with axSPA.

4.2.1 | Assessment of evidence

An enhanced CV risk profile has been observed in axSpA patients. We found "Low" grade quality of evidence to demonstrate significant long-term improvement of CV risks and cardiorespiratory function through exercise in axSpA. The association between AS specific exercises, CV risk and aerobic capacity in axSpA patients requires more research.

4.3 | Effect of exercise on bone mineral density (BMD)

People with rheumatological diseases are at greater risk of lower BMD because of inflammatory cytokines mediated bone loss, advanced age, physical inactivity, concomitant glucocorticoid therapy and so on. Patients with axSpA experience 2 enhanced but opposite bone remodeling processes: (a) new bone formation (syndesmophytosis)

around the vertebral cortex, zygapophyseal joints and entheses and (b) excessive loss of trabecular bone leading to spinal osteoporosis. Mitra et al[31] observed higher prevalence of osteoporosis in axSpA patients when compared with age and gender matched controls, even in early onset and mild disease groups. Loss of BMD is difficult to mitigate and warrants optimum control of disease activity, adequate calcium and vitamin D supplementation, appropriate bone protection strategies and long-term weight-bearing exercises (either by repetitive weight-bearing and/or strengthening exercises). There were no studies showing the positive impact of exercises in BMD in patients with axSpA; however, De Jong et al[32] have reported affirmative impact of combined and supervised high-intensity, weight-bearing exercises on BMD in patients with RA.

4.3.1 | Assessment of evidence

Osteoporosis is prevalent in patients with axSpA. We observed "Very low" grade quality of evidence to demonstrate a positive association between BMD and AS specific exercises in axSpA. Several short duration exercise training programs have failed to demonstrate any satisfactory improvement in BMD in axSpA. A combination of muscle strengthening and weight-bearing exercises are required to improve BMD.

4.4 | Effect of exercise on function, mood and quality of life

Patients with axSpA usually suffer from joint pain, stiffness, excessive fatigue and low mood which may impair their functional status and psychological well-being. South-Asian patients with axSpA also exhibited poorer quality of life when compared with the general population and RA patients.[4,5] It has been reported that non-pharmacological interventions such as exercise interventions are effective in reducing fatigue and depression in patients with AS.[33] Supervised group exercise programs have demonstrated greater improvement of spinal movements, quality of life, and patient satisfaction and global assessment when compared with unsupervised, individual exercise programs.[34,35] Patients receiving additional behavioral education programs were found to have better pain management ability, functional skills, fatigue and self-efficacy scores. [36]

4.4.1 | Assessment of evidence

We observed "Moderate" and "Low" grade quality of evidence to demonstrate positive impact of exercise on function in active AS and stable AS respectively. The ACR/SPARTAN/SAA network noticed similar quality of evidence to associate exercise and function in axSpA. Despite consistent observations that exercise intervention has been effective in axSpA, there was "Very low" grade quality of evidence exploring the psychological impact of exercise.

4.5 | Effect of home-based exercise programs (HEP) versus supervised group exercise programs (GEP)

Regular HEP has been shown to reduce pain, improve spinal stiffness, chest expansion, depression and quality of life in axSpA.[37] A Cochrane systematic review has suggested that individualized HEP or supervised exercises were superior to no intervention, supervised GEP were superior to HEP, and a combination of GEP and spa therapy was superior to GEP alone in improvement of pain, function and psychological status.[35] Cagliyan et al[38] reported significant improvement of range of cervical spine rotation, pain, BASDAI, ASQoL scores and depression in the GEP group immediately after 3 months of intervention, and during follow-up when compared to the HEP group. Karapotal et al[39] have observed that HEP were cheaper, easily performed and equivalent to supervised GEP groups in patients with AS. Helliwell et al[40] have shown that combination of exercises (aerobic, strengthening, and ROM) in HEP has significantly improved aerobic capacity and functional ability (BASFI) in patients with AS and was superior to HEP with ROM exercises alone.

4.5.1 | Assessment of evidence

We found "Moderate" grade quality of evidence to demonstrate positive effect of home exercise programs on pain, stiffness and function. The ACR/SPARTAN/SAA network has observed moderate quality of evidence to suggest positive impact of HEP on pain, spinal stiffness and function in active and stable AS. Although GEP is strongly recommended, a "Very low" grade quality of evidence was found to advocate the superior efficacy of GEP over HEP.

4.6 | Effect of exercise on non-radiographic axSpA versus radiographic axSpA

There were limited numbers of studies exploring the effectiveness of rehabilitation programs in non-radiographic axSpA. Levitova et al[41] demonstrated that an intensive therapeutic exercise program resulted in improvement of BASDAI, Ankylosing Spondylitis Disease Activity Score – C-reactive protein, BASMI scores and calprotectin levels in both non-radiographic axSpA and radiographic axSpA. A recent study involving the DESIR cohort from France reported no significant functional benefit of physical therapy in daily practice for patients with non-radiographic axSpA.[42] A meta-analysis of 8 RCTs concluded that therapeutic PT interventions showed a significant improvement of disease activity and functional status in radiographic and non-radiographic axSpA patients, and the impact was largest wherein aerobic and strengthening exercise programs predominate over stretching and breathing exercises.[43] Viitanen et al,[44] observed small but significant improvements in BASDAI, BAS-G, and stiffness-VAS but insignificant improvements in BASFI and Health Assessment Questionnaire scores after 3 months following an intensive 3-week inpatient exercise program in non-radiographic axSpA

patients. However these small changes had disappeared during 3 years of follow up.

4.6.1 | Assessment of evidence

We found "Moderate" and "Low" grade quality of evidence to demonstrate positive impact of exercise on AS and non-radiographic axSpA. The ACR/SPARTAN/SAA network has also observed moderate quality and low quality of data showing beneficial impact of any form of PT intervention in active AS and stable AS respectively. Low grade quality of evidence was available for PT intervention and non-radiographic axSpA. AS specific exercise dosages to address the strength, cardiorespiratory function and neuromotor skills have received little attention in the literature especially with non-radiographic axSpA.

4.7 | Effect of combination of exercise therapy with therapeutic agents

Yigit et al[45] reported that combination of HEP and anti-tumor necrosis factor (anti-TNF) therapy resulted in significant improvement of functional capacity, joint mobility, depression and quality of life when compared with anti-TNF therapy alone. Liang et al[46] in their meta-analysis of five studies comprising 221 participants have demonstrated that combination of intensive group exercise with an educational-behavioral program with anti-TNF therapy resulted in significant reduction of BASDAI, BASFI, BASMI, chest expansion, pain and fatigue, suggesting that intensive rehabilitation has a positive impact on axSpA clinically stabilized with biological therapy.

4.7.1 | Assessment of evidence

We observed "Low" grade quality of evidence to demonstrate the short-term beneficial impact of additional AS specific exercises on anti-TNF therapy. No studies have addressed the effect of long-term additional AS specific exercises on the therapeutic management of axSpA. In addition, other disease-modifying agents such as sulphasalazine have not been studied in this context.

4.8 | Effect of various PT modalities on axSpA

Data on the effectiveness of various physiotherapy modalities in the management of axSpA were sparse. Gemignani et al[47] studied the effect of TENS with sham TENS treatment over 3 weeks and reported significant short-term relief of pain in the treatment arm, but the results were statistically insignificant. Balneotherapy and spa therapy have been traditionally used in many centers across the world for rheumatic diseases and chronic ailments. In a meta-analysis, balneotherapy was found to be effective in improvement of pain perception in rheumatic diseases including AS, although the results were statistically insignificant.[48] Three RCTs have suggested that Tai Chi,[49] swimming,[50] and pilates[51] could have a short-term beneficial impact on mobility, strength and neuromotor training in patients with axSpA. Spinal manipulation should better be avoided in patients with axSPA.

4.8.1 | Assessment of evidence

We found "Very low" grade quality of evidence showing the beneficial effect of various PT modalities on the disease activity and function in axSpA. The ACR/SAA/SPARTAN network has observed very low quality of evidences to demonstrate positive impact of physiotherapy modalities in axSpA. They also observed moderate and very low quality of evidence to suggest that aquatic PT interventions were more effective (short-term) than land-based PT interventions in improving function in active AS and active non-radiographic axSpA respectively. There was insufficient evidence to advocate the superiority of one particular modality over the other. Any consensus regarding standardized protocols was lacking.

5 | EXERCISE PRESCRIPTION FOR axSpA

FITT-VP[52] (Table 2) is a widely used principle for exercise prescription consisting of frequency, intensity, type, timing, volume and progression of exercise. The TRA has prescribed a comprehensive exercise program for individuals with axSpA.[9] An individualized exercise program should be prescribed by a team of experienced multi-disciplinary professionals including rheumatologists, orthopedics rehabilitation personnel, occupational therapists, psychologists and so on, according to the patient's physiology, disease burden, functional status, psychological factors, culture and aspirations to

TABLE 2 FITT- VP principle of exercise prescription

FITT-VP	Translation
Frequency	How often? – eg number of sessions/da or d/wk
Intensity	How hard? - percentage of physiological maximum (heart rate, strength, VO_2 max)
Time (duration)	How long? – min, h, d
Type of exercise	Which type of exercise? – aerobic, strengthening, balance etc
Volume	eg. 150 min of moderate intensity or 75 min of combined moderate and vigorous intensity exercises
Progression	eg. increase, as tolerated up to 300 min/wk of moderate or 100 min/wk of moderate to vigorous exercise

Abbreviation: VO_2 max, maximum rate of oxygen consumption.

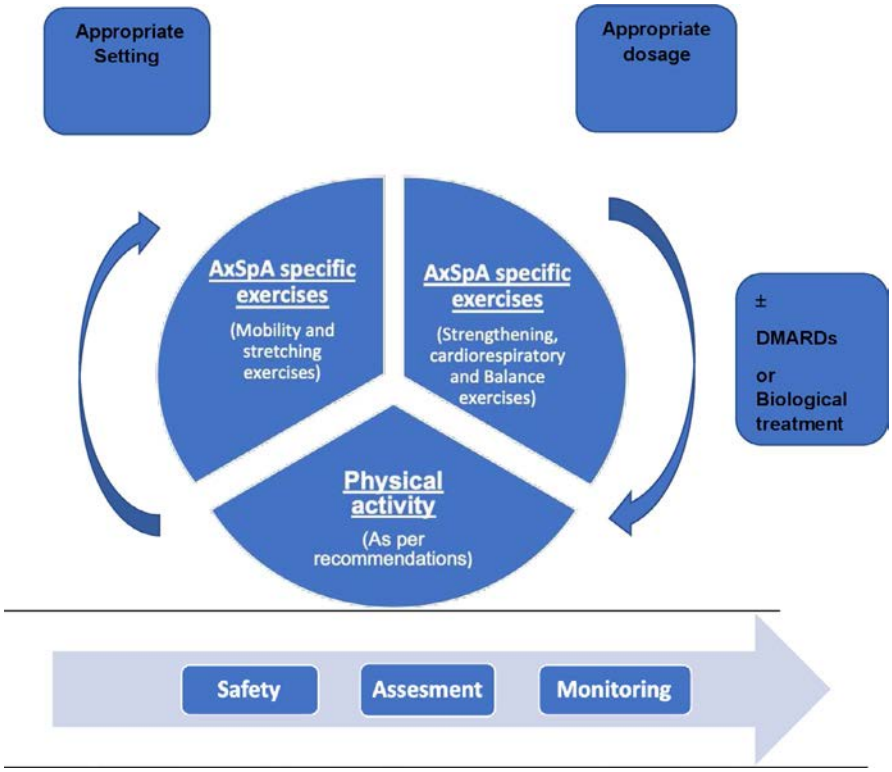

FIGURE 1 Framework of AS specific exercises

ensure adequate adherence. Ward et al[53] found that spinal exercises on more than 5 days per week, and recreational exercises for more than 200 minutes per week, lead to improvement of pain, stiffness and function and slower progression of functional disability over 5 years. Based on the present review of literature we have proposed a framework of AS specific exercises (Figure 1). In Table 3 we have proposed a comprehensive yet simple rehabilitation program for individuals with axSpA which could be easily adopted in most Asia-Pacific countries. This includes a combination of posture control techniques, ROM, muscle strengthening, stretching of commonly affected muscles, aerobic, balance training and cardiorespiratory exercises. We further propose that the clinical effectiveness of such approach should be studied formally. Spinal mobility exercises could be practiced as illustrated in the National Ankylosing Spondylitis Society guidebook (12146 NASS Guidebook.indd – VCU.edu).

Adherence is an important factor to determine the effectiveness of any intervention. Sufficient patient education and monitoring strategies, individualized feedback sessions, application of telecommunication facilities and behavior change techniques could be useful to improve motivation, acceptability and competence with exercise.

6 | RECOMMENDATIONS ON PHYSICAL ACTIVITY IN axSpA

There is a compelling body of population-based evidence that regular physical activity imparts multisystem benefits.[10,11] The World Health Organization (WHO),[54] has proposed internationally accepted recommendations to promote the awareness of regular physical activity among adult populations (18-64 years). Every adult should accumulate at least 150 minutes of moderate intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous intensity aerobic exercise along with muscle strengthening exercises. The American College of Sports Medicine (ACSM)[15] recommended additional inclusion of flexibility and neuromotor exercises such as balance or agility on at least 2 days a week. The EULAR, ACR/SAA/SPARTAN group, APLAR and TRA have also recommended regular physical activity for people with arthritis (including axSpA) which may constitute a bridge between arthritis-specific exercises and public health recommendations for physical activity.[6-9]

7 | CHALLENGES IN ASIA-PACIFIC COUNTRIES

It is clear that an efficient rheumatology and rehabilitation network is essential to ensure optimum dissemination of recommendations based PT interventions among healthcare professionals and patients with axSpA. In the Asia-Pacific countries there are a number of barriers as to why this is not happening.

There are wide variations in the healthcare expenditure and rehabilitation networks across countries in the Asia-Pacific region. The current health expenditure as a percentage of GDP is around 3%-5% in most Asia-Pacific countries. In contrast, the percent of expenditure in Western countries ranges 10%-17%.[55] Similarly, the average health spending per individual ranges from US$41 in low income

TABLE 3 Proposed rehabilitation program for patients with axSpA

Category of exercise	Interventions	Regime
Posture control	Walking tall and tucking the chin. Isometric shoulder bracing (when required). Chest - up and forward. Lying prone for 15-20 min twice a d. Apply principles of ergonomics at work and daily living (sitting upright in a chair reaching to the thoracic level, car seat adjustments while driving, lower margin of computer screen at eye level etc)	Incorporate posture control techniques in daily living
Pain	Aggravated by inactivity Reduced following exercise Hot packs, hot shower bath Ultrasound therapy, interferential therapy, transcutaneous electrical stimulation, etc (under supervision) (If pain increases in the latter stage of exercise, consider fracture assessment)	Practice regular exercise
Flexibility and spinal mobility	Stretching of sternocleidomastoid, trapezius, shoulder adductors and flexures, abdominals, hip adductors and flexors, hamstrings and gastrocnemius ± Tai Chi exercises yoga/Pilates Gymnastic ball may help Sitting cross legged	10-15 min To be practiced on a daily basis
Aerobic exercises	Cycling Walking Jogging Swimming Dance	20-30 min/session 3-5 d/wk Aerobic exercise could be performed by 5 min warm-up, 20-30 min aerobic exercise, and 5 min cooling-down.
Muscle strengthening exercises	Cervical spine, dorso-lumbar spine, shoulder, hip, knee, abdominal muscle, thoracic rotators@**Measures**@Free weights@Weight machines@Therabands@Core stability exercises	Each set of exercises should be performed at 10 repetitions, 2 sets each time, with a rest interval of 2 to 3 min between sets, at least 2 times per wk. Increase intensity over time
Cardiorespiratory exercises	Deep breathing exercise for apical, central and diaphragmatic breathing (with emphasis of full rib cage expansion) Encourage playing wind instruments, singing etc	Daily
Balance training	One leg stance Stability ball Strengthening core muscles	On a regular basis

countries to US$2937 in high income countries.[56] Data on rehabilitation services in Asia-Pacific countries are often fragmented and incomplete. Several challenges have been identified in the delivery of structured rehabilitation services in Asia-Pacific countries such as lack of resources and health infrastructure, limited number of trained specialists and rehabilitation personnel, lack of authorities responsible to administer and monitor services, insufficient health information systems, complex referral systems and poor accessibility, lack of awareness among the general population.[13,57]

The World Report on Disability published by WHO and the World Bank in 2011 has identified several shortcomings of rehabilitation networks and provision of assistive devices globally.[58] Individually too, APLAR countries such as China have reported on the specific rehabilitation needs.[59] Expansion and decentralization of rehabilitation services to the community is essential to improve accessibility and participation. Several countries such as China, India, Myanmar, Thailand, Viet Nam have established mid-level training programs to expand the workforce of rehabilitation personnel.[60] Health authorities and academic institutions from developed countries can collaborate with their developing counterparts to design a national musculoskeletal and rehabilitation network and organize training of educators, healthcare professionals and rehabilitation personnel based on the current situation, regional leadership, financial state, existing information and governance. Efforts should be taken to overcome the hurdles of research capacity by provision of infrastructure to mentor and train rehabilitation researchers and to build

TABLE 4 Challenges to rehabilitation services in the Asia-Pacific countries[13,55]

Components	Challenges	Proposed solutions
Healthcare infrastructure	1. Limited number of institutional or community-based rehabilitation centers. 2. Lack of communication between institutional, private and community healthcare.	1. Establish and expand high-quality and accessible rehabilitation centers. 2. Standardize national rehabilitation services.
Healthcare work force	Limited number of trained rheumatologists, physiatrists, physiotherapists, occupational therapists, social workers	Recruitment of trained personnel with professional degrees at each levels
Training and research opportunities	1. Lack of teaching modules on rheumatology and rehabilitation during undergraduate and postgraduate medical training. 2. Incoherent national training program in rheumatology 3. Lack of structured educational program in physical medicine and rehabilitation.	1. Strengthening of the teaching of rheumatology in undergraduate and postgraduate medical training curricula 2. Emphasis on modules on rehabilitation in postgraduate training in rheumatology 3. Promotion of professional degrees and educational programs for allied health professionals. 4. Strengthening of clinical governance; continued monitoring and assessment of training curriculum 5. Promote research facilities in Asia-Pacific countries
Awareness of physical activity	Poor awareness of physical activity among health professionals, rehabilitation personnel and general population	1. More commitment from health authorities and professional bodies to promote physical activity 2. Involvement of social media, television etc 3. Application of telecommunication facilities to raise awareness and monitor adherence to therapy.
Healthcare expenditure	A small proportion of health budget is spent on community-based rehabilitation and research	Policy makers should invest more to promote research collaborations and community rehabilitation

partnerships between relevant organizations and disciplines representing individuals with axSpA. We have summarized these unique challenges and their proposed solutions in Table 4. We hope that our review draws special attention to enhance the role of therapeutic exercise in the management of axSpA and underscores the need for a supportive national rehabilitation network to help patients in Asia-Pacific countries.

8 | CONCLUSIONS

Despite the mixed quality of available evidence the beneficial role of exercise in people with axSpA has been generally acknowledged. Although exercise in general seems to be safe and effective, their effects on non-radiographic SpA are still debated. Treating clinicians and allied health professionals should encourage their patients with axSpA to incorporate aerobic and cardiorespiratory exercises along with mobility and resistance training in conjunction with recommended therapeutic strategies. Additional supervision should be implemented to ensure adequate patient education and compliance toward exercise prescription. High-quality research is warranted on the optimal dosage, type, frequency and mode of delivery of exercises in the management of axSpA especially during active flares, patients with comorbidities such as CV diseases and with significant deformities and disabilities. It is important for health authorities and professional bodies to work in tandem to promote research collaborations and to establish a national rehabilitation network in Asia-Pacific countries.

CONFLICT OF INTERESTS

None of the authors have declared any conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design of the work, PD, VR. Data collection, PD. Data analysis and interpretation, PD, SS, VR. Drafting the article, PD. Critical revision of the article, SS, RH, VR. Final approval of the version to be published, PD, RH, SS, VR.

ORCID

Parthajit Das https://orcid.org/0000-0002-1788-846X
Sham Santhanam https://orcid.org/0000-0002-3672-9245
Vinod Ravindran https://orcid.org/0000-0001-5842-1877

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How to cite this article: Das P, Haldar R, Santhanam S, Ravindran V. Therapeutic exercises and rehabilitation in axial spondyloarthropathy: Balancing benefits with unique challenges in the Asia-Pacific countries. *Int J Rheum Dis*. 2021;24:170–182. https://doi.org/10.1111/1756-185X.14035

Received: 11 June 2020 | Revised: 19 July 2020 | Accepted: 16 August 2020

DOI: 10.1111/1756-185X.13963

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Fibromyalgia in patients with psoriatic arthritis: Relationship with enthesopathy, sleep, fatigue and quality of life

Firat Ulutatar[1] | Cagri Unal-Ulutatar[2] | Mehmet Tuncay Duruoz[3]

[1]School of Medicine, PMR Department, Pain Medicine Division, Cukurova University, Adana, Turkey

[2]PMR Department, Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital, Istanbul, Turkey

[3]School of Medicine, PMR Department, Rheumatology Division, Marmara University, Istanbul, Turkey

Correspondence
Cagri Unal-Ulutatar, MD, Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital, Physical Medicine and Rehabilitation Department, Emek Mahallesi, Namık Kemal Cad. No:54, 34785 Sancaktepe/İstanbul.
Email: drcagriunal1988@hotmail.com

Abstract

Objectives: To evaluate the relationship of fibromyalgia with enthesopathy, sleep, fatigue and quality of life in patients with psoriatic arthritis.

Methods: The psoriatic arthritis patients according to CASPAR criteria were included in the study. The diagnosis of fibromyalgia was based on 2016 ACR criteria. Demographic and clinical parameters were noted. Disease activity and enthesopathy were evaluated with Disease Activity Score-28 (DAS-28) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), respectively. Functional assessment scales in this study were Psoriatic Arthritis Quality of Life (PsAQoL), Pittsburgh Sleep Quality Index (PSQI), Multidimensional Assessment of Fatigue (MAF). Fibromyalgia Impact Questionnaire (FIQ) was used to assess the functional status of fibromyalgia. The Mann-Whitney U test and Spearman correlation coefficient (ρ) were used. Hierarchical multiple regression analysis used to examine the differential contributions to FIQ score. $P < .05$ was accepted as significant.

Results: We enrolled 50 PsA patients (31 female, 19 male) with a mean age of 49.5 years (SD: 10.2) and mean disease duration 7.5 years (SD: 7.5). Thirty-two patients (64% of PsA patients) fulfilled ACR criteria for fibromyalgia. The mean scores of MASES, PSQI, MAF and PsAQoL were significantly higher in patients with fibromyalgia ($P < .05$). The correlations between FIQ and other functional parameters were as follows; MASES ($\rho = 0.71$, $P < .0005$), PSQI ($\rho = 0.62$, $P < .0005$), MAF ($\rho = 0.60$, $P < .0005$), PsAQoL ($\rho = 0.61$, $P < .0005$). A moderate correlation was existing between FIQ and DAS-28 ($\rho = 0.42$, $P = .03$).

Conclusions: Coexistence of fibromyalgia in PsA patients is associated with the presence of enthesopathy, poor quality of life, sleep disturbance and fatigue.

KEYWORDS

clinical aspects, fibromyalgia, psoriatic arthritis, regional pain syndromes, soft tissue rheumatism

1 | INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease and is included in the spondyloarthropathy group. It affects 30% of patients with psoriasis.[1] Fibromyalgia is a chronic widespread pain condition which can cause fatigue and sleep problems. Central sensitization is one of the reasons to explain these symptoms. This is the state in which the spinal cord amplifies afferent signals out

of proportion to peripheral insults. Central pain is seen in these patients because continuous nociceptive stimulations are amplified via central pathways in rheumatic diseases. The prevalence of fibromyalgia syndrome (FMS) ranges from 2% to 8% in the general population.[2] Disease-modifying antirheumatic drugs are commonly used to control pain; however, they are not solely effective in controlling pain mechanisms. Although the joint inflammation in patients is controlled, a significant portion of the patients continues to have a deterioration in physical function and quality of life (QoL). This may be due to comorbid conditions accompanying patients, for instance, FMS.[3]

Pain, which is the most important finding of rheumatic diseases, occurs as a result of interaction between the peripheral and central nervous systems. Chronic pain is caused by the involvement of joints, skin, muscle and peripheral nerves in PsA patients. Chronic pain may be nociceptive, or neuropathic and it can be due to central sensitization. Pain caused by central sensitization is the result of the excessive increase in central nervous system pain processing. Central sensitization is an exaggerated sensation of pain due to amplified peripheral nociceptive inputs in PsA patients. Fibromyalgia is a kind of central pain syndrome. In FMS, somatic symptoms such as fatigue, forgetfulness, irritable bowel syndrome, insomnia, mood disorders, paresthesia can be seen as well as central pain.[4]

In rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS), FMS is usually present to an average of 15%-30%. Proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha are effective in these central pain pathways in animal studies. It was also reported that chronic pain and stress that may accompany chronic rheumatic diseases may trigger FMS.[4] Diagnosis and treatment of FMS patients are important in PsA. The disease activity in these patients may seem to be uncontrolled by drugs due to accompanied FMS and may lead us to overtreatment. On the other hand, QoL may be impaired and may lead to disability due to the development of somatization symptoms secondary to chronic central pain.[5] With the introduction of patient-reported outcome measures, parameters such as disease activity, response to treatment and QoL in rheumatic diseases were more easily assessed. In this study, we aimed to evaluate FMS in PsA patients and to investigate the relationship of FMS with clinical (disease activity, enthesopathy) and functional (QoL, fatigue, sleep) parameters.

2 | METHODS

2.1 | Participants and sample size

Patients aged 18 or older, diagnosed with PsA according to the classification criteria for PsA (CASPAR) were recruited into the study.[6] This was a cross-sectional study and data were collected prospectively from consecutive Marmara University Pendik Training and Research Hospital attendees to the rheumatology outpatient clinics. Exclusion criteria were the coexistence of other rheumatic diseases, severe psychiatric disorder, pregnancy, malignancy, end-stage renal/hepatic disease. Both written and verbal consents were taken. A formula based on G power version 3.0.10 was used to calculate the sample size. We calculated the relevant sample size in reference to a previous study, using a power of 80% and a significance level of 0.05, effect size 0.87.[7] The minimum sample size was found to be 36.

2.2 | Data collection

The demographic and clinical features of the patients were noted. The demographic data included age, gender, body mass index (BMI), education, marital and employment status. Clinical parameters were disease duration, active/latent psoriasis, presence of dactylitis, major organ involvement, number of swollen/tender joints, erythrocyte sedimentation rate, C-reactive protein, type of treatment (conventional synthetic disease-modifying antirheumatic drugs csDMARDs]; biological DMARDs [bDMARDs]). Disease Activity Score of 28 joints (DAS-28) was used to note disease activity. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was used as an instrument to assess enthesopathy.[8] Fibromyalgia was established based on 2016 fibromyalgia diagnostic criteria.[9] FMS was diagnosed in adults when all of the following criteria were met: generalized pain (at least 4 of 5 regions), symptoms were lasting at least 3 months, widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) ≥ 5 or WPI of 4-6 and SSS score ≥ 9, and a diagnosis of FMS was valid irrespective of other diagnoses.[9] Fibromyalgia impact questionnaire (FIQ) was developed and validated by Burckhardt et al to assess the disease impact in patients with fibromyalgia.[10] It was used to measure physical functioning, work status, depression, anxiety, morning stiffness, fatigue, pain, and well-being over the past week. Its score ranged from 0 to 100. Higher scores reflected more impact.[10]

Associations of FMS with enthesopathy, disease activity, QoL, sleep, and fatigue were analyzed. QoL, sleep, and fatigue in PsA were measured with Psoriatic Arthritis Quality of Life (PsAQoL), Pittsburgh Sleep Quality Index (PSQI), Multidimensional Assessment of Fatigue (MAF), respectively. PsAQoL is a disease-specific instrument assessing QoL defined as the extent to which patient needs were fulfilled and it reflects the impact from the perspective of the patient. It is composed of 20 items, and the participants give true/not true responses (scores 1 and 0, respectively). The total score ranged from 0 to 20, with a high score representing poor QoL.[11,12] It is a reliable and valid scale that has been developed specifically for PsA patients.[13] PSQI is composed of 7 dimensions which were sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The component scores were summed to produce a global score (range 0-21). Higher scores indicated worse sleep quality. Global score greater than 5 was accepted as “poor sleepers”. It has been validated in rheumatic diseases and it was correlated with clinical indices, FIQ and Short Form-36 (SF-36).[14,15] The Turkish version of PSQI was validated in depressive and sleep disorder patients.[16] MAF is a 16 item scale that measures fatigue according to 4 dimensions: degree

and severity, distress that it causes, the timing of fatigue (over the past week), and its impact on activities of daily living. Scores ranged from 0 (no fatigue) to 50 (severe fatigue).[17] MASES evaluates specific entheses at each anatomical location (based on 6 bilateral sites and a single spinous process). The score ranged between 0 and 13.[8] Although developed for use in RA, the MAF has also been validated in other rheumatologic conditions including osteoarthritis, ankylosing spondylitis (AS), SLE.[18] The Turkish version of MAF was validated in chronic musculoskeletal physical therapy patients and scleroderma.[17,19]

2.3 | Statistical analyses

SPSS® version 22 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The data were analyzed using descriptive statistical methods (mean, standard deviation, and frequency). Ordinal variables were compared by using Chi-square test and Fisher's exact test. Spearman's rank correlation coefficient was used to evaluate the relation between FIQ scores and clinical (MASES, DAS-28, disease duration) and functional parameters (PsAQoL, PSQI and MAF). The Mann-Whitney *U* test was performed to compare the scores of PsA patients with or without FMS. Hierarchical multiple regression analysis was used to examine the differential contributions of demographic variables (gender and BMI), clinical parameters (DAS-28 and MASES) and functional parameters (PsAQoL, PSQI and MAF). The variables were entered into 3 models including different categories of variables: demographic variables entered in Model 1, clinical parameters entered in Model 2, and functional parameters entered in Model 3. Scatterplots of the distribution of the residuals for the models were found to be acceptable. For all analyses, $P < .05$ accepted as significant.

3 | RESULTS

A total of 50 PsA patients (31 females, 19 males) were recruited into this study. The average age and duration of the illness of those who participated in the study were 49.5 ± 10.2 years and 7.5 ± 7.5 years, respectively. Demographic and clinical characteristics of the patients are outlined in Table 1. Six patients (12%) had dactylitis, and 27 (54%) patients had an active psoriatic lesion. The frequency of patients in symmetrical arthritis, asymmetrical oligoarthritis, and spondylitis predominant groups was 11 (22%), 35 (70%), 4 (8%), respectively. None of the patients had major organ involvement. PsA patients with FMS numbered 32 (64%) and patients without FMS numbered 18 (36%). Demographic, clinical and functional parameters in PsA patients with FMS were compared to patients without FMS which is depicted in Table 2. FMS frequency was higher among female patients (25 out of 31) compared to male patients (7 out of 12; $P = .002$). There was not a significant difference in FMS presence between the csDMARD and bDMARD users ($P = .09$). Poor sleepers among PsA patients numbered 27 (54%). Among these poor sleepers, 24 had FMS. FIQ scores were significantly higher in female PsA patients (40.1 ± 25.9) compared to male patients (25.2 ± 25.9; $P = .03$). Table 3 shows the relation of FIQ scores with other recorded parameters.

TABLE 1 Demographic and clinical characteristics of patients

	Mean (SD), min-max
Age	50 (10.3), 27-67
BMI, kg/m^2	26.8 (3.4), 20.5-36.6
Disease duration, y	7.5 (7.5), 0.08-36.9
DAS-28 score	3.2 (1.1), 1.5-5.7
	n (%)
Educational level	
Primary-secondary school	33 (66)
High school	7 (14)
University	10 (20)
Employment status	
Unemployed	27 (54)
Employed	16 (32)
Retired	7 (14)
Marital status	
Single	4 (8)
Married	46 (92)
Treatment	
csDMARD	36 (72)
bDMARD	14 (28)

Abbreviations: bDMARDs, biological DMARDs; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DAS, Disease Activity Score.

A hierarchical regression analysis was used to examine the differential contributions of different independent variables to FIQ scores. The full model of gender, BMI, DAS-28, MASES, PsAQoL, PSQI, and MAF to predict FIQ scores was statistically significant, $R^2 = 0.69$, $F_{(7,42)} = 13.17$, $P < .0005$, adjusted $R^2 = 0.64$. The overall model accounted for 69% of the variance in the FIQ scores. In hierarchical multiple regression, 3 models were used. Model 1, demographic variables (gender and BMI) predicted the FIQ scores since its contribution to the models was 24.4% of the variance ($F_{(2,47)} = 7.6$, $P = .001$). Controlling for gender and BMI, clinical parameters assessed by DAS-28 and MASES contributed significantly, accounting for an additional 33% of the variance ($F_{(2,45)} = 17.5$, $P < .0005$). The addition of scales that assessed QoL with PsAQoL, sleep with PSQI and fatigue MAF (Model 3) also led to a statistically significant increase in R^2 of 0.11, $F_{(3,42)} = 5.02$, $P = .005$. Table 4 shows the full details on each regression model.

4 | DISCUSSION

The prevalence of FMS accompanying other inflammatory rheumatic diseases such as RA, spondyloarthropathies (SpA), SLE, SS, and PsA

TABLE 2 Characteristics of PsA patients with FMS and without FMS

	Patients with FMS Mean (SD)	Patients without FMS Mean (SD)	*P* significance value
Age, y	49.1 (10.3)	50.4 (10.5)	.71
BMI, kg/m^2	26.6 (3.7)	27.1 (2.9)	.75
Disease duration, y	8.8 (8.7)	5.2 (4)	.20
DAS-28	3.4 (1)	2.8 (1.1)	.03*
MASES	7.1 (4.5)	0.6 (1.2)	<.0005*
PSQI total score	8.5 (4.5)	2.8 (3.1)	<.0005*
PsAQoL	9.1 (5.8)	3.9 (3.5)	.001*
MAF	26.8 (13.7)	11.7 (11.3)	.002*

Abbreviations: BMI, body mass index; DAS-28, Disease Activity Score; FMS, fibromyalgia syndrome; MAF, multidimensional assessment of fatigue; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PsA, psoriatic arthritis; PsAQoL, psoriatic arthritis quality of life; PSQI, Pittsburgh sleep quality index; SD, standard deviation.

*$P < .05$ accepted as significant.

TABLE 3 Correlation of FIQ scores with demographic, clinical and functional parameters

	Spearman's ρ	*P* significance value
Age	0.05	.74
BMI	−0.24	.09
Disease duration	0.17	.23
DAS-28	0.42	.003*
MASES	0.71	<.0005*
PsAQoL	0.61	<.0005*
PSQI total score	0.62	<.0005*
MAF	0.60	<.0005*

Abbreviations: BMI, body mass index; DAS-28, disease activity score; FIQ, fibromyalgia impact questionnaire; MAF, multidimensional assessment of fatigue; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PsAQoL, Psoriatic Arthritis Quality of Life; PSQI, Pittsburgh sleep quality index.

*$P < .05$ accepted as significant.

TABLE 4 Final model for the associations between FIQ and other variables entered in 3 models

Variables	R^2 change	F change	P value
Model 1: Demographic variables			
Gender BMI	0.24	7.6	.001*
Model 2: Clinical parameters			
DAS-28 MASES	0.33	17.5	<.0005*
Model 3: Functional parameters			
PsAQoL PSQI MAF	0.11	5	.005*

Abbreviations: BMI, body mass index; DAS-28, Disease Activity Score; FIQ, Fibromyalgia Impact Questionnaire; MAF, multidimensional assessment of fatigue; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PsAQoL, Psoriatic Arthritis Quality of Life; PSQI, Pittsburgh sleep quality index.

*$P < .05$ accepted as significant.

is usually higher than the general population.[2] FMS is seen in a significant proportion of SpA and PsA patients who are genetically and clinically predisposed to central sensitization.[2] This study has shown the relation of FMS in PsA patients with their clinical and functional status. This could guide us in which type of PsA patients we need to investigate for FMS.

The prevalence of FMS in PsA patients in the literature varies between 17.2%-53.3% when compared to our results.[20] Chronic widespread pain from FMS is observed in patients with several rheumatic diseases: RA (25%), SLE (30%), and SS (50%).[21] The variance of FMS prevalence might be due to the sample size and type of tool used to diagnose FMS. For instance, Magrey et al investigated 34 PsA patients and used the London Fibromyalgia Epidemiologic Study Screening Questionnaire and Symptoms Intensity scale to screen their patients for FMS.[3]

It has been previously reported that PsA patients with FMS had higher disease activity scores, especially DAS-28 scores.[7,22] Moreover, Joharatnam et al demonstrated that the presence of FMS in patients with RA is related to a higher DAS28.[23] Similarly, we found a moderate correlation between FIQ and DAS-28 score, and in hierarchical regression analyses both DAS-28 and MASES scores contributed significantly to FIQ scores. Also, patients with FMS had higher DAS-28 scores compared to FMS-free ones. It is important to differentiate FMS in these rheumatic disorders since disease activity measures which include subjective elements such as pain and patient global assessment may be exaggerated when fibromyalgia coexists, not reliably reflecting the patients' inflammatory disease activity. This can affect the treatment protocol of inflammatory rheumatic disease.[22] Brikman et al showed that PsA patients with FMS had higher enthesitis scores compared to the ones without

FMS.[7] Macchioni et al suggested that in terms of the diagnostic distinction between PsA and FMS, the presence of an individual ultrasound-positive enthesis is not helpful. On the contrary, a high number of ultrasound-involved entheses makes PsA a more likely diagnosis.[24] This could result in overdiagnosis of PsA. To the best of our knowledge, there is no adequate data investigating patients with ultrasonography (USG) in patients with concomitant existence of PsA and FMS. Moreover, ultrasound is underutilized being an operator-dependent method and for the absence of a standardized approach to study entheses.[20]

Female predominance shown in our study was similar to a previous study in which 92.3% of PsA patients with FMS were female.[7] Moreover, there was no significant difference in mean age or disease duration between the groups (PsA with vs. without FMS) in the same study in accordance with our results.

In hierarchical regression analysis, all of the functional parameters assessing QoL, sleep, and fatigue were found to be significantly related to FIQ scores. In a previous study evaluating the effect of the comorbidities in PsA, patients with FMS had lower scores in QoL assessed by SF-36.[25] However, the study did not compare the effect of severity in fibromyalgia symptoms (assessed by FIQ) to the clinical and functional alterations in PsA patients. Indeed, in our study as the severity of FMS increased, the clinical and functional outcomes of PsA became worse. It was previously reported that 50%-76% of PsA patients suffered from increased fatigue levels. Fibromyalgia, enthesitis and itching sensation from psoriatic plaques may disturb sleep quality in these patients, thereby increasing pain.[3,26] PsA patients with FMS suffered more fatigue in a previous study.[27] Lower SF-36 pain scores (higher levels of pain) and morning stiffness were significantly associated with increased fatigue levels.[27] We found that 54% of PsA patients suffered from sleep disturbance. Gezer et al investigated sleep quality in 41 PsA patients and found that 85.4% of them had sleep disturbance. Also, they found that subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, daytime dysfunction and total PSQI scores were significantly higher in patients with PsA compared to healthy controls.[28] The effect of FMS as comorbidity on sleep disturbance in PsA has not been investigated yet. PsA with FMS had significantly higher sleep disturbance compared to those without FMS. Sleep disturbance is a primary mediator between pain and QoL in PsA patients.[28] The presence of generalized pain, memory disturbances, moodiness, increased anxiety, and concentration problems were found to be related to sleep disorders in FMS.[29] Liedberg et al showed that FMS patients with poor sleep quality had worse pain intensity, disturbed psychological variables, and poor QoL.[30] A UK population-based epidemiological study demonstrated that age, baseline pain status, anxiety, poor QoL and sleep disturbances were all associated with the development of widespread pain.[31] Therefore, identifying and treating FMS in PsA patients might ameliorate the symptoms of fatigue and sleep disturbance, thereby decreasing pain levels.

There are few published data on the prevalence and effect of FMS in patients with PsA. We investigated the functional parameters that are commonly seen in FMS patients and thereby affecting PsA disease activity. Outcome measures directly assessing depression and anxiety was not used which was the limitation of our study. However, in PsAQoL there were questions which are related to the psychological aspect of the patients.

In conclusion, FMS is commonly seen as a comorbid disease in PsA similar to other inflammatory rheumatic diseases. Severity and impact of FMS in PsA patients increases (higher FIQ scores) with female gender, higher disease activity, greater scores of enthesopathy, worse QoL, poor sleep and increased fatigue levels. It is important to recognize and treat FMS in these patients because it can impair QoL, increase fatigue and sleep disturbances by affecting disease activity and entheseal involvement.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Cagri Unal-Ulutatar: collecting and analyzing the data, writing the manuscript. Firat Ulutatar: designing the study, collecting, analyzing the data, writing the manuscript. Mehmet Tuncay Duruoz: designing the study, analyzing the data and coordinating the study.

ORCID

Firat Ulutatar https://orcid.org/0000-0002-6109-6451
Cagri Unal-Ulutatar https://orcid.org/0000-0002-4571-8521
Mehmet Tuncay Duruoz https://orcid.org/0000-0003-3584-2788

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How to cite this article: Ulutatar F, Unal-Ulutatar C, Tuncay Duruoz M. Fibromyalgia in patients with psoriatic arthritis: Relationship with enthesopathy, sleep, fatigue and quality of life. *Int J Rheum Dis*. 2021;24:183–188. https://doi.org/10.1111/1756-185X.13963

Received: 5 August 2020 | Revised: 3 September 2020 | Accepted: 10 September 2020

DOI: 10.1111/1756-185X.13987

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Fibromyalgia in patients with psoriatic arthritis: Impact on disease activity indices, fatigue and health-related quality of life

Noha A. Elsawy | Abdel-Moneim H. Helal† | Hala A. Abd ElHamid | Yousra Hisham Abdel-Fattah

Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Correspondence
Yousra Hisham Abdel-Fatah, Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Alexandria University, Medan Khartoum Sultan Hussein St., Alexandria, Egypt.
Emails: yousra.moustafa@alexmed.edu.eg
yousrahisham@gmail.com

Abstract

Objective: To assess the frequency of fibromyalgia (FM) in patients with psoriatic arthritis (PsA) and its impact on disease activity indices, fatigue and health-related quality of life (QOL).

Methods: This cross-sectional study randomly recruited patients with PsA attending an outpatient clinic between June 2017 and December 2018. Disease activity, functional ability, fatigue, and QOL were assessed for all patients. The recruited PsA patients were screened for concomitant FM, then classified into group I, patients with PsA only, and group II, patients with FM-PsA. The severity and impact of FM were assessed for group II patients.

Results: A total of 60 patients with PsA were assessed with a mean age of 49.30 ± 11.69 years, of which 43.3% were female. A total of 23 PsA patients had concomitant FM (38.3%). Patients with FM-PsA showed a statistically higher disease activity in all aspects of PsA except for C-reactive protein, swollen joint count (SJC) and dactylitis count. Patients in both groups had similar functional levels, while fatigue and QOL were statistically worse in patients with FM-PsA than in patients with PsA only.

Conclusion: These results might highlight the importance of considering FM as a contextual factor in disease activity assessment in patients with PsA, especially in those with discrepancies in tender joint count/patient-reported outcomes vs SJC/inflammatory markers and those with persistently high disease activity indices.

KEYWORDS

disease activity, fatigue, fibromyalgia, psoriatic arthritis, quality of life

†Deceased.

1 | BACKGROUND

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis characterized by joint and entheseal pain and swelling that may lead to physical disability, emotional instability, and poor quality of life (QOL). The definite prevalence of PsA is still vague, it is said to occur in around 30% of patients with skin psoriasis (PsO).[1]

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread non-articular musculoskeletal pain and tenderness. Other associated symptoms include; disturbed sleep, fatigue, headache, stiffness and anxiety.[2] It is a common rheumatologic disorder that is underdiagnosed with a mean global prevalence of 2.7% in the general population.[3]

Fibromyalgia may coexist with various rheumatic diseases, including PsA, complicating their diagnosis and management.[4] The coexistence of FM among patients with rheumatoid arthritis (RA)[5-7] and systemic lupus erythematosus[8-10] has been vastly studied, and showed a higher prevalence than that found in the general population.[4] The pathogenesis of FM entails both central and peripheral mechanisms, with involvement of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Temporal summation and dysfunction in descending facilitatory and inhibitory pain pathways were also implicated in its pathogenesis.[11,12]

Fibromyalgia was shown to have a significant burden on the mental and physical health in patients with PsA.[13] Moreover, only a single study assessed the effect of the coexistence of FM on disease activity in patients with PsA,[14] with no published research on the effect of FM on fatigue or QOL in patients with PsA, and scarce research regarding this topic in Egyptian patients. Therefore, in the current study, we assessed the frequency of FM in patients with PsA and its impact on disease activity indices, fatigue and health-related QOL.

2 | MATERIALS AND METHODS

2.1 | Studied population

This cross-sectional study included 60 patients diagnosed with PsA according to the classification criteria for psoriatic arthritis (CASPAR).[15] All patients who fulfilled the CASPAR criteria and had no reason for exclusion were recruited from those attending the outpatient clinic between June 2017 and December 2108. Patients were further classified into two groups based on the absence or presence of coexisting FM: group I, patients with PsA only; and group II, patients with FM-PsA. FM was diagnosed according to the 2016 Revisions to the 2010/2011 FM diagnostic criteria.[16]

2.2 | Inclusion criteria

Adult patients with PsA ≥ 18 years of age, fulfilling a score of 3 or more of the CASPAR criteria with inflammatory articular disease (joint, spine, or enthesis) were included. Patients were excluded if they had musculoskeletal, neurological or connective tissue disorders other than PsA or if the patients had PsO but did not fulfill a score of 3 or more of the CASPAR criteria.

2.3 | Study design

All patients underwent demographic data collection, the duration and history of the disease were recorded and body mass index was calculated.[17] Musculoskeletal system examination was performed. The severity of the PsO was assessed using psoriasis area severity index (PASI).[18] The PsA disease activity was assessed by disease activity in psoriatic arthritis (DAPSA) index[19] and the composite psoriatic disease activity index (CPDAI).[20] Functional ability was assessed by the Health Assessment Questionnaire disability index (HAQ-DI),[21] fatigue was assessed using the Arabic translated version of the multidimensional assessment of fatigue (MAF) scale[22] and QOL was assessed using the dermatology life quality index (DLQI), psoriatic arthritis quality of life (PsAQOL) and ankylosing spondylitis QOL (ASQOL).[23]

Following the detailed assessment of disease activity, QOL and fatigue in the PsA patients, the patients were then evaluated for the presence or absence of concomitant FM, according to the 2016 Revisions to the 2010/2011 FM diagnostic criteria.[16] Those with FM-PsA were further evaluated to assess the severity and impact of FM.

In group II, assessment of FM was done by tender point count,[24] widespread pain index (WPI), symptom severity scale (SSS), fibromyalgia severity (FS) scale[16,25] and the Arabic translated version of the Fibromyalgia Impact Questionnaire (FIQ).[26]

2.4 | Statistical analysis

Statistical analysis was done using IBM SPSS software version 20.0. Number and percentage were used for qualitative data. The distribution of normality was assessed. The Chi-square (± Monte Carlo correction), Mann-Whitney and Student's *t* tests were the used as statistical tests and accordingly the range and median or the mean and standard deviation were used to express results. Pearson and Spearman coefficients were used to correlate between data. The kappa test was used to assess agreement between the diagnostic accuracy of the three criteria. Statistical significance was assigned at P value <.05.

2.5 | Power calculation

Group sample sizes of 37 and 23 patients achieved 90% power to detect a difference of 15 in DAPSA between the PsA group (12.7 ± 12.7) and FM-PsA group (27.7 ± 19), according to a previous study,[14] with a significance level (alpha) of 0.05 using a 2-sided

2-sample *t* test. The sample size was calculated using NCSS 2004 and PASS 2000 software.

3 | RESULTS

The mean age of the studied patients was 49.30 ± 11.69 years. Females constituted 43.3% of the enrolled patients. Most patients (80%) were on synthetic disease-modifying anti rheumatic medication (DMARDs) (mostly methotrexate and sulfasalazine), only one patient (1.7%) was on biological therapy (etanercept), while 11 patients (18.3%) required topical therapy for PsO.

Patients were divided into two groups; group I included 37 patients with PsA only (61.7%), while group II included 23 patients with FM-PsA (38.3%).

Demographic data and disease duration are demonstrated in Table 1. There was a statistically significant difference between the two groups as regards the patients' occupation, where 24.3% of patients with PsA were manual workers, as opposed to none of the FM-PsA patients. Also 13 (21.7%) patients retired at an early age (<60 years) as a consequence of the pain, eight of which were patients with FM-PsA. The only patient who received biologic therapy was in group II, while 78% received synthetic DMARDs and 17% only received topical therapy. Similar percentages were found in group I, where 81% received synthetic DMARDs and 18% only received topical therapy. The doses for the synthetic DMARDs were fairly similar in both groups.

Group II had a statistically higher number of patients with symmetrical polyarthritis (16 vs 13 respectively, $\chi^2 = 6.733$, $r = .009$) and mixed type (axial and peripheral joint involvement) of arthritis (15 vs 6 respectively, $\chi^2 = 14.97$, $r < .001$) compared to group I, while axial only type of arthritis was found in six patients (16.2%) only in group I.

The disease activity of PsO and PsA in both groups is demonstrated in Table 2. There was no statistically significant difference between the two groups as regards C-reactive protein (CRP), swollen joint count (SJC) and dactylitis count, while in group II, there were statistically higher PASI, DAPSA, CPDAI, tender joint count (TJC), Leeds Enthesitis Index (LEI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared to group I.

The HAQ, MAF scale and different QOL assessment tools are tabulated in Table 3. There was no statistically significant difference between the two groups as regards the HAQ score. Although the DLQI and PsAQOL were higher in group II than in group I, they did not reach statistical significance, while patients with FM-PsA had

TABLE 1 Comparison between the studied groups according to demographic data and disease duration

	Group I (N = 37)		Group II (N = 23)		Test of significance	*P*
	n	%	n	%		
Age, year, mean ± SD	48.38 ± 11.69		50.78 ± 11.8		$t = 0.772$	.443
Gender						
Males	23	62.2	11	47.8	$\chi^2 = 1.187$	.276
Females	14	37.8	12	52.2		
Occupation						
Housewife	14	37.8	12	52.2	$\chi^2 = 8.159^*$	$^{MC}P = .042^*$
Retired	9	24.3	9	39.1		
Manual work	9	24.3	0	0.0		
Office work	5	13.5	2	8.7		
BMI median (range)	28.9 (20.9-43)		29.4 (23.7-41.9)		$U = 405.5$	.761
Marital status						
Married	32	86.5	22	95.7	$\chi^2 = 2.54$	$^{MC}P = .599$
Single	3	8.1	0	0.0		
Divorced	1	2.7	0	0.0		
Widower	1	2.7	1	4.3		
Duration of PsO, year						
Median (range)	13 (0.25-75)		15 (2.5-50)		$U = 334.5$	.166
Duration of PsA, year						
Median (range)	5 (0.25-20)		2 (0.08-15)		$U = 357$	.295

Note: P value for comparing between the studied categories.

Abbreviations: BMI, body mass index; PsA, psoriatic arthritis; PsO, skin psoriasis; *t*, Student's *t* test; *U*, Mann-Whitney test.

* Statistically significant at $P \leq .05$.

TABLE 2 Comparison between the studied groups according to disease activity

	Group I (N = 37)	Group II (N = 23)	Test of significance	*P*
PASI				
Median (range)	8.3 (0.0-45.7)	14.4 (0.9-49.6)	$U = 292.5^{*}$	.043*
DAPSA				
Median (range)	29 (14-89)	45.5 (20.5-99)	$U = 226.0^{*}$	.002*
CPDAI				
Mean ± SD	8.68 ± 3.33	11.26 ± 2.03	$t = 3.735^{*}$	<.001*
CRP, mg/dL				
Median (range)	6.3 (0.3-72)	6 (0.8-61.6)	$U = 409.5$	.802
68 TJC				
Median (range)	7 (2-64)	23 (8-68)	$U = 112.0^{*}$	<.001*
66 SJC				
Median (range)	2 (0-23)	4 (0 –10)	$U = 300.5$	.055
LEI				
Median (range)	2 (0 –6)	6 (3 –6)	$U = 76.50^{*}$	<.001*
BASDAI				
Mean ± SD	4.88 ± 1.99	6.68 ± 1.40	$t = 3.784^{*}$	<.001*
Dactylitic count				
Median (range)	0 (0 –8)	0 (0 –7)	$U = 421.0$	.924

Note: P value for comparing between the studied categories.

Abbreviations BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CPDAI, composite psoriatic disease activity index; DAPSA, disease activity of psoriatic arthritis; LEI, Leeds enthesitis index; PASI, psoriasis area severity index; SJC, swollen joint count; TJC, tender joint count; *t*, Student's *t* test; *U*, Mann-Whitney test.

*Statistically significant at $P \leq .05$.

TABLE 3 Comparison between the studied groups according to functional level, QOL and fatigue assessment tools

	Group I (N = 37)	Group II (N = 23)	Test of significance	*P*
HAQ-DI				
Median (range)	0.47 (0-2)	0.79(0.1-1.95)	$U = 339.0$	.188
MAF				
Median (range)	26.5 (0-49.5)	34 (28-48.7)	$U = 172.5^{*}$	<.001*
DLQI				
Median (range)	9 (0-30)	13 (3-24)	$U = 308.0$	.073
ASQOL				
Mean ± SD	9.97 ± 4.82	13.87 ± 3.27	$t = 3.417^{*}$	.001*
PsAQOL				
Median (range)	12 (0-20)	15 (9-20)	$U = 306.0$	.068

Note: P value for comparing between the studied categories.

Abbreviations: ASQOL, ankylosing spondylitis quality of life; DLQI, dermatology life quality index; HAQ-DI, Health Assessment Questionnaire disability index; MAF, multidimensional assessment of fatigue; PsAQOL, psoriatic arthritis quality of lifel *t*, Student's *t* test; *U*, Mann-Whitney test.

* Statistically significant at $P \leq .05$.

a statistically higher MAF scale and ASQOL compared to patients with PsA only.

In group II patients the mean tender point count was 16.50 ± 1.84, ranging from 12 to 18 tender points, the mean WPI was 12.48 ± 3.20, the mean SSS was 8.22 ± 1.76, the mean FS scale was 20.7 ± 3.99 and the mean FIQ score was 57.22 ± 7.30.

The correlations between both the FS scale and FIQ and the other disease activity indices and assessment tools are demonstrated

TABLE 4 Correlation between FS and FIQ and the other parameters

	FS		FIQ	
	r_s	*P*	*r*	*P*
DAPSA	.590*	.003*	.178	.417
CPDAI	.402	.057	.216	.322
PASI	.143	.514	.488*	.018*
LEI	−.081	.715	.138	.529
BASDAI	.190	.385	.624*	.001*
Dactylitis count	−.082	.711	.014	.949
HAQ-DI	.613*	.002*	.557*	.006*
MAF	.341	.111	.619*	.002*
DLQI	.303	.160	.299	.166
ASQOL	.533*	.009*	.635*	.001*
PsAQOL	.640*	.001*	.576*	.004*

Abbreviations: ASQOL, ankylosing spondylitis quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CPDAI, composite psoriatic disease activity index; DAPSA, disease activity of psoriatic arthritis; DLQI, dermatology life quality index; FIQ, fibromyalgia impact questionnaire; FS, fibromyalgia symptoms scale; HAQ-DI, Health Assessment Questionnaire disability index; LEI, Leeds enthesitis index; MAF, multidimensional assessment of fatigue; PASI, psoriasis area severity index; PsAQOL, psoriatic arthritis quality of life; *r*, Pearson coefficient; r_s, Spearman coefficient.

* Statistically significant at $P \leq .05$.

in Table 4. There was a statistically significant correlation between FS scale and DAPSA, HAQ, ASQOL and PsAQOL. Also, there was a statistically significant correlation between FIQ and PASI, BASDAI, HAQ, MAF, ASQOL and PsAQOL.

4 | DISCUSSION

In this cross-sectional study we screened for FM in 60 PsA patients, followed by assessment of the effect of FM on the disease activity indices, fatigue and QOL in PsA patients. Out of the 60 PsA patients; 23 patients (38.3%) had concomitant FM (FM-PsA), while 37 patients (61.7%) had no concomitant FM.

These data are consistent with Magrey et al in 2013[27] and Ulus et al in 2020.[28] In the former; 37.5%-53.3% of PsA patients had concomitant FM using the London FM epidemiologic study screening questionnaire and symptoms intensity scale,[27] while in the latter 34% of PsA patients had concomitant FM according to the 2010 American College of Rheumatology (ACR) criteria for FM.[28]

In contrast, our results were higher than other studies, such as in Salaffi et al in 2014,[29] Graceffa et al in 2015,[30] Brikman et al in 2016,[14] Di Carlo et al[31] and Fan et al in 2017.[32] They found the prevalence of FM-PsA to be around 9%-19%; these contradictory findings may be explained by genetic and racial differences. Also, Salaffi et al[29] only assessed PsA patients with predominant axial involvement.

Males were more predominant in PsA only patients, while an equal gender distribution was found in FM-PsA patients, but this difference did not reach statistical significance. In the literature, FM was found to be more prevalent in females than in males, both in the general population[4] and in PsA patients.[29] While the newer published criteria were proven to increase the diagnosis of FM in men,[33] their theory is that men are less tender compared to women and thus any criteria that excludes tender points decreases the gender bias.[34]

None of the patients with FM-PsA were manual workers while 24% of the PsA only patients being manual workers. Moreover, eight FM-PsA patients (34.8%) requested early retirement from their jobs due to the pain, compared to four PsA only patients (10.8%). This is consistent with reports that patients with FM modify their work environment or change their occupation as a consequence of the disease.[35]

Symmetric polyarthritis and mixed arthritis were statistically higher in FM-PsA patients, while none of the patients with axial only type had concomitant FM. This could be explained by the small number of patients with axial only type of PsA enrolled in this study. Moreover, FM in PsA was found to be more likely to be associated with the peripheral form,[36] while less likely to be associated with the predominantly axial form.[29]

The wide pathogenetic and clinical heterogeneity found in PsO and PsA was emphasized by Scarpa et al in 2006,[37] who proposed the terminology psoriatic disease (PsoD). In 2019 Chimenti et al[38] highlighted the great heterogeneity of this condition again and proposed another terminology: systemic psoriatic disease. For that reason different indices were used to comprehensively assess the disease activity in both groups, as PsA involves the skin, as well as articular and extra-articular tissue.

All disease activity indices and tools reflecting pain and tenderness (DAPSA, CPDAI, TJC, LEI and BASDAI) were statistically higher in patients with FM-PsA, while the pure objective assessment tools of inflammation (CRP, SJC and dactylitis count) showed no statistically significant difference between the two groups. This is consistent with the single published research in this aspect, by Brikman et al in 2016.[14] They suggested that central sensitization and wind up that occurs in patients with FM could explain the higher patients' perception of tenderness or disease impact. Also, fibromyalgic pain and fatigue can simulate or overlap with PsA disease symptoms, while objective disease activity measures are not influenced by FM.[39]

The positive statistical correlation found between either FS scale or FIQ and some disease activity indices (DAPSA, PASI and BASDAI), may be explained by the similar symptoms assessed (such as pain, tenderness, stiffness and fatigue) by these tools with the lack of specificity to a certain disease or structure.[16,19,36]

Accordingly, it is essential to differentiate whether the increase in pain is due to actual increase in disease activity or the associated

FM (which causes overestimation of disease activity indices), which is important to avoid unnecessary change in the therapy or increase in its dose to control the disease and hence the pain.

In the past tenderness from enthesitis in PsA and the tender points from FM, used in the ACR 1990 Criteria for the Classification of FM,[24] might have caused difficulties in distinguishing between the two conditions. This may explain the statistically significant higher median LEI score in the FM-PsA patients compared to the PsA only patients, as this score uses tenderness at six common entheseal sites that overlap with some FM tender points. But now with the use of the 2016 Revisions to the 2010/2011 FM diagnostic criteria[16] (which was applied to diagnose our patients in the current study) tender points were excluded from the diagnostic criteria, decreasing the confusion. The use of musculoskeletal ultrasound and Doppler may also help in this dilemma as it has been proven to differentiate between PsA patients with active inflammation from those without,[40,41] while Marchesoni et al in 2012[41] clarified that the two conditions could also be distinguished solely on clinical findings, where the presence of more than six FM-related symptoms and more than eight tender points was predictive of FM rather than PsA.

In this study, PASI was statistically higher in patients with FM-PsA and it showed a positive statistically significant correlation with FIQ. This is supported by Sampogna et al in 2012,[42] but contradictory to the study by Brikman et al[14]. Brikman et al[14] found no statistically significant difference regarding PASI in patients with PsA only and FM-PsA. They attributed this to the objectivity of the PASI. On another note, PsO has been proven to have an extensive effect on patients' live, leading to depression,[43] anxiety and sleep disturbance,[44] with social difficulties, which in turn may predisposes to FM and its deleterious impact on the patient's life.[45,46]

As regards the functional assessment, fatigue and QOL assessment tools, although the DLQI and PsAQOL were higher in patients with FM-PsA they did not reach statistical significance, while MAF scale and ASQOL were both statistically higher in patients with FM-PsA. Moreover, most of these PsA assessment tools had a positive statistical significant correlation with the FM assessment tools.

This is consistent with the published research by Marchesoni et al,[41] who studied the similarities or overlap between FM and PsA symptoms. They found that both groups of patients had similar symptoms but patients with FM had more associated symptoms, tender points and fatigue than those with PsA.

5 | CONCLUSION

These results might highlight the importance of considering FM as a contextual factor in disease activity assessment in patients with PsA, especially in those with discrepancies in TJC/patient-reported outcomes vs SJC/inflammatory markers or persistently high disease activity indices.

5.1 | Limitations

- There was no control group to compare between the percentage and severity of FM in healthy volunteers and patients with PsA.
- A longitudinal study is recommended to assess the effect of adequate treatment of FM in patients with FM-PsA on disease activity indices, QOL and fatigue.

ACKNOWLEDGEMENTS

Our sincere gratification to our Professor and mentor the late Prof. Dr Abdel-Moneim Hussein Helal, whose vision and ideas enriched this work but was unable to see it through.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Noha A. Elsawy, Abdel-Moneim H. Helal, Hala A. Abd ElHamid, Yousra Hisham Abdel-Fattah: Concepts, Design, Definition of intellectual content, Literature search, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review. Noha A. Elsawy, Hala A. Abd ElHamid, Yousra Hisham Abdel-Fattah: Clinical studies, Experimental studies, Statistical analysis. Hala A. Abd ElHamid, Yousra Hisham Abdel-Fattah: Data acquisition.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

A written informed consent was obtained from all patients before enrollment in the study. The study was approved by the local ethics committee of Faculty of Medicine, Alexandria University. Ethics board approval number: 0105197.

Consent for publication: not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Noha A. Elsawy https://orcid.org/0000-0003-3670-8134
Hala A. Abd ElHamid https://orcid.org/0000-0002-3818-359X
Yousra Hisham Abdel-Fattah https://orcid.org/0000-0002-5692-3483

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How to cite this article: Elsawy NA, Helal A-MH, Abd ElHamid HA, Abdel-Fattah YH. Fibromyalgia in patients with psoriatic arthritis: Impact on disease activity indices, fatigue and health-related quality of life. *Int J Rheum Dis*. 2021;24:189–196. https://doi.org/10.1111/1756-185X.13987

Received: 19 October 2020 | Revised: 14 November 2020 | Accepted: 24 November 2020

DOI: 10.1111/1756-185X.14043

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

YouTube as a source of information on fibromyalgia

Tugba Ozsoy-Unubol[1] | Ebru Alanbay-Yagci[2]

[1]Department of Physical Medicine and Rehabilitation, Sultan II. Abdülhamid Han Training and Research Hospital, İstanbul, Turkey

[2]Department of Physical Medicine and Rehabilitation, Gaziosmanpaşa Training and Research Hospital, İstanbul, Turkey

Correspondence
Tugba Ozsoy-Unubol, Department of Physical Medicine and Rehabilitation, Sultan II. Abdülhamid Han Training and Research Hospital, İstanbul, Turkey.
Email: tugbaozsoyy@gmail.com

Abstract

Aim: The internet has gained popularity as a health information source for patients. YouTube is one of the biggest platforms used worldwide. Several studies showed that quality of the information on YouTube videos for patient information is poor. This study aimed to evaluate the content and quality of YouTube videos, as a source of patient information for fibromyalgia (FM).

Methods: In this cross-sectional study, a YouTube search with the keyword "fibromyalgia" was performed, and the first 200 videos were listed according to relevancy. Advertisements, duplicate videos, videos in languages other than English, and videos without audio were excluded. Video features (number of "likes", "dislikes", views, length of video), and source of upload were recorded. DISCERN and *Journal of the American Medical Association* (JAMA) benchmark criteria were used for quality analysis. Video quality was assessed according to the source of upload and video features. The correlation analysis was performed between video features, JAMA, and DISCERN scores.

Results: A total number of 102 videos were analyzed. The most common source of upload was physicians and majority of the content (55.8%) was about symptoms and treatment. Mean DISCERN and JAMA scores were 35.7 and 2.2, respectively. These scores were highest in videos uploaded by physicians (52.7 and 2.6, respectively). There is a positive correlation between the duration of the video, DISCERN, and JAMA scores.

Conclusion: The majority of YouTube content has poor quality. Health professionals should be aware of the importance of health-related information on YouTube and provide high-quality accurate and up-to-date content.

KEYWORDS

DISCERN, fibromyalgia, internet, quality, YouTube

1 | INTRODUCTION

Fibromyalgia (FM) is a clinical syndrome characterized by chronic widespread pain, prominent physical and psychological impairment including anxiety and depression.[1-3] After osteoarthritis, FM is the second most common "rheumatic" disorder with a prevalence among the general population within the 2%-8% range.[4,5] The pathogenesis and pathophysiology of FM are multifactorial and not understood in detail yet. They are reflected in the variety and complexity of symptoms experienced by fibromyalgia patients. The consistent feature is altered pain processing based on central and peripheral nervous system influences.[6,7]

Due to the complex nature of FM, there are many myths and misunderstandings so, patients tend to seek information.[8] Patients may want to know detailed information about their disease and treatment options for participating in the decision process. A well informed patient may have an active role in decision making and experience less anxiety.[9,10] On the other hand, without good quality information patients inconsistently discuss their findings with their physician and are unable to make informed choices. The internet has become a prominent source of health information in parallel with the accrual in its use in society.[11-13] Because the internet allows everyone to upload content, and is not regulated, it may contain misleading or inaccurate information.[11] So, a concern was aroused about the quality and accuracy of the online medical information.

YouTube is one of the largest media-sharing sites in the world. Because of its ease of use and anonymous accessibility, it is preferred for obtaining medical information. Several studies have examined the content and accuracy of YouTube videos on several topics such as hypertension, dialysis, and rheumatoid arthritis in hopes of elucidating the effectiveness of YouTube videos for patient education.[14-16] However, there is a lack of studies evaluating the quality of YouTube videos, as an information source for patients with FM.

This study aimed to assess the quality of the English YouTube video content as a source of patient information, by using the keyword "fibromyalgia".

2 | METHODS

The study was designed as a cross-sectional study. Since the study does not include any human participants or animals and the videos were available to everyone, ethics committee approval was not required.

2.1 | YouTube search

A search was performed on https://www.youtube.com/ on August 15, 2020, with the keyword “fibromyalgia”. The first 200 videos were listed by relevance (default option on YouTube). Search history was deleted before searching. Only videos in English were included. Advertisements, duplicate videos, videos in languages other than English, and videos without audio were excluded.

2.2 | Video features

The number of views, view ratio (number of views/d), total video duration, the total number of comments, the total number of “likes” and “dislikes”, number of comments/d, time since the upload date, and the source of upload were recorded. The source of upload was categorized as physician, non-physician health personnel, health-related websites, patient, trainer, TV program, and independent user. Additionally, like ratio and video power index (VPI) were used for the analysis of popularity of the videos. Like ratio was calculated by a formula ([number of likes/number of likes + number of dislikes] × 100) and VPI was calculated as like ratio*view ratio/100.[17] Video content was classified as general information (symptoms and treatment), general information (only symptoms), treatment (chiropractic, yoga, hydrotherapy, exercise, diet and drugs, etc), differential diagnosis, fibromyalgia and disability, etiology, fibromyalgia and sexual health, and localization of tender points.

2.3 | Video quality analysis

Video contents were evaluated by 2 independent physical medicine and rehabilitation (PMR) specialists. A consensus was achieved among the assessors for items with differences. DISCERN and *Journal of the American Medical Association* (JAMA) Benchmark Criteria were used for quality analysis of the videos.

The DISCERN instrument was developed to enable patients and information providers to judge the quality of information. It consists of 15 questions plus an overall quality rating. It is composed of 3 sections evaluating reliability (section 1), quality of information about treatment options (section 2), and the general quality of the information (section 3). The first section has 8 questions, the second section has 7 questions. Section 3 includes an overall rating (Table 1). Each question was scored on a 5-point (1-5) scale. If the quality criterion has been completely fulfilled, it was scored as 5, and if not fulfilled at all scored as 1. If it met the criterion in some extent, it scored as 2 to 4 according to assessors’ judgment.[18] The DISCERN manual contains detailed information for each question including instructions and examples.[19] The total DISCERN score was calculated by summing up the first 15 questions.[20] It can be categorized as excellent (63-75), good (51-62), fair (39-50), poor (27-38), and very poor (<27).[21,22]

JAMA benchmark criteria were published in order to evaluate the quality of internet information on health care. It assesses 4 criteria including authorship, attribution, disclosure, and currency. If the criteria is satisfied it gets 1 point. The maximum possible score is 4 which represents the highest quality.[23] The criteria are as follows: (a) authorship (authors and contributors, their affiliations, and relevant credentials should be provided); (b) attribution (references and sources for all content should be listed clearly, and all relevant copyright information noted); (c) disclosure (conflicts of interest, video ownership, funding, sponsorship, advertising, and support should be fully disclosed); and (d) currency (dates that content was posted and updated should be indicated).

2.4 | Statistical analysis

The Statistical Package for the Social Sciences 22 (IBM, Armonk, NY, USA) was used for the analysis of the data. Shapiro-Wilk test was performed to test the normality of data. Mean, SD, frequency, minimum, and maximum were used as descriptive methods. Kruskal-Wallis test was used to determine statistically significant differences

TABLE 1 DISCERN scoring system

	Question		Score
Section 1	1	Are the aims clear?	1-5
	2	Does it achieve its aims?	1-5
	3	Is it relevant?	1-5
	4	Is it clear what sources of information were used to compile the publication (other than the author or producer)?	1-5
	5	Is it clear when the information used or reported in the publication was produced?	1-5
	6	Is it balanced and unbiased?	1-5
	7	Does it provide details of additional sources of support and information?	1-5
	8	Does it refer to areas of uncertainty?	1-5
Section 2	9	Does it describe how each treatment works?	1-5
	10	Does it describe the benefits of each treatment?	1-5
	11	Does it describe the risks of each treatment?	1-5
	12	Does it describe what would happen if no treatment is used?	1-5
	13	Does it describe how the treatment choices affect overall quality of life?	1-5
	14	Is it clear that there may be more than 1 possible treatment choice?	1-5
	15	Does it provide support for shared decision making?	1-5
Section 3	16	Based on the answers to all of these questions, rate the overall quality of the publication as a source of information about treatment choices	1-5

between more than 2 groups of an independent variable. The Dunn-Bonferroni post-hoc method was used following a significant Kruskal-Wallis test for pairwise comparison. The Spearman test was performed for correlation analysis. The inter-rater agreement was assessed with the kappa coefficient. The results were evaluated at a 95% confidence interval and a significance level of $P < .05$. Bonferroni adjustment is performed automatically in SPSS version 22 by multiplying the Dunn's P value by the number of comparisons.

3 | RESULTS

Eighty-eight videos were excluded; 65 were off-topic, 27 were duplicates, 3 were in a language other than English, 2 had no audio and one was inappropriate. A total of 102 videos were analyzed. The characteristics of the videos were summarized in Table 2. A majority of the videos (28.43%) were uploaded by physicians. The most common video content was general information including symptoms and treatment options. The mean JAMA score was 2.23 and the mean DISCERN total score was 35.76. According to DISCERN classification 36.3% were "very poor", 29.4% were poor, 12.7% were "fair", 12.7% were "good" and 8.8% were "excellent". When the cutoff for the JAMA score was selected as ≥3, 43.1% met the quality criteria. The Cohen kappa score was calculated at 0.899 for the JAMA score and 0.787 for the DISCERN total. DISCERN scores were significantly higher in videos that were uploaded by physicians. According to Bonferroni adjustment, DISCERN reliability, quality and total scores of videos uploaded by physicians were significantly higher from other sources (except TV programs). DISCERN treatment scores of the videos uploaded by physicians were significantly higher from other sources (except TV programs and trainers) (Table 3). DISCERN classification according to the source and features of the videos are presented in Table 4.

There was no statistically significant correlation between DISCERN scores and like ratio, VPI, number of likes, dislikes, comments, views. The duration of video had a significant moderate correlation with the DISCERN reliability, treatment, quality and total score ($P < .0001$) ($r = 0.419$, 0.510, 0.447 and 0.490, respectively). JAMA score had a significantly weak correlation with the number of likes ($P = .006$, $r = .271$), dislikes ($P = .004$, $r = .281$), views ($P = .03$, $r = .216$), comments ($P = .004$, $r = .297$), VPI ($P = .017$, $r = .236$) and duration of video ($P = .003$, $r = .287$).

4 | DISCUSSION

This study aimed to evaluate the content and quality of YouTube videos, as an information source for patients with FM. The most frequently shared content was general information videos containing symptoms and treatment. The mean JAMA and DISCERN scores were 2.23 and 35.76, respectively. The majority of the videos were of low quality. Most common video source was physician and the videos uploaded by physicians had the highest quality scores. Duration of the videos was positively correlated with the DISCERN and JAMA score.

Since patients have tendency to seek online information and the quality of online information is variable and unregulated, this may cause misleading of patients and impairment of the relation between clinician and patient. On the other hand, accurate and reliable information may provide the patient taking an active role in decision

processes and provide lower levels of anxiety.[9,10] So, clinicians should know about the content and quality of online information.

There are studies evaluating YouTube as a source of patient information on many diseases including rheumatoid arthritis, ankylosing spondylitis, Sjögren's syndrome, and so on.[15,24-26] To the best of our knowledge, there is no study evaluating the YouTube content as a source of patient information on FM. However, there are studies investigating the content and quality of online information on FM.[8,12,27] These studies reported that the most commonly searched contents are "what is fibromyalgia" and "Which are the symptoms of fibromyalgia?"[8,27] Consistent with these studies, the most common video content was about symptoms and treatment in the current study.

According to the DISCERN ratings more than 50% of videos were classified as "very poor" and "poor". For JAMA score 43.1% were ≥3. Similarly, the quality of online information on FM was studied and 43% of webpages met these criteria.[27] In accordance with our results previous studies evaluating YouTube content and quality as a source of patient information on various diseases had similar results. They stated that the quality of the information on kyphosis, rotator cuff repair is poor, as well.[17,28]

In the current study, the most common video source was determined as physicians followed by health-related websites. JAMA and DISCERN scores were found highest in videos uploaded by the physicians. In studies evaluating YouTube video content on different topics, videos uploaded by physicians, universities, and academic

TABLE 2 Characteristics and quality assessments of YouTube videos

Source of upload	N	%
Physician	29	28.43
Non-physician health personnel	10	9.80
Health-related websites	20	19.60
Patient	16	15.68
Trainer	12	11.76
TV program	7	6.86
Independent user	8	7.84
Video content	**N**	**%**
General information (symptoms and treatment)	57	55.88
General information (symptoms)	14	13.72
Treatment (chiropractic, yoga, hydrotherapy, exercise, diet, drugs, etc)	24	23.52
Differential diagnosis	2	1.96
Fibromyalgia and disability	2	1.96
Etiology	1	0.98
Fibromyalgia and sexual health	1	0.98
Localization of tender points	1	0.98
Video features	**Mean ± SD**	**Min–Max**
Duration (s)	668.46 ± 894.16	74-4511
Time since upload (d)	1292.84 ± 992.23	21-4174
Number of views	43 262.95 ± 79 498.78	65-397 021
View ratio	40.62 ± 78.25	0.04-461.38
Number of comments	140.07 ± 283.63	0-1300
Number of likes	1151.73 ± 4317.20	1-41 000
Number of dislikes	31.55 ± 58.35	0-346
Like ratio	94.32 ± 6.33	66.66-100
VPI	38.88 ± 75.90	0.04-454.92
JAMA score	2.23 ± 0.85	1-4
DISCERN reliability	21.44 ± 8.54	9-39
DISCERN treatment	14.32 ± 8.38	7-35
DISCERN quality	2.37 ± 1.19	1-5
DISCERN total	35.76 ± 16.03	16-72

Abbreviation: VPI, video power index.

TABLE 3 Video quality assessments according to the source of the video

	Physician	Non-physician health personnel	Health-related websites	Patient	Trainer	TV program	Independent user	P^*
JAMA score	3 (1-3)	2 (1-3)	2 (1-4)	2 (1-4)	2 (1-3)	3 (1-4)	2 (1-3)	.314
DISCERN reliability	32 (20-37)	17 (9-33)	17 (9-39)	13.5 (9-25)	16.5 (9-27)	22 (13-34)	18 (10-24)	**.0001**
DISCERN treatment	24 (7-35)	8 (7-26)	9 (7-33)	8 (7-13)	10.5 (7-20)	10 (9-31)	7.5 (7-18)	**.0001**
DISCERN quality	4 (2-5)	2 (1-4)	2 (1-5)	1 (1-3)	2 (1-3)	2 (1-4)	2 (1-2)	**.0001**
DISCERN total	56 (28-71)	26 (16-57)	28 (16-72)	21.5 (16-33)	27 (17-46)	32 (22-65)	27.5 (17-36)	**.0001**

Note: Results are presented as median (min–max).
*Kruskal-Wallis test.

TABLE 4 Distribution of DISCERN classification according to video source and features

	DISCERN classification				
	Very poor	Poor	Fair	Good	Excellent
Source of the video (n)					
Physician	0	5	7	10	7
Non-physician health personnel	5	3	1	1	0
Health-related websites	9	6	2	2	1
Patient	11	5	0	0	0
Trainer	6	4	2	0	0
TV program	2	3	1	0	1
Independent user	4	4	0	0	0
	37	30	13	13	9
Video features (mean ± SD)					
Video duration (s)	449.3 ± 632.6	480.9 ± 430.4	343.7 ± 283.1	695.2 ± 722.8	2624.8 ± 1372.9
Number of views	39 423 ± 78 127.8	52 597.2 ± 93 625.4	19 332.5 ± 19 358.3	35 831.6 ± 70 047.7	73 235.3 ± 100 990.6
Number of likes	872.7 ± 1990.8	2126.2 ± 7586.4	385.6 ± 442.2	488.3 ± 89.2	1115.4 ± 1322.8
Number of dislikes	28.3 ± 56.2	29.3 ± 51.3	25.9 ± 31.5	41.2 ± 97	46.3 ± 55.1
Like ratio	95.6 ± 4.8	94.4 ± 7.2	90.9 ± 7.3	94.9 ± 4.3	92.2 ± 8.4
VPI	35.8 ± 85.1	50.1 ± 89.2	25.6 ± 28	40.6 ± 72.3	30.2 ± 36.5

Abbreviation: VPI, video power index.

sources were found to be of higher quality and more reliable.[24,29] Also, it has been stated that online FM information sources had low quality and poor readability.[8]

The duration of the video was correlated with both DISCERN and JAMA scores. According to DISCERN classification, "good" and "excellent" videos had longer length. As expected, when the duration was increased, the topic can be clearly explained. However, patients may lose interest when watching a longer video. Consistent with our study, some researchers found that the duration of high-quality videos was longer than those of poor.[30,31] They also stated that viewers lost interest in long videos despite increased video content.[31] So, video suppliers should provide high-quality relevant information in a reasonable duration.

One of the limitations of this study is interpreting only English videos and taking a snapshot of the information. Additionally, the use of one keyword; "fibromyalgia" is another limitation. Since the contents of the videos on FM were also evaluated, the keyword was kept as a broad term. On the other hand, all videos were analyzed by 2 independent PMR specialists and showed almost perfect agreement. In addition, the videos were not analyzed as animated or non-animated. The type of video may affect the video view rate and like ratio. In further studies, this video feature should be added as a criterion.

In conclusion, patients with FM have the interest to gather information on YouTube, and the quality of information on YouTube is variable. Physicians, academic institutions should be aware of this information-seeking interest. High-quality, reliable videos that shed light on patients' questions with an optimal duration should be provided by physicians and academic institutions. This will prevent patients from misleading information and provide support.

CONFLICT OF INTEREST

All the authors have no conflict of interest to declare.

ETHICS APPROVAL

Since the study does not include any human participants or animals and the videos were available to everyone, ethics committee approval was not required.

ORCID

Tugba Ozsoy-Unubol https://orcid.org/0000-0001-9538-9191

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How to cite this article: Ozsoy-Unubol T, Alanbay-Yagci E. YouTube as a source of information on fibromyalgia. *Int J Rheum Dis*. 2021;24:197–202. https://doi.org/10.1111/1756-185X.14043

Received: 10 August 2020 | Revised: 22 October 2020 | Accepted: 22 October 2020

DOI: 10.1111/1756-185X.14025

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Did Sejong the Great have ankylosing spondylitis? The oldest documented case of ankylosing spondylitis

JiHwan Lee

Department of Orthopedic Surgery, Konkuk University School of Medicine, Seoul, Korea

Correspondence
JiHwan Lee, Department of Orthopedic Surgery, Konkuk University School of Medicine, 120-1, Neungdong-ro, Gwangjin-gu, Seoul, 05030, Korea.
Email: metaphoricusjh@gmail.com

Abstract

Aim: Sejong the Great (May 7, 1397-March 30, 1450), a king during Korea's Choson Dynasty, is the most respected historical figure in South Korean society, and consequently, many studies have been conducted on his achievements and the disease he suffered. The dominant trend of scholarship claims that Sejong suffered from diabetic retinopathy. However, this interpretation has not been medically verified. The present analysis aimed to demonstrate that Sejong's is the oldest documented case of ankylosing spondylitis.

Methods: *The Annals of the Choson Dynasty* (hereafter, *The Annals*) are daily records of the king. *The Annals* were recorded for 472 years (1392-1865) and contain 49 646 667 Chinese characters. Records in *The Annals* on Sejong span 1418-1450; the present study author reviewed these records.

Results: Sejong's medical records are mentioned 40 times in the source text. The king first experienced musculoskeletal pain in his knee at the age of 22 years. Sejong's knee pain is mentioned 3 times, and his back pain, which he described as "stiff and immobile", is mentioned 6 times. He complained most frequently of ocular symptoms described as "prickly or tingling," which are mentioned 12 times.

Conclusions: Based on the analysis of official documentation, the author argues that there is a high probability that Sejong suffered from ankylosing spondylitis, making this the oldest officially documented case of the disease.

KEYWORDS

ankylosing, diabetes mellitus, diabetic retinopathy, spondylitis, spondyloarthropathies

1 | INTRODUCTION

Sejong the Great (May 7, 1397-March 30, 1450), a Choson Dynasty king, was a renowned linguist who created the Hangul alphabet; in honor of his achievements, UNESCO presents an eponymous award to organizations and groups that contribute to reducing illiteracy. Sejong is also believed to have suffered from various diseases, and several sources have confirmed his history of chronic back pain and irregular bouts of eye disease. Sejong enjoyed eating meat, avoided exercise, and experienced several instances of polydipsia. Consequently, some historians have hypothesized that Sejong suffered from diabetes and eventually developed diabetic retinopathy. In addition, several studies have claimed that Sejong suffered from gonorrhea, herniated nucleus pulposus, diabetic neuropathic arthropathy, and cerebral infarction.[1]

However, neither the back nor the knee pain that Sejong suffered from are symptoms caused by diseases such as vascular claudication, Charcot arthropathy, diabetic neuropathic arthropathy,

herniated nucleus pulposus, internal disc derangement, or spinal stenosis. Sejong's knee pain occurred at the age of 22 years and only in his right joint. He described his back pain in the following manner: "My waist and back are stiff and immobile, so it is hard to bend or straighten."[2] Sejong's eye disease does not match the symptoms of diabetic retinopathy either. Reports indicate that he suffered "painful or tingling symptoms" and his vision repeatedly worsened and improved.[3] These symptoms are starkly different from those of diabetic retinopathy.

This study claims that a single condition caused the arthralgia Sejong experienced, which began in one joint, developed into back pain (in an atypical pattern), and progressed further into eye disease, which had repeated cycles of exacerbation and relief. The present study author seeks to evaluate the adequacy of this claim by analyzing *The Annals of the Choson Dynasty* (hereafter, *The Annals*), the official records of the Choson Dynasty.

2 | METHODS

The Annals are daily records of the king and events of the period, written from the 15th century, and constitute fairly rare contemporary evidence that does not reflect the prejudice of the recorders or any other interested party of the period. *The Annals* established and operated a separate institution free from the influence of political interest groups, and access to kings or their descendants was prohibited to prevent distortion by the royal family. The objectivity of *The Annals* has been recognized by UNESCO and included in their *Memory of the World Register*. They are also recognized as thorough observations and are often cited in papers regarding climate or celestial events.[4-6] Other records offer information regarding Sejong's disease, but their objectivity and thoroughness fall short of *The Annals*. Therefore, the author only consulted the records found in *The Annals*.

The Annals are publicly available online. They were recorded for 472 years (1392-1865) and contain 49 646 667 Chinese characters. Among them, records on Sejong span the period from 1418 to 1450, and the present author reviewed all information captured within this timeframe.

There are several precautions to take when consulting these records. First, the medical context of the Choson Dynasty must be considered; for example, diseases recorded during this period as gonorrhea are different from modern gonorrhea. In the Choson Dynasty era, a tingling feeling during urination, the feeling of urine retention, or lower abdominal discomfort were all labeled as gonorrhea, although such symptoms are more indicative of cystitis.[1] Consequently, historical sources were consulted with a focus on symptoms rather than on medical terminology. In addition, symptoms that were not clearly understood were excluded.

3 | RESULTS

The frequency of Sejong's symptoms is shown in Figure 1. Sejong complained most frequently of ocular symptoms; diabetes-related symptoms are discussed only 3 times (polydipsia twice and unexpected weight loss once).

After sorting Sejong's symptoms by year, several patterns emerged. As shown in Figure 2, Sejong's musculoskeletal pain first developed at the age of 22 years, and back pain increased in frequency in his early 30s. The recorded eye symptoms increased in frequency after the age of 42 years.

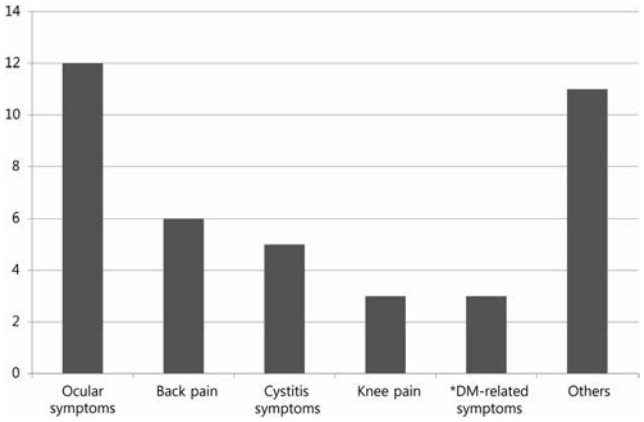

FIGURE 1 Frequency of symptoms

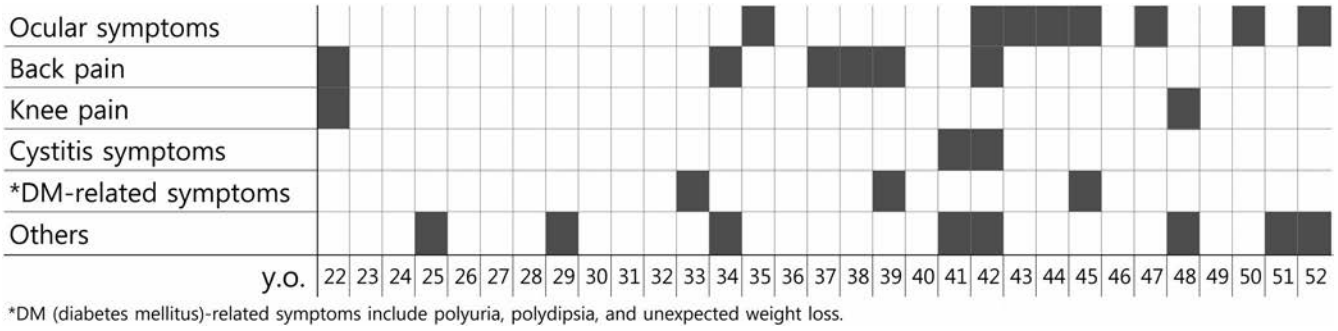

FIGURE 2 Age and symptoms

4 | DISCUSSION

The established theory is that Sejong's musculoskeletal pain and ocular symptoms were due to diabetes; however, this assertion is unlikely. First, there is little evidence that he had diabetes. Although Sejong complained of polydipsia and unexpected, occasional weight loss, there are limitations to interpreting this as a symptom of diabetes. In particular, unexpected weight loss is also observed in wasting diseases, such as rheumatic diseases.

Second, historians argue that Sejong's obesity and lack of exercise support their diagnosis of diabetes. However, fewer than 32% of South Koreans diagnosed with diabetes are overweight.[7] Finally, Koreans have a tendency to develop nephropathy as a complication of diabetes,[8] but there is no evidence of nephropathy in Sejong's symptoms, and most of the symptoms in Sejong's urogenital system may be explained by cystitis.

Moreover, in the 15th century, there was no insulin or any oral hypoglycemic agent to help manage diabetes. If Sejong indeed had had type 1 diabetes, it would have been difficult for him to survive without insulin administration from the age of 33 years, when the symptoms first occurred, until the age of 52 years, when he died. Even with type 2 diabetes, which would not have been controlled, Sejong would have been unlikely to survive for over 20 years and, even if he had, he would have likely experienced complications such as nephropathy or diabetic foot.

As Sejong's symptoms occurred at the age of 33 years, which is relatively early in life, maturity-onset diabetes of the young (MODY) is a plausible diagnosis. However, based on *The Annals*' records, there is no diabetes evidence in any of the 3 generations of Sejong's paternal line. Thus, MODY, which is characterized by dominant inheritance, does not fit the king's presentation.[9]

Finally, even if Sejong did have diabetes, the symptoms he suffered from did not match those of diabetic retinopathy. Diabetic retinopathy is painless, and Sejong reported decreased vision and tingling. These symptoms are similar to those of uveitis, which often accompanies autoimmune diseases. Diabetic retinopathy also does not manifest itself in repeated cycles of exacerbation and relief. Sejong's eye pain occurred alternately on the left and right sides, with repeated cycles of deterioration and improvement.

Given these symptoms, what disease might have plagued Sejong? The author claims that the knee pain, back pain, and eye disease occurring in sequence point to Sejong suffering from ankylosing spondylitis. Ankylosing spondylitis begins with either back pain or arthritis in one joint, after which various complications can develop.[10] Early symptoms develop at approximately 23 years of age while developing ankylosing spondylitis after 40 years is rare. Sejong's right knee pain occurred at the age of 22 years, and his back pain was exacerbated in his 30s. The most common symptom of an extra-articular manifestation of ankylosing spondylitis is acute uveitis, which relapses in more than 50% of patients with ankylosing spondylitis who experience it.[11] Uveitis causes pain and has repeated cycles of exacerbation and improvement, consistent with Sejong's symptoms.

The Annals provide excellent data, but there are limitations to using them diagnostically, and conclusions must be drawn with extreme caution. As modern medical knowledge was not available during the Choson Dynasty, the symptoms themselves may not have been correctly assessed, and the authors attempted to minimize Sejong's memory lapses. Sejong's complaints of symptoms were analyzed by weighting the records within 1 month of onset or records with the exact date of onset. However, *The Annals* are more of a daily record of salient events and not that of medical history, and confirming the diagnoses is impossible.

Despite these limitations, together, his knee pain, back pain, and acute uveitis point toward Sejong likely having had ankylosing spondylitis. Although Sejong is recorded to have avoided horseback riding because he was not interested in sports, this may have also been due to pain from ankylosing spondylitis.

Skeletal evidence of ankylosing spondylitis has been observed in Egyptian mummies.[12] However, the first record of an ankylosing spondylitis diagnosis based on the patient's clinical symptoms was published on February 11, 1898 by Pierre Marie.[13] As Sejong lived in the 15th century, his probable ankylosing spondylitis might be the earliest documented case with a contemporary recording of symptoms compatible with this diagnosis.

ACKNOWLEDGMENTS

The author would like to thank the National Institute of Korean History and the King Sejong Memorial Society for providing *The Annals of the Choson Dynasty* for free on their website. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR'S CONTRIBUTION

The author contributed to the literature search, figure creation, data interpretation, and writing of the manuscript.

ORCID

JiHwan Lee https://orcid.org/0000-0002-5335-9784

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How to cite this article: Lee J. Did Sejong the Great have ankylosing spondylitis? The oldest documented case of ankylosing spondylitis. *Int J Rheum Dis*. 2021;24:203–206. https://doi.org/10.1111/1756-185X.14025

Received: 4 August 2020 | Revised: 6 November 2020 | Accepted: 7 November 2020

DOI: 10.1111/1756-185X.14030

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

Prevalence of inflammatory back pain and radiographic axial spondyloarthritis in a semi-urban community of Lahore, Pakistan

Muhammad Ahmed Saeed[1,2,3,4,7] | Hina Ahmed[5] | Muhammad Faiq[6] | Zeeshan Aslam[6] | Saira Elaine Anwer Khan[6,7] | Shabnam Batool[6] | Sumaira Farman[3,4,7] | Nighat Mir Ahmad[2,3,4,7]

[1]Rheumatology, Al-Aleem Medical College, Lahore, Pakistan

[2]Department of Rheumatology, Gulab Devi Teaching Hospital, Al-Aleem Medical College, Lahore, Pakistan

[3]Department of Rheumatology, National Hospital and Medical Center, Lahore, Pakistan

[4]Adjunct Faculty Fatima, Jinnah Medical University, Lahore, Pakistan

[5]Department of Community Health Sciences, FMH College of Medicine and Dentistry, Lahore, Pakistan

[6]Department of Rheumatology, FMH College of Medicine and Dentistry, Lahore, Pakistan

[7]Arthritis Care Foundation, Lahore, Pakistan

Correspondence
Dr. Muhammad Ahmed Saeed, Rheumatology, Gulab Devi Teaching Hospital, Al-Aleem Medical College, Lahore, Pakistan.
Email: masaeed72@gmail.com

Funding information
This COPCORD study was funded through an APLAR COPCORD grant.

Abstract

Aims: To determine the prevalence of inflammatory back pain (IBP) and radiographic axial spondyloarthritis (SpA) in a semi-urban community of Lahore, Pakistan.

Methods: This cross-sectional household survey was designed as per the Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) model. In Phase 1, the subjects were interviewed for musculoskeletal (MSK) pain in the last 7 days by clinical assistants. In Phase 2, physiotherapists identified subjects with spinal/back pain and interviewed for Assessment in Spondyloarthritis International Working Group (ASAS) criteria for IBP. In Phase 3 subjects having IBP or chronic back pain (CBP) with an age at onset ≤45 years, were assessed and further investigated.

Results: A total of 4922 subjects with a mean age of 35.3 ± 14.5 years, including 2770 (56%) women were surveyed in Phase 1. MSK pain in last 7 days was reported by 1407 (28.6%) of whom 1034 (21%) had spinal pain. The ASAS criteria for IBP were met in 329 (6.7%, 95% CI 6.0-7.0). In Phase 3, 222 with IBP and 83 having CBP with age at onset ≤45 years were evaluated. Out of this total of 305, 144 (2.9%) were confirmed to have IBP by rheumatologists as per at least 1 of the 3 criteria. ASAS criteria were met in 107 (2.2%, 95% CI 1.8-2.6). ASAS criteria for radiographic axial SpA were met in 47 (1%, 95% CI 0.7-1.3) of the surveyed population.

Conclusion: Inflammatory back pain was reported in 6.7% by physiotherapists, confirmed in 3% by rheumatologists. The prevalence of radiographic axial SpA was 1%.

KEYWORDS

ankylosing spondylitis, community survey, COPCORD, epidemiology, inflammatory back pain

1 | INTRODUCTION

Inflammatory back pain (IBP) is the hallmark symptom of ankylosing spondylitis (AS) and other related diseases grouped as spondyloarthritis (SpA), afflicting young individuals leading to a lot of disability.[1,2] AS has been historically diagnosed as per modified New York criteria, which requires the presence of radiographic sacroiliitis.[3] Due to the advent of magnetic resonance imaging (MRI) and better insight into the course of AS, it has been classified by Assessment of Spondylo-Arthritis international Society (ASAS) into radiographic

axial SpA and non-radiographic axial SpA mandating newer studies for determining the prevalence.[4] The term radiographic axial SpA has been used interchangeably with AS in the literature as well as in clinical practice.[5]

Various IBP criteria have been used in a primary care setting as screening tools for early referral, but their utility in community-based surveys for case identification has not been widely studied.[6] In population-based estimates from the US National Health and Nutrition Examination Survey, the prevalence of IBP is 6% by applying Calin criteria.[7] While, IBP in the UK primary care population has been reported to be 1.7%, 3.0%, and 3.4% as per ASAS, Calin, and Berlin criteria respectively.[8]

Community Oriented Program for Control of Rheumatic Disorders (COPCORD) is a WHO-International League Against Rheumatism (ILAR) joint initiative that started in 1983 for generating epidemiological data.[9] Several stage 1 surveys from developing countries have been completed reporting back pain as one of the commonest self-reported symptoms but data on IBP are scarce.[10,11] A COPCORD study from Mexico reported IBP in 3%.[12] The worldwide prevalence of AS is around 0.5% to 1%.[13] However, COPCORD surveys from Pakistan, India, and Bangladesh have reported a very low prevalence of AS and other SpA (0.03%-0.1%), in that studies' focus was not on specifically identifying subjects with inflammatory back pain (IBP), and the diagnosis was ascertained mostly on clinical assessment alone.[10,14,15]

There is a lack of data on the prevalence of rheumatic diseases in general and especially of SpA spectrum diseases in Pakistan. The last COPCORD study in Pakistan was conducted more than 2 decades ago by Farooqi et al.[14]

This study aimed to determine the prevalence of IBP and radiographic axial SpA as per ASAS criteria in a semi-urban community of Lahore, Pakistan.

2 | METHODS

This was a cross-sectional, household survey, conducted by the Department of Rheumatology, FMH College of Medicine and Dentistry (FMHCM&D), in a semi-urban community of Nain Sukh, Sheikupura District, Lahore Division, Punjab, Pakistan, which is situated 15 km outside Lahore city on the bank of River Ravi. It was conducted from November 2018 to April 2019. The estimated population of Nain Sukh and its surroundings was around 40 000. The base camp of the household survey was the Primary Healthcare Center (PHC) of Nain Sukh, run by the Department of Family Medicine, FMHCM&D in collaboration with the district government.

This study was designed as per WHO-ILAR, COPCORD model having 3 phases. The original COPCORD Core Questionnaires (CCQ) of Phases 1 and 2, were translated from English to Urdu by a rheumatologist. The Urdu version was translated back to English by another rheumatologist, who was unaware of the original English questionnaire, both were not directly part of this research project. There was no significant difference between the CCQ and the back-translated version. The final version of the questionnaire was validated in a pilot study involving 50 Nain Sukh subjects.

The surveyed population included men and women older than 16 years who had been living at their place of residence for at least 6 months. Subjects were excluded if they were visiting Nain Sukh, were unable or unwilling to give informed consent, or not willing to give a blood sample.

Formal ethical approval was obtained from the FMHCM&D's Institutional Review Board. Verbal informed consent was taken from all participants.

2.1 | Selection and training of the COPCORD survey team

For Phases 1 and 2 of the household survey, 10 clinical assistants with matriculation and formal paramedic training and 8 physiotherapists were selected. The clinical assistants, physiotherapists, and 2 rheumatology fellows participated in class and field workshops to ensure the accuracy and uniformity of the questionnaire application.

2.2 | Measures taken to enhance the co-operation of the community

The Principal Investigator and the team arranged pre-survey meetings with the religious leaders, elected union council members, and the family physicians of the outreach program of the Family Medicine Department of FMHCM&D. Posters and banners were displayed highlighting the objectives and benefits of the survey and information leaflets were distributed in the houses a week before the survey. Announcements were made before and during the survey from the loudspeakers of the mosques and in Friday prayers congregation.

2.3 | Data collection in Phases 1 and 2

Phases 1 and 2 were conducted simultaneously. Phase 3 was started 4 weeks after the completion of Phase 2. The PHC of Nain Sukh was made the base camp. For Phase 1, random walk and quota sampling technique was used.'[16] Eight teams of clinical assistants and physiotherapists went from door to door to administer CCQs for data collection via interview in Phases 1 and 2 from household members of both genders aged 16 years and above. Each team was assigned a minimum interview quota of 600 for Phase 1.

The geographic map of Nain Sukh was divided into various areas. The principal investigator identified a focal point at the crossing in each specified geographical area of Nain Sukh. The next step was selecting the street randomly which was done by spinning a water bottle on the ground as used in vaccination surveys by WHO's Extended Program of Immunization.[17] The survey was started from the first house on the right in the street to which the bottle had pointed.[17]

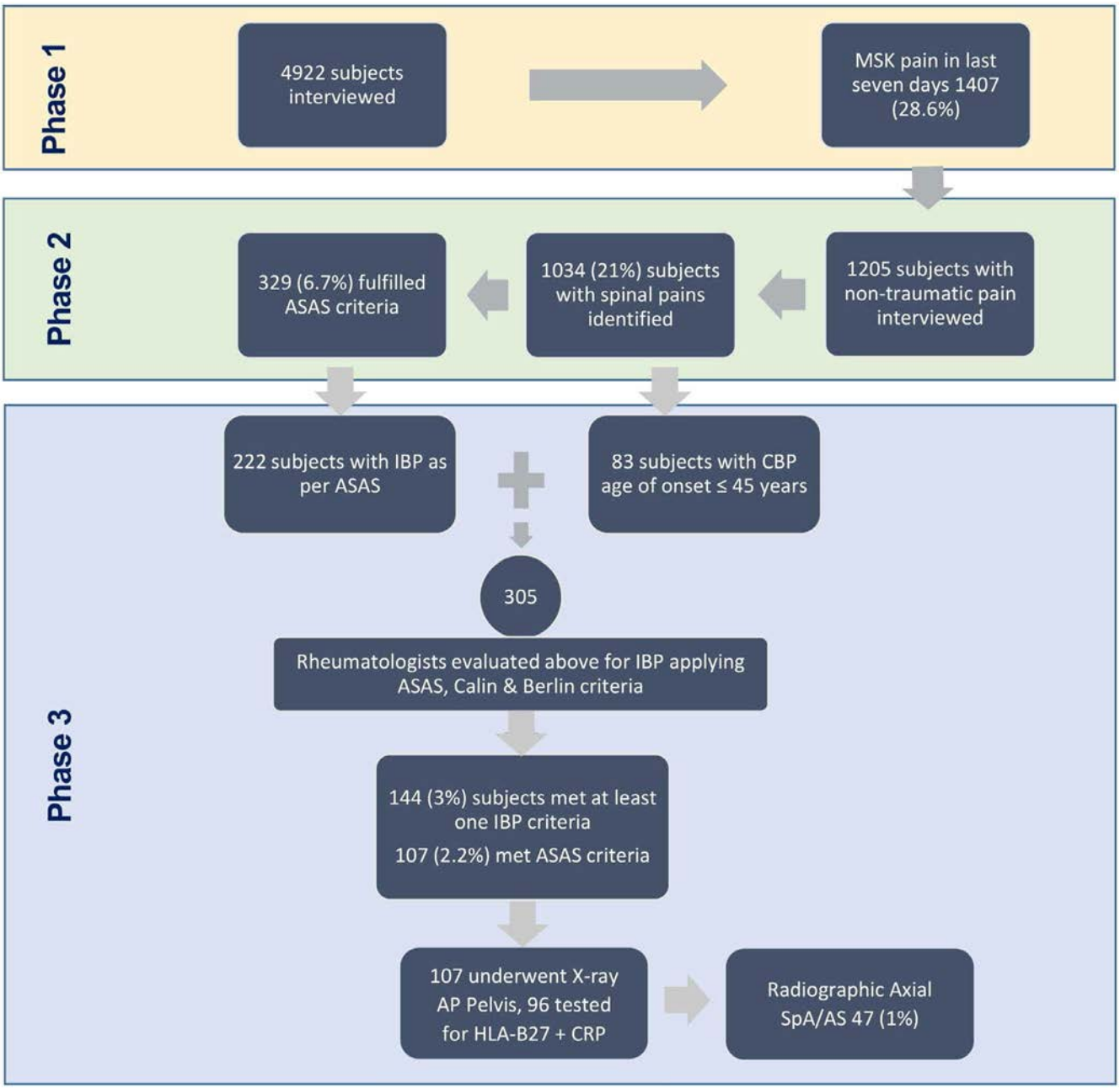

FIGURE 1 COPCORD study flow chart

The interviewers in each team interviewed each house beginning from their right. If the interviewer encountered any sidewalk, he or she continued to interview the house on the right hand and the same applied for the crossing street. In this way, the household survey continued until a predetermined quota of 600 subjects for each team had been achieved. Repeated call backs were done at different times of the day at the convenience of households to reduce the non-response rate.

Positive respondents were defined as those having body aches and joint pains during the last 7 days, not attributable to trauma. They were enrolled for Phase 2 through a purposive sampling. Subjects were asked to point to areas of pain, swelling, stiffness, and/or limitation, on a drawing of a mannequin, which they experienced in the last 7 days or prior. The subjects rated their pain on a Likert scale. Data on their health-seeking behaviors were also recorded. The impact of musculoskeletal (MSK) pain on functional disability was assessed by the Modified Health Assessment Questionnaire (MHAQ), administered via interview.[18] In addition to the CCQ for Phase 2 all participants were specifically asked for the presence of spinal/back pain defined as the history of pain, stiffness, and limitation of movement in neck, upper, lower back, and painful stiffness in shoulder and pelvic girdle muscles. They were further interviewed for individual items of ASAS criteria. Positive respondents of Phase 2 were those who fulfilled ASAS criteria for IBP or had chronic back pain (CBP) defined as back pain of 3 months or more with an age at onset ≤45 years.

2.4 | Phase 3

This phase was started 4 weeks after Phase 2. In the first round, all subjects with back pain fulfilling the ASAS criteria for IBP in Phase 2 were invited to visit the rheumatology clinic for evaluation. In the second round, the lead investigator scrutinized Phase 2 forms to identify individuals who had CBP with an age of onset ≤45 years for clinical assessment by the rheumatology team. Each subject was asked specific questions about the presence of IBP as per ASAS, Calin, and Berlin criteria to validate information collected by physiotherapists.[4] Subjects who did not meet any of the 3 criteria for IBP were labeled as non-inflammatory back pain (see Figure 1). A complete medical history with a focus on all SpA associated features defined by ASAS classification criteria for axial SpA like family history, history suggestive of inflammatory arthritis, enthesitis, uveitis, dactylitis, psoriasis, Inflammatory bowel disease, and good response to non-steroidal anti-inflammatory drugs were taken from each participant.[3] They were thoroughly examined including tests for spinal mobility like modified Schober's, finger-to-floor distance, chest expansion, tragus to the wall, and occiput to wall distance.[4] The examination also involved tender and swollen joint count, enthesis and especially looking for nail and skin psoriasis.[19] All subjects enrolled in Phase 3 also rated their back pain on a numeric scale.

The subjects fulfilling any of the IBP criteria were tested for human leukocyte antigen (HLA)-B 27 and C-reactive protein (CRP). Testing for HLA-B 27 was done on Clonit HLA-B27 allele real-time polymerase chain reaction assay, in a College of American Pathologists 2016 certified lab. Subjects with IBP present or prior, as per any of the 3 criteria also underwent anteroposterior (AP) pelvis X-ray in a nearby health facility. Each X-ray was scored as per New York criteria for grading of sacroiliitis, independently by a radiologist and the PI.[20] X-rays reported as bilateral grade 2, unilateral grade 3 or above were considered meeting the criteria for radiographic axial SpA or AS. In case of any discordance in reporting, a mutual agreement was reached after discussion.

For patients who had predominantly inflammatory arthritis with a present or prior history of IBP, were classified as having peripheral SpA as per ASAS criteria for peripheral SpA.[19,21]

Since this was a prevalence estimation study, recognizing the importance of accurate data collection, every effort was made to have detailed rheumatologic assessments on all selected subjects. Patients fulfilling modified New York criteria for AS were not subjected to further imaging. Subjects having IBP as per any of the criteria with X-ray AP pelvis either normal or inconclusive were offered MRI of the sacroiliac joints at the discretion of the PI, to look for active sacroiliitis defined as per ASAS.[22]

Those subjects who could not get an MRI because of cost or other logistical issues were labeled as unclassified IBP.

2.5 | Quality control and monitoring

A pilot study on 50 subjects of the same semi-urban community was undertaken to assess the training level of interviewers and the reliability of the Urdu translated versions of CCQs. A separate log of all subjects' demographic and contact details was also maintained. The PI used to regularly visit the base camp and the field. At each visit, all the filled CCQs of Phases 1 and 2 were scrutinized for any missing details which were later rectified through contacting the subject personally or by phone.

2.6 | Statistical analysis

The pre-test of the Urdu version of CCQ Phase 1 and Phase 2 was done to assess the feasibility and reliability in 50 subjects of Nain Sukh. To determine the reliability, Cronbach's alpha was calculated and the score was 0.87. These subjects were later included in the total count of 4922 subjects surveyed. At the end of the household survey, the data from the completed questionnaires were analyzed using SPSS software version 25. Proportions were calculated for all qualitative variables and all quantitative variables were presented as mean and standard deviation. One-way analysis of variance was applied for comparisons of means among different groups. For comparison of categorical variables between different sub-groups of diagnosis, a Chi-square test was applied. The level of significance was set at 95% (P value ≤.05). For calculating the relative risk (RR), Pearson's Chi-square test was applied. Prevalence figures were represented with a 95% confidence interval calculated by Wilson score.

3 | RESULTS

3.1 | Demography of the surveyed population

A total of 4922 subjects were interviewed in Phase 1. The mean age of the surveyed population was 35.3 ± 14.5 years (95% CI 34.9-35.7). Out of 4922 subjects, 2770 (56.3%) were female. For the sociodemographic characteristics of the participants refer to Table 1.

3.2 | Data on non-traumatic musculoskeletal pain

In the surveyed households, the point prevalence of MSK pain in the last 7 days was 1407 (28.6%; 95% CI 27.3-29.9). The regional distribution of MSK pain is shown in Table 2. Out of these 1407, 1205 (24.5%) of the surveyed population participants were enrolled for Phase 2 of the survey, having non-traumatic MSK pain. Most of the subjects who dropped out were those who were non-contactable or not available on the subsequent visit or withdrew their consent.

3.3 | Data on spinal/back pain

Lower back pain (755; 15.3%, 95% CI 14.4-16.4), was the most commonly reported MSK symptom within the last 7 days followed by neck pain in 420 (8.5%, 95% CI 8.5-7.8). There were 1034 (21%, 95% CI 19.8-22.2) subjects who reported having spinal pain, who were

TABLE 1 Sociodemographic characteristics of the surveyed population (N = 4922)

Age in y, mean ± SD	35.33 ± 14.47
	95% CI 34.9-35.7
Female n (%)	2770 (56.3)
Age group n (%)	
25 or less	1537 (31.2)
26-35	1391 (28.3)
36-45	1004 (20.4)
46-56	520 (10.6)
56 and older	470 (9.5)
Marital status n (%)	
Married	3711 (75.4)
Single	1003 (20.4)
Widowed	184 (3.7)
Divorced	16 (0.3)
Separated	8 (0.2)
Family size, mean ± SD	7.12 ± 3.80
Literacy level n (%)	
Read-only	384 (7.8)
Read and write	2439 (49.6)
Illiterate	2099 (42.6)
Y in school n (%)	
Primary	368 (7.5)
Secondary	419 (8.5)
Matric	767 (15.6)
Intermediate	243 (4.9)
Graduation	254 (5.2)
Masters	40 (0.8)
Non-formal education	2831 (57.6)
Smoking n (%)	449 (9.1)
Alcoholism n (%)	8 (0.2)
Current occupation n (%)	
Student	317 (6.4)
Farm work	148 (3.0)
Desk job	6 (0.1)
Fieldwork	938 (19.1)
Shop business	548 (11.1)
Household work	2526 (51.3)
Housemaid	59 (1.2)
Professional	71 (1.4)
Military	1 (0.0)
Retired	128 (2.6)
Unemployed	174 (3.5)
Monthly income n (%)	
Less than PKR 15 000 (USD 112)	2006 (40.8)
More than PKR 15 000 (USD 112)	2916 (59.2)

then interviewed for ASAS criteria for IBP, and 329 (6.7%, 95% CI 6.0-7.4) of these subjects fulfilled the criteria, administered by physiotherapists during Phase 2 of the survey. Subjects who had IBP were younger as compared to the ones with non-inflammatory back pain (34.8 ± 10.2 vs 41.4 ± 14.3, $P < .000$). There were 250 (76%) females out of total 329 subjects with IBP. In addition, 83 subjects were identified having CBP with age at onset ≤45 years.

In the first round of Phase 3, out of 329 with IBP as per ASAS, 222 subjects came for rheumatological examination; the rest either withdrew their consent or were non-contactable. However, ASAS criteria was confirmed in 86 (38.7%). Out of 83 subjects with CBP with age at onset ≤45 years identified from Phase 2, 21 (25.3%) met ASAS criteria. Finally, out of 305 subjects enrolled for Phase 3, 144 (2.9%, 95% CI 2.5-3.4) subjects were classified as confirmed IBP by a rheumatologist as per any of the above 3 criteria. IBP present or in the past was confirmed by a rheumatologist as per ASAS, Calin, or Berlin criteria in 107 (2.2%, 95% CI 1.8-2.6), 102 (2.1%, 95% CI 1.7-2.5), and 87 (1.8%, 95% CI 1.4-2.2), respectively (Figure 1, COPCORD survey flow chart).

One hundred and seven subjects underwent X-ray AP pelvis and 97 patients were tested for HLA-B 27 and CRP levels. ASAS criteria for radiographic axial SpA was met in 47 (1%, 95% CI 0.7-1.3) of the surveyed population and 15.4% of the subjects evaluated in Phase 3. MRI of sacroiliac joints was done in 5 patients with IBP and active sacroiliitis was found to be present in 3 patients as per the ASAS definition of active sacroiliitis. Thus, 53 subjects were finally found to have axial SpA as per ASAS criteria, yielding a prevalence estimate of 1.1% (95% CI 0.8-1.4). The rest of the patients with IBP were labeled as unclassified IBP (47; 1.0%). Around 10 (0.2%) patients fulfilled the ASAS criteria for peripheral SpA (Table 3).

Out of 53 patients fulfilling the ASAS criteria for axial SpA, 32 (60.4%) were females and 21 (39.6%) males. However, the percentages out of the total of the same gender were 60 for males (21/35) and 42.7 for females (32/75) resulting in a RR of 1.41 (95% CI 0.96-2.05). HLA-B27 was reported to be positive in 7 (7.2%) out of 97 tested. Out of these 7 patients, 3 met the New York criteria, and the rest fulfilled the ASAS criteria for axial SpA clinical arm. In the rest of the subjects with CBP and age at onset ≤45 years with or without joint pains, the commonest diagnosis was non-inflammatory lower back pain (LBP) in 141 (2.9%), followed by fibromyalgia in 33 (0.7%), and inflammatory arthritis in 12 (0.2%) (Table 3).

Patients with axial SpA or unclassified IBP had a lower age at onset of back pain as compared to subjects with non-inflammatory back pain ($P = .002$). Subjects with non-inflammatory pain had higher body mass index as compared to patients with axial SpA and unclassified IBP ($P = .000$). Subjects with axial SpA had significantly lower lumbar flexion on modified Schober's test and higher pain on visual analog scale as compared to the subgroup comprising of non-IBP (Table 4).

4 | DISCUSSION

Since its inception, COPCORD has generated a wealth of data on MSK symptoms and rheumatic diseases from the developing world.

TABLE 2 Regional distribution of musculoskeletal pain in the surveyed population (N = **4922)**

Region/joint area	n (%)
Neck	420 (8.5)
Upper back	88 (1.8)
Lower back	752 (15.3)
Shoulder joint	209 (4.2)
Elbow joint	71 (1.4)
Hand	96 (1.9)
Wrist joint	85 (1.7)
Hip joint	50 (1.0)
Knee joint	402 (8.2)
Calf pain	110 (2.2)
Ankle joint	108 (2.2)
Feet	54 (1.1)

TABLE 3 Prevalence of different rheumatic diseases in the semi-urban community of Nain Sukh (N = 4922)

Diagnosis	n (%; 95% CI)
Radiographic axial SpA/AS	47 (1; 1.0-1.3)
Non-radiographic axial SpA	6 (0.1; 0.04-0.26)
Unclassified inflammatory back pain	48 (1.0; 1.0-1.3)
Peripheral SpA	10 (0.2; 0.1-0.4)
Undifferentiated inflammatory arthritis	12 (0.2; 0.1-0.4)
Osteomalacia	1 (0)
Fibromyalgia	33 (0.7; 0.48-0.94)
Soft tissue rheumatism	5 (0.1)
Generalized benign hypermobility	2 (0)
Non-inflammatory back pain	141 (2.9; 2.4-3.4)

Abbreviations: AS, ankylosing spondylitis; SpA, spondyloarthritis.

The majority of the COPCORD surveys had reported back pain as one of the commonest symptoms. Despite the fact that the concept of IBP is more than 4 decades old, the prevalence of IBP has not been reported in most of these surveys. This survey is the first to the best of our knowledge which has applied ASAS criteria of IBP as a screening tool in the community for case identification and ascertaining the diagnosis of axial SpA.

The current survey had highlighted that every 4th person in the surveyed community had MSK pain (in the last 7 days) and spinal pain was reported in almost two-thirds of the positive respondents of Phase 1. The frequency of MSK pain in the last 7 days (point prevalence) in our survey had been almost double that of the previous survey from the north of Pakistan (28.6% vs 14.7%).[14] The COPCORD investigators from the neighboring country India in various COPCORD studies had reported MSK pain in 6.3%-23.7%.[15] Data from Iran showed a much higher point prevalence (44.7%) of MSK pain. Interestingly, they reported back pain (23.7%) as the second commonest reported symptom, which was close to our figure of 21% of subjects suffering from spinal pain.[23] In our survey, LBP was reported in 15.3% of the subjects. COPCORD surveys from across the globe had reported frequency of back pain around 11.5%-35%, which was closer to our figure.[24] In a Brazilian Study the point prevalence of MSK pain (26.9%) was almost the same as our reported figure with spinal pain as the most commonly reported symptom in almost two-thirds of positive respondents.[25] Nearly similar statistics on MSK pain (28.4% to 36.5%) were published a few years back from other parts of South America, in a female predominant surveyed population like ours.[26,27]

In this study, we used ASAS criteria for IBP as a screening tool for identifying patients with axial SpA. The utility of IBP in primary care for screening patients for early referral to rheumatologists is well established.[28] Its utility as a screening tool in community-based studies has been not well recognized.[29] Various algorithms had been developed over time but again they were applicable in a primary care setting and not in a community.[30] We found that almost 1 in every 3 persons with spinal pain had IBP (6.7% of the total population). A study from Mexico reported back pain in 8% while 3% had IBP, which was around 37% of the subjects with back pain which was close to our figure of 32%.[12] Weisman et al reported the prevalence rates of IBP to be 6% in a US population, which was close to our findings of 6.7%, as per ASAS criteria administered by physiotherapists.[31] This was noteworthy that they used Berlin criteria which were administered by trained interviewers, which was not verified by rheumatologists. There was a discordance of observation between physiotherapists and rheumatologists as out of 222 seen by the rheumatologist in Phase 3, with physiotherapist-diagnosed IBP, only 144 (64.8%) were confirmed to fulfill at least one IBP criterion. This discrepancy may be explained by different levels of expertise and settings.

The frequency of AS or radiographic SpA in the current study was 1%, which was higher than those reported in earlier COPCORD studies (0.07% to 0.26%) but almost the same as reported in Western literature.[13,32] A study from Mexico using the COPCORD model showed that the prevalence of IBP, SpA, and AS were 1.3%, 0.6%, and 0.1% respectively which is lower than our figure.[33] It is noteworthy that the investigators used Berlin criteria for IBP and European Spondyloarthropathy Study Group (ESSG) criteria for SpA. Studies from India had consistently reported very low standardized prevalence rates for AS and other SpA by clinical diagnosis.[15] A meta-analysis by Stolwijk et al[34] showed that the prevalence of AS was higher in studies that used ASAS or New York criteria for case ascertainment as compared to the clinical diagnosis. A recent study on university students from southern China used ASAS criteria for diagnosis and found a prevalence of axial SpA of 0.34%. This study like ours reported that IBP was more common in females but males and IBP more likely to be diagnosed with axial SpA.[35] Furthermore, this low prevalence reported in most COPCORD studies might be because early diagnosis of AS requires MRI and expensive tests like HLA-B27, while COPCORD

TABLE 4 Univariate comparison of demography and clinical characteristics of subjects with axial SpA, unclassified IBP, non-IBP and subgroup comprising of miscellaneous diagnosis

Variables	Axial SpA (n = 53)	Unclassified IBP (n = 48)	Non-IBP (n = 141)	Miscellaneous diagnosis[a] (n = 63)	*P* value
Age in y, mean ± SD	33.3 ± 7.0	33.5 ± 8.8	37.2 ± 8.8	33.8 ± 9.0	.293
Age at onset of back pain, mean ± SD	28.9 ± 6.7	28.9 ± 8.4	32.7 ± 7.5	29.1 ± 7.9	.002*
Female, n (%)	32 (60.4)	37 (77.1)	106 (75.2)	52 (82.5)	.048*
BMI, mean ± SD	27.4 ± 6.4	27.1 ± 6.9	28.2 ± 9.9	28.8 ± 7.8	.000*
Modified Schober's in cm, mean ± SD	14.8 ± 1.3	14.9 ± 1.2	15.4 ± 1.1	15.4 ± 1.4	.003*
Finger-to-floor distance in cm, mean ± SD	4.8 ± 9.1	5.5 ± 8.9	3.2 ± 7.4	5.4 ± 9.3	.206
Chest expansion in cm, mean ± SD	3.5 ± 1.1	3.9 ± 1.1	3.8 ± 0.9	3.4 ± 1.5	.093
Tragus to the wall in cm, mean ± SD	10.6 ± 2.7	10.5 ± 2.2	10.2 ± 1.6	9.7 ± 2.8	.182
Pain VAS numeric, mean ± SD	5.0 ± 2.7	4.8 ± 2.3	3.9 ± 2.2	4.9 ± 2.9	.004*
HAQ score, mean ± SD	0.8 ± 0.5	0.6 ± 0.4	0.7 ± 0.4	0.8 ± 0.5	.461

Abbreviations: BP, inflammatory back pain; HAQ, Health Assessment Questionnaire; ISpA, spondyloarthritis VAS, visual analog scale.

[a]Other diagnoses include patients with peripheral SpA, fibromyalgia, and inflammatory arthritis, etc (for detail see Table 3).

*P value significant at ≤.05.

studies have been historically low-cost low infrastructure, ascertaining diagnosis mostly on clinical grounds. Further, adding items addressing specifically IBP in the CCQ might have increased its sensitivity for the diagnosis of axial SpA. This needs to be validated further to suggest incorporating IBP individual item questions in Phase 2 CCQ.

In our study, 35% of the subjects enrolled in Phase 3 with CBP with an age at onset ≤45 years met ASAS criteria for IBP, and almost half of these subjects were classified as radiographic axial SpA or AS. Burgos-Vargas et al in their multi-centric study also reported that 38.7% of patients with chronic LBP had IBP of whom 53.7% met criteria for AS.[36]

In the current survey, the sensitivity of HLA-B27 was around 16% which was much lower than Western data.[37] There is a lack of data on the prevalence of HLA-B27 in the general population in Pakistan; however, an earlier study on prospective donors and recipients of renal transplant reported prevalence of HLA-B 27 in 5.5%.[38] Otsuka et al[39] from Japan reported a very low frequency of HLA-B27 (5.4%) in their SpA cohort with higher frequency of other HLA-B gene alleles. Studies from the Arab world had also reported prevalence of HLA-B27 to be as low as 13.87% from Lebanon to around 70% in Kuwait and Saudi Arabia.[40-42] Moreover, several other genes have been implicated in the pathogenesis of SpA that might be the case in our population and needs to be explored in future studies.[43] Because of the lower positivity rate of HLA-B27 in our cohort of IBP patients, we might not have been able to delineate the significance of the clinical arm of ASAS criteria for axial SpA in ascertaining the diagnosis which was in contrast to a study done in a population with a high prevalence of HLA-B27.[44]

One of the limitations of our study was high attrition rate (30%) from Phase 2 to Phase 3. The reasons for this might be the relatively younger population with IBP, the majority being women engaged in household work, while men being daily wage-earners found it difficult to come for clinical examination and imaging to a tertiary care hospital. However, dropouts for the clinical examination can be avoided in future surveys by using a fast track model as adopted by Chopra et al in their Bhigwan COPCORD project.[45] Second, our surveyed population was predominantly female which can be

addressed in the future by using controlled sampling. Moreover, the reason for higher prevalence of AS in our study might be because of over-reporting of the grade of sacroiliitis as both the rheumatologist as well as the radiologist were aware of the clinical history of IBP. Interestingly, in the follow-up of the previously described cohort developed for ASAS classification, Sepriano et al explained that subtle radiographic changes were amenable to measurement errors.[46] Another limitation of our study was that we were not able to get the MRI of sacroiliac joints on all patients with IBP who were not fulfilling ASAS criteria for radiographic axial SpA, because of logistical and budgetary constraints. Hence, the prevalence of non-radiographic axial SpA might have been higher than reported in this study. Data on disease activity and functional status were not available on all subjects so were not reported. We highly recommend a future COPCORD study using a randomized sampling technique with age and gender standardization to confirm our findings.

5 | CONCLUSIONS

In summary, ASAS criteria for IBP can be applied in community surveys to estimate the prevalence of axial SpA. The estimated prevalence of IBP in the semi-urban community of Nain Sukh was 6.7% as per ASAS criteria administered via interview by physiotherapists. IBP as per at least 1 of the 3 validated criteria was confirmed in 3% by the rheumatologist. The estimated prevalence of AS or radiographic axial SpA in this survey was around 1% which is higher than reported in previous COPCORD surveys but almost the same as reported in Western studies.

ACKNOWLEDGEMENTS

We cordially acknowledge the support of the Fellows of FMH, Department of Rheumatology, clinical staff of PHC Nain Sukh, clinical assistants, physiotherapists, especially Ms Fatima Attique for helping in data entry, Mr Tipu Sultan research assistant, for data analysis and Dr Sharoon Hanook for helping in statistical analysis.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualizing of the study. Data acquisition was done by MAS, MF, ZA. Data entry, analysis, and interpretation were done by MAS and HA. The manuscript was drafted by MAS and HA. The remaining authors gave their intellectual input and approved the final draft for submission.

ORCID

Muhammad Ahmed Saeed https://orcid.org/0000-0003-4771-4441

Hina Ahmed https://orcid.org/0000-0002-1946-2198

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How to cite this article: Saeed MA, Ahmed H, Faiq M, et al. Prevalence of inflammatory back pain and radiographic axial spondyloarthritis in a semi-urban community of Lahore, Pakistan. *Int J Rheum Dis*. 2021;24:207–215. https://doi.org/10.1111/1756-185X.14030

Received: 28 September 2020 | Revised: 10 November 2020 | Accepted: 12 November 2020

DOI: 10.1111/1756-185X.14036

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Cancer diagnosis and mortality in patients with ankylosing spondylitis: A Western Australian retrospective cohort study

Erin Kelty[1] | Warren Raymond[2] | Charles Inderjeeth[2,3] | Helen Keen[2,4] | Johannes Nossent[2,3] | David B. Preen[1]

[1]The School of Population & Global Health, The University of Western Australia, Perth, WA, Australia

[2]The School of Medicine, The University of Western Australia, Perth, WA, Australia

[3]Rheumatology Department, Sir Charles Gairdner Hospital, Perth, WA, Australia

[4]Rheumatology Department, Fiona Stanley Hospital, Perth, WA, Australia

Correspondence
Erin Kelty, School of Population & Global Health, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia.
Email: erin.kelty@uwa.edu.au

Funding information
This work was supported by an unrestricted grant from the Arthritis Foundation of Western Australia.

Abstract

Aim: Ankylosing spondylitis (AS) has been associated with a modest increase in the risk of cancer. However, little is known as to how AS influences risk of mortality following cancer diagnosis. This study compared the risk of cancer and subsequent mortality in patients with AS compared with a non-AS population group.

Methods: Patients diagnosed with AS in Western Australia (WA) between 1980 and 2014 were identified from the WA Rheumatic Disease Epidemiological Register (N = 2152; 31 099 patient-years). A non-AS comparison group (N = 10 760; 165 609 patient-years) was selected from hospital records, matched 1:5 on age, Aboriginality, and gender. Data on cancer diagnosis, comorbidities and mortality were extracted from state cancer, hospital, and mortality registers. The relative risk of cancer (overall and by type) and mortality following cancer diagnosis between AS and non-AS comparators was compared using Cox proportional hazard models, adjusting for risk factors and comorbidities.

Results: Ankylosing spondylitis patients had a 15% increase in the crude risk of cancer (hazard ratio [HR]: 1.15, 95% CI: 1.02-1.30). However, this association was attenuated following adjustment for smoking and common comorbidities (adjusted HR: 1.08, 95% CI: 0.95-1.22). Following a cancer diagnosis, patients with AS had an increased risk of 5-year mortality in the unadjusted (HR: 1.24, 95% CI: 1.03-1.49) and the adjusted models (adjusted HR: 1.37, 95% CI: 1.13-1.66).

Conclusion: Ankylosing spondylitis was not associated with an increased risk of cancer diagnosis. Following a cancer diagnosis, AS was associated with an increased risk of 5-year mortality.

KEYWORDS

ankylosing spondylitis, cancer, chronic arthritis, mortality, survival

1 | INTRODUCTION

Ankylosing spondylitis (AS) occurs as the result of an abnormal immune response, which triggers chronic inflammation in the spinal joints, particularly at the sacroiliac junction.[1,2] The effects of AS are not limited to the musculoskeletal system, it can also effect the eyes, heart, lungs, and colon.[3,4] AS has been associated with a modest increased risk of cancer, with a 14% increase in cancer risk observed in a 2016 meta-analysis.[5] In particular, AS has been associated with an increased risk of cancers of the lymphoid,

hematopoietic and related tissues (pooled relative risk [RR] 1.32; 95% CI, 1.11-1.57), as well as the digestive system (pooled RR 1.20; 95% CI, 1.01-1.42).[5] The increased risk of cancer is thought to be at least in part related to the chronic inflammation associated with AS.[6]

Systemic inflammation in cancer patients has also been associated with reduced survival.[7,8] Increases in markers of inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), has been associated with a reduction in 5-year diagnosis following cancer diagnosis.[8] The role that inflammation associated with AS may play in survival following cancer diagnosis has not been investigated. However, higher NLR has also been observed in patients with AS compared with controls.[9] Additionally, poorer survival outcomes following cancer diagnosis have been associated with other chronic autoimmune diseases, such as rheumatoid arthritis (RA).[10,11] In a study of 6309 patients diagnosed with cancer and RA, the risk of all-cause mortality was 31% higher in patients with RA compared with those without the condition.[11] As such, it is expected that mortality in patients with AS and cancer would be higher than for the general population.

This paper examines the risk of cancer in Western Australian (WA) patients with AS, and their 5-year mortality rates following cancer diagnosis, compared to non-AS population comparison group.

2 | MATERIALS AND METHODS

2.1 | Study cohort

The study included patients diagnosed with AS in WA between 1980 and 2014, as identified as part of the WA Rheumatic Disease Epidemiological Register (WARDER) study. The AS cohort was limited to patients diagnosed between the ages of 18 and 80 years. A non-AS comparison group matched 1:5 on age (within 1 year), gender, and Aboriginal status were sampled from hospital records. For patients with AS, the age at the first hospital or emergency department contact with a primary or additional diagnosis related to AS (International Classification of Diseases 9th edition [ICD-9]: 720.0, and ICD-10-CM [Clinical Modification]: M45) was used as time-0 for follow-up. For patients in the comparison group, the age at admission to hospital (a randomly selected admission) for any diagnosis was used.

2.2 | Study data

Data for this study were collated from statewide health registers by the WA Data Linkage Branch. Data for each participant were extracted from the WA Hospital Morbidity Data System (HMDS) (1980-2014), Emergency Department Data Collection (EDDC) (2002-2014), Cancer Register (1982-2014) and the Death Register (1980-2014).

The Cancer Register routinely collects statewide information on cancer diagnoses from pathology reports and oncology treatment records. This data combined with data from the Death Register were used to identify cancer cases. The Death Register contains complete information on the date of death, and a death certificate, which details the primary and underlying causes of death. Occasionally, this may contain cancers that are not included in the Cancer Register.

The HMDS and EDDC data were used to identify the following comorbidities: diabetes mellitus, cardiovascular disease, chronic lower respiratory infection, and inflammatory bowel disease (IBD). These comorbidities were selected for their association with AS and/or cancer. The HMDS was also used to identify patients with a history of tobacco smoking, which was routinely recorded as an additional diagnosis. The HMDC is a statutory data collection that compiles information, including the primary and additional diagnosis fields (up to 20) of all inpatient admissions from all hospitals in WA, while the EDDC contains data (including a single diagnosis code), related to emergency department activity in WA.

Data from the 4 datasets were coded using International ICD-9, ICD-9-CM and ICD-10 Australian Modification (ICD-10-AM) codes. The ICD codes used in this study are presented in Table S1.

2.3 | Data analysis

Comparison of the demographics of AS and the comparison group was initially made using univariable logistic and linear regression. Univariable Cox proportional hazard models were used to compare time to cancer diagnosis and survival in patients diagnosed with cancer, with and without AS. Subsequent multivariable models were used to control for history of smoking, prior cancer diagnosis, diabetes mellitus, cardiovascular disease, chronic lower respiratory infection, and IBD. For cancer survival, age at cancer diagnosis, gender, history of smoking, and year of cancer diagnosis were included in the multivariable analysis. Incidence and survival were also examined stratified by gender, age, and cancer site (breast, colorectal, lung, prostate and skin).

2.4 | Ethics considerations

The study received ethics approval from the WA Department of Health Human Research Ethics Committee (WADOH HREC#: 2016.24).

3 | RESULTS

3.1 | Demographics

The study included 2152 patients diagnosed with AS (with 31 099 patient-years of observation) and 10 760 comparison patients without AS (165 609 patient-years) matched on age, gender, and Aboriginality. AS patients were less likely to have been previously diagnosed with cancer (odds ratio [OR]: 0.57, 95% CI: 0.45-0.71),

but had higher rates of cardiovascular disease (OR: 1.95, 95% CI: 1.77-2.14), chronic lower respiratory infections (OR: 2.31, 95% CI: 2.03-2.63), diabetes (OR: 1.37, 95% CI: 1.18-1.58) and IBD (OR: 7.26, 95% CI: 5.63-9.37) than the comparison group. Additionally, the AS group had significantly higher rates of having smoked (OR: 1.62, 95% CI: 1.48-1.78) compared with the non-AS group (Table 1).

3.2 | Cancer incidence

The overall risk of cancer in patients with AS was significantly higher than patients without AS in unadjusted analysis (hazards ratio [HR]: 1.15, 95% CI: 1.02-1.30, $P = .020$) (Table 2). However, following adjustment for smoking and common comorbidities the difference was no longer significant (HR: 1.08, 95% CI: 0.95-1.22, $P = .238$). Similarly, in male patients a significant difference in cancer incidence was observed in the univariable model, but not the adjusted model. The incidence of cancer was not significantly different for females with and without AS in both the unadjusted and adjusted models. When stratified by age, the crude risk of cancer was higher in young (18-39 years) and middle-aged (40-59 years) AS patients compared with patients without AS, While in older patients (>60) there was no difference in the incidence of cancer.

There was no significant difference between the 2 groups in terms of the risk of breast, colorectal, lung or skin cancer. The incidence of prostate cancer was significantly higher in the males in the AS group compared with the comparison group ($P = .007$). The numbers of site-specific cancer patients with AS was too low for a robust multivariable model including all co-variates. Following adjustment for significant co-variates (smoking and cardiovascular disease), the risk of prostate cancer was still significantly higher in the AS group (HR: 1.37, 95% CI: 1.02-1.84).

When stratified by the year of AS diagnosis, patient diagnosed prior to 2005 had a significantly higher crude risk of cancer compared with patients without AS, while for AS patients diagnosed in 2005 or later the risk of cancer was significantly lower (Table 2).

3.3 | Mortality following cancer diagnosis

Mortality was examined in the 323 AS and the 1495 comparison patients diagnosed with cancer during the study period. There were fewer female patients (OR: 0.62, 95% CI: 0.48-0.81) and more patients have a history of smoking (OR: 2.16, 95% CI: 1.68-2.77) in the AS group compared with the comparison group (Table 3). However, the AS group were less likely to have been diagnosed with cancer prior to this event (OR: 0.37, 95% CI: 0.20-0.68).

Although 1-year mortality was not significantly different between the 2 groups, 3- and 5-year mortality following cancer diagnosis was significantly higher in patients diagnosed with AS compared with non-AS comparison group (Table 4). A 90% increase in mortality was observed in AS patients diagnosed with prostate cancer, while no differences in mortality were observed for the other cancer sites.

Over the study period, the prognosis following cancer diagnosis improved significantly with risk of death reducing by an average of 3.2% per year. In the comparison group, the average reduction in the risk of mortality was 2.2% (95% CI 1.8%-3.8%), while in the AS group the average reduction was 4.8% (2.2%-6.7%).

4 | DISCUSSION

In this large population-based study, AS was associated with a modest increase in the crude risk of cancer; however, following adjustment for smoking status and common comorbidities there was no significant difference in cancer risk between the 2 groups. Following diagnosis with cancer, patients with AS had a 37% increased risk of death in the 5 years following the cancer diagnosis compared with cancer in patients without AS.

TABLE 1 Characteristics and comorbidities of study participants with and without AS

	AS	Comparison	*P* value
Number	2152	10 760	NA
Follow-up, y, mean ± SD	14.5 ± 9.8	15.4 ± 10.2	<.001
Gender male, n (%)	1294 (60.1%)	6470 (60.1%)	.999
Age, y, mean ± SD	47.4 ± 16.0	47.4 ± 16.0	.934
Aboriginal, n (%)	16 (0.7%)	80 (0.7%)	.999
History of cancer, n (%)	87 (4.0%)	746 (6.9%)	<.001
History of smoking, n (%)	997 (46.3%)	3739 (34.8%)	<.001
Comorbidities, n (%)			
Cardiovascular disease	1243 (57.8%)	4437 (41.2%)	<.001
Chronic lower respiratory disease	383 (17.8%)	921 (8.6%)	<.001
Diabetes mellitus	257 (11.9%)	971 (9.0%)	<.001
Inflammatory bowel disease	145 (6.7%)	106 (1.0%)	<.001

Abbreviation: AS, ankylosing spondylitis.

TABLE 2 Hazards ratios (HR) for cancer and type specific cancer in patients with AS compared with an age and gender matched comparison group, unadjusted and adjusted models

	AS, n (%)	Comparisons, n (%)	HR (95% CI)	Adjusted HR[a] (95% CI)
AS vs non-AS group	323 (15.0%)	1495 (13.9%)	1.15 (1.02-1.30)	1.08 (0.95-1.22)
Age				
18-39	53 (6.7%)	243 (6.1%)	1.36 (1.01-1.84)	1.29 (0.95-1.75)
40-59	144 (18.4%)	561 (14.4%)	1.29 (1.07-1.55)	1.26 (1.04-1.52)
60+	126 (22.0%)	691 (24.0%)	0.92 (0.76-1.12)	0.97 (0.80-1.18)
Gender				
Male	231 (17.9%)	910 (14.1%)	1.16 (1.01-1.34)	1.06 (0.91-1.23)
Female	92 (10.7%)	585 (13.2%)	1.07 (0.86-1.34)	1.00 (0.79-1.26)
Cancer site[b]				
Breast	14 (0.7%)	124 (1.2%)	0.60 (0.35-1.04)	—
Colorectal	21 (1.0%)	163 (1.5%)	0.69 (0.44-1.09)	—
Lung	33 (1.5%)	131 (1.2%)	1.33 (0.91-1.95)	—
Prostate[c]	60 (4.6%)	184 (2.8%)	1.49 (1.11-2.00)	—
Skin	72 (3.4%)	333 (3.1%)	1.17 (0.91-1.51)	—
Year of AS diagnosis				
Prior to 2005	288 (19.3%)	1268 (16.8%)	1.25 (1.10-1.43)	1.12 (0.98-1.28)
2005 onward[b]	35 (5.3%)	227 (7.1%)	0.63 (0.44-0.90)	—

Abbreviation: AS, ankylosing spondylitis

[a]Adjusted for history of smoking, prior cancer diagnosis, diabetes, cardiovascular disease, inflammatory bowel disease and chronic lower respiratory infections.

[b]Number of cases too small for multivariable analysis.

[c]Percentage of males.

TABLE 3 Characteristics of AS and comparison patients diagnosed with cancer

	AS	Comparison	*P* value
Number	323	1495	
Male, n (%)	231 (71.5%)	910 (61.0%)	<.001
Age at cancer diagnosis, y, mean ± SD	65.1 ± 12.9	67.8 ± 13.1	.001
History of cancer, n (%)	12 (3.7%)	140 (9.4%)	.001
History of smoking, n (%)	208 (64.4%)	682 (45.6%)	<.001

Abbreviation: AS, ankylosing spondylitis.

4.1 | Cancer risk

While the unadjusted risk of cancer in AS patients was consistent with previous literature, with a 15% increase risk of cancer in this study and a 14% increase in a 2016 meta-analysis, this was no longer significant following adjustment for potential confounders.[5] In the meta-analysis adjusted measures were used; however, the studies varied substantially in the co-variates included. While most included age and gender, only 3of the 23 studies included smoking status, 1 controlled for diabetes and none controlled for prior cancer diagnosis, IBD or chronic lower respiratory infection. The absence of the variables may have contributed to the difference in findings between this study and the meta-analysis.

The relationship between cancer incidence and AS was modified by age. In patients diagnosed with AS for the first time between the ages of 18-39 and 40-59, the risk of cancer was increased by 29% and 26% respectively. In contrast, while the incidence of cancer was much higher in AS patients first diagnosed at 60-80 years of age, there was no difference between patients with and without AS. Similar findings have been observed previously in the literature.[12,13]

Ankylosing spondylitis was not associated with an increased risk of breast, colorectal, lung or skin cancer, consistent with a 2016 meta-analysis of cancer in AS patients which found no increased risk of breast cancer, skin cancer, or respiratory cancers. A significant increase in the risk of prostate cancer was observed in male AS patients. Increased risk of prostate cancer was also observed in a Taiwanese cohort (standardized incidence ratio [SIR] 1.64, 95% CI:

TABLE 4 Mortality risk following cancer diagnosis in patients with and without AS

	Number deceased (%)			
	AS	Comparisons	HR (95% CI)	Adjusted HR[a] (95% CI)
1 y	78 (24.2%)	321 (21.5%)	1.07 (0.83-1.37)	1.14 (0.88-1.46)
3 y	127 (39.3%)	428 (28.6%)	1.29 (1.06-1.58)	1.40 (1.14-1.71)
5 y	141 (43.7%)	499 (33.4%)	1.24 (1.03-1.49)	1.37 (1.13-1.66)
Age, y, at cancer diagnosis (deceased at 5 y post-diagnosis)				
18-39	5 (9.4%)	12 (4.9%)	1.58 (0.14-17.47)	—
40-59	46 (31.9%)	142 (25.3%)	1.95 (1.09-3.48)	1.41 (0.77-2.58)
60+	90 (71.7%)	345 (49.9%)	1.23 (1.01-1.50)	1.17 (0.96-1.43)
Gender (deceased at 5 y post-diagnosis)				
Male	104 (45.0%)	336 (36.9%)	1.12 (0.90-1.40)	1.24 (0.99-1.55)
Female	37 (40.2%)	163 (27.9%)	1.40 (0.98-2.00)	1.81 (1.26-2.60)
Site-specific (deceased at 5 y post-diagnosis)				
Breast	<5[b]	NS	0.77 (0.18-3.31)	—
Colorectal	11 (52.4%)	62 (38.0%)	1.60 (0.84-3.30)	—
Prostate	22 (36.7%)	36 (19.6%)	1.93 (1.13-3.28)	—
Lung	29 (87.9%)	108 (82.4%)	0.74 (0.49-1.11)	—
Skin	14 (19.4%)	33 (9.9%)	1.85 (0.99-3.46)	—

Abbreviations: AS, ankylosing spondylitis; NS, not specified to protect patient confidentiality.

[a]Adjusted for age, gender, smoking, year of diagnosis, and prior cancer diagnosis.

[b]Where the cell size if less than 5, "<5" was used to protect participant confidentiality.

1.04-2.47)[12] and a Korean cohort of AS patients (SIR 1.97, 95% CI: 1.59-2.35).[14] Given AS disproportionally effects males, the role of androgens has been investigated as a potential contributor to the increased risk of prostate cancer. However, research thus far has not produced strong evidence of a relationship between endogenous hormones and prostate cancer risk.[15] Additionally, serum levels of adrenal and gonadal hormones appear to be normal in patients with AS.[16] It has been proposed that the role of AS treatments such as nonsteroidal anti-inflammatory drugs may contribute to the risk of prostate cancer; however, this requires further investigation.[14]

When stratified by year of AS diagnosis, patients diagnosed prior to 2005 had an 30% increase in the crude risk of cancer, while patient diagnosed in 2005 and after were associated with a 35% reduction in cancer risk compared with the comparison group. Substantial changes in the diagnosis and management of AS occurred over the study period, resulting in earlier diagnosis, slower progression of the disease, and better health outcomes,[17] which may be contributing to a reduction in cancer risk. However, given the substantially shorter follow-up and fewer cases of cancer patients since 2005, further research is required to examine how cancer risk may have changed over time in patient with AS.

4.2 | Mortality following cancer diagnosis

Following cancer diagnosis, AS was associated with a 37% increase in mortality at 5 years (adjusted). This increase in mortality risk was not associated with a particular gender or age group. Similarly, the difference in mortality risk between groups did not appear to be associated with particular cancer types/sites, with the exception of prostate cancer which was associated with a 90% increase in mortality compared with prostate cancer patients without AS.

The increase in mortality following cancer diagnosis in AS may be attributable to the systemic inflammation associated with AS. Markers of inflammation including those included in the platelet-to-lymphocyte ratio, NLR, C-reactive protein (CRP) and mean platelet volume (MPV) have been found to be indicators of cancer prognosis.[18,19] Interestingly, many of these inflammatory markers are also significantly different in patient with AS compared with healthy controls.[9,20] For example, mean platelet volume was significant lower and CRP significantly higher in AS patients[20]; both low MPV and high CRP have been associated with increased mortality following cancer diagnosis.[21,22] Interestingly, in the same study RA patients also had lower MPV and higher CRP compared with the

control group.[20] RA has also been associated with an increase in 5-year mortality following cancer diagnosis.[11]

The difference in mortality may be associated with the presence of other comorbidities, cancer stage at diagnosis, or difference in uptake or response to cancer treatment. Unfortunately due to the number of cancer cases within each group, it was not possible to investigate or control for the role of comorbidities. Data were not available or did not include information on stage of cancer diagnosis and cancer treatment.

The first hospital admission with an AS diagnosis was used as a surrogate date of AS diagnosis; however, AS was likely to have been diagnosed prior to this event and managed in an ambulatory care setting. The gap between AS diagnosis and first AS hospitalization may have been substantial, particularly in older patients, given AS is generally diagnosed before the age of 40.[23]

4.3 | Limitations

While the use of statewide health data had a number of advantages in terms of the capture of data, it places some limitations on the scope of available data. In particular, clinical data (eg, AS severity, treatments, tumor staging) and data on other cancer risk factors (eg, diet and exercise) were not available. Additionally, while efforts were made to select a suitable comparison group and control for difference between the 2 groups, unmeasurable differences between the 2 groups may have influenced the findings.

5 | CONCLUSION

When adjusted for smoking and common comorbidities, AS was not associated with an increased risk of cancer. AS was also associated with a reduced survival following cancer diagnosis, potentially associated with chronic inflammation associated with AS.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of the Western Australian Data Linkage Branch, the Western Australian Department of Health, and the data custodians of the WA Cancer Register, the Hospital and Morbidity Data Collection, the WA Death Register, the Victorian Department of Justice, and the National Coronial Investigation System for their assistance with the study.

CONFLICT OF INTEREST

EK, WR and DP have no interested to declare. CI has received funds from Amgen for consultancy and speaker engagements. He has received fund from Eli Lilly Australia for a speaking engagement and Novartis Pharmaceutical Australia Pty Ltd for consultancy. HK received fund from Abbvie, and Roche for speaking and travel awards from Roche, Pfizer and Abbvie. JN received funds from Janssen-Cilag Pty Ltd in 2019 for a single speaker engagement.

DATA AVAILABILITY STATEMENT

Data were provided by the Western Australian Data Linkage Branch on behalf of the custodians of the respective data sets. As a condition of the use of this data, the data are unable to be shared publicly.

ORCID

Erin Kelty https://orcid.org/0000-0002-0841-2216
Warren Raymond https://orcid.org/0000-0002-2537-0070
Charles Inderjeeth https://orcid.org/0000-0003-0535-963X
Johannes Nossent https://orcid.org/0000-0002-2833-7997
David B. Preen https://orcid.org/0000-0002-2982-2169

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SUPPORTING INFORMATION

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

How to cite this article: Kelty E, Raymond W, Inderjeeth C, Keen H, Nossent J, Preen DB. Cancer diagnosis and mortality in patients with ankylosing spondylitis: A Western Australian retrospective cohort study. *Int J Rheum Dis*. 2021;24:216–222. https://doi.org/10.1111/1756-185X.14036

Received: 9 June 2020 | Revised: 19 November 2020 | Accepted: 19 November 2020

DOI: 10.1111/1756-185X.14041

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Assessment of loneliness in patients with inflammatory arthritis

Hakan Emmungil[1] | Ufuk İlgen[1] | Sezin Turan[1] | Ozge Kilic[2]

[1]Department of Rheumatology, Trakya University Medical School, Edirne, Turkey

[2]Department of Psychiatry, Bezmialem Vakif University Medical Faculty, İstanbul, Turkey

Correspondence
Ufuk İlgen, Department of Rheumatology, Trakya University Hospital, 22100, Edirne, Turkey.
Email: ufukilgen@gmail.com

Abstract

Aim: This study aimed to explore loneliness and associated factors in Turkish patients with inflammatory arthritis.

Method: Adult patients with rheumatoid arthritis (RA) (n = 58), ankylosing spondylitis (AS) (n = 53), and psoriatic arthritis (PsA) (n = 30), respectively, were included in the study. A single-item visual analog scale (VAS) for loneliness, UCLA Loneliness Scale-8 (ULS-8), Beck depression inventory (BDI), Beck anxiety inventory (BAI), revised multidimensional scale of perceived social support, Health Assessment Questionnaire-Disability Index (HAQ-DI) were used for the psychometric and functional assessments. Multiple regression models were generated for predicting the ULS-8 and HAQ-DI scores.

Results: There was no difference between disease groups in terms of the ULS-8 and HAQ-DI scores. Among demographic and clinical parameters, only the education status and number of drugs used had associations with the ULS-8 score. Single-item VAS score for loneliness did not predict the ULS-8 score well. There were significant correlations between the ULS-8 and HAQ-DI, depression, anxiety, social support, and physician global VAS scores. Only the education status significantly predicted ($\beta = -0.208$) the ULS-8 score in multiple regression analysis (adjusted $R^2 = 0.15$, $P < .001$). Beck depression, anxiety, and patient global VAS scores remained significant for predicting the HAQ-DI after multiple regression with the covariates ULS-8, depression, anxiety, social support, patient and physician global VAS scores, and the number of drugs used (adjusted $R^2 = 0.53$, $P < .001$). Disease activity and the ULS-8 scores were not found to be associated in any disease group.

Conclusion: Loneliness is associated with depression, anxiety, lack of social support, disability, higher number of drugs used, and lower education but not with disease activity in Turkish patients with RA, AS, and PsA. Perception and expression of loneliness vary according to the cultural background. Single-item scales for loneliness may lack reliability compared to the more comprehensive ULS-8.

An abstract of this study was presented at EULAR 2019 as a poster and published in the congress proceedings and *Annals of the Rheumatic Diseases* supplement (doi: 10.1136/annrheumdis-2019-eular.7548).

KEYWORDS
ankylosing spondylitis, inflammatory arthritis, loneliness, psoriatic arthritis, rheumatoid arthritis, social support

1 | INTRODUCTION

The biopsychosocial model examines how biological, psychological, and social aspects play a role in health and disease models. It is proposed to allow doctors to better grasp the emotional perspective of their patients on their disease and suffering.[1] Social aspects have usually been neglected not only in clinical practice but in research on rheumatic diseases.

Loneliness, defined as the painful emotional experience of a disparity between the real and the desired social contact,[2] may be one of the most overlooked aspects of the social domain and is associated with a negative self-assessment of health.[3,4] While it is closely related to other social issues such as lack of support, invalidation, and isolation, loneliness has also affective, cognitive, and behavioral correlates.[5,6] Most of the medical literature on loneliness has concentrated mainly on mental health and related issues.[5,7] Loneliness has been found to be inversely correlated with life satisfaction and associated with poor personality integration.[5] It has also been linked to anxiety and depression in numerous empirical investigations.[5,8,9] Loneliness may predict depression and may even be a vulnerability factor for suicide ideation, parasuicide, and suicide completion.[5,10] In addition to suicide risk, studies have found loneliness to be associated with alcohol abuse.[11] Moreover, as a risk factor for both mental and physical health problems,[12] it shows a harmful effect on all-cause mortality as well.[13] Loneliness may indicate an excess mortality risk even after control for age, gender, and subjective health in the elderly.[4] Studies also demonstrated the negative effects of loneliness on survival after myocardial infarction,[7] metastatic breast cancer,[14] and malignant melanoma.[15]

The impact of loneliness on rheumatic diseases (and vice versa) is largely unknown. Patients with inflammatory arthritis identified loneliness as a contributor to psychological distress.[16] In a study conducted in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthritis, other systemic rheumatic diseases, and fibromyalgia, lack of social support and invalidation were identified as the independent predictors of loneliness.[17] Of note, neither of these two studies explored clinical features of the disease and their association with loneliness. Further, they had mixed patient groups including those with inflammatory and degenerative rheumatic diseases and subgroups of inflammatory arthritis were not individually examined. Interestingly, when loneliness was explored in a cross-cultural context in RA, female Egyptian RA patients were found to experience more loneliness than Dutch patients.[18] However, low social support was important in explaining loneliness in the Netherlands but not in Egypt. In terms of disease-related features, this study examined only the disease duration and disability in relation to psychosocial factors and loneliness, and recruited RA patients only. Loneliness appears to share common features across cultures, yet culture shapes it and is shaped by it.[19] So, loneliness and culture are conceptually interrelated.[19] Perception and expression of loneliness and coping with it are all known to vary according to the cultural background.[19,20]

The origin of loneliness has been a focus of discussion. Some proposed a single-dimension view that loneliness was a core perception of an individual not primarily dependent on the changing relationships and felt in the same way by all lonely people.[2,21,22] Others proposed emotional (further divided into romantic and family categories) and social origins.[2,21] Thus, the measurement of loneliness by single- or multidimensional approaches has long been argued.[21] Single-item Likert-type or visual analog scales (VAS), multi-item single-dimensional scales (such as UCLA [University of California, Los Angeles] Loneliness Scale), and multidimensional scales composed of emotional and social sub-scales (such as Social and Emotional Loneliness for Adults [SELSA]) were used to explore loneliness in studies.[2-5,17,18,21,22]

Our study aims to explore loneliness and associated factors in patients with RA, AS, and psoriatic arthritis (PsA) with a focus on disease-related factors. Effects of demographic features, functional status, depression, anxiety, and social support on loneliness, and loneliness on functional status will also be evaluated. Since very little is known about loneliness in inflammatory arthritis and as loneliness is to be shaped by the culture, our study will contribute to the literature in the context of Turkish culture in which social bonds are expected to be strong. It is also expected to highlight loneliness and its predictors, increase awareness, and finally guide potential future interventions in the study population.

2 | METHODS

2.1 | Patients and design

Patients, 18 years of age or older, with RA, AS, and PsA, meeting the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)[23] modified New York criteria,[24] and Classification Criteria for Psoriatic Arthritis (CASPAR),[25] followed up at the Department of Rheumatology, Trakya University Hospital and admitted between May 2018 and December 2019, were included in the study. Sample size was determined using ClinCalc (www.clincalc.com/stats/samplesize.aspx) online statistics program. To detect 20% or more difference in the mean loneliness scores with 0.05 type I error and 80% power and when the standard deviations were set as 20% of the mean, at least 16 patients were found to be included in each study group. To decrease type II error, inclusion of at least 30 cases per study group was planned. Exclusion criteria were the presence of severe disease complications, comorbid diseases requiring hospitalization, and severe mental states that grossly affect cognition caused by disorders such as dementia, schizophrenia, and bipolar disorder.

2.1.1 | Demographic features

Age, gender, marital status, number of children, household size, education and working status, and comorbid diseases were determined.

2.1.2 | Clinical parameters

Disease duration, number of drugs being used, corticosteroid, non-steroidal anti-inflammatory and conventional or biological/targeted synthetic disease-modifying anti-rheumatic drug (DMARD) use, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and the relevant disease activity indices were identified for each patient. The Disease Activity Score of 28 joints (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) were used to assess the disease activity in patients with RA.[26] The Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and AS Disease Activity Score (ASDAS) were used to assess the disease activity in AS patients.[27] For patients with PsA, the number of swollen and tender joints, and 0-100 point VAS for pain and fatigue were used as indicators of disease activity in addition to ESR and CRP since no single disease activity index is available. VAS (0-100 points) for the global assessment of health by the patients themselves and the relevant physicians were also used. Additionally, the presence of enthesitis and uveitis for AS, active psoriasis for PsA, and hand deformities (Boutonniere, swan-neck, Z-thumb deformities, radioulnar, radiocarpal, carpometacarpal, and metacarpophalangeal subluxations and deviations, and arthritis mutilans) for RA and PsA patients were recorded.

2.1.3 | Psychometric assessment

Beck depression inventory (BDI), Beck anxiety inventory (BAI), revised multidimensional scale of perceived social support, and UCLA loneliness scale (ULS-8), all validated in Turkish populations,[28-31] were used for psychometric assessments. A 0-10 point VAS for loneliness was tested for the prediction of the ULS-8 score. A significant correlation existed between the ULS-8 score and VAS score for loneliness ($\rho = 0.386$, $P < .001$). But only 11% of the variance in the ULS-8 score was explained by the VAS score (Appendix S1). Since the magnitude of effect of this simple one-item VAS score on the validated and comprehensive ULS-8 score was so small, it was not found useful for the assessment of loneliness in our sample.

2.1.4 | Functional assessment

Health Assessment Questionnaire-Disability Index (HAQ-DI) was used for the functional assessement.[32]

ULS-8 and HAQ-DI scores were the primary outcome variables and the relationship between the demographic, clinical and psychological features with ULS-8 and HAQ-DI was assessed in a cross-sectional way.

2.2 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, v.19 (IBM Corp., Armonk, NY, USA). Data were expressed as numbers and percentages for the categorical, and medians and interquartile ranges (IQRs) for the continuous variables because of the small sample size and mostly non-normal distribution. Normality was assessed by the Shapiro-Wilk test. Non-parametric comparison (Wilcoxon-Mann-Whitney and Kruskal-Wallis) and correlation (Spearman) tests were used to evaluate the association of the ULS-8 score with the demographic data, clinical parameters, and depression, anxiety, social support, and HAQ-DI scores. Categorical comparisons were performed using Chi-square or Fisher's exact tests. Two multiple regression models to predict HAQ-DI and ULS-8 scores were generated for significant associations and standardized β coefficients were provided. P values less than .05 were considered statistically significant. Adjusted significance levels were provided in post hoc pairwise comparisons for continuous variables and Bonferroni corrections were made for the categorical ones.

3 | RESULTS

3.1 | Patient characteristics and clinical features

After exclusion of 12 patients due to severe medical conditions, dementia, and unwillingness to participate in the study, 141 patients (58, 53, and 30 with RA, AS, and PsA, respectively) were recruited into the study. The demographic data and clinical features of the disease groups are summarized in Table 1. RA patients were older compared to AS and PsA patients, female gender was also more frequent in the RA group. Corticosteroid and conventional DMARD use were less frequent in AS compared to RA and PsA, as expected.

3.2 | Psychometric and functional evaluation and global health assessment of the study groups

Most patients had minimal to mild depression regardless of the disease group (Table 2). There were 18.9%, 15.1%, and 6.6% of the patients in the RA, AS, and PsA groups, respectively, who had moderate to severe depression. Similar was true for anxiety except moderate anxiety was more frequent in RA compared to the AS group (Table 2). Median ULS-8 scores were 15, 15, and 14.5 in the RA, AS, and PsA groups, respectively ($P = .749$). Social support scores

TABLE 1 Demographic data and clinical parameters according to disease groups

	RA (n = 58)	AS (n = 53)	PsA (n = 30)	*P* value
Age, y	58 (IQR 12)[a,b]	42 (IQR 14)[a,b]	45 (IQR 20)[a,b]	<.001
Female, n (%)	41 (70.7)[a,b]	19 (35.8)[a,b]	21 (70)[a,b]	<.001
Married, n (%)	46 (79.3)	46 (86.8)	28 (93.3)	.196
Number of children	2 (IQR 0)	2 (IQR 1)	2 (IQR 1)	.102
Household size	3 (IQR 2)	4 (IQR 1)	4 (IQR 1)	.057
Education status, n (%)				
Primary school or lower	33 (56.9)[a,b]	13 (24.5)[a,b]	14 (46.7)	.002[d]
Higher education	25 (43.1)[a,b]	40 (75.5)[a,b]	16 (53.3)	
Actively working, n (%)	16 (27.6)[a,b]	31 (58.5)[a,b]	10 (33.3)	.003[d]
Comorbid disease present,[c] n (%)	36 (62.1)[a,b]	19 (35.8)[a,b]	12 (40)	.014[d]
Number of drugs	5 (IQR 3)[a,b]	2 (IQR 1)[a,b]	5 (IQR 3)[a,b]	<.001[d]
Disease duration, y	8 (IQR 8)	9 (IQR 9)	9,5 (IQR 14)	.555
ESR, mm/h	25 (IQR 26)[a,b]	13 (IQR 15)[a,b]	19 (IQR 22)	.014[d]
CRP, mg/L	6 (IQR 8.8)	7,6 (IQR 9.3)	5,1 (IQR 6)	.396
Corticosteroid use, n (%)	42 (72.4)[a,b]	6 (11.3)[a,b]	24 (80)[a,b]	<.001
csDMARD use, n (%)	52 (89.7)[a,b]	16 (30.2)[a,b]	24 (80)[a,b]	<.001
b/tsDMARD use, n (%)	6 (10.3)[a,b]	37 (69.8)[a,b]	16 (53.3)[a,b]	<.001
NSAID use, n (%)				
No	19 (32.8)	11 (20.8)	9 (30)	.298
On demand	34 (58.6)	31 (58.4)	18 (60)	
Daily	5 (8.6)	11 (20.8)	3 (10)	

Note: Disease group, age, gender, education and working status, presence of comorbid disease, number of drugs, and ESR were controlled for each other.

Abbreviations: AS, ankylosing spondylitis; b/tsDMARD, biological or targeted synthetic disease-modifying anti-rheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; IQR, interquartile range; n, number; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

[a,b]Denotes statistically significant pairs in the same row (post hoc adjusted $P < .05$).

[c]Psoriasis was excluded.

[d]No actual difference after control for the confounders.

were also similarly distributed among the groups (Table 2). There were 89.7%, 90.6%, and 96.7% of the patients in the RA, AS, and PsA groups who had mild disability (Table 2). The median patient VAS scores for the global assessment of health were 30 to 35/100 and the physician scores were 20 to 25/100 (Table 2).

3.3 | Loneliness and demographic and clinical features

The distributions of the ULS-8 score were similar across the categories of gender, marital and working status, presence of children, and comorbid disease. The median ULS-8 scores were 16.5 (IQR 6) and 14 (IQR 6) in primary school or lower and higher education categories of the education status, respectively ($P = .001$). Age, number of children, household size, number of comorbid diseases, disease duration, ESR, and serum CRP did not have a correlation with the ULS-8 score. The number of drugs used had a positive correlation with the ULS-8 score ($\rho = 0.22$, $P = .009$).

3.4 | Loneliness and psychometric and functional tests

The correlation matrix of the ULS-8, HAQ-DI, Beck depression, Beck anxiety, social support, and patient and physician global VAS scores are given in Table 3. The ULS-8 score had significant correlations with Beck depression ($\rho = 0.32$, $P < .001$), anxiety ($\rho = 0.33$,

TABLE 2 Psychometric test results, functional status, and patient and physician VAS scores for global disease assessment according to disease groups

	RA (n = 58)	AS (n = 53)	PsA (n = 30)	*P* value
Beck depression score	9 (IQR 13)	9 (IQR 11)	8.5 (IQR 11)	.924
Minimal depression, n (%)	41 (70.7)	37 (69.8)	22 (73.3)	.628
Mild depression, n (%)	6 (10.3)	8 (15.1)	6 (20)	
Moderate depression, n (%)	6 (10.3)	6 (11.3)	1 (3.3)	
Severe depression, n (%)	5 (8.6)	2 (3.8)	1 (3.3)	
Beck anxiety score	8.5 (IQR 16)	8 (IQR 13)	9.5 (IQR 10)	.626
Minimal anxiety, n (%)	30 (51.7)	31 (58.5)	17 (56.7)	.011
Mild anxiety, n (%)	15 (25.9)	16 (30.2)	9 (29.9)	
Moderate anxiety, n (%)	11 (19.9)[a]	1 (1.8)[a]	4 (13.4)	
Severe anxiety, n (%)	2 (3.5)	5 (9.5)	-	
Perceived social support score	67.5 (IQR 32)	72 (IQR 24)	77 (IQR 21)	.635
ULS-8 score	15 (IQR 7)	15 (IQR 5)	14.5 (IQR 7)	.749
HAQ-DI score	0.05 (IQR 0.45)	0.2 (IQR 0.58)	0.1 (IQR 0.29)	.495
Mild disability, n (%)	52 (89.7)	48 (90.6)	29 (96.7)	.637
Moderate disability, n (%)	5 (8.6)	5 (9.4)	1 (3.3)	
Severe disability, n (%)	1 (1.7)	-	-	
Patient global VAS score	35 (IQR 30)	35 (IQR 40)	30 (IQR 30)	.685
Physician global VAS score	20 (IQR 23)	25 (IQR 28)	20 (IQR 20)	.264

Note: Abbreviations: AS, ankylosing spondylitis; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, interquartile range; n, number; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ULS-8, UCLA Loneliness Scale-8; VAS, visual analog score.

[a]Denotes statistically significant pairs in the same row (post hoc adjusted $P < .05$).

$P < .001$), social support ($\rho = -0.22$, $P = .009$), and HAQ-DI ($\rho = 0.27$, $P = .001$) scores but not with the patient global VAS score ($\rho = 0.1$, $P = .224$). Beck depression and anxiety scores correlated with each other ($\rho = 0.6$, $P < .001$) and with the patient and physician global VAS, social support, and HAQ-DI. The HAQ-DI score also correlated with the social support ($\rho = -025$, $P = .003$), and patient ($\rho = 0.5$, $P < .001$) and physician ($\rho = 0.28$, $P < .001$) global VAS scores beside the Beck depression ($\rho = 0.53$, $P < .001$) and anxiety ($\rho = 0.53$, $P < .001$) scores. Among demographic and clinical parameters, only the number of drugs used had an association with the HAQ-DI score ($\rho = 0.18$, $P = .037$).

3.5 | Loneliness and disease activity measures

ULS-8 score did not correlate with the DAS28-ESR ($\rho = 0.03$, $P = .837$), DAS28-CRP ($\rho = 0.1$, $P = .464$) CDAI ($\rho = 0.12$, $P = 385$), and SDAI ($\rho = 0.18$, $P = 180$) in RA; BASDAI ($\rho = 0.02$, $P = .872$), BASFI ($\rho = 0.14$, $P = .319$), and ASDAS-ESR ($\rho = -0.14$, $P = .317$) ASDAS-CRP ($\rho = -0.07$, $P = .619$) in AS; and the number of swollen ($\rho = 0.06$, $P = .744$) and tender joints ($\rho = 0.05$, $P = .776$), ESR ($\rho = 0.02$, $P = .909$), serum CRP ($\rho = -0.30$, $P = .104$), patient global ($\rho = -0.07$, $P = .700$), physician global ($\rho = 0.04$, $P = .821$), pain ($\rho = -0.03$, $P = .867$), and fatigue ($\rho = -0.06$, $P = .758$) VAS scores in PsA groups. The presence of enthesitis and uveitis in AS, active psoriasis in PsA, and hand deformities in RA and PsA groups had also no association with the ULS-8 score.

3.6 | Predictors of functional status and loneliness

Two multiple regression models were generated for predicting the outcome variables (ie the HAQ-DI and ULS-8 scores) by including the singly associated variables. Depression ($\beta = 0.188$), anxiety ($\beta = 0.332$) and patient global VAS ($\beta = 0.433$) scores remained significant for predicting HAQ-DI after multiple regression with the covariates ULS-8, depression, anxiety, social support, patient and physician global VAS scores, and number of drugs used (adjusted

TABLE 3 Correlation matrix of the ULS-8, HAQ-DI, Beck depression, Beck anxiety, social support, and patient and physician global VAS scores

	Beck depression score	Beck anxiety score	Social support score	Patient global VAS score	Physician global VAS score	HAQ-DI score
ULS-8 score						
ρ	0.32	0.33	−0.22	0.1	0.16	0.27
P value	<.001	<.001	.009	.224	.058	.001
HAQ-DI score						
ρ	0.53	0.53	−0.25	0.5	0.28	
P value	<.001	<.001	.003	<.001	<.001	
Physician global VAS score						
ρ	0.29	0.23	-0.08	0.69		
P value	0.001	0.005	0.33	<0.001		
Patient global VAS score						
ρ	0.36	0.35	−0.2			
P value	<.001	<.001	.016			
Social support score						
ρ	-0.3	−0.22				
P value	<.001	.008				
Beck anxiety score						
ρ	0.6					
P value	<.001					

Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; ULS-8, UCLA Loneliness Scale-8; VAS, visual analog scale.

$R^2 = 0.53$, $P < .001$). In multiple regression with the covariates HAQ-DI, depression, anxiety, social support, physician global VAS scores, number of drugs used, and education status, only the education status ($\beta = -0.208$) significantly predicted the ULS-8 score (adjusted $R^2 = 0.15$, $P < .001$).

4 | DISCUSSION

We performed a comprehensive psychometric, clinical, and functional assessment to test the hypothesis of a significant relationship of loneliness with psychosocial and disease characteristics in Turkish patients with RA, AS, and PsA. One in six to seven patients with inflammatory arthritis had moderate to severe depression and anxiety. Those with depression and anxiety had higher loneliness scores. Besides depression and anxiety, we have found that loneliness was associated with social support, disability, the number of drugs used, and the education status. Education status was the only independent predictor of loneliness. Documentation of loneliness and related factors is an initial step to increase the awareness of such an overlooked aspect of the psychosocial status in inflammatory arthritis patients and may lead to consider research in other rheumatic diseases as well. It may also help to shape the psychosocial interventions, particularly in patients with functional disability.

In a cross-sectional study of over 1000 patients regarding psychological impact of inflammatory arthritis and support needs from regional rheumatology units across England, isolation, loneliness, poor communication (feeling unheard by family, friends, and physicians), and lack of psychological support (particularly from the physician) were identified as the categories of psychological distress.[16] This study showed that, in addition to valuing the support of peers and family, inflammatory arthritis patients looked to the rheumatology team for validation and support. Moreover, patients identified physicians' guide to appropriate support as helpful although often not provided.[16]

In another study from the Netherlands conducted in 927 patients with various rheumatic diseases including RA, AS, osteoarthritis, other systemic rheumatic diseases, and fibromyalgia, lack of social support and invalidation were identified as independent predictors of loneliness after control for age, gender, education, working, and relationship status.[17] Notably, loneliness scores, assessed by a 1-item Likert-type scale, were similar in different rheumatic disease groups except in patients with fibromyalgia who felt more lonely. We did not identify the lack of social support as a significant predictor of loneliness in multivariable analysis in our patient group with inflammatory arthritis although the social support and ULS-8 scores correlated. Different scales to measure loneliness (see below) and social support (revised multidimensional scale of perceived social support used in the present study was structured mainly on the source of support, whereas the social support survey used in the study by Kool and Geenen[17] was structured on the type of support), heterogenous patient groups, and sociocultural issues may be speculated to account for the discrepancy in the results. Perception of loneliness and its differential expression in terms of lack of social support may be explained by culturally unique expectations concerning relationships. This may

be supported by the observation that people from more individualist cultures value social networks more in coping with loneliness compared to people from more communal cultures which already provide such networks.[19,20] Interestingly, lower education was associated with loneliness in both populations, but age, working, and marital status were not so in our study group in contrast to Dutch patients.[17] This could be explained by social interconnectedness compensating for age, working, and marital status-related contribution to loneliness. In predominantly communal cultures, loneliness of an individual is usually considered a culturally determined social duty to be solved rather than a personal emotional experience to be suffered. These imply the necessity of culture-specific healthcare strategies in coping with loneliness and underline the importance of a multidisciplinary approach to patients with rheumatic diseases.

In a cross-cultural study comparing women with RA from the Netherlands and Egypt in terms of loneliness (assessed by a 1-item Likert-type scale), the leading predictor of loneliness in both populations was the worse affect (anxiety and depression).[18] Similar to the findings of the study conducted in the same population by Kool and Geenen,[17] lack of social support was important in explaining loneliness in the Netherlands but not in Egypt.[18] There were significant associations between the depression, anxiety, and loneliness scores in our study (Table 3), but these were confounded by the education status in multiple regression analysis.

Because of the methodological differences and to be able to make more direct comparisons with the prior research, we reperformed the analyses by using the 0-10 point VAS for loneliness instead of ULS-8. Loneliness VAS score was significantly associated with depression ($\rho = 0.335$), anxiety ($\rho = 0.239$), social support ($\rho = -0.431$), functional status ($\rho = 0.193$), patient global health assessment ($\rho = 0.148$), and the number of drugs used ($\rho = 0.189$), but not with the education status. Note that the correlation coefficients of the loneliness VAS score and ULS-8 score with the anxiety, patient global VAS, and the social support scores are quite different (Table 3). Thus, the 1-item VAS for loneliness and ULS-8 give different results and this may be related to education status, which was the single independent predictor of the ULS-8 but not even associated with the loneliness VAS score in our study group. Additionally, since loneliness VAS is a global self-reflection, it may be more sensitive to the current mood state and may lack reliability compared to the more comprehensive ULS-8. Interestingly, if we run a multiple regression to predict the loneliness VAS score with the above-mentioned associated variables, the worse affect does not significantly predict loneliness, and the social support score and number of drugs used would become the independent predictors of loneliness (β[social support score] = −0.333, β[number of drugs used] = 0.175, adjusted $R^2 = 0.131$, $P < .001$). Since loneliness is a perceived feeling, the Dutch and Egyptian patients with rheumatic diseases may feel lonely primarily affected by the worse affect while Turkish patients with inflammatory arthritis may feel so primarily affected by the lack of social support *when assessed by a 1-item tool*. The measurement tool for loneliness seems to be of substantial importance according to our findings as discussed previously in the literature.[21]

Notably, the results of a randomized (55 and 53 patients to intervention and waiting list groups, respectively), internet-based, multimodal, cognitive-behavioral intervention study for RA (RAHelp) demonstrated that self-efficacy may be improved while loneliness may be reduced after educational intervention covering the topics Overview and Rationale, RA Stressors, Effective Coping, Life Goals, Pain Management, Emotional Responses, Managing Change, Self-Esteem, Relationships, and Community Participation, although affective symptoms and arthritis scores did not significantly improve.[33] Quality of life was still better in the intervention group in the 9th month post-intervention.

Lastly, although no association between loneliness and the type of rheumatic disease (except fibromyalgia) was reported in previous studies,[16-18,34] to our knowledge, the relationship between loneliness and disease activity measures in separate disease groups was not previously reported.

Limitations of this study include a relatively small sample size with a potentially high type II error rate, particularly for the subgroup analyses and the cross-sectional design that prevents the proper interpretation of causality. The patients were from a single center and no healthy control group was present. Medical and psychiatric history of the participants were self-reported and not based on detailed examination. Patients with moderate to severe depression, anxiety, and disability were low in number. Direct comparisons and more conclusive interpretations were not possible because of the methodological differences with the previously published studies. Strengths of the study include a comprehensive evaluation of the disease activity measures in relation to loneliness and other psychosocial determinants in a particular patient group of RA, AS, and PsA which, to the best of our knowledge, has not been reported before.

In conclusion, loneliness is associated with depression, anxiety, lack of social support, disability, higher number of drugs used, and lower education but not with disease activity in Turkish patients with RA, AS, and PsA. Perception and expression of loneliness vary according to the cultural background. The assessment tool for loneliness is of substantial importance and single-item scales may lack reliability.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: HE OK. Data collection and processing: HE, Uİ, ST. Analysis and interpretation: HE, Uİ, OK. Literature review: HE, Uİ, ST, OK. Writing: HE, Uİ, ST. Critical review: HE, Uİ, ST, OK

INFORMED CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained from each patient to use clinical data for research purposes. Institutional Review Board of Trakya University Medical School approved the study (Date/Number: TÜTF-BAEK 2018/170-08/04).

ORCID

Hakan Emmungil https://orcid.org/0000-0001-5184-4404
Ufuk İlgen https://orcid.org/0000-0001-6443-6426
Sezin Turan https://orcid.org/0000-0001-5885-2036
Ozge Kilic https://orcid.org/0000-0001-9764-343X

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SUPPORTING INFORMATION

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

How to cite this article: Emmungil H, İlgen U, Turan S, Kilic O. Assessment of loneliness in patients with inflammatory arthritis. *Int J Rheum Dis*. 2021;24:223–230. https://doi.org/10.1111/1756-185X.14041

Received: 29 June 2020 | Revised: 3 November 2020 | Accepted: 7 November 2020

DOI: 10.1111/1756-185X.14031

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Higher serum levels of autotaxin and phosphatidylserine-specific phospholipase A_1 in patients with lupus nephritis

Yasunori Iwata[1,2] | Shinji Kitajima[2] | Junya Yamahana[3] | Shuji Shimomura[2] | Shiori Yoneda-Nakagawa[2] | Norihiko Sakai[2,4] | Kengo Furuichi[5] | Hisayuki Ogura[2] | Koichi Sato[2] | Tadashi Toyama[2] | Yuta Yamamura[2] | Taro Miyagawa[2] | Akinori Hara[2] | Miho Shimizu[2] | Ryunosuke Ohkawa[6] | Makoto Kurano[7] | Yutaka Yatomi[7] | Takashi Wada[2]

[1]Division of Infection Control, Kanazawa University, Kanazawa, Japan

[2]Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan

[3]Noto General Hospital, Ishikawa, Japan

[4]Division of Blood Purification, Kanazawa University, Kanazawa, Japan

[5]Division of Nephrology, Kanazawa Medical University School of Medicine, Ishikawa, Japan

[6]Department of Analytical Laboratory Chemistry, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

[7]Department of Clinical Laboratory Medicine, University of Tokyo, Tokyo, Japan

Correspondence
Yasunori Iwata, Division of Infection Control, Department of Nephrology and Laboratory Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan.
Email: iwatay@staff.kanazawa-u.ac.jp

Funding information
Japan Society for the Promotion of Science KAKENHI (18K08426, YI)

Abstract

Background: Recent studies revealed that lysophospholipids (LPLs) and related molecules, such as autotaxin (ATX) and phosphatidylserine-specific phospholipase A_1 (PS-PLA_1), are candidates for novel biomarkers in melanoma, glaucoma and diabetic nephropathy. However, it is not clear whether serum levels of ATX/ PS-PLA_1 would be associated with pathological and clinical findings of lupus nephritis (LN).

Methods: In this retrospective cohort study, serum samples were collected from 39 patients with LN and 37 patients with other glomerular diseases. The serum levels of ATX and PS-PLA_1 were evaluated for an association with renal pathology and clinical phenotypes of LN.

Results: The serum levels of ATX and PS-PLA_1 were higher in the patients with LN as compared to those with other glomerular diseases. Among the classes of LN, the patients with class IV showed the trend of lower serum levels of ATX. Moreover, the patients with lower levels of ATX exhibited higher scores of activity index (AI) and chronicity index (CI). The level of ATX tended to be negatively correlated with AI and CI. These results might be explained by the effect of treatment, because the serum levels of ATX and PS-PLA_1 were inversely correlated with the daily amount of oral prednisolone. Moreover, they did not reflect the level of proteinuria or kidney survival in LN patients.

Conclusion: Although the serum levels of ATX and PS-PLA_1 were affected by the treatment, these levels were higher in the patients with LN. The potential clinical benefits of these markers need to be clarified in further studies.

KEYWORDS

ATX, lupus nephritis, pathology, PS-PLA_1

1 | BACKGROUND

Lupus nephritis (LN) is one of the major clinical manifestations of systemic lupus erythematosus (SLE). The frequency of LN in SLE patients has been reported to be 40%-82% in Asian patients.[1] Although some therapeutic agents, such as glucocorticoid and immunosuppressant drugs are available, LN is still at high risk for end stage renal disease (ESRD). Accumulated studies revealed that 10%-20% of LN patients progress to ESRD.[2,3] Especially, patients with class IV showed a higher rate of ESRD compared to those with other classes in long-term observation.[2] Accordingly, the evaluation of kidney pathology is critical for the appropriate therapy and for the prediction of renal survival.

Although kidney biopsy is performed to assess the pathology in LN, it sometimes carries possible complications, such as bleeding. Therefore, a novel biomarker is required to diagnose and manage LN patients without kidney biopsy. In this regard, some molecules including cytokines/chemokines, tubular injury markers and micro RNAs are raised as candidates for novel biomarkers.[4] However, further studies are needed to identify more specific and sensitive biomarkers for LN.

Lysophospholipids (LPLs) are a family of phospholipids and are involved in signal transduction via G protein coupled receptor.[5] Recent studies have revealed that LPLs play a pathophysiological role in cancer,[6] atherosclerosis[7] and diabetes.[8] Moreover, LPLs and related molecules are candidates for novel biomarkers in some diseases. Autotaxin (ATX) is the enzyme that produces lysophosphatidic acid (LPA) from the substrate LPLs. Phosphatidylserine-specific phospholipase A_1 (PS-PLA_1) is involved in the production of lysophosphatidylserine (LysoPS). These molecules are evaluated in melanoma,[9] glaucoma[10] and diabetic nephropathy[11] and showed the ability to reflect disease activity/progression. However, little is known in the patients with LN. Therefore, we assessed the serum levels of ATX and PS-PLA_1 and explored whether these molecules could reflect the clinical features of LN.

2 | METHODS

2.1 | Patients

We retrospectively enrolled 76 Japanese subjects suffering from glomerular diseases. The patients were admitted to the Department of Nephrology, Kanazawa University Hospital, or its affiliated hospitals, between 1977 and 2018. SLE was diagnosed by adequate evaluations of 1982 or 1997 revised American College of Rheumatology SLE classification criteria.[12,13] The serum levels of PS-PLA_1 and ATX were evaluated in 39 and 35 patients, respectively (Figure 1). The values of healthy controls were used from pooled datasets.[9,14,15] The study protocol was approved by the medical ethics committee of Kanazawa University (approval number; 1590).

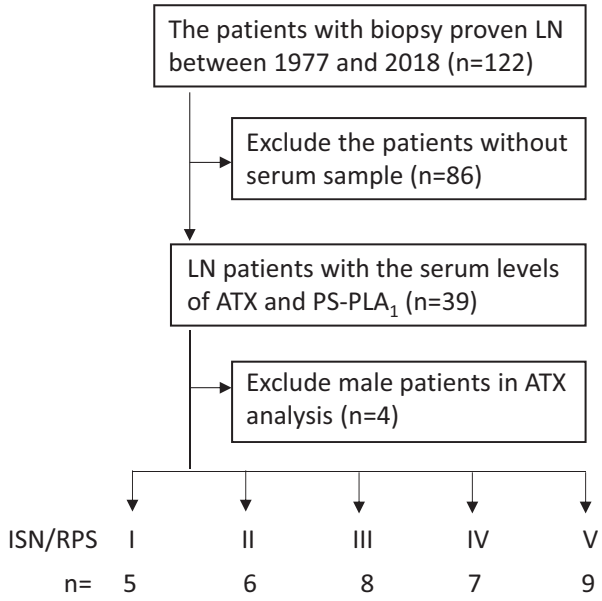

FIGURE 1 Patients flow diagram. ATX, autotaxin; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; PS-PLA_1, phosphatidylserine-specific phospholipase A_1

2.2 | Histopathologic studies

For light microscopic examination, renal biopsy specimens were fixed in 10% phosphate-buffered formalin (pH 7.4), embedded in paraffin, and sliced into 4-μm sections. These specimens were stained with hematoxylin and eosin, periodic acid Schiff reagent, Mallory-azan, and periodic acid silver methenamine, and were examined by light microscopy. LN was evaluated with the criteria of the new International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification.[16]

2.3 | Renal outcome

The renal outcome for this study was ESRD, which was defined as the need for dialysis or renal transplantation.

2.4 | Measurement of serum ATX and PS-PLA_1 levels

The concentrations of ATX/PS-PLA_1 were determined in serum samples that were collected at the time of renal biopsy (baseline) and stored at −20°C until the analyses were performed. The serum ATX/PS-PLA_1 level was determined using a 2-site immunoenzymetric assay with a commercial automated immunoassay analyzer (TOSOH AIA system, TOSOH, Tokyo, Japan).[9-11,17,18] The assay system has been validated and satisfactory results were obtained for the within-run and between-run precision, interference, detection limit, and linearity.[17,18]

TABLE 1 The characteristics and renal function of the patients

	LN	DN	MN	RPGN
Age	34.1 ± 2.4	52.5 ± 2.7***	54.4 ± 2.6***	70.4 ± 2.3***
M/F	4/35	14/1	11/8	2/1
Serum creatinine (mg/dL)	0.70 ± 0.05	1.16 ± 0.12***	1.49 ± 0.29*	1.28 ± 0.08
Proteinuria (g/g creatinine)	1.9 ± 0.4	3.6 ± 2.2	2.0 ± 0.9	N/A

Note: Abbreviations: DN, diabetic nephropathy; LN, lupus nephritis; MN, membranous nephropathy; N/A, not applicable; RPGN, rapidly progressive glomerulonephritis.

*$P < .05$

***$P < .001$ as compared to LN.

2.5 | Statistics

Data are presented as the mean ± SEM. We used the unpaired Student's *t* test and a *P* value of less than .05 was considered significant. To evaluate the effect of the serum ATX/PS-PLA$_1$ levels on the pathological parameters and renal composite events, the patients were divided into 2 groups according to whether the serum ATX/PS-PLA$_1$ levels were above or below the average value of the total cohort. For multiple group comparisons, one-way analysis of variance with Tukey's multiple comparison test were performed. The coefficient determination was obtained with Excel software. The renal composite events were compared by the log-rank test. Statistics were performed using GraphPad Prism 8.0.

3 | RESULTS

3.1 | Characteristics of enrolled patients

The patients with LN were younger than those with diabetic nephropathy (DN), membranous nephropathy (MN) and rapidly progressive glomerulonephritis (RPGN). Also the serum levels of creatinine were lower in LN patients as compared to those with DN and MN (Table 1). In LN patients, 13 of 39 cases were treatment naïve. Thirteen patients had antiphospholipid syndrome (APS). The existence of APS did not show the differences of the serum levels of ATX and PS-PLA$_1$ (Figure S1). The average dose of prednisolone (PSL) was 12.3 ± 3.0 mg/d. The dose of PSL in class IV was higher than that of class V. Ten patients were treated with immunosuppressant drugs, such as cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil and mizoribine (Table 2).

3.2 | Serum levels of ATX and PS-PLA$_1$ are increased in patients with LN

We evaluated the serum levels of ATX and PS-PLA$_1$ in the patients with LN and compared them to those with DN, MN and RPGN. Interestingly, the patients with LN showed higher levels of PS-PLA$_1$ as compared to those with DN or MN. The level of PS-PLA$_1$ was similar between the patients with other glomerular diseases and healthy controls (Figure 2A). Since the serum level of ATX is known to be higher in females than in males,[18] we evaluated the level of ATX in each gender separately. Although the level of ATX was higher both in female and male patients with LN than those with other glomerular diseases, there was no difference between the healthy controls (Figure 2B).

3.3 | Patients with LN class IV show the trend of lower levels of ATX than those with the other classes of LN

Next, we explored whether serum levels of ATX/PS-PLA$_1$ would be associated with renal pathology. We evaluated the serum levels of ATX/PS-PLA$_1$ in each class of LN. In the patients with LN class IV, the serum level of ATX was lower or tended to be

TABLE 2 The clinical features of the patients with lupus nephritis

Duration of SLE, y	2.3 ± 0.7
Naïve/relapse	13/26
APS	13
C3 (mg/dL)	50.9 ± 3.6
C4 (mg/dL)	12.6 ± 2.5
Anti-DNA Ab (IU/mL)	164.4 ± 59.8
PSL (mg/d)	12.3 ± 3.0
Class I	10.0 ± 10.0
Class II	11.5 ± 7.3
Class III	23.3 ± 12.0
Class IV	25.4 ± 6.4*
Class V	7.1 ± 3.0
Immunosuppressant	10

Note: Relapse indicated the frequency of the patients who relapsed at the time of the examination. Immunosuppressant indicated the frequency of the patients who were treated with immunosuppressant, such as cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil and mizoribine.

Abbreviations: Ab, antibody; APS, anti-phospholipid syndrome; APS, anti-phospholipid syndrome; PSL, prednisolone.

*$P < .05$ as compared to class V

lower than those of classes II, III or V in females. However, the level of PS-PLA$_1$ in serum was similar between the LN classes (Figure 3).

3.4 | Patients with lower levels of ATX show higher AI/CI in the pathology of LN

The scoring of AI and CI has been documented to correlate with the progression to ESRD in LN.[2,19,20] Therefore, we analyzed whether the serum levels of ATX/ PS-PLA$_1$ could reflect the AI/CI. Patients with low serum levels of ATX showed higher AI/CI in renal pathology (Figure 4A). The serum level of PS-PLA$_1$ was not correlated with AI nor CI on renal pathology (Figure 4B).

3.5 | Serum levels of ATX and PS-PLA$_1$ are affected by medication

Next, we investigated the effect of treatment on the serum levels of ATX and PS-PLA$_1$. Serum levels of PS-PLA$_1$ tended to be decreased after induction therapy concomitant with the decreased amount of proteinuria (Figure 5A). Moreover, the serum levels of ATX and PS-PLA$_1$ are inversely correlated with the daily amount of oral PSL (Figure 5B).

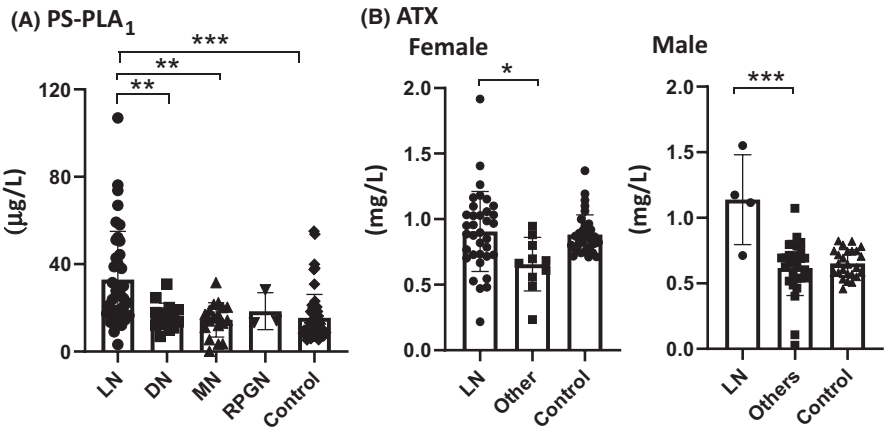

FIGURE 2 The serum levels of autotaxin (ATX) and phosphatidylserine-specific phospholipase A$_1$ (PS-PLA$_1$) in the patients with kidney diseases. The sample was collected at the time of renal biopsy. The serum ATX/PS-PLA$_1$ level was determined using a 2-site immunoenzymetric assay with a commercial automated immunoassay analyzer (TOSOH AIA system, TOSOH, Tokyo, Japan). One-way analysis of variance with Tukey's multiple comparison test were performed. $^*P < .05$, $^{**}P < .01$, $^{***}P < .001$

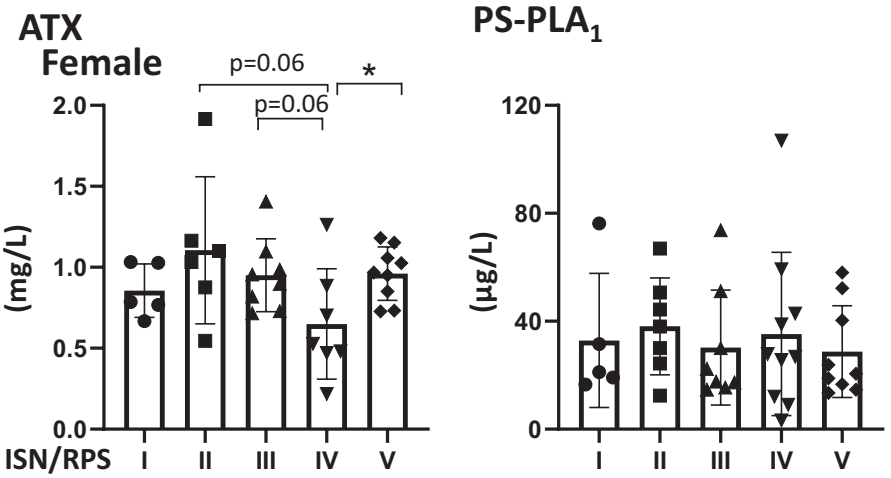

FIGURE 3 The serum levels of autotaxin (ATX) and phosphatidylserine-specific phospholipase A$_1$ (PS-PLA$_1$) in the patients with lupus nephritis (LN). Kidney pathology was evaluated with the criteria of the new International Society of Nephrology/Renal Pathology Society classification[16] in the patients with LN. The serum level of ATX was lower or tended to be lower in the patients with LN class IV as compared to those with classes II, III or V. The serum level of PS-PLA$_1$ was not different between the classes. One-way analysis of variance with Tukey's multiple comparison test were performed

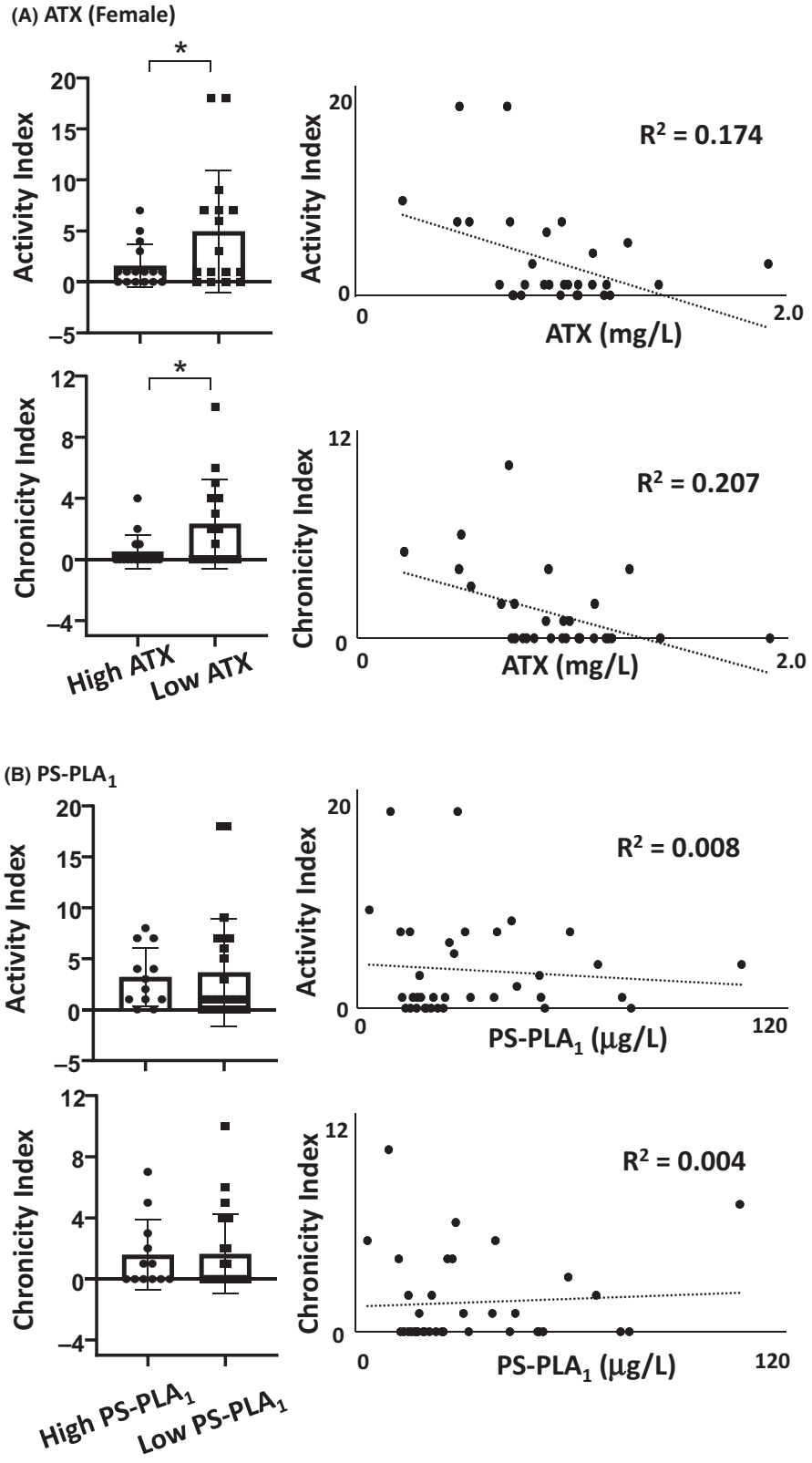

FIGURE 4 The association between serum levels of autotaxin/phosphatidylserine-specific phospholipase A_1 (ATX/PS-PLA_1) and disease activity/chronicity on pathology of lupus nephritis (LN). Low level/high level was defined as the level below/over the average both in ATX and PS-PLA_1, respectively. Activity index/ chronicity index (AI/CI) were evaluated with the criteria of the new International Society of Nephrology/Renal Pathology Society classification.[16] A, The patients with low serum level of ATX showed higher AI in renal pathology. Moreover, the serum level of ATX tended to be negatively correlated with AI. Also, the patients with low level of ATX exhibited the trend of higher values of CI. The level of ATX tended to be negatively correlated with CI. B, The serum level of PS-PLA_1 was not correlated with AI or CI on renal pathology. *$P < .05$, Student's *t* test. The coefficient determination was obtained with Excel software

3.6 | Serum levels of ATX and PS-PLA_1 do not reflect the level of proteinuria or survival rate in LN patients

Then we explored the relation between serum levels of ATX/ PS-PLA_1 and clinical manifestations, such as proteinuria and kidney survival. Neither the serum levels of ATX nor PS-PLA_1 were correlated with proteinuria. Also kidney survival was not associated with the levels of ATX or PS-PLA_1 in LN patients (Figure 6). Moreover, the levels of ATX and PS-PLA_1 did not show the correlation with the score of SLE Disease Activity Index (SLEDAI) or clinical laboratory data, such as anti-double-stranded DNA antibody and complements (Figure S2A,B).

4 | DISCUSSION

Here, we reported that the serum levels of ATX and PS-PLA$_1$ were higher in the patients with LN as compared to those with DN and MN. Among the classes of LN, the patients with class IV showed lower serum levels of ATX. Moreover, the patients with lower levels of ATX exhibited higher AI and CI scores. The level of ATX tended to be negatively correlated with AI and CI. Induction therapy for LN tended to reduce the serum level of PS-PLA$_1$. The levels of ATX and PS-PLA$_1$ were negatively correlated with daily dose of oral prednisolone. However, they did not reflect the levels of proteinuria or kidney survival in LN patients.

The patients with LN class IV or higher AI/CI are at high risk for progression to ESRD.[2,21] These findings rely on pathology, obtained by renal biopsy, which sometimes carries the risk of complications. Therefore, novel biomarkers have been required to predict the pathological findings. In this regard, the serum levels of PS-PLA$_1$ and ATX could be candidate molecules based on our findings.

Recent studies revealed LPL, especially sphingosine-1-phosphate (S1P), is involved in the pathogenesis of SLE. S1P is produced by Th17 cells and promotes endothelial transmigration by activating the S1P receptor 3 in lupus-prone mice.[22] S1P also plays a key role in dying cell clearance. Dying cell-released S1P induced phagocytosis of macrophages via erythropoietin receptor (EPOR) signaling. Macrophage-specific EPOR knock-out mice showed lupus-like phenotype along with impaired dead cell phagocytosis of macrophages.[23] Moreover, the increased concentration of S1P was observed in human SLE patients.[24,25] Although the pathogenesis of S1P has been reported on SLE, the involvement of ATX/LPA is still not clear in SLE.

The serum level of ATX was higher in the patients with LN as compared to other kidney diseases such as DN and MN. Nevertheless, the level of ATX was lower in patients with LN class IV. Moreover, the level of ATX tended to be inversely correlated with AI/CI on renal pathology. The patients with class IV, who showed high activity and chronicity, were already treated with higher doses of PSL in this cohort. Also, higher dose of PSL was associated with lower level of ATX. Therefore, the treatment of higher doses of PSL might decrease the serum levels of ATX in the patients with LN class IV in this study. Consistent with these findings, oral PSL has been reported to decrease serum levels of ATX.[26,27] In terms of the regulation of ATX, some studies have reported that LPA and S1P have inhibitory effects for ATX expression.[28,29] Given that circulating S1P level is correlated with disease activity in SLE patients,[25] the suppressed expression of ATX could be explained in part by increased circulation levels of S1P in patients with higher LN activity. However, we did not analyze the levels of S1P or LPA in this study. More detailed experiments are needed to clarify the mechanisms of suppressed ATX expression in the patients with higher activity of LN.

As for PS-PLA$_1$, Sawada et al reported that serum level of PS-PLA$_1$ was correlated with disease activity in SLE patients.[30] Consistent with this finding, our result also showed increased level of PS-PLA$_1$ in LN patients. However, the level of PS-PLA$_1$ is not associated with pathological findings or clinical characteristics such as proteinuria and decline of renal function in LN. Although they described the serum levels of PS-PLA$_1$ was higher in the patients with

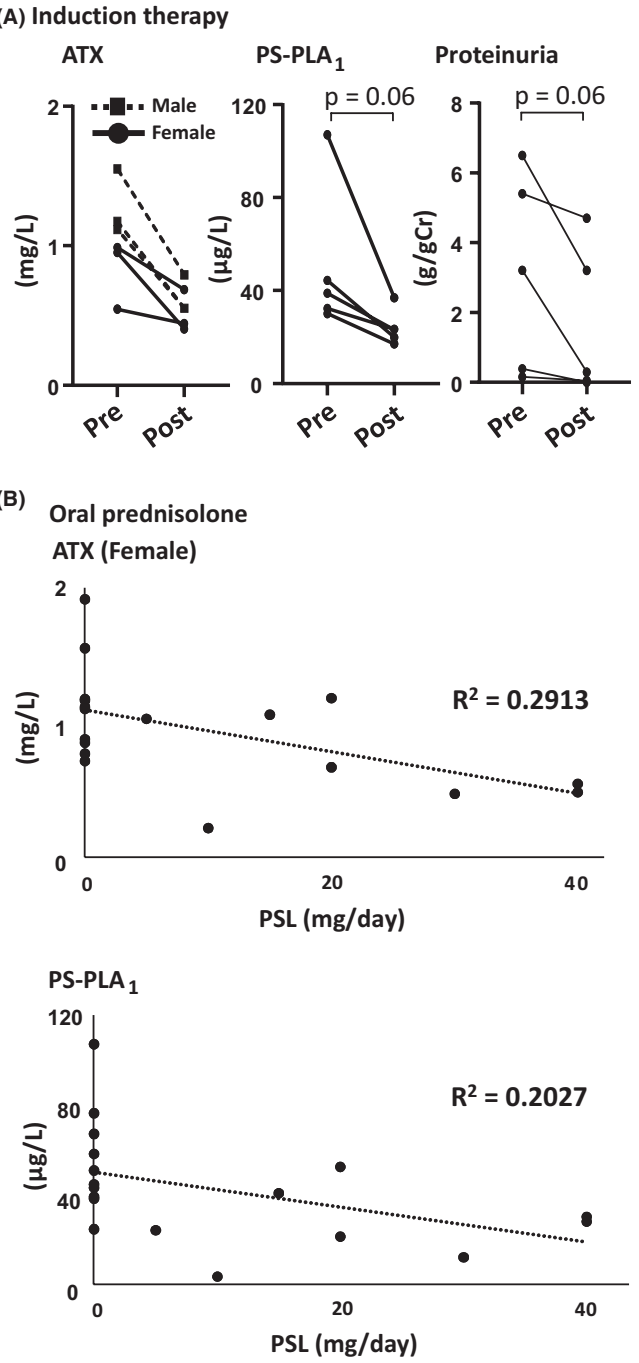

FIGURE 5 The effect of therapy for the serum levels of autotaxin/phosphatidylserine-specific phospholipase A$_1$ (ATX/PS-PLA$_1$). A, Serum levels of PS-PLA$_1$ tended to be decreased after induction therapy concomitant with the decreased amount of proteinuria. Induction therapy were performed with oral prednisolone (PSL) and/or methyl PSL pulse therapy with/without immunosuppressant drugs, such as cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil and mizoribine. B, The serum levels of ATX and PS-PLA$_1$ are inversely correlated with the daily amount of oral PSL

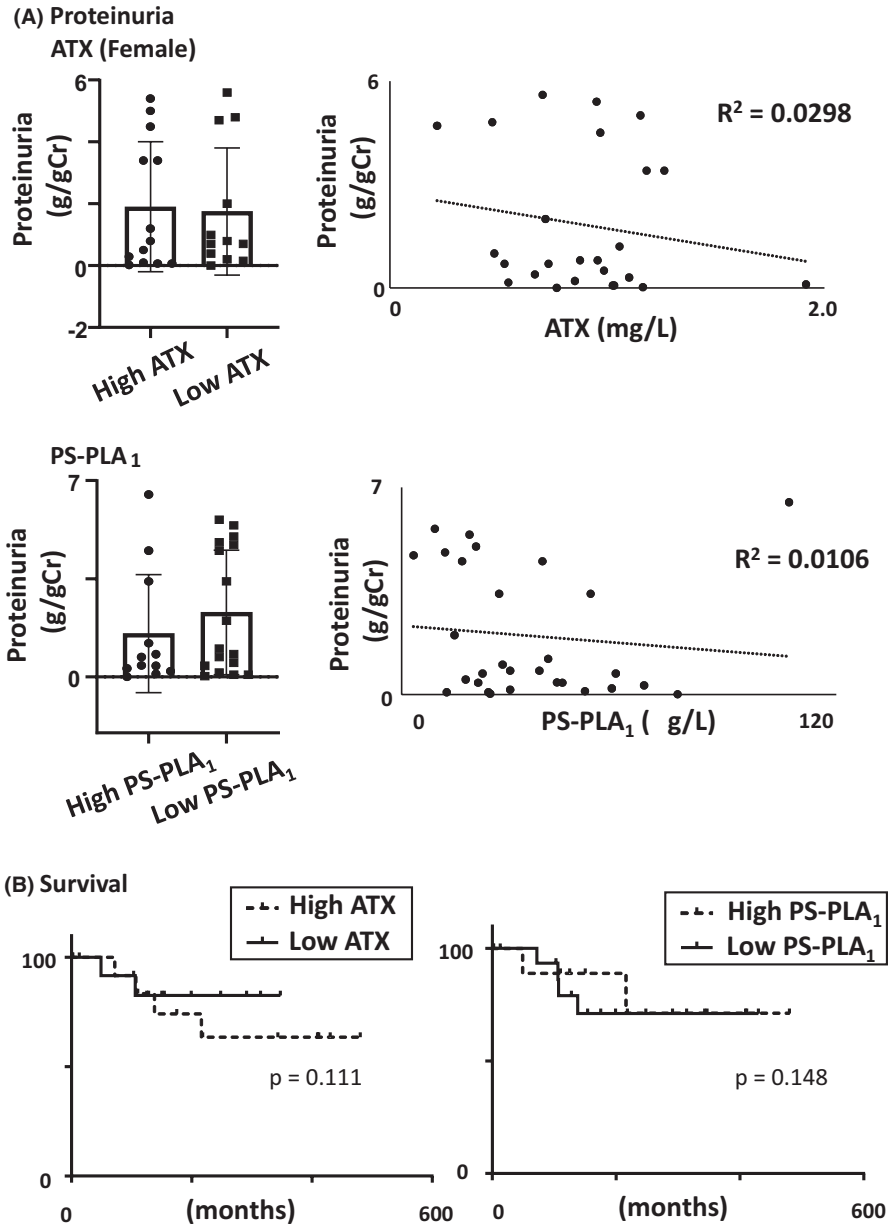

FIGURE 6 The association between serum levels of autotaxin/phosphatidylserine-specific phospholipase A_1 (ATX/PS-PLA_1) and proteinuria and renal survival. A, Neither the serum levels of ATX nor PS-PLA_1 were associated with the amount of urine protein. B, Also neither the serum levels of ATX nor PS-PLA_1 were associated with renal survival. The groups were compared by Student's *t* test or log-rank test. The coefficient determination was obtained with Excel software

renal manifestation than those without, the correlation between the level of PS-PLA_1 and kidney pathology was not analyzed in the study.[30] While PS has been reported to regulate the function of immune cells,[31] the pathophysiological role of PS-PLA_1 is still unclear on inflammation. Given that various immune cells are involved in the disease progression of LN, the levels of PS would be a more accurate biomarker to reflect disease activity of LN.

The limitation of this study is the relatively small sample size. Some analysis showed not the significance but just the trend of difference between the groups. Especially, the relation between the levels of ATX/ PS-PLA_1 and clinical manifestations such as proteinuria and kidney survival need to be clarified with increased sample numbers. Moreover, we used the pooled datasets of healthy controls in this study. While both ATX and PS-PLA_1 were analyzed with the same assays as ours in these manuscripts, the sera of healthy controls should be evaluated side by side with our disease samples to compare the levels of these molecules. In addition, we did not explore the pathophysiological roles of ATX and PS-PLA_1 on LN. Since little is known about the involvement of ATX and PS-PLA_1 in LN, to understand the mechanisms may strengthen their potential as novel biomarkers.

5 | CONCLUSION

We wish to highlight the findings that the serum levels of ATX and PS-PLA_1 were high in the patients with LN. Moreover, the level of ATX was inversely correlated with AI and CI in LN. Although the serum levels of ATX and PS-PLA_1 were affected by the treatment, these levels were higher in the patients with LN. The potential clinical benefits of these markers need to be clarified in further studies.

CLINICAL SIGNIFICANCE

A novel biomarker is required to diagnose and manage LN patients. Based on our findings, the serum levels of ATX and PS-PLA$_1$ were higher in the patients with LN as compared to those with other glomerular diseases. The patients with lower levels of ATX exhibited higher scores of activity index and CI in renal pathology. Our data raised the possibility of serum levels of ATX and PS-PLA$_1$ as novel biomarkers for LN.

ACKNOWLEDGEMENTS

This work was supported by the Japan Society for the Promotion of Science KAKENHI (18K08426, YI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

AUTHOR CONTRIBUTIONS

YI, SK and JY designed and performed the experiments. SS, SYN, NS KF, HO, KS, TT, Y. Yamamura, TM, AH, and MS collected the samples and analyzed the clinical data. RO, MK performed enzyme-linked immunosorbent assay to quantify autotaxin and PS-PLA$_1$. YI and TW wrote the manuscript. Y. Yatomi and TW supervised the work.

ETHICAL APPROVAL

Ethics approval and consent to participate: the study protocol was approved by the medical ethics committee of Kanazawa University (approval number; 1590).

Consent for publication: not applicable.

DATA AVAILABILITY STATEMENT

Please contact authors for data requests (Iwata Y, MD, PhD, email address: iwatay@staff.kanazawa-u.ac.jp).

ORCID

Yasunori Iwata https://orcid.org/0000-0002-4756-5207
Ryunosuke Ohkawa https://orcid.org/0000-0002-8584-133X

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SUPPORTING INFORMATION

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

How to cite this article: Iwata Y, Kitajima S, Yamahana J, et al. Higher serum levels of autotaxin and phosphatidylserine-specific phospholipase A_1 in patients with lupus nephritis. *Int J Rheum Dis*. 2021;24:231–239. https://doi.org/10.1111/1756-185X.14031

Received: 7 September 2020 | Revised: 30 September 2020 | Accepted: 26 October 2020

DOI: 10.1111/1756-185X.14027

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Association between Graves' disease and risk of incident systemic lupus erythematosus: A nationwide population-based cohort study

Cho Lee[1] | Shih-Fen Chen[2] | Yu-Cih Yang[3] | Chung Y. Hsu[4] | Yu-Chih Shen[1,5]

[1]Department of Psychiatry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

[2]Department of Obstetrics and Gynecology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

[3]Management Office for Health Data, China Medical University Hospital, and College of Medicine, China Medical University, Taichung, Taiwan

[4]Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

[5]School of Medicine, Tzu Chi University, Hualien, Taiwan

Correspondence
Yu-Chih Shen, Department of Psychiatry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Sec. 3, Chung Yang Rd, Hualien 970, Taiwan.
Email: shengmp@gmail.com

Funding information
This study is supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004); MOST Clinical Trial Consortium for Stroke, Taiwan (MOST 108-2321-B-039-003); Tseng-Lien Lin Foundation, Taichung, Taiwan. The funding sources had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Abstract

Objective: Previous case reports have linked Graves' disease to incident systemic lupus erythematosus (SLE). It has also been reported that antithyroid drugs used to treat Graves' disease can induce SLE development. The purpose of this study was to investigate the risk of SLE in patients with Graves' disease.

Methods: A total of 8779 patients with Graves' disease and 8779 controls (without Graves' disease) matched by age, gender, index year, and Charlson Comorbidity Index (CCI) score were enrolled between 2000-2012. Patients were then followed until the end of 2013 using Taiwan's National Health Insurance Research Database, at which time participants who developed SLE were identified. Cox regression analysis was used to calculate the hazard ratio (HR) with a 95% confidence interval (CI) of SLE incidence rate between patients with Graves' disease and unaffected controls.

Results: Patients with Graves' disease had a significantly increased risk of SLE than unaffected controls (8.81 vs 2.83 per 10 000 person-years, HR: 5.45, 95% CI: 1.74-17.0) after adjusting for antithyroid therapies (antithyroid drugs, radioactive iodine ablation, and surgery). Diagnostic bias may be present as patients with Graves' disease may seek more help from healthcare providers. After excluding the first 0.5 and 1 year of observation period, similar results were obtained (excluding 0.5 year - HR: 4.30, 95% CI: 2.78-8.57; excluding 1 year - HR: 4.63, 95% CI: 2.33-7.79).

Conclusion: This study shows that Graves' disease is associated with an increased risk of incident SLE. Further studies on the underlying pathogenesis linking Graves' disease and SLE are warranted.

KEYWORDS
cohort, Graves' disease, systemic lupus erythematosus

1 | INTRODUCTION

Graves' disease is an autoimmune disease with autoantibodies against the thyroid-stimulating hormone receptor, which act as agonists and induce excessive thyroid hormone secretion.[1] Systemic lupus erythematosus (SLE) is another autoimmune disease in which autoantibodies against a panoply of self-antigens can affect multiple systems, including the skin, joints, and kidneys.[2] Some case reports have linked Graves' disease to incident SLE.[3,4] It has also been reported that antithyroid drugs used to treat Graves' disease

can induce SLE.[5] Whether the existence of Graves' disease and its treatment poses an increased risk of incident SLE has not been widely studied. To more fully determine their relationship, Taiwan's National Health Insurance Research Database (NHIRD), a nationally representative database of medical claims, was used to conduct a longitudinal follow-up study of SLE risk in patients with Graves' disease.

2 | METHODS

2.1 | Data source

The National Health Insurance Program of Taiwan (NHIP) was established in 1995 to offer national healthcare via a single-payer government-mandated insurance coverage plan. The NHIP covers 23 million individuals in Taiwan and is one of the world's largest and most extensive population databases. The NHIRD contains all insurance coverage claims data and associated medical information for >99% of Taiwan's population. The database consists of extensive data for covered individuals, including demographic data, disease diagnoses, medical procedures, and other related information. Disease diagnoses were coded to reflect the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coding. Several subsets of data have been created within the NHIRD, including the one used for this study (The Longitudinal Health Insurance Database 2000 [LHID2000]). LHID2000 includes all healthcare information for 1 000 000 individuals randomly chosen from NHIRD between 1995 and 2013 (roughly 4% of Taiwan's population). The population was selected to be representative of the overall NHIRD population and the country as a whole.

2.2 | Inclusion criteria

Patients newly diagnosed with Graves' disease (ICD-9-CM code: 242.0, toxic diffuse goiter) between 2000 and 2012 in LHID2000 were considered for inclusion in the case cohort. Although patients diagnosed with Graves' disease may be coded as ICD-9-CM: 242.9 (thyrotoxicosis without mention of goiter or other cause), for a more accurate diagnosis, this study did not include these patients. For a reliable diagnosis, the case cohort included only those individuals who had been treated with antithyroid drugs (propylthiouracil, thiamazole, and carbimazole), radioactive iodine ablation, or surgery (thyroidectomy) during the follow-up period. In terms of timing, the first diagnosis of Graves' disease was defined as the index date. Individuals with a history of SLE (ICD-9-CM code: 710.0) between 1995 and the index date were eliminated from the case cohort.

For each patient in the case cohort, one control subject matched by age, gender, index year, and Charlson Comorbidity Index (CCI) score was identified from the LHID2000 database (control cohort). Individuals diagnosed with Graves' disease or those treated with the above treatment for Graves' disease at any time, and those with a history of SLE between 1995 and the index date were excluded from consideration in the control cohort.

2.3 | Outcome

In Taiwan, SLE is usually diagnosed by rheumatologists, and rheumatologists can request a certificate of catastrophic disease from NHIP for patients who meet the diagnostic criteria for SLE. In this study, patients newly diagnosed with SLE by board-certified rheumatologists were considered incidents. To ensure the SLE diagnosis was valid, we used the catastrophic disease registry database to confirm the SLE diagnosis. Each patient in the study was followed until diagnosed with SLE, death, removal from the NHIP, or the end of 2013 (whichever came first).

2.4 | Covariates

Baseline demographic information on age (<40 and ≥40 years), gender, and CCI score (0 and ≥1) were collected for each subject. The CCI score was calculated by summing the weight scores for 19 medical conditions based on their potential influence on mortality and was used to quantify the overall burden of physical comorbidities.[6] During the follow-up period, information on antithyroid drugs (propylthiouracil, thiamazole, and carbimazole), radioactive iodine ablation, or surgery (thyroidectomy) in the case cohort was collected.

2.5 | Statistical analysis

For comparisons of demographic characteristics between the case cohort and the control cohort, Wilcoxon's rank sum was used for continuous variables and the Chi-square test for nominal variables.

The SLE incidence rate was estimated by the number of incidents divided by the person-years of follow-up. Kaplan-Meier analysis with a log-rank test was used to determine the difference in SLE cumulative incidence for the 2 cohorts.

Cox regression analysis was used to calculate the crude and adjusted hazard ratio (HR) with a 95% confidence interval (CI) of the SLE incidence rate between the 2 cohorts. In calculating the adjusted HR, antithyroid therapies (antithyroid drugs, radioactive iodine ablation, and surgery) were fitted into the model and treated as time-dependent covariates.

Diagnostic bias may be present as patients with Graves' disease may seek more help from healthcare providers. We performed sensitivity analyses to minimize potential bias by excluding the first 0.5 and 1 year of the observation period. The significance level of all tests was set at .05. SAS 9.4 software (SAS Institute Inc, Cary, NC, USA) was used to conduct these analyses.

3 | RESULTS

3.1 | Demographic status

The baseline demographic characteristics of patients with Graves' disease (case cohort) and the comparative controls (control cohort) are shown in Table 1. Overall, 8779 patients with Graves' disease were matched to 8779 controls by age, gender, index year, and CCI score. The age distribution in the 2 cohorts was 52.7% for those <40 years, and 47.3% for those ≥40 years of age. The 2 cohorts had more females than males (76.6% vs 23.4%). The distribution of CCI scores in both cohorts was 91.8% for 0, and 8.2% for ≥1. During follow-up, antithyroid drugs (99.3%) were the most commonly used treatment in the case cohort, followed by surgery (10.2%), and radioactive iodine ablation (1.9%). The mean age at diagnosis of SLE (around 43-44 years) and duration of follow-up (8.0 years) were similar for the 2 cohorts. At the end of the follow-up, the frequency of incident SLE was significantly higher in the case cohort than in the control cohort (0.7% vs 0.2%).

3.2 | Risk of SLE

The incidence rates for SLE were 8.81 (case cohort) and 2.83 (control cohort) per 10 000 person-years, respectively (Table 2). The case cohort had a significantly higher risk of SLE compared to the control cohort (HR: 3.06, 95% CI: 1.85-5.07) in the crude analysis. Kaplan-Meier analysis with a log-rank test also revealed a significant association between having Graves' disease and the subsequent risk of SLE ($P < .01$; Figure 1). After adjustment for the covariates mentioned above, the case cohort still had a significantly higher risk of SLE compared to the control cohort (HR: 5.45, 95% CI: 1.74-17.0).

3.3 | Sensitivity analysis

As shown in Table 2, after excluding the first 0.5 year of observation, the case cohort had a significantly higher risk of SLE compared to the control cohort both in the crude analysis (HR: 2.90, 95% CI:

TABLE 1 Demographic characteristics of patients with Graves' disease and comparative controls at baseline and during the follow-up period

Variable	Patients with Graves' disease N = 8779		Patients without Graves' disease N = 8779		*P* value
	n	%	n	%	
Baseline					
Age					
<40	4629	52.7	4629	52.7	—
>40	4150	47.3	4150	47.3	
Mean (SD), y[a]	40.7 (15.5)		40.7 (15.6)		.79
Gender					
Female	6721	76.6	6721	76.6	—
Male	2058	23.4	2058	23.4	
CCI score					
0	8056	91.8	8056	91.8	—
≥1	723	8.2	723	8.2	
Follow-up period					
Treatment					
Antithyroid drugs	8719	99.3			—
Radioactive iodine ablation	172	1.9			
Surgery	896	10.2			
Systemic lupus erythematosus[b]	62	0.7	20	0.2	<.01
Age at diagnosis (SD), years[a]	43.1 (16.9)		44.7 (13.4)		.56
Mean duration between enrollment and diagnosis (SD), years[a]	8.0 (3.6)		8.0 (3.9)		.71

Abbreviation: CCI, Charlson comorbidity index.

[a]Wilcoxon's rank sum test.

[b]Chi-square test.

TABLE 2 Sensitivity analyses of incident systemic lupus erythematosus among patients with Graves' disease and comparative controls

Hyperthyroidism	Systemic lupus erythematosus	Person years	IR[a]	Crude[b] HR (95% CI)	Adjusted[c] HR (95% CI)
Not excluding					
No	20	70 451	2.83	1 (Reference)	1 (Reference)
Yes	62	70 353	8.81	3.06 (1.85-5.07)*	5.45 (1.74-17.0)*
>0.5 y					
No	18	70 441	2.55	1 (Reference)	1 (Reference)
Yes	53	70 342	7.53	2.90 (1.70-4.95)*	4.30 (2.78-8.57)*
>1 y[f]					
No	17	70 415	2.41	1 (Reference)	1 (Reference)
Yes	50	70 324	7.10	2.89 (1.67-5.02)*	4.63 (2.33-7.79)*

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rates.

[a]Per 10 000 person-years.

[b]Relative HR.

[c]Adjusted for antithyroid therapies in Cox regression analyses (antithyroid therapies, including antithyroid drugs, radioactive iodine ablation, and surgery, were treated as time-dependent covariates).

[e]Excluding the first 0.5 y of observation period.

[f]Excluding the first year of observation period.

*$P < .05$.

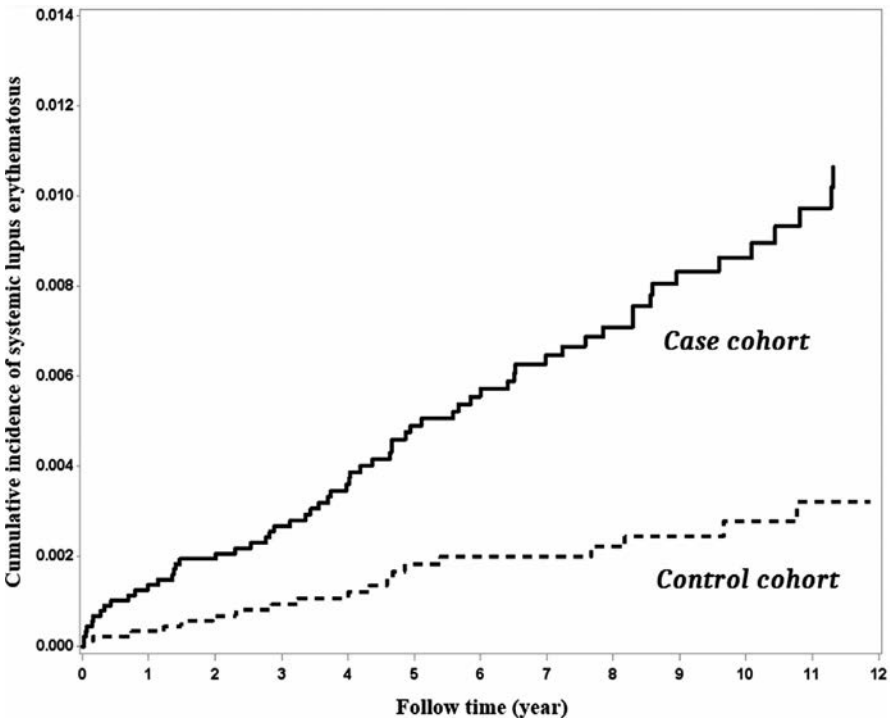

FIGURE 1 Cumulative incidence of systemic lupus erythematosus (SLE) in patients with Graves' disease (case cohort) and comparative controls (control cohort). Kaplan-Meier analysis with a log-rank test revealed a significant association between the case cohort and the subsequent risk of SLE ($P < .01$)

1.70-4.95) and after adjustment for the above-mentioned variables (HR: 4.30, 95% CI: 2.78-8.57).

After adjusting for the first 1 year of observation, similar results were obtained. Significant risk associations between the case cohort and incident SLE were noted in the crude analysis (HR: 2.89, 95% CI: 1.67-5.02) and after adjustment for the above-mentioned variables (HR: 4.63, 95% CI: 2.33-7.79).

4 | DISCUSSION

This population-based cohort study examined the risk of SLE in patients with Graves' disease using an age-, gender-, index year-, and CCI score-matched cohort with a maximum follow-up period of 13 years in a nationally representative sample. The study demonstrated that patients with Graves' disease had an increased risk

of incident SLE compared with unaffected controls. There are possible explanations that may account for the mechanisms underlying this observation. However, it should be noted that this is an observational study which does not directly deal with the mechanism.

First, a shared genetic predisposition between Graves' disease and SLE could be a possible explanation.[7] For example, some genetic association studies have revealed that certain gene loci, such as polymorphisms in the *PTPN22*, *IFIH1*, and *ITPR3* genes, are associated with susceptibility to both Graves' disease and SLE.[8-10] Amplified autoimmune reactions of Graves' disease via shared genetic pathways may contribute to the development of SLE.

Second, Graves' disease is characterized by hyperthyroidism, and there is a body of evidence indicating that hyperthyroidism could greatly increase oxidative stress.[11] Since persistent oxidative stress has been linked to both initiation and progression of SLE,[12] Graves' hyperthyroidism may serve as a contributing factor in patients with subclinical vulnerability to SLE.

Third, there is a possibility of drug-induced SLE after treatment with antithyroid drugs.[5] This could be supported by the fact that after adjusting for the impact of baseline demographics and antithyroid therapies, a further increased risk of incident SLE was observed. The mechanism could be associated with drug-induced structural changes of the histone-DNA complex.[13] The changes lead to histone not being easily hydrolyzed, allowing it to retain its immunogenicity or expose new epitopes. Many drugs are metabolized into cytotoxic metabolites, which lead to cell death and abnormal degradation of chromatin. This could induce an autoimmune response against histone-DNA complexes leading to incident SLE.

This study's strengths include the large population-based cohort, adjustment for antithyroid therapies, and a long observation period. Certain limitations of the study should be addressed here. First, only patients who sought medical help for the diagnosis and treatment of Graves' disease or SLE were included. Also, this study did not include patients with Graves' disease being coded as ICD-9-CM: 242.9. Therefore, patient identification may have been biased and may have weakened the observed association. However, the patients identified in the present study were confirmed by their treatment or certificate of catastrophic disease, which improved diagnostic validity. Second, diagnostic bias may be present as patients with Graves' disease may seek more help from healthcare providers. Although sensitivity analyses were performed to minimize the influence of potential bias by excluding the first 0.5 and 1 year of the observation period, the existence of diagnostic bias should still be of concern. Third, the presentation of symptoms and detailed laboratory data for Graves' disease and SLE are not available in the Taiwan NHIRD database. Therefore, additional analyses could not be applied, such as the relationship between thyroid hormone levels and autoantibody detection of SLE. Fourth, the influence of individual medical comorbidities was not taken into account as this study only weighted them according to the CCI score. Finally, the reasons for choosing a particular antithyroid therapy (ie, antithyroid drugs, radioactive iodine ablation, and surgery) were not available. This study took all antithyroid therapies as a whole and treated them as time-dependent covariates, which reduces the chances of showing the effect of individual antithyroid treatment on the risk of SLE.

In conclusion, this study shows that Graves' disease is associated with an increased risk of incident SLE. Further prospective studies on the underlying pathogenesis linking Graves' disease and SLE are warranted.

ACKNOWLEDGEMENTS

The authors thank Shinn-Zong Lin for cross-hospital integration.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

C. Lee and SF Chen managed the literature searches and wrote the Introduction of the manuscript. YC Yang and CY Hsu did all the analyses and wrote the Method and Results of the manuscript. YC Shen conceived the study and wrote the Discussion of the manuscript. All authors have approved the final manuscript.

ETHICAL APPROVAL

This research was monitored by the Institutional Review Board of China Medical University (CMUH104-REC2-115). All study approaches followed the appropriate standards and policies. The need for informed consent from individual subjects was waived because the LHID2000 contains only anonymized secondary data.

DATA AVAILABILITY STATEMENT

The data are available on request from the corresponding author.

ORCID

Yu-Chih Shen https://orcid.org/0000-0002-3503-5778

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How to cite this article: Lee C, Chen S-F, Yang Y-C, Hsu C-Y, Shen Y-C. Association between Graves' disease and risk of incident systemic lupus erythematosus: A nationwide population-based cohort study. *Int J Rheum Dis*. 2021;24:240–245. https://doi.org/10.1111/1756-185X.14027

Received: 19 August 2020 | Revised: 20 October 2020 | Accepted: 7 November 2020

DOI: 10.1111/1756-185X.14033

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Relationships of the stand-up time to falls and fractures in patients with rheumatoid arthritis: Results from the CHIKARA study

Masahiro Tada[1] | Yutaro Yamada[2] | Koji Mandai[2] | Noriaki Hidaka[1]

[1]Department of Orthopedic Surgery, Osaka City General Hospital, Osaka, Japan

[2]Department of Orthopedic Surgery, Osaka City University Medical School, Osaka, Japan

Correspondence
Masahiro Tada, Department of Orthopedic Surgery, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima-ku, Osaka 534-0021, Japan.
Email: m-tada@med.osaka-cu.ac.jp

Funding information
Grant-in-aid for Osteoporosis and Quality of Life 2015 from the Japan Osteoporosis Foundation

Abstract

Aim: Patients with rheumatoid arthritis (RA) have a higher risk of falls and fractures due to muscle weakness and painful joints of the lower extremities. Evaluation of muscle functions is important to predict falls and fractures. The aim was to investigate the relationships of muscle functions with falls and fractures in RA patients.

Methods: Stand-up muscle power, speed, and stabilizing time were evaluated by a muscle function analyzer in 90 RA patients in the CHIKARA study (UMIN000023744). The relationships of the muscle functions with falls, fractures, body composition, Disease Activity Score of 28 joints - erythrocyte sedimentation rate (DAS28-ESR), modified Health Assessment Questionnaire (mHAQ) scores, Steinbrocker class, stage, sarcopenia, and frailty were investigated in a cross-sectional study.

Results: Each parameter of muscle function was related to age, falls, frailty, and the leg muscle score. However, only stabilizing time was related with fractures ($r = .217$, $P = .04$). When stabilizing time was ≥ 1.13 and ≥1.36 seconds, the odds ratios for falls and fractures were increased 6.2-fold compared to < 1.13 seconds (95% CI: 1.2-20.1, $P = .002$) and 11.4-fold compared to <1.36 seconds (95% CI: 1.7-92.5, $P = .071$), respectively. Sarcopenia and skeletal muscle mass were not significantly related to each muscle function. There was a negative correlation between DAS28-ESR and power. Steinbrocker class and mHAQ had negative correlations with power and speed.

Conclusions: Sarcopenia and skeletal muscle mass were not adequate indicators of muscle functions in RA patients. Analyzing muscle functions is helpful to predict falls and fractures. Patients with extended stabilizing times should recognize the increased risk of falls and fractures.

KEYWORDS

dynapenia, fall, fracture, muscle function analysis, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is one of the risk factors for secondary osteoporosis[1] and a high prevalence of fragility fractures. RA patients were found to have an increased risk of fractures, which was most marked at the hip and spine compared with controls (relative ratios: 2.0 and 2.4, respectively).[2] The incidence of fractures is not decreased in patients with RA who are treated with biological and targeted synthetic disease-modifying antirheumatic drugs and show improved disease activity by the treat-to-target approach.[3]

Moreover, RA patients have a higher risk of fall-induced fractures than the general population,[4] and their annual incidence of falls is relatively high.[5] Falls are a main factor related to fragility fractures induced by osteoporosis. Therefore, reduction of falls is important to avoid fractures. Muscle function loss caused by muscle weakness and decreased balance ability, and some diseases such as osteoarthritis, cerebrovascular disorder, Parkinson's syndrome, orthostatic hypotension, dizziness, and some drugs such as antidepressants or diuretics have been found to be risk factors for falls. A recent study reported that postural sway is associated with falls in community-dwelling elderly individuals.[6] In particular, postural sway on standing up from a chair frequently leads to falls.

Sarcopenia, which is defined by low muscle mass, muscle power, and muscle quality,[7] is reportedly an independent risk factor for falls.[8] We previously reported that the prevalence of sarcopenia was 28%,[9] and sarcopenia incidence over a year was 13%[10] in a prospective cohort study. Grip strength, gait speed, the stand-up test, and the short physical performance battery (SPPB) test are used to diagnose sarcopenia with the new criteria of the European Working Group on Sarcopenia in Older People (EWGSOP)[11] and the Asia Working Group for Sarcopenia (AWGS).[12] However, these tests are not sufficient to quantify muscle function, especially balancing function, such as postural sway. Recently, muscle function loss has been defined as dynapenia, which is different from sarcopenia.[13] Sarcopenia is described as the age-related loss of muscle mass. On the other hand, dynapenia was described as the age-related loss of muscle strength and power.[14] However, accurate diagnostic criteria have not been defined. Evaluation focused on muscle function is important to predict falls and fractures.

Muscle function has generally been evaluated by the gait speed test, grip test, timed-up-and-go (TUG) test, chair stand test, and SPPB test.[11,12] These tests need a large space and time to perform. A muscle function analyzer easily evaluates muscle function by the patient placing the feet on the machine and standing from a chair. Power, speed, and stabilizing time of the lower limb and trunk are measured within a short time and a small space. The aim of this study was to investigate the relationships between lower limb and trunk muscle functions and falls and fractures, body composition, and disease activity with a muscle function analyzer.

2 | MATERIALS AND METHODS

2.1 | Participants

A prospective, observational study was started in 2016 to investigate correlations between sarcopenia, locomotive syndrome, and disease activity of RA, as part of the Correlation research of sarcopenia, skeletal muscle and disease activity in rheumatoid arthritis (CHIKARA) study.[9] This study was registered with the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) (UMIN000023744). Correlations between muscle functions and falls and fractures, body composition, and disease activity measured by the lower limb and trunk muscle function analyzer were investigated by cross-sectional analysis using the 1-year follow-up data of the CHIKARA study.

This study included 100 consecutive RA patients (78 women, 22 men) seen in general clinical practice at our hospital. The details of the study protocol and inclusion criteria were presented in our previous report.[9] All RA patients were ≥20 years old and fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[15] At 1-year follow-up, 10 cases (8 cases, personal choice; 1 case, relocation; 1 case, entered retirement home) dropped out. Therefore, 90 patients with RA were available for this analysis. The flowchart of this study and patient disposition are shown in Figure 1.

2.2 | Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee (No. 1505018; July 7, 2015) and with the 1964 Helsinki

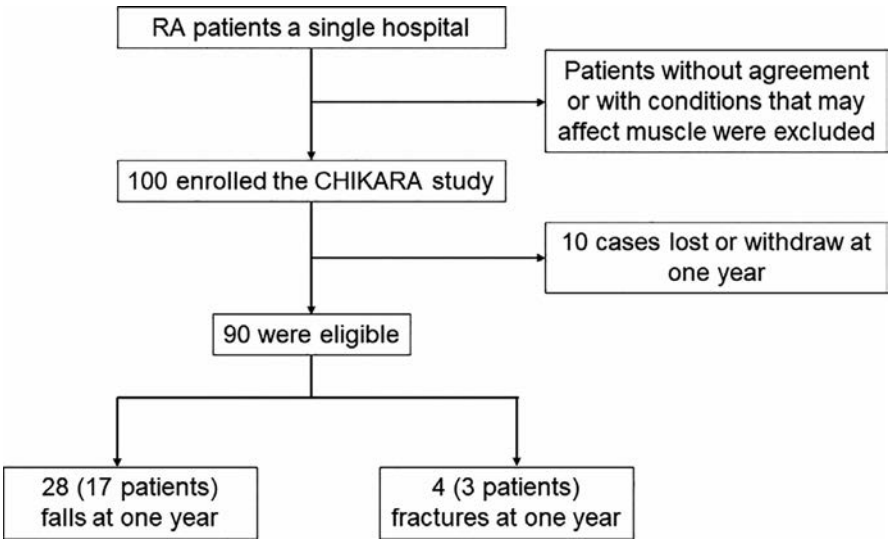

FIGURE 1 Flowchart of this study and patient disposition. RA, rheumatoid arthritis

Declaration and its later amendments or comparable ethical standards. Written, informed consent to participate in this study was obtained from all patients.

2.3 | Body composition and diagnosis of sarcopenia and frailty

Body compositions were measured using a body composition analyzer (MC-780A; TANITA, Tokyo, Japan). Weight, body mass index, muscle mass, body fat mass, total body water, estimated bone mass, and basal metabolic rate were measured by this device. Gait speed was determined by a 3-m walk test, and grip strength was measured for each hand using a digital hand-held isokinetic dynamometer (TKK-5401; Takei Scientific Instruments, Niigata, Japan). Sarcopenia was diagnosed using the AWGS criteria 2014.[16] The cut-off values used were <0.8 m/s for gait speed and <26 kg in men and <18 kg in women for grip strength. Sarcopenia was diagnosed when appendicular skeletal mass index from the bioelectrical impedance analysis method was <7.0 kg/m^2 in men and <5.7 kg/m^2 in women. Frailty was diagnosed using the frailty checklist. It is a simple, self-reported, yes/no survey consisting of 25 questions. The worst score is 25, and the best score is 0. According to a report, frailty was defined as a score from 8 to 25, with pre-frailty from 4 to 7 and normal from 0 to 3.[17]

2.4 | Muscle function analyzer

Muscle functions were measured using a muscle function analyzer (BM-220; TANITA, Tokyo, Japan). This device was connected to a body composition analyzer. The measuring position is shown in Figure 2. The patients sat on the edge of the chair that was 40 cm high and put their feet on this device. They folded their arms in front of their chest, bent their knee 70 degrees, and stood up as soon as possible without swaying. They were measured twice to obtain accurate results. Pressure sensors were built into the footrests, and the power, speed, and stabilizing time (balance function) of the lower limb and trunk were evaluated simultaneously. Higher values for power and speed were considered better. On the other hand, lower stabilizing time was considered better. The details are indicated in Figure 3. The calculated scores correlated with the TUG test, which measures the ability to stand up and move. Physical ability and muscle functions were measured easily, and the measurement results reflected the muscle function and mass of the lower limb and trunk.

2.5 | Clinical assessments

All patients were treated based on the treat-to-target (T2T) concept[18] during the observation period, and they completed a self-administered questionnaire about falls and fractures over a year of observation. Laboratory examinations included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). RA activity was measured as a Disease Activity Score (DAS) composite of the ESR and the 28-joint score (DAS28-ESR).[19] Functional status was also measured in patients with RA based on modified Health Assessment Questionnaire (mHAQ) scores.[20]

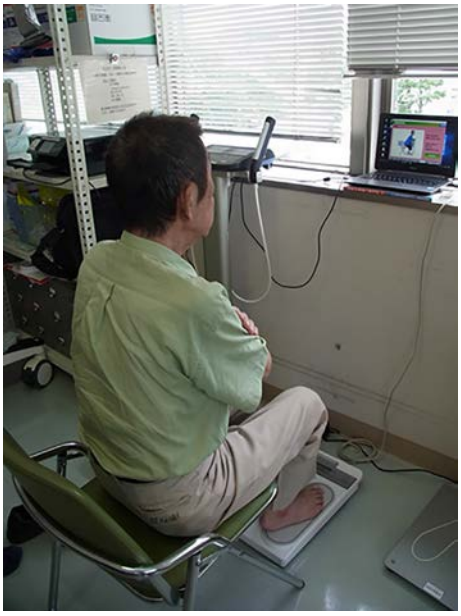

FIGURE 2 The lower limb and trunk muscle function analyzer is connected to the body composition analyzer. After body composition is measured, the patients put their feet on this device. The personal computer shows the timing of standing up, and this device measures power, speed, and stabilizing time of the lower limb and trunk

2.6 | Statistical analysis

The characteristics of patients with RA are presented as means ± standard deviation (SD) for those with a normal distribution or as medians (25th, 75th percentiles) for those not normally distributed. Continuous variables were analyzed using an unpaired Student's t test or the Mann-Whitney *U* test, and categorical variables were analyzed using Fisher's exact test when comparing men and women. Associations between lower limb and trunk muscle functions (power, speed, and stabilizing time) and disease activity, laboratory data, body composition, presence of sarcopenia and frailty, and incidences of falls and fractures were examined using Spearman's correlation coefficients on univariate analyses. Multiple regression analysis was performed to investigate the independent factors related to lower limb and trunk muscle functions. Explanatory variables considered in the models were age, gender, mHAQ score, Steinbrocker class, skeletal muscle index, leg score (ratio of leg muscle weight per total body weight, best score: 100, worst score: 0), grip strength, frailty, and falls. Receiver operating characteristic (ROC) curve analysis for stabilizing time and presence

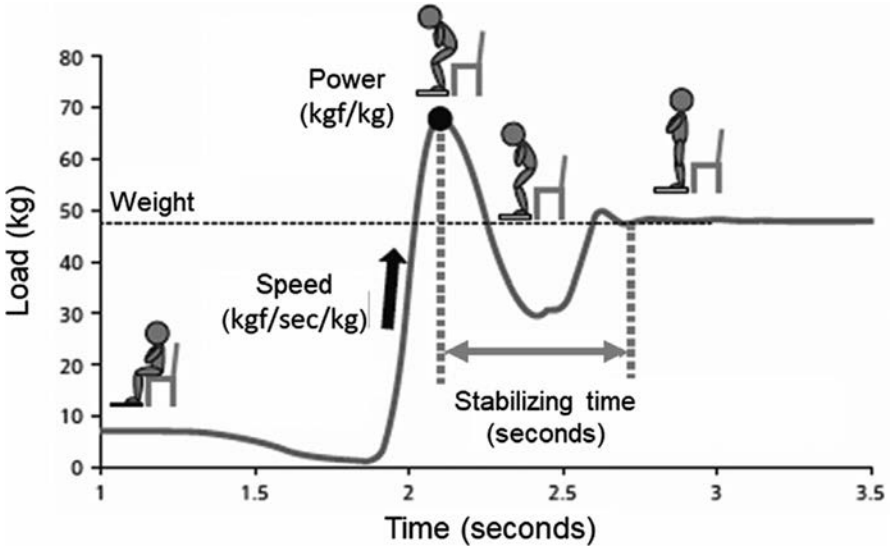

FIGURE 3 This figure shows the conceptual scheme. It defines power as force divided by weight and speed as the power divided by the seconds for standing up. Stabilizing time was the time from standing up to standing still in all directions

of falls or fractures was performed, and the cut-off value was calculated to maximize the sum of sensitivity and specificity. All statistical analyses were performed with IBM SPSS Statistics version 26 (IBM, Armonk, NY, USA). Values of $P < .05$ were considered significant.

3 | RESULTS

3.1 | Characteristics of all RA patients, male RA patients, and female RA patients

The details of the clinical data, body composition, physical assessment, muscle functions, and presence of sarcopenia and frailty of the 90 patients with RA are presented in Table 1. The median age was 69.0 years, and disease duration was 6.5 years. Disease activity was low (DAS28-ESR, 3.08). The positive rates of anti-cyclic citrullinated peptide antibody and rheumatoid factor were 78.9% and 64.4%, respectively. The percentage of methotrexate use was 83.3%, at a mean dosage of 8.0 mg/week, and that of glucocorticoid was 18.9%, at a mean dosage of 4.0 mg/day. The body mass index (BMI) was slightly low (21.8 kg/m^2), and the leg score that was calculated from the ratio of lower extremity per body weight was relatively high (89.2 points). BMI and muscle mass were significantly higher in men than women. On the other hand, the leg score was significantly lower in men than women. Grip strength and power were significantly higher in men than women. However, there were no significant differences in gait speed, speed, and stabilizing time (Table 1). The numbers of falls and fractures were 28 (17 patients) and 4 (3 patients) per year, respectively; there were no significant differences between men and women.

The average age of fracture cases was 73.2 ± 3.5 years, and all cases were women. The fracture sites were one each of femoral neck, lumbar vertebra, rib, and fifth metatarsal. The outpatient doctor diagnosed them on X-ray examination. Only the rib fracture was not due to falls; the other fractures were caused by falls.

3.2 | Factors associated with muscle functions

The results of univariate analysis are shown in Table 2. Age, leg score, gait speed, frailty, and falls were significantly correlated with all muscle functions. Gender (women), DAS28-ESR, and muscle mass were significantly negatively correlated only with power. Power and speed showed the same tendency as the mHAQ scores and Steinbrocker class, whereas stabilizing time did not have significant correlations with them. SMI and sarcopenia were not significantly correlated with all lower limb and trunk muscle functions. For fractures, there were no relationships with power and speed. However, there was a positive correlation with stabilizing time.

The results of multivariate analysis are shown in Table 3. Age and frailty were the independent factors related to power and speed. The aged RA patients with frailty had lower power and speed. On the other hand, stabilizing time showed a different tendency. Falls and leg scores were the independent factors related to stabilizing time. RA patients who had some falls and lower leg scores by the body composition analyzer had long stabilizing times; this indicates that these patients had postural sway on standing up.

3.3 | Relationship between stabilizing time and presence of falls or fractures

The ROC curves for stabilizing time and the presence of falls or fractures are shown in Figure 4. The area under the ROC curve (AUC) for falls was 0.72 (95% CI: 0.57-0.86, $P = .005$), and the cut-off value was 1.13 seconds. When stabilizing time was ≥ 1.13 seconds, the odds ratio (OR) for falls increased 6.2-fold (95% CI: 1.2-20.1) compared to that at < 1.13 seconds using Fisher's exact test ($P = .002$). The AUC for fractures was 0.85 (95% CI: 0.75-0.95, $P = .041$), and the cut-off value was 1.36 seconds. When stabilizing time was ≥ 1.36 seconds, the OR for fractures increased 11.4-fold (95% CI: 1.7-92.5) compared to that at < 1.36 seconds ($P = .071$).

TABLE 1 Characteristics of all RA patients, male RA patients, and female RA patients

	All RA patients (n = 90)	Men (n = 20)	Women (n = 70)	*P* value
Clinical data				
Women (%)	77.8			
Age, y	69.0 (61.0, 77.0)	69.0 (65.0, 79.0)	67.0 (56.0, 75.0)	.185**
Disease duration, y	6.5 (2.3, 12.2)	5.1 (1.6, 11.1)	7.1 (2.4, 12.4)	.195**
Stage, I/II/III/IV	32/26/16/16	7/4/5/4	25/22/11/12	.675***
Class, 1/2/3/4	42/43/5/0	11/9/0/0	31/34/5/0	.396***
CRP, mg/dL	0.09 (0.03, 0.27)	0.17 (0.08, 0.31)	0.06 (0.03, 0.26)	.053**
DAS28-ESR	3.08 ± 0.98	2.95 ± 1.09	3.13 ± 0.95	.477*
mHAQ	0.125 (0, 0.5)	0.125 (0, 0.5)	0.125 (0, 0.375)	.976**
MTX, mg/weight, rate (%)	8.0 ± 3.0 (83.3)	8.5 ± 2.9 (70.0)	7.8 ± 3.1 (87.1)	.133*
GC, mg/d, rate (%)	4.0 ± 1.7 (18.9)	4.1 ± 1.5 (20.0)	3.9 ± 1.8 (18.5)	.306*
bDMARD or tsDMARD use, rate (%)	31.1	25	32.3	.592***
Body composition				
BMI, kg/m^2	21.8 ± 3.4	22.4 ± 2.7	21.5 ± 3.6	.284*
Muscle mass, kg	35.8 ± 5.8	44.2 ± 4.3	33.4 ± 3.5	<.001*
SMI, kg/m^2	6.4 ± 0.8	7.3 ± 0.8	6.1 ± 0.7	<.001*
Leg score, points	89.2 ± 8.6	85.1 ± 5.0	90.4 ± 9.1	.015*
Physical assessment				
Grip strength, kg	17.1 ± 7.0	20.6 ± 6.5	14.8 ± 6.0	.001*
Gait speed, m/s	1.1 ± 0.3	1.2 ± 0.2	1.1 ± 0.4	.543*
Muscle functions				
Power, kgf/kg	1.23 ± 0.13	1.29 ± 0.12	1.22 ± 0.13	.039*
Speed, kgf/s/kg	8.93 ± 2.42	9.65 ± 2.32	8.72 ± 2.43	.126*
Stabilizing time, s	1.19 ± 0.42	1.21 ± 0.20	1.18 ± 046	.809*
Status and events				
Sarcopenia, n (%)	28 (31.1)	9 (45)	19 (27.1)	.171***
Frailty number (%)	39 (43.3)	6 (30)	33 (47.1)	.207***
Falls, n (%)	28 (31.1)	2 (10)	26 (37.1)	.685***
Fractures, n (%)	4 (4.4)	0 (0)	4 (5.7)	.642***

Note: Data are shown as mean ± SD or median (25th, 75th percentile).

Continuous variables were analyzed using an unpaired Student's t test* or the Mann-Whitney *U* test**. Categorical variables were analyzed using Fisher's exact test***.

Abbreviations: CRP, C-reactive protein; BMI, body mass index; bDMARDs, biological disease-modifying antirheumatic drugs; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; SMI, skeletal muscle index; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

4 | DISCUSSION

This study investigated the relationships between muscle functions and disease activity, laboratory data, muscle mass, sarcopenia, frailty, falls, and fractures in RA patients in a cross-sectional analysis using the 1-year follow-up data of the CHIKARA study. The lower limb and trunk muscle functions were not correlated with muscle mass, but they were correlated with falls and fractures. Of the lower limb and trunk muscle functions, stabilizing time was correlated with both falls and fractures, and cut-off values were calculated by ROC curve analysis.

Power and speed reflected the muscle strength and function of the quadriceps femoris muscle, and the stabilizing time reflected those of the gluteus maximus and iliopsoas muscles on the muscle function analyzer. Spinal malalignment by deformity, scoliosis, and kyphosis, and so on, affected imbalance on standing up.[21] Lower

TABLE 2 Univariate analysis of factors potentially related to lower limb and trunk muscle functions

	Power		Speed		Stabilizing time	
	R value	*P* value	*R* value	*P* value	*R* value	*P* value
Age, y	−.556	<.001	−.522	<.001	.452	<.001
Gender, women	−.214	.042	−.161	.129	−.026	.809
DAS28-ESR	−.277	.008	−.170	.110	.135	.205
mHAQ	−.241	.022	−.299	.004	.184	.082
Steinbrocker class	−.243	.021	−.299	.004	.109	.308
Muscle mass, kg	.273	.009	.200	.058	.162	.126
SMI, kg/m^2	.106	.320	.057	.592	.164	.123
Leg score, points	.413	<.001	.302	.004	−.433	<.001
Grip strength, kg	.417	<.001	.341	.001	−.194	.067
Gait speed, m/s	.387	<.001	.351	.001	−.283	.019
Sarcopenia	−.107	.315	−.084	.431	−.007	.945
Frailty	−.470	<.001	−.435	<.001	.307	<.001
Falls, n	−.253	.016	−.278	.008	.304	.004
Fractures, n	−.107	.314	−.120	.261	.217	.040

Note: Abbreviations: DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; SMI, skeletal muscle index

TABLE 3 Multiple regression analysis of factors potentially related to lower limb and trunk muscle functions

	Power		Speed		Stabilizing time	
	β value	*P* value	*β* value	*P* value	*β* value	*P* value
Age, y	−0.443	<.001	−0.336	<.001	0.062	.634
Frailty	−0.335	<.001	−0.260	.005	0.033	.744
Leg score, points	−0.023	.838	−0.072	.523	−0.231	.022
Falls, yes	−0.183	.282	−0.141	.105	0.295	.004

Note: We performed multivariate regression analysis using age, gender, modified Health Assessment Questionnaire, Steinbrocker class, skeletal muscle index, leg score, grip strength, frailty, and falls as explanatory variables.

limb joint (hip, knee, and ankle) contractures were also important factors related to postural sway. Postural sway has been used as a tool for assessing fall risk in elderly individuals.[6,22] Postural instability and imbalance were associated with future fall risk in RA.[5,23] Therefore, the stabilizing time, which reflects imbalance and postural sway, is especially important to predict falls.

Polypharmacy is an important problem for RA patients in step with the rapidly aging population in our country. It has been reported that polypharmacy is a risk factor for fall occurrence in geriatric outpatients.[24] Oh et al reported that the presence of 5 or more prescriptions increases the risk of falls, and this was included in the screening test to assess the risk of falls in RA patients in a large cohort study (IORRA study).[25] Loop diuretics, antidepressants, and antiepileptics were significantly associated with an increased risk of falling in a meta-analysis.[26-28] In the present study, no patients were treated with these medicines.

DAS28-ESR and mHAQ were negatively correlated with power and speed. Therefore, patients with high disease activity and low activities of daily living (ADL) have decreased muscle functions. Controlling disease activity and maintaining ADL are also important to maintain lower limb and trunk muscle functions. On the other hand, they did not correlate with stabilizing time, which was related with falls and fractures. Stabilizing time might have different implications than power and speed.

RA patients have deformities and joint destruction of the hip, knee, ankle, and foot due to the disease itself, and they affected lower limb and trunk muscle functions in this study. The diagnostic criteria of sarcopenia are composed of both muscle mass (SMI) and muscle function (grip strength and gait speed). The grip strength and gait speed correlated with power, speed, and stabilizing time as measured by the device used in the present study. However, SMI was not correlated with them. This is the reason for no correlation between sarcopenia and muscle functions.

The diagnostic criteria of sarcopenia have been defined[11,12] and coded in the International Classification of Diseases-10. On the other hand, those for dynapenia have not been clearly defined.

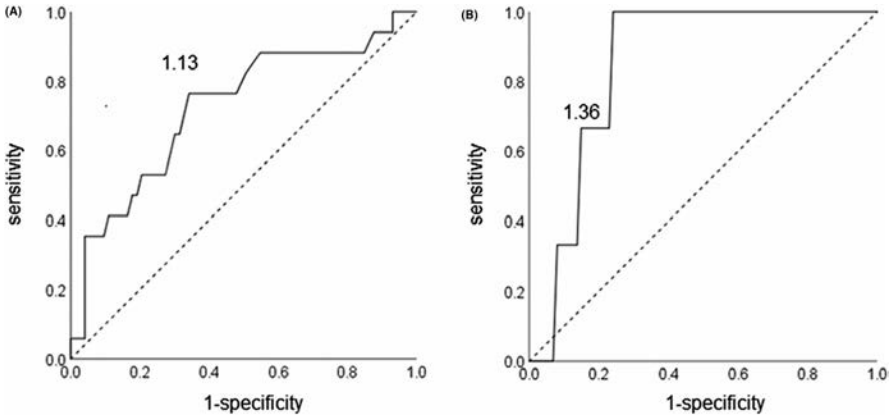

FIGURE 4 Receiver operating characteristic (ROC) curve analysis for stabilizing time in relation to falls (A) and fractures (B); the cut-off values of stabilizing time are 1.13 and 1.36 s, respectively, and the area under the ROC curve (AUC) is 0.72 (95% CI: 0.57-0.86, $P = .005$) for falls and 0.85 (95% CI: 0.75-0.95, $P = .041$) for fractures

Grip strength or gait speed was used to evaluate muscle function. However, evaluation method, criteria, and cut-off values differed by study.[29,30] It has been reported that sarcopenia did not always correspond with dynapenia, and the related factors differed between them.[31] Grip strength or gait speed were old criteria for sarcopenia in EWGSOP[7] and AWGS.[16] However, in the new criteria, a balance test, such as the SPPB test, was added.[11,12] This matches the present study's finding of the importance of not only power and speed, but also stabilizing time (balance).

The present study has some limitations that must be considered. First, all diseases that can result in muscle weakness and decreased balancing ability were not examined. However, patients were asked about some diseases, such as osteoarthritis, cerebrovascular disorders, Parkinson's syndrome, orthostatic hypotension, and dizziness, that are known risk factors for falls, and they were excluded in this study. Second, this study was not a comparative study and did not have data for healthy controls. Third, the design of this study was cross-sectional, and the follow-up period was short. A longitudinal study is necessary to clarify the relationships between falls and fractures and changes of muscle functions. Fourth, the sample size was too small to conclusively determine the effects of the stand-up stabilizing time on falls and fractures. A large cohort study is needed in the future. Fifth, a comparison of men and women might not be appropriate, because the sample size was small. On the other hand, muscle mass and function were different by gender, and the separate analysis and description were helpful to recognize them.

In conclusion, the present study showed that sarcopenia and skeletal muscle mass were not correlated with lower limb and trunk muscle functions. The sarcopenia criteria and muscle mass might not adequately reflect lower limb and trunk muscle functions and predict falls and fractures. Power and speed were related to falls, and stabilizing time was correlated with both falls and fractures. Therefore, analyzing muscle functions is helpful to predict falls and fractures. In particular, patients with extended stabilizing times should recognize the increased risk of falls and fractures.

ACKNOWLEDGEMENTS

The authors greatly appreciate the cooperation of the patients with RA in the CHIKARA study.

CONFLICT OF INTEREST

Masahiro Tada, Yutaro Yamada, Koji Mandai, and Noriaki Hidaka declare that they have 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. Dr Tada 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 design and conduct: MT Data collection: MT, YY, and KM Data analysis: MT and NH Data interpretation: MT and NH Drafting the manuscript: MT

ORCID

Masahiro Tada https://orcid.org/0000-0003-3161-3929

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How to cite this article: Tada M, Yamada Y, Mandai K, Hidaka N. Relationships of the stand-up time to falls and fractures in patients with rheumatoid arthritis: Results from the CHIKARA study. *Int J Rheum Dis*. 2021;24:246–253. https://doi.org/10.1111/1756-185X.14033

Received: 28 September 2020 | Revised: 3 November 2020 | Accepted: 7 November 2020

DOI: 10.1111/1756-185X.14034

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-α therapy

Sami Fidan[1] | Erhan Capkın[2] | Deniz Aksu Arıca[3] | Serdar Durak[1] | Ilyas Ercan Okatan[4]

[1]Department of Gastroenterology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

[2]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

[3]Department of Dermatology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

[4]Department of Rheumatology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Correspondence
Sami Fidan, MD, Karadeniz Technical University, Faculty of Medicine, Department of Gastroenterology, 61080, Trabzon, Turkey.
Email: fidansami@yahoo.com

Abstract

Objective: The purpose of this study was to determine hepatitis B virus (HBV) screening rates in patients receiving anti-tumor necrosis factor (TNF)-α therapy and the frequency of HBV reactivation in patients with resolved hepatitis B virus infection (hepatitis B surface antigen [HBsAg] negative, hepatitis B core antibody [Anti-HBc] positive).

Patients and methods: Data from 1834 patients who underwent anti-TNF-α therapy in the Rheumatology, Gastroenterology and Dermatology Departments of our hospital between 2010 and 2020 were retrospectively analyzed. Within 6 months before the initial anti-TNF-α therapy, performing a HBsAg and/or anti-HBc test is defined as HBV screening. HBV reactivation is defined as the presence of detectable serum HBV DNA or HBsAg seroconversion from negative to positive.

Results: The overall HBV screening rate was 82.3% before starting anti-TNF-α therapy. There was an increasing trend in HBV screening rates during the years analyzed (64% in 2010, 87.4% in 2019) ($P < .001$). Before anti-TNF-α therapy was initiated, 272 patients were HBsAg negative and anti-HBc positive. Among these patients, HBV reactivation did not occur in 31 patients who received antiviral prophylaxis, whereas HBV reactivation occurred in only 1 (0.4%) of the 241 patients who did not receive antiviral prophylaxis.

Conclusion: Hepatitis B virus screening rates prior to starting anti-TNF-α therapy were relatively high, and its trend was increased by year. HBV reactivation because of anti-TNF-α use rarely occurred in patients with resolved HBV infection. Further studies are needed on whether routine anti-HBc screening and/or HBV DNA follow-up are necessary in these patients aside from HBsAg.

KEYWORDS

antirheumatic therapy, anti-tumor necrosis factor therapy, hepatitis B, hepatitis B virus reactivation, hepatitis B virus screening

1 | INTRODUCTION

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine, which is produced mainly by monocytes, macrophages, and T-lymphocytes, and has important roles in the pathogenesis of many diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel diseases.[1] Nowadays, different TNF-α inhibitors are widely used in the treatment of these chronic inflammatory diseases. Infliximab, adalimumab, and golimumab are monoclonal antibodies against human TNF-α, certolizumab is a monoclonal antibody component against human TNF-α, and etanercept is a fusion protein derived from human TNF-α receptors.[1,2] These drugs have strong immunosuppressive affects and are first-line agents in the treatment of many diseases. However, patients who are treated with TNF-α inhibitors are at risk of developing some opportunistic infections and hepatitis B virus (HBV) reactivation.[1,3] HBV reactivation (HBVr) can progress from asymptomatic clinical course to severe hepatitis and even fulminant hepatic insufficiency in these patients.[3,4] Therefore, it is recommended that patients should be screened for HBV before treatment with TNF-α inhibitors.[5-9] However, there are insufficient data on rates of HBV screening prior to starting TNF-α inhibitor therapy.

The current guidelines recommend antiviral prophylaxis before anti-TNF-α treatment since the risk of HBVr is relatively high in HBsAg positive patients who receive anti-TNF-α treatment.[5-9] However, data on HBV management and HBVr risk are limited in patients receiving anti-TNF-α therapy and with serological evidence of resolved HBV infection (negative HBsAg, positive anti-HBc, variable hepatitis B surface antibody [anti-HBs], and negative HBV DNA). In addition, there are differences between current guidelines regarding the management of these patients. The American Gastroenterological Association recommends antiviral prophylaxis instead of preemptive treatment in these patients, and the European Crohn's and Colitis Organization and the American College of Rheumatology guidelines recommend preemptive treatment instead of antiviral prophylaxis.[6,7,9] This leads to conflict between doctors who initiate anti-TNF-α therapy and doctors who initiate antiviral prophylaxis. Hence the purpose of this single-site retrospective cohort study was to determine HBV screening rates in patients receiving anti-TNF-α therapy initiated between 2010 and 2020, and the frequency of HBV reactivation in patients with resolved hepatitis B virus infection.

2 | MATERIALS AND METHODS

2.1 | Study populations and data source

This single-site retrospective cohort study was conducted using data from patients who received anti-TNF-α therapy at Rheumatology, Dermatology, and Gastroenterology Departments at Karadeniz Technical University Medical Faculty Hospital between January 1, 2010, and December 30, 2019. First of all, patients who were diagnosed with disease likely to receive anti-TNF-α treatment using ICD-9 (International Classification of Diseases-9) codes were searched electronically. Among these patients, those who had a drug report for anti-TNF-α and/ or prescribed anti-TNF-α were determined. Then, using the files of these patients and the electronic record system of our hospital, the diagnoses, demographic characteristics, initial anti-TNF-α start dates and treatment durations, HBV serology before and after treatment, clinical and laboratory results of the patients were evaluated. Data among these patients were screened from the first anti-TNF-α administration to the last visit to our hospital. First, we evaluated the pre-treatment HBV screening rates in patients who received anti-TNF-α treatment, then we evaluated patients with resolved HBV infection in terms of HBVr. The patients who did not receive anti-TNF-α treatment, those who received anti-TNF-α treatment for less than 2 months, the patients under the age of 18, those who were diagnosed with cancer, who received simultaneous rituximab treatment, patients whose viral markers were not examined, those with inadequate clinical data or follow-up and patients with hepatitis C virus (HCV) RNA positivity were excluded from the study. The flow chart of the study participants is shown in Figure 1. The study was conducted in line with the principles of the Helsinki Declaration, and was approved by the Local Ethics Committee (No. 2019/262) of the Karadeniz Technical University.

2.2 | Methods and definitions

Performing of HBsAg and/or anti-HBc tests in 6 months before the first course of anti-TNF-α agents was identified as HBV screening.[10] The patients with HBsAg positivity were identified as chronic hepatitis B infection, and those with HBsAg negative/anti-HBc positive patients were identified as resolved HBV infection.[10,11] During the follow-up of the patients, the positivity of basal HBV DNA from negativity, or increased viral load by 10 times compared to basal values, and/or the positivity of HBsAg from negativity were identified as HBVr.[10-12] The increase in serum alanine aminotransferase (ALT) levels at least 3 times higher than the normal upper limit (45 U/L for serum ALT) was identified as hepatitis.[11] HBV-associated hepatitis was defined as clinical, biochemical evidence of hepatitis with an increase in HBV DNA.[10] The duration in anti-TNF-α treatment was identified as the time from the first anti-TNF-α prescription to the last dose. During the study period, the HBV serological markers that contained HBsAg, anti-HBs, and anti-HBc levels were assessed with the electrochemiluminescence immunoassay method using Roche Cobas E601 Device (Japan). The serum HBV DNA levels were measured in Roche Cobas AmpliPrep (Japan) with a real-time polymerase chain reaction method (lower detection limit was 12 IU/mL). The routine biochemical parameters were tested by using Roche Hitachi Cobas 8000 Autoanalyzer (Roche).

2.3 | Statistical analysis

All statistical analyses were performed with the Statistical Program for Social Sciences software (SPSS 23.0 for Windows; IBM, Armonk,

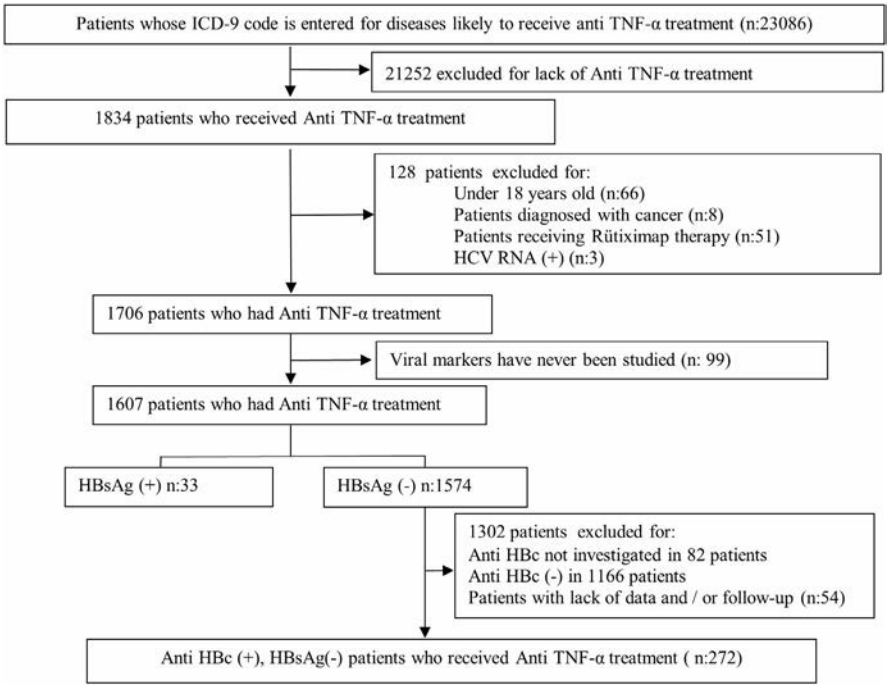

FIGURE 1 Flow-charts of the patients enrolled in this analysis. Anti-HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD, International Classification of Diseases; TNF, tumor necrosis factor

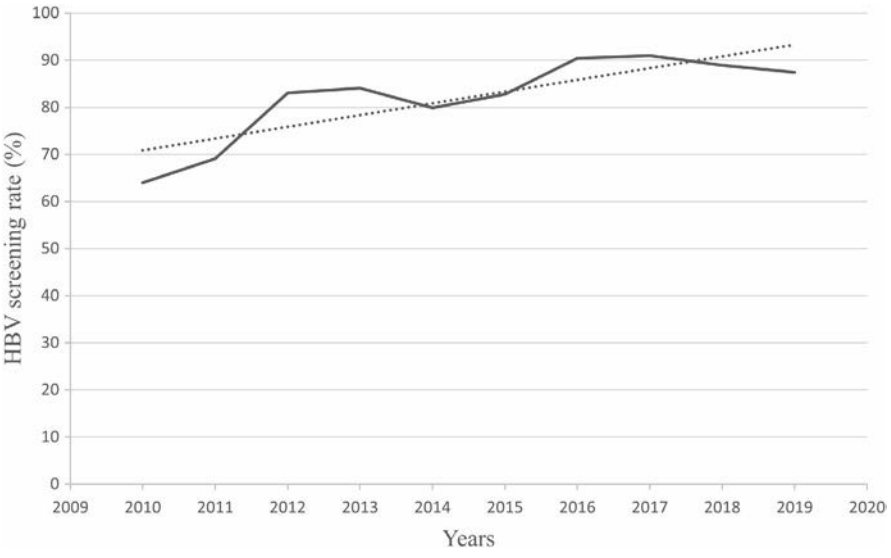

FIGURE 2 Serial annual change in HBV screening rates before anti-TNF-α treatment. HBV, hepatitis B virus; TNF, tumor necrosis factor

NY, USA). The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as number and percentage for categorical variables and as mean ± SD and median (interquartile range [IQR]) for numerical variables. Linear-by-linear association test (Chi-square for trend) was used to evaluate HBV screening rates prior to starting anti-TNF-α therapy over the years. Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | HBV screening rates

The results of 1834 patients who received anti-TNF-α treatment in the Rheumatology, Gastroenterology, and Dermatology Departments of our hospital were evaluated retrospectively. In these patients, the overall hepatitis B screening rate before anti-TNF-α therapy was 82.3% (82% for HBsAg, 69.8% for anti-HBc). The HBV screening rates increased at significant levels over the years ($P < .001$) (Figure 2). Among patients who were screened for HBV serological markers, HBsAg and anti-HBc positivity rates were 2% and 18.2%, respectively.

3.2 | HBVr rates

The results of 272 patients with resolved HBV infection before anti-TNF therapy were evaluated for HBVr. Anti-HBs was positive in 241 of these patients (88.6%). The mean age of the patients was 52.0 ± 12.6 years, and 47% were women. The mean anti-TNF-α

treatment duration was 33 months (IQR: 10.2-73.0). The clinical and demographic characteristics of the patients are given in Table 1. The majority of the patients were receiving anti-TNF-α treatment for rheumatic diseases. Among these patients, 31 (11.4%) received antiviral prophylaxis before anti-TNF-α treatment (16 tenofovir, 12 entecavir, and 3 lamivudine), 241 (88.6%) did not receive antiviral prophylaxis. HBVr did not occur in the patients who had received antiviral prophylaxis, and it was detected in only 1 (0.4%) of the 241 patients who did not receive antiviral prophylaxis (Table 1). Hepatitis developed in 4 (12.9%) patients who had received antiviral prophylaxis, and in 25 (10.4%) patients who had not received prophylaxis, which made a total of 29 patients (10.6%) (20 of them were drug-related toxic hepatitis, 6 were nonalcoholic fatty liver disease, 2 were cholecystitis, and 1 was cholangitis). None of the patients had HBV-related hepatitis. HBV DNA was examined in 66 patients (24.3%) before the start of anti-TNF-α and were all negative. HBV DNA was examined in a total of 219 (80.5%) patients after the commencement of anti-TNF-α; HBVr was negative in all of them except for the patient who developed HBVr.

TABLE 1 Demographic and clinical characteristics of 272 HBsAg negative/ anti-HBc positive patients treated with TNF-α inhibitors

Clinical characteristics	n (%)
Age, mean ± SD	52.0 ± 12.6
Gender	
Female	128 (47)
Male	144 (53)
Time on anti-TNF, mo, median (IQR)	33.0 (10.2-73.0)
Indication for anti-TNF-α	
Spondyloarthropathy	162 (59.5)
Rheumatoid arthritis	66 (24.3)
Psoriatic arthritis	28 (10.3)
Inflammatory bowel disease	10 (3.7)
Behçet's disease	6 (2.2)
Anti-TNF-α agent	
Adalimumab only	67 (24.6)
Etanercept only	63 (23.2)
Infliximab only	22 (8)
Golimumab only	19 (7)
Certolizumab only	8 (3)
2 or more agents	93 (34.2)
Concomitant immunosuppressants	70 (25.7)
Methotrexate	36
Leflunomide	18
Azathioprine	7
Cyclosporine	2
2 or more agents	7
Prophylactic antiviral therapy	31 (11.4)
Tenofovir	16
Entecavir	12
Lamivudine	3
HBV-related hepatitis	0
HBV reactivation	1 (0.4)[a]

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TNF, tumor necrosis factor.
[a]Shows the ratio among patients not taking antiviral prophylaxis

3.3 | Characteristics of a case who developed HBVr

The patient who developed HBVr was a 78-year-old woman with a diagnosis of psoriatic arthritis. Although the patient was receiving prednisolone, hydroxychloroquine, and methotrexate treatments due to psoriatic arthritis for 2 years, she was treated with adalimumab (40 mg at every 2 weeks) due to inadequate response to former treatment. In the examinations before the adalimumab treatment, the following values were detected: HBsAg(−), anti-HBc-immunoglobulin G (IgG)(+), anti-HBs(+), serum ALT 10 U/L, serum aspartate aminotransferase (AST) 18 U/L and HBV DNA(−). Antiviral prophylaxis was not initiated for the patient, and HBsAg and HBV DNA were followed-up with 3-month intervals. Her test results in the examinations made in the 28th month of adalimumab treatment were HBsAg(−), anti-HBc-IgG(+), anti-HBs(+), ALT 11 U/L, AST 20 U/L, total bilirubin 0.9 mg/dL, and HBV DNA 244 IU/mL, and these were interpreted as HBVr, and tenofovir therapy was initiated. In the 3rd month of tenofovir treatment for the patient who continued to be treated with adalimumab, the following values were detected: ALT 10 U/L, AST 18 U/L, and HBV DNA(−). The patient continued to receive adalimumab and concurrent tenofovir therapy.

4 | DISCUSSION

It is estimated that more than one-third of the world's population is infected with HBV.[13] Since the "covalent closed circular DNA" (cccDNA), which acts as a template for HBV replication in the hepatocyte nuclease of HBV-infected individuals, remains permanent, these patients have the risk of HBVr when immunosuppressive agents are used.[10] Yet, considering the current increasing use of anti-TNF-α agents, it is very important to estimate the effect of anti-TNF-α agents on HBVr, especially in countries where the total positivity of anti-HBc is relatively high. In our study, we presented real-life data of HBsAg(−)/ anti-HBc(+) patients who were initiated into anti-TNF-α therapy. To the best of our knowledge, our study has the largest number of cases in this patient group. In our study, HBV reactivation developed in only 1 (0.4%) of the 241 patients who did not receive antiviral prophylaxis, and HBVr was not detected in patients receiving antiviral prophylaxis. However, no clinical findings were detected in the patient who developed HBVr except for HBV DNA positivity.

HBVr rates up to 40% due to the use of anti-TNF-α in chronic hepatitis B patients and HBV-related mortality of 5% were reported in previous studies.[3,14] However, there are few studies

on HBVr in patients with resolved HBV infection and anti-TNF-α treatment in the literature, and the results obtained are quite contradictory. In a review by Alvarez et al[3] conducted with patients receiving anti-TNF-α, 35 (39%) of 87 patients with HBsAg(+) developed HBVr; however, HBVr was reported in 9 (5%) of 168 patients with HBsAg(−)/anti-HBc(+). One of the HBsAg(−)/anti-HBc(+) patients in this review died due to fulminant liver failure. The results of the latest study are worrying in terms of HBVr. Similarly, in a recent retrospective observational study with 152 patients who had rheumatoid arthritis and HBsAg(-)/anti-HBc(+), HBVr was reported in 3 of the 98 patients treated with anti-TNF-α drugs (3.1%), and in 4 (7.4%) of the 54 patients treated with other biologic agents.[15] In this study, no patients with HBVr developed de novo hepatitis. However, unlike these studies, HBVr did not develop in any of the 72 patients receiving anti-TNF-α and were anti-HBc(+) in a prospective study conducted by Caporali et al[16] In a review of Lee et al[17] evaluating a total of 468 HBsAg(−)/anti-HBc(+) patients receiving anti-TNF-α treatment for rheumatic diseases, it was reported that HBVr was detected in 1.7% of the patients, and none of the 8 patients who developed HBVr had clinical deterioration. In a prospective observational study conducted by Barone et al[18] with 179 patients who had past HBV infection and those receiving biological treatment for rheumatic diseases (14 were treated with rituximab, 146 with anti-TNF-α, and 19 with other biological treatment modalities), none of the patients had HBVr. Similarly, in recent years, in a retrospective study conducted by Pauly et al[12] with patients who received anti-TNF-α therapy for autoimmune diseases, HBVr was detected in 9 (39%) of the 23 patients with HBsAg positivity at the start of the treatment; however, none of the 178 patients with HBsAg(−)/anti-HBc(+) developed HBVr. As a result of this study, the authors emphasized that HBsAg(+) patients prior to therapy should receive prophylactic antiviral treatment for anti-TNF-α treatment and that patients who are HBsAg(−)/anti-HBc(+)should not receive antiviral prophylaxis.

When the studies are evaluated together, the HBV reactivation rates are detected at extremely low rates in HBsAg(−)/anti-HBc(+) patients receiving anti-TNF-α treatment, and clinical worsening and progression to hepatic failure are seen extremely rarely in patients where reactivation occurs.[12,17,18] For this reason, it should be discussed whether this patient group requires routine anti-HBc screening, antiviral prophylaxis, and regular HBV DNA monitoring. However, it should not be ignored that these patients may receive other immunosuppressive treatments, especially corticosteroids, which may have potential risks for HBVr in addition to anti-TNF-α treatment. As a matter of fact, most of the HBV reactivation cases reported in HBsAg(−)/anti-HBc(+) patients were combined with an anti-TNF-α agent and another immunosuppressive drug.[14,15,19] Based on the available data, Perillo proposed an algorithm for patients with planned anti-TNF-α treatment.[20] According to this algorithm, it is recommended that HBsAg screening is carried out for those receiving anti-TNF-α monotherapy, and if positivity is found, then antiviral prophylaxis should be started. However, in cases where anti-TNF treatment and other immunosuppressors are combined, it is recommended that HBsAg and anti-HBc are screened, transaminases are followed-up in HBsAg(−)/anti-HBc(+) patients every 2-3 months, and if these values are elevated, HBV DNA is examined.

When the risk of HBVr and the effectiveness of antiviral prophylaxis were considered, it is recommended in the guidelines that all patients scheduled for anti-TNF-α therapy should be screened for HBV infection.[6,7,9] Despite this recommendation, previous studies showed that HBV screening rates in patients receiving anti-TNF therapy ranged between 8.1% and 49%.[21-23] In these studies, it was emphasized that HBV screening rates increased over years. In our study, HBV screening rates increased from 60% in 2010 to 87.4% in 2019 ($P < .001$). However, we noticed a minor fall in HBV screening rates in 2014 and 2019. We think that this decrease in screening rates may be due to the lack of a protocol for HBV screening in relevant clinics including our Institute. In addition, the fact that these patients are not followed up by the same doctors and the difference in HBVr awareness among doctors may be the reason for the decrease in screening rates. The awareness on HBVr can be further increased with meetings, web presentations, seminars, and training brochures for patients who use anti-TNF-α agents. In addition, the use of routine screening programs and/or alarm systems in these patients for HBV can increase HBV screening rates further. A study conducted by Sampedro et al[24] with patients receiving biological treatment showed that the use of the alarm system before the treatment increased from 50% to 94% for HBsAg and the anti-HBc screening rate from 30% to 85%. In a recent survey study conducted by Toka et al[25] among the members of the Turkish Rheumatology Association, it was reported that 93.8% of doctors screened all patients, and 6.2% screened only patients at high risk of HBV infection before immunosuppressive treatment. The results of our study are in line with these survey results and revealed higher screening rates, which may depend on the publication of increased literature on HBVr cases and updated clinical practice guidelines in recent years.

The strengths of our study are that it is a study that includes the most HBsAg(-)/anti-HBc(+) patients who received anti-TNF-α treatment, has a long follow-up period and presents real-life data. However, our study also has some limitations that should be considered. Since the study patients were determined by using ICD-9 codes, it is prone to coding-related inaccuracies. Also, because our study had a retrospective design, there was no study protocol in which patients were followed regularly. For this reason, we cannot exclude the possibility of temporary HBVr during the follow-ups in some patients. However, we believe there was no HBVr with significant clinical manifestation.

In conclusion, the HBV screening rates prior to therapy initiation were relatively high in patients receiving anti-TNF-α therapy, and its trend increased over the study time period. This shows that there is a high awareness of HBVr among doctors who prescribe anti-TNF-α agents. HBV reactivation because of anti-TNF-α use is rarely detected in patients with resolved HBV infection, and usually does not cause symptoms. For this reason, studies are needed on whether routine anti-HBc screening and/or HBV DNA follow-up are necessary for these patients aside from HBsAg.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sami Fidan, Serdar Durak, Erhan Çapkın, Deniz Aksu Arıca and Ercan İlyas Okatan. The first draft of the manuscript was written by Sami Fidan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ORCID

Sami Fidan https://orcid.org/0000-0002-7412-4319
Erhan Capkın https://orcid.org/0000-0003-2728-5934
Deniz Aksu Arıca https://orcid.org/0000-0003-3755-4325
Serdar Durak https://orcid.org/0000-0002-8175-9611
Ilyas Ercan Okatan https://orcid.org/0000-0003-2547-0626

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How to cite this article: Fidan S, Capkın E, Arıca DA, Durak S, Okatan IE. Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-α therapy. *Int J Rheum Dis*. 2021;24:254–259. https://doi.org/10.1111/1756-185X.14034

Received: 2 September 2020 | Revised: 3 November 2020 | Accepted: 12 November 2020

DOI: 10.1111/1756-185X.14037

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Association of serum CXCL12 levels with arthropathy in patients with systemic sclerosis

Tetsuya Ikawa | Takuya Miyagawa | Yuki Fukui | Satoshi Toyama | Jun Omatsu | Kentaro Awaji | Yuta Norimatsu | Yusuke Watanabe | Ayumi Yoshizaki | Shinichi Sato | Yoshihide Asano

Department of Dermatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Correspondence
Yoshihide Asano, Department of Dermatology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan.
Email: yasano-tky@umin.ac.jp

Funding information
This work was supported by a grant for Research in Intractable Diseases from the Ministry of Health, Labor, and Welfare of Japan. The funder is not involved in study design, data collection, data analysis, manuscript preparation, and publication decisions.

Abstract

Aim: Systemic sclerosis (SSc) is an autoimmune connective tissue disease, in which extensive fibrotic change and vasculopathy affect the skin and various internal organs. It also involves the joints, causing stiffness, arthralgia, and arthritis. Although arthropathy is commonly observed in SSc, its underlying mechanism remains unknown. CXCL12, also known as stromal cell derived factor 1, is associated with inflammation, mesenchymal cell recruitment, angiogenesis, and collagen production, and is implicated in the development of various joint diseases. To assess the potential contribution of CXCL12 to SSc development, we investigated the clinical association of serum CXCL12 levels in patients with SSc.

Method: We conducted a cross-sectional analysis of 68 patients with SSc and 20 healthy controls recruited in a single center over 9 years. Serum CXCL12 levels were measured by enzyme-linked immunosorbent assay.

Results: Serum CXCL12 levels were significantly higher in patients with SSc than in healthy controls (median 1554.0 pg/mL, 25th-75th centiles 1313.0-1914.0 pg/mL vs 967.4 pg/mL, 608.8-1271.0 pg/mL, $P < 0.001$). Patients with SSc with elevated CXCL12 levels had significantly more cases of arthropathy than those with normal CXCL12 levels (85.7% vs 25.0%, $P = 0.01$). Furthermore, patients with SSc with elevated CXCL12 levels showed an increased trend in the prevalence of limited range of motion of the finger joints compared with those with normal CXCL12 levels (60.0% vs 18.6%, $P = 0.07$). Moreover, serum CXCL12 levels were significantly correlated with the titers of rheumatoid factor in patients with SSc ($r = .41$, $P = 0.001$).

Conclusion: Elevated serum CXCL12 levels may be related to the development of SSc arthropathy.

KEYWORDS

arthropathy, CXCL12, rheumatoid factor, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a multisystem autoimmune disease with unknown etiology, characterized by vasculopathy and fibrosis of the skin and various internal organs.[1,2] In addition to a range of organ involvement, joint involvement is another common complication of SSc, such as joint stiffness, arthralgia, arthritis, joint contracture, and deformity.[3] The underlying mechanisms of SSc-associated joint involvement are not fully understood.

Chemokines are substances originally found as mediators of cell recruitment. Accumulating evidence has demonstrated that chemokines affect many biological processes other than chemotaxis, such as cell growth, embryonic development, autoimmunity, inflammation, and angiogenesis.[4,5] Altered expression profiles of chemokines have been shown in various pathological conditions, including autoimmune diseases, and SSc is no exception. For example, CCL3 and CCL5 contribute to the early stage of SSc by recruiting mononuclear cells and causing related tissue damage.[4] In the later stages of SSc, CCL2, CCL7, CXCL10, and CXCL12 work together in promoting sclerotic changes across multiple organs.[4] In addition, serum levels of CCL18 and CXCL4 serve as useful markers for the activity of interstitial lung disease associated with SSc.[6,7] Hence, chemokines have been proven to be related to SSc pathogenesis.

In this study, we focused on CXCL12 (also known as stromal cell derived factor 1), which belongs to the CXC chemokine group and binds to CXCR4 and possibly to CXCR7.[8] Six splicing variants have been identified in human CXCL12 (CXCL12a to CXCL12f).[8] CXCL12 is constitutively expressed in mesenchymal cells, fibroblasts, bone marrow stromal cells, vascular endothelial cells, and periosteum,[9,10] and is detected at higher levels in the liver, heart, pancreas, spleen, and skin.[11] CXCL12 had been known as a homeostatic chemokine until recently—trafficking hematopoietic and lymphoid progenitor cells, promoting hematopoiesis and B-cell lymphopoiesis, and playing a part in embryogenesis and tissue regeneration via facilitating angiogenesis.[8,12] Numerous studies have now demonstrated the association of CXCL12 with inflammatory and autoimmune diseases through attracting T cells, B cells, monocytes, and mesenchymal stem cells.[8] Also, CXCL12 contributes to extracellular matrix remodeling independent of transforming growth factor-β.[13] The expression of CXCL12 can be enhanced by several factors, most importantly by tissue hypoxia.[8,14,15] Given that tissue hypoxia occurs throughout the body as a result of the impairment of peripheral circulation in SSc,[16] CXCL12 is potentially linked to the pathogenesis of this disease, which is characterized by autoimmune inflammation, vasculopathy, and tissue fibrosis.[2,8]

Based on this background, we examined if serum CXCL12 levels serve as a potential biomarker of disease activity and/or severity in SSc.

2 | METHODS

2.1 | Patients

Serum samples, frozen at −80°C until assayed, were obtained from 68 patients with SSc on their first visit to our hospital (60 women, 8 men; median [25th-75th centiles], age 59 years [46.5-68.0 years]; disease duration 3.0 years [1.0-8.6 years]) and 20 healthy controls (17 women, 3 men; age 52 years [38.3-67.5 years]) after obtaining informed consent and institutional approval (University of Tokyo Graduate School of Medicine). When samples were obtained, nearly half of the patients were already medicated with vasodilators before referral to our facility, but no patients were treated with corticosteroids, other immunosuppressants, or bosentan (Table 1). Patients were grouped by the LeRoy's classification system:[17] 38 diffuse cutaneous SSc (dcSSc) and 30 limited cutaneous SSc (lcSSc). All patients fulfilled the new classification criteria of SSc.[18] The following procedures were conducted in accordance with the Declaration of Helsinki.

2.2 | Clinical assessment

Disease onset was defined as the first clinical event of SSc other than Raynaud's phenomenon. Disease duration was determined as an interval between the disease onset and the time of blood sampling. Skin score was measured by modified Rodnan total skin thickness score (mRSS).[19] Interstitial lung disease was evaluated by pulmonary function test results, such as the percentage of predicted vital capacity (%VC) and the percentage of predicted diffusion lung capacity for carbon monoxide (%DL_{CO}). Esophageal dysfunction was defined as distal esophageal hypomotility on barium-contrast radiography. Heart involvement was defined as symptomatic pericarditis, clinical evidence of left ventricular congestive heart failure, and/or arrhythmias requiring treatment. Elevated right ventricular systolic pressure (RVSP) was defined as 35 mm Hg or more on echocardiogram.[20-23] Arthropathy was clinically assessed, including complaints of joint stiffness or arthralgia, and objectively swollen joints. Limited range of motion was defined as restricted range of motion due to joint contracture or deformity. Thyroid involvement was defined as having Hashimoto thyroiditis. Skeletal muscle involvement was defined as proximal muscle weakness and elevated serum creatine kinase levels, plus abnormal electromyographic findings consistent with myopathy and/or histopathological changes in inflammatory myopathy.

2.3 | Measurement of serum CXCL12 levels

Enzyme-linked immunosorbent assay kit for human CXCL12/SDF-1α (R&D Systems, Minneapolis, MN, USA) was used to measure serum

TABLE 1 Association of CXCL12 levels with demographic features, clinical manifestations, and laboratory data in patients with systemic sclerosis

	Patients with elevated CXCL12 levels (n = 8)	Patients without elevated CXCL12 levels (n = 60)	*P* values
Demographic features			
Sex, male:female	0:8	8:52	0.58
Age, y	62.5 [49.25-72.0] (n = 8)	58.0 [45.25-68.0] (n = 60)	0.55
Disease duration, y	4.0 [1.25-6.50] (n = 8)	3.1 [1.0-1.0] (n = 60)	0.96
dcSSc:lcSSc	4:4 (n = 8)	17:13 (n = 60)	0.72
Clinical findings			
mRSS	8.0 [2.0-13.75] (n = 8)	8.0 [4.25-12.0] (n = 56)	0.86
Raynaud's phenomenon	87.5 (7/8)	91.5 (54/59)	0.55
Nail-fold bleeding	62.5 (5/8)	78.3 (47/60)	0.38
Telangiectasia	40 (2/5)	34 (16/47)	>0.99
Digital ulcers	0 (0/8)	18.3 (11/60)	0.34
Arthropathy	85.7 (6/7)	25.0 (14/56)	0.0090
ROM limitation of joints	60.0 (3/5)	18.6 (11/59)	0.070
Laboratory findings			
RF	28.0 [8.0-41.0] (n = 7)	5.0 [5.0-16.0] (n = 53)	0.020
MMP-3	61.0 [47.0-63.0] (n = 7)	66.0 [50.5-78.5] (n = 29)	0.42
CRP	0.095 [0.025-0.265] (n = 8)	0.095 [0.05-0.24] (n = 60)	0.52
ESRssc	32.5 [9.0-54.75] (n = 8)	21.0 [14.5-47.0] (n = 57)	0.66
%VC	90.45 [70.53-111.8] (n = 8)	93.5 [76.5-102.4] (n = 60)	0.96
$\%DL_{CO}$	80.4 [69.0-87.2] (n = 8)	86.5 [74.65-101.8] (n = 60)	0.29
KL-6	491.5 [346.5-832.0] (n = 8)	427.5 [227-775.5] (n = 60)	0.30
SP-D	147.2 [59.53-219.6] (n = 8)	101.2 [54.55-177.5] (n = 53)	0.39
RVSP	26.5 [17.25-31.25] (n = 8)	28.0 [22.75-34.0] (n = 58)	0.42
Organ involvements			
Esophagus dysfunction	75(6/8)	83.3(50/60)	0.62
Interstitial lung disease	62.5 (5/8)	56.7 (34/60)	>0.99
Decreased $\%DL_{CO}$ (<70%)	37.5 (3/8)	18.3 (11/60)	0.35
Decreased %VC (<80%)	37.5 (3/8)	33.3 (20/60)	>0.99
Elevated RVSP (RVSP ≥35 mm Hg)	12.5 (1/8)	19 (11/58)	>0.99
Heart involvement	0 (0/8)	1.7 (1/60)	>0.99
Scleroderma renal crisis	12.5 (1/8)	0 (0/60)	0.12
Thyroid involvement	37.5 (3/8)	8.6 (5/58)	0.055
Muscle involvement	0 (0/8)	3.3 (2/60)	>0.99
Autoantibodies			
Anti-topoisomerase I	12.5 (3/8)	55 (33/60)	0.46
Anti-centromere	50 (4/8)	36.7 (22/60)	0.47
Anti-RNA polymerase III	0 (0/8)	6.7 (4/60)	>0.99
Medications			
Prostacyclin analog	25 (2/8)	35 (21/60)	0.71
Prostaglandin E_1	25 (2/8)	8.3 (5/60)	0.19
Phosphodiesterase inhibitor	0 (0/8)	6.7 (4/60)	>0.99
Serotonin blocker	12.5 (1/8)	23.3 (14/60)	0.67
Vitamin E	25 (2/8)	26.7 (16/60)	>0.99
Calcium channel blocker	0 (0/8)	5 (3/60)	>0.99

Note: Data are given as median [25th-75th centiles] (number of patients) for each group. For frequent analyses, percentage (number of patients applicable/number of population) are shown.

Abbreviations: mRSS, modified Rodnan total skin thickness score; ROM, range of motion; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; %VC, % vital capacity; $\%DL_{CO}$, % diffusing capacity for carbon monoxide; KL-6, Krebs Von Den Lugen-6; SP-D, pulmonary surfactant protein-D; RVSP, right ventricle systolic pressure.

CXCL12 levels. Briefly, a polystyrene 96-well plate coated with anti-CXCL12 antibody was incubated with sera for 2 hours at room temperature. The wells were washed and incubated at room temperature for 2 hours with horseradish peroxidase-conjugated anti-CXCL12 antibody. After a further wash, the wells were impregnated with tetramethylbenzidine and incubated at room temperature for 30 minutes. Finally, sulfuric acid was added to terminate the reaction. The absorbance was measured at 450 nm. Serum CXCL12 levels were calculated from a standard curve.

2.4 | Statistical analysis

Statistical analysis was performed using Mann-Whitney *U* test to compare two unpaired data with skewed distribution. The comparisons among more than three groups with skewed distribution were conducted with the Kruskal-Wallis test, followed by the Dunn's multiple comparison test. The data with skewed distribution were shown as median with 25th-75th centiles. The Fisher's exact probability test was carried out for frequency analyses. The Spearman's rank correlation coefficient was used for clinical correlations. Statistical significance was defined as a *P* value of <0.05.

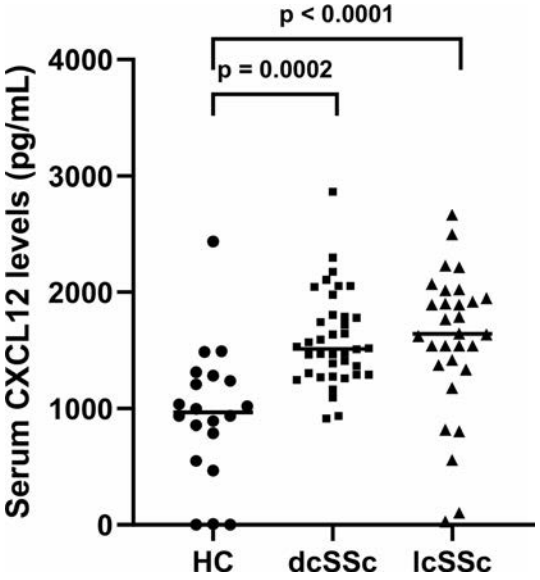

FIGURE 1 Serum CXCL12 levels of patients with systemic sclerosis (SSc) and healthy controls. Serum CCL20 levels were measured by ELISA in diffuse cutaneous SSc (dcSSc) (n = 38), limited cutaneous SSc (lcSSc) (n = 30) and healthy control (HC) participants (n = 20). Horizontal bars represent median of each group. Statistical analysis was conducted with the Kruskal-Wallis test. The Dunn's multiple comparison test was used to compare each group

3 | RESULTS

3.1 | Association of serum CXCL12 levels with clinical and laboratory findings in patients with SSc

Serum CXCL12 levels were significantly higher in patients with SSc than in healthy controls (median [25th-75th centiles]: 1554.0 pg/mL [1313.0-1914.0 pg/mL] versus 967.4 pg/mL [608.8-1271.0 pg/mL], *P* <0 .001). As the expression profiles of disease-associated molecules are often different between dcSSc and lcSSc subtypes, we also evaluated serum CXCL12 levels in the two groups, demonstrating that patients with dcSSc and lcSSc had serum CXCL12 levels significantly elevated compared with healthy controls (1512.6 pg/mL [1290.2-1792.4 pg/mL] for dcSSc, 1641.0 pg/mL [1363.7-1965.0 pg/mL] for lcSSc, *P* <0 .0001 [Kruskal-Wallis test]; *P* = 0.0002 for dcSSc versus healthy controls and *P* <0 .0001 for lcSSc versus healthy controls [Dunn's multiple comparison test]; Figure 1). There was no significant difference in serum CXCL12 levels between dcSSc and lcSSc subtypes. These results suggest a possible contribution of increased CXCL12 expression to the development of SSc.

Demographic characteristics, clinical findings, and laboratory variables were compared between patients with SSc with increased serum CXCL12 levels and those with normal levels (Table 1). Cut-off value was set at 2100.7 pg/mL, which is equal to mean + 2 standard deviations, calculated from serum CXCL12 levels of healthy controls. There was no significant difference in sex, age, disease duration, and ratio of disease subtypes. Values of mRSS and the frequencies of cutaneous vascular complications, such as Raynaud's phenomenon, nailfold bleeding, telangiectasia, and digital ulcers, were comparable between the two groups. The frequency of arthropathy was significantly higher in SSc patients with elevated CXCL12 levels. Relevant to this, titers of rheumatoid factor (RF) were significantly enhanced in SSc patients with elevated CXCL12 levels compared with the other patients. In contrast, matrix metalloproteinase-3 (MMP-3) and C-reactive protein levels, and erythrocyte sedimentation rate were comparable in the two groups. The prevalence of internal organ involvement, such as esophageal dysfunction, interstitial lung disease, elevated RVSP, heart involvement, and scleroderma renal crisis; thyroid and muscle involvement; and the values of %VC, $\%DL_{CO}$, Krebs Von Den Lugen-6, and surfactant protein D did not differ in the two groups. Also, the prevalence of SSc-associated autoantibodies, including antibodies against topoisomerase I, centromere, and RNA polymerase III antigens, was comparable in the two groups.

3.2 | Correlation of serum CXCL12 levels with numeric clinical parameters in patients with SSc

We further examined if serum CXCL12 levels were correlated with numeric clinical parameters in patients with SSc. With respect to mRSS, %VC, $\%DL_{CO}$, Krebs Von Den Lugen-6, surfactant protein-D, and RVSP, we failed to detect any significant correlations (data not shown). On the other hand, serum CXCL12 levels had a positive correlation with RF titers ($r = 0.41$, $P = 0.001$; Figure 2), but

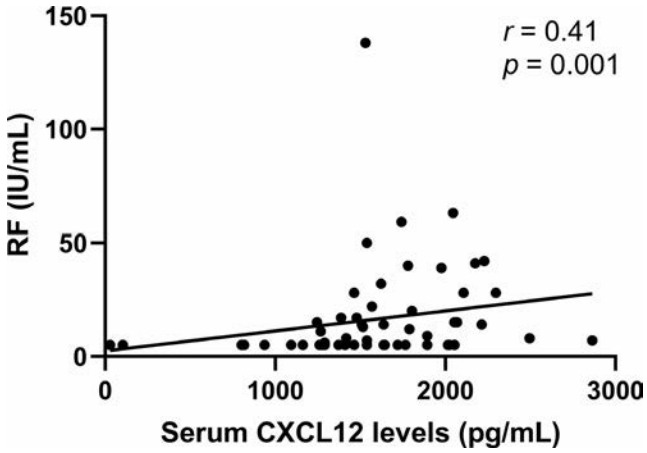

FIGURE 2 The correlation of serum CXCL12 levels with rheumatoid factor (RF) titers in patients with systemic sclerosis (SSc). Serum CXCL12 levels were positively correlated with RF titers in SSc patients. The solid line represents the regression line

other parameters related to arthropathy, including matrix metalloproteinase-3, C-reactive protein, and erythrocyte sedimentation rate, did not correlate with serum CXCL12 levels (data not shown).

4 | DISCUSSION

A major interest in SSc research has been the mechanisms underlying the life-threatening complications, but joint involvement is a common manifestation largely affecting the morbidity of this disease. A meta-analysis by Avouac et al[24] reported that 48%-61% of patients with SSc had joint pain. EULAR Scleroderma Trials and Research registry showed that the prevalence of clinical synovitis and joint contracture was 16% and 31%, respectively.[25] The clinical characteristics of SSc arthropathy are as follows: (a) it is oligoarticular or polyarticular, and acute or insidious,[25] (b) all joints may be affected, but the fingers, wrists, and ankles are predominantly affected,[24] (c) joint effusions are generally less frequent and mild.[26] In radiological studies, SSc arthropathy displays diverse findings, such as low-grade erosive arthritis, bone necrosis, bone marrow edema, joint space narrowing, synovitis, and tenosynovitis,[3,24,27] suggesting that this complication consists of inflammation and ischemia.[3,27] So far, the molecular mechanism underpinning SSc arthropathy remains unknown.

CXCL12 involvement has been reported in many diseases associated with aberrant inflammation and/or dysregulated angiogenesis, such as cancer, inflammatory bowel disease, diabetic retinopathy, and connective tissue diseases.[28-32] Regarding SSc, as far as we know, Dziankowska-Bartkowiak et al[33] reported the only study, but they failed to show any clinical association with serum CXCL12 levels. In the current study, we found a relationship between elevated serum CXCL12 levels and SSc arthropathy, which gives us a new insight into the developmental mechanism of this complication. This result is plausible because CXCL12 has been profoundly implicated in the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA). For example, CXCL12 concentration in synovial fluid is 10 times higher in RA patients and three times higher in OA patients than in healthy controls.[34] Hence, CXCL12 seems to contribute to the development of a broad range of joint disorders.

Rheumatoid arthritis is characterized by the generation of autoantibodies, chronic synovitis, aberrant angiogenesis, and the degradation of cartilage and bone.[8,9] Xu et al[35] showed that synovial levels of CXCL12 were correlated with the severity of RA. On the other hand, Hansen et al[32] reported that plasma CXCL12 levels were independent of disease activity, although elevated in patients with RA. These previous studies suggest the critical role of synovial CXCL12 in joint inflammation related to RA. Indeed, CXCL12 is produced by fibroblast-like synoviocytes in the synovial tissue,[29,30,34,36] suggesting that the leukocyte-trafficking function of CXCL12 facilitates synovitis.[8] In addition, CXCL12 augments the expression of Receptor activator of nuclear factor-κB ligand (RANKL) in $CD4^+$ T cells, leading to joint absorption by promoting the production of MMP-9 and MMP-13 from osteoclasts.[11,36,37] Thus, CXCL12 potentially functions as a critical mediator of RA-associated joint inflammation and absorption. On the other hand, the mechanism underlying the cartilage and bone loss of OA is different from that of RA, as represented by evidence that OA is associated with aging and less inflammatory than RA.[9] In the early phase of experimental OA, CXCL12 seems to activate CXCR4-overexpressing chondrocytes,[38] resulting in the induction of matrix degenerative substances, such as MMP-1, -3, -9, and -13.[34,39-42] In parallel, CXCL12 enhances the proliferation of dysregulated osteoblasts, leading to the formation of osteophytes.[11] Hence, CXCL12 is one of the key molecules involved in the development of a wide range of joint diseases, and several CXCL12-CXCR4 antagonists have been shown to be beneficial in slowing the progression of subchondral bone loss by reducing proteolytic enzymes, such as MMPs, in animal models.[39]

In this study, serum CXCL12 levels were significantly related to joint involvement in SSc. As serum CXCL12 levels were not linked to any other vascular and fibrotic symptoms, the joints are suspected to be the major source of CXCL12 in SSc. Further supporting this notion, serum CXCL12 levels were positively correlated with the titers of RF, which is produced by synovial B cells in response to the local environment in the rheumatoid joint.[43] Given that the association of RF positivity with SSc arthropathy is also reported in a previous study,[44] our current data suggest that CXCL12 is involved in the development of SSc arthropathy, like RA and OA.

With respect to SSc vasculopathy, there is an interesting report regarding the potential role of CXCL12. Manetti et al[45] demonstrated the association of a *CXCL12* gene polymorphism (a G-to-A transition at position 801 in the 39-untranslated region of cDNA encoding CXCL12B [*CXCL12*-G801A]) with the high prevalence of SSc-related vascular complications, such as pulmonary arterial hypertension and digital ulcers. However, the interpretation of this result is complicated because the influence of this polymorphism on CXCL12 expression is obscure. Kimura et al[46] demonstrated the major contribution of other polymorphisms in linkage disequilibrium

with the *CXCL12*-G801A, rather than *CXCL12*-G801A itself, to the altered levels of transcripts. Importantly, the expression of CXCL12 and CXCR4 is enhanced in endothelial cells of early edematous SSc-involved skin compared with those of healthy control skin, but their expressions are progressively decreased in parallel with disease duration irrespective of disease subtype.[47] Hence, the activation of the CXCL12-CXCR4 axis seems to be involved in the development of SSc vasculopathy, especially in its early stages. In our study, serum CXCL12 levels were not linked to vascular complications, but this result does not deny the involvement of CXCL12 in SSc vasculopathy because CXCL12 likely affects the behaviors of endothelial cells by acting on them locally without the elevation of its circulating levels. Our current results indicate that circulating CXCL12 levels reflect joint symptoms, rather than vascular complications, associated with SSc.

A limitation of our study was the lack of data on the association of serum CXCL12 levels with the severity of SSc arthropathy, which is important to assess whether CXCL12 is a central driver of this complication. Further studies are required to clarify this point.

In summary, this is the first report revealing the significant association of serum CXCL12 levels with joint involvement in SSc. Our current results shed new light on the pathogenesis of SSc arthropathy and the ubiquitous role of CXCL12 in various forms of joint involvement.

ACKNOWLEDGMENTS

This work was supported by a grant for Research in Intractable Diseases from the Ministry of Health, Labor, and Welfare of Japan. The funder is not involved in study design, data collection, data analysis, manuscript, preparation, and publication decisions.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

TI, YA, and SS conceived and designed the study, and analyzed and interpreted the data. Acquisition of data was by TI, TM, YF, ST, JO, KA, YN, YW, and AY, and acquisition of funding was by YA and SS. YA, AY, and SS supervised the study. All authors have read and approved the manuscript.

ORCID

Yoshihide Asano https://orcid.org/0000-0001-5560-9778

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How to cite this article: Ikawa T, Miyagawa T, Fukui Y, et al. Association of serum CXCL12 levels with arthropathy in patients with systemic sclerosis. *Int J Rheum Dis*. 2021;24:260–267. https://doi.org/10.1111/1756-185X.14037

Received: 20 August 2020 | Revised: 20 November 2020 | Accepted: 21 November 2020

DOI: 10.1111/1756-185X.14046

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

Risk factors for cancer-associated myositis: A large-scale multicenter cohort study

Yimin Li[1] | Xiaohui Jia[2] | Xiaolin Sun[1] | Lianjie Shi[3] | Fuan Lin[4] | Yuzhou Gan[1] | Xuewu Zhang[1] | Xiaojuan Gao[5] | Miao Miao[1] | Daojun Hong[6] | Yuhui Li[1] | Jing He[1]

[1]Department of Rheumatology and Immunology, Beijing Key Laboratory for Rheumatism and Immune Diagnosis (BZ0135), Peking University People's Hospital, Beijing, China

[2]Department of Rheumatology, The First Hospital of Hebei Medical University, Shijiazhuang, China

[3]Department of Rheumatology, Peking University International Hospital, Beijing, China

[4]Department of Rheumatology, People's Hospital of Jianyang City, Jianyang, China

[5]Department of Rheumatology, Ningde Hospital, Affiliated Hospital of Fujian Medical University, Ningde, China

[6]Department of Neurology, The First Affiliated Hospital of Nanchang University, Nanchang, China

Correspondence
Yuhui Li and Jing He, Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China.
Emails: liyuhui84@163.com; hejing1105@126.com

Abstract

Aim: The aim of this study was to identify the risk factors and prognosis of patients with cancer-associated myositis (CAM).

Method: Four hundred and eighty-seven patients with dermatomyositis (DM), clinical amyopathic dermatomyositis (CADM) and polymyositis (PM) from 3 clinical centers were enrolled retrospectively in this study. Clinical and laboratory data of CAM and non-CAM patients were compared. Logistic regression analysis was used to identify risk factors of CAM.

Results: Out of the 487 patients with DM/CADM/PM, 7.0% (34/487) of patients were classified as CAM. Older age (53.91 ± 13.32 vs. 48.76 ± 14.34 years), heliotrope rash (61.8% vs. 41.9%), shawl sign (41.2% vs. 22.1%), V sign (58.8% vs. 38.6%) were observed significantly more commonly in patients with CAM than those without CAM (all $P < .05$). Fever (17.7% vs. 37.8%), arthralgia/arthritis (23.5% vs. 45.7%), interstitial lung disease (ILD, 38.2% vs 68.9%) were significantly less common in the CAM group than the non-CAM group. Age at onset (odds ratio [OR] 1.036, 95% CI 1.001-1.072, $P = .042$), shawl sign (OR 2.748, 95% CI 1.107-6.822, $P = .029$), anti-transition initiation factor (TIF)-1γ antibody (OR 4.012, 95% CI 1.268-12.687, $P = .018$) were identified as the initial risk factors for the onset of CAM, and ILD was identified as a protective factor for CAM (OR 0.292, 95% CI 0.115-0.739, $P = .009$). All-cause mortality was significantly higher in CAM patients compared with non-CAM patients ($P = .001$).

Conclusion: The mortality of patients with CAM was higher than DM/CADM/PM patients without cancer. Malignancy should be screened in DM/CADM/PM patients especially with risk factors, including older age, shawl sign, anti-TIF-1γ antibody, and lack of ILD.

KEYWORDS

autoantibodies, cancer-associated, interstitial lung disease, myositis, risk factors

Yimin Li and Xiaohui Jia are equal contributions and are designated as co-first authors. Yuhui Li and Jing He are equal contributions as corresponding authors directing this study.

1 | INTRODUCTION

Dermatomyositis (DM), clinical amyopathic dermatomyositis (CADM) and polymyositis (PM) are heterogeneous systemic autoimmune rheumatic disorders characterized by cutaneous manifestations, muscle weakness or extra-muscle manifestations such as interstitial lung disease (ILD) and malignancy. Previous reports have specified an increased incidence of malignancy in patients with PM/DM, especially with DM.[1-3] The prevalence of malignancy has been reported to be 7% ~ 60% in DM and 0% ~ 28% in PM in different studies. Clinical and immunological characteristics such as older age, anti-translation initiation factor (TIF)-1γ, anti-nuclear matrix protein (NXP2), and anti-small ubiquitin-like modifier enzyme (SAE) antibodies have been reported associated with cancer-associated myositis (CAM).[4-7] However, the prevalence and risk factors of CAM have varied widely in different studies due to the rarity of disease.[8-11]

In this study, we compared clinical and immunological features between CAM and non-CAM patients, and identified risk factors of cancer in patients with PM/DM/CADM by analysis of multicenter large-scale cohorts in China.

Key points

- The mortality of patients with CAM was higher than DM/CADM/PM patients without cancer.
- Older age, the presence of shawl sign, and anti-TIF-1γ antibody at diagnosis predict the onset of CAM.
- ILD might be a protective factor for CAM.

2 | MATERIALS AND METHODS

Four hundred and eighty-seven patients with confirmed diagnoses of DM/CADM/PM in 3 academic centers (Department of Rheumatology and Immunology in Peking University People's Hospital, Peking University International Hospital, People's Hospital of Jianyang City) from July 2000 to July 2017 were enrolled in this retrospective study. DM/PM patients were diagnosed according to Bohan and Peter criteria,[12] and CADM according to criteria proposed by Sontheimer.[13] CAM was defined as cancer diagnosed within 3 years before or after the diagnosis of myositis.[14,15] Patients with definite autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis were excluded. The total observation time was defined as the duration from disease diagnosis to the last follow-up: either death or their last visit prior to June 2020. The study was approved by the ethics committee of Peking University People's Hospital.

Clinical and laboratory data were collected from the medical records of patients at the diagnosis of myositis. Clinical data included age at onset, gender, disease duration, fever, dysphagia, arthralgia/arthritis, Raynaud's phenomenon, Gottron's sign/papules, mechanic's hands, heliotrope rash, shawl sign, V-neck sign, skin ulceration, subcutaneous calcinosis, malignancy history and ILD. Laboratory data including serum levels of creatine kinase (CK), lactate dehydrogenase (LDH), alanine transaminase (ALT), ferritin were collected at the initial diagnosis. Myositis-specific autoantibodies (MSAs, antigens including Jo-1, EJ, OJ, PL-7, PL-12, KS, SAE, Mi-2, NXP2, melanoma differentiation-associated 5 [MDA5] and TIF-1γ), and myositis-associated autoantibodies (MAAs, antigens including Ro-52 and PM-Scl) were detected by immunoblotting according to manufacturer's instructions (Euroimmun, Germany).

2.1 | Statistical analysis

All statistical calculations were performed using SPSS 20.0 software for Windows. Categorical variables were expressed as frequency (percentages). Numerical data were reported as the mean ± standard error. Continuous data were compared by Student's *t* test or the Mann-Whitney *U* test. The Fisher exact test or Chi-square test was used for categorical variables. Risk factors of CAM were confirmed by logistic regression analyses based on significant variables in comparison of clinical and laboratory data between CAM and non-CAM groups; subsequently, variables in the univariate analyses (with $P < .05$) were entered into binary logistic regression analysis to identify independent risk factors for CAM. Patient survival was analyzed by Kaplan-Meier curve. $P < .05$ was considered a statistically significant difference.

3 | RESULTS

3.1 | Comparison of clinical and laboratory features of CAM and non-CAM patients

Among 487 cases enrolled, 10.3% (50/487) of patients were diagnosed with cancer, and 7.0% (34/487) of patients were classified as CAM (Table 1). There were 16 patients, including 11 females, and 5 males, who developed malignancy outside the 3 year period in total. Out of 34 patients with CAM, malignancy was diagnosed in 85.3% (29/34) of patients within 1 year as idiopathic inflammatory myositis (IIM) diagnosis. And 5.9% (2/34) and 8.8% (3/34) of patients were diagnosed with malignancy before and after IIM diagnosis, respectively (Figure S1). We divided patients into CAM and non-CAM groups, and compared clinical and laboratory characters of the 2 groups. In CAM, 67.7% (23/34) of patients had DM, 26.5% (9/34) had CADM, 5.9% (2/34) had PM. Age at disease onset of CAM patients was significantly older than non-CAM patients (53.9 ± 13.3 vs. 48.8 ± 14.3 years, $P = .043$). Fever and arthralgia/arthritis were observed less frequently in the CAM group than non-CAM group, with incidence rates of 17.7% vs 37.8% and 23.5% vs 45.7%, respectively (both $P < .05$). Heliotrope rash, shawl sign, V sign were observed significantly more common in CAM patients than in the non-CAM patients, with incidence rates of 61.8% vs 41.9%, 41.2% vs 22.1%, 58.8% vs 38.6%, respectively (all $P < .05$). Elevated ALT was significantly less common in the CAM group than the non-CAM

TABLE 1 Comparison of clinical and laboratory characteristics between patients with CAM and non-CAM

Features at diagnosis of IIM	CAM (n = 34)	Non-CAM (n = 453)	*P*
Diagnosis			
DM, n (%)	23 (67.7)	189 (41.7)	.012
CADM, n (%)	9 (26.5)	199 (43.9)	
PM, n (%)	2 (5.9)	65 (14.4)	
Demographics			
Mean age at onset, y (±SD)	53.9 (±13.3)	48.8 (±14.3)	.043
Female, n (%)	24 (70.6)	346 (76.4)	.446
Duration from onset to diagnosis, mo (±SD)	51.2 (±61.9)	60.0 (±65.3)	.251
Clinical characteristics			
Fever, n (%)	6 (17.7)	171 (37.8)	.019
Dysphagia, n (%)	3 (8.8)	15 (3.3)	.241
Arthralgia/arthritis, n (%)	8 (23.5)	207 (45.7)	.012
Raynaud's phenomenon, n (%)	0 (0)	20 (4.42)	.385
Myalgia, n (%)	7 (20.6)	68 (15.0)	.385
Heliotrope rash, n (%)	21 (61.8)	190 (41.9)	.024
Shawl sign, n (%)	14 (41.2)	100 (22.1)	.011
V sign, n (%)	20 (58.8)	175 (38.6)	.020
Gottron's sign/ papules, n (%)	23 (67.7)	285 (62.9)	.581
Mechanic's hands, n (%)	7 (20.6)	131 (28.9)	.299
Periungual telangiectasia, n (%)	8 (23.5)	67 (14.8)	.173
Skin ulceration, n (%)	2 (5.9)	23 (5.1)	1.000
Subcutaneous calcinosis, n (%)	0 (0)	8 (1.8)	1.000
Laboratory characteristics, mean (± SD)			
Elevated ALT, n (%)	8 (23.5)	202 (44.6)	.017
CK, U/L	811.1 ± 1627.2	847.4 ± 1611.3	.822
LDH, U/L	435.9 ± 307.3	404.6 ± 332.7	.618
Elevated ferritin, n (%)[a]	1 (14.3)	50 (51.0)	.137
ESR, mm/1 h	28.8 ± 22.3	30.1 ± 25.2	.780
CRP, mg/L	12.5 ± 20.2	15.7 ± 28.8	.560
ILD, n (%)	13 (38.2)	312 (68.9)	<.001

Abbreviations: ALT, alanine transaminase; CADM, clinical amyopathic dermatomyositis; CAM, cancer-associated myositis; CK, creatine kinase; CRP, C-reactive protein; DM, dermatomyositis; PM, polymyositis; ESR, erythrocyte sedimentation rate; IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; LDH, lactate dehydrogenase.

[a]Seven cases of 34, 27 values missing in CAM group, 98 cases of 453, 355 values missing in non-CAM group.

group (23.5% vs 44.6%, $P = .017$). Furthermore, ILD was found significantly less commonly in patients with CAM than those with non-CAM (38.2% vs 68.9%, $P < .001$). Malignancy types are showed in Table 2. The most common types of malignancy in female patients were ovarian cancer (20.8%, 5/24), followed by breast cancer (16.7%, 4/24) and colon cancer (12.5%, 3/24). The most common types of malignancy in male patients was lung cancer (30.0%, 3/10), followed by nasopharyngeal carcinoma (20%, 2/10).

3.2 | Immunological characteristics in patients with CAM

Out of 487 cases included in this study, MSAs were available for 300 patients, including 24 patients with CAM and 276 patients with non-CAM. We compared the prevalence of MSAs and MAAs between CAM and non-CAM groups (Table 3). The prevalence of anti-TIF-1γ antibody was significantly higher in patients with CAM than in the non-CAM group (29.2% vs 5.1%, $P = .000$). No significant differences were found between the CAM and non-CAM groups for the prevalence of anti-aminoacyl-tRNA synthetase, anti-MDA5, anti-NXP2, anti-SAE, or other MAAs.

3.3 | Risk factors for malignancy in patients with CAM

We identified the independent risk factors for malignancy in patients with CAM by binary logistic regression analysis (Table 4). Significantly

TABLE 2 Malignancy types in patients with CAM

Malignancy types	Total (n = 34)	Female (n = 24)	Male (n = 10)
Ovarian cancer, n (%)	5 (14.7)	5 (20.8)	0 (0)
Cervical carcinoma, n (%)	1 (2.9)	1 (4.2)	0 (0)
Esophageal cancer, n (%)	2 (5.9)	1 (4.2)	1 (10.0)
Pancreatic cancer, n (%)	1 (2.9)	0 (0)	1 (10.0)
Colon cancer, n (%)	3 (8.8)	3 (12.5)	0 (0)
Gastric cancer, n (%)	2 (5.9)	1 (4.2)	1 (10.0)
Malignant thymoma, n (%)	3 (8.8)	2 (8.3)	1 (10.0)
Lung cancer, n (%)	4 (11.8)	1 (4.2)	3 (30.0)
Nasopharyngeal carcinoma, n (%)	4 (11.8)	2 (8.3)	2 (20.0)
Thyroid carcinoma, n (%)	1 (2.9)	1 (4.2)	0 (0)
Breast cancer, n (%)	4 (11.8)	4 (16.7)	0 (0)
Hematologic malignancies, n (%)	1 (2.9)	0 (0)	1 (10.0)
Spinal schwannoma, n (%)	1 (2.9)	1 (4.2)	0 (0)
Ureter carcinoma, n (%)	1 (2.9)	1 (4.2)	0 (0)
Retroperitoneal tumor, n (%)	1 (2.9)	1 (4.2)	0 (0)

Abbreviations: CAM, cancer-associated myositis.

TABLE 3 Comparison of MSAs/MAAs between patients with CAM and non-CAM

Autoantibodies	CAM (n = 34)	Non-CAM (n = 453)	*P*
Anti-ARS, n (%)	7/24 (29.2)	104/276 (37.7)	.407
Anti-TIF-1γ, n (%)	7/24 (29.2)	14/276 (5.1)	<.001
Anti-MDA5, n (%)	2/24 (8.3)	56/276 (20.3)	.249
Anti-NXP2, n (%)	1/24 (4.2)	16/276 (5.8)	1.000
Anti-SAE, n (%)	1/24 (4.2)	8/276 (2.9)	1.000
Anti-Mi2, n (%)	3/24 (12.5)	13/276 (4.7)	.248
Anti-Ro-52, n (%)	10/24 (41.7)	140/276 (50.7)	.395
Anti-PM/Scl75/100, n (%)	0/24 (0)	22/276 (8.0)	.149
ANA, n (%)	22/30 (73.3)	311/428 (72.7)	.937
RF, n (%)	3/29 (10.3)	89/387 (23.0)	.177

Abbreviations: ANA, anti-nuclear antibody; ARS, aminoacyl-tRNA synthetase, include Jo-1, EJ, OJ, PL-7, PL-12, KS; TIF-1γ, translation initiation factor-1γ; CAM, cancer-associated myositis; MAAs, myositis-associated autoantibodies; MDA5, melanoma differentiation-associated 5; MSAs, myositis-specific autoantibodies; NXP2, nuclear matrix protein 2; PM/Scl, polymyositis/scleroderma; RF, rheumatoid factor; SAE, small ubiquitin-like modifier enzyme.

TABLE 4 Multivariate analysis of risk factors associated with CAM

	Odds ratio	95% CI	*P*
Univariate			
Age at onset	1.027	1.001-1.053	.044
Subtypes of IIM			
DM	Reference		
CADM	0.372	0.168-0.824	.015
PM	0.253	0.058-1.102	.067
Fever	0.353	0.143-0.871	.024
Arthralgia/arthritis	0.366	0.162-0.825	.015
Heliotrope rash	2.236	1.092-4.577	.028
Shawl sign	2.471	1.205-5.067	.014
V sign	2.269	1.117-4.610	.023
ILD	0.28	0.136-0.575	.001
Anti-TIF-1γ	7.706	2.747-21.615	<.001
Multivariate			
Age at onset	1.036	1.001-1.072	.042
Shawl sign	2.748	1.107-6.822	.029
ILD	0.292	0.115-0.739	.009
Anti-TIF-1γ	4.012	1.268-12.687	.018

Abbreviations: CAM, cancer-associated myositis; CI, confidence intervals; ILD, interstitial lung disease; TIF-1γ, translation initiation factor-1γ; CADM, clinical amyopathic dermatomyositis; CAM, cancer-associated myositis; DM, dermatomyositis; PM, polymyositis; IIM, idiopathic inflammatory myositis.

different initial clinical and immunological factors were used in univariate analysis, including age at onset, subtypes of myositis, fever, arthralgia/arthritis, shawl sign, ILD and anti-TIF-1γ antibody. Subsequently, 3 variables were identified as independent risk factors of CAM in the multivariate model, including age at onset (odds ratio [OR] 1.036, 95% CI 1.001-1.072, *P* = .042), shawl sign (OR 2.748, 95% CI 1.107-6.822, *P* = .029), anti-TIF-1γ antibody (OR 4.012, 95% CI 1.268-12.687, *P* = .018), while ILD was identified as a protective factor for CAM (OR 0.292, 95% CI 0.115-0.739, *P* = .009).

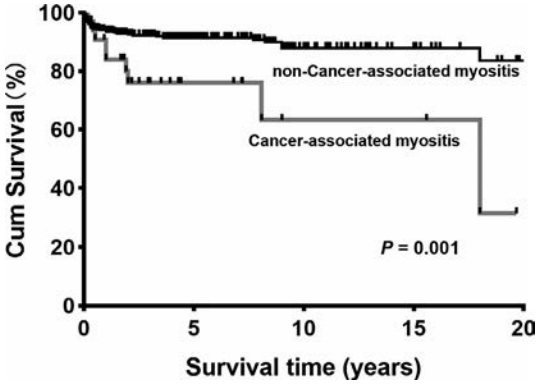

FIGURE 1 Survival rates for all-cause mortality in CAM and non-CAM patients. CAM, cancer-associated myositis

3.4 | Survival analyses for all-cause mortality in CAM patients

The initial treatment regimes of patients with CAM and non-CAM are compared in Table S1. Glucocorticoid pulse was used more commonly in patients with non-CAM compared with patients with CAM (*P* = .028). Cyclosporine (15.7% vs 2.9%, *P* = .044), cyclophosphamide (39.7% vs 20.6%, *P* = .027) were used more commonly in the non-CAM group compared with CAM group. The survival rates of CAM patients were 84.0% at 1 year and 76.0% at 5 years after the onset of the disease, while the survival rates of non-CAM group were 93.6% at 1 year and 91.5% at 5 years. All-cause mortality was significantly higher in CAM patients compared with non-CAM patients (*P* = .001) (Figure 1). In terms of the cause of mortality, the principal cause of death in CAM was malignancy (88.9%, 8/9), followed by respiratory failure due to rapidly progressive ILD (11.1%, 1/9) (Table 5). In contrast, out of 40 fatalities in non-CAM, 55% (22/40) of patients died from respiratory failure, and 37.5% (15/40) died from infection.

4 | DISCUSSION

The association between myositis and an increased risk of malignancy has been established by previous research.[3,9] This retrospective study represents multicenter large data sets from the perspective of a multicenter inpatient rheumatology setting in China.

The incidence of malignancy in patients with myositis varied with the duration of myositis. In our study, 68% (34/50) of malignancy was detected within 3 years before or after the diagnosis

TABLE 5 Cause of death in patients with CAM and non-CAM

Variables	CAM (n = 34)	non-CAM (n = 453)	*P*
Non-survived, n (%)	9 (26.5)	40 (8.8)	.004
Cause of death			
Respiratory failure, n (%)	1 (11.1)	22 (55.0)	.026
Malignancy, n (%)	8 (88.9)	0 (0.0)	<.001
Infection, n (%)	0 (0.0)	15 (37.5)	.042
CMV, n (%)	0 (0.0)	3 (7.5)	1.000
Bacterial, n (%)	0 (0.0)	5 (12.5)	.569
Bacterial + *Aspergillus*, n (%)	0 (0.0)	2 (5.0)	1.000
Bacterial + CMV, n (%)	0 (0.0)	2 (5.0)	1.000
Bacterial + CMV+*Aspergillus*, n (%)	0 (0.0)	3 (7.5)	1.000
Others	0 (0.0)	3 (7.5)	1.000

Abbreviations: CAM, cancer-associated myositis; CMV, cytomegalovirus.

of IIM, and 58% (29/50) of cancer was observed within 1 year within the diagnosis of myositis. The clustering of malignancy cases in myositis suggests that myositis might be of paraneoplastic origin.

In the present study, we have demonstrated that the prevalence of CAM in patients with PM/DM/CADM was 7.0%, which was consistent with the prevalence of 7%-32% reported in previous studies.[16] In terms of phenotypes of myositis, the risk of CAM is the greatest for DM, followed by CADM and PM.

Elevated ALT was observed less likely in CAM groups in our study. Elevation of liver enzymes including ALT, aspartate aminotransferase, CK, lactic dehydrogenase can be attributed to muscle inflammation, it might also be attributed to liver injury. The results indicated that liver might be involved in non-CAM.

Our study confirmed some initial risk factors associated with CAM reported in previous studies,[17-19] including age at onset, lack of arthralgia/arthritis and ILD, anti-TIF-1γ antibody. Most studies[17,18] reported that patients developed malignancy with an average age older than 45 years, while a large cohort study enrolled 705 patients from Scotland reported that the risk of malignancy was highest in PM patients aged 15-44 years.[19] Our study identified that age at onset provided a high OR, with a 1.036-fold increase in risk. In addition, the presence of ILD has been reported as a protective factor for malignancy in previous studies,[3,20] and this study also identified this as also relevant to patients with CAM. Anti-TIF-1γ antibody was first reported as an autoantibody directed against a 155-kDa protein in 2006.[21] It has been reported that anti-TIF-1γ was one of the cancer-associated antibodies, and the rate of TIF-1γ-associated cancer ranged from 60% to 80% in IIM patients.[22,23] Best et al. reported that the pooled prevalence of CAM in patients with anti-TIF-1γ antibody was 41% by meta-analysis,[24] while our study showed the prevalence of CAM in patients with anti-TIF-1γ antibody was 33.3% (7/21), which was lower compared to previous studies. However, Yang et al.[4] reported 38.2% of patients with anti-TIF-1γ antibody diagnosed with cancer in 3 years in China. The inclusion of patients from a single center and a relatively small sample of patients with malignancy may lead to the bias.

Severe cutaneous manifestations are frequently observed in patients with CAM, especially observed in patients with anti-TIF-1γ antibody.[21] Okiyama et al. showed that interface dermatitis was observed in more than half of the skin specimens in patients with anti-TIF-1γ antibody, and vascular injury could also be observed in 44% of anti-TIF-1γ groups.[25] András et al. showed that V sign and Gottron's papules were observed more commonly in patients with CAM.[26] Kaneko et al. reported that more patients with CAM had shawl sign than those without CAM (27% vs 19%, $P = .62$) [27]; Liu et al. showed that shawl sign was more common in myositis patients with malignancy compared with patients without malignancy (44.19% vs 30.61%, $P = .109$) [28]; however, the difference was not statistically significant in these studies. In comparison, we found that shawl sign was an independent risk factor for CAM. Therefore, patients with these clinical features should receive intensive malignancy screening.

In our study, the mortality rate of CAM patients was 26.5%, which is significantly higher than non-CAM patients (8.8%). This result was consistent with previous studies.[11,17,20] The main cause of death for CAM patients in this study was malignancy, so it may be reasonable to suggest that patients with initial risk factors be screened for malignancy in clinical practice.

There are several limitations in our study. First, in this retrospective study, a patient selection bias cannot be avoided due to all data being collected from inpatient medical records in referral hospitals. Second, 38.4% of patients had not received the testing of MSAs/MAAs which may lead to statistical bias of the study. Third, anti-signal repetition particle and anti-3-hydroxy-3-mathylglutaryl-CoA reductase antibodies were missing which lead to the incomplete classification of myositis in our study.

In conclusion, the mortality of patients with CAM was higher than patients without CAM. Malignancy should be screened in myositis patients especially with risk factors, including older age, shawl sign, anti-TIF-1γ antibody, and lack of ILD. These results also indicated potential differences in pathogenesis and therapeutic strategies between patients with and without CAM.

ACKNOWLEDGEMENTS

S.X. and L.Y. conceived and designed the study. J.X., L.Y., S.L., L.F., G.X, Z.X. and G.Y. collected the data. J.X. and L.Y. analyzed the data. L.Y. and M.M. wrote the paper. H.J. and L.Y. designed the study and revised the manuscript.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

ORCID

Yimin Li https://orcid.org/0000-0002-0134-218X
Lianjie Shi https://orcid.org/0000-0001-8882-8870

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SUPPORTING INFORMATION

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

How to cite this article: Li Y, Jia X, Sun X, et al. Risk factors for cancer-associated myositis: A large-scale multicenter cohort study. *Int J Rheum Dis*. 2021;24:268–273. https://doi.org/10.1111/1756-185X.14046

Received: 24 October 2020 | Revised: 4 December 2020 | Accepted: 4 December 2020

DOI: 10.1111/1756-185X.14047

EXPERT COMMENTS

International Journal of Rheumatic Diseases

WILEY

Recent advances in pediatric rheumatology: July to September 2020

Sathish Kumar Loganathan | **Sanjib Mondal** | **Surjit Singh**

Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence: Surjit Singh, Department of Pediatrics, Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.
Email: surjitsinghpgi@rediffmail.com

1 | UVEITIS IN JUVENILE IDIOPATHIC ARTHRITIS: 18-YEAR OUTCOME IN THE POPULATION-BASED NORDIC COHORT STUDY

Veronika Rypdal, MD, Mia Glerup, MD, PhD, Nils Thomas Songstad, MD, PhD, Geir Bertelsen, MD, PhD, Terje Christoffersen, MD, Ellen D. Arnstad, MD et al. *Ophthalmology*. 2020 Aug 28; S0161-6420(20)30842-3. https://doi.org/10.1016/j.ophtha.2020.08.024

Rypdal et al. conducted a multicenter, prospective, cross-sectional study to assess long-term outcome in juvenile idiopathic arthritis-associated uveitis (JIA-U), 18 years after onset of JIA. Of 434 enrolled patients from 4 Nordic countries, 96 patients (22.1%) had uveitis. Of these, the majority (n = 89) developed uveitis during the first 8 years of follow-up while 12 developed uveitis between 8-18 years. Uveitis was diagnosed at median age of 5.8 years, and median interval between diagnosis of JIA to onset of uveitis was 1.8 years. Development of uveitis was noted in 14/45 patients with enthesitis-related arthritis, 21/71 with rheumatoid factor (RF)-negative polyarthritis, 8/28 with psoriatic arthritis and 21/119 with persistent oligoarthritis. It is noteworthy that uveitis was not documented in any patient with systemic JIA or RF-positive polyarthritis. Authors found that human leukocyte antigen (HLA)-B27 positivity was more common in patients with uveitis. Bilateral anterior uveitis was more common than unilateral uveitis. Only 8 patients required biologicals by end of the first year. Twenty-one required biologicals, in 8 years from the onset of JIA. Common complications noted in this cohort included cataract and glaucoma. Over 18 years of follow-up period, 76/96 required systemic disease-modifying antirheumatic drugs (DMARDs) and 52/96 received biologicals. Risk factors for ocular complications were short interval between JIA onset and diagnosis of uveitis, and anti-nuclear antibody positivity (odds ratio [OR] 3.0; 95% CI 1.2-7.7). This is a landmark study that provides long-term follow-up data on JIA-U.

2 | PREFILLED PEN VERSUS PREFILLED SYRINGE: A PILOT STUDY EVALUATING TWO DIFFERENT METHODS OF METHOTREXATE SUBCUTANEOUS INJECTION IN PATIENTS WITH JIA

Justyna Roszkiewicz, Zbigniew Swacha and Elżbieta Smolewska. *Pediatr Rheumatol Online J*. 2020 Aug 12; 18 (1): 64. https://doi.org/10.1186/s12969-020-004554

Roszkiewicz et al. conducted a single-center pilot study on 2 subcutaneous methotrexate delivery systems and compared prefilled syringe with prefilled pen. Parameters that were analyzed included therapy-related side effects, pain at injection site, and ease of use. Twenty-three patients (17 girls; 6 boys) with JIA receiving methotrexate by prefilled syringe were enrolled in this study. Study population comprised of 23 patients. While 12 had oligoarticular JIA, 6 had polyarticular JIA, 4 had enthesitis-related arthritis and 1 had systemic JIA. Mean treatment duration of methotrexate prior to enrollment was 18 months. Before enrollment, patients had been taking methotrexate through a prefilled syringe. They were asked to complete a questionnaire. The patients were then administered methotrexate through prefilled pen and were again asked to fill the questionnaire. Dose of injected methotrexate ranged 10-20 mg. In this cohort 19/23 patients and 82.6% of caregivers were more satisfied with prefilled pen compared to prefilled syringe. After using prefilled pen confidence levels were increased, stress level was less and it was found to be more user friendly. Level of pain and side effects were significantly lower with prefilled pen. This is a small,

albeit important, study on preferred mode of administration of methotrexate

3 | RECURRENT SYNOVITIS OF HIP AND MEFV GENE RELATED ARTHRITIS IN CHILDREN

Salehzadeh F and Mirzarahimi M. *Pediatr Rheumatol*. 2020; 18: 63. https://doi.org/10.1186/s12969-020-00456-3

Recurrent synovitis of hip (RSH) is an uncommon clinical entity in children. It is not clear if idiopathic RSH and recurrent arthritis seen in context of familial Mediterranean fever (FMF) have a clinical overlap. This is especially important in regions where FMF is common as *MEFV* variants have been linked to several rheumatic diseases. Salehzadeh and Mirzarahimi conducted a single-center retrospective study on 195 children with chronic oligoarticular JIA and selected 3 patients with RSH who had at least 3 attacks per year. All 3 had no clinical phenotype suggestive of FMF (Tel-Hashomer criteria). These patients were screened for 12 common *MEFV* pathogenic variants that are usually found with FMF. Results showed that all 3 children had a single variant in *MEFV* (A744S, V726A and R761H). This study suggests that RSH may be a *MEFV*-related arthritis but is clinically distinct from FMF. This is a novel finding. However, it is not clear whether these affected children would go on to develop FMF later in life.

4 | UTILITY OF THE EULAR SJÖGREN SYNDROME DISEASE ACTIVITY INDEX IN JAPANESE CHILDREN: A RETROSPECTIVE MULTICENTER COHORT STUDY

Naomi Iwata, Minako Tomiita, Ichiro Kobayashi, Yusaburo Inoue, Yukiko Nonaka, Nami Okamoto et al. *Pediatr Rheumatol Online*. 2020 Sep 17; 18 (1): 73. https://doi.org/10.1186/s12969-020-00458-1

Iwata et al. conducted this multicenter retrospective study to assess the usefulness of European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) in Japanese children with primary Sjögren's syndrome (pSS). The authors enrolled 31 patients (3 boys; 28 girls) in this cohort. Median age of diagnosis was 10 years. Overall median ESSDAI at first visit was 7.0 (interquartile range [IQR]: 5.0-15.0). Nine patients had high disease activity (>14), 15 patients had medium activity index (5-13), and 7 patients had a low disease activity index (<4). After first visit, 14 patients (45.2%) were treated with glucocorticoids (4 high dose; 8 medium dose; and 2 low dose) and 19.4% received various other immunosuppressants (eg, methotrexate, mycophenolate mofetil and tacrolimus). Median ESSDAI was found to be higher in patients given high/medium doses of prednisolone when compared with patients receiving no/low dose prednisolone (16.5 [IQR 10.5-18.0] vs 5.0 [IQR 3.0-8.5]). ESSDAI score showed no difference between presence/absence of sicca symptoms. This study shows that the ESSDAI score is a robust assessment tool and is useful even in Japanese children.

5 | NORMAL HIP JOINT FLUID VOLUMES IN HEALTHY CHILDREN OF DIFFERENT AGES, BASED ON MRI VOLUMETRIC QUANTITATIVE MEASUREMENT

Vanessa Quinn-Laurin, Bashiar Thejeel, Nancy A. Chauvin, Timothy G. Brandon et al. *Pediatr Radiol*. https://doi.org/10.1007/s00247-020-04744-8

Laurin et al. conducted a single-center study to evaluate synovial fluid volumes in normal hip joints of healthy children in different age groups by magnetic resonance imaging (MRI) volumetric quantitative measurement. All individuals in this cohort underwent MRI of pelvis and sacroiliac joints with fat-saturated T_2-weighted turbo spin echo imaging. Seventy healthy volunteers were enrolled. Male : female ratio was 1:1. Majority were Afro-American with mean age 12.8 years. Results showed that mean fluid volume in normal hip joints was 2.1 mL (0.38-5.41 mL). Mean volume was higher in males compared to females (average 2.25 ± 0.96; 1.86 ± 0.56 mL, $P = .004$). Femoral head diameter was also larger in males compared to females (4.19 ± 0.39; 3.82 ± 0.27 cm, $P < .0001$). This study gives normative values for hip joint fluid volume in a pediatric age group. There is paucity of such data in children.

6 | WHOLE-BODY MRI QUANTIFICATION FOR ASSESSMENT OF BONE LESIONS IN CNO PATIENTS TREATED WITH PAMIDRONATE: A PREVALENCE, REPRODUCIBILITY, AND RESPONSIVENESS STUDY

Jyoti Panwar, Mirkamal Tolend, Lillian Lim, Shirley M. Tse, Andrea S. Doria, Ronald M. Laxer et al. *J Rheumatol*. 2020 Sep 15; jrheum.200329. https://doi.org/10.3899/jrheum.200329

Imaging a child with chronic non-bacterial osteomyelitis (CNO) for diagnosis and monitoring of therapy has been always contentious. Jyoti et al. conducted a single-center, retrospective study of whole-body MRI quantification to assess the inter-observer variation in assessment of inflammatory bone lesions in patients with CNO and to evaluate responsiveness of MRI-detected CNO lesions after pamidronate therapy. In this cohort, 32 patients were included and 387 bone lesions were detected on whole-body MRI short-T_1 inversion recovery imaging before initiating pamidronate. Lower limbs were more commonly involved than upper limbs. Usual sites were distal tibial meta-epiphysis (60%); proximal tibial meta-epiphysis and distal femur meta-epiphysis (50%); and distal fibular meta-epiphysis (31%). Commonest bony lesions that were seen in this cohort were high signal intensity within surrounding soft tissue seen adjacent to tubular bones of lower limbs, bony expansion typically seen in clavicle and mandible and collapsed

bone seen commonly in thoracic spine vertebrae. Authors reported excellent inter-reader agreement in detecting bone marrow lesions in all body regions and quantifying size and signal intensity of bone lesions in arms and legs. Post-pamidronate imaging assessment showed good responsiveness in spine, skull and thorax. While 34% of lesions showed resolution after first dose of pamidronate, 76% had resolved after second dose. However, 7.5% of lesions showed worsening after first dose of pamidronate but the majority of these showed resolution after the second dose. This is a very useful clinical study which may help pediatric rheumatologists in assessment of patients with CNO.

7 | HIGH PREVALENCE OF RARE FBLIM1 GENE VARIANTS IN AN ITALIAN COHORT OF PATIENTS WITH CHRONIC NON-BACTERIAL OSTEOMYELITIS (CNO)

Pio d'Adamo A, Bianco AM, Ferrara G, Bianca ML, Insalaco A, Tommasini A et al. Pediatr Rheumatol. 2020;18: 55. http://doi.org/10.1186/s12969-020-00447-4

CNO is a rare autoinflammatory disorder. Although its precise etiology is not known, it is presumed to have a genetic basis. Pio d'Adamo et al. conducted a multicentric observational study on 80 patients with CNO, diagnosed on the basis of Jansson criteria and evaluated frequency of *FBLIM1* variants by Sanger sequencing. The authors showed that 22.5% (18/80) had at least 1 pathogenic variant of the gene. Of these, 15 showed 1 variant, 2 had 2 variants and 1 showed 5 variants. Furthermore, novel pathogenic variants were noted in 8 patients. However, no significant difference was found in terms of clinical symptoms and outcome between children with *FBLIM1* variants and without variants. This study suggests that children with *FBLIM1* variants are susceptible to developing CNO. This is an important advancement in a subject that is still poorly understood.

8 | SAFETY AND EFFICACY OF INTRAVENOUS BELIMUMAB IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM A RANDOMISED, PLACEBO-CONTROLLED TRIAL

Brunner HI, Abud-Mendoza C, Viola D, Penades IC, Levy D, Anton J et al. *Ann Rheum Dis*. 2020; 0: 1–9. https://doi.org/10.1136/annrheumdis-2020-217101

Childhood-onset systemic lupus erythematosus (cSLE) is an autoimmune disease that may lead to significant minor and major organ damage over time. Several newer drugs are undergoing trials either as initial therapy or as add-on therapy in cSLE. Brunner et al. conducted a phase-2, randomized, double-blind, placebo-controlled trial with intravenous belimumab in 53 children with cSLE. In this study the authors compared its efficacy, disease response and safety with those patient with cSLE (n = 40) who were on placebo. At start of the trial, all children included in the cohort were on standard therapy. Children with neurolupus, severe acute lupus nephritis, on high doses of prednisolone (>1.5 mg/kg/d) or those having received rituximab in the past were excluded. Authors showed that SLE responder index (52.8% vs 43.6%, OR 1.49), Pediatric Rheumatology International Trials Organization (PRINTO) - American College of Rheumatology (ACR) 30 (52.8% vs 27.5%, OR 2.92), PRINTO-ACR 50 (60.4% vs 35%, OR 2.74) and parent global response scores (59.1% vs 33.3%, OR 2.74) were much better with belimumab than the placebo group. Adverse effects with belimumab were fewer (17% vs 35%) in comparison to placebo. This study is likely to significantly impact treatment protocols for childhood lupus in the years to come.

9 | CLINICAL FEATURES, DISEASE ACTIVITY AND OUTCOMES OF MALAYSIAN CHILDREN WITH PAEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS: A COHORT FROM A TERTIARY CENTRE

Lim SC, Ling Chan EW and Tang SP. *Lupus*. 2020; 0 (0): 1–9. https://doi.org/10.1177/0961203320939185

Ethnicity and genetic background play a crucial role in diverse clinical manifestations and outcome in patients with SLE. Lim et al. conducted this retrospective single-center study on 141 Malaysian children of different ethnicities: Malay (n = 87; 61.7%); Chinese (n = 40; 28.4%) and Indian (n = 5; 3.5%) and others with pSLE diagnosed on the basis of Systemic Lupus International Collaborating Clinics 2012 criteria. Authors analyzed clinical manifestations, disease activity and final outcome of all children in the cohort. Results revealed that most children in this cohort were female (87.9% vs 12.1%, M:F = 7.3:1) and had early age of disease onset (median 10.8 years). It was also found that the majority (99.3%) had high disease activity at diagnosis. However, the majority (62.4%) achieved remission within 6 months. Among all major organs involved in these children, renal involvement was the commonest (45.4%). More than half of these (53.1%) had sustained renal remission, and end stage renal disease was noted in only 3.1%. Authors have used a regimen of 12 months pulse cyclophosphamide therapy in patients with proliferative lupus nephritis. Cerebral lupus (17%) and ocular damage (29%) were more frequent in this cohort from Malaysia as compared to previously published studies from other regions. Aggressive use of systemic steroids was probably responsible for high frequency of ocular damage as well as for growth retardation (38.2%). Mortality was only 1.4% during 6 months of follow-up. We need more data on pediatric lupus from developing countries. This study by Lim et al. is a step in the right direction.

10 | NEUROLOGICAL INVOLVEMENT IN KAWASAKI DISEASE: A RETROSPECTIVE STUDY

Liu X, Zhou K, Hua Y, Wu M, Liu L, Shao S et al. *Pediatr Rheumatol*. 2020; 18: 61. https://doi.org/10.1186/s12969-020-00452-7

Neurological involvement in Kawasaki disease (KD) is uncommon, albeit well documented in the literature. In this single-center retrospective study, Lin et al. reviewed 1582 children with KD (diagnosed by 2 experts based on American Heart Association 2004 criteria). Of these, 80 (5.1%) had neurological symptoms. These included extreme irritability (21/80, 26.3%), somnolence (40/80, 50%), meningeal irritation (15/80, 18.8%), convulsions (14/80, 17.5%), headache (13/80, 16.3%), bulged fontanelle (7/80, 8.8%) and facial nerve palsy (1/80, 1.3%). The authors compared clinical profiles of such children with gender and admission date matched children with KD (n = 512) who had no neurological symptoms. Inflammatory markers were higher in a subset of children with neurological involvement. It was also found that KD shock syndrome ($P < .001$), intravenous immunoglobulin resistance ($P = .003$) and requirement for steroids ($P = .016$) were significantly higher in children with KD having neurological involvement. However, no significant correlation was noted between development of coronary artery lesions and neurological involvement. This study provides an important clinical perspective for children with KD who have a neurological presentation.

11 | WHAT DOSE OF ASPIRIN SHOULD BE USED IN THE INITIAL TREATMENT OF KAWASAKI DISEASE? A META-ANALYSIS

Jia X, Du X, Bie S, Li X, Bao Y and Jiang M. Rheumatology. 2020; 0: 1–8. https://doi.org/10.1093/rheumatology/keaa050

High-dose intravenous immunoglobulin (IVIg) has been found to be effective in significant reduction of coronary artery lesions (CALs) in KD. Aspirin is used along with IVIg for its synergistic antipyretic and anti-inflammatory effects. Jia et al. conducted a meta-analysis from 8 retrospective studies (Newcastle-Ottawa scale > 6) with 12 176 KD patients and compared outcome between patients who received low-dose aspirin (n = 2497, <10 mg/kg/d) and those who received high doses of aspirin (n = 9679, 5 studies used >80 mg/kg/d and 3 studies used >30 mg/kg/d). Authors showed no significant difference for development of CALs ($P = .19$), IVIg resistance ($P = .59$) and duration of hospital stay ($P = .71$) with different doses of aspirin. However, resolution of fever was significantly ($P = .04$) faster with higher doses of aspirin. Furthermore, frequency of adverse effects was more with high doses of aspirin. This study suggests that low-dose aspirin is well tolerated and equally effective as high doses of aspirin in management of KD. The result of this study would likely impact treatment regimens of KD the world over.

12 | OPEN LABEL, PHASE II STUDY WITH ANAKINRA IN INTRAVENOUS IMMUNOGLOBULIN-RESISTANT KAWASAKI DISEASE

Isabelle Kone-Paut, Stéphanie Tellier, Alexandre Belot, Karine Brochard, Corinne Guitton, Isabelle Marie, et al. *Arthritis Rheumatol*. 2020; 10.1002/art.41481. https://doi.org/10.1002/art.41481

Kone-Paut et al. have conducted a multicenter open-label clinical trial (KAWAKINRA) to assess safety and efficacy of anakinra in patients with IVIg resistant KD. This trial was conducted in France and recruited patients from 4 centers. The study enrolled 16 IVIg resistant patients (14 boys; 2 girls) with KD. Median age at presentation was 31 months. While 13 patients had received a single dose of IVIg, 2 had received 2 doses and 1 had received 3 doses. Doses of anakinra used in this cohort varied 2-10 mg/kg/d and duration of therapy was 1-15 days. Fever subsided within 48 hours and C-reactive protein levels showed a prompt decrease. Coronary artery Z scores were <2.5 at 6 weeks of follow-up. The authors concluded that anakinra was well tolerated and efficacious in reducing fever, systemic inflammation and coronary artery dilatation. This is a landmark study and would likely impact therapeutic decision making in patients with KD who show less than adequate response to first dose of IVIg.

ORCID

Surjit Singh https://orcid.org/0000-0002-6716-1883

How to cite this article: Loganathan SK, Mondal S, Singh S. Recent advances in pediatric rheumatology: July to September 2020. *Int J Rheum Dis*. 2021;24:274–277. https://doi.org/10.1111/1756-185X.14047

Received: 6 September 2020 | Revised: 8 September 2020 | Accepted: 12 September 2020

DOI: 10.1111/1756-185X.13989

COCHRANE CORNER

International Journal of Rheumatic Diseases

WILEY

Are down-titration and discontinuation strategies of tumour necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity possible? - A Cochrane Review summary with commentary

Giovanni Morone

Santa Lucia foundation IRCCS, Rome, Italy

Correspondence: Giovanni Morone, Santa Lucia foundation IRCCS, Via ardeatina, 306 – 00142 Rome, Italy.
Email: g.morone@hsantalucia.it

Cochrane Rehabilitation

http://rehabilitation.cochrane.org

The aim of this commentary is to discuss in a rehabilitation perspective the published Cochrane Review "Down-titration and discontinuation strategies of tumour necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity"[1] by Verhoef LM et al,[1] under the direct supervision of the Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with the *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

1 | BACKGROUND

Anti–tumor necrosis factor (TNF) agents are effective in treating people with rheumatoid arthritis (RA), but are associated with dose-dependent adverse effects and high costs. Adverse effects include increased risk of infection and a dose-dependent increased risk of malignancy and other rare severe adverse events.[2] Dose reduction or discontinuation in people with RA and low disease activity status is important for reducing adverse events and costs and for this reason these methodologies have been described in current guidelines for the treatment of RA.[3,4] Anti-TNF dose modifications may lead to changes in RA disease activity, conditioning patients' functional activity and quality of life. In this context, an up-to-date Cochrane Systematic Review (CSR) about down-titration and discontinuation strategies of anti-TNF agents for RA in patients with low disease activity was needed.

2 | DOWN-TITRATION AND DISCONTINUATION STRATEGIES OF TUMOUR NECROSIS FACTOR–BLOCKING AGENTS FOR RHEUMATOID ARTHRITIS IN PATIENTS WITH LOW DISEASE ACTIVITY

Verhoef LM, van den Bemt BJF, van der Maas A, Vriezekolk JE, Hulscher ME, van den Hoogen FHJ, Jacobs WCH, van Herwaarden N, den Broeder AA, 2019.

2.1 | What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to evaluate the benefits and harms of down-titration (dose reduction, discontinuation, or disease activity-guided dose tapering) of anti-TNF agents on disease activity, functioning, costs, safety, and radiographic damage compared with usual care in people with RA and low disease activity.

[1]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 5, Art. No.: CD010455, 10.1002/14651858.CD010455.pub3 (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.

2.2 | What was studied in the Cochrane Review?

The population addressed in this review was people with RA with low disease activity using a standard (or lower) dose of anti-TNF agents for longer than 6 months. The interventions studied were dose reduction, discontinuation or disease activity-guided dose tapering of anti-TNF agents. The intervention was compared to usual care/no down-titration/anti-TNF continuation. The major outcomes studied were disease activity, proportion of participants with persistent remission, proportion of participants switched to another biologic, proportion of participants with minimal radiographic progression, function, number of serious adverse events, withdrawals due to adverse events.

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 March 2018. The following electronic databases were searched: MEDLINE, Embase, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). Other research sources were proceedings of conferences from 2005 to 2017 of the American College or Rheumatology, and from 2005 to 2017 of the European League Against Rheumatism (EULAR) for abstracts of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), with reference lists of identified clinical trials. Moreover, experts (first authors of included studies) were asked about additional trials.

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

The CSR included 14 studies (13 RCTs and 1 CCT; 3315 participants in total) of 3 down-titration strategies of anti-TNF agents (anti-TNF dose reduction, anti-TNF discontinuation, and anti-TNF disease activity-guided dose tapering) in people with RA with low disease activity. Included studies reported data on all anti-TNF agents, but primarily adalimumab and etanercept. Study durations ranged from 6 months to 3.5 years.

The CSR included 6 studies (1148 participants) reporting anti-TNF dose reduction compared with anti-TNF continuation, highlighting the following.

- There is little or no difference in mean Disease Activity Score in 28 joints (DAS28) after 26-52 weeks (2 studies, 501 participants, high-certainty evidence, mean difference [MD] 0.06, 95% confidence interval [CI] −0.11 to 0.24, absolute risk difference [ARD] 1% higher) compared with continuation, with a risk ratio (RR) of persistent remission after 52 weeks of 1.01 (2 studies, 612 participants, 95% CI 0.80-1.28, ARD 1% higher, low-certainty evidence).
- It does not result in an important deterioration in function (Health Assessment Questionnaire Disability Index [HAQ-DI]) after 26-52 weeks (2 studies, 501 participants, high-certainty evidence, MD 0.09, 95% CI 0.00-0.19, ARD 3%).
- It may slightly reduce the proportion of participants switched to another biologic after 3.5 years (1 study, 323 participants, RR 0.40, 95% CI 0.17-0.93, low-certainty evidence).
- It may probably slightly increase the proportion of participants with minimal radiographic progression after 52 weeks (2 studies, 553 participants, moderate-certainty evidence, RR 1.22, 95% CI 0.76-1.95, ARD 2% higher).
- It may cause little or no difference in number of serious adverse events after 26-52 weeks (5 studies, 1084 participants, RR 1.09, 95% CI 0.65-1.82, ARD 0%, low-certainty evidence) and withdrawals due to adverse events after 52 weeks (3 studies, 937 participants, RR 1.07, 95% CI 0.51-2.24, ARD 0%, low-certainty evidence).

The CSR included 8 studies (2111 participants) reporting anti-TNF discontinuation compared with anti-TNF continuation highlighting the following.

- It may probably slightly increase the mean DAS28 (2 studies, 733 participants, moderate-certainty evidence, MD 0.96, 95% CI 0.67-1.25, ARD 14%), and that the RR of persistent remission (6 studies 1188 participants) lies between 0.16 and 0.77 (low-certainty evidence) after 28-52 weeks.
- It increases the proportion of participants with minimal radiographic progression after 52 weeks (3 studies, 549 participants, high-certainty evidence, RR 1.69, 95% CI 1.10-2.59, ARD 7%).
- It may lead to a slight deterioration in function (HAQ-DI) after 28-52 weeks (4 studies, 1498 participants, MD 0.18, CI 0.05-0.31, ARD 6%, low-certainty evidence).
- It is uncertain whether anti-TNF discontinuation influences the number of serious adverse events after 28-52 weeks (8 studies, 2095 participants, RR 1.29, 95% CI 0.82-2.03, ARD 2% higher, very low-certainty evidence).
- It probably slightly increases the number of withdrawals due to adverse events after 28-52 weeks (4 studies, 1116 participants, moderate-certainty evidence, RR 1.46, 95% CI 0.75-2.84, ARD 1% higher, moderate-certainty evidence).

The CSR included 3 studies (365 participants) assessing disease activity-guided anti-TNF dose tapering, highlighting the following.

- It may result in little or no difference in mean DAS28 after 72-78 weeks (3 studies, 357 participants, MD 0.25, 95% CI −0.17 to 0.67, ARD 4%, low-certainty evidence).
- It results in little or no difference in the proportion of participants with persistent remission after 18 months (1 study, 180 participants, high-certainty evidence, RR 0.89, 95% CI 0.75-1.06, ARD −9%).
- It may result in little or no difference in switching to another biologic after 18 months (2 studies, 317 participants, RR 0.62, 95% CI 0.25-1.54, low-certainty evidence).

- It may slightly increase proportion of participants with minimal radiographic progression after 18 months (2 studies, 312 participants, RR 1.45, 95% CI 0.77-2.73, ARD 11%, low-certainty evidence).
- It probably leads to a slight deterioration of function after 18 months after 18 months (1 study, 123 participants, moderate-certainty evidence, MD 0.2 higher, 0.02 lower to 0.42 higher, ARD 7% higher).
- It is uncertain whether anti-TNF disease activity-guided dose tapering influences the number of serious adverse events after 18 months (2 studies, 317 participants, RR 1.24, 95% CI 0.42-3.70; 3% higher, very low-certainty evidence).

2.5 | What did the authors conclude?

The authors concluded that fixed-dose reduction of anti-TNF is comparable to continuation of the standard dose regarding disease activity and function, and may be comparable in proportion of participants with persistent remission. Discontinuation of anti-TNF is probably inferior to continuation of treatment with respect to disease activity and function, rate of patients' persistent remission, and radiographic damage. Anti-TNF disease activity-guided dose tapering may be comparable to continuation of treatment regarding disease activity and is comparable with respect to the proportion of participants with persistent remission.

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

From a rheumatology perspective, anti-TNF (particularly etanercept) fixed-dose reduction in patients with RA with low disease activity may be associated to little or no difference in disease activity compared with continuation, with no function and global health reduction. Anti-TNF discontinuation is an inferior strategy compared with continuation in term of disease subjects' function and the proportion of participants with minimal radiographic progression.

Anti-TNF disease activity-guided dose tapering may result in little or no difference in mean disease activity score, may slightly increase proportion of participants with minimal radiographic progression. Authors highlighted that this strategy is probably more feasible from a clinical point of view and has the best cost-effectiveness. Indeed, anti-TNF dose reduction may cause little or no difference in the number of serious adverse event and in the number of withdrawals due to adverse events.

This is an important topic with rheumatology and rehabilitation implications due to the large number of subjects treated with anti-TNF agents. Current evidence on RA treatment suggests the importance of an early and effective reduction/suppression of the inflammation. This leads to reduced radiologically assessed long-term joint damage, an increase of subjects' function and related quality of life. This CSR suggests that a dose reduction of TNF inhibitors may be an appropriate strategy for subjects affected by RA who have achieved low activity of the disease. This finding is important because it is commonly believed that inflammatory conditions worsen if therapy is discontinued.

Limitations of the review include: studies were limited mainly to adalimumab and etanercept, the low presence through articles of cost-effectiveness, and the limited availability of long-term follow-up studies (more than 1 year) affect the interpretation of study findings and its applicability to clinical practice. In addition, it is noteworthy that the treatment decision is made in the light of patient factors such as progression of structural damage, comorbidities and safety issues and not only to disease activity factors.

It is important for rheumatology and rehabilitation professionals knowing that patients undertaking modification of anti-TNF might experience changes in disease activity and function. This aspect is fundamental to plan safe rheumatological drug management, to plan safe rehabilitation approaches and rigorous disease activity and function monitoring in these patients.

ACKNOWLEDGEMENTS

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

CONFLICT OF INTEREST

The author declares no conflicts of interest.

ORCID

Giovanni Morone https://orcid.org/0000-0003-3602-4197

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Received: 19 October 2020 | Revised: 27 November 2020 | Accepted: 27 November 2020

DOI: 10.1111/1756-185X.14044

International Journal of Rheumatic Diseases

WILEY

CORRESPONDENCE

The association between gout and the risk of urological cancers: A pooled analysis of population-based studies

Dear Editor,

Gout is a disorder of purine metabolism, and is characterized by inflammation and hyperuricemia, which are considered to be associated with carcinogenesis and anti-carcinogenesis, respectively.[1-3] Insofar as can be ascertained, both gout and hyperuricemia are conspicuously related to metabolic syndrome, which has been hypothesized to be associated with carcinogenesis.[4] Some researchers argue that high serum uric acid levels are related to increased risk of cancer, although uric acid was thought to be protective in tumorigenesis because of its systemic antioxidant properties.[4] Recent epidemiological studies report conflicting relationships between gout or gout therapy and the risk of urological cancers, even when analyzing the same databases.[1-3,5-10] Given these contradictory reports, we conducted this meta-analysis to elucidate the risk of urological cancers among individuals with gout.

Electronic databases including PubMed, Web of Science, the Cochrane Library, and Embase were retrieved from inception to 13 September 2020 to identify eligible studies without language limitations. The reference lists of relevant reviews were searched manually. Studies were included if they reported: (a) patients who developed or were diagnosed with bladder carcinoma (BCa), renal carcinoma (RCa), or prostate carcinoma (PCa) after diagnosis of gout; (b) standard incidence ratio (SIR) and hazard ratio (HR) with corresponding 95% confidence intervals (CIs) were used to assess the risk of urological cancers among patients; (c) population-based cohort studies or case-control studies; (d) the sample size included in this study is more than 1000; (e) the follow up should be more than 1 year after diagnosis of gout. We incorporated the most recent or most informative study if more than one article studied the same population. Exclusion criteria were: (a) any study that did not satisfy the inclusion criteria; (b) meeting abstracts, review or meta-analysis; and (c) data not available. Two independent authors screened the search results based on the title, abstract, and final full text. Disagreements were resolved through discussion or a third party. Two authors independently evaluated the methodological quality of the studies according to the Newcastle-Ottawa Scale. The fixed effects model was used unless there was heterogeneity ($P < 0.1$), and significance was set at $P < 0.05$. Additionally, we performed a subgroup analysis based on allopurinol use or not. This meta-analysis was accomplished using STATA version 14.2 (StataCorp, College Station, TX, USA).

A total of 1801 studies were identified, and five articles[6-10] containing 562 178 participants were incorporated into the final analysis. The enrolled patients were from Sweden, Korea, Finland, and China. No significant difference was found between the case group and the control group in terms of the risk of PCa (HR 0.95, 95% CI 0.80-1.12). The result remained unchanged in a subgroup analysis of allopurinol use or not (HR 1.05, 95% CI 0.94-1.17). A pooled analysis of two studies including 203, 980 people in the case group and 256, 059 people in the control group found that the risk of BCa among individuals with gout was increased by 1.18 times compared with controls (HR 1.18; 95% CI 1.05-1.32). A fixed-effect model was used because there was no significant between-study heterogeneity ($I^2 = 0.0\%$, $P = 0.433$). Similarly, individuals with gout were at a substantially higher risk of RCa (HR 1.27, 95% CI 1.12-1.44). With reference to SIR of the risk of urological cancers, two of five studies[8,9] reported on RCa and BCa among individuals with gout, showing a significantly higher risk of RCa (SIR 1.92, 95% CI 1.25-2.58; $P < 0.001$), and of BCa (SIR 1.77, 95% CI 0.78-2.75; $P < 0.001$). However, no apparently increased risk of PCa (SIR 2.15, 95% CI −0.05 to 4.34; $P = 0.06$) was observed when compared with the background population. Figure 1 showed the outcomes in this meta-analysis.

Our report is limited by the available data and we were unable to analyze the association between the risk of urological cancers and gout therapy. The limited number of studies, and the inherent limitations of the included studies discouraged us from reaching a definite conclusion. Notably, most of the contemporary studies derived from the National Health Insurance database of Taiwan, and thereby, evidence from other countries is warranted.

In conclusion, we observed that individuals with gout appear to have an increased risk of BCa and RCa, but not of PCa. Whether anti-gout medications can play a role in decreasing the risk of urological cancers remains to be further investigated.

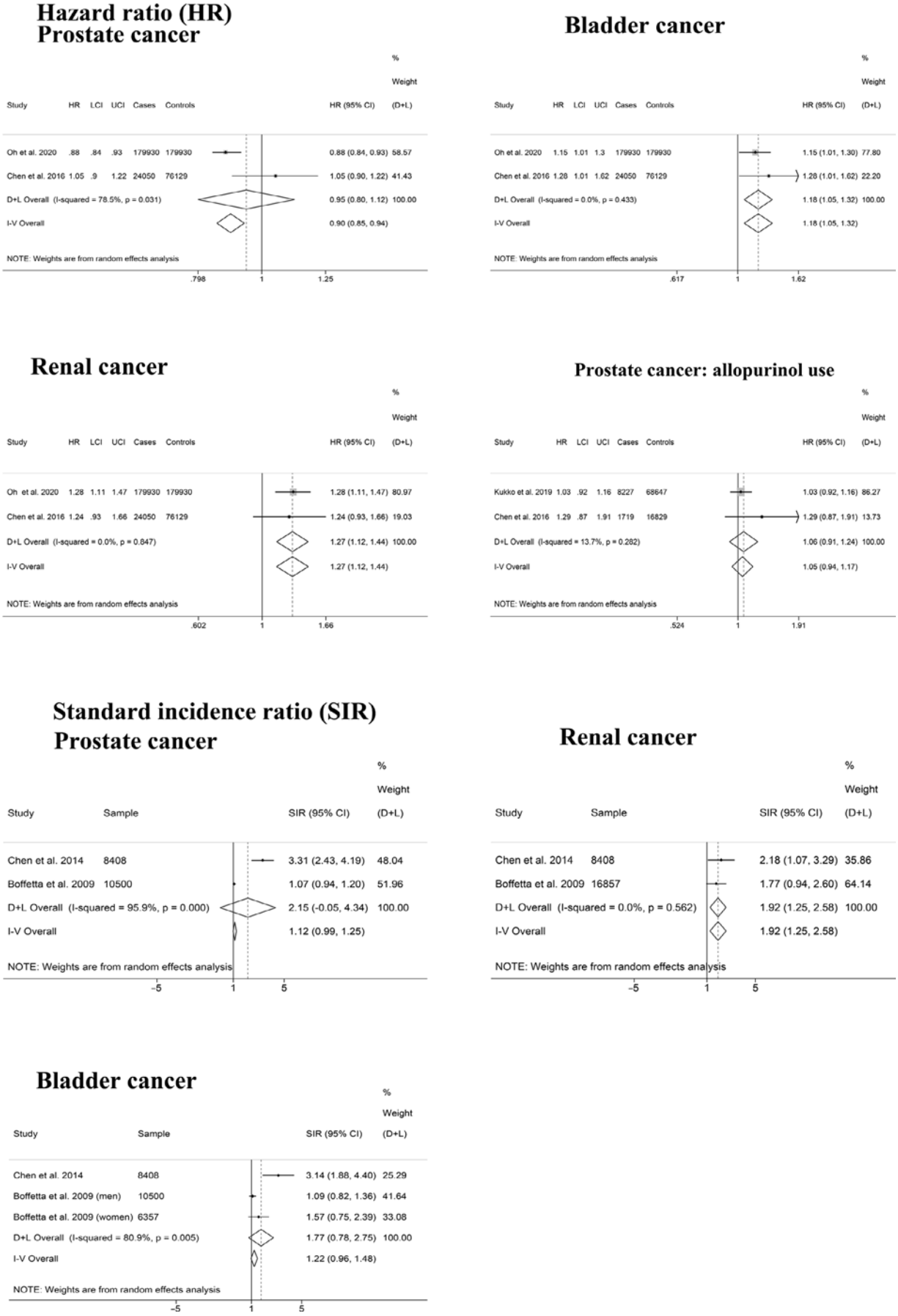

FIGURE 1 Outcomes evaluated in this meta-analysis

KEYWORDS
allopurinol, bladder cancer, gout, prostate cancer, renal cancer

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

DCF conceived and designed the study. LY and WRW provided administrative support. DCF and XH contributed to provision of study materials or patients, and analyzed and interpreted the data. DCF and YBY collected and assembled the data. All authors contributed to writing the manuscript and gave their final approval of the manuscript.

FUNDING INFORMATION

This work was supported by the Department of Science and Technology of Sichuan Province (2020YFH0099).

ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and re-solved.

Dechao Feng
Xiao Hu
Yubo Yang
Lu Yang
Wuran Wei

Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China

Correspondence
Wuran Wei, Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Guoxue Xiang #37, Chengdu, 610041, Sichuan, China.
Email: weiwuran@126.com

Dechao Feng and Xiao Hu contributed equally to this work and should be considered as co-first authors.

ORCID

Dechao Feng https://orcid.org/0000-0002-8267-9920

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Received: 13 December 2020 | Accepted: 19 December 2020

DOI: 10.1111/1756-185X.14054

CORRESPONDENCE

International Journal of Rheumatic Diseases

WILEY

C-reactive protein concentrations as predictors of glucocorticoid-free remission in patients with polymyalgia rheumatica

Dear Editor,

I have read with great interest Hattori et al.'s article, recently published in the *International Journal of Rheumatic Diseases*.[1]

Conflicting results have been reported in published literature on the usefulness of C-reactive protein (CRP) concentrations and erythrocyte sedimentation rate (ESR) as predictors of glucocorticoid (GC)-free remission in patients affected with polymyalgia rheumatica (PMR). For instance, some researchers reported that normal values of CRP at 6 months (but not at 1 month) from baseline were independently associated with complete remission of PMR at 12 months in a multivariate analysis.[2] In Hattori's retrospective study, instead, the achievement of CRP concentrations < 0.17 mg/dL at 1 month from baseline was associated – when compared to CRP concentrations > 0.17 – with a higher probability, at 30 months, of GC-free remission. CRP was considered normal if < 0.3 mg/dL. ESR was not instead a predictive variable.[1]

In a bi-centric, retrospective case-series study published in 2019, among 460 PMR patients, we identified 7 with normal values of both ESR and CRP concentrations at the time of diagnosis. Diagnosis of PMR was confirmed during follow-up lasting from 29 to 120 months.[3] In 6 of these 7 patients, we diagnosed a relapse of PMR according to the modified PMR-Activity Score proposed by Devauchelle-Pensac et al.[4] Proportion of GC-free remission at 29 months from the initiation of GC treatment in the group of patients with normal baseline values of ESR and CRP was not statistically different when compared to patients with raised baseline ESR and CRP (unpublished data).

More recently, among 454 patients affected with PMR, Marsman et al. identified 62 with normal baseline values of both ESR and CRP. The number of patients with relapse of PMR and the proportion of GC-free remission during 24 months follow-up were not significantly different in patients with baseline normal versus baseline elevated ESR and CRP.[5]

It is worth highlighting that all patients enrolled in Marsman et al.'s and in our study followed a uniform treatment protocol in line with the recommendations for the management of PMR proposed in 2015 by a European League Against Rheumatism / American College of Rheumatology collaborative initiative,[6] and received 12.5-20 mg/d prednisolone as the initial dose. Despite a different methodological approach,[7] both studies highlight that PMR without baseline increase of both ESR and CRP exists, and that CRP values have no significance as predictor of GC-free remission.

In conclusion, according to these brief remarks, CRP baseline values seemed not to have always the significance of predictor of GC-free remission in patients with PMR treated with prednisolone. Moreover, the CRP normalization timing proposed by Hattori et al. diverges from the same timing suggested by another research group.[2]

I agree with Hattori et al. that a prospective study with a well-defined protocol would be very useful.

CONFLICT OF INTEREST

The author declares no conflict of interest.

Ciro Manzo

Azienda Sanitaria Locale Napoli 3 sud. Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic, Poliambulatorio "Mariano Lauro", Sant'Agnello, Naples, Italy

Correspondence

Ciro Manzo, Rheumatology, Poliambulatorio "Mariano Lauro" viale dei Pini, 1 – 80065 – Sant'Agnello, Naples, Italy.

ORCID

Ciro Manzo https://orcid.org/0000-0002-4800-1817

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DOI: 10.1111/1756-185X.14073

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.

APLAR aims to improve standards of clinical practice, teaching, and research in rheumatology across Asia Pacific. We are recognising the long-term efforts and dedication of centers in the region with a similar goal for excellence in the field. The certification programme we have initiated will award leading centers in Asia Pacific as Centers of Excellence based on three pillars (research, clinical practice, academia), pre-defined by a list of criteria set by APLAR.

We hope the centers in the region with an excellent track record in any of these pillars will participate in this programme as our goal is to establish reference centers that are best in class models for practice, teaching, and research in rheumatology. We believe this will enhance and enrich the 'best in class' experience for our trainees involved in the APLAR Fellowship programme. Further, this will also help us build a strong network of reference centers for collaborations and consultation within and among countries in the region.

APLAR awarded Centers of Excellence have been updated and information about these centers can be found on the website. Center of Excellence 2020 application has been launched. Interested applicant may get in contact with APLAR's Member National Organisation for more information and application form. Application information has been made available through the Member National Organisations of APLAR. Application is now closed. Look for updates by visiting the APLAR website.

APLAR Grants – Opened for application now!

Closing date: 31st March 2020

APLAR FELLOWSHIP GRANT

APLAR Fellowship Grant supports Science and Medical graduates to undertake intensive or advanced study in clinical aspects or research methodology of either adult or paediatric rheumatology in a rheumatic disease unit outside his own country, preferably at an APLAR Center of Excellence, or others, for a minimum period of six (6) months. The APLAR Executive Committee will consider the option of extending the Fellowship duration to twelve (12) months if there is a clinical need.

Applicant must have a long-term commitment to continue research or clinical work in his/her own country at the conclusion of the Fellowship. The grant is to cover accommodation and subsistence costs.

APLAR RESEARCH GRANT

APLAR Research Grant gives science and medical graduates the opportunity to start and do research within their own country of residence. It hopes to promote and support basic and clinical research directed to the causes, prevention, and treatment of rheumatic diseases in the APLAR member society countries. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset.

APLAR-COPCORD GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) invites applications from physicians from APLAR member societies for its APLAR Community Oriented Program for Control of Rheumatic Diseases (COPCORD) research grant. The aims of the grant are to give the researcher an opportunity to study rheumatic disease in the community of their own country of residence. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset.

APPLICATION FOR APLAR GRANTS 2021

The APLAR Grants is now **opened for application** from **1st January to 31 March 2021**. We are pleased to inform you that up to 3 grants each, will be awarded for the APLAR Fellowship Grant and APLAR Research Grant, while up to 2 grants will be awarded for the COPCORD Grant.

For information **on eligibility, criteria, and application requirement,** kindly visit our official website at https://www.aplar.org/education/.