ISSN 1756-1841 VOLUME 24 NUMBER 9 2021

International Journal of Rheumatic Diseases

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

WILEY

Indexed by ISI (SCI-E), MEDLINE

International Journal of Rheumatic Diseases

APL.JEB.May21

WILEY

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

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

International Journal of Rheumatic Diseases

Volume 24 | Number 9 | September 2021

Contents

EDITORIAL

Metabolic syndrome, rheumatoid and psoriatic arthritis: Managing cardiovascular risk 1103
M. K. Piya

REVIEWS

Rheumatoid arthritis management in the APLAR region: Perspectives from an expert panel of rheumatologists, patients and community oriented program for control of rheumatic diseases 1106
A. Chopra, H.-Y. Lin, S. V. Navarra, M. A. Saeed, S. Sockalingam, S. Thongpooswan, R. Jois, B. Salim, K. W. Gavin Lee, T. C. Lau and J. Wee

Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis 1112
A. Loganathan, N. Kamalaraj, C. El-Haddad and K. Pile

ORIGINAL ARTICLES

Prevalence of metabolic syndrome in patients with rheumatoid arthritis in eastern China—A hospital based study 1121
C.-y. Kong, C.-l. Wang, K.-j. Niu and W. Qi

A Benchmarking Study Evaluating Axial Spondyloarthritis Burden in Spain and Other European Countries. Results from the Spanish Atlas and the European Map of Axial Spondyloarthritis (EMAS) Studies. 1127
M. Garrido-Cumbrera, J. Gratacós, E. Collantes-Estevez, P. Zarco-Montejo, C. Sastre, L. Christen, S. Sanz-Gómez, J. Correa-Fernández and V. Navarro-Compán

Clinical characteristics of non-radiographic axial spondyloarthritis: Results of the Korean Nonradiographic Axial SPondyloArthritis (KONASPA) data 1137
H. Jeong, Y.-G. Kim, T.-H. Kim, T.-J. Kim, M.-C. Park, M. R. Seo, K. Shin, J. S. Oh, S.-H. Lee, Y.-A. Lee, E. Y. Lee, H. J. Baek and H.-S. Cha

Static foot posture and its relation to clinical variables in ankylosing spondylitis 1148
N. Gokcen, A. Sariyildiz and I. Coskun Benlidayi

Cross-cultural adaptation and validation of revised WHO-ILAR-COPCORD core English questionnaire translated to Bangla 1153
M. E. Islam, S. Ahmed, M. A. Shahin, M. A. Islam, M. N. Shazzad and S. A. Haq

Performance of myositis-specific antibodies detected on myositis line immunoassay to diagnose and sub-classify patients with suspected idiopathic inflammatory myopathy, a retrospective records-based review 1167
T. J. Beaton, D. Gillis, K. Prain, K. Morwood, J. Anderson, J. Goddard and T. Baird

The implication of interferon-γ-producing immunocompetent cells for evaluating disease activity and severity in adult-onset Still's disease 1176
T. Ichikawa, Y. Shimojima, D. Kishida, K.-i. Ueno and Y. Sekijima

Prevalence and factors associated with low back pain in schoolchildren in Cameroon, sub-Saharan Africa 1186
F. Kemta Lekpa, D. Enyama, D. Noukeu Njinkui, A. Ngongang Chiedjio, S. R. Simeni Njonnou, C. Ngongang Ouankou, H. Namme Luma and S. P. Choukem

The relationship between common variants in the* DPEP1 *gene and the susceptibility and clinical severity of osteoarthritis 1192
Z. Zhang, Y. Mei, M. Feng, C. Wang, P. Yang and R. Tian

Effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial 1200
H. Yakut, S. Özalevli, R. Aktan, A. Özgen Alpaydın, A. Merih Birlik and G. Can

APLAR GRAND ROUND CASE

Coexistence of Takayasu arteritis and chronic myeloid leukemia: Coincidental or paraneoplastic phenomenon? 1213
T. Yuce Inel, A. Gulcu, A. Karakas, E. Erdogan Yucel and F. Onen

CORRESPONDENCE

What is behind the elevated neutrophil to lymphocyte ratio in glucocorticoid-resistant polymyalgia rheumatica? 1217
H. Ito

Arthritis of the left elbow joint after vaccination against SARS-CoV-2 infection 1218
C. Baimukhamedov

COVID-19 pneumonia can cause irreversible lung damage in dermatomyositis with pre-existing interstitial lung disease 1221
S. Hama, M. Akiyama, T. Shimada, M. Higashida-Konishi, H. Takei, K. Izumi, H. Oshima and Y. Okano

APLAR MATTERS 1224

Received: 23 July 2021 | Accepted: 25 July 2021

DOI: 10.1111/1756-185X.14197

International Journal of Rheumatic Diseases

WILEY

EDITORIAL

Metabolic syndrome, rheumatoid and psoriatic arthritis: Managing cardiovascular risk

There is an increased risk of cardiovascular disease (CVD) and mortality in people with rheumatoid arthritis (RA) and psoriatic arthritis (PsA).[1-4] There have been improvements in disease-specific rheumatological outcomes in these conditions, aided by earlier recognition, tighter control approaches and more effective treatments. The focus is now shifting to concurrently preventing and managing co-morbidities, with some international rheumatology and dermatology guidelines now incorporating advice on co-morbidity management.[5-8] However, it remains uncertain if the increased CVD risk is simply due to an increased clustering of established risk factors, or whether people with RA and PsA have a higher intrinsic risk of CVD.

Metabolic syndrome (MetS) is one such established CVD risk factor. It is defined as a cluster of 3 out of 5 risk factors including central obesity, hyperglycemia, raised triglyceride levels, reduced high-density lipoprotein (HDL) levels or hypertension.[9,10] Both central obesity/adiposity and MetS are linked to chronic inflammation and insulin resistance,[11,12] with inflammation also being linked to CVD risk.[13,14] According to the World Health Organization, the worldwide prevalence of obesity in adults has tripled since 1975, and in 2016 the prevalence of overweight and obesity was 39% and 13% respectively.[15] The prevalence does vary significantly by country or region, and in the USA, the obesity prevalence in adults was much higher at 42.4%.[16] With the increasing prevalence of obesity, the prevalence of MetS has also been increasing over time in the USA from 25.3% in 1988-1994 to 34.2% in 2007-2012.[17]

A systematic review by Loganathan et al.[18] in this issue of the *Journal* has clearly demonstrated a higher prevalence of MetS in patients with PsA (46%) compared to psoriasis (31%). The higher disease activity and inflammation in PsA compared to psoriasis may explain this difference in prevalence. Interestingly, in this study, the prevalence of MetS in RA is significantly lower (34%) than PsA, and is comparable to psoriasis. In another hospital-based study from Eastern China by Kong et al.,[19] also published in this issue of this *Journal*, the prevalence of MetS in RA was actually very similar to healthy comparators, 31% vs 34%, and similar to the prevalence in the systematic review. These findings do raise some questions, given that RA is clearly an inflammatory condition, and as previously mentioned, is associated with a higher CVD risk.

A higher prevalence of MetS in PsA may potentially account for a higher CVD risk, although other factors could still be at play. However, there certainly seem to be factors beyond the traditional risk factors and MetS that drive the higher CVD risk in RA. The European League Against Rheumatism (EULAR) guidelines recommend early and aggressive screening and management of traditional CVD risk factors and components of MetS for all inflammatory joint disorders including PsA and RA.[5] While CVD risk management is a sensible first step in high-risk populations, the strength of these recommendations are moderate to low in PsA or RA. There is a lack of good-quality evidence that this risk management actually results in reduced CVD events or death in PsA or RA. The limited use of nonsteroidal anti-inflammatory drugs and corticosteroids is also suggested due to the potential of increased CVD risk and/or worsening of hypertension/hyperglycemia. Given that the prevalence of CVD in RA is significantly higher than the general population, the current studies support these EULAR guidelines that also suggest that CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor. Another factor to consider is that the presence of MetS is often considered as binary – present or absent, based on whether 3 of 5 of the criteria are met.[9,10] However, age or gender may have a role in the significance of the presence of MetS, as may clustering of the individual components of MetS.[20] For example, a person with 0 or 2 risk factors would be considered to have no MetS, while a person with 3, 4 or 5 risk factors would all be considered to have MetS, with actual risk of CVD being on a spectrum. Findings from the study by Kong et al.[19] showed that although the prevalence of MetS in those with and without RA was similar, there was a greater prevalence of hypertension and low HDL levels in the RA patients, and they also had lower body mass indexes and triglyceride levels compared to patients without RA.

Regular screening for MetS components as well as lifestyle advice on smoking cessation, healthy eating and increased physical activity where practical, should be offered to all patients. This may be with the rheumatologist or general practitioner or other healthcare professional, depending on the healthcare setting. The arrival of statins was a major game changer when it came to reducing CVD risk, but the arrival of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has the potential to take lipid lowering to the next level.[21] And in people with type 2 diabetes mellitus (T2DM), the evidence that sodium glucose transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) agonists help with weight loss and improved glycemia, and also independently reduce cardiovascular risk makes them an attractive therapeutic option.[22] These new medications are

not without cost implications, and some of these may require the involvement of healthcare providers other than rheumatologists.

Given that central obesity and adiposity are integrally linked to inflammation and insulin resistance in MetS, significant weight loss may be an option to reduce CVD risk. In addition to the metabolic improvements, weight loss could also reduce the mechanical load on joints. However, there is ample evidence that just asking people to improve lifestyle and attempt to lose weight does not work, and specific targeted interventions with appropriate support are more likely to result in change. This may be in the form of intensive lifestyle interventions, low energy diets, pharmacotherapy or bariatric surgery. While low or very low energy diets can result in significant weight loss, they are not always sustained, whereas bariatric surgery is often linked to significant and sustained weight loss and improvement in glycemia. Current pharmacotherapy results in modest weight loss but new and emerging therapies have been shown to result in significant weight loss of around 15% body weight, that is sustained with once a week subcutaneous injections.[23,24] These options, along with the increasing availability of bariatric surgery present significant weight loss as an achievable option for many people with RA or PsA. However, data from the prospective Swedish Obesity Study on patients without RA or PsA at baseline showed a reduced risk of developing psoriasis in those who had bariatric surgery compared to controls but no difference in development of PsA or RA during follow-up.[25,26] The total number of people developing these conditions was very low in this study though, despite up to 26 years follow-up data. There are a few studies of bariatric surgery in people with pre-existing psoriasis or PsA[27-29] or RA,[30,31] but the results of these studies are mixed with no clear benefit in RA or PsA following bariatric surgery. Moreover, the number of patients were quite small, and the follow-up duration limited.

The other question that remains is whether treatments targeting inflammation itself which improve inflammatory arthritis, also influence inflammation linked to obesity, MetS and CVD. There is limited evidence of the effect of the newer biological therapies on CVD risk. Previous attempts to treat inflammation have had mixed results with some suggestion that methotrexate reduces CVD risk in RA, and tumor necrosis factor inhibitors reduce CVD risk in psoriasis/PsA as well as RA.[32,33] Results from the trial on the monoclonal antibody targeting interleukin-1b, canakinumab, showed reduced CV events with 150 mg dose but not 50 mg or 300 mg, and it had a higher risk of fatal infection compared to placebo.[34]

In summary, while chronic inflammation may link PsA and RA with an increased CVD risk, the prevalence of MetS alone may not account for this, particularly in RA where the prevalence of MetS was comparable to the background population. Attention may need to be paid to the individual components of MetS as well as the influence of age and gender when considering CVD risk. Early screening for and aggressive management of traditional CVD risk factors including the components of MetS are recommended. However, good-quality long-term studies are needed to demonstrate if managing risk factors brings CVD risk down to the level of the background population. Newer therapeutic options may help achieve these goals, particularly with the availability of PCSK9 inhibitors for lipid lowering, and of SGLT2 inhibitors and GLP1 agonists for glycemic control in T2DM. And although options for significant weight loss are available, including bariatric surgery and newer pharmacological options, further studies are required to determine if this weight loss results in improvement in disease activity in inflammatory arthritis. The use of anti-inflammatory therapies for the reduction of CVD risk may not be recommended at the moment, due to the prohibitive cost and risk of side effects, but they may influence the decision to start biological therapies in patients with RA or PsA if they have a higher CVD risk. With existing and emerging therapies to help reduce inflammation and manage CVD risk factors, rheumatologists need to be prepared for the increasingly expanding role beyond simply managing the inflammatory joint disease itself.

KEYWORDS

cardiovascular risk, inflammation, metabolic syndrome, psoriatic arthritis, rheumatoid arthritis

Milan K. Piya[1,2]

[1]*School of Medicine, Western Sydney University, Sydney, NSW, Australia*

[2]*Camden and Campbelltown Hospitals, Sydney, NSW, Australia*

Correspondence

Milan K. Piya, 2nd Floor, Macarthur Clinical School, Western Sydney University, Parkside Crescent, Campbelltown, NSW 2560, Australia.

Email: m.piya@westernsydney.edu.au

REFERENCES

1. Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis*. 2011;70(6):929-934.
2. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. *Nat Rev Rheumatol*. 2015;11(12):693-704.
3. Gupta S, Syrimi Z, Hughes DM, Zhao SS. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. *Rheumatol Int*. 2021;41(2):275-284.
4. van den Hoek J, Boshuizen HC, Roorda LD, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int*. 2017;37(4):487-493.
5. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17-28.
6. Eder L, Dey A, Joshi AA, Boehncke WH, Mehta NN, Szentpetery A. Cardiovascular diseases in psoriasis and psoriatic arthritis. *J Rheumatol Suppl*. 2019;95:20-27.
7. Dauden E, Blasco AJ, Bonanad C, et al. Position statement for the management of comorbidities in psoriasis. *J Eur Acad Dermatol Venereol*. 2018;32(12):2058-2073.
8. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073-1113.

9. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
10. National Cholesterol Education Program (NCEP) Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.
11. Piya MK, McTernan PG, Kumar S. Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin. *J Endocrinol*. 2013;216(1):T1-T15.
12. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*. 2014;105(2):141-150.
13. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med*. 2004;351(25):2599-2610.
14. Libby P, Ridker PM, Hansson GK, Atherothrombosis LTNo. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54(23):2129-2138.
15. WHO. World Health Organisation Overweight and Obesity Factsheet 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
16. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. 2020. Available from: https://www.cdc.gov/nchs/products/databriefs/db360.htm
17. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination Survey, 1988–2012. *Prev Chronic Dis*. 2017;14:E24.
18. Loganathan A, Kamalaraj N, El-Haddad C, Pile K. Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis. *Int J Rheum Dis*. 2021;24:1112–1120.
19. Kong CY, Wang CL, Niu KJ, Qi W. Prevalence of metabolic syndrome in patients with rheumatoid arthritis in eastern China-A hospital based study. *Int J Rheum Dis*. 2021;24:1121–1126.
20. Devers MC, Campbell S, Simmons D. Influence of age on the prevalence and components of the metabolic syndrome and the association with cardiovascular disease. *BMJ Open Diabetes Res Care*. 2016;4(1):e000195.
21. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol*. 2019;16(3):155-165.
22. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet*. 2021;398(10296):262-276.
23. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
24. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet*. 2021;398(10295):143-155.
25. Maglio C, Zhang Y, Peltonen M, et al. Bariatric surgery and the incidence of rheumatoid arthritis - a Swedish Obese Subjects study. *Rheumatology*. 2020;59(2):303-309.
26. Maglio C, Peltonen M, Rudin A, Carlsson LMS. Bariatric surgery and the incidence of psoriasis and psoriatic arthritis in the Swedish Obese Subjects Study. *Obesity*. 2017;25(12):2068-2073.
27. Laskowski M, Schiöler L, Ottosson J, et al. Impact of Bariatric surgery on moderate to severe psoriasis: a retrospective nationwide registry study. *Acta Derm Venereol*. 2021;101(6):adv00487.
28. Mahil SK, McSweeney SM, Kloczko E, McGowan B, Barker JN, Smith CH. Does weight loss reduce the severity and incidence of psoriasis or psoriatic arthritis? A critically appraised topic. *Br J Dermatol*. 2019;181(5):946-953.
29. Egeberg A, Sørensen JA, Gislason GH, Knop FK, Skov L. Incidence and prognosis of psoriasis and psoriatic arthritis in patients undergoing bariatric surgery. *JAMA Surg*. 2017;152(4):344-349.
30. Xu F, Yu C, Li DG, et al. The outcomes of bariatric surgery on rheumatoid arthritis disease activity: a prospective cohort study. *Sci Rep*. 2020;10(1):3167.
31. Sparks JA, Halperin F, Karlson JC, Karlson EW, Bermas BL. Impact of bariatric surgery on patients with rheumatoid arthritis. *Arthritis Care Res*. 2015;67(12):1619-1626.
32. Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(3):480-489.
33. Yang ZS, Lin NN, Li L, Li Y. The effect of TNF inhibitors on cardiovascular events in psoriasis and psoriatic arthritis: an updated meta-analysis. *Clin Rev Allergy Immunol*. 2016;51(2):240-247.
34. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119-1131.

Received: 25 April 2021 | Revised: 7 July 2021 | Accepted: 12 July 2021

DOI: 10.1111/1756-185X.14185

INVITED REVIEW

International Journal of Rheumatic Diseases

WILEY

Rheumatoid arthritis management in the APLAR region: Perspectives from an expert panel of rheumatologists, patients and community oriented program for control of rheumatic diseases

Arvind Chopra[1] | Hsiao-Yi Lin[2] | Sandra V. Navarra[3] | Muhammad Ahmed Saeed[4] | Sargunan Sockalingam[5] | Supat Thongpooswan[6] | Ramesh Jois[7] | Babur Salim[8] | Ka Wing Gavin Lee[9] | Tang Ching Lau[10] | James Wee[11]

[1]Center for Rheumatic Diseases, Pune, India

[2]Clinical Research Center and Division of Allergy, Immunology and Rheumatology, Department of Medicine, Cheng Hsin General Hospital, Taipei, Taiwan

[3]Rheumatology Center, University of Santo Tomas Hospital, Manila, Philippines

[4]Al-Aleem Medical College, Lahore, Pakistan

[5]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[6]Bumrungrad Hospital, Bangkok, Thailand

[7]Department of Rheumatology & Clinical Immunology, Vikram Hospital, Bangalore, India

[8]Fauji Foundation Hospital Rawapindi Pakistan, Rawapindi, Pakistan

[9]Hong Kong Sanatorium & Hospital, Hong Kong, China

[10]Division of Rheumatology, Department of Medicine, National University Hospital, Singapore, Singapore

[11]Pfizer Inc., Makati City, Philippines

Correspondence
Arvind Chopra, APLAR COPCORD Coordinator, Director and Chief Rheumatologist, Centre for Rheumatic Diseases, Pune, India.
Email: arvindchopra60@hotmail.com

Abstract

Rheumatoid arthritis (RA) is a major health burden in Asia Pacific affecting the quality of life of patients and consuming healthcare resources. According to recent estimates from the World Health Organization-International League Against Rheumatism-Community Oriented Program for Control of Rheumatic Diseases, prevalence is around 0.3%-0.5%. Management guidelines have helped to improve treatment across this diverse region. To gain better insight into current real-world management applications in view of these guidelines, virtual meetings were conducted in mid-2020 to explore perspectives of rheumatologists and patients, as well as discuss the impact of coronavirus disease 2019 on RA management. Patients and rheumatologists from Hong Kong, Malaysia, Singapore, the Philippines, Thailand, India, Pakistan, and Taiwan were included, representing a diverse mix of healthcare systems, wealth, ethnicity and culture. Despite many countries having prospered in recent years, similar challenges in RA diagnosis and treatment were identified. The daily impact and patient experience of RA were also similar across countries, marked by "silent" pain and disability, and universal misunderstanding of the disease. Late diagnosis and treatment, and barriers to access to appropriate treatment, remain problematic. The experience shared by Taiwan offers a glimmer of hope, however, wherein patient advocacy groups have succeeded in being included in policy-making decisions and securing access to advanced treatment. Real-world solutions that pay heed to the unique local needs and diversity of Asia Pacific are required to improve RA management, which will take time. In the interim, help can be sought from the trained, non-rheumatologist community to reduce some of the disease burden.

KEYWORDS

APLAR region, current management, patient journey, rheumatoid arthritis

1 | INTRODUCTION

Asia Pacific is a vast, diverse region, with a sizeable burden of rheumatoid arthritis (RA), which affects the quality of life of patients and consumes healthcare resources[1-3] The prevalence of RA in Asia Pacific (around 0.30%-0.50%) compared with North America (0.70%) and Europe (0.59%) is relatively lower but, given the large populations, this translates to a huge burden in the region (Figure 1).[4-8]

The World Health Organization-International League Against Rheumatism-Community Oriented Program for Control of Rheumatic Diseases (WHO-ILAR-COPCORD) survey data were collected in phases using a near-similar methodology and in particular a uniform core set of questions (to identify respondents), thereby allowing comparison of point prevalence across countries and regions. The surveys were planned and supervised by rheumatologists and the diagnosis of rheumatic disorders was essentially clinical.

In some countries there is an urban-rural divide but this is likely to become blurred over time with rapid urbanization and modern development, and migration of people to the cities.[9]

In 2007, the opportunities and challenges for rheumatology in Asia Pacific were discussed in an editorial, which noted that "many countries in the Asia Pacific region have failing economies, and are still struggling to establish rheumatology as a medical subspecialty. There is a general lack of awareness about musculoskeletal diseases and their effect on society. Diagnosis and treatment are often delayed because primary-care physicians have limited knowledge of the clinical evaluation and management of rheumatic diseases, and trained rheumatologists are few and far between."[10]

Since 2007, healthcare infrastructure has markedly improved in many low- and middle-income countries (LMICs) in Asia Pacific, whereas higher-income countries (HICs) have become more systematic in their approach to healthcare delivery. In 2015, the Asia Pacific League of Associations for Rheumatology (APLAR) took the lead to develop treatment guidelines specific for the region, which took into account the diversity in healthcare delivery, and other differences across countries. Indeed, the APLAR executive has been at the forefront of improving the rheumatology landscape and has established special interest groups for RA and COPCORD epidemiology, with recent COPCORD publications being readily available online.[11]

From the patient perspective, the management of RA has evolved to incorporate more shared decision-making, individualized therapy, and patient-centered outcomes. Treatment options have increased significantly with the availability of newer advanced disease-modifying antirheumatic drugs (DMARDs). How have these developments benefited RA patients and rheumatology practice in Asia Pacific? To gain more insight into current real-life management and the perspectives of RA patients, a series of virtual meetings was held with experienced rheumatologists (the authors of this article) and their patients (N = 7) from Hong Kong, Malaysia, Singapore, Philippines, Thailand, India, Pakistan, and Taiwan in July 2020, and we expected there to be disparities between affluent countries (eg, Taiwan, Hong Kong, and Singapore) and LMICs (eg, India, Pakistan).

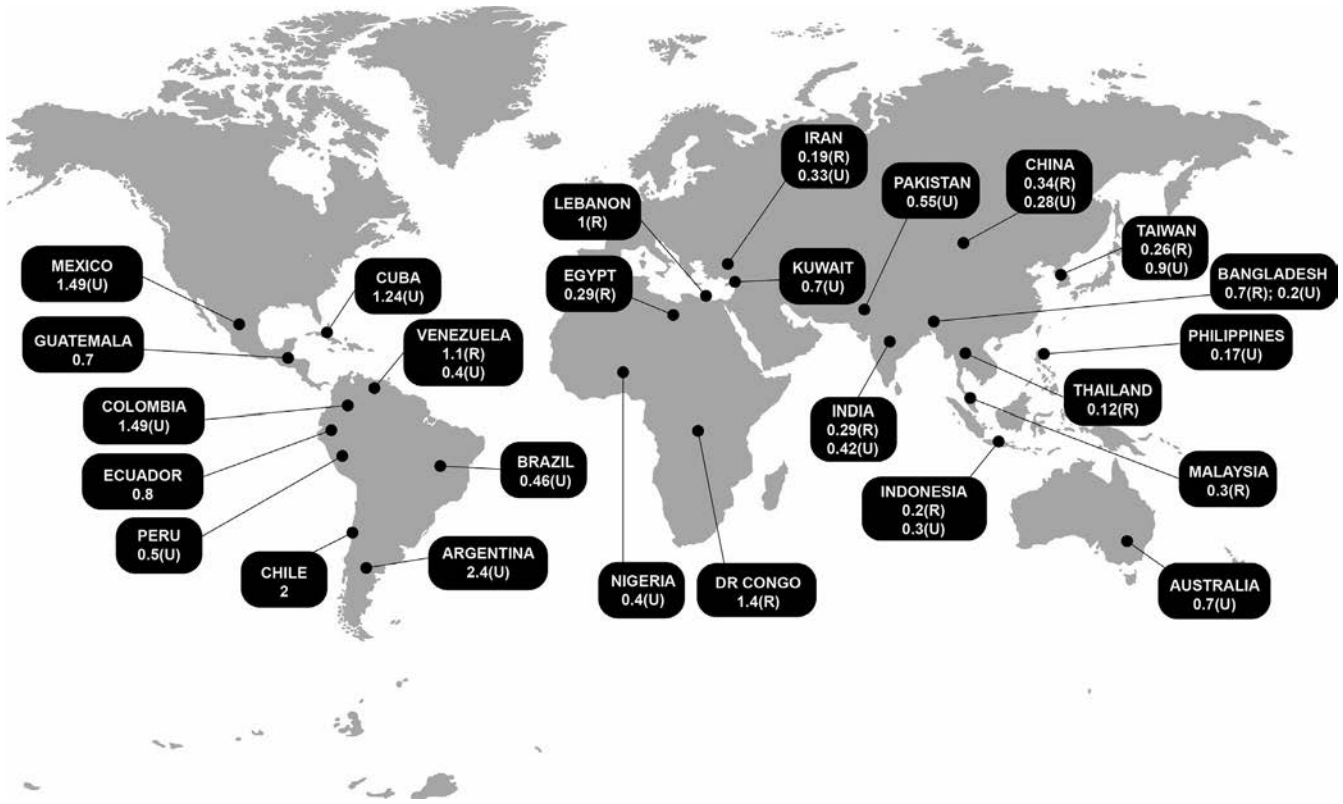


FIGURE 1 WHO-ILAR-COPCORD prevalence map of rheumatoid arthritis.[4] Prevalence rates for Asia-Pacific countries were determined from population surveys conducted from 1988 to 2015. U, urban; R, rural

Previously unpublished data from WHO-ILAR-COPCORD (available at www.copcord.org), courtesy of Arvind Chopra, one of the authors, were included to support this commentary.

2 | THE RA PATIENT JOURNEY, MARKED BY "INVISIBLE" PAIN AND DISABILITY, AND LOW AWARENESS

Patients were asked to describe their journey from diagnosis to treatment, and how RA had impacted their lives and that of their families. Very similar experiences emerged regardless of where patients came from, their personal means and background. Notably, the majority of patients were diagnosed late, some beyond 2 years from symptom onset. Patients had difficulty finding the right information about RA or sought treatment solely for pain relief including use of traditional Chinese medicines and acupuncture, which delayed diagnosis. All the patients were on DMARD treatment, but this may not be the case in large stretches of the region where medical services are sparse and medical practice is non-specialized. In these scenarios, patients tend to be managed with painkillers and steroids for prolonged periods, which is consistent with several COPCORD population surveys that reported surreptitious and often rampant use of steroids (sometimes mixed with herbal remedies) to treat RA. In terms of advanced DMARD therapy (biologics and targeted-synthetic DMARDs), some had received biologic therapy in the past, some were still receiving biologic therapy, and some had never tried because of cost, but felt that this type of treatment would be beneficial. Moreover, the RA patient journey was shown to be an isolating and lonely one. RA can be perceived as an "invisible" illness, and it is difficult to imagine the severity and type of pain that RA patients feel when, on the outside, they "look normal". Patients referred to having "silent pain" that was difficult even for family members to believe, let alone comprehend.

Throughout the work day, an RA patient may feel morning stiffness, breakthrough pain, and occasional nausea or other medication adverse effects while appearing "normal". The lack of understanding around RA extends further to employers and the workplace, and there are no concessions for RA patients when they are feeling unwell. It is not surprising that many RA patients give up work prematurely, often at the height of their careers, as the result of symptoms and increasing disability. In the last decade, despite goals of inclusivity and diversity having been indoctrinated into most workplaces, there remains a growing need for recognition from employers, as well as protection of RA patients in the workplace. Moreover, this loss in peak productivity and its consequences on the economic and social health of a country have yet to be fully appreciated by governments.[12-17]

Individuals with RA can also be misinformed and lack understanding on the pathophysiology of their disease, which can hamper outcomes by delaying diagnosis and the provision of adequate treatment. In the minds of many RA patients, the pain caused by RA *is* the disease, which is a double-edged sword. While pain alerts patients and reminds them to be compliant with their medication, the reverse—stopping medication—often happens when they are not in pain. It is very important that patients are educated about the "silent" progression of RA even when pain is absent. Many RA patients also do not grasp that, despite the absence of pain, poor disease control can still increase the risk of bone destruction and disability. More needs to be done to ensure that patients understand why it is important to reach treatment goals.

Perhaps the defining feature of the RA patient journey in Asia Pacific is invisibility: the pain is invisible, the damage is invisible until it has progressed to significant disability, the patient population is often invisible, and the patient voice is imperceptible and fragmented because there are few patient support and advocacy groups. Where patient groups exist, activities tend to center on lifestyle support and experience sharing. In the arena of advocacy, patient groups in Singapore, Hong Kong, the Philippines, and Malaysia have tried to get involved, but their influence has been limited, with little say in the decisions that directly affect them. In India, patient support (eg, Mission Arthritis India) mainly focuses on education but patients have no influence on public health policy. Yet, to increase awareness and understanding of RA and to improve outcomes, patients in Asia Pacific must be seen and heard. The success of RA patient advocacy groups in Taiwan, which have made good use of social media platforms such as LINE, WeChat, and Facebook to stay connected and vocal—and through which they have been included in policy decision-making and secured greater and longer access to effective advanced DMARD therapy[18]—demonstrates that patients, given the opportunity, have a valid voice, and can work with physicians and policy-makers to improve their own outcomes. Taiwan serves as an effective model for multi-stakeholder collaboration, which can be applied to both HICs and LMICs in Asia Pacific.

3 | CHALLENGES IN THE MANAGEMENT OF RA IN ASIA PACIFIC

Rheumatologists were asked to provide their opinion on RA management in their respective countries to illuminate challenges in current practice. They also provided specific details on epidemiology, diagnosis of RA, the treatment pathway for patients and access to advanced DMARD therapy.

The challenges in RA management in HICs and LMICs in Asia Pacific are interlinked, like pillars underlying a vast structure. Viewed this way, improvements to one pillar should benefit and strengthen the support of the whole structure, and the more pillars that are improved, the greater and stronger the structure becomes. Hence, improvements in RA management, ideally, should not be made in isolation, although small isolated improvements are still beneficial.

The first major challenge lies in the shortage of rheumatologists in some Asia-Pacific countries, which contributes to late diagnosis and delayed appropriate treatment. This challenge was also mentioned in the APLAR guidelines.[1] Indeed, in countries like India, RA is largely neglected in public health, there are no national arthritis

programs,[19] and public funding is often diverted to other diseases (eg, infectious diseases, diabetes, hypertension, cancer). In this respect, the comments of the 2007 editorial still ring true in 2020.[10] The shortage of rheumatologists is more evident in LMICs like the Philippines, Thailand, India, and Pakistan where an urban-rural divide exists. Rural areas are at a major disadvantage in terms of availability of and access to rheumatologists and rheumatology services, which often leads to misdiagnosis or late diagnosis.

To address the shortage of rheumatologists in some countries, healthcare providers have found creative solutions, such as the training of non-rheumatologists to help with diagnosis and parts of routine follow up. In Thailand, the Thai Rheumatism Association developed evidence-based recommendations on RA diagnosis and management for non-rheumatologists,[20] and local medical societies in India and Pakistan are working with associations such as APLAR and COPCORD to develop and implement formal training courses for non-rheumatologists. For example, in Pakistan, a tertiary-care rheumatology center developed a 9-month course for family physicians using a blended learning technique, which was partly funded by a grant from ILAR. The curriculum was developed using American College of Rheumatology Rheum 2 modules and international guidelines.[21] This model can be replicated to address the extreme shortage of experts in the field of rheumatology in other LMICs. Meanwhile, in some centers, such as the one at the University of Santo Tomas Hospital in the Philippines, education workshop modules to establish efficient networking with non-rheumatologists, as well as trained clinic assistants, have increased resources for providing physician and patient education.

A second challenge lies in the implementation of the treat-to-target (T2T) approach—the reference standard for RA management—in which individualized care and the attainment of treatment goals are prioritized.[22-25] However, in the public health sector of Asia-Pacific countries, regardless of wealth, most rheumatologists do not have sufficient consultation time to implement a T2T approach. This is compounded by the shortage of rheumatologists in some countries as mentioned above, a shortage of facilities to enable regular follow up, and resistance towards intensification of treatment, which is discussed further in the third challenge, below. In LMICs where RA is managed at the primary-care level, the management needs to be surveyed and evaluated, because it is likely that no specific, consistent strategy is being followed to treat the disease. Only a small fraction of RA patients in these countries are likely to be treated with reasonable standards of care.

In short, the many limitations in healthcare infrastructure and delivery that exist currently in Asia Pacific, particularly in LMICs, combine to make the T2T approach difficult to implement in real-life practice. A solution may be to modify the T2T approach, tailoring it to RA clinical practice in Asia Pacific, without compromising effectiveness. Another may be to use the T2T approach with conventional DMARDs earlier in the course of disease, which can lead to remission in up to one-third of patients.[26]

A third challenge involves the under-utilization of biologics and other advanced DMARDs in the region. In real-life practice, the usage of biologics and other advanced DMARD therapies amount to around 5% in the represented countries, whereas the data would suggest that a greater proportion of the RA population is indicated for advanced DMARD treatment.[27] This implies considerable undertreatment of a proportion of patients with moderate to severe RA, though more data are needed to support this. The APLAR guidelines give more attention to the role of conventional DMARDs, as these are more accessible and affordable for many countries in the APLAR region.[1] The guidelines also highlight the elevated risk of biologic-associated infection in Asian populations, particularly tuberculosis,[28] which must be taken into account when managing RA patients in the region, but which may also deter use.

Cost is an obvious barrier to greater uptake of advanced DMARD therapy in all countries, regardless of wealth or resources.[29] Other barriers include clinical inertia on the part of physicians, and reluctance of patients to intensify treatment even in the presence of active disease, some of whom are unwilling to "risk" new treatments.[22,30] These barriers underscore the fact that the value and clinical benefits of advanced DMARD therapy are under-appreciated, even though biologics have been available for almost two decades and the development of biosimilars has the potential to expand access to more patients. The best approach to overcome these barriers may be to continue to reinforce evidence from clinical trials and real-world data to convince clinicians and patients, and change behaviors, prejudices, and mindsets.

Several ethnic and traditional medicinal systems are in popular practice in the APLAR region and many have existed since antiquity. Some of these (such as the Chinese traditional system and Indian Ayurveda) are encouraged and promoted by the respective national healthcare systems. These treatments are considered holistic and individualized, but often compete with modern medicine, because they are widely perceived by the general public to be safer with some patients taking these medicines for prolonged periods. As such, it is important to determine and evaluate the clinical benefits of some of these alternative therapies using modern science, necessitating a comprehensive, integrative research agenda.

It is prudent to add, however, that several non-pharmacologic modalities of treatment are important in the management of RA. Diet, exercise, and physiotherapy are pivotal to patients but are often neglected by doctors in clinical practice. Traditional methods of physical and mental fitness (such as tai chi and yoga) are popular and their potential benefits should be recognized and integrated into guidelines and recommendations.

3.1 | The impact of COVID-19 on RA management in Asia Pacific

At the time of our meetings in 2020, it was imperative to include the impact of coronavirus disease 2019 (COVID-19) into the discussions. Every aspect of healthcare has been affected by COVID-19 and rheumatology practice is no exception.[31,32] Rheumatologists have had to adapt rapidly to an evolving situation, as clinics closed

and fear among patients set in. Through this process, a major lesson has been the utilization of telemedicine in rheumatology, with increasing understanding among clinicians regarding its capacity to support practice, especially in providing continuity of care.[33] Most rheumatologists in the region have used telemedicine during the COVID-19 pandemic and patients have responded well, with some even expressing a preference to continue with telemedicine after COVID-19. On the one hand, telemedicine's obvious limitation lies in confirming a new diagnosis, which usually requires in-person consultation (indeed, COVID-19 has likely created a sizeable backlog of new cases, which countries will have to prepare for once the pandemic subsides). On the other hand, telemedicine will likely continue to play a role in the routine follow up of patients with stable RA, which is more convenient for patients and reduces the in-clinic burden on doctors and staff. Moreover, as digital technology continues to advance, new opportunities for telemedicine will arise. For example, in Malaysia, an automated repeat-prescription system linked to pharmacies, without the need for a face-to-face doctor consultation, greatly supported the use of telemedicine during lockdown, enabling patients with stable disease to continue getting their medications without having to set foot in a clinic. Nevertheless, in some LMICs, patients may live in areas that are remote or underdeveloped, and without internet access or even reliable sources of electricity; many of these patients may also not be digitally savvy. Hence, the uptake of telemedicine should be guided by individual patients' preferences, access to digital resources, and their level of comfort with using telemedicine.

4 | WHERE DO WE GO FROM HERE?

The experience shared by both patients and rheumatologists allows us to qualitatively assess and discuss how far we have come in the management of RA in Asia Pacific and the challenges that still need to be overcome, as well as providing important insight into the patient journey. In the development of the APLAR guidelines, the views of one patient representative were consulted;[1] perhaps to increase the applicability of guidelines in real-life practice in the future, this approach should continue to be incorporated to ensure that management recommendations are sensitive to the needs of the people they seek to help. In the APLAR guidelines, problems with access to advanced DMARD treatment, largely related to affordability, were noted, and alternatives to these agents were provided. It is beyond the scope of guidelines to recommend other approaches for overcoming issues of access but, from our discussions, there may be a real opportunity to effect change through patient advocacy in countries where governments and public health systems are beginning to realize that involving patients in policy decisions can improve long-term outcomes and care. Many countries in Asia Pacific, on face value, claim to include patients in their healthcare policy-making; however small the window, this opportunity should be explored further with more organized, consolidated patient group efforts. Greater collaborations with bodies such as APLAR, and learning from patient groups in places like Taiwan on how to amplify the patient voice, may also help to improve awareness, disease education, and patient autonomy and responsibility, and may improve treatment and care, including increasing access to advanced DMARD therapy when needed.

From the rheumatologists' perspective, many challenges remain the same, such as the shortage of rheumatologists, late diagnosis, and late or suboptimal treatment. Real-world, tailored, and pragmatic solutions are needed in Asia Pacific to improve outcomes, such as the training of and networking with non-rheumatologists; it may be a while before the rheumatology workforce is sufficient to meet the disease burden. WHO-ILAR-COPCORD needs to further explore ways to serve its primary purpose in determining disease burden and risk factors, imparting education to the community and doctors, and implementing control and preventive strategies at a grass-root level.

One legacy of COVID-19 is the march of telemedicine onto the global stage and, post-pandemic, rheumatologists must determine how and in whom telemedicine should be best used. Finally, if we are to improve patient outcomes on a wider scale, the RA population of Asia Pacific must become "visible". Policy-makers need to hear and see these patients, and understand how their decisions profoundly affect not only the individual and their families, but also the health and productivity of a state or nation. Reducing the RA burden means that a whole society benefits, and actions must be taken to achieve this.

ACKNOWLEDGEMENTS

We would like to thank all the patients who completed the pre-meeting survey to share their experience with RA and who joined the meetings to give additional insight and feedback. Cathy Chow, PhD, at Weber Shandwick Hong Kong is acknowledged for editorial support, with funding from Pfizer.

CONFLICT OF INTEREST

AC, HYL, MAS, SS, RJ, BS, and KWGL all have no conflicts of interest; SVN is on the speaker bureau for Pfizer, Johnson & Johnson, and Novartis; ST has received consultant fees, speaking fees, and honoraria from Novartis, Pfizer, Roche, and Zuellig Pharma, and serves on advisory board for Pfizer; LTC has received speaker fees and honoraria from Amgen, Johnson & Johnson, Pfizer, and Eli Lilly; JW is an employee of Pfizer.

ORCID

Arvind Chopra https://orcid.org/0000-0002-4347-9651

REFERENCES

1. Lau CS, Chia F, Harrison A, et al. APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis*. 2015;18:685-713.
2. Cross M, Smith E, Hoy D et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73:1316–1322.
3. Rudan I, Sidhu S, Papana A, et al. Prevalence of rheumatoid arthritis in low- and middle-income countries: a systematic review and analysis. *J Glob Health*. 2015;5:010409.

4. Chopra A. The COPCORD world of musculoskeletal pain and arthritis. *Rheumatology (Oxford)*. 2013;52:1925-1928.
5. Chopra A. Disease burden of rheumatic diseases in India: COPCORD perspective. *Indian J Rheumatol*. 2015;10:70-77.
6. Chopra A. The WHO ILAR COPCORD Latin America: consistent with the world and setting a new perspective. *J Clin Rheumatol*. 2012;18:167-169.
7. Chopra A, Abdel-Nasser A. Epidemiology of rheumatic musculoskeletal disorders in the developing world. *Best Pract Res Clin Rheumatol*. 2008;22:583-604.
8. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int*. 2021;41:863-877.
9. Joshi VL, Chopra A. Is there an urban-rural divide? Population surveys of rheumatic musculoskeletal disorders in the Pune region of India using the COPCORD Bhigwan model. *J Rheumatol*. 2009;36:614-622.
10. Lau C-S, Kim HY, Nishioka K. Rheumatology in the Asia Pacific region–opportunities and challenges. *Nat Clin Pract Rheumatol*. 2007;3:119.
11. COPCORD publications. Available at. 2021. Accessed on June 3 http://copcord.org/publications.asp
12. Gong G, Mao J. Health-related quality of life among Chinese patients with rheumatoid arthritis: The predictive roles of fatigue, functional disability, self-efficacy, and social support. *Nurs Res*. 2016;65:55-67.
13. Michaud K, Strand V, Shadick NA, et al. Outcomes and costs of incorporating a multibiomarker disease activity test in the management of patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2015;54:1640-1649.
14. Olofsson T, Petersson IF, Eriksson JK, et al. Predictors of work disability during the first 3 years after diagnosis in a national rheumatoid arthritis inception cohort. *Ann Rheum Dis*. 2014;73:845-853.
15. Wallman JK, Eriksson JK, Nilsson J-A, et al. Costs in relation to disability, disease activity, and health-related quality of life in rheumatoid arthritis: observational data from Southern Sweden. *J Rheumatol*. 2016;43:1292-1299.
16. Zhu TY, Tam LS, Li EK. Societal costs of rheumatoid arthritis in Hong Kong: a prevalence-based cost-of-illness study. *Rheumatol*. 2011;50:1293-1301.
17. Kobelt G, Woronoff AS, Richard B, et al. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study. *Joint Bone Spine*. 2008;75:408-415.
18. Press release. National health insurance pays 8+1 items on cancer-related drug list and relaxes the restriction on dose reduction of rheumatoid arthritis drugs. 2021. Accessed on February 2 https://www.nhi.gov.tw/News_Content.aspx?n=FC05EB85BD57C709&s=9382655DEF2D21C9
19. Mathew AJ, Rahim A, Bina T, Paul BJ, Chopra A. A call to integrate musculoskeletal disorders into the national programme for non-communicable diseases (NCD). *Indian J Med Res*. 2012;136:499-501.
20. Katchamart W, Narongroeknawin P, Chevaisrakul P, et al. Evidence-based recommendations for the diagnosis and management of rheumatoid arthritis for non-rheumatologists: Integrating systematic literature research and expert opinion of the Thai Rheumatism Association. *Int J Rheum Dis*. 2017;20:1142-1165.
21. Khan SEA, Saeed MA, Batool S, et al. A rheumatology curriculum in Pakistan for empowering family physicians and fighting disability. *Clin Rheumatol*. 2020;39:681-687.
22. Batko B, Batko K, Krzanowski M. Żuber Z (2019) Physician adherence to treat-to-target and practice guidelines in rheumatoid arthritis. *J Clin Med*. 2019;8:1416.
23. Taylor PC, Criado AB, Mongey A-B, et al. How to get the most from methotrexate (MTX) treatment for your rheumatoid arthritis patient? – MTX in the treat-to-target strategy. *J Clin Med*. 2019;8:515.
24. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75:3-15.
25. Brinkmann GH, Norvang V, Norli ES, et al. Treat to target strategy in early rheumatoid arthritis versus routine care – A comparative clinical practice study. *Semin Arthritis Rheum*. 2019;48:808-814.
26. Farman S, Ahmad NM, Saeed MA, et al. Treat-to-target approach in daily clinical practice in Pakistani patients with early rheumatoid arthritis. *J Coll Physicians Surg Pak*. 2015;25:129-133.
27. Edwards CJ, Kiely P, Arthanari S, et al. Predicting disease progression and poor outcomes in patients with moderately active rheumatoid arthritis: a systematic review. *Rheumatol Adv Pract*. 2019;3:rkz002.
28. Chiu Y-M, Tang C-H, Hung S-T, Yang Y-W, Fang C-H, Lin H-Y. A real-world risk analysis of biological treatment (adalimumab and etanercept) in a country with a high prevalence of tuberculosis and chronic liver disease: a nationwide population-based study. *Scand J Rheumatol*. 2017;46:236-240.
29. Lang H-C, Lee H-C, Lee S-S, Lin H-Y, Chiu Y-M. The impact of introducing biologics to patients with rheumatoid arthritis in Taiwan: a population-based trend study. *Int J Rheum Dis*. 2016;19:1112-1118.
30. Pappas DA, Gerber RA, Litman HJ, et al. Delayed treatment acceleration in patients with rheumatoid arthritis who have inadequate response to initial tumor necrosis factor inhibitors: data from the Corrona Registry. *Am Health Drug Benefits*. 2018;11:148-158.
31. Ladani AP, Loganathan M, Danve A Managing rheumatic diseases during COVID-19. *Clinical Rheumatology*. 2020;39(11):3245–3254. https://doi.org/10.1007/s10067-020-05387-8
32. Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. *Nat Rev Rheumatol*. 2021;17:71-72.
33. ACR Releases. Position Statement on Telemedicine. June 29, 2020. Available at: https://www.rheumatology.org/About-Us/Newsroom/Press-Releases/ID/1087. Accessed on 19 January 2020

How to cite this article: Chopra A, Lin H-Y, Navarra SV, et al. Rheumatoid arthritis management in the APLAR region: Perspectives from an expert panel of rheumatologists, patients and community oriented program for control of rheumatic diseases. *Int J Rheum Dis*. 2021;24:1106–1111. https://doi.org/10.1111/1756-185X.14185

Received: 23 January 2021 | Revised: 1 May 2021 | Accepted: 6 May 2021

DOI: 10.1111/1756-185X.14147

REVIEW

International Journal of Rheumatic Diseases | WILEY

Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis

Aravinthan Loganathan[1,2,3] | Narainraj Kamalaraj[1,4] | Carlos El-Haddad[1] | Kevin Pile[1,3]

[1]Rheumatology Department, Campbelltown Hospital, Campbelltown, NSW, Australia

[2]Rheumatology, Wollongong Hospital, Campbelltown, NSW, Australia

[3]University of Western Sydney – Campbelltown Campus, Campbelltown, NSW, Australia

[4]School of Medicine, Western Sydney University – Campbelltown Campus, Campbelltown, NSW, Australia

Correspondence
Aravinthan Loganathan, Rheumatology, Campbelltown Hospital, Campbelltown, NSW, Australia.
Email: aravi.loganathan@gmail.com

Abstract

Background: Psoriatic arthritis (PsA), rheumatoid arthritis (RA) and psoriasis (PsO) are associated with systemic inflammation and increased cardiovascular mortality and morbidity. Metabolic syndrome (MetS) is associated with systemic inflammation, and conditions associated with MetS, such as obesity, are associated with difficulty in attaining minimal disease activity (MDA) in individuals with inflammatory arthritis. This systematic review aims to determine whether there is an increased prevalence of MetS in PsA populations compared with PsO and RA populations.

Methods: A systematic review was conducted to assess the prevalence of MetS in PsA, PsO, and RA populations following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The quality of the studies reviewed was assessed using the Joanna Briggs Institute Checklist for Prevalence Studies.

Results: The pooled prevalence of MetS in PsA populations was 0.46 ± 0.06 (95% CI 0.40-0.51). In comparison, the prevalence of MetS in PsO and RA populations was 0.34 ± 0.03 (95% CI 0.32-0.37) and 0.31 ± 0.04 (95% CI 0.27-0.35), respectively. Patients with PsA were 1.62 ± 0.036 (95% CI 1.50-1.74) and 1.66 ± 0.038 (95% CI 1.54-1.79) times more likely to have MetS compared with PsO and RA populations.

Conclusion: The prevalence of MetS is significantly increased in PsA populations compared with PsO and RA populations. Further studies should be performed using a standardized definition of MetS in PsA, RA, and PsO populations to determine whether addressing the metabolic components in MetS offers any therapeutic benefits and in terms of attaining MDA and improving cardiovascular health.

KEYWORDS

psoriatic arthritis, rheumatoid arthritis, psoriasis, metabolic syndrome, cardiovascular risk

1 | INTRODUCTION

Psoriasis (PsO) is an immune-mediated chronic inflammatory disease of the skin that affects 2%-3% of the world's population.[1] The concept of the "psoriatic march" supports the presence of systemic inflammation in PsO due to inappropriate activation of the innate and adaptive immune system. Persistent activation of the immune system in psoriatic patients results in disease expression and systemic inflammation through cytokine release. Sustained inflammation is associated with insulin resistance, which increases the risk of

endothelial dysfunction, atherosclerosis, myocardial infarction (MI) and cerebrovascular accident (CVA).[2-4]

Psoriatic arthritis (PsA) is a seronegative inflammatory arthropathy with a prevalence of 25%-30% in psoriatic populations.[5,6] The estimated prevalence of PsA in the general population is 6-25 per 10 000.[5] While there are several different subtypes of PsO, plaque, scalp, and inverse and psoriatic nail involvement are all associated with a high risk of developing PsA. Psoriatic patients with higher Psoriasis Area and Sensitivity Index (PASI) scores are more likely to develop PsA, which could be due to the burden of increased systemic inflammation. The presence of psoriatic plaque is an important biomarker for future risk of developing synovio-entheseal inflammation. Metabolic risk factors that increase the risk of PsA include obesity, hyperlipidemia, and hyperuricemia, while non-metabolic risk factors include first-degree family relatives with PsA, smoking, infections (eg, streptococcal) and retinoid medications.[7]

More than 10% of newly diagnosed PsA patients develop cardiovascular disease (CVD) within 10 years of developing new-onset inflammatory arthritis.[8] PsA patients, like PsO patients, are more likely to suffer significant mortality from CVD, including MI, angina, CVA, heart failure, atherosclerosis, and hypertension.[9] The presence of diabetes, hyperlipidemia, hypertension, obesity, and PsO are known predictors of cardiovascular morbidity.[9,10] A systematic review involving 26 studies showed that psoriatic patients were more likely to suffer from hypertension (odds ratio [OR] 2.31, 95% CI 1.12-4.74), abdominal obesity (OR 1.9, 95% CI 1.45-2.5) and hypertriglyceridemia (OR 1.8, 95% CI 1.29-2.51) compared with non-psoriatic patients.[3]

Traditional cardiovascular risk factors in patients suffering from rheumatoid arthritis (RA) are not entirely representative of these patients' increased cardiovascular mortality and morbidity risks. Patients with RA are twice as likely to develop CVD in comparison to the general population, which is similar to diabetic populations.[11-13] Recent European League Against Rheumatism (EULAR) recommendations for CVD risk management in patients with RA and other forms of inflammatory joint disorders stress that rheumatologists should manage traditional CVD risk factors while optimizing RA treatment concurrently.[14] CVD risk assessments should be performed every 5 years and reviewed each time there is a change in the management of inflammatory arthritis.[14] Systemic inflammation plays a role in accelerated atherosclerosis, as plaque formation is triggered by endothelial dysfunction, which is often impaired in RA patients. Circulating inflammatory proteins and antibodies, such as anticyclic citrullinated peptide antibodies and rheumatoid factor, increase the likelihood of endothelial dysfunction.[15] In addition, certain medications, such as non-steroidal anti-inflammatory drugs and glucocorticoids, can exacerbate hypertension and lead to impaired glucose tolerance and lipid profiles.[11]

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that includes hypertension, obesity, increased waist circumference, insulin resistance, and dyslipidemia. Patients with MetS have higher levels of baseline inflammation, as demonstrated by elevated inflammatory markers, such as C-reactive protein.[16] Pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, which promote insulin resistance, also contribute to abdominal obesity. Visceral fat modulates and secretes adipocytokines, such as leptin, adiponectin, plasminogen activator inhibitor 1, IL-6 and resistin. These inflammatory proteins play critical roles in the inflammation cascade and can induce hypertension, atherosclerotic vascular disease, and endothelial dysfunction.[17]

The purpose of the present systematic review is to analyze whether there is an increased prevalence of MetS in patients with PsA compared with patients with RA and PsO. Previous studies have demonstrated that MetS and obesity are poor prognostic indicators in the minimal disease activity (MDA) state in patients with PsA, despite recent advancements in disease-modifying anti-rheumatic drugs therapy.[2,18,19]

2 | METHODOLOGY

2.1 | Protocol and registration

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, and the methodology is available to review on the PROSPERO database (CRD42019129131).

2.2 | Search strategy and study selection

The databases MEDLINE, PubMed, EMBASE, Google Scholar, ProQuest, Ebsco CINAHL, Scopus, ScienceDirect, Web of Science, and the Cochrane Library were searched, with a date range of January 1990 to 19 August 2019. The search parameters used during database searches included human studies only, while no restrictions were placed on geography or language (non-English language articles were only included if an English translation was available). The databases listed above were searched using the following medical subject headings (MeSH): "MetS," "Dysmetabolic Syndrome," "Insulin Resistance Syndrome", and "Cardiovascular Syndrome." Various MeSH search terms for PsA, RA, and PsO were also utilized. Detailed information on the search strategy is provided in Table S1.

2.3 | Inclusion criteria

The inclusion criteria for the studies for all 3 population groups are listed in Table S2.

In the PsA group, the following classification criteria were accepted for inclusion: Classification Criteria for Psoriatic Arthritis (CASPAR), Moll and Wright, Bennett, Vasey and Espinoza, Modified

European Spondyloarthropathy Study Group, Modified McGonagle, Fournie et al. Criteria and rheumatologist diagnosis. In RA, studies used the American College of Rheumatology (ACR)/EULAR 2010, 1987 ACR Classification criteria or included patients diagnosed with RA by a rheumatologist.

2.3.1 | Types of studies

Cross-sectional studies, randomized controlled trials, cohort studies, and case-control studies were included. The studies included data collected both prospectively and retrospectively.

2.4 | Exclusion criteria

Published conference abstracts, literature reviews, and editorials were excluded; however, references from these articles were screened for suitability for inclusion. Studies with 20 or fewer patients were also excluded. Articles that included multiple studies with primary data were excluded, although each study in these articles was considered separately. If the studies met the Joanna Briggs minimal quality checklist and were not included in the initial preliminary search, they were manually added to the list of accepted articles.

2.5 | Study records

One reviewer (AL) screened all the titles and abstracts of the identified records. Covidence© online software was used during the initial screening stage to determine which studies to include or exclude. Accepted abstracts underwent a full-text review to determine whether they met the eligibility criteria for inclusion. Endnote™ X9 software was used to maintain a comprehensive database of all the studies included in the review.

2.6 | Data extraction

For each study included, the following data were collected in a Microsoft Excel data extraction spreadsheet: year of study; country of the study population; number of patients included in the study; prevalence of MetS in PsA, PsO, and RA; criteria used to diagnose MetS in PsA, PsO, and RA populations and the prevalence of the different metabolic components of MetS in PsA, PsO, and RA populations. Extracted data for the included studies are available in the appendix (Table S8a–c). The ORs and relative risk were not extracted from individual studies. Studies that applied more than one MetS criteria to report multiple prevalence values recorded each prevalence value separately. A sensitivity analysis was conducted to check for bias and over/under-estimation due to bias. When multiple MetS criteria were used in the same study population, the most-used MetS criteria was used to determine the prevalence values at the end of the entire data extraction period.

2.7 | Bias assessment

The Critical Appraisal Checklist for Studies Reporting Prevalence Data by the Joanna Briggs Institute was used to conduct a quality assessment of the studies and assess for the presence of bias. Publication bias and the effect of smaller studies were evaluated for asymmetry using the Doi plot rather than an Egger's regression. This is because the Egger's regression has lower power in relation to detecting asymmetry compared with a Doi plot, particularly when smaller studies are included. In addition, the Egger's regression requires the interpretation of a funnel plot, and the Luis Furuya-Kanamori (LFK) index from the Doi plot has been shown to outperform the Egger's *P* value. LFK values outside the range −1 to +1 were suggestive of asymmetry and publication bias.[20]

2.8 | Statistical analysis

Statistical analysis was conducted using Microsoft Excel and MetaXL. The statistical heterogeneity of the population was assessed using an I^2 index. A random-effects model was used to calculate the prevalence in MetS for an I^2 index of >0.6.[21] I^2 values >75% were considered as having significant heterogeneity.[22] As there was a high level of heterogeneity within the study populations, a sensitivity analysis was conducted to investigate whether the study design could account for this. The ORs and 95% CIs for MetS in PsA, RA, and PsO were calculated based on the different classification criteria and gross national income (GNI; Table S3) from the June 2018 World Bank list of economies.[23] The OR was calculated using a Chi-squared table and the cumulative prevalence of MetS across PsA, RA, and PsO populations.

3 | RESULTS

3.1 | Search results

Figure 1 shows the PRISMA flow diagrams. The initial literature search yielded an initial 3156, 3181 and 7555 studies in the PsA, PsO, and RA cohorts, respectively. After screening, removing duplicate studies and conducting a full-text review of studies that met the eligibility criteria, 24, 89 and 53 studies were included in the final analysis for PsA, PsO, and RA, respectively.

3.2 | Heterogeneity

There was a high degree of heterogeneity between the studies in all the analyses performed. The I^2 values for PsA, PsO, and RA

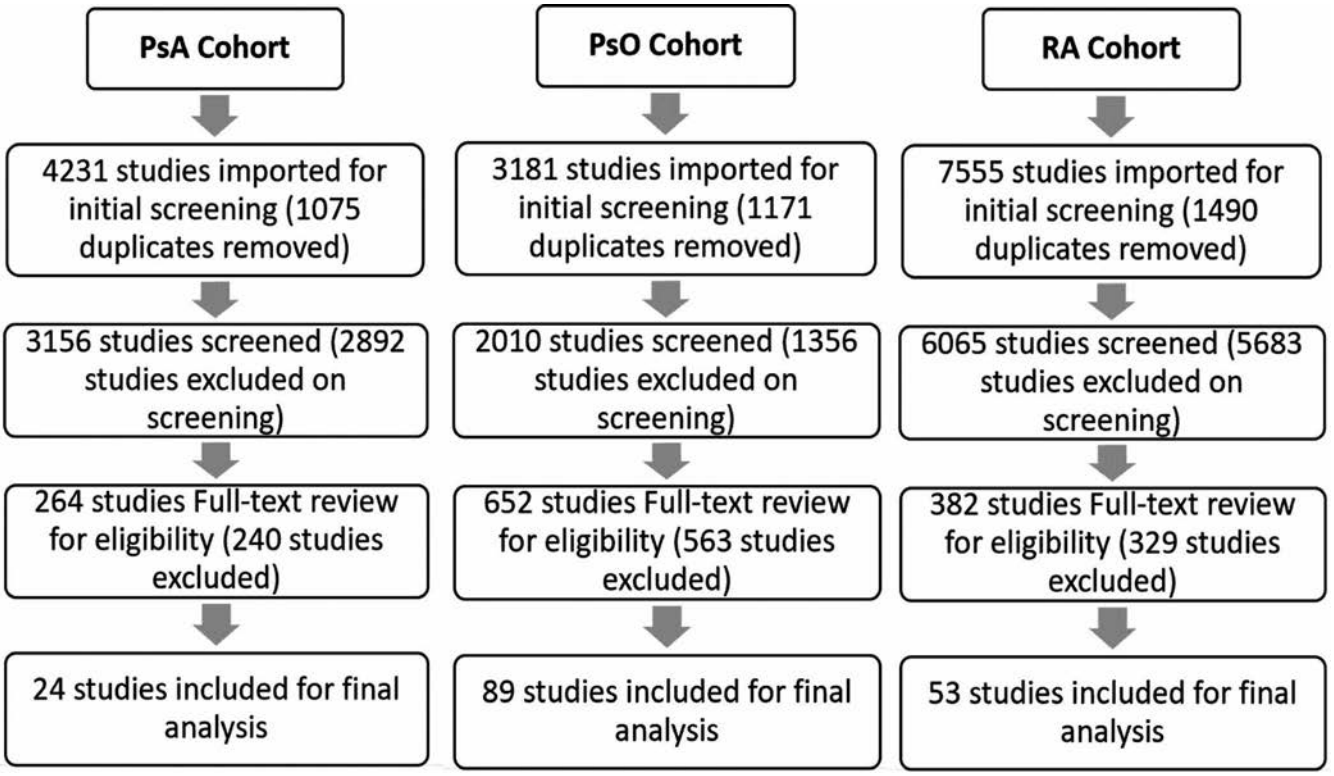


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

populations were 91%, 95% and 91%, respectively. The studies included had different sample sizes and definitions for MetS and classification criteria, which explained the studies' heterogeneity (Figure 2).

3.3 | Prevalence of MetS in PsA

Using the random-effects model (Table 1), the prevalence of MetS in patients classified as having PsA was 0.46 ± 0.06 (95% CI 0.40-0.51). When duplicate prevalence data sets using different criteria for MetS were removed, and only the prevalence of MetS according to the National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) was included (Table S4), the pooled prevalence reduced to 0.43 ± 0.07 (95% CI 0.37-0.5). Among the different criteria used to define MetS, harmonized and International Diabetes Federation (IDF) criteria showed the highest prevalence of MetS at 0.52 ± 0.16 (95% CI 0.36-0.68) and 0.52 ± 0.12 (95% CI 0.40-0.63; Table S4).

When different classification criteria were used to define PsA (Table S4), the prevalence of MetS when using the CASPAR, Moll and Wright, and diagnosis by a rheumatologist was 0.42 ± 0.07 (95% CI 0.36-0.49), 0.60 ± 0.06 (95% CI 0.54-0.66) and 0.47 ± 0.27 (95% CI 0.21-0.75), respectively.

The prevalence of MetS in patients with PsA was higher in study populations from lower GNI countries (Table S4). While there were only 2 studies in the GNI 2 group, the prevalence was 0.60 ± 0.09 (95% CI 0.51-0.68). In comparison, in populations from countries classified as GNI 3 and GNI 4, the prevalence of MetS was 0.52 ± 0.07 (95% CI 0.45-0.59) and 0.39 ± 0.09 (95% CI 0.29-0.47), respectively.

3.4 | Prevalence of MetS in PsO

The pooled prevalence (Table 1) of MetS in the PsO population was 0.34 ± 0.03 (95% CI 0.32-0.37) using the random-effects model. This value did not significantly change when duplicate MetS prevalence values were removed and remained the same at 0.34 ± 0.03 (95% CI 0.31-0.37; Table S5). When defined using the NCEP-ATP criteria, the prevalence of MetS was 0.34 ± 0.04 (95% CI 0.30-0.37). Unlike the PsA groups, the prevalence of MetS showed no clear trend according to GNI.

3.5 | Prevalence of MetS in RA

The pooled prevalence (Table 1) for RA was 0.31 ± 0.04 (95% CI 0.27-0.35), and when multiple MetS criteria were removed, the prevalence remained the same at 0.31 ± 0.06 (95% CI 0.26-0.36; Table S6). As with the PsO cohort, the RA population showed no clear trend according to the population's GNI. When the NCEP-ATP criteria were used, the prevalence of MetS was 0.32 ± 0.06 (95% CI 0.27-0.3).

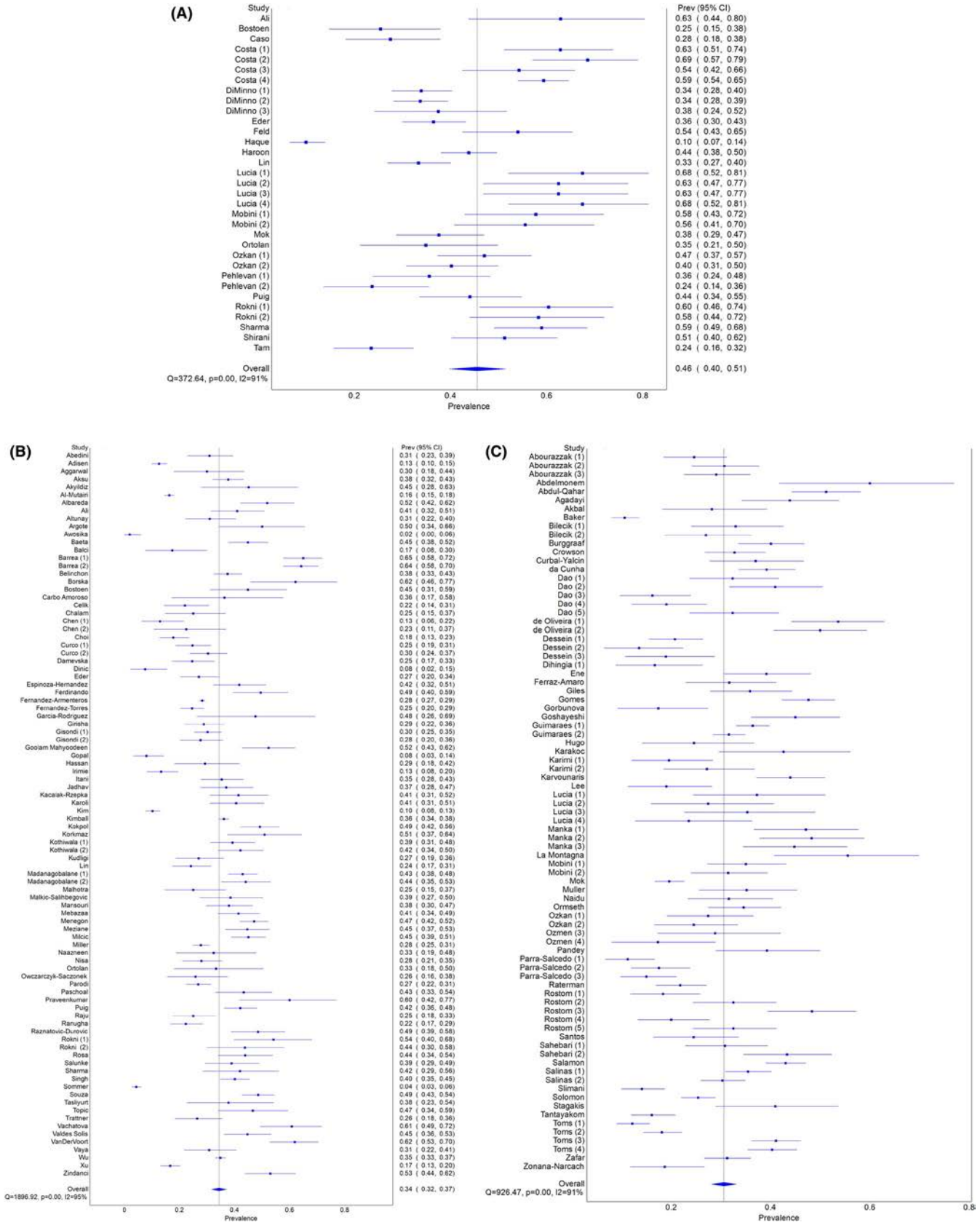


FIGURE 2 (A-C) Forest plot for psoriatic arthritis, psoriasis, and rheumatoid arthritis [Colour figure can be viewed at wileyonlinelibrary.com]

3.6 | Comparison of PsA, PsO, and RA populations

Patients with PsA were 1.61 ± 0.036 (95% CI 1.49-1.74) and 1.66 ± 0.038 (95% CI 1.54-1.79) times more likely to have MetS compared with patients with PsO and RA, respectively (Table 2).

3.7 | Prevalence of individual components of MetS in PsA, PsO, and RA

Data were also collected on the presence of the individual components of MetS (Table 3). These definitions varied based on the definition of MetS used in studies that reported relevant data.

While the prevalence rates of the individual components of MetS among the PsA, PsO, and RA populations were similar, MetS was significantly more prevalent in the PsA population. This suggests that patients with PsA are at higher risk of suffering from more than one cardiovascular risk factor compared with patients with RA and PsO.

TABLE 1 Prevalence of metabolic syndrome in psoriatic arthritis, psoriasis and rheumatoid arthritis (random-effects model)

Population group	Prevalence	SE	95% CI	I^2
Psoriatic arthritis	0.46	0.06	0.40-0.51	91
Psoriasis	0.34	0.03	0.32-0.37	95
Rheumatoid arthritis	0.31	0.04	0.27-0.35	91

TABLE 2 Odds ratios (OR) for metabolic syndrome for psoriatic arthritis vs psoriasis and rheumatoid arthritis

	MetS		
Disease	Yes	No	OR (95% CI)
Psoriatic arthritis	1447	2003	N/A (reference group)
Psoriasis	8718	19 448	1.61 (1.49-1.73)
Rheumatoid arthritis	4625	10 628	1.66 (1.54-1.79)

3.8 | Prevalence of MetS in PsA populations based on area of study

The prevalence of MetS in the PsA population based on the geographical location of the studies included in the present research was calculated. The different geographical areas included Europe, Asia, North America, and the Middle East. The countries included in the Europe group were Italy, Spain, Belgium, Ireland, and Romania. Hong Kong and India were included in the Asia group; the USA made up the North America group; and Turkey, Iran, and Israel comprised the Middle East group. The percentages of patients with PsA and MetS in the Europe, Asian, North American, and Middle Eastern groups were 47.2%, 45.78%, 34.88% and 48.4%, respectively.

3.9 | Sensitivity analysis PsA

A sensitivity analysis (Table S7) was conducted to determine the influence of certain variables on the prevalence of MetS in PsA populations. The variables assessed were the different classification criteria for PsA, the criteria for MetS and countries' GNI. There was no significant difference in the prevalence of MetS when duplicate studies were removed, and the studies were compared with different classification criteria for PsA (CASPAR classification vs rheumatologist diagnosis) or MetS criteria (Harmonized vs NCEP-ATP). However, patients with PsA who were classified according to Moll and Wright were more likely to have MetS when compared with patients classified using CASPAR and those diagnosed by a rheumatologist.

Studies that used the NCEP-ATP criteria were more likely to suggest the presence of MetS compared with studies that used the WHO and American Heart Association / National Heart and Blood Institute (AHA/NHLBI) criteria. However, the IDF criteria were more likely to predict MetS compared with NCEP-ATP. Populations from countries with a lower socioeconomic status were more likely to have MetS compared with those from countries with a higher socioeconomic status.

4 | DISCUSSION

4.1 | Synthesis of the findings

MetS was significantly more prevalent in PsA populations (0.46 ± 0.06 [95% CI 0.40-0.52]) compared with PsO populations

TABLE 3 Prevalence of individual characteristics of metabolic syndrome in psoriatic arthritis, psoriasis and rheumatoid arthritis

Population group	Central obesity/ elevated WC (%)	Hyper-triglyceridemia (%)	Reduced HDL (%)	DM/insulin resistance (%)	Impaired fasting glucose (%)	HTN (%)
Psoriatic arthritis	62.1	35.6	36.6	20.6	25.8	50.2
Psoriasis	49.5	37.3	42.6	21.3	32.9	40.2
Rheumatoid arthritis	62.5	35.4	43.6	19.9	26.4	51.9

Abbreviations: HDL, high-density lipoprotein; HTN, hypertension; WC, white cells.

(0.34 ± 0.03 [95% CI 0.32-0.37]) and RA (0.31 ± 0.04 [95% CI 0.27-0.35]) by 1.61- and 1.66-fold, respectively. The prevalence of MetS varied depending on different population groups, and a pooled analysis conducted using similar MetS definitions to those used in the present study suggested a prevalence of MetS in young adults of 4.8%, 5.2%, 7% and 6.5%.[24] Research by Sigit et al., who used the IDF and AHA/NHLBI criteria, noted a prevalence of MetS in an Indonesian population (GNI 2) of 39% and a Dutch population (GNI 4) of 29.2%.[25]

Recent research has suggested that the risk of CVD mortality is similar in RA and PsA populations.[26-28] However, the use of traditional CVD risk scores, such as the Framingham Risk Score, underestimates the true risk of CVD in PsA cohorts because the presence of CVD risk factors, including obesity, dyslipidemia, and hypertension, are higher in PsA populations compared with the general population. In addition, traditional CVD risk-scoring systems do not consider chronic inflammation, which can lead to endothelial dysfunction and atherosclerosis.[8] Chronic inflammation may play an essential role in maintaining MetS and may be influenced by white adipose tissue (WAT). WAT provides energy and promotes inflammation through adipokines, which affects both PsA inflammation and the metabolic state, such as by causing insulin resistance.[29] PsO has been identified as an independent risk factor for MI, with patients with severe PsO at higher risk.[30]

PsO severity correlates with body mass index (BMI), with a higher BMI associated with severe PsO. In addition, PsO patients with a higher BMI are more likely to show an impaired response to systemic therapy.[31] Research has shown an increased prevalence of obesity in patients with PsO and notably higher rates of obesity in PsA populations compared with RA populations; however, no significant difference was noted in the present systematic review. Studies have identified obesity as an important risk factor for the development of PsO and PsA.[27,32,33] Obesity, depending on age, gender, and serological status, can increase a patient's predisposition to RA by 40%–70%.[34,35] An elevated BMI also promotes low-grade inflammation through the production of cytokines, such as TNF and IL-6, in adipose tissue. The presence of obesity makes it more difficult for RA patients to reduce their overall disease activity and decreases the likelihood of remission using TNF-α inhibitors.[18]

In their systematic review, Shan et al. reported a correlation between obesity and the reduced efficacy of anti-TNF agents. In RA patients, reaching MDA was reduced in obese RA patients on TNF therapies compared with non-obese RA patients. PsO and PsA patients with obesity treated with anti-TNF agents also showed reduced efficacy in the study. Weight loss using a low-calorie diet has been shown to improve the response to anti-TNF agents in overweight and obese patients with PsA and PsO, which suggests that addressing obesity could represent an essential therapeutic strategy in managing obese patients with inflammatory arthritis.[36] Costa et al. assessed the correlation between MetS and the attainment of MDA in 330 patients who met the CASPAR classification criteria for PsA. At the end of the study period, 134/330 patients did not attain MDA, of whom 77.4% had MetS. The univariate and multivariate analyses conducted in the present study found that the presence of MetS resulted in a lower likelihood of attaining MDA.[19]

Evidence regarding the impact of MetS on RA is mixed. Several studies that assessed patients with RA with MetS showed this population is more likely to have higher Health Assessment Questionnaire (HAQ) scores than patients without MetS; however, other studies have not shown a significant difference.[37-41] Two large-scale studies that included 100 patients showed that MetS was associated with high systemic inflammatory markers, disease activity, and disability scores compared with patients with RA but without MetS.[42,43] Disease Activity Score of 28 joints (DAS-28) in patients with RA varied, with some studies showing a statistically insignificant increase in disease activity with the presence of MetS and others failing to demonstrate any link.[38,44] Some small studies have failed to show any correlation between disease activity using different disease activity scores, such as PASI, DAS28, Multidimensional HAQ – Routine Assessment of Patient Index Data 3 [MDHAQ-RAPID3], and other parameters in MetS using NCEP and WHO definitions.[45]

4.2 | Strengths of systematic review

This is the first systematic review to examine the prevalence of MetS in PsA populations. A variety of studies that included different validated definitions of MetS were included. Different classification criteria for RA and PsA were included in this study to best reproduce patients seen in the community. Studies that did not state how the study population was defined and studies that used International Classification of Diseases coding were excluded to improve diagnostic accuracy of the study population. There were also no geographical and language limitations placed on studies included in this systematic review.

4.3 | Limitations of the systematic review

In the PsO group, determining how many patients with PsO had concurrent PsA was difficult. Publication bias should also be considered, as studies that report positive outcomes are more likely to be published than those that do not, which could, in this case, lead to an over-estimation of MetS. Some data, specifically those relating to the prevalence of different MetS criteria, were not always available. The Doi plot suggested in both PsA and PsO study groups was minor (LFK = 1.71), and there was major asymmetry (LFK = 2.02), which indicated bias. Potential sources of bias included the sample variance sizes included and the different definitions of MetS, PsA, and RA used.[46] The asymmetry noted could be attributable to the multiple classification criteria for inflammatory arthritis and diagnostic criteria of MetS used. Lastly, there was geographic variance in the prevalence of MetS, which may have also resulted in bias.

4.4 | Implications for clinical practice

This systematic review found that the prevalence of MetS was significantly elevated in PsA populations compared with PsO and RA cohorts; in addition, it showed that the true prevalence was higher than that reported previously in the literature. MetS is often not assessed for by rheumatologists as part of routine assessments in patients with inflammatory arthritis. This systematic review showed that the presence of MetS is high, particularly in PsA populations. This should be addressed because different metabolic risk factors, including obesity (present in 62%), can affect the efficacy of disease-modifying therapy and the attainment of MDA and can increase the risk of cardiovascular morbidity and mortality. Managing CVD mortality and morbidity in rheumatoid populations through stringent CVD risk assessment and risk stratification in PsA populations should be routinely performed by rheumatologists.

Further, studies that utilize standardized definitions of MetS in PsA populations should be conducted to determine whether the presence of MetS can explain the increased CVD risk and mortality in psoriatic patients. In addition, the presence of MetS and its impact on MDA should be reviewed, given that obesity has already been identified as a poor prognostic indicator in MDA attainment, despite the use of biologics. Research should also examine whether aggressive management of CVD risk factors can increase the likelihood of attaining MDA without changing the pharmacological therapy. At present, no data on whether biological agents can positively influence cardiovascular outcomes and metabolic parameters, such as insulin resistance in patients with inflammatory arthritis, are available. Future studies should examine whether the use of biological therapies and tight disease control can modify patients' metabolic characteristics to improve CVD outcomes.

5 | CONCLUSION

This systematic review showed that the prevalence of MetS in PsA patients is 1.62 and 1.66 higher than patients diagnosed with PsO and RA. In PsA populations, patients from countries with a lower GNI tended to have a higher prevalence of MetS, and the prevalence of the disease was also higher when matched to RA and PsO populations from matched GNI groups. While the present study does not suggest a therapeutic benefit from the effective management of MetS in PsA populations, it does show that MetS is highly prevalent in the PsA population and should, therefore be assessed for, given the known association of MetS with increased cardiovascular morbidity and mortality. In addition, further studies should be conducted to determine whether optimizing these metabolic risk factors can improve disease activity in PsA populations and whether such an approach should be considered part of rheumatologists' standard of care for patients with PsA to enhance patient outcomes and promote MDA attainment.

ORCID

Aravinthan Loganathan https://orcid.org/0000-0003-3576-7204

REFERENCES

1. Gisondi P, Ferrazzi A, Girolomoni G. Metabolic comorbidities and psoriasis. *Acta Dermatovenerol Croat*. 2010;18(4):297-304.
2. Boehncke WH. Systemic inflammation and cardiovascular comorbidity in psoriasis patients: causes and consequences. *Front Immunol*. 2018;9:579.
3. Choudhary S, Patel R, Pradhan D, et al. Psoriasis and cardiovascular disorders: association or epiphenomenon? Meta-analysis of observational studies. *3 Biotech*. 2020;10(3):104.
4. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol*. 2011;20(4):303-307.
5. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med*. 2017;376(10):957-970.
6. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol*. 2019;80(1):251-65 e19.
7. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol*. 2019;15(3):153-166.
8. Ernste FC, Sanchez-Menendez M, Wilton KM, Crowson CS, Matteson EL, Maradit KH. Cardiovascular risk profile at the onset of psoriatic arthritis: a population-based cohort study. *Arthritis Care Res (Hoboken)*. 2015;67(7):1015-1021.
9. Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis*. 2009;68(7):1131-1135.
10. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum*. 1997;40(10):1868-1872.
11. Jagpal A, Navarro-Millan I. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. *BMC Rheumatol*. 2018;2:10.
12. Hansildaar R, Vedder D, Baniaamam M, Tausche A-K, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *Lancet Rheumatol*. 2021;3(1):e58-e70.
13. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ*. 2018;361:k1036.
14. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17-28.
15. Hong J, Maron DJ, Shirai T, Weyand CM. Accelerated atherosclerosis in patients with chronic inflammatory rheumatologic conditions. *Int J Clin Rheumtol*. 2015;10(5):365-381.
16. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2(5–6):231-237.
17. Feld J, Nissan S, Eder L, et al. Increased prevalence of metabolic syndrome and adipocytokine levels in a psoriatic arthritis cohort. *J Clin Rheumatol*. 2018;24(6):302-307.
18. Schafer M, Meissner Y, Kekow J, et al. Obesity reduces the real-world effectiveness of cytokine-targeted but not cell-targeted disease-modifying agents in rheumatoid arthritis. *Rheumatology (Oxford)*. 2020;59(8):1916–1926.
19. Costa L, Caso F, Ramonda R, et al. Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. *Immunol Res*. 2015;61(1–2):147-153.

20. Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc*. 2018;16(4):195-203.
21. Charidimou A, Boulouis G, Shams S, Calvet D, Shoamanesh A, International M-MI. Meta-analysis methodology in the microbleeds field: the relevance of the clinical question and study quality in choosing the most appropriate model. *J Neurol Sci*. 2017;381:348-349.
22. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
23. World Bank. *World Bank list of economies World Bank List of Economies*. The World Bank; 2018. https://databank.worldbank.org/data/download/site-content/CLASS.xls
24. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Prev Med Rep*. 2017;7:211-215.
25. Sigit FS, Tahapary DL, Trompet S, et al. The prevalence of metabolic syndrome and its association with body fat distribution in middle-aged individuals from Indonesia and the Netherlands: a cross-sectional analysis of two population-based studies. *Diabetol Metab Syndr*. 2020;12(1):2.
26. Jindal S, Jindal N. Psoriasis and cardiovascular diseases: a literature review to determine the causal relationship. *Cureus*. 2018;10(2):e2195.
27. Johnsson H, McInnes IB, Sattar N. Cardiovascular and metabolic risks in psoriasis and psoriatic arthritis: pragmatic clinical management based on available evidence. *Ann Rheum Dis*. 2012;71(4):480-483.
28. Weijers JM, Rongen-Van Dartel SAA, Hoevenaars DMGMF, Rubens M, Hulscher MEJL, Van Riel PLCM. Implementation of the EULAR cardiovascular risk management guideline in patients with rheumatoid arthritis: results of a successful collaboration between primary and secondary care. *Ann Rheum Dis*. 2018;77(4):480-483.
29. Caso F, Chimenti MS, Navarini L, et al. Metabolic Syndrome and psoriatic arthritis: considerations for the clinician. *Exp Rev Clin Immunol*. 2020;16(4):409-420.
30. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735.
31. Naldi L, Addis A, Chimenti S, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. *Dermatology*. 2008;217(4):365-373.
32. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Arch Intern Med*. 2007;167(15):1670-1675.
33. Gulati AM, Salvesen O, Thomsen RS, et al. Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trondelag Health Study (HUNT). *RMD Open*. 2018;4(1):e000630.
34. George MD, Baker JF. The obesity epidemic and consequences for rheumatoid arthritis care. *Curr Rheumatol Rep*. 2016;18(1):6.
35. Lu B, Hiraki LT, Sparks JA, et al. Being overweight or obese and risk of developing rheumatoid arthritis among women: a prospective cohort study. *Ann Rheum Dis*. 2014;73(11):1914-1922.
36. Shan J, Zhang J. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine*. 2019;86(2):173-183.
37. Abourazzak FE, Mansouri S, Najdi A, Tahiri L, Nejjari C, Harzy T. Prevalence of metabolic syndrome in patients with rheumatoid arthritis in Morocco: a cross-sectional study of 179 cases. *Clin Rheumatol*. 2014;33(11):1549-1555.
38. Eldin AB, ElBakry SA, Morad CS, Abd-El-Samie AM. The impact of metabolic syndrome on rheumatoid arthritis in a cohort of Egyptian patients. *Egyptian Rheumatol*. 2018;40(1):7-10.
39. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: case control study. *BMC Musculoskelet Disord*. 2013;14(1):147.
40. de Oliveira BMGB, Medeiros MMdC, de Cerqueira JVM, de Souza Quixadá RT, de Oliveira ÍMAX. Metabolic syndrome in patients with rheumatoid arthritis followed at a University Hospital in Northeastern Brazil. *Rev Brasil Reumatol*. 2016;56(2):117-125.
41. Ozmen M, Yersal O, Ozturk S, Soysal D, Koseeoglu MH. Prevalence of the metabolic syndrome in rheumatoid arthritis. *Eur J Rheumatol*. 2014;1(1):1-4.
42. Dao H-H, Do Q-T, Sakamoto J. Increased frequency of metabolic syndrome among Vietnamese women with early rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther*. 2010;12(6):R218.
43. Bilecik NA, Tuna S, Samancı N, Balcı N, Akbaş H. Prevalence of metabolic syndrome in women with rheumatoid arthritis and effective factors. *Int J Clin Exp Med*. 2014;7(8):2258-2265.
44. Ghazaly AHAH, El-Moez KMA, El Shorbagy MS, El-Nahrery EM. Angiopoietin-2 as a biomarker for metabolic syndrome and disease activity in rheumatoid arthritis patients. *Egyptian Rheumatol*. 2016;38(1):9-13.
45. Pehlevan S, Yetkin DO, Bahadır C, et al. Increased prevalence of metabolic syndrome in patients with psoriatic arthritis. *Metab Syndr Relat Disord*. 2014;12(1):43-48.
46. Lin L. Bias caused by sampling error in meta-analysis with small sample sizes. *PLoS ONE*. 2018;13(9):e0204056.

SUPPORTING INFORMATION

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

How to cite this article: Loganathan A, Kamalaraj N, Elhaddad C, Pile K. Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis. *Int J Rheum Dis*. 2021;24:1112–1120. https://doi.org/10.1111/1756-185X.14147

Received: 31 December 2020 | Revised: 7 May 2021 | Accepted: 9 May 2021

DOI: 10.1111/1756-185X.14148

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Prevalence of metabolic syndrome in patients with rheumatoid arthritis in eastern China—A hospital based study

Chun-yu Kong[1] | Chang-lei Wang[2] | Kai-jun Niu[3,4] | Wufang Qi[1]

[1]Tianjin First Center Hospital, Tianjin, China

[2]Tianjin University of Traditional Chinese Medicine, Tianjin, China

[3]Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, Tianjin, China

[4]Health Management Centre, Tianjin Medical University General Hospital, Tianjin, China

Correspondence
Wufang Qi, Tianjin First Center Hospital, No.24 Fukang Road, Nankai District, Tianjin 300192, China.
Email: wufangqi2021@sina.com

Funding information
This study was funded by Science and technology project of Tianjin Health Committee (No. ZC20043).

Abstract

Objective: The purpose of this hospital clinic based study was to evaluate the potential risk factors associated with the prevalence of MetS in RA population.

Methods: From January 2015 to October 2018, 717 patients with RA and 717 healthy controls who were treated or performed physical examination in Tianjin First Central Hospital were enrolled in this study. The basic disease diagnoses were recorded. A questionnaire was performed on all participants to assess the demographic details of the RA cohort. Moreover, laboratory indicators related to glucose and lipid metabolism in patients with RA were also detected. The potential risk factors for MetS were also analyzed.

Results: The prevalence of MetS were 31.2% and 34.2% in case and control groups, respectively ($P = .22$). There were lower levels of HDL-C, obesity, TG, LDL-C and TC in case group than control group (all $P < .05$). The hypertension levels in healthy controls was decreased in compared with patients with RA ($P < .05$). Nevertheless, in patients with RA, complement 3 (OR: 1.02; 95% CI: 1.01-1.03, $P = .007$) and less glucocorticoids use (OR: 0.63, 95% CI: 0.39-0.99, $P = .046$) were associated with MetS.

Conclusion: The prevalence of MetS was not associated with RA. Complement 3 may be associated with the higher prevalence of MetS in patients with RA. Glucocorticoids treatment may be associated with MetS.

KEYWORDS

influencing factors, metabolic syndrome, prevalence, rheumatoid arthritis

1 | INTRODUCTION

Metabolic syndrome (MetS) is a state of aggregation of multiple metabolic risk factors of cardiovascular disease (CVD). MetS includes high blood sugar, hypertension (HBP), central obesity, dyslipidemia.[1] A previous study has suggested that all-cause mortality and CVD prevalence are both associated with MetS.[2] Furthermore, MetS is also associated with cholelithiasis,[3] chronic kidney disease,[4] hyperuricemia,[5] obstructive sleep apnea (OSA),[6] and nonalcoholic fatty liver disease.[7]

For rheumatoid arthritis (RA), the risk factors for MetS include higher levels of inflammation, functional status, disease activity (DAS28), pain, disability score, the drugs used and rheumatoid cachexia.[8-14] An American study has indicated that several chronic inflammatory diseases, such as RA, have higher incidence of MetS.[15] However, this result is contrary to an Iranian study.[16] Therefore, it needs to further explore the prevalence of MetS in patients with RA in comparison with healthy controls in different regional population.

Therefore, we aimed to investigate the prevalence of MetS in patients with RA, and to evaluate the potential risk factors for MetS.

2 | PATIENTS AND METHODS

2.1 | Patients

This study obtained the approval of the Ethics committee of Tianjin First Central Hospital. Informed consent provided by all participants. There were 717 patients with RA in Tianjin First Central Hospital between January 2015 to October 2018 and 717 healthy controls who were randomly selected from the Physical Examination Center. The healthy population were age-sex matched without rheumatological disease, and they were the population in the health examination center of the hospital in the same period. Patients with RA were admitted to the Department of Rheumatology and immunology of the hospital during the investigation period. Inclusion criteria: (a) patients with RA who met the diagnostic criteria of the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [17]; (b) subjects who were 18 or older; (c) patients signed informed consent; and (d) patients were seropositive with newly diagnosed RA. Exclusion criteria: (a) patients who were combined with other immune diseases, (b) patients with malignant tumor or benign tumor affecting endocrine function, (c) pregnant and lactating women. The list of medications was obtained for all patients and included in the analysis.

2.2 | Assessments

Patients with RA were provided with a questionnaire, which included information regarding age, sex, lifestyle, RA medications, disease duration, and history of obesity, high blood pressure (HBP), diabetes mellitus (DM). The levels of blood pressure, TC, HDL-C, TG, and LDL-C were measured. ESR, hs-CRP, WBC, serum complement 3(C3), serum complement C4(C4), AKA, ACPA, D-Dimer, and plasma fibrinogen (Fib) were also measured.

2.3 | Definition of MetS

Chinese Diabetes Society (CDS) has defined the MetS,[18] and Asian criteria of central obesity was also used.[19] Three or more of the following are defined as MetS. (a). Blood pressure is more than 130/85 mmHg; (b) fasting blood glucose is more than 5.6 mmol/L) or there is a history of DM; (c) BMI is more than 25 kg/m^2; (d) serum TG level is more than 1.7 mmol/L; (e) HDL-C level is less than 1.0 mmol/L for male or 1.3 mmol/L for female.

2.4 | Statistical analysis

The continuous variables of normal distribution were described as means and 95% confidence interval (CI) and compared by *t*-test. Categorical variables were presented as percentage or frequency and compared by chi-square test. The potential risk factors of MetS were analyzed by multivariate logistic regression model. All covariates in the present study were chosen referring to the previous studies.[20-24]

Propensity scores were obtained by a logistic regression model and the following covariates, including Erythrocyte sedimentation rate, high-sensitivity C-reactive protein (CRP), Complement 3, Anti-keratin antibody, Anti-cyclic citrullinated peptide antibodies, plasma fibrinogen, drugs, glucocorticoid, and disease duration. Statistical Analysis System version 9.3 (SAS Institute Inc.) was used for statistical analysis. $P < .05$ was showed notable difference.

3 | RESULTS

3.1 | Descriptive characteristics of the subjects

The characteristics of subjects were presented in Table 1. The difference in the prevalence of MetS between RA and healthy controls was NOT statistically significant in our study ($P = .22$). However, patients with RA had higher percentages of HBP and diastolic blood pressure than healthy controls ($P < .05$). Additionally, the levels of BMI, TG, HDL-C, LDL-C and TC were all higher in control group than RA group ($P < .05$).

3.2 | Analysis of potential factors associated with metabolic syndrome in patients with RA

The potential risk factors of MetS in RA were shown in Table 2. Higher C3 level and obesity prevalence were both risk factors of MetS in patients with RA (OR: 1.02 and 1.03; 95% CI: 1.03-1.10 and 1.01-1.04; $P < .05$). However, we found that GCs were inversely related to MetS and DM (OR: 0.63 and 0.46; 95% CI: 0.39-0.99 and 0.25-0.84; $P < .05$). Furthermore, higher C3, higher ESR and less DMARDS use were associated with the frequency of the HBP in patients with RA (OR: 1.02, 1.06 and 1.78; 95% CI: 1.01-1.04, 1.01-1.12 and 1.30-3.09; $P < .05$). Furthermore, higher AKA and higher Fib were both risk factors for DM in patients with RA (OR: 1.61 and 1.56; 95% CI: 1.01-2.56 and 1.004-2.42; $P < .05$). C3 level was related to TG level in patients with RA (OR: 1.03, 95% CI: 1.02-1.04, $P < .0001$).

4 | DISCUSSION

The prevalence of MetS is 31.2% in patients with RA and 34.2% in healthy controls, respectively. In this study, we analyzed the characteristics of subjects, and explored the related risk factors of MetS in patients with RA. We found that patients with RA had lower levels of TC, TG, HDL-C, LDL-C and BMI in comparison with healthy controls. In addition, the prevalence of HBP in patients with RA was higher than healthy controls. Higher complement 3 and less glucocorticoids were associated with MetS.

TABLE 1 Clinical characteristics of patients with RA and healthy controls (Age- and sex- matching) (n = 2108)

Characteristics	RA		F/χ^2 value	*P* value
	No	Yes		
No. of RA	n = 717	n = 717	—	—
Age (year)	60.6 (59.8, 61.5)	61.0 (60.2, 61.8)	0.33	.56
Sex (female, %)	79.7	78.8	0.22	.64
MetS (%)	34.2	31.2	1.49	.22
DBP (mm Hg)	78.7 (77.9, 79.6)	82.8 (82.0, 83.6)	46.38	<.0001
SBP (mm Hg)	130.9 (129.4, 132.4)	132.5 (131.0, 133.9)	2.15	.14
HBP (%)	58.4	69.6	20.55	<.0001
BMI (kg/m^2)	25.3 (25.1, 25.6)	23.4 (23.1, 23.7)	96.82	<.0001
TG (mmol/L)	1.60 (1.54, 1.67)	1.20 (1.14, 1.27)	70.25	<.0001
HDL-C (mmol/L)	1.45 (1.42, 1.48)	1.27 (1.24, 1.30)	78.40	<.0001
LDL (mmol/L)	3.27 (3.21, 3.34)	2.95 (2.89, 3.02)	43.01	<.0001
TC (mmol/L)	5.42 (5.34, 5.5)	4.60 (4.52, 4.68)	208.69	<.0001
C3 (mg/dL)	103.7 (102.0, 105.3)	98.9 (97.2, 100.6)	15.55	<.0001
C4 (mg/dL)	22.6 (22.1, 23.1)	21.6 (21.0, 22.1)	7.35	<.01
DM (%)	16	16.2	0.01	.94
WBC ($\times 10^9/L$)	5.56 (5.42, 5.70)	6.39 (6.22, 6.56)	55.57	<.0001
hs-CRP (mg/L)	2.12 (1.72, 2.52)	2.67 (2.22, 3.11)	3.24	.07

Note: Data are expressed as Geometric mean (95% confidence interval).

Abbreviations: BMI, body mass index; C3, Complement 3; C4, Complement 4; DBP, diastolic blood pressure; DM, diabetes; HBP, hypertension; HDL, high-density lipoprotein-cholesterol; hs-CRP, Hypersensitive C-reactive protein; LDL, low density lipoprotein cholesterol; MetS, Metabolic syndrome; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol; TG, Triglyceride; WBC, white blood cell count.

The frequency of MetS varies depending on the geographical region of the population.[25] The prevalence of MetS in patients with RA ranges from 10.6% to 55.5%.[26] For example, the prevalence of MetS is 27.2% in Iran,[27] 31.3% in Pakistan[21] and 39.28% in India.[20] Moreover, different diagnostic criteria of MetS also leads to different prevalence.[25,28] Yi KH et al[29] pointed out that the prevalence of MetS in patients with RA was not widespread in Asia than that in non-Asian populations. It might be related to ethnic differences in the prevalence of obesity and dairy-related product consumption.[30,31]

MetS components include HBP, hyperglycemia, decreased HDL-C level, elevated TG level, and central obesity. We found that there was a high prevalence of HBP in RA group in comparison with the healthy controls, which was similar to previous studies.[9,32,33] Patients with RA had many risk factors related to HBP, including chronic inflammation and disease duration.[34,35] Inflammatory cytokines may increase the incidence of arterial stiffness, which lead to the possibility that higher levels of inflammatory cytokines could contribute to increased frequency of HBP in patients with RA.[36] Additionally, medicines, including GCs, NSAIDs and leflunomide, might induce the prevalence of HBP in patients with RA. GCs increase the cardiac output and the circulatory volume, which make vascular tissues more sensitive to catecholamine.[37] Side effects of NSAIDs, including blocking the synthesis of prostaglandins, result in increased water retention and serum sodium.[37] Therefore, when prescribing drugs that may affect blood pressure, doctors should prescribe patients to check blood pressure regularly and take relevant measures.[37]

In addition, we find that the patients in the control group is overweight. This may be contributed to the nutritional status or the cachexia caused by RA.[38] It has been pointed out that excessive levels of inflammatory factors are contributed to the cachexia in patients with RA,[39] which may be due to increased hydrolysis of muscle protein by acting on nuclear factor (NF)-κB through the ubiquitin-proteasome pathway.[40] These cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), influence on energy and protein metabolism.[41] In addition to IL-1β and TNF-α, IL-6 and interferon-γ are also involved in the pathogenesis of cachexia.[41] The GCs are also associated with BMI, which are related to steroid myopathy by acting on the transcription factor FOXO and increased protein catabolism that cause muscle atrophy.[42]

In the present study, patients with RA had lower TG level compared with the healthy controls. However, some researchers reported contradictory TG levels in patients with RA.[43,44] Antirheumatic drugs, including prednisolone, hydroxychloroquine and methotrexate, can reduce TG levels.[45] Hydroxychloroquine is one of the disease-modifying antirheumatic drugs, which is frequently used in patients with RA. It has a positive effect on the levels of serum lipids, so that it can decrease the TG level.[45] Another meta-analysis has pointed out that statin could reduce the TG level.[46] However, decreased PON1 activity, increasing BMI, the presence of diabetes,

TABLE 2 Multivariate logistic regression of the odds ratios (95% confidence interval) or variance for the Characteristic of patients with RA according to presence or absence of metabolic syndrome

Characteristics	Mets (%)	*P* value	Obesity (%)	*P* value	TG (mmol/L)	*P* value	HDL (mmol/L)	*P* value	HBP (%)	*P* value	DM (%)	*P* value
Age (year)	1.01 (0.99, 1.04)	.3	1.00 (0.98, 1.03)	.89	1.04 (1.01, 1.07)	<.01	0.95 (0.93, 0.98)	<.0001	1.06 (1.03, 1.09)	<.0001	1.06 (1.03, 1.10)	<.001
Sex	0.53 (0.16, 1.62)	.27	1.10 (0.36, 3.37)	.87	0.45 (0.12, 1.56)	.22	1.72 (0.58, 5.28)	.33	0.53 (0.17, 1.67)	.28	0.57 (0.07, 3.06)	.54
ESR (mm/h)	1.00 (0.95, 1.04)	.81	0.95 (0.91, 1.00)	.06	0.96 (0.91, 1.01)	.18	1.03 (0.99, 1.08)	.21	1.06 (1.01, 1.12)	.04	0.92 (0.83, 1.00)	.07
hs-CRP (mg/L)	0.99 (0.91, 1.07)	.83	1.00 (0.92, 1.08)	.99	1.03 (0.94, 1.12)	.54	1.01 (0.93, 1.10)	.83	0.92 (0.84, 1.00)	.06	1.08 (0.98, 1.20)	.1
C3 (mg/dL)	1.02 (1.01, 1.03)	<.01	1.03 (1.01, 1.04)	<.001	1.03 (1.02, 1.04)	<.0001	1.00 (0.99, 1.01)	.76	1.02 (1.01, 1.04)	<.01	0.99 (0.98, 1.01)	.45
AKA	0.91 (0.63, 1.31)	.62	0.87 (0.60, 1.26)	.46	1.08 (0.73, 1.60)	.69	0.91 (0.64, 1.31)	.62	0.98 (0.66, 1.48)	.92	1.61 (1.01, 2.56)	.045
ACC (μ/mL)	1.00 (1.00, 1.00)	.68	1.00 (1.00, 1.00)	.056	1.00 (1.00, 1.00)	.84	1.00 (1.00, 1.00)	.86	1.00 (1.00, 1.00)	.7	1.00 (1.00, 1.00)	.046
D-Dimer (μL)	1.00 (1.00, 1.00)	.2	1.00 (1.00, 1.00)	.26	1.00 (1.00, 1.00)	.19	1.00 (1.00, 1.00)	.56	1.00 (1.00, 1.00)	.73	1.00 (1.00, 1.00)	.04
Fib (g/l)	1.01 (0.73, 1.41)	.94	0.79 (0.56, 1.10)	.16	0.81 (0.56, 1.17)	.27	1.20 (0.87, 1.68)	.28	1.27 (0.88, 1.87)	.21	1.56 (1.00, 2.42)	.047
DMARDS	1.40 (0.83, 2.40)	.21	0.89 (0.53, 1.51)	.67	1.22 (0.70, 2.14)	.49	1.36 (0.82, 2.24)	.23	1.78 (1.03, 3.09)	.04	0.81 (0.43, 1.57)	.53
GC	0.63 (0.39, 0.99)	.046	0.82 (0.52, 1.29)	.39	0.82 (0.50, 1.34)	.42	0.94 (0.60, 1.47)	.79	1.39 (0.85, 2.28)	.19	0.46 (0.25, 0.84)	.01
NSAIDs	1.17 (0.75, 1.83)	.49	1.22 (0.78, 1.91)	.38	0.91 (0.56, 1.47)	.69	1.05 (0.67, 1.62)	.84	0.66 (0.41, 1.08)	.1	1.34 (0.74, 2.44)	.33
Amenorrhea	1.64 (0.64, 4.51)	.32	1.46 (0.58, 3.72)	.43	1.27 (0.44, 4.08)	.68	0.80 (0.30, 2.03)	.64	1.08 (0.44, 2.66)	.86	1.33 (0.29, 9.58)	.74
Smoke	0.95 (0.53, 1.71)	.88	0.92 (0.50, 1.67)	.78	0.85 (0.45, 1.60)	.63	1.75 (0.99, 3.15)	.055	0.91 (0.48, 1.76)	.78	1.24 (0.60, 2.51)	.56
Course (year)	0.99 (0.96, 1.01)	.36	0.98 (0.95, 1.00)	.09	1.00 (0.97, 1.03)	1.00	1.02 (0.99, 1.04)	.24	0.997 (0.97, 1.03)	.85	0.99 (0.96, 1.03)	.72

Note: Data were expressed as Odds ratios (95% confidence interval).

Abbreviations: ACCP, Anti-cyclic citrullinated peptide antibodies; AKA, Anti-keratin antibody; C3, Complement 3; Course, Course of the disease; DMARDS, disease-modifying anti-rheumatic drugs; ESR, Erythrocyte sedimentation rate; Fib, plasma fibrinogen; GC, glucocorticoid; hs-CRP, Hypersensitive C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

and systemic inflammation outcome on TNF-α blockade can increase TG levels.[47,48] Therefore, medication and treatment used in patients with RA have a potential effect on the levels of the serum lipids.[45]

C3 plays an important role not only in immune complexes and microorganisms, but also in inflammation.[49] Previous studies have indicated that the inflammatory pathway is activated, especially the complement factor, which is responsible for the increased prevalence of MetS.[50] We found that C3 was a risk factor for MetS. At the same time, we found that C3 was positively correlated with TG level in patients with RA. C3 can generate C3a, a C3 fragment consisting of 77 amino acids, by interacting with factor B and factor D. Its terminal arginine is excised to form C3adesArg, such as ASP.[51] ASP can increase the synthesis and release of TG in fat cells,[52] that is, the C3 level increases, the TG level also increases.

We found that GCs are inversely related to MetS. The relationship between GCs and the prevalence of MetS remains controversial. GCs promote the proliferation and differentiation of adipocytes.[53] However, Peckett AJ et al[54] pointed out that the effect of GCs on adipose tissue depended on the duration of exposure and dose. GCs also are associated with HBP,[55] central obesity,[56] and induction of blood glucose fluctuations.[57] These factors can increase the prevalence of MetS.[26] Whereas others studies have suggested that GCs were not notably related to the prevalence of MetS.[58] This may be due to immunological intervention that effectively improves the patient's lipid mass spectrometry, especially the level of HDL-C.[59]

There are also some limitations in this study. For example, patients take many kinds of drugs to treat the disease, and those drugs may affect the efficacy and the patient's condition. Drugs produced by different manufacturers may have different efficacy, which cannot be corrected one by one. Second, the prednisone dose was not collected.

5 | CONCLUSION

In conclusion, there was no statistically significant difference in prevalence of MetS in our population. Complement 3 may be increase the prevalence of MetS in patients with RA. Glucocorticoids treatment may be associated with MetS.

ORCID

Wufang Qi https://orcid.org/0000-0003-0774-3934

REFERENCES

1. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469-480.
2. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113-1132.
3. Grundy SM. Cholesterol gallstones: a fellow traveler with metabolic syndrome? *Am J Clin Nutr*. 2004;80:1-2.
4. Kitiyakara C, Yamwong S, Cheepudomwit S, et al. The metabolic syndrome and chronic kidney disease in a Southeast Asian cohort. *Kidney Int*. 2007;71:693-700.
5. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med*. 2007;120:442-447.
6. Theorell-Haglow J, Berne C, Janson C, Lindberg E. The role of obstructive sleep apnea in metabolic syndrome: a population-based study in women. *Sleep Med*. 2011;12:329-334.
7. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143:722-728.
8. Dao HH, Do QT, Sakamoto J. Increased frequency of metabolic syndrome among Vietnamese women with early rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther*. 2010;12:R218.
9. Karvounaris SA, Sidiropoulos PI, Papadakis JA, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. *Ann Rheum Dis*. 2007;66:28-33.
10. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation*. 2005;111:1448-1454.
11. Nakanishi N, Shiraishi T, Wada M. Association between C-reactive protein and insulin resistance in a Japanese population: the Minoh Study. *Intern Med*. 2005;44:542-547.
12. Sidiropoulos PI, Karvounaris SA, Boumpas DT. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. *Arthritis Res Ther*. 2008;10:207.
13. Zonana-Nacach A, Santana-Sahagun E, Jimenez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. *J Clin Rheumatol*. 2008;14:74-77.
14. da Cunha VR, Brenol CV, Brenol JC, Xavier RM. Rheumatoid arthritis and metabolic syndrome. *Rev Bras Reumatol*. 2011;51:260-268.
15. Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis*. 2008;196:756-763.
16. Sahebari M, Goshayeshi L, Mirfeizi Z, et al. Investigation of the association between metabolic syndrome and disease activity in rheumatoid arthritis. *Scientific World J*. 2011;11:1195-1205.
17. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581.
18. Chinese Medical Association, Diabetes Society, Metabolic Syndrome Research Collaboration Group. Chinese Medical Association Diabetes Society advice on metabolic syndrome. *Chin J Diabetes*. 2004;3:5-10.
19. Heng D, Ma S, Lee JJ, et al. Modification of the NCEP ATP III definitions of the metabolic syndrome for use in Asians identifies individuals at risk of ischemic heart disease. *Atherosclerosis*. 2006;186:367-373.
20. Pandey PK, Swami A, Biswas TK, Thakuria R. Prevalence of metabolic syndrome in treatment naive rheumatoid arthritis and correlation with disease parameters. *Arch Rheumatol*. 2017;32:46-52.
21. Zafar ZA, Mahmud TH, Rasheed A, Wagan AA. Frequency of metabolic syndrome in Pakistani cohort of patients with rheumatoid arthritis. *J Pak Med Assoc*. 2016;66:671-676.
22. de Oliveira BM, Medeiros MM, de Cerqueira JV, de Souza Quixada RT, de Oliveira IM. Metabolic syndrome in patients with rheumatoid arthritis followed at a University Hospital in Northeastern Brazil. *Rev Bras Reumatol Engl Ed*. 2016;56:117-125.
23. Ozmen M, Yersal O, Ozturk S, Soysal D, Koseeoglu MH. Prevalence of the metabolic syndrome in rheumatoid arthritis. *Eur J Rheumatol*. 2014;1:1-4.
24. Salinas MJ, Bertoli AM, Lema L, et al. Prevalence and correlates of metabolic syndrome in patients with rheumatoid arthritis in Argentina. *J Clin Rheumatol*. 2013;19:439-443.

25. Zhang J, Fu L, Shi J, et al. The risk of metabolic syndrome in patients with rheumatoid arthritis: a meta-analysis of observational studies. *PLoS One*. 2013;8:e78151.
26. Hallajzadeh J, Safiri S, Mansournia MA, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: a comprehensive updated systematic review and meta-analysis. *PLoS One*. 2017;12:e0170361.
27. Karimi M, Mazloomzadeh S, Kafan S, Amirmoghadami H. The frequency of metabolic syndrome in women with rheumatoid arthritis and in controls. *Int J Rheum Dis*. 2011;14:248-254.
28. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: case control study. *BMC Musculoskelet Disord*. 2013;14:147.
29. Yiu KH, Tse HF, Mok MY, Lau CS. Ethnic differences in cardiovascular risk in rheumatic disease: focus on Asians. *Nat Rev Rheumatol*. 2011;7:609-618.
30. Chiu M, Austin PC, Manuel DG, Tu JV. Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. *CMAJ*. 2010;182:E301-E310.
31. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr*. 2008;87:1914-1925.
32. Panoulas VF, Douglas KM, Milionis HJ, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2007;46:1477-1482.
33. Gomes KWP, Luz AJP, Felipe MRB, Beltrao LA, Sampaio AXC, Rodrigues CEM. Prevalence of metabolic syndrome in rheumatoid arthritis patients from Northeastern Brazil: Association with disease activity. *Mod Rheumatol*. 2018;28:258-263.
34. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension*. 2005;46:1118-1122.
35. Bajraktari IH, Rexhepi S, Berisha I, et al. Prevalence of asymptomatic arterial hypertension and its correlation with inflammatory activity in early rheumatoid arthritis. *Open Access Maced J Med Sci*. 2017;5:641-644.
36. Dulai R, Perry M, Twycross-Lewis R, Morrissey D, Atzeni F, Greenwald S. The effect of tumor necrosis factor-alpha antagonists on arterial stiffness in rheumatoid arthritis: a literature review. *Semin Arthritis Rheum*. 2012;42:1-8.
37. Diaconu CC, Dediu GN, Iancu MA. Drug-induced arterial hypertension - a frequently ignored cause of secondary hypertension: a review. *Acta Cardiol*. 2018;1-7.
38. Malecka-Massalska T, Majdan A. Malnutrition and obesity among patients with rheumatoid arthritis and chronic inflammatory process. *Wiad Lek*. 2018;71:52-58.
39. Roubenoff R, Roubenoff RA, Cannon JG, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J Clin Invest*. 1994;93:2379-2386.
40. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr*. 2006;83:735-743.
41. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology (Oxford)*. 2004;43:1219-1223.
42. Schakman O, Gilson H, Thissen JP. Mechanisms of glucocorticoid-induced myopathy. *J Endocrinol*. 2008;197:1-10.
43. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Metabolic syndrome in rheumatoid arthritis. *Maedica (Buchar)*. 2012;7:148-152.
44. Garcia-Gomez C, Nolla JM, Valverde J, Gomez-Gerique JA, Castro MJ, Pinto X. Conventional lipid profile and lipoprotein(a) concentrations in treated patients with rheumatoid arthritis. *J Rheumatol*. 2009;36:1365-1370.
45. Karimifar M, Sepehrifar MS, Moussavi H, et al. The effects of conventional drugs in the treatment of rheumatoid arthritis on the serum lipids. *J Res Med Sci*. 2018;23:105.
46. Li GM, Zhao J, Li B, et al. The anti-inflammatory effects of statins on patients with rheumatoid arthritis: a systemic review and meta-analysis of 15 randomized controlled trials. *Autoimmun Rev*. 2018;17:215-225.
47. Rodriguez-Carrio J, Alperi-Lopez M, Lopez P, et al. High triglycerides and low high-density lipoprotein cholesterol lipid profile in rheumatoid arthritis: a potential link among inflammation, oxidative status, and dysfunctional high-density lipoprotein. *J Clin Lipidol*. 2017;11:1043-1054.e2.
48. Davis LA, Whitfield E, Cannon GW, et al. Association of rheumatoid arthritis susceptibility gene with lipid profiles in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53:1014-1021.
49. Morgan BP, Gasque P. Extrahepatic complement biosynthesis: where, when and why? *Clin Exp Immunol*. 1997;107:1-7.
50. Liu Z, Tang Q, Wen J, et al. Elevated serum complement factors 3 and 4 are strong inflammatory markers of the metabolic syndrome development: a longitudinal cohort study. *Sci Rep*. 2016;6:18713.
51. Baldo A, Sniderman AD, St-Luce S, et al. The adipsin-acylation stimulating protein system and regulation of intracellular triglyceride synthesis. *J Clin Invest*. 1993;92:1543-1547.
52. Yasruel Z, Cianflone K, Sniderman AD, Rosenbloom M, Walsh M, Rodriguez MA. Effect of acylation stimulating protein on the triacylglycerol synthetic pathway of human adipose tissue. *Lipids*. 1991;26:495-499.
53. Rebuffe-Scrive M, Walsh UA, McEwen B, Rodin J. Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. *Physiol Behav*. 1992;52:583-590.
54. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. *Metabolism*. 2011;60:1500-1510.
55. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2008;47:72-75.
56. Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension*. 1999;33:1364-1368.
57. Panthakalam S, Bhatnagar D, Klimiuk P. The prevalence and management of hyperglycaemia in patients with rheumatoid arthritis on corticosteroid therapy. *Scott Med J*. 2004;49:139-141.
58. Toms TE, Panoulas VF, Douglas KM, Griffiths HR, Kitas GD. Lack of association between glucocorticoid use and presence of the metabolic syndrome in patients with rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther*. 2008;10:R145.
59. Georgiadis AN, Papavasiliou EC, Lourida ES, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment–a prospective, controlled study. *Arthritis Res Ther*. 2006;8:R82.

How to cite this article: Kong C-Y, Wang C-L, Niu K-J, Qi W. Prevalence of metabolic syndrome in patients with rheumatoid arthritis in eastern China—A hospital based study. *Int J Rheum Dis*. 2021;24:1121–1126. https://doi.org/10.1111/1756-185X.14148

Received: 5 May 2021 | Revised: 17 June 2021 | Accepted: 21 June 2021

DOI: 10.1111/1756-185X.14173

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

A Benchmarking Study Evaluating Axial Spondyloarthritis Burden in Spain and Other European Countries. Results from the Spanish Atlas and the European Map of Axial Spondyloarthritis (EMAS) Studies

Marco Garrido-Cumbrera[1,2] | Jordi Gratacós[3] | Eduardo Collantes-Estevez[4,5] | Pedro Zarco-Montejo[6] | Carlos Sastre[7] | Laura Christen[8] | Sergio Sanz-Gómez[1] | José Correa-Fernández[1] | Victoria Navarro-Compán[9]

[1]Health & Territory Research, Universidad de Sevilla, Seville, Spain

[2]Spanish Federation of Spondyloarthritis Associations (CEADE), Madrid, Spain

[3]Hospital Universitari Parc Taulí, Barcelona, Spain

[4]Reina Sofia University Hospital, Cordova, Spain

[5]Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Universidad de Córdoba, Cordova, Spain

[6]Hospital Universitario Fundación Alcorcón, Madrid, Spain

[7]Novartis Farmacéutica S.A, Barcelona, Spain

[8]Novartis Pharma AG, Basel, Switzerland

[9]Hospital Universitario La Paz, IdiPaz, Madrid, Spain

Correspondence
Marco Garrido-Cumbrera, Centro Internacional de la Universidad de Sevilla, Avenida Ciudad Jardín 20-22, 41005, Sevilla, Spain.
Email: mcumbrera@us.es

Funding information
Novartis Pharma AG

Abstract

Aim: To compare the burden of disease in Spanish patients with axial spondyloarthritis (axSpA) vs other European countries (OEC).

Methods: Data from 2846 unselected patients from the European Map of Axial Spondyloarthritis (EMAS) and the Atlas of Axial Spondyloarthritis in Spain (Atlas) were collected through online surveys. Comparative analysis was carried out between Spanish patients (2016) and patients from 12 OEC (2017-2018). Socio-demographic characteristics, life habits, and patient-reported outcomes (Bath Ankylosing Spondylitis Disease Activity Index 0-10, spinal stiffness 3-12, functional limitation 0-54, the 12-Item General Health Questionnaire [GHQ-12] for psychological distress 0-12) were compared. Chi-square and Mann-Whitney tests were used for qualitative and quantitative variables respectively.

Results: 680 (23.9%) Spanish axSpA patients were compared to 2166 axSpA patients (76.1%) from OEC. Compared to Spain, the OEC group had a higher percentage of females (64.1% vs 52.5%; $P < .001$) and university-educated participants (51.7% vs 36.9%; $P < .001$). Spanish patients showed a greater diagnostic delay (8.5 ± 7.7 vs 7.2 ± 8.6 years; $P < .001$), visits to orthopedic specialists before diagnosis (56.9% vs 25.3%; $P < .001$), human leukocyte antigen-B27 carriership (77.1% vs 70.1%; $P = .003$), disease activity (5.7 ± 2.0 vs 5.4 ± 2.0; $P = .024$), and higher unemployment rates (21.7% vs 9.2%; $P < .001$). Despite lower rates of diagnosed anxiety and depression, Spanish patients were at higher risk of psychological distress according to the GHQ-12 (5.7 ± 4.5 vs 4.8 ± 4.0; $P < .001$).

Conclusion: Compared to European axSpA patients, Spanish patients experience a longer diagnostic delay and greater psychological distress. Being wrongly referred to orthopedic specialists and facing a more precarious labor scenario appear as

possible causal factors, highlighting the need to increase the number of rheumatologists, the training of healthcare professionals, and improving axSpA patients' working conditions.

KEYWORDS

ankylosing spondylitis, axial spondyloarthritis, diagnostic delay, employment status, patient-reported outcomes, psychological distress

1 | INTRODUCTION

Axial spondyloarthritis (axSpA) is a disease associated with a high degree of disease burden and disability,[1] and consequently with a high cost per patient to European national health systems.[2-4] This disease has been the focus of extensive research in recent decades. From this growing interest in axSpA, different research registries and cohorts have emerged at national levels in Europe. Some examples are the DANBIO,[5] DESIR,[6] GESPIC,[7] OASIS,[8] SPACE,[9] SWISS,[10] or REGISPONSER,[11] the objectives of which are to study the characteristics of axSpA and understand the clinical aspects to improve patient management and treatment. However, despite the relevant clinical value of these studies, which allowed researchers to reach a better understanding of the functioning of axSpA and related conditions, these records have some limitations in providing answers to further research questions. On the one hand, there is a trend in these studies to leave aside life spheres that are of key importance from the patient's perspective, such as work experience or mental health. On the other hand, most of these registries and cohorts have been carried out on a national level and it is therefore not possible to compare data between different countries.

The systematic study of other life spheres, also affected by the disease either in a direct or indirect way, escapes clinical studies almost entirely. To give an example, only the DESIR cohort study collects some data on the impact of axSpA on working life for the total study population, based on indirect measures such as absenteeism through sick leave or level of disability.[6] There is a wide research gap not only on the disease's impact on working life, but also in the association of the condition with poorer psychological health or the patient's perspective with respect to their own disease.

Additionally, despite the rigor of the studies presented, they utilize different methodologies in terms of sample inclusion criteria, sampling method and variables collected, so a comparison of the disease characteristics and status of patients with axSpA between European countries is not possible. Some studies are international, like the OASIS. However, its scope covers only 3 countries of similar geographical and socio-economic conditions (France, Belgium, and the Netherlands).[8] Even if great efforts are being made in order to carry out joint studies of different registries that allow for greater generalizability of results, this research is still subject to problems due to the different methodologies used by said registries, leading to sample bias [12] or lack of comparability of the relevant indicators for axSpA patients' health.[13]

All of these reasons made it necessary to conduct a study on axSpA from the patient's perspective, collecting representative country samples under 1 common methodology, thereby allowing comparisons of national data in relation to a European framework. That is one of the main objectives of the European Map of Axial Spondyloarthritis (EMAS), upon which data for this study is based.

Benchmarking studies in axSpA may provide evidence of disparities, making it necessary to improve the healthcare and management of these patients. The aim of this study is to analyze the burden of the disease in axSpA patients in Spain compared with that of patients from other European countries (OEC) in terms of sociodemographic characteristics, diagnostic journey, disease activity, function, and psychosocial wellbeing.

2 | MATERIALS AND METHODS

2.1 | The Atlas and EMAS working groups

The Atlas of Axial Spondyloarthritis in Spain is an initiative of the Spanish Federation of Spondyloarthritis Associations (CEADE), carried out by the Health & Territory Research (HTR) group of the University of Seville and the Max Weber Institute, with the collaboration of the Spanish Society of Rheumatology (SER), and the support of Novartis Spain. Results from the Atlas raised international interest and thus, an equivalent research following the same methodology was carried out. This extension of the project to OEC was addressed as EMAS, and it was also led by HTR in collaboration with the Axial Spondyloarthritis International Federation (ASIF), along with patient organizations in participating countries, and the support of Novartis headquarters. The EMAS project continues expanding, being currently carried out in additional countries in Africa, America, Asia, and Europe under the new brand International Map of Axial Spondyloarthritis (IMAS). More information about the Atlas[14] and EMAS[15] can be found in their seminal studies.

2.2 | Design and survey development

The Atlas of Axial Spondyloarthritis in Spain is a cross-sectional study gathering data through an online survey of 680 unselected patients with self-reported axSpA diagnosis.[14] This Spanish survey was adapted into the EMAS survey, which recruited an additional 2166 axSpA patients from 12 different European countries other than Spain: Austria,

Belgium, France, Germany, Italy, the Netherlands, Norway, Russia, Slovenia, Sweden, Switzerland, the United Kingdom. To develop the EMAS questionnaire, the steering committee and participating countries were asked to assess and modify questions for local relevance, with guidance to only make essential changes in order to maintain consistency between the Atlas and EMAS studies, on a pan-European level. The EMAS questionnaire was developed in English and subsequently translated into the languages of the other European countries involved (Dutch, French, German, Italian, Russian, Swedish, and Slovenian). The final EMAS patient questionnaire included 108 items of the original 116 of the Atlas, related to 12 different areas: socio-demographic and anthropometric characteristics, disability and performance, work life, daily life, lifestyle habits, diagnostic process, healthcare resource use, treatment, other disorders/diseases, psychological health, disease outcomes, and patient experience of living with the disease. All indicators collected for the EMAS survey were patient-reported outcomes.

In addition, a range of supplementary indices were collected in the questionnaire to assess specific areas.

1. BASDAI (Bath Ankylosing Spondylitis Disease Activity Index): a validated self-administered questionnaire assessing disease activity in axSpA patients.[16]
2. Spinal Stiffness Index: this index assessed the degree of stiffness experienced in the spinal column, distinguishing between the cervical, dorsal, and lumbar areas. The scale ranges from 3 (no stiffness) to 12 (maximum level of stiffness).[14]
3. Functional Limitation Index: it assessed the degree of functional limitation in 18 activities of daily life through a 4-point Likert scale (0 to 3). Total scores range from 0 (no limitation) to 54 (maximum level of functional limitation).[14]
4. GHQ-12 (The 12-Item General Health Questionnaire): this validated scale evaluates psychological distress using 12 questions. The cut-off point of 3 implied those with a score of 3 or more may be experiencing psychological distress.[17]

2.3 | Sample selection and recruitment

Sample selection inclusion criteria for both the Atlas and EMAS studies were the same: to be aged ≥18 years, resident in any of the 13 participating European countries, have a diagnosis of axSpA, including ankylosing spondylitis (also known as radiographic axSpA) and non-radiographic axSpA, and to have paid an axSpA-related visit to a healthcare professional in the 12 months prior to participation.

Participants from the Atlas were recruited from January to March 2016. Survey dissemination of the Atlas was made through press releases, e-mails and website and social media announcements. EMAS participants were recruited between July 2017 and March 2018 by Ipsos SA (formerly GfK) through its online panel of respondents. This firm ensures that patients are fully validated through their connected healthcare professionals around the world who refer patients for research. In Austria, Norway, Slovenia, Sweden, the Netherlands, Italy, Russia, and Spain, patient organizations supported recruitment by distributing the survey link to their members. The questionnaire was completed via an online platform for survey data collection. In addition, the database from the Atlas[18] was adapted to fit the EMAS database in order to allow comparisons between Spanish and the OEC axSpA patients.

2.4 | Statistical analysis

Socio-demographic characteristics, life habits, and patient-reported outcomes (BASDAI, spinal stiffness, functional limitation and psychological distress through GHQ-12) were compared between Spanish and OEC axSpA patients. Chi-square test was used for qualitative variables and Mann-Whitney test for quantitative variables. All analyses were carried out using the Statistics Package for Social Sciences (SPSS) v. 25.0.

3 | RESULTS

The Spanish sample was characterized by a slightly higher age and lower presence of women than in the OEC sample. The number of people with university studies and the overall income level was lower than the European average. Regarding harmful lifestyle habits, compared to the OEC, a higher percentage of Spanish axSpA patients declared that they smoke. However, although both groups followed a similar trend regarding regular alcohol consumption (more than twice a week), the Spanish sample less frequently reported moderate consumption (between 1 and 2 times a week) and more participants reported occasional drinking or abstinence compared to their European counterparts (Table 1).

The average mean age of onset of first symptoms of Spanish axSpA participants was more than 3 years lower than in the OEC, overall disease duration was reported to be around 4 years longer, and diagnostic delay more than 1 year greater. As for patient-reported outcomes, the Spanish sample also reported a higher rate of human leukocyte antigen (HLA)-B27 positivity. Moreover, the Spanish sample had a slightly higher BASDAI score. However, BASDAI differences were not clinically relevant according to rheumatologic standards. Additionally, Spanish axSpA patients declared a much greater functional limitation than the OEC. They also reported half the rate of inflammatory bowel disease than the OEC (Table 2).

A total of 21.7% of the Spanish sample in the active population was unemployed, while for OEC this figure drops to 9.2%. Moreover, unemployed patients were asked whether they considered that they had to leave or lost their job due to axSpA, to which 62.8% of Spanish and 65.3% of OEC respondents answered “yes”. Furthermore, 95.5% of Spanish axSpA patients stated that their disease made it or would make it difficult to find a job compared to 70.3% of the OEC. However, in the case of Spanish patients who had a job, they reported fewer work-related issues, and less need for workplace adaptation than their European counterparts. Although the reported prevalence of mental disorders (anxiety, depression, and sleep disorders) was significantly lower in the Spanish sample compared to the OEC, the average GHQ-12 score was higher in Spanish axSpA patients. Finally,

TABLE 1 Sociodemographic, anthropometric characteristics, and lifestyle habits (N = 680 for Spain and N = 2,166 for OEC, unless otherwise specify)

Variable	Spain mean ± SD; n (%)	OEC mean ± SD; n (%)	*P* value
Sociodemographic			
Age, years	45.7 ± 10.8	43.4 ± 12.6	<.001*
Gender, female	357 (52.5)	1389 (64.1)	<.001*
Marital status			
Single	126 (18.5)	475 (21.9)	.152
Married	486 (71.5)	1447 (66.8)	
Separated/divorced	60 (8.8)	213 (9.8)	
Widowed	8 (1.2)	31 (1.4)	
Educational level			
No schooling completed	9 (1.3)	23 (1.1)	<.001*
Primary school	119 (17.5)	144 (6.6)	
High school	301 (44.3)	880 (40.6)	
University	251 (36.9)	1119 (51.7)	
Monthly income (euros) per household member	823.2 ± 656.4; n = 333	1173.5 ± 928.8; n = 1956	<.001*
Patient organization, member	301 (44.3)	806 (37.2)	.001*
Anthropometric characteristics			
Body mass index			
Underweight, <18.5	17 (2.5)	91 (4.2)	.069
Normal weight, 18.5-24.9	309 (45.4)	943 (43.5)	
Overweight, 25-29.9	240 (35.3)	713 (32.9)	
Obese, >30	114 (16.8)	419 (19.3)	
Lifestyle habits			
Smoking			
Non-smoker or socially	417 (71.3); n = 585	1679 (77.5)	<.001*
<10 cigarettes/day	24 (4.1); n = 585	111 (5.1)	
More than 10 cigarettes/day	144 (24.6); n = 585	376 (17.4)	
Alcohol			
Never or occasionally	503 (86.0); n = 585	1723 (79.5)	<.001*
1-2 times per week	37 (6.3); n = 585	292 (13.5)	
More than twice per week	45 (7.7); n = 585	151 (7.0)	

Abbreviation: OEC, other European countries.

*P-value ≤.05.

95.6% of the Spanish sample reported benefiting from public health insurance while for OEC this figure fell to 77.7% ($P < .001$; Table 3).

With respect to EMAS data, Spanish patients show a systematically longer diagnostic delay than their European counterparts over the last 2 decades (Table 4).

4 | DISCUSSION

The results of the EMAS survey allow us to verify a series of unmet needs at the European level as well as particular needs of Spanish patients, such as long diagnostic delay and psychosocial consequences including the deterioration of mental health and high impact of axSpA on working life.

4.1 | Country profiles

Despite the organizational heterogeneity of European health systems, some peculiarities of the Spanish health system can be highlighted. Spain has more physicians than the European average (381 vs 353 per 100 000 inhabitants).[19] In fact, this figure places Spain

TABLE 2 Disease characteristics and functioning (N = 680 for Spain and N = 2,166 for OEC, unless otherwise specify)

Variable	Spain mean ± SD; n (%)	OEC mean ± SD; n (%)	*P* value
Diagnosis			
Age at onset of first symptoms, years	24.4 ± 8.8; n = 555	27.2 ± 11.6	<.001*
Age at diagnosis, years	32.9 ± 9.6; n = 556	33.9 ± 11.9	.053
Diagnostic delay, years	8.5 ± 7.7; n = 550	7.2 ± 8.6; n = 2,102	<.001*
Disease duration, years	20.9 ± 12.2; n = 555	16.2 ± 12.3; n = 2,161	<.001*
Extra-musculoskeletal manifestations			
Uveitis	122 (17.9)	347 (18.2); n = 1,902	.860
Crohn's disease	21 (3.1)	133 (6.8); n = 1,961	<.001*
Ulcerative colitis	22 (3.2)	153 (7.7); n = 1,981	<.001*
Human leukocyte antigen-B27			
Positive	391 (77.1); n = 507	892 (70.1); n = 1,272	.003*
Disease activity			
BASDAI, 0-10	5.7 ± 2.0; n = 418	5.4 ± 2.0	.024*
BASDAI, <4	81 (19.4); n = 418	484 (22.3)	.179
BASDAI, ≥4	337 (80.6); n = 418	1682 (77.7)	
Spinal stiffness index, 3-12			
Overall spinal stiffness	7.5 ± 2.7; n = 494	7.8 ± 2.4	.009*
Maximum degree of spinal stiffness			
No stiffness	59 (10.9); n = 541	128 (5.9)	<.001*
Mild	102 (18.9); n = 541	369 (17.0)	
Moderate	182 (33.6); n = 541	752 (34.7)	
Severe	198 (36.6); n = 541	917 (42.3)	
Functional limitation index, 0-54			
Overall limitation	27.7 ± 13.2; n = 605	14.3 ± 11.8	<.001*
Low, 0-17	152 (25.1); n = 605	1383 (63.9)	<.001*
Medium, 18-35	282 (46.6); n = 605	660 (30.5)	
High, 36-54	171 (28.3); n = 605	123 (5.7)	

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; OEC, other European countries.

*P-value ≤ .05.

among the 10 countries within the Organization for Economic Co-operation and Development (OECD) with the highest number of doctors per inhabitant.[20] However, in relation to the number of rheumatologists, it has been estimated that Spain has 2.0 per 100 000 inhabitants.[21] According to workforce planning models for the year 2021, the as yet unreached estimate required to meet the needs of rheumatic patients is 3.5 per 100 000 inhabitants for Spain (calculated for 2021), while for the United Kingdom the need is only 0.7 rheumatologists per 86 000 inhabitants (calculated for 1988).[22] In other healthcare systems the needed rates may be higher. For example, in Austria the needed rate has been established as 4.3 rheumatologists per 100 000 inhabitants (calculated for 2017). [23]

According to the data presented, the situation of Spanish patients with axSpA is more precarious than that of their European neighbors. On the one hand, Spanish statutory health insurance is universal in coverage and financed almost entirely through the public sector,[24] with a private spending in health that could match that of the Russian Federation (both comprising less than 5%) while surpassing that of Norway (<1%), and being much lower than that of France (>10%).[25] On the other hand, it is important to acknowledge that compared to other EMAS participating countries, Spain is among the countries that spend a lower percentage of its gross domestic product (GDP) on health. In fact, 9.2% of Spain's total GDP is allocated to the health sector. This percentage surpasses only that of Italy (9.0%), Slovenia (8.5%), and Russia (5.6%), and differs by about 2% with the largest health investors: France (11.5%), Germany (11.2%) and Sweden (11.0%).[26]

Additionally, Spanish expenditure per capita on health is $2354, the 3rd lowest among EMAS countries, only above Slovenia and Russia;[27] it is also 3rd with the lowest numbers of hospital beds per 100 000 inhabitants (297.28, while the Euro 28 average is 504.02).[28] Furthermore, in comparison with the OEC sample, Spanish axSpA patients were characterized by being less educated

TABLE 3 Patient-reported outcomes for working life, psychological health, and disease-related perceptions (N = 680 for Spain and N = 2166 for OEC, unless otherwise specified)

Variable	Spain mean ± SD; n (%)	OEC mean ± SD; n (%)	*P* value
Employment status of labor force	n = 415	n = 1247	
Employed	325 (78.3)	1132 (90.8)	<.001*
Unemployed	90 (21.7)	115 (9.2)	
Employment status of economically inactive	n = 238	n = 804	
Temporary sick leave	63 (26.5)	241 (30.0)	.308
Permanent sick leave	64 (26.9)	228 (28.4)	
Retired	63 (26.5)	167 (20.8)	
Early retirement	10 (4.2)	33 (4.1)	
Homemaker	29 (12.2)	85 (10.6)	
Student	9 (3.8)	50 (6.2)	
Work-related issues due to axSpA	170 (54.3); n = 313	795 (71.6); n = 1111	<.001*
Workplace adaptation due to axSpA	116 (23.9); n = 485	1047 (48.3)	<.001*
axSpA influenced job choice	186 (33.8); n = 551	970 (49.1); n = 1976	<.001*
Difficulties finding a job due to axSpA	294 (95.5); n = 308	1240 (70.3); n = 1763	<.001*
Psychological health			
Sleep disorder	134 (19.7)	924 (45.5); n = 2033	<.001*
Anxiety	135 (19.9)	674 (33.1); n = 2038	<.001*
Depression	100 (14.7)	610 (30.0); n = 2034	<.001*
GHQ-12 score, 0-12	5.7 ± 4.5; n = 474	4.8 ± 4.0	<.001*
At risk for psychological distress, GHQ-12 ≥3	310 (65.4); n = 474	1314 (60.7)	.055
Disease-related perceptions			
Talked with your physician about treatment goals	338 (75.8); n = 446	1325 (64.6); n = 2050	<.001*
Main health insurance			
Public health insurance	526 (95.6); n = 550	1110 (77.7); n = 1428	<.001*
Private health insurance	22 (4.0); n = 550	214 (15.0); n = 1428	
Private care, self-pay	2 (0.4); n = 550	104 (7.3); n = 1428	

Abbreviations: axSpA, axial spondyloarthritis; GHQ-12, The 12-Item General Health Questionnaire; OEC, other European countries.

*P-value ≤ .05.

and having a lower income level per household member. Low public investment coupled with low income levels means that Spanish axSpA patients face a disabling disease with limited resources.

The Spanish sample also had a lower representation of female members, slightly older and with a higher rate of membership to national patient organizations. These facts, in particular educational level, income and gender, may mediate the differences found in the burden of disease across Europe.

4.2 | Diagnostic delay

The Spanish sample shows an average diagnostic delay of 8.5 years and a median of 6 years, a figure higher than that reported by the Spanish REGISPONSER study (mean 6.3 years and median 3.0 years) conducted in 2007.[11] This could lead to the unlikely conclusion of an increase in diagnostic delay in Spain in recent years. However, a more plausible explanation would be the longer disease duration for participants in the Atlas study with respect to that of REGISPONSER (6 years longer on average). Therefore, the Atlas study, although more recent, would be reporting adiagnostic delay in patients with longer disease duration.

Comparison of the Atlas and EMAS studies showed that the diagnostic delay in Spain was significantly longer than in the OEC, with an average of more than 18 months. This difference is even more significant when considering there is a higher percentage of HLA-B27 positive patients and a lower proportion of women in the Spanish sample, as these 2 characteristics have been associated with

TABLE 4 Distribution of diagnostic delay of Spanish and European Map of Axial Spondyloarthritis patients through the decades

	OEC			Spain		
	n	Mean ± SD	Median [Q1, Q3]	n	Mean ± SD	Median [Q1, Q3]
≤1980	154	14.9 ± 14.2	10 [2, 27]	77	12.7 ± 11.3	9 [5, 16]
1981-1990	275	14.8 ± 10.9	15 [4, 25]	90	12.3 ± 8.3	11 [5, 19]
1991-2000	447	10.2 ± 7.6	10 [3, 17]	162	9.2 ± 6.8	8 [3, 15]
2001-2010	668	4.9 ± 4.0	4.5 [1, 8]	156	6.2 ± 4.2	6 [2, 9]
>2010	551	1.4 ± 1.5	1 [0, 2]	65	2.3 ± 1.9	2 [1, 4]
Total	2095	7.2 ± 8.6	4 [1, 10]	550	8.5 ± 7.7	6 [3, 12]

Abbreviation: OEC, other European countries; Q1, quartile 1; Q3, quartile 3.

a shorter diagnostic delay in other studies.[29] In fact, a meta-analysis conducted on the Spanish population finds that women with axSpA are diagnosed later.[30]

With respect to the diagnosis of axSpA in Spain, patients should first visit their general practitioner who, after clinical examination, would decide to refer them to a rheumatologist,[18] as in many OEC. Additional delay to diagnosis could be influenced by a higher percentage in the Spanish sample of referrals to orthopedic specialists (56.9% of Spanish axSpA patients visited orthopedic specialists prior to diagnosis, compared to only 25.3% in the OEC). However, when examining the total number of healthcare professionals visited before diagnosis, both Spain and the OEC reported a similar average of 2 visits to different physicians before diagnosis. It would be necessary throughout Europe to improve disease education related to inflammatory vs mechanical back pain among healthcare professionals, specifically among those responsible for referring patients to rheumatologists. More precisely, Spanish general practitioners should be better trained to identify suspicious cases of axSpA in order to refer them to a rheumatologist, rather than an orthopedic specialist.

More specifically, general practitioners need to be better trained in axSpA clinical patterns and the typical features of the disease, such as disease onset <45 years old, extra-articular manifestations and response to nonsteroidal anti-inflammatory drug treatment,[31] while also understanding that axSpA is not a disease exclusive to older men, affecting young people of both genders,[32] with the potential to manifest in both radiographic and non-radiographic forms.[33] This could be achieved by training medicine students in general practice consultations where they could encounter axSpA patients [34] or through training activities aimed at general practitioners and conducted by rheumatologists, as in the case of the ESPeranza program.[35] Moreover, general practitioners should have easier access to medical tests for detecting axSpA features, such as imaging of the sacroiliac joints or HLA-B27 testing, and procedures should be habilitated in order to allow preferential referral to the rheumatologist of suspected cases. Additionally, it would be of utmost importance for Spain to increase its rate of rheumatologists per 100 000 inhabitants to meet the healthcare demand. Nevertheless, optimizing collaboration between different specialties should shorten the patient journey to diagnosis, and ultimately effective treatment.

4.3 | Burden of the disease

The burden of disease reported by both samples was significant, declaring high levels of disease activity, spinal stiffness and functional limitation overall. However, Spanish axSpA patients reported an even higher BASDAI score than the EMAS OEC average, even higher than the values recorded by other Spain-based axSpA registries like the REGISPONSER.[11] However, mean differences, although statistically significant, were not clinically relevant. Spanish patients also reported greater functional limitation. However, we cannot be sure whether this is due to longer disease duration or whether it is actually associated with the longer diagnostic delay of these patients.

4.4 | Working impact

Unemployment rates differ greatly from the Spanish general population (17.2%) to that estimated for the EU-28 (6.8%).[36] When employment status is examined for axSpA patients, an increase in unemployment rates is appreciated in both Spain and Europe despite both samples reporting a higher level of education than the general population.[37] However, Spanish axSpA patients' unemployment rates show a steeper increase than that of their European counterparts, and the unemployment gap becomes larger between both groups.

When examining employed patients, the Spanish were less likely to report interference of the disease in their work performance compared to the OEC. Spanish participants declared fewer work-related issues overall, fewer workplace adaptations, and a smaller influence of axSpA on work choice. This is striking, as research points to a strong relationship between problems and needs in working life and burden of disease.[38] If burden of disease is equivalent between Spain and OEC, interference of the condition at work should also be similar.

Therefore, it is more likely that work outcomes reported by the Spanish sample are due to a more precarious labor scenario (characterized by high unemployment rates, short-term duration jobs, low salaries, and gender inequalities), compared to the European Union context.[39] Thus, Spanish axSpA patients would not report an influence of axSpA on work choice in an already constrained market,

would not have access to as many workplace adaptations as in OEC, and would refrain from asking for sick days or reductions in working hours for fear of losing their job. Additional data from the Atlas and EMAS surveys would indicate that this fear may be common among those with the condition, especially in the Spanish context: if we consider what European axSpA patients stated about job hunting, 70% of OEC patients stated they found or expected to find difficulties in job searches, compared to 95% of the Spanish sample. This difficult labor scenario could be influencing the levels of psychological distress reported by Spanish survey participants as it has been noted how the financial crisis has been involved in the increased prevalence of mental disorders in Spain.[40]

4.5 | Mental burden

The impact of axSpA on mental health is well documented.[41,42] The EMAS sample showed a high prevalence of mental health issues among axSpA patients, higher than those collected by the World Health Organization for the European region, which situates the prevalence of anxiety and depression in the general population below 5%.[43] However, Spanish axSpA patients showed particularities regarding their self-reported mental health, declaring lower rates of the mental disorders explored (anxiety, depression, and sleep disorders), while reporting much higher levels of psychological distress through the GHQ-12, a validated screening scale. The fact that Spanish participants reported fewer diagnosed mental disorders (anxiety, depression, and sleep disorders) than OEC axSpA patients, while ranking much higher in the GHQ-12 score, points to an underdiagnosis of mental disorders in Spain.

4.6 | Strengths and limitations

The EMAS project represents the largest axSpA patient survey to date, including 2846 respondents from 13 European countries. Its main objective was to understand the patient's perspective through a holistic approach using a questionnaire developed for patients by patients. As such, EMAS collected not only clinical characteristics of the disease but also the patient-reported impact on psychological health, daily activities, work, and lifestyle, all of which are considered relevant aspects by axSpA patients. The focus of its design added to its international scope, enables a head-to-head comparison of patient-reported outcomes at the pan-European level in areas that are often overlooked by research.

We acknowledge that EMAS has some limitations. First, the survey was based on self-reported data and did not attempt to confirm participant diagnosis, nor did it seek to support participant responses with clinician-reported assessments. Nevertheless, the characteristics of the sample matched those of previous cohorts including patients with confirmed axSpA, and as the aim of the survey was to better understand the patient perspective, direct feedback was preferred. Second, as 1 of the inclusion criteria was to have had at least 1 visit to a rheumatologist in the last 12 months, the sample could be biased in excluding patients not requiring a follow-up appointment and thus, with controlled disease activity. In this way, this study could have overestimated the severity of some disease outcomes, especially those related to disease activity.

Additionally, non-validated indices were used for assessing functional limitations in daily activities and spinal stiffness. This was due to patients expressing their concern during the preliminary phase of the survey development about not being able to report relevant aspects of their disease not included in other scales or indices considered. In any case, Cronbach alpha values obtained for the indices employed in EMAS showed good reliability of these instruments in this sample.[14] Lastly, the 2 recruitment methods employed (GfK patient panel and patient organizations) resulted in differences in sample sizes between countries, naturally skewing the aggregated European data toward the experiences of patients in countries with a greater sample weight.

Despite these limitations, EMAS adopts a multidisciplinary approach, including the medical and patient community within the research team aiming to understand the patient experience from a holistic perspective.

5 | CONCLUSIONS

The EMAS results show how, compared to OEC, Spanish axSpA patients show longer diagnostic delay. The results highlight the need to improve the diagnostic pathway of axSpA patients as well as psychological care within the Spanish health system in order to deal with the high psychological distress levels reported by Spanish patients and the rates of underdiagnosed mood disorders suggested by the present study. Low numbers of rheumatology specialists, in addition to a high percentage of erroneous referrals to orthopedic specialists in Spanish patients, has highlighted the need to increase human resources for health in order to adapt international recommendations to the national context.

However, the unmet needs of Spanish axSpA patients are not only limited to the quality of health care. Compared to the EMAS sample, the Spanish cohort had much higher unemployment rates. Additionally, workers with axSpA with a similar burden of disease, as their European counterparts, receive less support in the workplace. All this could be affecting patients' levels of psychological distress.

Managing axSpA from a holistic approach, including the perspective of health psychologists, rehabilitation therapists, social workers, and related professions, should be key for clinical improvement and quality of life in these patients in Spain, as well as in Europe.

ACKNOWLEDGEMENTS

We would like to thank all patients and patient organizations who participated in the EMAS study. This study was funded by Novartis Pharma AG.

CONFLICT OF INTEREST

Dr Jordi Gratacós has received unrelated honoraria or research grants from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB. Dr Eduardo Collantes-Estévez has received unrelated honoraria or research grants from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB. Mrs Laura Christen is an employee of Novartis Pharma AG. Dr Carlos Sastre is an employee of Novartis Farmacéutica Spain. Dr Victoria Navarro-Compán has received unrelated honoraria or research grants from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB.

AUTHORS' CONTRIBUTIONS

Marco Garrido-Cumbrera, Laura Christen, Sergio Sanz-Gómez, José Correa-Fernández and Victoria Navarro-Compán designed the study, José Correa-Fernández carried out data analysis. All authors contributed to interpretation of the data, helped to draft the manuscript and approved its final version to be submitted; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL

The manuscript does not contain clinical studies.

CONSENT TO PARTICIPATE

All participants were asked to provide explicit opt-in consent prior to participating in the survey.

DATA AVAILABILITY STATEMENT

Data are available via the corresponding author upon reasonable request.

ORCID

Marco Garrido-Cumbrera https://orcid.org/0000-0001-9727-1189
Jordi Gratacós https://orcid.org/0000-0003-4007-4103
Eduardo Collantes-Estevez https://orcid.org/0000-0002-7647-6289
Pedro Zarco-Montejo https://orcid.org/0000-0002-3039-187X
Carlos Sastre https://orcid.org/0000-0002-1577-7838
Sergio Sanz-Gómez https://orcid.org/0000-0001-6801-0836
José Correa-Fernández https://orcid.org/0000-0002-7788-5391
Victoria Navarro-Compán https://orcid.org/0000-0002-4527-852X

REFERENCES

1. López-Medina C, Molto A, Claudepierre P, Dougados M. Clinical manifestations, disease activity and disease burden of radiographic versus non-radiographic axial spondyloarthritis over 5 years of follow-up in the DESIR cohort. *Ann Rheum Dis*. 2019;79(2):209-216. https://doi.org/10.1136/annrheumdis-2019-216218
2. Kobelt G, Sobocki P, Mulero J, Gratacos J, Pocovi A, Collantes-Estevez E. The burden of ankylosing spondylitis in Spain. *Value Heal*. 2008;11(3):408-415. https://doi.org/10.1111/j.1524-4733.2007.00252.x
3. Ara RM, Packham JC, Haywood KL. The direct healthcare costs associated with ankylosing spondylitis patients attending a UK secondary care rheumatology unit. *Rheumatology*. 2008;47(1):68-71. https://doi.org/10.1093/rheumatology/kem296
4. Merino M, Braçe O, González-Domínguez A, et al. Social economic costs of ankylosing spondylitis in Spain. *Clin Exp Rheumatol*. 2021;39(2):357-364. Epub. PMID: 32662412.
5. Glintborg B, Sorensen IJ, Ostergaard M, et al. Ankylosing spondylitis versus nonradiographic axial spondyloarthritis: Comparison of tumor necrosis factor inhibitor effectiveness and effect of HLA-B27 Status. An observational cohort study from the nationwide DANBIO registry. *J Rheumatol*. 2017;44(1):59-69. https://doi.org/10.3899/jrheum.160958
6. Dougados M, D'Agostino MA, Benessiano J, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: Study design and baseline characteristics of the 708 recruited patients. *Jt Bone Spine*. 2011;78(6):598-603. https://doi.org/10.1016/j.jbspin.2011.01.013
7. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum*. 2012;64(5):1388-1398. https://doi.org/10.1002/art.33465
8. Ramiro S, Stolwijk C, Van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: A 12 year prospective follow-up of the OASIS study. *Ann Rheum Dis*. 2015;74(1):52-59. https://doi.org/10.1136/annrheumdis-2013-204055
9. Van Lunteren M, Ez-Zaitouni Z, De Koning A, et al. In early axial spondyloarthritis, increasing disease activity is associated with worsening of health-related quality of life over time. *J Rheumatol*. 2018;45(6):779-784. https://doi.org/10.3899/jrheum.170796
10. Molnar C, Scherer A, Baraliakos X, et al. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: Results from the Swiss Clinical Quality Management cohort. *Ann Rheum Dis*. 2018;77(1):63-69. https://doi.org/10.1136/annrheumdis-2017-211544
11. Miranda-García M, Font-Ugalde P, Muñoz-Gomariz E, Collantes-Estévez E, Zarco-Montejo P, González-Fernández C. National Register of Patients with Spondyloarthritis (REGISPONSER). Descriptive analysis of 2367 Spanish patients included. *Reum Clin Supl*. 2008;4(4):48-55.
12. Ørnbjerg LM, Brahe CH, Askling J, et al. Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis*. 2019;78(11):1536-1544. https://doi.org/10.1136/annrheumdis-2019-215427
13. Lindström U, Glintborg B, Di Giuseppe D, et al. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. *RMD Open*. 2019;5(2):1-8. https://doi.org/10.1136/rmdopen-2019-001079
14. Garrido-Cumbrera M, Navarro-Compán V, Zarco P, et al. Atlas of axial spondyloarthritis in Spain 2017: Study design and population. *Reumatol Clin*. 2019;15(3):127-132. https://doi.org/10.1016/j.reuma.2018.08.003
15. Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. The European Map of Axial Spondyloarthritis: capturing the patient perspective—an analysis of 2846 patients across 13 countries. *Curr Rheumatol Rep*. 2019;21(19):1-9. https://doi.org/10.1007/s11926-019-0819-8
16. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21(12):2286-2291.

17. Cano A, Sprafkin RP, Scaturo DJ, Lantinga LJ, Fiese BH, Brand F. Mental health screening in primary care: a comparison of 3 brief measures of psychological distress. *Prim Care Companion J Clin Psychiatry*. 2001;3(5):206-210. https://doi.org/10.4088/PCC.v03n0503
18. Garrido-Cumbrera M, Gálvez-Ruiz D, Chacón García J, et al. *Atlas of Axial Spondyloarthritis in Spain 2017*. : Profile of the Disease. Max Weber Institute: Madrid; 2017.
19. EUROSTAT. Practising Physicians - Statistics Explained. https://ec.europa.eu/eurostat/databrowser/view/tps00044/default/table?lang=en. Published 2017. Accessed February 11, 2020
20. Barber-Pérez P, González-López-Valcárcel B. Estimación de la Oferta y Demanda de Médicos Especialistas. España. 2018–2030; 2019.
21. Sanchez-Piedra C, Yoldi B, Valero M, Andreu J, Díaz-González F, Gómez-Reino J. Status of rheumatology in Spain in 2017: 2.0 rheumatologists per 100 000 population. *Reumatol Clínica*. 2018;14:311-312. https://doi.org/10.7547/0960272
22. Dejaco C, Lackner A, Buttgereit F, Matteson EL, Narath M, Sprenger M. Rheumatology workforce planning in western countries: a systematic literature review. *Arthritis Care Res*. 2016;68(12):1874-1882. https://doi.org/10.1002/acr.22894
23. Puchner R, Vavrovsky A, Pieringer H, Hochreiter R, Machold KP. The Supply of rheumatology specialist care in real life. results of a nationwide survey and analysis of supply and needs. *Front Med*. 2020;7:1-8. https://doi.org/10.3389/fmed.2020.00016
24. García-Armesto S, Abadía-Taira MB, Durán A, Hernández-Quevedo C, Bernal-Delgado E. Spain: health system review. *Health Syst Transit*. 2010;12(4):1-295.
25. Sagan A, Thomson S. Voluntary health insurance in Europe. 2016; http://www.euro.who.int. Published 2017. Accessed February 11, 2020
26. EUROSTAT. Government expenditure on health - Statistics Explained. https://ec.europa.eu/eurostat/statistics-explained/index.php/Government_expenditure_on_health. Published 2017. Accessed February 11, 2020
27. Data World Bank. Current Expenditure per Capita on Health (US Dollars). https://data.worldbank.org/indicator/SH.XPD.CHEX.PC.CD. Published 2018. Accessed July 8, 2019
28. EUROSTAT. Hospital Beds - Statistics Explained. https://ec.europa.eu/eurostat/databrowser/view/tps00046/default/table?lang=en. Published 2017. Accessed February 11, 2020
29. Jovani V, Blasco-Blasco M, Pascual E, Ruiz-Cantero MT. Challenges to conquer from the gender perspective in medicine: The case of spondyloarthritis. *PLoS One*. 2018;13(10):1-14. https://doi.org/10.1371/journal.pone.0205751
30. Jovaní V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E. Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and metaanalysis. *J Rheumatol*. 2017;44(2):174-183. https://doi.org/10.3899/jrheum.160825
31. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis*. 2011;70(1):25-31. https://doi.org/10.1136/ARD.2010.133645
32. Garrido-Cumbrera M, Navarro-Compán V, Bundy C, et al. Identifying parameters associated with delayed diagnosis in axial spondyloarthritis : data from the European Map of axial spondyloarthritis. *Rheumatol*. 2021;1–19.
33. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet*. 2017;390(10089):73-84. https://doi.org/10.1016/j.mpmed.2018.01.005
34. Otón T, Sastre C, Carmona L. The journey of the non-radiographic axial spondyloarthritis patient: the perspective of professionals and patients. *Clin Rheumatol*. 2021;40(2):591-600. https://doi.org/10.1007/s10067-020-05269-z
35. Fernández CC. Diagnosing early spondyloarthritis in Spain: the ESPeranza program. *Reumatol Clin*. 2010;6(Suppl 1):6-10. https://doi.org/10.1016/j.reuma.2009.12.005
36. EUROSTAT. Employment Statistics. http://ec.europa.eu/eurostat/statistics-explained/index.php/Fertility_statistics. Published 2018. Accessed November 21, 2018
37. Organisation for Economic Co-operation and Development. OECD Statistics - Educational Attaintment and Labour-Force Status. https://stats.oecd.org/. Published 2017. Accessed February 11, 2020
38. Garrido-Cumbrera M, Bundy C, Navarro-Compán V, et al. Patient-reported Impact of Axial Spondyloarthritis on Working Life: Results from the EMAS survey. *Arthritis Care Res*. 2020; https://doi.org/10.1002/acr.24426
39. *European Comission Directorate-General for Employment Social Affairs and Inclusion. Joint Employment Report 2019*. Brussels: 2019.
40. Gili M, García-Campayo J, Roca M. Crisis económica y salud mental. Informe SESPAS 2014. *Gac Sanit*. 2014;28:104-108.
41. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis*. 2018;77(1):3-17. https://doi.org/10.1136/annrheumdis-2017-211734
42. Garrido-Cumbrera M, Delgado-Domínguez CJ, Gálvez-Ruiz D, Blanch-Mur C, Navarro-Compán V. The effect of axial spondyloarthritis on mental health: Results from the Atlas. *J Rheumatol*. 2019;46(10):1284-1289. https://doi.org/10.3899/jrheum.180868
43. World Health Organization. Depression and Other Common Mental Disorders. Global Health Estimates; 2017. doi:CC BY-NC-SA 3.0 IGO

How to cite this article: Garrido-Cumbrera M, Gratacós J, Collantes-Estevez E, et al. A benchmarking study evaluating axial spondyloarthritis burden in Spain and other European countries. Results from Spanish Atlas and European Map of axial sponydoarthritis studies. *Int J Rheum Dis*. 2021;24:1127–1136. https://doi.org/10.1111/1756-185X.14173

Received: 23 March 2021 | Revised: 2 June 2021 | Accepted: 25 June 2021

DOI: 10.1111/1756-185X.14175

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Clinical characteristics of non-radiographic axial spondyloarthritis: Results of the Korean Nonradiographic Axial SPondyloArthritis (KONASPA) data

Hyemin Jeong[1] | Yong-Gil Kim[2] | Tae-Hwan Kim[3] | Tae-Jong Kim[4] | Min-Chan Park[5] | Mi Ryoung Seo[6] | Kichul Shin[7] | Ji Seon Oh[2] | Sang-Hoon Lee[8] | Yeon-Ah Lee[9] | Eun Young Lee[10] | Han Joo Baek[6] | Hoon-Suk Cha[11]

[1]Department of Internal Medicine, Soonchunhyang University Hospital, Bucheon, South Korea

[2]Division of Rheumatology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

[3]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

[4]Department of Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

[5]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

[6]Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea

[7]Division of Rheumatology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea

[8]Division of Rheumatology, Department of Internal Medicine, Kyung Hee University, College of Medicine, Kyung Hee University Hospital at Gangdong, Seoul, South Korea

[9]Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul, South Korea

[10]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

[11]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Correspondence
HoonSuk Cha, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.
Email: hoonsuk.cha@samsung.com

Funding information
Celltrion Healthcare

Abstract

Aim: To evaluate clinical characteristics and natural history of non-radiographic axial spondyloarthritis (nr-axSpA) using KOrean Nonradiographic Axial SPondyloArthritis (KONASPA) data.

Methods: Data were collected from 11 centers in South Korea. A total of 278 patients with nr-axSpA from January 2018 to July 2020 were included. Demographic data, clinical features, comorbidities, disease activity, medications, and laboratory results were collected.

Results: Mean age at symptom onset was 28.2 ± 14.2 years. Of 278 patients, 152 (54.7%) were male. Mean Bath Ankylosing Spondylitis Disease Activity Index at diagnosis was 3.5 ± 2.1. Dyslipidemia was the most common comorbidity (8.4%), followed by hypertension (6.1%). Mean age at diagnosis of nr-axSpA was older in female patients than in male patients (31.8 ± 15.8 years vs 24.9 ± 12.0 years, $P < 0.001$). Enthesitis and uveitis were more frequently found in female patients than in male patients. Thirty-one (11.1%) participants with nr-axSpA progressed to ankylosing spondylitis. The median follow-up duration was 48 months. In multivariable Cox regression analysis, age at symptom onset (hazard ratio [HR] 0.93, 95% confidence

interval (CI) 0.88-0.97, $P = 0.006$), body mass index (BMI) (HR 1.24, 95% CI 1.06-1.44, $P = 0.005$) and sacroiliitis grade (HR 1.86, 95% CI 1.19-2.92, $P = 0.006$) were associated with progression to ankylosing spondylitis.

Conclusions: Results of nationwide data revealed that women with nr-axSpA showed a late disease onset and more extra-articular manifestations than men. Young age at symptom onset, high BMI, and presence of radiographic sacroiliitis at diagnosis were risk factors for progression to AS.

KEYWORDS

ankylosing spondylitis, body mass index, disease progression, sacroiliitis, spondyloarthritis

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects sacroiliac joints and spine with clear radiographic changes in the sacroiliac joint. In 1985, Khan et al first described spondylitic disease showing no radiographic damage in the sacroiliac joint.[1] Magnetic resonance imaging (MRI) was introduced for the diagnosis of spondyloarthritis (SpA) in 2005.[2] Reversible inflammatory changes can be detected by MRI before irreversible joint damage appears on X-ray. MRI was first included in the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria for spondyloarthritis.[3] After the introduction of the 2009 ASAS classification criteria, axial spondyloarthritis is classified as radiographic axial spondyloarthritis (r-axSpA) or non-radiographic axial spondyloarthritis (nr-axSpA). Also known as AS, r-axSpA is mandatorily defined by evident radiographic structural damage in the conventional X-ray that satisfied modified New York criteria;[4] nr-axSpA is ax-SpA without definitive structural damage on X-ray. Several studies have compared nr-axSpA and AS. Patients with nr-axSpA and AS show similar disease activity and functional activity assessed by the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI), respectively.[5-8] However, patients with nr-axSpA show shorter disease duration, lower C-reactive protein, and a lower Bath AS Mobility Index than patients with AS.[6,9] Patients with nr-axSpA also have lower proportions of male patients and smokers than AS patients.[9] There are heterogeneous results about the evolution of nr-axSpA into AS. Studies have reported that progression to AS occurs in 5%-28% of nr-axSpA patients.[10-12] Smoking, human leukocyte antigen (HLA) -B27 positivity, and inflammation of the sacroiliac joint on MRI were risk factors for sacroiliac joint progression.[13] The concept of nr-axSpA is still under debate. Some researchers have suggested that nr-axSpA is an early form of AS. Other researchers have considered nr-axspA to be a mild form of AS with favorable clinical outcome. Although considerable research has identified clinical characteristics of nr-axSpA from nationwide cohorts in western European populations, the natural history and characterization of nr-axSpA are not completely known. The aim of the present study was to evaluate the clinical characteristics and natural course of nr-axSpA using KOrean Nonradiographic Axial SPondyloArthritis (KONASPA) data.

2 | MATERIALS AND METHODS

2.1 | Study population

KONASPA is a retrospective and prospective cohort of nr-axSpA organized by the Korean Society of Spondyloarthritis Research. The KONASPA registry is a multicenter database representing 11 tertiary academic hospitals across Korea. Patients were included in the KONASPA cohort if they met the following conditions: (a) age over 18 years; (b) fulfillment of the ASAS classification criteria for axial SpA;[3] and (c) not fulfilling the radiologic modified New York criteria for AS, which required either bilateral grade 2 or unilateral grade 3 or 4 sacroiliac joint changes.[4] KONASPA was started in January 2018. It is an ongoing cohort. Patients who met the above inclusion criteria for nr-axSpA at the first rheumatologic outpatient clinic were enrolled. These enrolled patients were followed up every year. Patients who progressed to AS by fulfilling the modified New York criteria during the follow-up period were defined as progressors. Non-progressors were defined as remaining patients with nr-axSpA who did not fulfill the radiologic modified NY criteria during the follow-up period. This study was approved by the institutional review boards of all participating sites. Informed consent was obtained from each patient before registration.

2.2 | Data collection

Demographic profile, socioeconomic characteristics, comorbidities, clinical features of SpA, disease activity, medications, and laboratory results were collected on a Case Record Form. Data were obtained through interview by rheumatologists or expert nurses. Physical examinations were performed by a physician. Data on age, gender, income, region, education, alcohol consumption, and smoking status were obtained. Medical comorbidities including cardiovascular

disease, infectious disease—such as pulmonary tuberculosis and varicellar zoster, endocrine disease, and malignancy were noted. Main clinical features of SpA, including peripheral arthritis, enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, non-steroidal anti-inflammatory drug (NSAID) response, and family history of SpA, were assessed. Ongoing treatment and past medications including NSAIDs, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and systemic glucocorticoid were collected.

2.3 | Disease activity parameters

Patients were asked to complete a self-assessed questionnaire. Disease activity parameters including BASDAI,[14] BASFI,[15] and Visual Analog Scale for global assessment of patients on a numerical rating scale (range: 0-10) were assessed. Modified Schober's test and chest expansion were also measured. Physical examination was performed to assess the presence of swelling or tenderness for 64 joints.

2.4 | Laboratory findings

Results of laboratory tests performed during their initial visits to the rheumatology clinic as a part of their usual diagnostic work up were collected. Laboratory parameters included erythrocyte sedimentation rate, C-reactive protein (CRP), and HLA-B27.

2.5 | Imaging

Plain X-rays of the sacroiliac joint, lumbar spine, and cervical spine were obtained at baseline for patients. MRI images were not essential for cohort registration. Rheumatologists or radiologists scored the sacroiliitis from grade 0 to grade 4 according to the modified New York criteria.[4] Spine radiography was scored using the modified Stoke Ankylosing Spondylitis Spine Score.[16] Information about the presence of syndesmophytes in the cervical or lumbar spine was also collected.

2.6 | Statistical analysis

Descriptive statistics were used to describe characteristics of the population using absolute frequencies and percentages. Categorical variables were compared using χ^2 test or Fisher's exact test. Continuous variables were compared using *t* test and presented as mean (standard deviation). Univariable and multivariable Cox regressions were used to identify factors associated with radiographic progression from nr-axSpA to AS over time. Variables associated with *P* value outcomes of 0.10 or less were included in the multivariable analysis. All analyses were performed using SPSS software, version 26.0 (IBM, Armonk, NY, USA). Statistical significance was considered when *P* values were less than 0.05.

3 | RESULTS

A total of 278 patients with nr-axSpA in the KONASPA cohort from January 2018 to July 2020 were analyzed. Demographic data of these 278 patients are shown in Table 1. Mean age at symptom onset was 28.2 years. About half (54.7%) of patients were male. In this registry, more than 86% of patients lived in urban areas. Table 2 shows clinical manifestations and comorbidities of nr-axSpA. Peripheral arthritis, enthesitis, and uveitis were common features of patients with nr-axSpA. Forty-six (16.5%) patients had a family history of SpA. The sum of two sacroiliac joints grades was 0 in 69 (24.8%) patients, 1 in 32 (11.5%) patients, 2 in 92 (33.1%) patients, and 3 in 69 (24.8%) patients. Two patients had syndesmophytes. The median time from onset of inflammatory back pain to the diagnosis of SpA was 12 months (interquartile range 2-48 months). The initial mean BASDAI score was 3.5 ± 2.1. Dyslipidemia was the most common comorbidity in nr-axSpA, followed by hypertension.

Naproxen and celecoxib were frequently used drugs as the first NSAIDs (Table 3). About half of patients discontinued their first NSAIDs after 8 months. The most common reason for discontinuation of first NSAIDs was inefficacy. Sulfasalazine was the most frequently used as a first csDMARD. Infliximab was the most common bDMARD in this registry. The number of users was almost the same for adalimumab, etanercept, and golimumab. Among 49 patients using biologics, 12 patients discontinued the first biologics. Among 12 patients who discontinued the first bDMARD, five patients discontinued the bDMARD due to inefficacy. One patient discontinued the bDMARD after 2 months, which was referred to as primary failure. The remaining four patients discontinued the bDMARD after 8, 22, 45, and 52 months, respectively, which was referred to as secondary failure. Patients with peripheral arthritis more frequently used csDMARDs and glucocorticoid than patients without peripheral arthritis, (68.9% vs 43.0%, P <0.001 and 33.3% vs 14.8%, P <0.001, respectively).

Clinical characteristics of male patients in comparison with female patients are shown in Table 4. Mean age at symptom onset and diagnosis of SpA was older for female patients than for male patients. Enthesitis and uveitis were more frequently found in female patients than in male patients. Although neither BASDAI nor BASFI was significantly different between male and female patients, initial CRP was lower in female patients than in male patients. Among 278 participants, 31 patients progressed to AS. The median duration from the diagnosis of nr-axSpA to the diagnosis of AS was 48 months (interquartile range 23-77 months). There was no significant difference in the proportion of AS progressors between male and female patients. Table 5 shows the results of a comparison of baseline clinical characteristics between non-progressors and progressors. The mean age of symptom onset was younger for AS progressors than for non-progressors. The prevalence of current smokers was higher for progressors. Alcohol consumption was more common in progressors. Erythrocyte sedimentation rate was higher in non-progressors. Baseline sacroiliitis grade was higher for progressors. Risk factors of progression to AS from nr-axSpA are shown in Table 6. In univariable

TABLE 1 Demographic features of the study population in KONASPA

Variables	
Age at symptom onset, y, mean ± SD, median (IQR)	28.2 ± 14.2 26.5 (20.0-35.0)
Age at diagnosis, y, mean ± SD, median (IQR)	32.2 ± 12.2 29.0 (23.0-39.0)
Male, n (%)	152 (54.7)
Smoking, n (%)	
Never smoker	179 (64.4)
Ex-smoker	27 (9.7)
Current smoker	45 (16.2)
Missing	27 (9.7)
Alcohol, frequency, n (%)	
Never	94 (33.8)
≤1/wk	78 (28.1)
2-3/wk	48 (17.3)
≥4/wk	16 (5.8)
Missing	42 (15.1)
Education, n (%)	
Elementary school	2 (0.7)
Middle school	4 (1.4)
High school	71 (25.5)
College graduation	67 (24.1)
Missing	134 (48.2)
Living area, n (%)	
Urban	239 (86.0)
Rural	33 (11.9)
Missing	6 (2.2)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Cox regression analysis, age at symptom onset (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.93-0.99, P =0.037), body mass index (BMI) (HR 1.16, 95% CI 1.04-1.30, P =0.006), and sacroiliitis grade (HR 1.56, 95% CI 1.08-2.27, P =0.017) were associated with radiographic progression. In multivariable Cox regression analysis, age at symptom onset (HR 0.93, 95% CI 0.88-0.97, P =0.006), BMI (HR 1.24, 95% CI 1.06-1.44, P =0.005), and sacroiliitis grade (HR 1.86, 95% CI 1.19-2.92, P =0.006) were significantly associated with progression to AS.

4 | DISCUSSION

We evaluated clinical features and natural history of nr-axSpA using a nationwide real-life cohort. Male and female patients with nr-axSpA accounted for 54.7% and 45.3%, respectively. These percentages were compatible with results of the GESPIC, Canada, CORRONA, and DESIR studies, [6,17-19] reporting a male to female ratio of nr-axSpA of approximately 1:1. HLA-B27 positivity was 79.5% in the current study, similar to the results of the GESPIC, Canada, CORRNA, and DESIR cohort studies.[6,17-19] In KONASPA, mean values of BASDAI and BASFI were 3.5 and 1.6, respectively, lower than results of above-mentioned western cohorts' data that reported a BASDAI range of 3.9 to 4.7 and a BASFI range of 2.5 to 3.3. Recently, Lopez-Medina et al[9] have performed a meta-analysis and analyzed the clinical characteristics of nr-axSpA. They reported that 35.2%, 14.3%, and 9.3% of patients with nr-axSpA had peripheral arthritis, uveitis, and psoriasis, respectively. In the current study, peripheral arthritis (48.6%) was more frequently observed, psoriasis (3.9%) was less frequently observed, and uveitis was similar compared with the results of their meta-analysis. In the current study, most (95.6%) patients with nr-axSpA were taking NSAIDs. This percentage was compatible with the Herne cohort, which reported that 94% patients used NSAIDs.[5] However, the proportion of patients using NSAIDs seemed to be higher than results of the meta-analysis and other western cohorts, which revealed that approximately 40%-70% of patients were treated with NSAIDs.[9,17-19] Patients in KONASPA more frequently used both csDMARDs (55.8%) and systemic glucocorticoids (23.7%) but less frequently used bDMARDs (19.4%) compared with the meta-analysis, which reported that 28.5% of nr-axSpA patients used csDMARDs, 26.2% of patients used bDMARDs, and 10.1% of patients used systemic glucocorticoids. The reason to explain the

TABLE 2 Clinical characteristics and comorbidities of the study population

Variables	
SpA features, ever, n (%)	
Peripheral arthritis	135 (48.6)
Enthesitis	83 (29.8)
Uveitis	47 (16.9)
Dactylitis	14 (5.0)
Psoriasis	11 (3.9)
Inflammatory bowel disease	13 (4.7)
NSAID response	189 (68.0)
Family history of SpA	46 (16.5)
Sum of both sacroiliitis grades, n (%)	
0	69 (24.8)
1	32 (11.5)
2	92 (33.1)
3	69 (24.8)
Missing	16 (5.8)
Syndesmophytes, n (%)	2 (0.7)
mSASSS, (n = 49), mean ± SD	0.6 ± 1.8
Duration from onset of IBP to diagnosis, median, mo (n = 254), median (IQR)	12 (2-48)
Schober's test, cm (n = 71), mean ± SD	5.2 ± 2.0
Chest expansion, cm (n = 57), mean ± SD	4.3 ± 1.6
VAS for patient`s global assessment (n = 171), mean ± SD	4.1 ± 2.3
BASDAI (n = 176), mean ± SD	3.5 ± 2.1
BASFI (n = 167), mean ± SD	1.5 ± 1.9
ESR, mm/h, mean ± SD, median (IQR), (n = 265)	33.4 ± 30.7, 23.0 (10.0-49.0)
CRP, mm/h, mean ± SD, median (IQR), (n = 255)	1.91 ± 3.82, 0.46 (0.10-1.94)
BMI, kg/m^2, mean ± SD	23.3 ± 3.6
HLA-B27, positive, n (%)	221 (79.5)
Comorbidities, n (%)	
Dyslipidemia	23 (8.3)
Hypertension	17 (6.1)
Diabetes	8 (2.9)
Ischemic heart disease	3 (1.1)
Peptic ulcer	5 (1.8)
Pulmonary tuberculosis	3 (1.1)
Varicellar zoster	1 (0.4)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IBP, inflammatory back pain; IQR, interquartile range; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SpA, spondyloarthritis; VAS, Visual Analog Scale.

relative lower proportion of bDMARDs might be an insurance issue. Currently, unlike patients with AS, patients with nr-axSpA cannot receive special insurance benefit in Korea. Therefore, it is not easy for patients with nr-axSpA to use bDMARDs. Recommendations for use of bDMARDs published by the Korean College of Rheumatology do not include nr-axSpA patients.[20]

This study reported that the age at diagnosis of SpA and the age at symptom onset were older in women than in men. This corresponded well with a previous study showing that age at disease onset and age at diagnosis were older in female patients with nr-axSpA than in male patients.[21] In KONASPA, there was no statistical difference in the duration from onset of inflammatory back pain to diagnosis of nr-axSpA Hence, there was no worsening of diagnostic delay in female patients compared with male patients in this cohort. However, these findings were different from those of the Swiss Clinical Quality Management Cohort study, which reported that women with nr-axSpA had longer diagnostic delay and that the age at symptom onset was comparable between male and female patients.[22] A meta-analysis has shown that female patients have a longer diagnostic delay of 2.3 years compared with male patients.[23] Slower progression of radiographic change of lower frequency of typical inflammatory back pain as a presenting manifestation might be the reason for such diagnostic delay in female patients.[24]

This study found that female patients more often presented enthesitis and uveitis than male patients, corresponding well with previous studies reporting that female patients more often presented peripheral enthesitis.[22,25] Uveitis seemed to be more frequently found among male patients.[26,27] However, a meta-analysis has reported that uveitis is more common in female patients than in male patients.[24,28] There was no difference in disease activity assessed by BASDAI or BASFI between male and female patients. Initial CRP levels were higher in male than in female patients in this cohort. Among patients with AS, female patients showed higher disease burden and BASDAI score for measuring fatigue, total back pain, and duration of morning stiffness than male patients.[26,29,30] However, previous studies have shown no significant difference in BASFI score between male and female patients.[22,25] Studies have shown that baseline CRP levels are higher in male patients than in female patients,[25,26,30] corresponding well with the current study.

The present study found that 11.2% of patients progressed to AS. The median duration from diagnosis of nr-axSpA to diagnosis of AS was 48 months. Younger age at symptom onset was associated with radiographic progression in patients with nr-axSpA in this study. Dougados et al reported that mean age was younger in patients with radiographic progression of the sacroiliac joint than patients without radiographic progression.[13] HLA-B27 positivity and smoking were risk factors for radiographic progression in AS.[13,31] Early disease onset was significantly higher in HLA-B27-positive patients and late disease onset was significantly higher in HLA-B27-negative patients.[32] Patients with late-onset AS more often showed involvement of peripheral arthritis whereas those with early-onset AS more

TABLE 3 Medications used by the study population

Variables	
Initiation of NSAIDs, n (%)	266 (95.6)
Naproxen	86 (32.3)
Celecoxib	83 (31.2)
Meloxicam	52 (19.5)
Aceclofenac	21 (7.9)
Nabumetone	14 (5.3)
Indomethacin	4 (1.5)
Others	6 (2.3)
Not use of NSAIDs	6 (2.2)
Missing	6 (2.2)
First NSAID adherence, n (%)	
Continue	112 (42.1)
Stop	142 (53.4)
Missing	12 (4.5)
Mean duration of use of first NSAID, mo, mean ± SD	8.7 ± 13.1
Reason for discontinuation (n = 142), n (%)	
Adverse event	8 (5.6)
Inefficacy	75 (52.8)
Improved symptom	46 (32.4)
Missing or unknown	13 (9.2)
Initiation of csDMARDs	155 (55.8)
Sulfasalazine	139 (89.7)
Methotrexate	15 (9.7)
Hydroxychloroquine	1 (0.6)
Not use of csDMARDs	123 (44.3)
First csDMARDsadherence, n (%)	
Continue	87 (56.1)
Stop	68 (43.9)
Reason for discontinuation (n = 68), n (%)	
Adverse event	5 (7.4)
Inefficacy	30 (44.1)
Improved symptom	26 (38.2)
Missing or unknown	7 (10.3)
Initiation of bDMARDs	49 (17.6)
Infliximab	18 (36.7)
Adalimumab	10 (20.4)
Etanercept	9 (18.4)
Golimumab	11 (22.4)
Secukinumab	1 (2.1)
Not use of bDMARDs	229 (82.4)
First bDMARDs adherence, n (%)	
Continue	37 (75.5)
Stop	12 (24.5)
Mean time of first biologic use, mo, mean ± SD	24.9 ± 32.6
Reason for discontinuation (n = 12), n (%)	
Adverse event	3 (25.0)
Inefficacy	5 (41.7)
Improved symptom	0 (0.0)
Missing or unknown	4 (33.3)
Initiation of systemic glucocorticoids, n (%)	66 (23.7)

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

often showed axial symptoms.[33] More frequent smoking, HLA-B27 positivity, and tendency for axial involvement may contribute to radiographic progression in patients with younger age onset nr-axSpA.

Baseline sacroiliitis and BMI were associated with progression to AS. High BMI is an independent predictor of spinal radiographic progression in patients with AS.[34,35] Adipokines are cytokines secreted by white adipose tissues. They can modulate inflammation and immune responses.[36] Adipokines such as leptin, resistin, and visfatin are associated with radiographic progression.[37,38] Biomechanical factors could influence radiographic progression. Jacques et al [39] demonstrated that mechanical strain can drive entheseal inflammation and new bone formation in SpA via the Erk1/2 signaling pathway. Occupational exposure to vibration or physical activity is associated with radiographic damage.[40,41] The rapid radiographic progression in obese patients could be explained by inflammation associated with mechanotransduction and immune response factors.

Baseline sacroiliitis grade was a risk factor for progression to AS from nr-axSpA. Previous studies have also identified that baseline radiographic damage is a marker of future radiographic progression.[31] A Rochester population-based cohort study has shown that progression from nr-axSpA to AS is significantly more frequent and faster in patients in the imaging arm than in those in the clinical arm.[12] In patients with early inflammatory back pain, a combination of sacroiliitis on MRI and HLA-B27 positivity is a strong predictor of the development of AS.[42]

The current study has some limitations. First, we did not use central reading. Sacroiliitis grade and classification of nr-axSpA and AS were done in each hospital. Although the rheumatologist or radiologist in each tertiary center scored X-ray images, reliability might not be good in grading radiographic sacroiliitis because different readers scored the X-ray images. Second, X-rays for sacroiliac joint were not performed yearly in all study population. Pelvis X-rays were performed at various intervals for each patient. Therefore, the inherent bias should be considered in this study design. Third, KONASPA was a retrospective and prospective cohort. Patients who were diagnosed with nr-axSpA at their first visit to the rheumatology clinic can be included, regardless of their condition at the time of cohort enrollment. Therefore, for some patients who were enrolled retrospectively, pre-existing data were not sufficient with possible recall

TABLE 4 Comparison of baseline characteristics between male and female patients

Variable	Male patients (n = 152)	Female patients (n = 126)	*P* value
Age at symptom onset, y, mean ± SD	24.9 ± 12.0	31.8 ± 15.8	<0.001
Age at diagnosis, y, mean ± SD	29.7 ± 9.7	35.1 ± 14.1	<0.001
Smoking (n = 251), n (%)			< 0.001
never smoker	77 (56.6)	102 (88.7)	
ex-smoker	21 (15.4)	6 (5.2)	
current smoker	38 (27.9)	7 (6.1)	
Alcohol, frequency (n = 236), n (%)			< 0.001
Never	31 (23.8)	63 (59.4)	
≤1/wk	48 (36.9)	30 (28.3)	
2-3/wk	40 (30.8)	8 (7.5)	
≥4/wk	11 (8.5)	5 (4.7)	
Peripheral arthritis, n (%)	70/146 (47.9)	65/124 (52.4)	0.464
Enthesitis, n (%)	36/146 (24.7)	47/121 (38.8)	0.013
Dactylitis, n (%)	5/145 (3.4)	9/123 (7.3)	0.156
Uveitis, n (%)	17/146 (11.6)	30/123 (24.4)	0.006
Psoriasis, n (%)	4/146 (2.7)	7/123 (5.7)	0.355
Inflammatory bowel disease, n (%)	6/146 (4.1)	7/123 (5.7)	0.547
Family history of SpA	23/143 (16.1)	24/122 (19.7)	0.446
Duration from onset of IBP to diagnosis, mo, mean ± SD	152.4 ± 392.8	78.6 ± 249.7	0.072
VAS for patient`s global assessment, mean ± SD	3.9 ± 2.4	4.4 ± 2.3	0.228
BASDAI (n = 176)	3.4 ± 2.2	3.5 ± 1.9	0.620
BASFI (n = 167)	1.5 ± 1.8	1.7 ± 1.9	0.524
BMI, kg/m^2, mean ± SD	24.1 ± 3.4	22.2 ± 3.7	<0.001
ESR, mm/h, mean ± SD	31.0 ± 31.7	36.5 ± 29.2	0.148
CRP, mg/dL, mean ± SD	2.48 ± 4.82	1.23 ± 1.91	0.006
HLA-B27 positive, n (%)	120/152 (78.9)	101/126 (80.2)	0.803
SIJ grade, total, mean ± SD	1.6 ± 1.1	1.5 ± 1.1	0.252
NSAIDs, n (%)	148 (97.4)	118 (93.7)	0.148
csDMARDs, n (%)	87 (57.2)	68 (54.0)	0.585
bDMARDs, n (%)	30 (19.7)	19 (15.1)	0.310
Systemic glucocorticoids, n (%)	31 (20.4)	35 (27.8)	0.150
Progression to AS, n (%)	18 (11.8)	13 (10.3)	0.688

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IBP, inflammatory back pain; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SIJ, sacroiliac joint; SpA, spondyloarthritis; VAS, Visual Analog Scale.

bias. As the study design is actually not a prospective study, it is necessary to analyze the characteristics of progressors among the patients who were enrolled prospectively. Fourth, the number of patients who had radiographic progression is small. Thirty-one patients progressed to AS and were used to assess factors for radiographic progression. A small sample size may estimate the effect imprecisely. The strength of our study was that we evaluated characteristics, disease burden, and treatment modality, and comorbidities of nr-axSpA in detail using a nationwide cohort.

In conclusion, characteristics of nr-axSpA in KONASPA were comparable with those shown in western cohort studies. This study revealed that women with nr-axSpA showed a late disease onset and more extra-articular manifestations than men. Younger age at symptom onset, high BMI, and the presence of radiographic sacroiliitis at

TABLE 5 Comparison of baseline characteristics between non-progressors and AS progressors

Variable	Non-progressor (n = 247)	Progressor (n = 31)	*P* value
Male, n (%)	134 (54.3)	18 (58.1)	0.688
Age at symptom onset, y, mean ± SD	29.1 ± 14.5	22.5 ± 10.2	0.016
Age at diagnosis, y, mean ± SD	32.7 ± 12.4	27.6 ± 9.8	0.028
Smoking (n = 251), n (%)			0.016
never smoker	161 (72.9)	18 (60.0)	
ex-smoker	26 (11.8)	1 (3.3)	
current smoker	34 (15.4)	11 (36.7)	
Alcohol, frequency (n = 236), n (%)			0.040
Never	89 (42.8)	5 (17.9)	
≤1/wk	67 (32.2)	11 (39.3)	
2-3/wk	39 (18.8)	9 (32.1)	
≥4/wk	13 (6.2)	3 (10.7)	
Peripheral arthritis, n (%)	118 (49.4)	17 (54.8)	0.567
Enthesitis, n (%)	78 (32.9)	5 (16.7)	0.070
Dactylitis, n (%)	13 (5.5)	1 (3.2)	1.000
Uveitis, n (%)	41 (17.2)	6 (19.4)	0.769
Psoriasis, n (%)	11 (4.6)	0 (0.0)	0.622
Inflammatory bowel disease, n (%)	12 (5.0)	1 (3.2)	1.000
Family history of SpA, n (%)	43 (18.3)	4 (13.3)	0.618
Duration from onset of IBP to diagnosis, mo, mean ± SD	117.2 ± 335.2	125.2 ± 342.5	0.902
Schober, cm (n = 71), mean ± SD	5.3 ± 1.9	5.1 ± 2.5	0.838
Chest expansion, cm (n = 57), mean ± SD	4.3 ± 1.6	4.4 ± 1.3	0.780
VAS for patient's global assessment (n = 171), mean ± SD	4.2 ± 2.3	3.6 ± 2.3	0.251
BASDAI (n = 176), mean ± SD	3.4 ± 2.1	3.5 ± 2.0	0.818
BASFI (n = 167), mean ± SD	1.6 ± 1.2	1.9 ± 1.6	0.553
BMI, kg/m^2, mean ± SD	23.3 ± 3.6	23.5 ± 4.1	0.774
Systolic blood pressure, mmHg, mean ± SD	122.8 ± 14.0	123.9 ± 15.8	0.981
Diastolic blood pressure, mmHg, mean ± SD	74.3 ± 11.7	76.1 ± 11.5	0.441
ESR, mm/hr, mean ± SD	35.3 ± 31.5	19.2 ± 19.1	<0.001
CRP, mg/dL, mean ± SD	2.03 ± 3.91	1.04 ± 1.98	0.183
HLA-B27-positive, n (%)	198 (80.2)	23 (74.2)	0.438
SIJ grade, total, mean ± SD	1.5 ± 1.1	2.3 ± 0.9	<0.001
NSAIDs, n (%)	235 (95.1)	31 (100)	0.373
csDMARDs, n (%)	133 (53.8)	22 (71.0)	0.070
bDMARDS, n (%)	40 (16.2)	9 (29.0)	0.077
Systemic glucocorticoids, n (%)	55 (22.3)	11 (35.5)	0.103

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IBP, inflammatory back pain; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SIJ, sacroiliac joint; SpA, spondyloarthritis; VAS, Visual Analog Scale.

TABLE 6 Predictors of progression to AS from nr-axSpA

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male	1.09 (0.53-2.27)	0.800		
Age at symptom onset	0.96 (0.93-0.99)	0.037	0.93 (0.88-0.97)	0.006
Age at diagnosis	0.98 (0.94-1.01)	0.267		
Smoking	1.12 (0.53-2.35)	0.758		
Alcohol consumption	1.85 (0.75-4.58)	0.181		
Peripheral arthritis	0.95 (0.35-2.53)	0.924		
Enthesitis	0.25 (0.05-1.11)	0.070		
Dactylitis	3.12 (0.39-25.03)	0.283		
Uveitis	0.90 (0.29-2.75)	0.856		
Inflammatory bowel disease	0.61 (0.08-4.66)	0.640		
Family history of SpA	0.28 (0.03-2.12)	0.291		
Duration from onset of IBP to diagnosis	1.00 (1.00-1.01)	0.235		
Schober (n = 71)	1.15 (0.85-1.55)	0.345		
VAS for patient's global assessment (n = 171)	1.03 (0.85-1.24)	0.713		
BASDAI (n = 176)	1.08 (0.90-1.30)	0.395		
BASFI (n = 167)	1.16 (0.90-1.50)	0.237		
BMI	1.16 (1.04-1.30)	0.006	1.24 (1.06-1.44)	0.005
ESR	0.98 (0.96-1.00)	0.056	0.99 (0.97-1.01)	0.681
CRP	0.91 (0.75-1.12)	0.404		
HLA-B27-positive	1.04 (0.45-2.38)	0.920		
SIJ grade, total	1.56 (1.08-2.27)	0.017	1.86 (1.19-2.92)	0.006
csDMARDs	1.40 (0.63-3.08)	0.401		
bDMARDs	0.95 (0.43-2.09)	0.915		
Systemic glucocorticoids	0.85 (0.40-1.80)	0.681		

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; HR, hazard ratio; IBP, inflammatory back pain; nr-axSpA, non-radiographic axial spondyloarthritis; SIJ, sacroiliac joint; VAS, Visual Analog Scale.

diagnosis were associated with progression to AS. KONASPA is an ongoing cohort. A larger number of patients and follow-up data are expected to be collected in the future. KONASPA will contribute to the identification of characteristics and natural course of nr-axSpA.

ACKNOWLEDGEMENTS

The KOrean Nonradiographic Axial SPondyloArthritis (KONASPA) registry is run by the Korean Society of Spondyloarthritis Research, which is supported by the Korean College of Rheumatology and by CELLTRION.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The author and co-authors contributed equally to this paper; study design, participants recruitment, data collection, analysis and/or interpretation of data, drafting of the manuscript or revising it critically. All authors finally approved the current manuscript.

ORCID

Hyemin Jeong https://orcid.org/0000-0001-6227-681X
Yong-Gil Kim https://orcid.org/0000-0002-8029-7355
Tae-Hwan Kim https://orcid.org/0000-0002-3542-2276
Min-Chan Park https://orcid.org/0000-0003-1189-7637
Kichul Shin https://orcid.org/0000-0002-6749-7598
Yeon-Ah Lee https://orcid.org/0000-0001-8007-9131

REFERENCES

1. Khan MA, van der Linden SM, Kushner I, Valkenburg HA, Cats A. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. *Arthritis Rheum*. 1985;28:40-43.
2. Benavent D, Navarro-Compan V. Understanding the paradigm of non-radiographic axial spondyloarthritis. *Clin Rheumatol*. 2021;40(2):501–512. https://doi.org/10.1007/s10067-020-05423-7
3. Sieper J, van der Heijde D, Landewe R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis*. 2009;68:784-788.
4. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27:361-368.
5. Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res (Hoboken)*. 2012;64:1415-1422.
6. Wallis D, Haroon N, Ayearst R, Carty A, Inman RD. Ankylosing spondylitis and nonradiographic axial spondyloarthritis: part of a common spectrum or distinct diseases? *J Rheumatol*. 2013;40:2038-2041.
7. Wallman JK, Kapetanovic MC, Petersson IF, Geborek P, Kristensen LE. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients–baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther*. 2015;17:378.
8. Malaviya AN, Kalyani A, Rawat R, Gogia SB. Comparison of patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) from a single rheumatology clinic in New Delhi. *Int J Rheum Dis*. 2015;18:736-741.
9. Lopez-Medina C, Ramiro S, van der Heijde D, Sieper J, Dougados M, Molto A. Characteristics and burden of disease in patients with radiographic and non-radiographic axial Spondyloarthritis: a comparison by systematic literature review and meta-analysis. *RMD Open*. 2019;5:e001108.
10. Dougados M, Sepriano A, Molto A, et al. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis*. 2017;76:1823-1828.
11. Costantino F, Zeboulon N, Said-Nahal R, Breban M. Radiographic sacroiliitis develops predictably over time in a cohort of familial spondyloarthritis followed longitudinally. *Rheumatology (Oxford)*. 2017;56:811-817.
12. Wang R, Gabriel SE, Ward MM. Progression of Nonradiographic Axial Spondyloarthritis to Ankylosing Spondylitis: A Population-Based Cohort Study. *Arthritis Rheumatol*. 2016;68:1415-1421.
13. Dougados M, Demattei C, van den Berg R, et al. Rate and Predisposing Factors for Sacroiliac Joint Radiographic Progression After a Two-Year Follow-up Period in Recent-Onset Spondyloarthritis. *Arthritis Rheumatol*. 2016;68:1904-1913.
14. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21:2286-2291.
15. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol*. 1994;21:2281-2285.
16. Creemers MC, Franssen MJ, Gribnau FWJ, van de Putte LBA, van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis*. 2005;64:127-129.
17. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum*. 2009;60:717-727.
18. Mease PJ, Heijde DV, Karki C, et al. Characterization of Patients With Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis in the US-Based Corrona Registry. *Arthritis Care Res (Hoboken)*. 2018;70:1661-1670.
19. Lopez-Medina C, Molto A, Claudepierre P, Dougados M. Clinical manifestations, disease activity and disease burden of radiographic versus non-radiographic axial spondyloarthritis over 5 years of follow-up in the DESIR cohort. *Ann Rheum Dis*. 2020;79:209-216.
20. Park E-J, Kim H, Jung SM, et al. The Use of Biological Disease-modifying Antirheumatic Drugs for Inflammatory Arthritis in Korea: Results of a Korean Expert Consensus. *J Rheumat Dis*. 2020;27:4-21.
21. Jeong H, Yoon JY, Park EJ, et al. Clinical characteristics of nonradiographic axial spondyloarthritis in Korea: a comparison with ankylosing spondylitis. *Int J Rheum Dis*. 2015;18:661-668.
22. Neuenschwander R, Hebeisen M, Micheroli R, et al. Differences between men and women with nonradiographic axial spondyloarthritis: clinical characteristics and treatment effectiveness in a real-life prospective cohort. *Arthritis Res Ther*. 2020;22:233.
23. Jovani V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E. Understanding How the Diagnostic Delay of Spondyloarthritis Differs Between Women and Men: A Systematic Review and Metaanalysis. *J Rheumatol*. 2017;44:174-183.
24. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Curr Rheumatol Rep*. 2018;20:35.

25. Tournadre A, Pereira B, Lhoste A, et al. Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. *Arthritis Care Res (Hoboken)*. 2013;65:1482-1489.
26. Webers C, Essers I, Ramiro S, et al. Gender-attributable differences in outcome of ankylosing spondylitis: long-term results from the Outcome in Ankylosing Spondylitis International Study. *Rheumatology (Oxford)*. 2016;55:419-428.
27. Braakenburg AM, de Valk HW, de Boer J, Rothova A. Human leukocyte antigen-B27-associated uveitis: long-term follow-up and gender differences. *Am J Ophthalmol*. 2008;145:472-479.
28. Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. *Ann Rheum Dis*. 2008;67:955-959.
29. Landi M, Maldonado-Ficco H, Perez-Alamino R, et al. Gender differences among patients with primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease in an iberoamerican spondyloarthritis cohort. *Medicine (Baltimore)*. 2016;95:e5652.
30. Shahlaee A, Mahmoudi M, Nicknam MH, Farhadi E, Fallahi S, Jamshidi AR. Gender differences in Iranian patients with ankylosing spondylitis. *Clin Rheumatol*. 2015;34:285-293.
31. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum*. 2012;64:1388-1398.
32. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int*. 2003;23:61-66.
33. Montilla C, Del pino-montes J, Collantes-estevez E, et al. Clinical Features of Late-onset Ankylosing Spondylitis: Comparison with Early-onset Disease. *J Rheumatol*. 2012;39:1008-1012.
34. Deminger A, Klingberg E, Geijer M, et al. A five-year prospective study of spinal radiographic progression and its predictors in men and women with ankylosing spondylitis. *Arthritis Res Ther*. 2018;20:162.
35. Jeong H, Bea EK, Lee J, Koh EM, Cha HS. Body mass index and estrogen predict radiographic progression in the spine in ankylosing spondylitis. *Joint Bone Spine*. 2015;82:473-474.
36. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. *Nat Clin Pract Rheumatol*. 2007;3:716-724.
37. Park J-H, Lee S-G, Jeon Y-K, Park E-K, Suh Y-S, Kim H-O. Relationship between serum adipokine levels and radiographic progression in patients with ankylosing spondylitis: A preliminary 2-year longitudinal study. *Medicine*. 2017;96:e7854-e.
38. Syrbe U, Callhoff J, Conrad K, et al. Serum adipokine levels in patients with ankylosing spondylitis and their relationship to clinical parameters and radiographic spinal progression. *Arthritis Rheumatol*. 2015;67:678-685.
39. Jacques P, Lambrecht S, Verheugen E, et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. *Ann Rheum Dis*. 2014;73:437-445.
40. Ward MM, Reveille JD, Learch TJ, Davis JC Jr, Weisman MH. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. *Arthritis Rheum*. 2008;59:822-832.
41. Ramiro S, Landewe R, van Tubergen A, et al. Lifestyle factors may modify the effect of disease activity on radiographic progression in patients with ankylosing spondylitis: a longitudinal analysis. *RMD Open*. 2015;1:e000153.
42. Bennett AN, McGonagle D, O'Connor P, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum*. 2008;58:3413-3418.

How to cite this article: Jeong H, Kim Y-G, Kim T-H, et al. Clinical characteristics of non-radiographic axial spondyloarthritis: Results of the Korean Nonradiographic Axial SPondyloArthritis (KONASPA) data. *Int J Rheum Dis*. 2021;24:1137–1147. https://doi.org/10.1111/1756-185X.14175

Received: 19 April 2021 | Revised: 4 June 2021 | Accepted: 7 July 2021

DOI: 10.1111/1756-185X.14180

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Static foot posture and its relation to clinical variables in ankylosing spondylitis

Neslihan Gokcen[1] | Aylin Sariyildiz[2] | Ilke Coskun Benlidayi[2]

[1]Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Cukurova University Faculty of Medicine, Adana, Turkey

[2]Department of Physical Medicine and Rehabilitation, Cukurova University Faculty of Medicine, Adana, Turkey

Correspondence
Neslihan Gokcen, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Cukurova University, Adana, Turkey.
Email: drngokcen@hotmail.com

Abstract

Aim: Postural abnormalities of the foot are common in rheumatic diseases. Static foot posture is a poorly studied clinical parameter in ankylosing spondylitis (AS). The aim of the study was to evaluate static foot posture in patients with AS and to determine the potential impact of clinical variables on foot posture.

Method: Fifty patients with AS and 40 age- and sex-matched healthy controls were enrolled in the study. Disease activity was measured using the Ankylosing Spondylitis Disease Activity Score. Axial mobility was evaluated with the Bath Ankylosing Spondylitis Metrology Index three-point answer scale. Functional status was assessed by the Bath Ankylosing Spondylitis Functional Index and Health Assessment Questionnaire-Disability Index. Enthesitis and foot posture were evaluated by the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Foot Posture Index-6, respectively.

Results: Patients with AS revealed significantly higher scores of foot posture index when compared with controls ($P = 0.005$). Abnormal foot posture (pronated and supinated) was more common in the patient group ($P < 0.01$). According to the multinomial logistic regression analysis, a higher MASES score was associated with supinated foot posture in AS patients (odds ratio 1.47, 95% confidence interval 1.03-2.09, $P = 0.035$). In addition, supinated foot posture was associated with enthesitis of the Achilles tendon ($P = 0.002$).

Conclusion: Enthesitis is related to deteriorated static foot posture in patients with AS. Enthesitis of the Achilles tendon is closely associated with the supinated foot posture.

KEYWORDS

Ankylosing spondylitis, enthesitis, foot posture, foot posture index, Maastricht Ankylosing Spondylitis Enthesitis Score

1 | INTRODUCTION

Spondyloarthritis (SpA) is an umbrella term including arthritic diseases with similar pathophysiological, clinical, and imaging features.[1] It is classified according to the predominant clinical sign as peripheral SpA and axial SpA. Ankylosing spondylitis (AS), the prototype of axial spondyloarthritis, is a chronic inflammatory disease characterized by primarily axial skeleton involvement. Although arthritis and enthesitis are the most common manifestations of peripheral spondyloarthritis, these are also observed in axial spondyloarthritis (30%-50%).[2,3]

Ankylosing spondylitis contributes to several postural changes during the disease course. Frequently expected postural changes are cervical flexion, decreased lumbar lordosis, pelvic

anteversion along with hip and knee flexion, and ankle dorsiflexion.[4,5] Accordingly, foot posture may also change in view of the misalignment of axial skeleton, hip and knee joint. Not only can the ankle joint be affected, but also other parts of the foot (hindfoot, forefoot) may be influenced.[1,5]

Arthritis and enthesitis may contribute to abnormal foot posture in patients with AS. Sahli et al[1] studied foot involvement in SpA. The authors found that 39% of the AS patients had foot involvement. A recent study conducted by Koca et al[6] investigated the relationship between foot function and clinical variables, particularly enthesitis. Consequently, impaired foot function due to enthesitis, tarsitis, and deformities was found to be more frequent in AS patients than in healthy controls. Although the influence of enthesitis on foot function has been discussed, its effect on foot posture has not been mentioned in the literature. Given the limited data in the literature, the aim of the present study was to assess static foot posture and its relation to clinical variables in patients with AS.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

This case-control study was conducted between May 2018 and May 2019. The inclusion criteria were as follows; (a) AS patients who met the 2010 Assessment of SpondyloArthritis International Society classification criteria,[7] (b) being between the ages of 18 and 65 years, and (c) having sufficient cognitive skills to be effectively questioned. The control group comprised 40 age- and sex-matched healthy participants. Patients with (a) hip, knee, or ankle joint involvement, (b) history of major trauma and/or surgery to the ankle-foot complex, (c) congenital deformities of the foot/ankle, or (d) distal polyneuropathies were excluded. Written informed consent was obtained from each patient according to the Declaration of Helsinki. The local ethics committee of Cukurova University approved the study protocol (Date: April 13, 2018, Ethical approval number: 76).

2.2 | Foot posture evaluation

Static foot posture was assessed by the Foot Posture Index-6 (FPI-6) while the patient was standing barefoot. FPI-6 includes six anatomical evaluations: (a) talar head palpation, (b) supra- and infra-lateral malleolar curvature, (c) calcaneal frontal plane position, (d) prominence in the region of talonavicular joint, (e) congruence of the medial longitudinal arch, (f) abduction/adduction of forefoot on the rearfoot. Each anatomical assessment is scored from −2 to +2. The total score ranges from −12 to +12. The foot posture is categorized into five as follows: (a) normal/neutral (from 0 to +5), (b) pronated foot (from +6 to +9), (c) highly pronated foot (from +10 to +12), (d) supinated foot (from −1 to −4), (e) highly supinated foot (from −5 to −12).[8-10] Further categorization was performed by merging the highly pronated and pronated feet, and the highly supinated and supinated feet. FPI-6 from 0 to +5, ≥+6 and ≤−1 were regarded as neutral, pronated, and supinated, respectively.[10]

2.3 | Evaluation of the clinical variables

The disease activity was calculated based on Ankylosing Spondylitis Disease Activity Score (ASDAS). According to ASDAS, back pain, peripheral pain/swelling, patient assessment of global disease activity, and duration of morning stiffness were evaluated by a numerical rating scale (from 0 to 10). Additionally, C-reactive protein level was added to the ASDAS formula before final calculation. Results were classified into four disease activity states including inactive disease (<1.3), moderate disease activity (≥1.3 to <2.1), high disease activity (≥2.1 to ≤3.5), and very high disease activity (>3.5) proposed by the Assessment of SpondyloArthritis of the International Society.[11,12]

The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used to evaluate physical function. The HAQ-DI comprises 20 items in eight categories including dressing, rising, eating, walking, hygiene, reach, grip, and daily activities. The index assesses physical function during the previous week. Each item is scored from 0 to 3, where 0 represents the capability of doing the activity and 3 states the highest incapability to perform the activity. Higher scores indicate impaired function.[13-15]

The Bath Ankylosing Spondylitis Metrology Index (BASMI) three-point answer scale was used to assess the axial mobility of patients. Accordingly, tragus to wall distance, lumbar flexion (modified Schober), lateral lumbar flexion, and maximum intermalleolar distance, and cervical rotation are evaluated. Each of the five clinical parameters is graded from 0 to 2. Total score is calculated from 0 to 10 with higher scores indicating impaired mobility.[16,17]

The Bath Ankylosing Spondylitis Functional Index (BASFI) was used to evaluate the functional status of patients. It includes 10 items assessing daily activities. Each item is scored on a 0-10 scale and high scores indicate decreased function. The mean score of the sum of all items is recorded as the final score. Increased scores indicate impaired function.[17-19]

Enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). A total of 13 entheses including the spinous process of the fifth lumbar vertebra, bilateral of first and seventh costochondral joint, spina iliaca anterior superior, crista iliaca, spina iliaca posterior superior, and proximal insertion of Achilles tendons are assessed. Each site is scored as 0 or 1 point, which is calculated according to the presence or absence of pain by local pressure. The sum of all sites is noted as the final score (from 0 to 13). High scores are related to clinically important enthesitis.[17,20]

2.4 | Statistical analysis

Data distribution was evaluated by the Shapiro-Wilk test. Descriptive analysis was used to analyze the demographic variables. Comparative analyses between groups were performed using

Fisher's exact test and Mann-Whitney *U* test for categorical and continuous variables, respectively. Comparison of continuous variables among foot posture groups was done by the Kruskal-Wallis test. Spearman's correlation analysis was used to evaluate potential correlations between foot posture and clinical variables. Univariate analysis was performed as a means of identifying the predictive variables for foot posture. Multinomial logistic regression analysis was performed to determine the risk factors related to impaired foot posture. Results with *P* values less than 0.05 were considered statistically significant. SPSS version 20.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

3 | RESULTS

Fifty patients (29 males, 21 females) and 40 age- and sex-matched controls (19 males, 21 females) were included in the study. The demographic and clinical characteristics of the participants are given in Table 1. Median age of the patients was 44 years. Of the patients, 42% were taking biological disease-modifying anti-rheumatic drugs, and the rest were on non-steroid anti-inflammatory drug therapy.

According to FPI-6, 36 (72%), 8 (16%), and 6 (12%) patients had neutral (from 0 to +5), pronated (≥+6), and supinated (≤−1) foot posture, respectively. Of the healthy controls, only two showed supinated foot posture and the rest had neutral FPI-6. When foot posture was compared between groups, abnormal posture (pronated and supinated) was significantly more frequent in patients than that in controls (28 vs 5, Fisher's exact test, $P < 0.01$). Additionally, the FPI-6 score was significantly higher in patients than in controls ($P = 0.005$) (Table 2).

TABLE 1 The baseline and clinical characteristics of the study population

	Patients (n = 50)	Controls (n = 40)
Age (years)[a]	44.0 (35.0-50.3)	43.0 (35.8-51.0)
BMI (kg/m^2)[a]	27.9 (24.3-32.0)	26.4 (24.0-28.0)
Female/male[b]	21 (42.0)/29 (58.0)	21 (52.5)/19 (47.5)
CRP (mg/dL)[a]	0.86 (0.38-1.44)	—
HAQ-DI[a]	6.0 (0.8-10.3)	—
ASDAS[a]	2.4 (1.8-3.2)	—
BASMI[a]	1.0 (0-4.0)	—
BASFI[a]	2.9 (1.0-4.4)	—
MASES[a]	2.0 (0-3.0)	—

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score.

[a]Values are given as median (interquartile range).

[b]Values are given as n (%).

TABLE 2 The comparison of the static foot posture between groups

	Patients (n = 50)	Controls (n = 40)	*P*
FPI-6 score[a]	2.0 (0-5.0)	0 (0-1.0)	0.005*
Supinated[b]	6 (12)	2 (5)	0.007*
Neutral[b]	36 (72)	38 (95)	
Pronated[b]	8 (16)	0	

Abbreviation: FPI-6, Foot Posture Index-6.

[a]Values are given as median (interquartile range). *P* value is derived from the Mann-Whitney *U* test.

[b]Values are given as n (%). *P* value is derived from the Fisher's exact test.

*$P < 0.05$.

In the patient group, there were no statistically significant differences in clinical variables among static foot posture groups (Table 3). In addition, the FPI-6 score showed no correlation with the clinical variables including HAQ-DI, ASDAS, BASMI, BASFI, and MASES (Table 4). However, patients with Achilles enthesitis revealed significantly higher rates of supinated foot posture (Fisher's exact test, $P = 0.002$). In univariate analysis, MASES and BASFI scores were found as the candidates for regression analysis ($P = 0.025$ and $P = 0.003$, respectively). Multinomial logistic regression analysis was used to evaluate the potential risk factors for impaired foot posture. Accordingly, a higher MASES score appeared as a risk factor for supinated foot posture in AS patients (odds ratio 1.47, 95% confidence interval 1.03-2.09, $P = 0.035$). In addition, further multinomial logistic regression analysis was performed by including other potentially affecting variables with *P* values below 0.50. In this respect, a higher MASES score continued being a risk factor for supinated foot posture after adjusting for age, BMI, BASMI, BASFI, and HAQ-DI (odds ratio 1.69, 95% confidence interval 1.03-2.78, $P = 0.038$).

4 | DISCUSSION

A number of studies so far have investigated foot involvement in SpA.[1,21] Foot involvement includes bone erosions, para-articular enthesophyte formation, and Achilles enthesitis.[21] Achilles enthesitis was found to be associated with higher BASFI and HAQ-DI scores.[22] Koca et al[6] studied the determinants of foot function in patients with AS. Both the foot function index total score and the subscores were significantly higher in the AS group when compared with controls. The foot function index subscores for pain, disability, and activity limitation showed significant correlation with BASFI and the Bath Ankylosing Spondylitis Disease Activity Index scores.[6] Another study found that late-onset SpA, peripheral SpA, shorter disease duration, and higher CRP were associated with foot involvement. However, there was no association with BASFI score.[1] In the present study, patients with AS revealed impaired foot posture and those with Achilles enthesitis revealed higher impairment

TABLE 3 The evaluation of clinical variables in accordance with static foot posture in patients with ankylosing spondylitis

	Supinated (n = 6)	Neutral (n = 36)	Pronated (n = 8)	*P*
Age (years)	47.5 (34.5-58.0)	44.5 (35.5-49.8)	37.5 (22.8-54.5)	0.612
BMI (kg/m^2)	29.3 (26.6-31.9)	28.0 (24.8-31.6)	24.4 (20.7-36.3)	0.537
CRP (mg/dL)	0.6 (0.4-0.9)	1.0 (0.4-1.5)	0.5 (0.3-2.3)	0.459
HAQ-DI	8.5 (0.8-12.5)	6.0 (0-10.5)	4.0 (1.5-13.0)	0.620
ASDAS	2.7 (1.5-3.5)	2.4 (1.8-3.2)	2.2 (1.7-3.3)	0.975
BASMI	1.0 (0.8-4.0)	1.0 (0-4.0)	3.0 (0.3-4.8)	0.838
BASFI	3.6 (1.8-4.4)	2.8 (0.5-4.4)	3.1 (1.2-4.4)	0.675
MASES	2.0 (2.0-7.3)	1.5 (0-3.0)	1.5 (0.3-6.0)	0.137

Note: Values are given as median (interquartile range). *P* value represents Kruskal-Wallis test.

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, Body Mass Index; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score.

TABLE 4 Intercorrelation of study variables in patients with ankylosing spondylitis

	1	2	3	4	5	6	7	8	9
1. Age (years)	1								
2. BMI (kg/m^2)	0.376**	1							
3. CRP (mg/dL)	0.082	0.071	1						
4. HAQ-DI	0.146	0.172	0.183	1					
5. ASDAS	−0.009	0.076	0.544***	0.606***	1				
6. BASMI	0.416**	0.204	0.072	0.371**	0.050	1			
7. BASFI	0.097	0.079	0.200	0.867***	0.584***	0.512***	1		
8. MASES	−0.194	0.086	0.203	0.452***	0.567***	−0.048	0.367**	1	
9. FPI-6	−0.194	−0.043	0.005	−0.078	−0.095	0.094	−0.107	0.022	1

Note: Values represent Spearman's correlation coefficients. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C-reactive protein; FPI-6, Foot Posture Index-6; HAQ, Health Assessment Questionnaire-Disability Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score.

in physical function. On the other hand, Achilles enthesitis was not correlated with BASFI scores or disease activity.

The biomechanical background of impaired foot function in AS has been studied by a number of researchers. Sawacha et al[5] assessed balance and posture using a pocket compass needle goniometer and stereo-photogrammetric imaging system. They found that decreased pelvic anteversion and hip flexion could cause increased knee flexion and ankle dorsiflexion. Overall lower extremity alignment may also be important and may affect the posture of the foot. Further studies evaluating the effect of hip and knee alignment on foot posture are required. Another study investigating the link between static foot posture and plantar pressure in healthy participants showed that lower arch posture was related to greater pressure under the hallux along with medial mid-foot.[23] Aydin et al[24] evaluated static and dynamic foot postures of AS patients by using pedobarography. There was no difference between AS patients and healthy controls in terms of static foot posture. However, during dynamic assessment, increased plantar pressure was observed at the forefoot and mid-foot in AS patients. Accordingly, the foot posture is influenced not only by stable position but also by movement. In the present study, only the static component of foot posture was assessed and Achilles enthesitis appeared as a determinant of supinated foot posture.

There are some limitations of the current study. The study examined static foot posture. Therefore, the results do not provide any insight into the dynamic component of foot posture in AS. Besides, enthesitis was evaluated only by physical examination. No imaging techniques such as ultrasound or magnetic resonance imaging were performed to further support the examination findings. In addition, radiographic evaluation that would allow us to determine potential foot abnormalities such as epin calcanei was not carried out. Although the results revealed a close relationship between enthesitis and foot posture, the case-control study design was unable to provide any causative relation.

In conclusion, the present study revealed that static foot posture is impaired in patients with AS. Achilles enthesitis is closely related to supinated foot posture. Preventive measures would be of importance for AS patients, particularly for those presenting with enthesitis.

CONFLICT OF INTEREST

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

NG, AS, and ICB contributed to the study design and collected the data. NG and ICB analyzed the data and take responsibility for the accuracy of the data analysis. NG, AS, and ICB interpreted the data, drafted the manuscript, and critically revised it for important contents. All authors read and approved the final manuscript.

ORCID

Neslihan Gokcen https://orcid.org/0000-0003-3022-493X
Ilke Coskun Benlidayi https://orcid.org/0000-0001-6517-5969

REFERENCES

1. Sahli H, Bachali A, Tekaya R, et al. Involvement of foot in patients with spondyloarthritis: prevalence and clinical features. *Foot Ankle Sur.* 2019;25:226-230.
2. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet*. 2017;390:73-84.
3. Haroon N. Thinking positive in spondyloarthritis. *Arthritis Rheumatol.* 2019;71:839-841.
4. Uckun A, Sezer I. Ankylosing spondylitis and balance. *Eurasian J Med*. 2017;49:207-210.
5. Sawacha Z, Carraro E, Del Din S, et al. Biomechanical assessment of balance and posture in subjects with ankylosing spondylitis. *J Neuroeng Rehabil*. 2012;9:63.
6. Koca TT, Göğebakan H, Koçyiğit BF, Nacitarhan V, Yildir CZ. Foot functions in ankylosing spondylitis. *Clin Rheumatol*. 2019;38:1083-1088.
7. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis*. 2011;70:25-31.
8. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index. *Clin Biomech*. 2006;21:89-98.
9. Carvalho BKG, Penha PJ, Penha NLJ, Andrade RM, Ribeiro AP, João SMA. The influence of gender and body mass index on the FPI-6 evaluated foot posture of 10- to 14-year-old school children in São Paulo, Brazil: a cross-sectional study. *J Foot Ankle Res*. 2017;10:1.
10. Al-Bayati Z, Coskun Benlidayi I, Gokcen N. Posture of the foot: don't keep it out of sight, out of mind in knee osteoarthritis. *Gait Posture*. 2018;66:130-134.
11. Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011;70:47-53.
12. Machado PM, Landewé R, Heijde D, Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis*. 2018;77:1539-1540.
13. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9:789-793.
14. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol*. 2005;23:14-18.
15. Ozcan E, Yilmaz O, Tutoglu A, Bodur H. Validity and reliability of the Turkish version of the Health Assessment Questionnaire for the Spondyloarthropathies. *Rheumatol Int*. 2012;32:1563-1568.
16. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol*. 1994;21(9):1694-1698.
17. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009;68:1-44.
18. Calin A, Jones SD, Garrett SL, Kennedy LG. Bath ankylosing Spondylitis Functional Index. *Br J Rheumatol*. 1995;34(8):793-794.
19. Ozer HT, Sarpel T, Gulek B, Alparslan ZN, Erken E. The Turkish version of the Bath Ankylosing Spondylitis Functional Index: reliability and validity. *Clin Rheumatol*. 2005;24(2):123-128.
20. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis*. 2003;62(2):127-132.
21. Erdem CZ, Sarikaya S, Erdem LO, Ozdolap S, Gundogdu S. MR imaging features of foot involvement in ankylosing spondylitis. *Eur J Radiol*. 2005;53(1):110-119.
22. Laatiris A, Amine B, Ibn Yacoub Y, Hajjaj-Hassouni N. Enthesitis and its relationships with disease parameters in Moroccan patients with ankylosing spondylitis. *Rheumatol Int*. 2012;32(3):723-727.
23. Jonely H, Brismée JM, Sizer PS Jr, James CR. Relationships between clinical measures of static foot posture and plantar pressure during static standing and walking. *Clin Biomech*. 2011;26(8):873-879.
24. Aydin E, Turan Y, Tastaban E, Kurt Omurlu I, Sendur OF. Plantar pressure distribution in patients with ankylosing spondylitis. *Clin Biomech*. 2015;30(3):238-242.

How to cite this article: Gokcen N, Sariyildiz A, Coskun Benlidayi I. Static foot posture and its relation to clinical variables in ankylosing spondylitis. *Int J Rheum Dis*. 2021;24:1148–1152. https://doi.org/10.1111/1756-185X.14180

Received: 2 February 2021 | Revised: 1 June 2021 | Accepted: 29 June 2021

DOI: 10.1111/1756-185X.14176

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Cross-cultural adaptation and validation of revised WHO-ILAR-COPCORD core English questionnaire translated to Bangla

Md Ekramul Islam[1] | Shamim Ahmed[2] | Md Abu Shahin[2] | Md Ariful Islam[2] | Md Nahiduzzamane Shazzad[2] | Syed Atiqul Haq[2]

[1]Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh

[2]Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Correspondence
Shamim Ahmed, Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
Email: drshamim.bsmmu@gmail.com

Abstract

Background: The Community-Oriented Program for Control of Rheumatic Diseases (COPCORD) is intended to reduce the information deficit about the epidemiology of rheumatic diseases, particularly in rural communities in high-income countries. Multiple studies have been conducted using the WHO-International League of Associations for Rheumatology (ILAR)-COPCORD core questionnaire in Bangladesh using the translated version in the Bangla language. Cross-cultural adaptation and validation of the questionnaire are important to achieve better outcomes.

Aim: To develop a culturally adapted, valid, and reliable Bangla version of the WHO-ILAR-COPCORD Core English Questionnaire to use as a rheumatic screening instrument among Bangla-speaking people.

Methods: The original English WHO-ILAR-COPCORD questionnaire was translated into Bangla and adapted in the local socio-cultural context maintaining idiomatic, semantic, experiential, and conceptual equivalence between the English and Bangla versions. Pretesting was carried out among 30 patients and healthy attendants, following standard international recommendations. Content validity of the adapted Bangla version was assessed by the item- and scale-level content validity indices (I-CVI and S-CVI). The adapted Bangla version of the WHO-ILAR-COPCORD questionnaire was used to assess 120 patients with rheumatic problems and healthy individuals. Test-retest reliability was assessed using intraclass correlation coefficients.

Results: The Bangla version of the WHO-ILAR-COPCORD questionnaire showed excellent content validity (I-CVI = 1, S-CVI = 1). The test-retest reliability was also acceptable (intraclass correlation coefficient > 0.7).

Conclusion: The adapted Bangla version of the WHO-ILAR-COPCORD questionnaire demonstrated acceptable psychometric properties, in terms of content validity and test-retest reliability, for evaluating rheumatic problems in Bangladeshi patients.

KEYWORDS

arthritis, infection, rheumatoid arthritis

1 | INTRODUCTION

Rheumatic diseases, which have been identified as a major cause of disability worldwide, are associated with substantial personal, family, and socio-economic burden.[1] The individual and social burden of these diseases has a substantial negative impact on the quality of life of the patients and the use of healthcare resources.[2] The World Health Organization (WHO) in collaboration with the International League of Associations for Rheumatology (ILAR) founded the Community-Oriented Program for Control of Rheumatic Disorders (COPCORD) in 1981(Appendix 1) to recognize, prevent, and control rheumatic and allied musculoskeletal disorders.[3] The program is intended to collect data on the burden associated with rheumatic disorders and to provide preventive measures including educational interventions.[4] The COPCORD comprises three main stages. Stage 1 has the following three phases to collect the community data on rheumatic musculoskeletal disorders based on house-to-house survey—phase I: collection of demographic data and identifying cases/respondents, phase II: data on pain and disability, and phase III: rheumatologic examination/evaluation. Phases I and II are conducted by community health workers/nurses (WHO-ILAR-COPCORD Questionnaire 2006). The phase I questionnaire includes basic demographic data with questions on age, gender, marital status, physical activity, the nature of the respondent's work/employment, monthly income, chronic medical illness, and presence/nature of traumatic events. In phase II, respondents who answered 'yes' to the presence of pain for ≤7 days are requested to mark the location and the severity of the pain (graded as mild, moderate, severe, and very severe) on a human manikin. The respondents are also asked to complete the sections of the questionnaire regarding functional disability, difficulty in performing specific tasks, and the treatment received.[5]

The past decade has witnessed newer insights regarding the epidemiology and comorbidity associated with rheumatic diseases.[6] It has been projected that the health burden of rheumatic diseases will increase in the new millennium. Prevalence data for the major rheumatic diseases are available from high-income countries, but figures from low- and middle-income countries are still emerging. The COPCORD methodology is designed to be simple and cost effective, and local health workers are designated to perform a house-to-house survey, collecting data on rheumatic complaints and disability from the adult population. COPCORD has been adapted and validated in Iran,[3] China,[9,10] the Philippines,[9] Indonesia,[5,10] Taiwan,[11] Thailand,[12] Canada,[13] Brazil, Chile, Mexico,[14] and Pakistan.[15] Although, there were some previous efforts for the translation and adoption of the questionnaire into Bangla, it has not yet been published because of problems with data collection and determining the prevalence of rheumatic diseases. The present study is intended to develop a version of the revised WHO-ILAR-COPCORD questionnaire to evaluate its validity and reliability among Bangladeshi patients.

2 | MATERIALS AND METHODS

2.1 | Type of study

The observational study was conducted in two phases: phase I and phase II. Phase I consisted of translation and cross-cultural adaptation of the original English WHO-ILAR-COPCORD questionnaire to Bangla based on the recommendations by Beaton et al.[16] Phase II consisted of assessment of the psychometric properties of the adapted Bangla version of the WHO-ILAR-COPCORD questionnaire i.e, testing its content validity and test-retest reliability.

2.2 | Study population

The study was conducted at the Department of Rheumatology (outpatient and inpatient), Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka. The study included adult Bangladeshi patients with rheumatic problems, healthy attendants, and volunteers. The criteria for exclusion were severely ill patients, individuals with intellectual and physical disabilities, and persons who were not willing to participate in the study. The estimated sample size for phase I pretest was 30 individuals (15 patients with rheumatic disorders and 15 healthy volunteers).

Sample size for phase II was determined based on the test-retest reliability. This was measured by the intraclass correlation coefficient (r). The expected r of the Bangla version of the Revised WHO-ILAR-COPCORD Core English Questionnaire was 0.8 with an r of 0.7 or higher being acceptable. The defined H0:ρ0 was 0.7 and H1:ρ1 was 0.8. Using a two-sided test, as suggested by Walter et al [17], with β (probability of type II error) = 0.2 (80% power) and α (probability of type I error) = 0.05, the sample size was estimated to be at least 117 individuals.

2.3 | Translation procedure

Translation and adaptation of the English WHO-ILAR-COPCORD questionnaire to Bangla was accomplished in five stages, namely forward translation, synthesis of Bangla version, back translation, expert committee review, and test of the pre-final Bangla version (as per the recommendations by Beaton et al[16]). The forward translation was carried out by two translators whose mother tongue was Bangla. One of the translators was the first author and the other was a Bangla teacher working at the University of Dhaka. A synthesized Bangla version was generated from both the translations and the same was back translated into English by two English linguistic professionals working at the University of Dhaka. An expert committee, comprising two rheumatologists, a language professional, a translator (forward and back translators), and a translation synthesis recorder reviewed all the translations and compared them with the original English WHO-ILAR-COPCORD questionnaire. The

committee verified the idiomatic, semantic, experiential, and conceptual equivalence between the English and Bangla versions, and a consensus was reached to form the pre-final Bangla version of the questionnaire.

2.4 | Testing of pre-final Bangla version

The pre-final Bangla version of the WHO-ILAR-COPCORD questionnaire was tested in a sample of 30 adults (15 patients with rheumatic disorders and 15 healthy attendants). The expert committee review was carried out before and after cross-cultural adaptation. Each individual who completed the questionnaire was interviewed to investigate what he or she meant by each questionnaire item and the chosen response. This ensured that the adapted version had retained its equivalence in an applied situation.

2.5 | Assessment of psychometric properties

In the second phase, validity and reliability testing of the Bangla version of the questionnaire were carried out among 120 patients. Content validity was assessed by the item-level content validity index (I-CVI) and the scale-level content validity index (S-CVI).[18] For test-retest reliability, the Bangla version of the WHO-ILAR-COPCORD questionnaire was reapplied to the participants 7 days after the first interview.

2.6 | Statistical analysis

Data were assessed using SPSS 23.0 (IBM, Armonk, NY, USA). A *P* value less than 0.05 was considered statistically significant. Content validity was assessed by the I-CVI and the S-CVI. Test-retest reliability was assessed by demonstrating the correlation between the test and retest responses using intraclass correlation coefficient (*r*). The expected *r* was at least 0.7 for good test-retest reliability.

2.7 | Ethical clearance

The participants were informed in detail about the non-interventional nature of the study. There were no physical, psychological, and social risks to the participants and a detailed interview was performed in each case. Ethical clearance was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University before the study. Spontaneous informed written consent was taken from the participants and an informed consent form in Bangla (completed by the participant) was attached to the questionnaire. Each patient was free to withdraw from the study at any stage, and privacy, anonymity, and confidentiality of data were strictly maintained.

3 | RESULTS

During phase I pretesting, several Bangla words were given to respondents for their input on better understandability, chosen responses and any alternate suggestions. During probing, individual questions of the COPCORD questionnaire were labelled as individual items. There were 11 items in phase I and seven items in phase II, and each item corresponded with that in the original WHO-ILAR-COPCORD questionnaire translated to Bangla. In phase I, items 1, 2, 7, and 9 were understood by all (100%) of the respondents. The expert committee decided to keep two Bangla options for the term "rheumatic musculoskeletal disorder" [8(a) and 8(b)] for item 8 of the English questionnaire during pretesting and 8(b) was found to be more understandable (100%) when compared with 8(a) (20%). Hence, the committee decided to retain item 8(b), so that all the target population would be able to understand the item. Item 4 represented literacy status of the respondents. Understandability by the respondents was 66%, as the educational qualification of the remaining participants (34%) was below the higher educational option given in item 4. The expert committee decided to retain item 4. The adapted version was made by compiling the items, which were best understood and best chosen. Understandability and chosen responses were also tested for two alternate Bangla translations given for item 3, 5, 6, 10, and 11—the corresponding words were "widowed", "drugs", "housework" and "housemaid", "high BP" and "paralysis". The best understood words (100%) and the best-chosen items by the participants were chosen from the pre-final version to frame the adapted version. According to the decision of the expert committee, necessary modifications were made to achieve conceptual and experiential forms of equivalence for the items 4, 10, 11, and item ka-3 (which is a Bengali alphabet ক, translated into Bangla from the original COPCORD questionnaire A3 in stage I, Phase II).

During probing of phase II, understandability and chosen responses were tested by providing three alternate Bangla translations of the word "stiffness" for item ka-1 (Bangla term of A1 of original phase II questionnaire) and ka-2 (Bangla term of A2 of original phase II questionnaire), and two alternate Bangla words for English word "severe" of items ka-1 and ka-2. Item ka-3 (Bangla term of A3 of original phase II questionnaire) was understood by all the respondents. Item kha (Bangla term of Section B of original questionnaire) with two parts (kha-1, B1 and kha-2, B2) represented the impact of functional disability. As this section was marked as optional in the original English WHO-ILAR-COPCORD core questionnaire (asking to strike out any activity that is not applicable or of interest), and there was no specific definition of impact of functional disability and considering the increased time taken, the expert committee decided to omit the item 'kha' (Bangla term of Section B) from the adapted version. Difficulty in performing specific tasks, which can be measured by a health assessment questionnaire, was translated and validated earlier in Bangla (Section C). The item "ga" (Bangla term of Section D of original phase II questionnaire) was understood by all (100%) respondents. Hence, the expert committee decided to provide item "ga" of the pre-final version as item "kha" in the adapted version.

Content validity of the adapted version was assessed by four rheumatologists. Both the I-CVI (Table 1 and 2) for each item and the S-CVI were estimated as 1 by the averaging calculation method. Tables 1 and 3 depict the rating of each item by the experts, corresponding to I-CVI and S-CVI.

Statistical analysis showed a strong correlation of Item 8a* (stop work) with 8a** (rs = 0.891, $P \leq 0.001$), item 8b*(change work) with 8b** (rs = 1.000), item 11*(trauma) with 11**(rs = 0.939, $P < 0.001$), item ka-1* (pain in 7 days) with ka-1** (*rs* = 0.929, $P < 0.001$), Item Ka-2* (pain before 7 days) with ka-2** (rs = 0.704, $P < 0.001$), Item ka 3* (recurrent pain) with ka-3** (rs = 0.922, $P < 0.001$), item kha*(past treatment) with kha** (rs = 1.000).

The test-retest reliability of the Bangla version of the WHO-ILAR-COPCORD questionnaire items was measured by intraclass correlation coefficient, which was found to be greater than 0.7 ($P < 0.001$), indicative of strong correlation between test and retest scores, and hence giving acceptable test-retest reliability (Table 4).

.

4 | DISCUSSION

Rheumatic disorders are the most common cause for long-term disabilities, morbidity, substantial healthcare expenditures, and loss of work. The clinical and socio-economic burden of rheumatic disorders has been reported to be higher in Bangladeshi rural and urban communities. The corresponding point prevalence of musculoskeletal pain reported by the Bangladesh COPCORD study group in rural, urban slum, and affluent urban communities were 26.2%, 24.9%, and 27.9%, respectively.[19]

Questionnaires are frequently used tools in medical research for data collection and evaluation. Several multinational and multicultural research studies have adopted questionnaires in local languages to improve the interaction and response of the participants.[20] The present study used a standard approach[16] to adapt the questionnaire with respect to translation, cross-cultural equivalence, back translation, and reliability. The study enrolled 120 individuals (patients of rheumatic diseases and healthy attendants) and the cross-cultural adaptation of the original WHO-ILAR-COPCORD English questionnaire was mainly concentrated on semantic and conceptual forms of equivalence. The adapted version of the questionnaire was found to have acceptable content validity in the form of I-CVI (=1), S-CVI (=1). At the first visit, the COPCORD questionnaire was given to patients with rheumatic diseases and healthy attendants and the answers to each individual item were recorded. Retest was conducted after 7 days for the same respondents.

A study by Islam et al assessed translation and validation of the COPCORD questionnaire into Bangla.[21] The study, comprising forward translation, back translation and validation, was carried out among a Bangladeshi population. Face validity was not done and during test-retest reliability some questions showed poor correlation using Spearman's correlation, and Phase I and Phase II of the questionnaire were merged during translation. However, the current

TABLE 1 Content validity of the adapted Bangla version of the WHO-ILAR-COPCORD questionnaire (phase I)

Item	Rating by expert 1	Rating by expert 2	Rating by expert 3	Rating by expert 4	I-CVI[a]
Item 1	4	4	4	3	1.0
Item 2	4	3	4	4	1.0
Item 3	4	3	4	4	1.0
Item 4	4	4	4	3	1.0
Item 5	4	4	4	4	1.0
Item 6	3	3	3	3	1.0
Item 7	3	4	3	3	1.0
Item 8	4	3	3	4	1.0
Item 9	4	4	4	3	1.0
Item 10	3	4	3	4	1.0
Item 11	3	4	3	4	1.0
Proportion relevant[c]	4/4 = 1.0	4/4 = 1.0	4/4 = 1.0	4/4 = 1.0	S-CVI/Ave[b] (Mean I-CVI) = 1.0

Abbreviations: COPCORD, Community-Oriented Program for Control of Rheumatic Disorders; I-CVI, item-level content validity index; ILAR, International League of Associations for Rheumatology; S-CVI, scale-level content validity index; WHO, World Health Organization.

Rating by each expert (rheumatologist) for all four questions: 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant; S-CVI/Ave[b] = (1.0 + 1.0 + 1.0 + 1.0)/4 = 1.0; [I-CVIa], item-level content validity index; I-CVI is the proportion of expert giving a rating of either 3 or 4; S-CVI/Ave[b], scale-level content validity index, averaging calculation method; Proportion relevant[c], proportion of questions that are quite or highly relevant; Excellent content validity means S-CVI/Ave ≥0.9; Item, individual question. (Each item indicates corresponding questionnaire in original phase I questionnaire translated to Bangla).

TABLE 2 Content validity of the adapted Bangla version of the WHO-ILAR-COPCORD questionnaire (phase II)

Item	Rating by expert 1	Rating by expert 2	Rating by expert 3	Rating by expert 4	Mean I-CVI[a]
Item Ka-1	3	3	3	3	1.0
Item Ka-2	4	3	3	4	1.0
Item Ka-3	4	4	3	4	1.0
Item Kha	4	4	3	3	1.0
Proportion relevant[c]	4/4 = 1.0	4/4 = 1.0	4/4 = 1.0	4/4 = 1.0	S-CVI/Ave[b] (Mean I-CVI) = 1.0

Abbreviations: COPCORD, Community-Oriented Program for Control of Rheumatic Disorders; I-CVI, item-level content validity index; ILAR, International League of Associations for Rheumatology; S-CVI, scale-level content validity index; WHO, World Health Organization.

Rating by each expert (rheumatologist) for all four questions: 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant; S-CVI/Ave[b] = (1.0 + 1.0 + 1.0 + 1.0)/4 = 1.0; I-CVI[a], item-level content validity index; I-CVI is the proportion of expert giving a rating of either 3 or 4; S-CVI /Ave[b], scale-level content validity index, averaging calculation method; Proportion relevant[c], proportion of questions that are quite or highly relevant; Excellent content validity means S-CVI/Ave ≥0.9; Item, individual question. (Each item indicates corresponding questionnaire in Phase II questionnaire).

study has shown good face validity and test-retest reliability was assessed using intraclass correlation coefficient (ICC). The ICC of all questions ranged from 0.704 to 1.00, which was indicative of a strong correlation between test response and retest response. To maintain the basic structural framework of the questionnaire, the adapted Bangla version was also segregated as Phase I and Phase II, as in the original English questionnaire.

A study by Anshory et al[20] assessed the validity of a modified Indonesian version of the COPCORD questionnaire for screening joint pain and musculoskeletal disease compared with examination by rheumatologists. The study involved adaptation of the COPCORD questionnaire in stage 1 and the community validation in stage 2 to evaluate the usefulness of the modified questionnaire to detect joint pain and musculoskeletal diseases compared with physical examination performed by rheumatologists. The reliability study showed that ICC analysis was good for all questions (range 0.754-1.000).

A study by Al-Awadhi et al evaluated the use of the Arabic version of the WHO-ILAR COPCORD Core Questionnaire for community screening of rheumatic diseases in Kuwaiti citizens including translation, back translation, and assessment of cross-cultural equivalence. The study concluded that the questionnaire is a promising screening tool for Arabic-speaking communities with satisfactory reliability of 0.800-1.000.[4] In the current study, the Bangla version of the WHO-ILAR-COPCORD questionnaire showed excellent content validity (I-CVI = 1, S-CVI = 1). The test-retest reliability was also acceptable (ICC > 0.7). Cross-cultural adaptation was performed following standard recommendations by Beaton et al[16] and on the basis of statistical calculations, an optimum number of patients was enrolled in the second phase of the study. Patients from all parts of the country were included to avoid bias due to minor differences in the local languages while using the valid Bangla version of the WHO-ILAR-COPCORD questionnaire. Nearly 49% of the study population had education up to primary level. Understandability by all the respondents indicated its simplicity as well as its applicability to a wider range of patients in larger studies. The adapted Bangla version demonstrated excellent content validity as well as good reliability.

TABLE 3 Brief description of each of the items considered in phases I and II

Item 1	Personal data (question 1 of phase I)
Item 2	Religion (question 2 phase I)
Item 3	Marital status (question 3 phase I)
Item 4	Literacy (question 4 phase I)
Item 5	Habit (question 5 phase I)
Item 6	Current occupation (question 6 phase I)
Item 7	Nature of work (question 7 phase I)
Item 8	Stopped work/change work (question 8 phase I)
Item 9	Monthly family income (question 9 phase I)
Item 10	Chronic medical illness/disorders question 10 phase I)
Item 11	Trauma (question 11 phase I)
Item ka 1 (Bangla term of A1)	Painful joint and/or soft tissue, swollen joints, less movement during last 7 days (question A1 phase II)
Item ka 2 (Bangla term of A2)	Painful joint and/or soft tissue, swollen joints, less movement in the past (question A2 phase II)
Item ka 3 (Bangla term of A3)	Intensity of pain (question A3 phase II)
Item kha (Bangla term of Section D)	Treatment (question D phase II)

Though the present study showed acceptable validity and reliability of the Bangla version of the WHO-ILAR-COPCORD questionnaire, there were a few limitations. As the study was carried

TABLE 4 Test-retest reliability (intraclass correlation coefficients, *r*)

Items	ICC	*P*-value
Item 8a (stopped work) Item 8a**	0.891	<0.001
Item 8b*(change work) Item 8b**	1.000	—
Item 11*(trauma) Item 11**	0.939	<0.001
Item Ka-1*(pain in 7 days) Item Ka-1**	0.929	<0.001
Item Ka-2*(pain before 7 days) Item Ka-2**	0.704	<0.001
Item Ka-3*(recurrent pain) Item Ka-3**	0.922	<0.001
Item Kha*(past treatment) Item Kha**	1.000	

Abbreviation: ICC, intraclass correlation coefficient;* at first visit of patient; **at second visit of patient; $P < 0.05$ indicates significance.

out in a tertiary-level hospital, it was not fully representative of the whole population of Bangladesh. As there were no self-reported or composite tools, including any reference standard tool other than the COPCORD questionnaire, construct validity and internal consistency could not be assessed. This study has some weak points and limitations. Some questions in the questionnaire pertaining to the recall of complaints by the interviewed individual may not be precise enough obtain the exact information. For example, there would be variation in data on musculoskeletal pain, especially disease duration, when the person was interviewed for the second time.

5 | CONCLUSION

The Bangla version of the WHO-ILAR-COPCORD questionnaire, being a valid and reliable tool with acceptable psychometric properties, may be used to determine the prevalence of rheumatic diseases. A community validation study is highly warranted to assess the validity of the Bangla version of the COPCORD questionnaire in screening joint pain and musculoskeletal diseases compared with examination by rheumatologists.

ORCID

Shamim Ahmed https://orcid.org/0000-0002-0616-5821
Md Nahiduzzamane Shazzad https://orcid.org/0000-0002-8535-4259
Syed Atiqul Haq https://orcid.org/0000-0003-4154-7283

REFERENCES

1. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewé R. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(6):995-1003.
2. Beasley RP, Bennett PH, Lin CC. Low prevalence of rheumatoid arthritis in Chinese. Prevalence survey in a rural community. *J Rheumatol Suppl*. 1983;10:11-15.
3. Davatchi F, Tehrani Banihashemi A, Gholami J, Faezi ST. The prevalence of musculoskeletal complaints in a rural area of Iran. *Clin Rheumatol*. 2009;28(4):1267-1274.
4. Awadhi A, Olusi S, Moussa M. Validation of the Arabic version of the WHO-ILAR COPCORD core questionnaire for community screening of rheumatic diseases in Kuwaitis. *J Rheumatol*. 2002;29:8.
5. Awadhi A, Olusi S, Moussa M. Musculoskeletal pain, disability and health-seeking behavior in adult Kuwaitis using a validated Arabic version of the WHO-ILAR COPCORD Core Questionnaire" *Clin Exp Rheumatol*. 2004;22:177-183.
6. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality and comorbidity of the rheumatic diseases. *Arthritis Res Ther*. 2009;11:229.
7. Xiang YJ, Dai SM. Prevalence of rheumatic disease & disability in China. *Rheumatol Int*. 2009;29(5):481-490.
8. Wigley R, Zhang NZ, Zeng QY. Rheumatic diseases in China: ILAR-China study comparing the prevalence of rheumatic symptoms in northern and southern rural populations. *J Rheumatol*. 1994;21:1484-1490.
9. Dans LF, Tankeh-Torres S, Amanta CM, Penserga EG. The prevalence of rheumatic disease in a Filipino urban population: a WHO-ILAR COPCORD study. *J Rheumatol*. 1997;24:1814-1819.
10. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. Epidemiology of rheumatic disease in rural and urban populations in Indonesia: a World Health Organization International League Against Rheumatism COPCORD study, stage 1, phase 2. *Ann Rheum Dis*. 1992;51:525-528.
11. Chou CT, Pei L, Chang DM, Lee CF, Schumacher HR, Liang NH. Prevalence of rheumatic disease in Taiwan: a population study of urban, suburban, rural differences. *J Rheumatol*. 1994;21:302-306.
12. Chaiamnuay P, Darmawan J, Muirden KD, Assawatanabodee P. Epidemiology of rheumatic disease in rural Thailand: a WHO-ILAR COPCORD study. *J Rheumatol*. 1998;25:1382-1387.
13. Lee P, Helewa A, Smythe HA, Bombardier C, Goldsmith CH. Epidemiology of musculoskeletal diseases and related disability in Canada. *J Rheumatol*. 1985;1985(12):1169-1173.
14. Bennett K, Cardiel MH, Ferraz MB, Riedemann P, Goldsmith CH, Tugwell P. Community screening for rheumatic disorders: cross cultural adaptation and screening characteristics of the COPCORD Core Questionnaire in Brazil, Chile and Mexico. *J Rheumatol*. 1997;24:160-168.
15. Farooqi A, Gibson T. Prevalence of the major rheumatic disorders in the adult population of North Pakistan. *Br J Rheumatol*. 1998;37:491-495.
16. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine*. 2000;25(24):3186-3191.
17. Walter AI, Helgenberger S, Wiek A, Scholz RW. Measuring societal effects of transdisciplinary research projects: design and application of an evaluation method. *Eval Program Plann*. 2007;30:325-338.
18. Polit DF, Beck CT. The Content Validity Index: are you sure you know what's being reported? Critique and recommendations. *Res Nurs Health*. 2006;29:489-497.

19. Haq SA, Darmawan J. Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study. *J Rheumatol*. 2005;32:348-353.
20. Anshory M, Wahono CS, Kalim H, Al Rasyid H. Validation of modified COPCORD Questionnaire Indonesian version as screening tool for joint pain and musculoskeletal diseases. *Indonesian J Rheumatol*. 2018;10(1):24-30.
21. Islam MA, Islam MN, Haq SA, et al. Translation of revised WHO international league against rheumatism community oriented program for the control of rheumatic diseases core English questionnaire into Bengali and its cross-cultural adaptation and validation. *Int J Adv Med*. 2021;8(2):235-240.

How to cite this article: Islam ME, Ahmed S, Shahin MA, Islam MA, Shazzad MN, Haq SA. Cross-cultural adaptation and validation of revised WHO-ILAR-COPCORD core English questionnaire translated to Bangla. *Int J Rheum Dis*. 2021;24:1153–1166. https://doi.org/10.1111/1756-185X.14176

APPENDIX 1

PROPOSED WHO-ILAR COPCORD QUESTIONNAIRE 2006 STAGE I – PHASE I

STAGE I – PHASE I

VILLAGE/TOWN/REGION:_____CENTER: _____

ID No. :_____House No_____ ☐ Self Completed ☐ Interview Based : Date:

INSTRUCTIONS: *This is a self filled form to be completed in the presence of the Health Worker. The Health Worker may be required to provide explanations BUT should not influence the individual in any manner to obtain an answer. However, if the survey is interview based, the Health Worker must ensure that the answer volunteered by an individual is correctly entered.*
Tick the correct entry in the box with ✓ mark. For some questions multiple entries may be used. Use 'Remark' space below to add anything else that you may find important for this survey; **Indicates Data required from each person*

*1. PERSONAL DATA

Last name First name Middle Name/Initial

_____

Age:____Years; **Sex :** ☐Male ☐Female; **Family**: Single ☐ Joint, Size (e.g. 4)____; **Diet:** Veg ☐ Non-veg,_____

Address:_____**Tel (O):**_____(R) _____

2. RELIGION: ☐ Hindu ☐ Islam ☐ Christian ☐ Buddhist ☐ Others, Specify _____

3. MARITAL STATUS: ☐ Single ☐ Married ☐ Widowed ☐ Divorced ☐ Separated ☐ Others_____

*4. LITERACY: ☐ Read only ☐ Read & Write ☐ None; Years in school_____ ☐ Graduate, Others_____

*5. HABIT: a) ☐ **PAST;** Smoking (begun_____, stopped_____) ☐ Tobacco (begun_____stopped_____)

☐ Alcohol (begun_____stopped_____) ☐ Drugs (begun_____stopped_____) ☐ Others_____

b) ☐ **CURRENT**; Smoking (begun_____) Tobacco (begun_____) ☐ Alcohol (begun_____)

☐ Drugs (begun_____) ☐ Others_____

*6. CURRENT OCCUPATION (*Multiple occupations may be marked):* ☐ Student ☐ Farm work ☐ Service – Desk job

☐ Service – Field work ☐ Shop/Business ☐ Housework ☐ Housemaid ☐ Professionals _____

☐ Military ☐ Retired,_____ ☐ Unemployed_____ ☐ Other_____

*7. NATURE OF WORK (as per individual thinking): ☐ Light ☐ Moderate ☐ Heavy, Other_____

*8. A) Have you **stopped work** due to any illness? ☐ NO ☐ YES, If YES: ☐ Rheumatic musculoskeletal disorder ☐ Non-Accident Injury ☐ Accident Injury ☐ Other Illness; Stopped since_____ Any other Information_____

B) Have you **changed work** due to any illness? ☐ NO ☐ YES, If YES ☐ Rheumatic musculoskeletal disorder ☐ Non Accident Injury ☐ Accident Injury ☐ Other Illness; stopped since_____ Any other Information_____

*9. MONTHLY FAMILY INCOME :_____

*10. CHRONIC MEDICAL ILLNESS/ DISORDERS: (Name the illness (e.g. hypertension) if known or else state disorder (e.g. high blood pressure). *Ask for 'trauma' from every person, and if present complete the reverse sheet*

	PAST (Prior 7 days)		PRESENT (within 7 days)	
	ONSET	DURATION	ONSET	DURATION
☐ Body aches & pain				
☐ Joint pain·				
☐ Trauma, Specify				
☐ High BP				
☐ Diabetes				
☐ Others, Specify				
☐ Others, Specify				

REMARK (You may add questions to obtain more information e.g. dietary habits/ survey, parity in lieu of family size, individual member income, height and weight [may be more suitable in the case record form], etc)

***11. TRAUMA** (*You may fill data on multiple injuries; fill extra information under remarks*)
(1) What did you suffer? Accident ☐ No ☐ Yes; Injury ☐ No ☐ Yes Others_____

(2) IF YES, how did the injury occur? Indicate year of onset in bracket e.g. Accident (1994)

a) Accident (Year_____) ☐ Vehicle ☐ Agriculture / Field ☐ Industrial ☐ Others _____

(i) If Vehicle, specify ☐ Driving ☐ Passenger ☐ Pedestrian ☐ Others _____

(ii) If Agriculture, specify ☐ Farming ☐ Tractor ☐ Others_____

(iii) If Industrial, specify ☐ Machinery ☐ Work site ☐ Others _____

b) Fall (Year_____) ☐ Ground Level (e.g. slip) ☐ From Height (☐Tree ☐ Building ☐ Stair☐ Others,_____

(3) IF YES, Identify part of the body injured by placing a cross **'X'** on the adjoining figure →

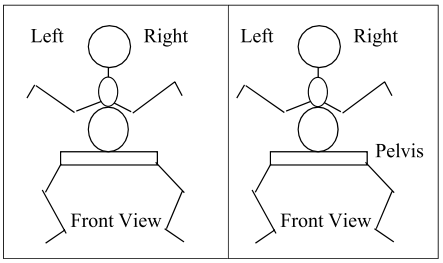
(4)Nature of Injury: a) Fracture - ☐ (open) with wound ☐ No wound, Number☐ Single☐ Multiple, Indicate Sites

_____

_____

b) ☐ Sprain c)☐ Paralysis d) ☐ others, specify_____

_____



(5) Who treated you? a) ☐ Bone setter b) ☐ Hospital, Period admitted _____ ☐ days ☐ weeks ☐ months c) Treatment Setting ☐ Govt ☐ Private d) ☐ Others, specify _____

(6) What is the result of Injury? a) ☐ Cured b) ☐ Disability i) Nature ☐ Pain ☐ Stiffness ☐ Deformity ☐ Others, specify_____

(ii) Duration of disability :☐weeks ☐ months ☐ years,_____

c) Loss of job ☐ No ☐ Yes,_____d) Change of job ☐No ☐Yes, _____

(7) Approximate Cost of Treatment (you may use different cost heads eg doctor fees, hospital bill, investigations, etc or give the approximate Total: _____

(8) REMARK

Thank you for your cooperation.

NAME OF HEALTH WORKER: _____

Qualification of Health Worker ☐Completed School ☐ Graduate ☐ Post –Graduate, Others_____;Occupation ☐ Trained Health Worker ☐ Volunteer Health Worker ☐Nurse ☐Others, specify_____Residential Village/ Town :_____TIME :_____DATE :

Background:

COPCORD was launched by WHO (World Health Organization) and ILAR (International League of Associations for Rheumatology). The earlier versions of COPCORD Core Questionnaire (CCQ) were based on ILAR experience [HA Valkenburg (The Netheland), Richard Wigley (New Zealand), KD Muirden (Australia), & others). The CCQ was later modified and developed [APLAR COPCORD Workshop Korea,1991, Prof S. van der Linden (The Netherlands), J Darmawan (Indonesia), and others). Maintaining basic framework, CCQ was modified and further developed by the fast track COPCORD Bhigwan (India) model and published (APLAR J Rheumatol 1997; 1: 145-154). The current proposed CCQ is based on the latter experience, review at the WHO-ILAR BJD Meeting Vienna, Austria 2005 (Clin Rheumatol 2007; 26: 1217-1227), inputs from several COPCORD investigators and experts, and discussions in the APLAR 2006 (Kuala Lumpur) COPCORD Session (Arvind Chopra, India, and others).

The WHO & UN supported '**The Bone & Joint Decade (BJD)** 2000 – 2010 (www.bjdonline.org) has included '**trauma**' along with arthritis & osteoporosis amongst the disease target conditions. The BJD program aims to create awareness and empower patients. It will measure the burden of rheumatic and other musculoskeletal disorders and reduce it in time through various community and medical programs.

The investigator is advised not to change the basic CCQ framework template and questions so to ensure standardization and comparability with other similar surveys. Modifications and Additions may be dictated by regional requirements and need investigator discretion. Translations should be carefully made into the local language/ dialect, and further back translated into 'English' by an independent expert to ensure the most appropriate meaning and interpretation before actual use in population survey. The investigator is encouraged to initially test both the Phase I and II questionnaires in a small sample pilot study.

PROPOSED WHO-ILAR COPCORD QUESTIONNAIRE 2006 STAGE I – PHASE II

STAGE I – PHASE II

Village/Town/Center :_____ **ID No**_____ **Serial No**_____ **Date**_____

Last Name_____ Name_____ Middle Name/Initial_____

Explanation of study *: Rheumatic or musculoskeletal diseases affect a large portion of our population -- both in the rural and urban sector. This COPCORD community project was designed by World Health Organization (WHO)/ International League against Rheumatism (ILAR) to find out the 'extent' of these diseases / problems in different parts of the World. A similar model is being used in this project to study your problem. Subsequently, better health services can be planned & provided to the community. All information provided by you will be treated as confidential, and not affect your ongoing medical care in any way. The entire information collectedwill be analyzed and used for purposes of medical research, health education and planning of health services.*

INSTRUCTIONS: The respondent should be encouraged to complete this questionnaire. The Health Worker should provided necessary explanations but should not prompt answers or bias the respondent in any manner. In case, the Health Worker is asked to complete this questionnaire, serious effort must be made to correctly fill the information as volunteered by the respondent.

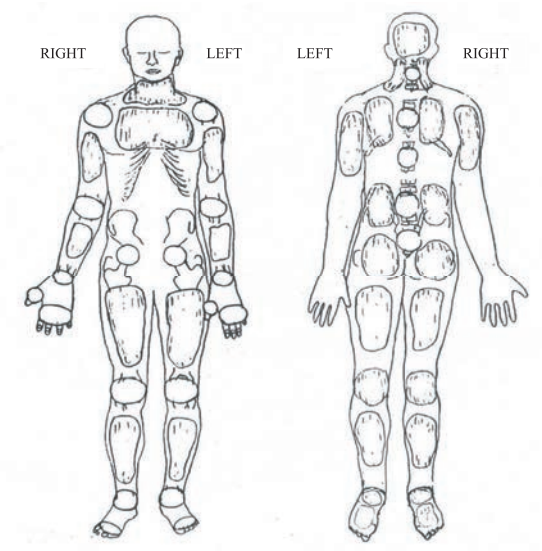
Please tick the correct entry in the box or indicate on the human manikin (see figure below) with " √ " mark. Circles on the human manikin generally indicate well known regions of joints or back bone. Shaded areas on the manikin generally indicate areas of soft tissues that are often painful. But YOU may mark anywhere on the manikin to indicate your pain/or swelling. YOU may make multiple 'marks' on the manikin. When describing a joint or other body site, please indicate 'R' for right, 'L' for left, and 'B' for both sides.

☐ SELF COMPLETED ☐ INTEVIEW BASED

SECTION 'A': JOINT PAIN, SOFT- TISSUE / MUSCLE PAIN, SWELLING, STIFFNESS

*A1. **Do you have painful joint &/or soft tissue/musculoskeletal pain &/or swollen joints &/or stiff joints &/or stiff back &/or less movement in any joint &/or less movement of the back or neck during the LAST 7 days (Current)?**

☐ NO ☐ YES, If YES, indicate your pain by " √ ", and swelling by "+" in the figure below.



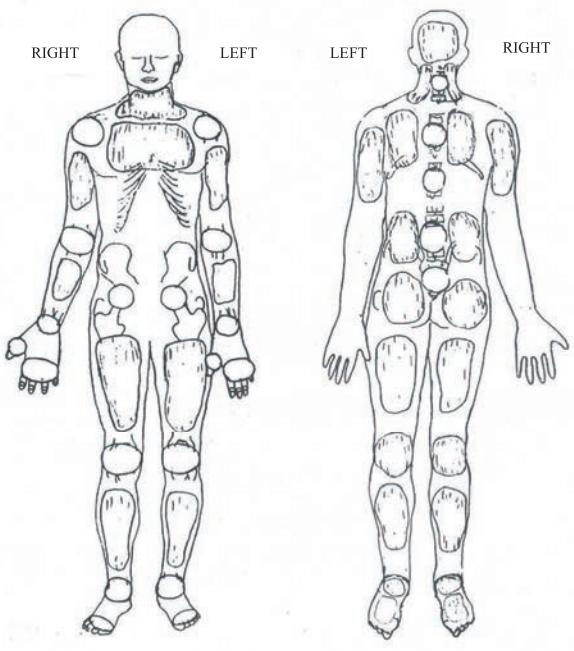
Sites of maximum current pain : _____

Sites of current Stiffness_____

Sites of current limited movement_____

*A2. **Do you have painful joint &/or soft tissue/musculoskeletal pain &/or swollen joints &/or stiff joints &/or stiff back &/or less movement in any joint &/or less movement of the back or neck in the PAST (earlier than 7 days)?**

☐ NO ☐ YES, If YES, indicate your pain by " √ ", and swelling by "+" in the figure below



Sites of maximum past pain : _____

Sites of past Stiffness_____

Sites of past limited movement_____

(a) When did you first suffer from pain ? _____

(b) If you had pain in the past, how long was the last episode ? _____

(c) If you had pain in the past, since when are you free from pain ? _____

(d) If your pain is recurrent, how long does the episode last ☐few days ☐4 – 6 weeks ☐6 – 12 weeks ☐ more than 3 months

*A3. Intensity of your pain ?

(i) IN THE PAST ☐ NIL ☐ MILD ☐ MODERATE ☐ SEVERE ☐ VERY SEVERE

(ii) CURRENT (PAST 7 DAYS) ☐ NIL ☐ MILD ☐ MODERATE ☐ SEVERE ☐ VERY SEVERE

SECTION 'B': IMPACT OF FUNCTIONAL DISABILITY (optional) :

*B1.What is the effect if any of pain / disability on your life activities as outlined below?
(NOTE: Strike out (---) any activity that is not applicable or of interest. There is no specific definition of mild, moderate, severe. It is according to your understanding and perception.)

	NONE	MILD	MODERATE	SEVERE
FAMILY RELATIONS	☐	☐	☐	☐
SOCIAL RELATIONS	☐	☐	☐	☐
MARITAL RELATIONS (including sexual activities)	☐	☐	☐	☐
FINANCIAL POSITION	☐	☐	☐	☐
BUSINESS	☐	☐	☐	☐
ABILITY TO WORK	☐	☐	☐	☐
ABILITY TO ATTEND SCHOOL / COLLEGE	☐	☐	☐	☐
HOBBY	☐	☐	☐	☐
GAMES	☐	☐	☐	☐
OTHERS, SPECIFY	☐	☐	☐	☐

*B2.(i) Have you stopped work due to pain / disability?
☐ NO ☐ YES, If YES, please specify reason:- _____

(ii) Have you altered / changed your work / job due to pain / disability?
☐ NO ☐ YES, If YES, please specify _____

B3. Are you depressed easily? ☐ NO ☐ YES: - If yes, is it due to rheumatic pain ? Clarify _____

_____

REMARK: (You may consider other issues like 'effect on sleep', etc)

***SECTION 'C': DIFFICULTY PERFORMING SPECIFIC TASKS :**

Note: You may address individual items such as walk, drive, lift weights, bathing, toilet, etc. Or else preferably, you may use any standard validated instrument to assess disability/ impairment/difficulty in performing tasks. It is advised that you chose a broad based popular instrument such as the 'Stanford Modified Health Assessment Questionnaire' (HAQ). You may also prefer to use a generic health instrument like the WHO-QOL (Brief) or SF-36. But the instrument should be suitable for local/regional use.

Here we illustrate the modified HAQ (CRD Pune, India Version) that was developed and validated for Indian use and in COPCORD Bhigwan/Pune (India) (Ref. www.rheumatologyindia.org for details/scoring) ☐ SELF REPORTED ☐ INTERVIEW

ARE YOU ABLE TO	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO	NA	SCORE
I) DRESSING 1. Dress yourself plus doing button ? 2. Wash your hair? 3. Comb your hair?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
I) RISING 4. Stand up straight from a chair? 5. Get in & out of bed ? 6. Sit cross-legged on floor & get up?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
III) EATING 7. Cut vegetable ? 8. Lift a full cup or glass to your mouth ? 9. Break chapatti with one hand ?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
IV) WALKING 10. Walk outdoors on flat ground? 11. Climb up five steps?	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	
V) HYGIENE 12. Take a bath? 13. Wash & dry your body? 14. Get on & off the toilet? Toilet: ☐ Indian ☐ WC/ Raised Seat Mode: ☐ Sit & Support ☐ Stand ☐ Stand & Support	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
VI) REACHING 15. Reach & get down a 2 kg. object (such as bag of sugar) from just above your head ? 16. Bend down to pick up clothing from the floor ?	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	
VII) GRIP 17. Open a bottle previously opened? 18. Turn taps on and off? 19. Open door latches?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
VIII) ACTIVITIES/ OCCUPATION 20. Work in office / house? 21. Run errands and shop? 22. Get in & out of a bus? 23. Get in & out of a car /Auto rickshaw?	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	

NA: Not applicable / relevant — Total Score

Please check any AIDS or DEVICES that you usually use for any of these activities :
☐ Cane ☐ Walker ☐ Crutches ☐ Wheelchair ☐ Special Built Up Chair ☐ Raised Toilet Seat

Categories for which you need HELP FROM ANOTHER PERSON :
☐ Dressing & Grooming ☐ Eating ☐ Arising ☐ Walking ☐ Hygiene ☐ Reach ☐ Grip ☐ Errands

SECTION 'D' : TREATMENT :
(Note: You may add other details like 'diet', 'medical aid systems e.g. insurance, etc')

*D1. WHICH TYPE OF TREATMENT HAVE YOU TAKEN IN THE PAST (*Adapt to regional needs*):-

☐ ALLOPATHY / MODERN MEDICINE	☐ HERBAL
☐ PHYSIOTHERAPY	☐ YOGA
☐ HOMEOPATHY	☐ MEDICATION
☐ MASSAGE	☐ UNKNOWN
☐ OTHER_____	☐ OTHER _____
☐ OTHER_____	☐ OTHER _____

D2. Any further information from patient? _____

_____

_____

_____

Thank you for your co-operation & assistance

NAME OF HEALTH WORKER: _____

Qualification of Health Worker ☐Completed School ☐ Graduate ☐ Post –Graduate, Others_____

Occupation ☐ Trained Health Worker ☐Volunteer Health Worker ☐Nurse ☐Others, specify_____

Residential Village/ Town :_____TIME :_____DATE : _____

Background:
COPCORD was launched by WHO (World Health Organization) and ILAR (International League of Associations for Rheumatology). The community data on rheumatic musculoskeletal disorders is to be collected in a house-house survey (Stage 1) in three phases-demographic data and identifying cases/respondent (Phase I), data on pain and disability (Phase II), and rheumatological examination/evaluation (Phase III). Phase I & II are to be conducted by community health worker/nurse. The earlier versions of COPCORD Core Questionnaire (CCQ) were based on ILAR experience [HA Valkenburg (The Netheland), Richard Wigley (New Zealand), KD Muirden (Australia), & others). The CCQ was later modified and developed [APLAR COPCORD Workshop Korea,1991, Prof S. van der Linden (The Netherlands), J Darmawan (Indonesia), and others). Maintaining basic framework, CCQ was modified and further developed by the fast track COPCORD Bhigwan (India) model and published (APLAR J Rheumatol 1997; 1: 145-154). The current proposed CCQ is based on the latter experience, review at the WHO-ILAR BJD Meeting Vienna, Austria 2005 (Clin Rheumatol 2007; 26: 1217-1227), inputs from several COPCORD investigators and experts, and discussions in the APLAR 2006 (Kuala Lumpur) COPCORD Session (Arvind Chopra, India, and others, Unpublished).

The WHO & UN supported '**The Bone & Joint Decade (BJD)** 2000 – 2010 (www.bjdonline.org) has included '**trauma**' along with arthritis & osteoporosis amongst the disease target conditions. The BJD program aims to create awareness and empower patients. It will measure the burden of rheumatic and other musculoskeletal disorders and reduce it in time through various community and medical programs.

The investigator is advised not to change the basic CCQ framework template and questions so to ensure standardization and comparability with other similar surveys. Modifications and Additions may be dictated by regional requirements and need investigator discretion. Translations should be carefully made into the local language/ dialect, and further back translated into 'English' by an independent expert to ensure the most appropriate meaning and interpretation before actual use in population survey. The investigator is encouraged to initially test both the Phase I and II questionnaires in a small sample pilot study.

Received: 18 April 2021 | Revised: 19 June 2021 | Accepted: 24 June 2021

DOI: 10.1111/1756-185X.14174

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Performance of myositis-specific antibodies detected on myositis line immunoassay to diagnose and sub-classify patients with suspected idiopathic inflammatory myopathy, a retrospective records-based review

Thomas J. Beaton[1] | David Gillis[1,2] | Kerri Prain[2] | Karen Morwood[1] | James Anderson[3] | John Goddard[3] | Timothy Baird[3]

[1]Department of Clinical Immunology, Sunshine Coast University Hospital, Sunshine Coast, Qld, Australia

[2]Department of Immunology, Pathology Queensland, Brisbane, Qld, Australia

[3]Department of Respiratory Medicine, Sunshine Coast University Hospital, Sunshine Coast, Qld, Australia

Correspondence
Thomas J. Beaton, Department of Clinical Immunology, Sunshine Coast University Hospital, Sunshine Coast, Qld, Australia.
Email: thomas.beaton2912@gmail.com

Present address
Thomas J. Beaton, Department of Clinical Immunology, Princess Alexandra Hospital, Woolloongabba, Qld, Australia

Abstract

Aim: To evaluate myositis line immunoassay (LIA) for diagnosis and sub-classification of suspected idiopathic inflammatory myopathy (IIM). To investigate if test performance is improved by increasing signal strength cut-off for myositis-specific antibody (MSA) or combining MSA with indirect immunofluorescence (IIF).

Methods: A retrospective, consecutive case series of patients investigated for MSAs from June 2013 to June 2020 for suspected IIM. Specificity, sensitivity, positive predictive value, and negative predictive value were calculated with 95% confidence intervals for diagnosis of IIM. Association of IIM diagnosis with increased signal strength and presence of an expected IIF pattern on Hep-2 cells was assessed by Fisher's exact test in MSA-positive patients.

Results: A total of 195 patients were evaluated. IIM was diagnosed in 32/195 (16.4%) patients. MSAs were detected in 41/195 (21%) patients, 18/41 (43.9%) patients with an MSA had a diagnosis of IIM. The probability of an IIM diagnosis was increased in MSA-positive patients with high compared with low signal strength (83.3% vs 43.5%; $P = 0.01$) and an expected compared with unexpected IIF pattern (61.5% vs 23.8%; $P = 0.04$). Specificity for IIM was not significantly improved by increasing signal strength cut-off (85.9% vs 93.8%). Positive predictive value of myositis LIA was only modest and not significantly improved by either increasing signal strength cut-off or requiring an expected IIF pattern for determination of MSA positivity (43.9% vs 60% vs 61.5%). Sub-classification of IIM correlated closely for respective MSAs (88.9%).

Conclusion: Increased MSA signal strength on myositis LIA and the presence of an expected IIF pattern were associated with IIM diagnosis. Test performance was non-significantly improved by these methods. Prevalence of IIM in this patient cohort was low; it is not excluded that LIA performance could be improved by these methods in a higher prevalence cohort.

KEYWORDS
anti-synthetase syndrome, autoantibodies, idiopathic inflammatory myopathy, immunoblot, line immunoassay, myositis-specific antibody

1 | INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are rare, heterogeneous immune-mediated disorders that were initially characterized by muscle inflammation and proximal muscle weakness. However, other organ involvement is common, particularly cutaneous disease and interstitial lung disease (ILD). This heterogeneity has led to sub-classification of IIM including polymyositis, dermatomyositis, sporadic inclusion body myositis, immune-mediated necrotizing myopathy (IMNM), and the anti-synthetase syndrome (ASS).[1,2]

Autoantibodies are frequently associated with IIM and have been proposed to both aid diagnosis and further sub-classify IIM patients.[3] Developments of technology and especially the development of a commercially available line immunoassay (LIA) have lent support to their use. These autoantibodies are considered either myositis-associated antibodies, that are not specific for IIM and are commonly present in overlap disease and other systemic autoimmune diseases, or myositis-specific antibodies (MSAs), which are reported to be highly specific for IIM.[4] The association of MSAs with specific clinical syndromes, pattern of organ involvement, and prognostic information has been well described by previous authors.[3,5-8]

Myositis-specific antibodies were initially described using immunoprecipitation (IP); however, these techniques are not performed on a routine basis for diagnosis and classification due to the laborious nature of testing and level of expertise required.[9] Commercially available myositis LIA have the potential to allow the identification of most described MSAs with greater ease.[10] Cohort studies assessing myositis LIA for IIM patients have reported very high specificity, (up to 100% for anti-Jo-1, PI-7, and PI-12).[4,10] Despite the high specificity reported in these studies, LIA testing has limitations. Agreement between myositis LIA and IP techniques can be poor, varying between individual MSAs.[11,12] Frequent false-positive MSA results have been identified by some authors, particularly in populations with relatively lower disease prevalence.[13-15] Furthermore, discordant results occur on direct comparison of different manufacturers' commercially available LIAs.[15,16] Accuracy of individual antibodies (as studied in comparison with clinical presentation) on different manufacturers' LIAs can vary with rarer MSAs in general being less reliable.[12,16,17] The association of positive MSA with clinical IIM can potentially be improved by increased LIA signal intensity cut-off for a positive result and is supported by small patient series.[14,15]

Combining myositis LIA with a second technique for measuring autoantibodies may also reduce the frequency of false-positive MSA results. Widely available antinuclear antibody testing in conjunction with line immunoassay has been investigated.[15,18,19] Antinuclear antibody reporting alone as a screening test for MSA is insensitive and complicated by the presence of cytoplasmic staining rather than nuclear correlation with several MSAs.[20] Cytoplasmic staining is problematic in view of the lack of consensus on reporting cytoplasmic staining results.[9,21] Counter immune electrophoresis (CIEP) or IP are highly specific methods for MSA detection; however, they are labor intensive and only available in highly specialized centers. CIEP is not available for all MSAs.[22]

This retrospective series examines MSA results from a consecutive series of patients suspected of having IIM and referred for MSA testing at a tertiary health service. We hypothesized that of patients who have a positive MSA by the LIA technique, those with increased signal strength on semi-quantitative analysis and an expected indirect immunofluorescence (IIF) pattern on Hep-2 cells are more likely to fulfill clinical criteria for IIM. As a result of this association, we hypothesized that the specificity and positive predictive value (PPV) of myositis LIA for the diagnosis of IIM may be improved by increasing the signal intensity cut-off for MSA to >1+ or the presence of an expected IIF on Hep-2 result in conjunction with MSA.

2 | MATERIALS AND METHODS

Consecutive patients who had MSA testing performed at an Australian tertiary hospital for the period June 2013 to June 2020 were included in this retrospective series. Patients were identified from the pathology reporting system AUSLAB. All patients who had myositis LIA completed or who had an MSA identified by extractable nuclear antigen testing using CIEP (anti-Jo-1 antibody) were included. Tests were ordered by hospital specialty teams with no pre-specified criteria.

A chart review of identified participants was completed. IIM was diagnosed and sub-classified if patients met the 2017 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IIM.[23] Criteria were retrospectively applied to documented clinical information and pathology results. Patients with a sub-classification of sporadic inclusion body myositis were excluded from diagnosis of IIM for the purposes of this study. ASS was diagnosed in patients who did not meet 2017 ACR/EULAR criteria for IIM but met proposed criteria for ASS by Connors et al[24] Diagnosis was made by the primary investigator and confirmed on independent review of clinical and pathological information by an associate investigator with expertise in IIM. ILD was required to be diagnosed and recorded in the clinical notes by a thoracic physician. The radiological pattern of ILD was reviewed by two thoracic physicians independently with a third reviewer if there was disagreement in pattern.

The myositis LIA performed on patient serum for the period of 2013 and early 2014 was the Euroline myositis profile 3 (Euroimmun, Lübeck, Germany). MSA antigens on this LIA are anti-Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2α, and Mi-2β, and four

myositis-associated antibodies: Ro52, Ku, PM/Scl-100, and PM/Scl-75. The Euroline autoimmune inflammatory myopathies 16Ag (Euroimmun) was used from 2014 onwards. This includes the same antigens with the addition of anti-MDA5, TIF1γ, SAE, and NXP2. In patients with anti-Jo1 antibody identified by CIEP, Myositis LIA with Euroline autoimmune inflammatory myopathies 16Ag (Euroimmun) was performed on serum stored from the time of initial antibody testing to assess LIA signal intensity. Results were recorded in a semi-quantitative fashion using EUROLINE software (Euroimmun) as low (1+), moderate (2+), and high (3+). If myositis LIA was repeated in a patient, the first result was considered as the MSA result. An in-house enzyme-linked immunosorbent assay performed at an external laboratory was used for reported anti-HMGCA antibodies.

Indirect immunofluorescence was performed on Hep-2 cells on stored serum of MSA-positive patients using the NOVA lite DAPI antinuclear antibody kit (Werfen Ltd., Warrington, UK). Samples were diluted to a starting concentration of 1:40. Results were confirmed by two laboratory scientists.

Sensitivity, specificity, PPV, and negative predictive value for MSA were calculated for a diagnosis of IIM (including those diagnosed with ASS). Exact (Clopper-Pearson) method was used for 95% confidence intervals.

Fisher exact test was used to assess the association of a diagnosis of IIM (including those diagnosed with ASS) with increased signal strength and expected IIF pattern on Hep-2 cells in MSA-positive patients. The *P* value was set at less than 0.05.

The study plan was approved by the local ethics committee LNR/2020/QPCH/65164 (Jul ver 3).

3 | RESULTS

In total, 251 myositis LIAs were performed in 195 patients during the prescribed period. Three patients were identified by CIEP result. Fifty-six myositis LIAs were repeated in 42 patients with a single change (positive Mi2 antibody became negative on repeat). An MSA was detected in 41/195 (21%) patients. IIF on Hep-2 cells was performed on 34 of 41 patients with a detectable MSA. Stored serum was unavailable for the remaining seven patients (Figure 1).

Idiopathic inflammatory myopathy was diagnosed in 32/195 (16.4%) patients, which included 31 adults. Average age of diagnosis in adults was 60.8 years. Thirteen patients had a sub-group of dermatomyositis, five with polymyositis, eight with ASS, and six had IMNM. IIM was associated with cancer in five patients. ILD was present in 11 patients, of whom eight had radiological non-specific interstitial pneumonia and/or organizing pneumonia and three had unclassifiable radiological ILD patterns (Tables 1 and 2). Patients with alternative diagnoses are detailed in Tables 3 and 4.

An MSA was detected in 18/32 (56.3%) IIM patients (Table 1) and 23/163 (14.1%) patients with an alternative diagnosis (Table 3). In patients with a detectable MSA, IIM patients were significantly more likely to have signal strength >1+ compared with patients with another diagnosis (15/18, 83.3% vs 10/23, 43.5%; $P = 0.01$).

Indirect immunofluorescence was assessed in 13/18 MSA-positive IIM patients (Table 1) and 21/23 MSA-positive patients with an alternative diagnosis (Table 3). In patients with a detectable MSA and IIF completed, IIM patients were significantly more likely to have an expected IIF pattern compared with patients with another diagnosis (8/13, 61.5% vs 5/21, 23.8%; $P = 0.04$).

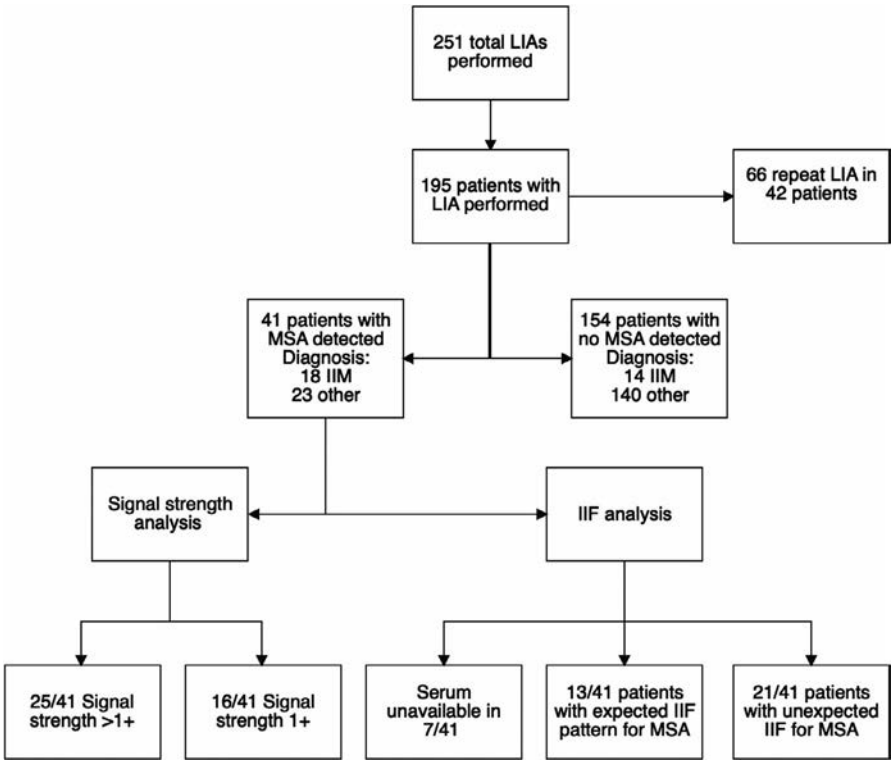


FIGURE 1 Flow diagram of patients with myositis LIA testing including further analyses performed and diagnosis. Abbreviations: IIF, indirect immunofluorescence; IIM, idiopathic inflammatory myopathy; LIA, line immunoassay; MSA, myositis-specific antibody

TABLE 1 MSA-positive IIM patients

Age/sex	MSA	Signal intensity	IIF pattern[b]	MAA	Criteria led diagnosis[a]	Sub-group	Clinical features
46M	NXP2	>1+	Centriole (U)	–	pIIM	PM	Myositis (proximal myopathy, raised CK), no cutaneous signs of DM
63M	NXP2	>1+	NA	–	dIIM	DM	Myositis (muscle biopsy), shawl sign, Gottron's papules, heliotrope rash
45F	Jo-1	>1+	Negative (U)	Ro52	dIIM	ASS	ILD (OP and NSIP), myositis (muscle biopsy), arthritis, mechanics hand
46M	Jo-1	>1+	NA	–	dIIM	ASS	ILD (NSIP), myositis (muscle biopsy), arthritis
83F	Jo-1	1+	Cytoplasmic(E)	Ro52	dIIM	ASS	ILD (NSIP), raised CK, malignancy-associated (cervical) Deceased: malignancy
79M	PL-12, SRP	>1+,1+	Cytoplasmic (E)	–	dIIM	ASS	ILD (unclassifiable), myositis (proximal myopathy, raised CK)
76F	PL-12, Mi2	1+,1+	Homogeneous (U)	–	ASS	ASS	ILD (unclassifiable), Raynaud syndrome
46M	PL-7	>1+	Cytoplasmic dots (U)	–	dIIM	ASS	Myositis (muscle biopsy), ILD (NSIP)
72M	PL-7	>1+	Cytoplasmic (E)	–	dIIM	IMNM	Necrotizing myositis (muscle biopsy)
87F	OJ, Mi2	>1+,1+	Cytoplasmic (E)	–	ASS	ASS	ILD (NSIP)
75F	EJ	>1+	NA	Ro52	dIIM	DM	Myositis (muscle biopsy), ILD (unclassifiable), Gottron's papules, heliotrope rash
60F	EJ, PL-12	1+,1+	Homogeneous (U)	Ro52	dIIM	ASS	Myositis (muscle biopsy), Raynaud syndrome, ILD (OP)
7M	MDA-5	>1+	NA	Ro52	dIIM	JDM	Inflammatory arthritis, Gottron's sign, heliotrope rash, raised CK
58F	MDA-5, PL-7	>1+,1+	Negative (E)	–	dIIM	DM	Amyopathic DM, peripheral ulcerating lesions
58F	MDA-5	>1+	Negative (E)	–	dIIM	DM	Amyopathic DM, ILD (OP), inflammatory arthritis, esophageal dysmotility
78F	Tif1y	>1+	Speckled (E)	Ro52	dIIM	DM	Myositis (raised CK, proximal myopathy), erythroderma, heliotrope rash Gottron's papules, dysphagia, malignancy-associated (lung). Deceased: malignancy
50F	Tif1y	>1+	Speckled (E)	–	dIIM	DM	Erythema, Gottron's sign and papules, heliotrope rash, raised CK malignancy-associated (melanoma)
67F	Mi2	>1+	NA	–	dIIM	DM	Myositis (proximal myopathy, raised CK), Gottron's sign

Abbreviations: ASS, anti-synthetase syndrome; CK, creatinine kinase; DM, dermatomyositis; IIF, indirect immunofluorescence; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myositis; JDM, juvenile dermatomyositis; MAA, myositis-associated antibody; MSA, myositis-specific antibody; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PM, polymyositis.

[a]Diagnostic criteria: ACR/EULAR classification criteria[23] used for diagnosis of definite or probable IIM (dIIM or pIIM), Connors et al criteria[24] for anti-synthetase syndrome (ASS) if not meeting criteria for IIM.

[b]IIF pattern on Hep-2 cells at lowest concentration of 1:40. Reported as expected (E) if IIF pattern for MSA with strongest signal strength present on IIF analysis or unexpected (U) if not present. Expected IIF patterns for MSAs as per Damoiseaux et al (2019) and Palterer et al (2018).[9,22] NA if serum unavailable for evaluation.

Test specificity for an MSA detected by LIA for the diagnosis of IIM in this series of patients was 85.9%, with a sensitivity of 56.3%, and a PPV of 43.9% (Table 5). MSA specificity and PPV for a diagnosis of IIM was not significantly improved when considering only MSA with signal strength >1+ positive. PPV was not significantly improved by requiring an expected IIF pattern with an MSA to consider the test positive (Table 5).

Clinical syndrome and sub-classification of IIM patients were predicted by MSA result in 16/18 (88.9%) cases (Table 1). Unexpected sub-classification occurred in a patient with

TABLE 2 MSA-negative IIM patients

Age/sex	Antibody	Criteria-led diagnosis	Sub-group	Clinical features
36F	–	dIIM	IMNM	Necrotizing myositis (muscle biopsy)
27F	Pm/Scl	dIIM	PM	Myositis (muscle biopsy), dysphagia, no cutaneous features of scleroderma
43M	Ro-52	dIIM	PM	Myositis (muscle biopsy), ILD (OP + NSIP), fever
60M	Ro-52	dIIM	DM	Myositis (muscle biopsy), heliotrope rash, Gottron's sign, dysphagia—malignancy-associated (melanoma) Deceased: malignancy
32F	–	dIIM	DM	Myositis (raised CK, proximal myopathy), dysphagia, Gottron's sign, heliotrope rash, shawl sign
49F	–	dIIM	DM	Myositis (muscle biopsy), Gottron's papules, heliotrope sign
60F	–	dIIM	DM	Myositis (proximal myopathy, raised CK), Gottron's sign, heliotrope rash, shawl sign, erythema (skin biopsy consistent with DM)
48M	–	dIIM	PM	Myositis (proximal myopathy, raised CK)
64F	–	dIIM	PM	Myositis (muscle biopsy)
78F	–	dIIM	IMNM	Necrotizing myositis (muscle biopsy)
91F	–	dIIM	DM	Myositis (proximal myopathy, raised enzymes), heliotrope rash, malignancy-associated (lymphoma) Deceased: malignancy
63M	–	dIIM	IMNM	Necrotizing myositis (muscle biopsy), dysphagia Deceased: comorbidities
71F	HMGCA	dIIM	IMNM	necrotizing myositis (muscle biopsy)
74M	HMGCA	dIIM	IMNM	necrotizing myositis (muscle biopsy)

Abbreviations: CK, creatine kinase; dIIM, definite idiopathic inflammatory myopathy; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; IVIg, intravenous immunoglobulin; MSA, myositis-specific antibody; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PM, polymyositis.

anti-NXP2 presenting with polymyositis and a patient with anti-PL-7 and IMNM. Two patients with IMNM and a negative myositis LIA had anti-HMGCA antibodies identified on enzyme-linked immunosorbent assay.

4 | DISCUSSION

In view of the increased availability and use of myositis LIA in clinical practice, it is important to assess its performance in different population groups. Myositis LIA performs well in high pre-test probability populations studied in cohort studies but less consistently in consecutive series of patients with a lower prevalence of disease. Approaches that could improve test performance were assessed in this study.

In this retrospective series, patients who had a detectable MSA had an increased probability of a diagnosis of IIM if MSA signal strength was >1+ (83.3% vs 43.5%). Test specificity, however, did not significantly improve by increasing the signal cut-off for a positive result to >1+ (from 85.9% to 93.9%). PPV of a detectable MSA on LIA was relatively low (43.5%), increasing the cut-off to >1+ did not significantly improve the PPV (60%). Of patients with a detectable MSA, there was an increased probability of a diagnosis of IIM in patients with an expected IIF pattern compared with an unexpected IIF pattern (61.5% vs 23.8%). The PPV was not significantly improved if only MSA results with an expected IIF pattern were considered positive (61.5%). Sensitivity of MSA in this series was low and too underpowered to assess accurately. The detection of an MSA in IIM patients was predictive of sub-classification in the majority of cases (88.9%). The prevalence of IIM in this cohort was 16.4% as a result of the inclusion of consecutive patients tested for MSA with no limitations or clinical criteria required to be referred for MSA testing. It is not ruled out that such approaches could improve test performance (especially PPV) in a higher prevalence population.

The association of increased MSA signal strength and a diagnosis of IIM has previously been reported in small studies with comparable patient numbers, prevalence of IIM in their cohorts, and definition of increased signal strength.[14,15] One of the studies observed increased specificity (from 88% to 96%); however, confidence intervals were not reported.[14] Neither study, in similarly low-prevalence populations, significantly improved the diagnostic performance of myositis LIA by increasing the signal intensity cut-off for a positive MSA result.

There are limitations for comparing studies investigating signal strength associations for myositis LIAs. Commercially available

TABLE 3 MSA-positive patients with an alternative diagnosis

MSA	Signal strength	IIF pattern, expected/unexpected pattern (E/U)	Diagnosis
NXP2	1+	NA	Infection-induced myositis
	1+	Homogeneous (U)	Scleroderma
PL-12	1+	Speckled (U)	Scleroderma
	>1+	Negative (U)	Polyarteritis nodosa
	1+	Cytoplasmic (E) + speckled	Lymphoma
PL-7	>1+	Negative (U)	Myalgia without other diagnosis
	>1+	Speckled (U)	Unclear diagnosis—no evidence of myositis
Tif1y	>1+	Speckled (E)	Myalgias—no evidence of myositis
Mi2α/β	>1+	Negative (U)	Cramp syndrome
	1+	Homogeneous (U)	Croglobulinemic vasculitis
	1+	Cytoplasmic + speckled (U)	Statin-induced myopathy
	>1+	NA	Limited scleroderma (myositis not meeting IIM criteria)
	1+	Nucleolar (U)	Transient CK elevation
	>1+	Negative (U)	Hepatitis C
SRP	1+	Cytoplasmic (U)	Idiopathic pulmonary fibrosis
	1+	Speckled (U)	Lung infiltrates of unclear cause
	>1+	Homogeneous (U)	Febrile illness—unclear diagnosis
SAE	1+	Speckled (E) + Cytoplasmic	Hepatitis C
	1+	Speckled (E)	Systemic lupus erythematosus
Multiple antibodies			
(NXP2, Tif1y, MDA-5)	>1+,1+,1+	Negative (U)	Myalgia
(Jo-1, Tif1y)	1+,1+	Dense fine speckled (U)	Chronic infection
(Tif1y, SRP)	>1+,>1+	Negative (U)	No disease
(Pl-12, Mi-2)	1+,1+	Cytoplasmic (E)	Pneumonia

Abbreviations: CK, creatinine kinase; IIF, indirect immunofluorescence; IIM, idiopathic inflammatory myopathy; MSA, myositis-specific antibody.

[a]IIF pattern on Hep-2 cells at lowest concentration of 1:40. Reported as expected (E) if IIF pattern for MSA with strongest signal strength present on IIF analysis or unexpected (U) if not present. Expected IIF patterns for MSAs as per Damoiseaux et al (2019) and Palterer et al (2018).[9,22] NA if serum unavailable for evaluation.

products perform differently for individual antibodies.[16] The lack of analyte controls for myositis LIA makes individual laboratory auditing of variability in performance a necessity.[25] A universal signal intensity cut-off value for positive MSA on LIA may not be appropriate.[26,27] Minimal validation of normal MSA signal intensity among normal and disease populations, particularly in different regions and across patient demographics, is needed. Other individual laboratory factors, such as temperature, may also influence results.[4]

The association of an MSA with an expected IIF pattern and a diagnosis of IIM is supported by other small studies. A series of MSA-positive patients with high prevalence (79.8%) of IIM found that 59% of IIM patients had an expected IIF pattern compared with 21% of non-IIM patients.[19] A higher starting dilution of 1:80 was used for IIF compared with our series.[19] Another series with a low prevalence (26%) of IIM found that 88% of MSA-positive IIM patients had an expected IIF pattern compared with 54% of MSA-positive patients with another diagnosis. A starting dilution of 1:40 was used for IIF.[15] It is unclear if an MSA with expected IIF pattern significantly improves the specificity or PPV of myositis LIA from these studies.

Comparing findings of IIF patterns across studies is limited by cohort and laboratory differences, including other autoantibodies in patients' serum impacting their ability to detect IIF patterns, different strength of correlation between IIF pattern and MSA in individual antibodies and a lack of international consensus on reporting cytoplasmic IIF staining present in many MSAs.[15,18,20,28]

This cohort had no clinical criteria required for ordering myositis LIA reflecting current practices of specialist teams in a tertiary hospital. Common alternative diagnoses in this patient group included other systemic autoimmune diseases, primary lung diseases, neurological disease, and other muscle disease in MSA-positive and MSA-negative patients. Chronic infections and malignancy occurred less commonly. Other studies with inclusion criteria of myositis LIA

TABLE 4 MSA-negative patients with an alternative diagnosis

System diagnosis (N, %)	Specific diagnosis (N)
Primary lung disease (17, 13.3%)	Idiopathic pulmonary fibrosis (10)
	Cryptogenic organizing pneumonia (2)
	Idiopathic ILD (2) (Radiological pattern: NSIP (1), unclassifiable (1))
	Hypersensitivity pneumonitis (1)
	Alveolar proteinosis (1)
	CTD – ILD (1)
Muscle disease (28, 21.9%)	Sporadic inclusion body myositis (7)
	Toxic myopathy (7)
	Inherited myopathy (2)
	Rhabdomyolysis (5)
	Muscular dystrophy (2)
	Fasciculation-cramp syndrome (3)
	Focal myositis (2)
Neurological disease (15, 11.7%)	Peripheral neuropathy (5)
	Acute demyelinating encephalomyelopathy (1)
	Parkinson's disease (2)
	Motor neuron disease (3)
	Multiple sclerosis (1)
	Functional neurological disorder (1)
	Myoclonus (1)
	Myasthenia gravis (1)
Systemic autoimmune disease (39, 30.5%)	Systemic lupus erythematosus (10)
	Scleroderma (6)
	Inflammatory arthritis (14)
	Undifferentiated CTD (1)
	Mixed CTD (1)
	Sjögren syndrome (2)
	Sarcoidosis (1)
	IgG4-related disease (1)
	Inflammatory bowel disease (2)
	Behçet's disease (1)
	Large-vessel vasculitis (1)
Infectious disease (4, 3.1%)	Non-tuberculous mycobacterium (1)
	Hepatitis C (1)
	Infective enteritis (1)
	HIV (1)
Malignancy (6, 4.7%)	Hematological (3)
	Lung (1)
	Mesothelioma (1)
	Cholangiocarcinoma (1)
No diagnosis (24, 18.8%)	Acute febrile/inflammatory illness (3)
	Myalgia/elevated CK without diagnosis (15)
	Unclear diagnosis from documentation (6)
Miscellaneous (5, 3.9%)	Erythroderma (1)
	Acute kidney injury (1)
	Pericarditis (2)
	Thrombotic microangiopathy (1)

Abbreviations: CK, creatinine kinase; CTD, connective tissue disease; HIV, human immunodeficiency virus; ILD, interstitial lung disease; MSA, myositis-specific antibody; NSIP, non-specific interstitial pneumonia.

testing rather than myositis diagnosis have limited information on diagnosis of MSA-negative patients although other systemic autoimmune diseases are common.[14,15]

The low prevalence of IIM (16.4%) in this cohort impacts its PPV and therefore its utility as a diagnostic test. This is consistent with disease prevalence of IIM in studies including consecutive myositis LIA testing, which is similar to the prevalence in this series, suggesting that myositis LIA is frequently used in low to moderate pre-test probability patients in clinical practice around the world.[13-15] In contrast, cohorts with very high pre-test probability have reported improved correlation of IIM classification criteria and clinical IIM diagnosis with addition of other MSAs.[29,30] Assessing patients' pre-test probability is particularly important in ASS-associated ILD without other features of IIM due to the low incidence of MSAs in idiopathic ILD, the heavy reliance on the presence of ASS antibodies in current proposed criteria, and the lack of a clinical reference standard for diagnosis.[24,31,32]

Despite low prevalence, this series had a relatively high percentage of MSA-positive IIM patients (56.3%) compared with large Indian and European cohorts (38% and 43%).[3,8] Differences may be explained by lower age in other cohorts, numerous overlap myositis in other cohorts, racial differences, and differences in pathology technique with IP in the European cohort and increased LIA signal cut-off in the Indian cohort.[3,8]

This study is limited by its small number of MSA-positive patients and patients with IIM. Sub-analysis of individual MSA performance is not possible because of the low numbers. Retrospective diagnosis increases the risk of bias; this was mitigated by application of published clinical criteria and a second clinician independently confirming diagnosis. This study was further limited by unavailability of stored serum for IIF analysis for seven

TABLE 5 Diagnostic performance of MSAs for the diagnosis of IIM

	MSA positive as per manufacturers' guidelines % [95% CI]	MSA positive only with signal strength >1+ % [95% CI]	MSA positive only with an expected IIF pattern % [95% CI]
Sensitivity	56.3% [37.7%-73.6%]	46.9% [29.1%-65.3%]	[a]
Specificity	85.9% [79.6%-90.8%]	93.9% [89.0%-97.0%]	[a]
PPV	43.9% [32.5%-56.0%]	60% [42.6%-75.2%]	61.5% [36.1%-81.9%]
NPV	90.9% [87.0%-93.7%]	90% [86.6%-92.6%]	89.1% [86.5%-91.3%]

Abbreviations: CI, confidence interval; IIF, indirect immunofluorescence; IIM, idiopathic inflammatory myopathy; MSA, myositis-specific antibody; NPV, negative predictive value; PPV, positive predictive value.

[a]Not calculated due to inability to perform IIF on serum of seven MSA-positive patients

patients with a positive MSA. This series is, however, reflective of the practical use of myositis LIA in a tertiary hospital setting and highlights the issue of frequent false-positive results in a relatively low-prevalence population despite the high specificity reported in cohort studies.

5 | CONCLUSION

At present, the use of MSA testing by myositis LIA has a limited diagnostic role with the exception of populations with high pre-test probability. Myositis LIA is, however, a valuable tool for sub-classification of patients with high suspicion of IIM. Improving accuracy and understanding the limitations of MSA testing is imperative for clinicians managing patients with suspected IIM.

ACKNOWLEDGEMENT

No acknowledgements.

AUTHOR CONTRIBUTIONS

TJB designed the study protocol, collected and analyzed data, and wrote the manuscript. DG was the primary supervisor on the project and confirmed indirect immunofluorescence analyses. KP performed the indirect immunofluorescence analyses. KM confirmed diagnosis of IIM. JA, JG, and TB analyzed the chest radiology.

ORCID

Thomas J. Beaton https://orcid.org/0000-0001-8283-3169

REFERENCES

1. Lundberg IE, Miller FW, Tjärnlund A, Bottai M. Diagnosis and classification of idiopathic inflammatory myopathies. *J Intern Med*. 2016;280(1):39-51.
2. Witt LJ, Curran JJ, Strek ME. The diagnosis and treatment of antisynthetase syndrome. *Clin Pulm Med*. 2016;23(5):218-226.
3. Betteridge Z, Tansley S, Shaddick G, et al. Frequency, mutual exclusivity and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients. *J Autoimmun*. 2019;101:48-55.
4. Rönnelid J, Barbasso Helmers S, Storfors H, et al. Use of a commercial line blot assay as a screening test for autoantibodies in inflammatory myopathies. *Autoimmun Rev*. 2009;9(1):58-61.
5. Targoff IN. Laboratory testing in the diagnosis and management of idiopathic inflammatory myopathies. *Rheum Dis Clin North Am*. 2002;28(4):859-890, viii.
6. Ghirardello A, Borella E, Beggio M, Franceschini F, Fredi M, Doria A. Myositis autoantibodies and clinical phenotypes. *Auto Immun Highlights*. 2014;5(3):69-75.
7. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med*. 2016;280(1):8-23.
8. Gupta L, Naveen R, Gaur P, Agarwal V, Aggarwal R. Myositis-specific and myositis-associated autoantibodies in a large Indian cohort of inflammatory myositis. *Semin Arthritis Rheum*. 2021;51(1):113-120.
9. Damoiseaux J, Vulsteke JB, Tseng CW, et al. Autoantibodies in idiopathic inflammatory myopathies: clinical associations and laboratory evaluation by mono- and multispecific immunoassays. *Autoimmun Rev*. 2019;18(3):293-305.
10. Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. *Rheumatology (Oxford)*. 2010;49(12):2370-2374.
11. Cavazzana I, Fredi M, Ceribelli A, et al. Testing for myositis specific autoantibodies: comparison between line blot and immunoprecipitation assays in 57 myositis sera. *J Immunol Methods*. 2016;433:1-5.
12. Tansley SL, Li D, Betteridge ZE, McHugh NJ. The reliability of immunoassays to detect autoantibodies in patients with myositis is dependent on autoantibody specificity. *Rheumatology (Oxford)*. 2020;59(8):2109-2114.
13. Knitza J, Schenker H, Schett G, Distler J. Only a minor proportion of individuals with anti-aminoacyl-tRNA synthetase autoimmunity presents with the clinical picture of "antisynthetase-syndrome" [abstract]. *Arthritis Rheumatol*. 2018;70(suppl 10).
14. Lecouffe-Desprets M, Hémont C, Néel A, et al. Clinical contribution of myositis-related antibodies detected by immunoblot to idiopathic inflammatory myositis: a one-year retrospective study. *Autoimmunity*. 2018;51(2):89-95.
15. Piette Y, De Sloovere M, Vandendriessche S, et al. Pitfalls in the detection of myositis specific antibodies by lineblot in clinically suspected idiopathic inflammatory myopathy. *Clin Exp Rheumatol*. 2019;38:212-219.
16. Vulsteke JB, De Langhe E, Claeys KG, et al. Detection of myositis-specific antibodies. *Ann Rheum Dis*. 2019;78(1):e7.
17. Ghirardello A, Bettio S, Bassi N, et al. Autoantibody testing in patients with myositis: clinical accuracy of a multiparametric line immunoassay. *Clin Exp Rheumatol*. 2017;35(1):176-177.
18. Picard C, Vincent T, Lega JC, et al. Heterogeneous clinical spectrum of anti-SRP myositis and importance of the methods of detection of anti-SRP autoantibodies: a multicentric study. *Immunol Res*. 2016;64(3):677-686.
19. Infantino M, Tampoia M, Fabris M, et al. Combining immunofluorescence with immunoblot assay improves the specificity of autoantibody testing for myositis. *Rheumatology (Oxford)*. 2019;58(7):1239-1244.

20. Aggarwal R, Dhillon N, Fertig N, Koontz D, Qi Z, Oddis CV. A negative antinuclear antibody does not indicate autoantibody negativity in myositis: role of anticytoplasmic antibody as a screening test for antisynthetase syndrome. *J Rheumatol*. 2017;44(2):223-229.
21. Hoffman IEA, Peene I, Veys EM, De Keyser F. Detection of specific antinuclear reactivities in patients with negative antinuclear antibody immunofluorescence screening tests. *Clin Chem*. 2002;48(12):2171-2176.
22. Palterer B, Vitiello G, Carraresi A, Giudizi MG, Cammelli D, Parronchi P. Bench to bedside review of myositis autoantibodies. *Clin Mol Allergy*. 2018;16:5.
23. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955-1964.
24. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest*. 2010;138(6):1464-1474.
25. Mahler M, Fritzler MJ. Detection of myositis-specific antibodies: additional notes. *Ann Rheum Dis*. 2019;78(5):e45.
26. Bundell C, Rojana-udomsart A, Mastaglia F, Hollingsworth P, McLean-Tooke A. Diagnostic performance of a commercial immunoblot assay for myositis antibody testing. *Pathology*. 2016;48(4):363-366.
27. Ronnelid J, Espinosa-Ortega F, Lundberg IE. Response to: 'Semi-quantitative analysis of line blot assay for myositis-specific and myositis-associated antibodies: a better performance?' by Cavazzana et al. *Ann Rheum Dis*. 2020;79(11):e153.
28. Damoiseaux J, von Mühlen CA, Garcia-De La Torre I, et al. International consensus on ANA patterns (ICAP): the bumpy road towards a consensus on reporting ANA results. *Auto Immun Highlights*. 2016;7(1):1.
29. Greco M, García de Yébenes MJ, Alarcón I, et al. Idiopathic inflammatory myopathies and antisynthetase syndrome: contribution of antisynthetase antibodies to improve current classification criteria. *Ann Rheum Dis*. 2019;78(9):1291-1292.
30. To F, Parker MJS, Ventín-Rodríguez C, Lilleker JB, Chinoy H. Including myositis-specific autoantibodies improves performance of the idiopathic inflammatory myopathies classification criteria. *Rheumatology (Oxford)*. 2019;58(12):2331-2333.
31. Watanabe K, Handa T, Tanizawa K, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. *Respir Med*. 2011;105(8):1238-1247.
32. Debray MP, Borie R, Revel MP, et al. Interstitial lung disease in antisynthetase syndrome: initial and follow-up CT findings. *Eur J Radiol*. 2015;84(3):516-523.

How to cite this article: Beaton TJ, Gillis D, Prain K, et al. Performance of myositis-specific antibodies detected on myositis line immunoassay to diagnose and sub-classify patients with suspected idiopathic inflammatory myopathy, a retrospective records-based review. *Int J Rheum Dis*. 2021;24:1167–1175. https://doi.org/10.1111/1756-185X.14174

Received: 7 April 2021 | Revised: 13 June 2021 | Accepted: 22 June 2021

DOI: 10.1111/1756-185X.14171

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

The implication of interferon-γ-producing immunocompetent cells for evaluating disease activity and severity in adult-onset Still's disease

Takanori Ichikawa | Yasuhiro Shimojima | Dai Kishida | Ken-ichi Ueno | Yoshiki Sekijima

Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan

Correspondence
Yasuhiro Shimojima, Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan.
Email: yshimoji@shinshu-u.ac.jp

Abstract

Objective: To investigate the relationship between interferon-γ (IFN-γ), IFN-γ-producing immunocompetent cells, their related cytokines, and the clinical features in adult-onset Still's disease (AOSD).

Methods: Twenty-five patients with AOSD before initiating treatment (acute AOSD), 9 patients after remission (remission AOSD), and 12 healthy controls (HC) were included. Circulating IFN-γ-producing CD4+ and CD8+ cells, natural killer (NK) cells, and IFN-γ production in NK cells were evaluated by flow cytometry. Serum levels of IFN-γ, interleukin (IL)-6, IL-12, IL-15, and IL-18 were also measured. The obtained results were statistically analyzed with clinical findings.

Results: Serum levels of IFN-γ, IL-6, IL-12, IL-18, intracellular expression of IFN-γ in CD4+, CD8+, and NK cells were significantly higher in acute AOSD than in HC. The proportion of NK cells was significantly lower in acute AOSD than in HC. Serum levels of IFN-γ and IFN-γ expression in CD4+ cells were significantly correlated with serum ferritin levels. The proportion of NK cells had a significant inverse correlation with serum IFN-γ levels. A lower proportion of NK cells was significantly noted in patients refractory to initial immunosuppressive treatment. In remission AOSD, serum levels of IL-6, IL-12, and IL-18 were significantly higher than in HC.

Conclusion: Increased serum levels of IFN-γ, increased expression of IFN-γ in CD4+ cells, and decreased NK cell proportion correlate with disease activity in AOSD. Moreover, a lower proportion of NK cells may be useful for predicting a refractory clinical course. Meanwhile, increased serum levels of IL-6, IL-12, and IL-18 may persist after clinical remission.

KEYWORDS

adult-onset Still's disease, CD4+ cells, interferon-γ, interleukin-12, interleukin-18, NK cells

1 | INTRODUCTION

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder with characteristic symptoms such as high fever, polyarthritis, evanescent rash, and increases in inflammatory laboratory parameters, including high serum ferritin levels. Considering the clinical course of AOSD, there is a concern that some patients may show resistance to initial immunosuppressive treatment, relapse, or life-threatening involvement. It is still difficult to determine the prognosis of patients with AOSD, although the candidates for prognostic disease factors have been suggested in some previous studies.[1,2] The pathogenic mechanism underlying AOSD development may be composed of diverse immunological interactions, including enhancing proinflammatory cytokine profiles, innate and adaptive immune systems. Notably, macrophage activation contributes to the occurrence of disease as a pathogenic hallmark in AOSD.[3] In the process of activating macrophages, interferon-γ (IFN-γ) is a crucial cytokine that is predominantly produced by natural killer (NK) cells and effector T cells.[4,5] Increase in serum levels of IFN-γ and frequency of IFN-γ-producing CD4+ cells (type 1 T helper [Th1] cells) were significantly found in AOSD.[6-8] In our recent investigation, increased expression of IFN-γ in NK cells was also significantly demonstrated in the acute phase of AOSD,[9] whereas a decreased frequency of NK cells was observed, similar to previous studies.[9-11] Accordingly, it was suggested that secreted IFN-γ and IFN-γ-producing immunocompetent cells might be implicated in developing the disease. However, it is still uncertain how these key mediators are relevant to clinical features and prognosis in AOSD.

In this study, we investigated how serum levels of IFN-γ and the kinetic profiles of IFN-γ-producing cells, including Th1 cells and NK cells, are related to the clinical features of AOSD. In addition, the participation of IL-12, IL-15, and IL-18, which play a role in IFN-γ production in both Th1 cells and NK cells,[12-15] was also evaluated.

TABLE 1 Clinical characteristics of patients with adult-onset Still's disease (N = 25)

Epidemiological findings	
Age, y, median [IQR]	51 [39–66]
Gender, M/F	6/19
Physical findings, n (%)	
Fever	25 (100)
Eruption	23 (92)
Sore throat/pharyngitis	19 (76)
Lymphadenopathy	12 (48)
Arthritis	22 (88)
Myalgia	18 (72)
Pleuritis	5 (20)
Pericarditis	1 (4)
Hepatomegaly	9 (36)
Splenomegaly	13 (52)
Clinical evaluation	
Pouchot's score, median [IQR]	6 [4–6]
Fulfilled MAS criteria, n (%)	7 (28)
Refractory course, n (%)	18 (72)
Laboratory findings, median [IQR]	
White blood cells, /μL	15 380 [10 600–19 080]
Neutrophils, /μL	13 396 [7935–17 668]
AST, U/L	60 [41–78]
ALT, U/L	51 [29–91]
C-reactive protein, mg/dL	9.66 [3.85–13.1]
ESR, mm/h	48 [31–96]
Ferritin, ng/mL	8191 [2863–11 080]

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ESR, erythrocyte sedimentation rate; IQR, interquartile range; MAS, macrophage activation syndrome.

2 | METHODS

2.1 | Patients and samples

Blood samples from 25 patients with AOSD before initiating immunosuppressive treatments (acute AOSD) and 12 healthy controls (HC) were included in this study. The diagnosis of AOSD was definitively made according to the criteria proposed by Yamaguchi et al.[16] in our hospital. The clinical findings in acute AOSD are shown in Table 1, in which the overall disease activity score (Pouchot's score)[17] and the complication of macrophage activation syndrome (MAS)[18,19] were also evaluated. These findings in Table 1 were obtained and evaluated as the baseline when blood samples were provided. Patients resistant to initial immunosuppressive treatment were defined as having a refractory course, which was determined by requiring additional treatment before tapering initial immunosuppressive agents: (1) increase in corticosteroid; (2) another immunosuppressant; (3) biologics; and/or (4) plasmapheresis. There were no significant differences in age and gender distribution between acute AOSD and HC (median age: 43.5 years; interquartile range [IQR] 40.8–60.0; 6 men and 6 women). Of the 25 patients, blood samples were provided from 9 patients who achieved remission with the Pouchot's score of 0 (remission AOSD) to evaluate the remission phase results. Blood samples were obtained at a median period of 18 months (IQR 10–28) after initiating immunosuppressive therapy. The maintenance therapies at the point of obtaining blood sample were as follows: prednisolone (PSL; n = 7), cyclosporine (n = 3), methotrexate (n = 3), and tocilizumab (n = 2). The local ethics committee in Shinshu University approved this study (the approval number: 601/4294). All participants provided informed consent.

2.2 | Flow cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples collected into ethylenediaminetetraacetic acid-coated tubes by gradient centrifugation with Ficoll-Hypaque

PLUS (GE Healthcare, Pittsburgh, PA, USA). CD4+ cells, NK cells, and intracellular IFN-γ expression in CD4+ cells or NK cells were determined by flow cytometric analysis. CD8+ cells and their IFN-γ expression were also evaluated. PBMCs were stimulated with 0.5 μg/mL of ionomycin, 0.04 μg/mL of phorbol myristate acetate (both from Sigma-Aldrich, St. Louis, MO, USA), and 2 μmol/L monensin (BD Bioscience, San Diego, CA, USA) at 37℃ for 4 hours. To detect CD4+ cells, CD8+ cells, or NK cells that were phenotypically defined as CD3−CD16+CD56+ cells, stimulated PBMCs were stained with phycoerythrin (PE)/Cy7 anti-CD4 (BioLegend, San Diego, CA, USA), fluorescein isothiocyanate (FITC)-conjugated anti-CD8 (Beckman Coulter, Brea, CA, USA), or Pacific blue-conjugated anti-CD3 (BioLegend) together with FITC-conjugated anti-CD16 (Beckman Coulter) and PE-conjugated anti-CD56 (Beckman Coulter). PBMCs stained with the above-mentioned cell-surface markers were permeabilized with Cytofix/Cytoperm (BD Bioscience) to determine intracellular IFN-γ expression. Permeabilized cells were subsequently stained with allophycocyanin-conjugated anti-IFN-γ (BioLegend) in NK cells or CD8+ cells, or FITC-conjugated anti-IFN-γ (Beckman Coulter) in CD4+ cells. Treated cells were acquired on a FACSCanto II flow cytometer (BD Bioscience), and the acquired data were analyzed using FlowJo version 7.6.5 software (Tree Star Inc, Ashland, OR, USA).

2.3 | Enzyme-linked immunosorbent assay (ELISA)

Serum samples were stored at −80℃ until ELISA was performed. Serum concentrations of IFN-γ, IL-6, IL-12 (R&D System, Minneapolis, MN, USA), IL-15 (Abcam, San Francisco, CA, USA), and IL-18 (Medical and Biological Laboratories, Nagoya, Japan) were assayed using commercially available ELISA kits.

2.4 | Statistical analysis

All data are presented as the median with IQR. *P* values of less than .05 were defined as statistically significant. The Mann-Whitney *U* test was used to compare 2 independent groups. In comparing the results of subsequent patients before and after treatment, the Wilcoxon signed ranked test was employed. A correlation coefficient test was performed to evaluate a significant relationship. All statistical analyses were performed using BellCurve for Excel (SSRI, Tokyo, Japan).

3 | RESULTS

3.1 | Clinical findings in patients with AOSD

The median Pouchot's score before initiating treatment was 6 (IQR 4–6) in acute AOSD (Table 1). Of the 25 patients, 7 (28%) fulfilled the criteria of MAS at baseline, and 18 (72%) were defined as having a refractory course (refractory patients). In the comparison of clinical and laboratory findings between refractory patients and those who did not have a refractory course (non-refractory patients), the number of white blood cells (WBC) was significantly higher in refractory patients than in non-refractory patients (P =.034), despite no other significant differences (Table 2). MAS ultimately developed in 11 refractory patients until they were defined as having a refractory course, whereas no MAS occurrence was newly shown in non-refractory patients except for 3 presenting with MAS at baseline. In the initial therapy, intravenous infusion of methylprednisolone (mPSL: 1 g daily for 3 days) was administered to 11 refractory patients, while non-refractory patients did not entirely require mPSL (P =.007). The initial dosage of oral PSL was significantly higher in refractory patients than in non-refractory patients (P =.001). Immunosuppressive agents were concomitantly initiated in 6 refractory patients, and not in non-refractory patients, resulting in no significant difference (P =.080). Of the 18 refractory patients, mPSL was additionally required in 16 (89%), and increase in the dosage of PSL was given in 7 (39%) (Table S1). Immunosuppressive agents, intravenous immunoglobulin, and plasma exchange were additionally administered for 11 (61%), 4 (22%), and 7 (39%), respectively. In remission AOSD, improved laboratory findings were significantly demonstrated as follows: WBC counts (7120/μL; IQR 6610–7560; P =.005), serum levels of C-reactive protein (0.03 mg/dL; IQR 0–0.04; P <.0001), and ferritin (71 ng/mL; IQR 54–83; P <.0001).

3.2 | Expression of IFN-γ-producing cells and serum IFN-γ in AOSD

The proportion of CD4+ cells was not significantly different between patients with AOSD and HC (Table 3). The proportion of CD4+IFN-γ+ cells was significantly higher in acute AOSD than in HC (P =.0002). In addition, the frequency and median fluorescence intensity (MFI) of IFN-γ in CD4+ cells were significantly higher in acute AOSD than in HC (P =.0002 and P <.0001, respectively) (Table 3, Figure 1A,B). The frequency and MFI of IFN-γ in CD8+ cells, as well as the proportion of CD8+IFN-γ+ cells, were significantly higher in acute AOSD than in HC (P =.0002, P =.0002, P =.041, respectively), whereas the proportion of CD8+ cells was significantly lower in acute AOSD than in HC (P =.003) (Table S2, Figure S1). The proportion of NK cells was significantly lower in acute AOSD than HC (P =.0026) (Table 3, Figure 1C), whereas the frequency and MFI of IFN-γ in NK cells were significantly higher in acute AOSD than in HC (P =.0001 and P <.0001, respectively) (Table 3, Figure 1D,E). Serum levels of IFN-γ were also significantly higher in acute AOSD than in HC (P <.0001). Meanwhile, there were no significant differences in these results between remission AOSD and HC.

In comparison with consecutive results of 9 patients before and after treatment, decreases in the proportion of CD4+IFN-γ+ cells, frequencies and MFI of IFN-γ expression in CD4+ cells and NK cells, serum levels of IFN-γ, and increase in the proportion of NK cells were significantly demonstrated (P <.05) (Figure 2). The frequency and MFI

TABLE 2 Comparison of clinical findings and initial treatment between refractory and non-refractory patients

	Refractory patients (N = 18)	Non-refractory patients (N = 7)	*P* values
Epidemiological findings			
Age, y, median [IQR]	54 [38–75]	43 [42–53]	.467
Gender, M/F	3/15	3/4	.194
Physical findings, n (%)			
Fever	18 (100)	7 (100)	.623
Eruption	16 (89)	7 (100)	.510
Sore throat/pharyngitis	15 (83)	4 (57)	.194
Lymphadenopathy	10 (56)	2 (29)	.223
Arthritis	17 (94)	6 (86)	.820
Myalgia	5 (28)	2 (29)	.663
Pleuritis	5 (28)	0 (0)	.161
Pericarditis	1 (6)	0 (0)	.720
Hepatomegaly	7 (39)	2 (29)	.501
Splenomegaly	11 (61)	2 (29)	.155
Clinical evaluation			
Pouchot's score, median [IQR]	5.5 [4–6]	6 [4–7]	.828
Fulfilled MAS criteria			
at baseline	4 (22)	3 (42)	.934
throughout the clinical course	11 (61)	3 (42)	.351
Laboratory findings, median [IQR]			
White blood cells, /μL	17 595 [11 430–25 390]	11 520 [8295–13 035]	.034
Neutrophils, /μL	15 182 [9433–23 078]	10 138 [6453–11 879]	.061
AST, U/L	65 [42–88]	54 [41–62]	.397
ALT, U/L	63 [34–99]	19 [14–57]	.090
C-reactive protein, mg/dL	9.74 [4.75–14.35]	8.51 [3.58–12.29]	.468
ESR, mm/h	48 [33–100]	48 [31–80]	.507
Ferritin, ng/mL	8293 [3846–17 757]	2863 [891–8548]	.090
Initial treatment			
mPSL, n (%)	11 (61)	0	.007
Oral PSL, mg/kg/d, median [IQR]	1.00 [0.90–1.02]	0.47 [0.38–0.68]	.001
Immunosuppressive agents, n (%)	6 (33)	0	.105
CsA	4 (22)	0	.242
TAC	1 (1.25)	0	.617
MTX	1 (1.25)	0	.617

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CsA, cyclosporin; ESR, erythrocyte sedimentation rate; IQR, interquartile range; MAS, macrophage activation syndrome; mPSL, intravenous infusion of methylprednisolone (1g daily for 3 d); MTX, methotrexate; PSL, prednisolone; TAC, tacrolimus.

of IFN-γ in CD8+ cells also significantly decreased after treatment (*P* =.027) (Figure S1). In remission AOSD, 7 refractory patients were included. Of the 7 refractory patients, decrease in the proportion of CD4+IFN-γ+ cells and increase in that of NK cells were shown in 6 after treatment, whereas neither the proportion of CD4+IFN-γ+ cells nor that of NK cells were significantly different from those before treatment (*P* =.062) (Figure S2). MFI of IFN-γ in CD4+ cells and NK cells significantly decreased after treatment (*P* =.018).

3.3 | Serum IL-6, IL-12, IL-15, and IL-18 expression, and their participation in AOSD

Serum levels of IL-6, IL-12, and IL-18 were significantly higher in acute and remission AOSD than in HC (Table 3). In comparisons between acute and remission AOSD, serum levels of IL-6 and IL-18 were significantly decreased (*P* =.008, *P* =.011, respectively), whereas those of IL-12 were not significantly different (*P* =.313). Serum levels of

TABLE 3 Phenotypes of lymphocytes and IFN-γ expression in patients with acute adult-onset Still's disease (AOSD), remission AOSD, and HC

	Acute AOSD	Remission AOSD	HC	*P* value	
	(n = 25)	(n = 9)	(n = 12)	Acute vs HC	Rem vs HC
In total lymphocytes					
% CD4+ cells	52.9 [38.9–57.4]	48.7 [36.4–61.5]	53.8 [38.9–58.6]	.990	.840
% CD4+IFN-γ+ cells	5.89 [2.63–11.86]	1.26 [0.68–2.28]	1.06 [0.47–1.72]	.0002	.693
% CD3- cells	45.0 [35.8–56.1]	39.8 [29.5–55.6]	41.9 [39.9–44.3]	.807	.531
% NK cells	8.42 [2.54–12.34]	10.75 [9.13–15.44]	14.28 [11.71–19.05]	.0026	.201
In CD4+ cells					
%IFN-γ	5.84 [2.41–9.17]	2.84 [1.95–5.25]	1.75 [0.55–2.68]	.0002	.174
In NK cells					
%IFN-γ	41.5 [32.2–73.7]	17.5 [12.2–18.5]	23.1 [18.5–28.8]	.0001	.077
In the serum					
IFN-γ (pg/mL)	15.41 [6.81–40.89]	4.16 [1.18–4.82]	1.12 [0.39–3.50]	<.0001	.254
IL-6 (pg/mL)	15.84 [7.58–181.3]	3.53 [2.19–12.38]	1.82 [1.29–2.36]	<.0001	.024
IL-12 (pg/mL)	1.55 [1.32–1.76]	1.34 [1.21–1.56]	0.59 [0.54–0.67]	<.0001	.0001
IL-15 (pg/mL)	6.97 [5.20–9.61]	5.20 [4.32–7.85]	5.20 [4.09–8.06]	.174	.971
IL-18 (pg/mL)	2271 [1798–2554]	98.5 [73.7–213.9]	71.6 [70.7–74.1]	<.0001	.006

Note: Data are presented as median with interquartile range.

Abbreviations: Acute, acute AOSD; HC, healthy controls; IFN-γ, interferon-γ; IL, interleukin; NK cells, natural killer cells; Rem, remission AOSD.

IL-15 were not significantly different in acute AOSD, remission AOSD, and HC. In the regression analyses with serum levels of IFN-γ, intracellular expression of IFN-γ in CD4+ and NK cells, and the proportion of CD4+IFN-γ+ and NK cells, serum levels of IL-12, IL-15, and IL-18 demonstrated no significant correlations (data not shown). Meanwhile, serum levels of IL-6 had a significant correlation with frequency of IFN-γ in CD4+ cells (P =.009) (Table S3).

3.4 | Relationship between IFN-γ-producing cells and clinical findings

We analyzed the statistical relationship between the experimental results and clinical findings shown in Table 1. Serum ferritin levels were significantly correlated with serum levels of IFN-γ, frequency, and MFI of IFN-γ in CD4+ cells (P =.026, P =.016, P =.035, respectively) (Figure 3A-C). Serum levels of IFN-γ had a significant reverse correlation with NK cells (P =.038) (Figure 3D). There were no other significant relationships between the experimental data and clinical findings.

Next, we compared the experimental data obtained between refractory and non-refractory patients. A lower proportion of NK cells was significantly demonstrated in refractory patients than in non-refractory patients (median 5.6%, IQR 2.4–10.9 vs. 14.1%, IQR 10.1–16.2; P =.025) (Figure 3E). Meanwhile, there were no significant differences between patients with and without MAS at baseline in the comparison of experimental data (data not shown).

4 | DISCUSSION

In this study, we focused on the participation of IFN-γ expression and IFN-γ-producing immunocompetent cells in the clinical features of AOSD. Some investigations previously demonstrated an increase in serum levels of IFN-γ in the acute phase of AOSD.[3,6,7,20] It was also assumed that IFN-γ might be implicated in the pathogenic mechanism underlying AOSD development as the promoter of macrophage and neutrophil activation.[3,21-23] However, the role of IFN-γ in evaluating the disease activity and prognosis of AOSD has not been evaluated thus far, whereas the correlation between disease activity markers and IFN-γ-induced chemokines was significantly demonstrated.[20] In our study, serum levels of IFN-γ were significantly correlated with ferritin, suggesting that serum levels of IFN-γ may be regarded as an indicator of disease activity because serum ferritin is a well-known biomarker for estimating disease activity and prognosis.[24-26]

Moreover, it has been known that macrophage activation leads to increased serum levels of ferritin in AOSD;[1,2,27] namely, IFN-γ expression may participate in disease activity by activating macrophages. Further, IFN-γ production in CD4+, CD8+, and NK cells was significantly increased in acute AOSD. Although a previous study reported the predominance of Th1 cells in the active phase of AOSD,[8] our investigation found that the intracellular expression of IFN-γ in CD4+ cells was significantly correlated with serum ferritin levels. The imbalance or implication of adaptive immunity in the pathogenesis of AOSD has been described to date.[2,3] The relationship between circulating effector T cells and disease activity has been described in previous investigations of AOSD.[8,28,29] The proportion

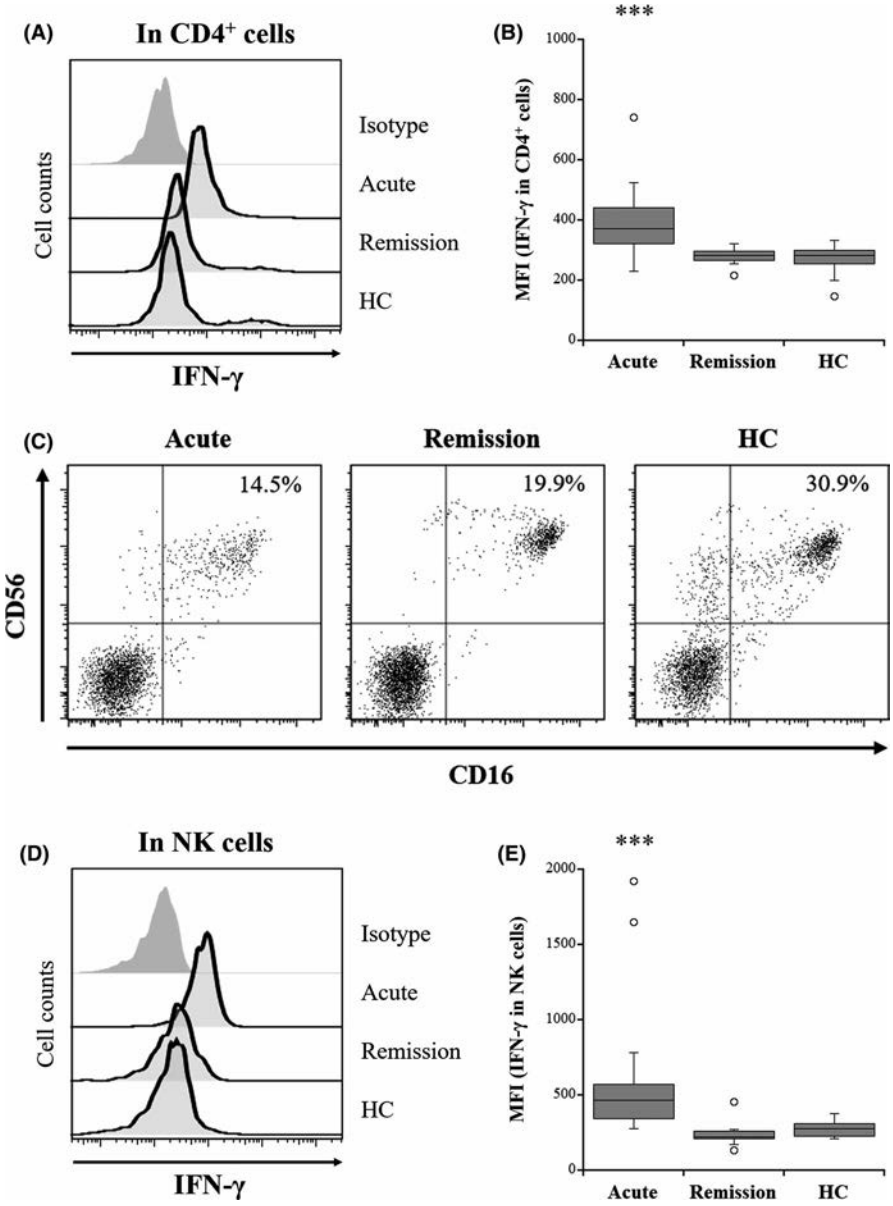


FIGURE 1 Comparisons of intracellular IFN-γ expression and NK cells. A, The representative histogram of IFN-γ expression in CD4+ cells. B, Comparison of MFI of IFN-γ in CD4+ cells. C, The representative dot-plots of CD16+CD56+ cells in the population of CD3− cells. D, The representative histogram of IFN-γ expression in NK cells. E, Comparison of MFI of IFN-γ in NK cells. Acute, acute adult-onset Still's disease (AOSD); Remission, remission AOSD; HC, healthy controls; IFN-γ, interferon-γ; MFI, median fluorescence intensity; NK cells, natural killer cells. ***P <.0001

of circulating IL-17-producing CD4+ (Th17) cells was found to be significantly correlated with serum ferritin levels in the acute phase of AOSD,[29] whereas our results first demonstrated a significant relationship between Th1 cells and serum ferritin levels, suggesting that the intracellular expression of IFN-γ in CD4+ cells is correlated with disease activity in AOSD. In our recent investigation, the production of IFN-γ, which is usually shown mainly in the $CD56^{bright}$ NK cell population in healthy individuals, was predominant in the $CD56^{dim}$ NK cell population in AOSD,[9] ultimately resulting in significantly increased IFN-γ in NK cells in acute AOSD. The percentage of $CD56^{dim}$ NK cell population is known to be around 90% in total circulating NK cells[14] despite not being significantly different between acute AOSD and healthy individuals,[9] allowing increased expression of IFN-γ in NK cells because a majority of the NK cell population can produce IFN-γ in AOSD. In addition, the proportion of circulating NK cells was significantly decreased in acute AOSD and inversely correlated with serum levels of IFN-γ. However, intracellular IFN-γ in NK cells was not correlated with serum ferritin levels or the proportion of NK cells (data not shown). Accordingly, IFN-γ produced in NK cells may not be a parameter that correlates with disease activity even though NK cells possess the ability to promote IFN-γ production in acute AOSD. Taken together, a decreased proportion of NK cells, increased serum levels of IFN-γ, and intracellular IFN-γ expression in CD4+ cells may be mediators that contribute to disease activity in AOSD.

Serum levels of IL-18 were found to be implicated in the disease activity,[2,3,30] and those of IL-12 were also increased in AOSD;[31] however, the participation of serum IL-15 has remained obscure in AOSD. Our study ultimately demonstrated that serum levels of IL-12 and IL-18 were significantly higher in AOSD than in HC, but those of IL-15 showed no significant difference. Although serum levels of these cytokines were not correlated with those of IFN-γ, intracellular IFN-γ expression, and the proportion of CD4+IFN-γ+ and NK cells, serum levels of IL-12 and IL-18 were significantly higher in remission AOSD than in HC. Moreover, this suggested that persistent

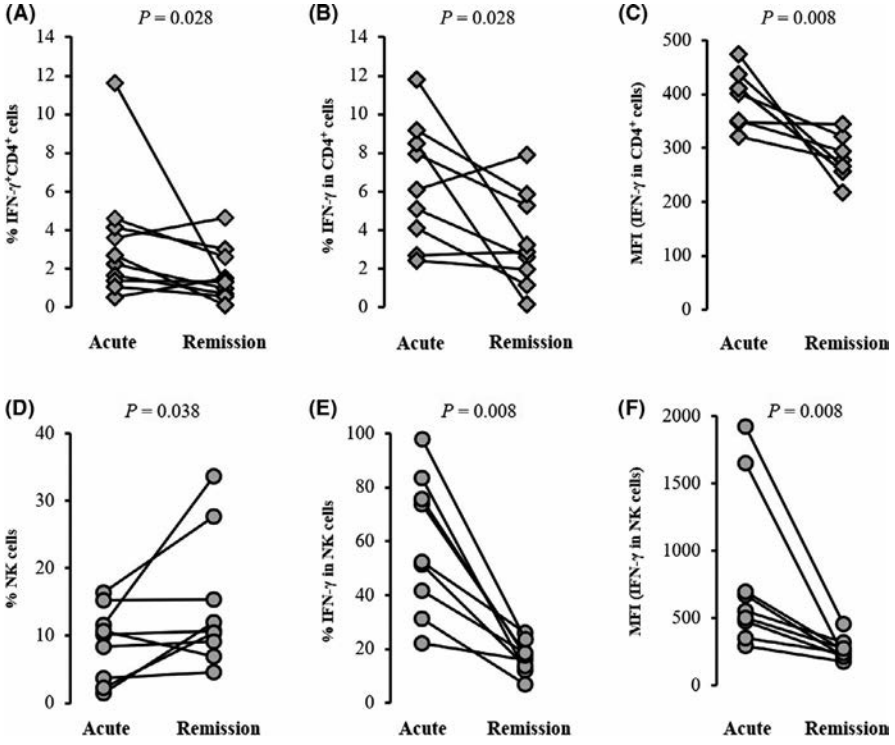


FIGURE 2 Alteration of IFN-γ and IFN-γ-producing cells before and after treatment. Acute, acute adult-onset Still's disease (AOSD); Remission, remission AOSD; HC, healthy controls; IFN-γ, interferon-γ; MFI, median fluorescence intensity; NK cells, natural killer cells

increased serum levels of IL-12 and IL-18 may be the cause of relapse, because IL-18 in combination with IL-12 upregulates IFN-γ-producing signals in CD4+ and NK cells.[13,32-34] Serum levels of IL-6, which were found to be associated with disease activity of AOSD,[1-3,35] were also significantly higher in acute and remission AOSD than in HC. It was previously shown that exposure to high concentrations of IL-6 might lead to suppressing NK cell cytotoxicity,[36] suggesting that IL-6 may partially affect NK cell activation in the pathogenesis of AOSD.

Refractory patients were classified in this study to determine the predictive factors of severity. The frequency of mPSL administration and PSL dosage was significantly higher in the initial treatment of refractory patients than in non-refractory patients, demonstrating insufficient therapeutic efficacy even in the more potent initial treatment. The previous cohort indicated that a high dose of PSL was usually required to achieve remission in AOSD,[37,38] even though there is a concern that the total dose of corticosteroid was ultimately accumulated in refractory patients.[37] Herein, a lower proportion of circulating NK cells was also significantly indicated in refractory patients. Namely, the frequency of circulating NK cells may be valuable for predicting the severity of AOSD. It has been shown that impaired function of NK cells may result in the inability to regulate the immune system, leading to the activation of lymphocytes and macrophages in systemic juvenile idiopathic arthritis (s-JIA) and AOSD.[10,11,39-41] Given our results and these immunological disorders, the induction of NK cells may regulate the pathological signaling underlying the development of AOSD. Further, the dysfunction of NK cells was found to be implicated in developing MAS, which affects the prognosis of s-JIA and AOSD.[40,42,43] The development of MAS was sequentially observed in refractory patients despite no occurrence of that in non-refractory patients after initiating treatment, suggesting that a lower proportion of NK cells at the onset of AOSD may also be predictive of MAS development. However, no significant differences were found between patients with and without MAS at the diagnosis of AOSD in the analyses of experimental results. It has been shown that multiple mediators are implicated in the development of MAS,[2,19,44] suggesting it may be insufficient to predict the occurrence of MAS only by estimating the expression of NK cells and/or IFN-γ.

In conclusion, serum levels of IFN-γ and intracellular expression of IFN-γ in CD4+, CD8+, and NK cells were significantly increased in acute AOSD. Notably, the expression of IFN-γ in the serum and CD4+ cells was significantly correlated with serum ferritin; meanwhile, a decreased proportion of NK cells was significantly correlated with serum IFN-γ levels, suggesting that IFN-γ and IFN-γ-producing immunocompetent cells are the parameters of disease activity. Furthermore, a lower proportion of NK cells may be a useful indicator for predicting an intractable clinical course. Further, there is a concern that sustained increases in serum IL-6, IL-12, and IL-18 levels, which were significantly higher in remission AOSD than in HC, may be responsible for relapse. On the other hand, precise machinery for NK cell reduction is still uncertain in AOSD. The generation of NK cells is dependent on response to internal or external pathogens, neoplasm antigens, and immunological signals in the host.[45,46] Some investigations suggested possible mechanisms leading to NK cell reduction, such as the implication of inhibitory receptors,[47] reduced expression of activating receptors,[48] or apoptosis mediated by induction of FcγR under IL-2 stimulation.[49] However, this study focused on the limited area of the immune system; thus, further investigations are required to clarify more precise indicators

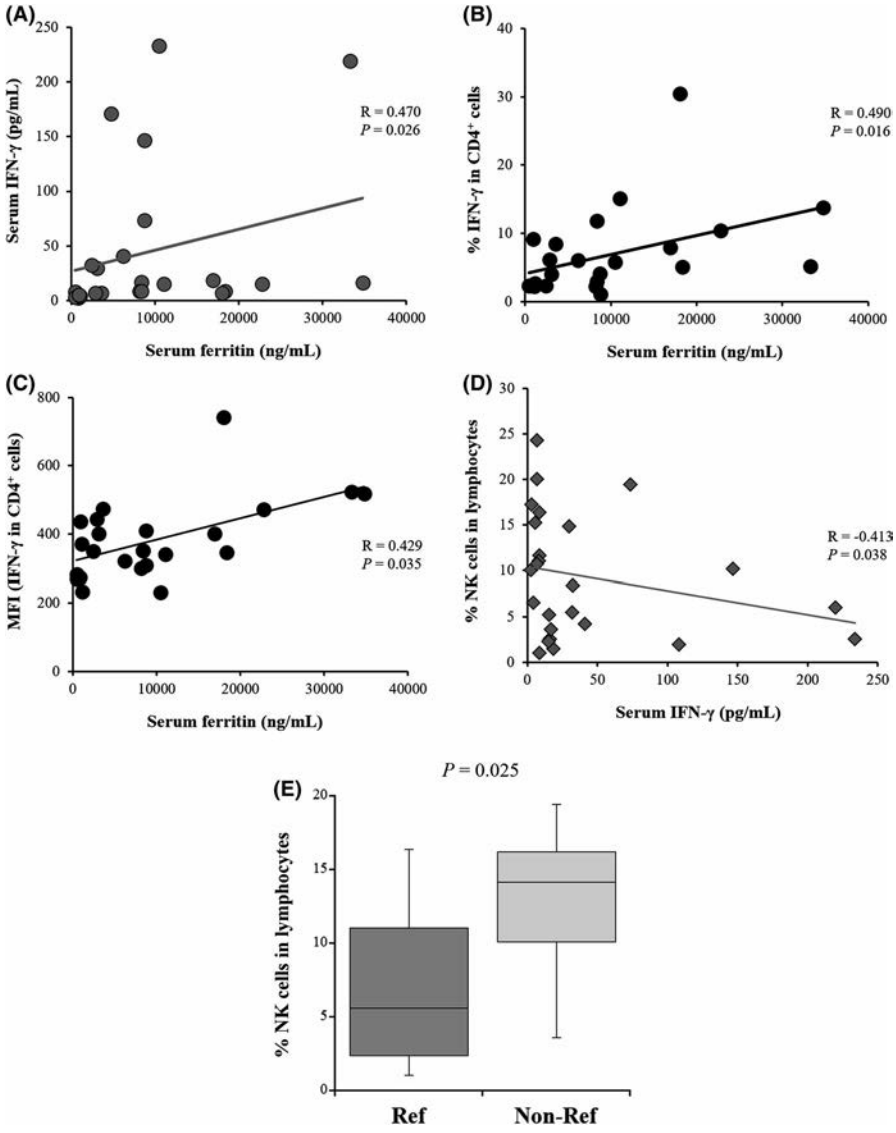


FIGURE 3 Regression analyses related to disease activity, and comparison between refractory and non-refractory patients. IFN-γ, interferon-γ; MFI, median fluorescence intensity; NK cells, natural killer cells; Ref, refractory patients; Non-Ref, non-refractory patients

of severity and prognosis in a wide range of immune mechanisms underlying AOSD.

ACKNOWLEDGEMENTS

We thank all members of the Department of Medicine (Neurology and Rheumatology), Shinshu University Hospital, for treating the patients. This study was supported by the Shinshu Public Utility Foundation for the Promotion of Medical Science, and a Health and Labor Sciences Research Grant on Rare and Intractable Diseases from the Ministry of Health, Labor and Welfare of Japan.

CONFLICTS OF INTEREST

The authors declare they have no financial or personal conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in the design of this study, developed the structure and argument for this study. Y-Shi, T-I, D-K, K-U recruited blood samples and clinical data. Y-Shi and T-I performed laboratory investigations, and analyzed obtained data. Y-Shi and T-I prepared the draft of this manuscript. Y-Shi and Y-Se contributed to revising the manuscript. All authors revised and approved of the final manuscript.

ORCID

Yasuhiro Shimojima https://orcid.org/0000-0001-7100-1121

REFERENCES

1. Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. *Nat Rev Rheumatol*. 2018;14:603-618.
2. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. *J Autoimmun*. 2018;93:24-36.
3. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still's disease. *Autoimmun Rev*. 2014;13:708-722.
4. Billiau A, Matthys P. Interferon-gamma: a historical perspective. *Cytokine Growth Factor Rev*. 2009;20:97-113.
5. Pollard KM, Cauvi DM, Toomey CB, Morris KV, Kono DH. Interferon-γ and systemic autoimmunity. *Discov Med*. 2013;16:123-131.
6. Hoshino T, Ohta A, Yang D, et al. Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease. *J Rheumatol*. 1998;25:396-398.

7. Choi JH, Suh CH, Lee YM, et al. Serum cytokine profiles in patients with adult onset Still's disease. *J Rheumatol*. 2003;30:2422-2427.
8. Chen DY, Lan JL, Lin FJ, Hsieh TY, Wen MC. Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease. *Ann Rheum Dis*. 2004;63:1300-1306.
9. Shimojima Y, Kishida D, Ueno KI, Ushiyama S, Ichikawa T, Sekijima Y. Characteristics of Circulating Natural Killer Cells and Their Interferon-γ Production in Active Adult-onset Still Disease. *J Rheumatol*. 2019;46:1268-1276.
10. Park JH, Kim HS, Lee JS, et al. Natural killer cell cytolytic function in Korean patients with adult-onset Still's disease. *J Rheumatol*. 2012;39:2000-2007.
11. Lee SJ, Cho YN, Kim TJ, et al. Natural killer T cell deficiency in active adult-onset Still's Disease: correlation of deficiency of natural killer T cells with dysfunction of natural killer cells. *Arthritis Rheum*. 2012;64:2868-2877.
12. Pawlak M, Ho AW, Kuchroo VK. Cytokines and transcription factors in the differentiation of CD4(+) T helper cell subsets and induction of tissue inflammation and autoimmunity. *Curr Opin Immunol*. 2020;67:57-67.
13. Kaplanski G. Interleukin-18: Biological properties and role in disease pathogenesis. *Immunol Rev*. 2018;281:138-153.
14. Berrien-Elliott MM, Wagner JA, Fehniger TA. Human Cytokine-Induced Memory-Like Natural Killer Cells. *J Innate Immun*. 2015;7:563-571.
15. Borger P, Kauffman HF, Postma DS, Esselink MT, Vellenga E. Interleukin-15 differentially enhances the expression of interferon-gamma and interleukin-4 in activated human (CD4+) T lymphocytes. *Immunology*. 1999;96:207-214.
16. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol*. 1992;19:424-430.
17. Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)*. 1991;70:118-136.
18. Ravelli A, Minoia F, Davi S, et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Arthritis Rheumatol*. 2016;68:566-576.
19. Ahn SS, Yoo BW, Jung SM, Lee SW, Park YB, Song JJ. Application of the 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome in Patients with Adult-onset Still Disease. *J Rheumatol*. 2017;44:996-1003.
20. Han JH, Suh CH, Jung JY, et al. Elevated circulating levels of the interferon-γ-induced chemokines are associated with disease activity and cutaneous manifestations in adult-onset Still's disease. *Sci Rep*. 2017;7:46652.
21. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features, predictive factors, and prognosis in 21 patients. *Medicine (Baltimore)*. 2015;94:e451.
22. Komiya A, Matsui T, Nogi S, et al. Neutrophil CD64 is upregulated in patients with active adult-onset Still's disease. *Scand J Rheumatol*. 2012;41:156-158.
23. Matsui K, Tsuchida T, Hiroishi K, et al. High serum level of macrophage-colony stimulating factor (M-CSF) in adult-onset Still's disease. *Rheumatology (Oxford)*. 1999;38:477-478.
24. Lee SW, Park YB, Song JS, Lee SK. The mid-range of the adjusted level of ferritin can predict the chronic course in patients with adult onset Still's disease. *J Rheumatol*. 2009;36:156-162.
25. Kong XD, Xu D, Zhang W, Zhao Y, Zeng X, Zhang F. Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. *Clin Rheumatol*. 2010;29:1015-1019.
26. Zeng T, Zou YQ, Wu MF, Yang CD. Clinical features and prognosis of adult-onset still's disease: 61 cases from China. *J Rheumatol*. 2009;36:1026-1031.
27. Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev*. 2007;6:457-463.
28. Jung JY, Choi B, Sayeed HM, et al. Characteristic patterns of HLA presentation and T cell differentiation in adult-onset Still's disease. *Int J Immunopathol Pharmacol*. 2018;32:2058738418791284.
29. Chen DY, Chen YM, Lan JL, Lin CC, Chen HH, Hsieh CW. Potential role of Th17 cells in the pathogenesis of adult-onset Still's disease. *Rheumatology (Oxford)*. 2010;49:2305-2312.
30. Colafrancesco S, Priori R, Alessandri C, et al. IL-18 Serum Level in Adult Onset Still's Disease: A Marker of Disease Activity. *Int J Inflam*. 2012;2012:156890.
31. Rau M, Schiller M, Krienke S, Heyder P, Lorenz H, Blank N. Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis. *J Rheumatol*. 2010;37:2369-2376.
32. Wawrocki S, Druszczynska M, Kowalewicz-Kulbat M, Rudnicka W. Interleukin 18 (IL-18) as a target for immune intervention. *Acta Biochim Pol*. 2016;63:59-63.
33. Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. *Front Immunol*. 2013;4:289.
34. Fehniger TA, Shah MH, Turner MJ, et al. Differential cytokine and chemokine gene expression by human NK cells following activation with IL-18 or IL-15 in combination with IL-12: implications for the innate immune response. *J Immunol*. 1999;162:4511-4520.
35. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. *J Rheumatol*. 2004;31:2189-2198.
36. Scheid C, Young R, McDermott R, Fitzsimmons L, Scarffe JH, Stern PL. Immune function of patients receiving recombinant human interleukin-6 (IL-6) in a phase I clinical study: induction of C-reactive protein and IgE and inhibition of natural killer and lymphokine-activated killer cell activity. *Cancer Immunol Immunother*. 1994;38:119-126.
37. Hu QY, Zeng T, Sun CY, et al. Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China. *Clin Exp Rheumatol*. 2019;37(Suppl 121):52-57.
38. Mimura T, Kondo Y, Ohta A, et al. Evidence-based clinical practice guideline for adult Still's disease. *Mod Rheumatol*. 2018;28:736-757.
39. de Jager W, Vastert SJ, Beekman JM, et al. Defective phosphorylation of interleukin-18 receptor beta causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;60:2782-2793.
40. Villanueva J, Lee S, Giannini EH, et al. Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. *Arthritis Res Ther*. 2005;7:R30-37.
41. Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: Comparison with systemic juvenile idiopathic arthritis. *Clin Immunol*. 2016;169:8-13.
42. Vandenhaute J, Wouters CH, Matthys P. Natural Killer Cells in Systemic Autoinflammatory Diseases: A Focus on Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome. *Front Immunol*. 2019;10:3089.
43. Yang XP, Wang M, Li TF, Li W, Zhang L, Liu SY. Predictive factors and prognosis of macrophage activation syndrome associated with adult-onset Still's disease. *Clin Exp Rheumatol*. 2019;37(Suppl 121):83-88.
44. Efthimiou P, Kadavath S, Mehta B. Life-threatening complications of adult-onset Still's disease. *Clin Rheumatol*. 2014;33:305-314.
45. Cooper MA, Yokoyama WM. Memory-like responses of natural killer cells. *Immunol Rev*. 2010;235:297-305.
46. O'Sullivan TE, Sun JC, Lanier LL. Natural Killer Cell Memory. *Immunity*. 2015;43:634-645.
47. Lanier LL. Up on the tightrope: natural killer cell activation and inhibition. *Nat Immunol*. 2008;9:495-502.

48. Zhou J, Tang X, Ding Y, An Y, Zhao X. Natural killer cell activity and frequency of killer cell immunoglobulin-like receptors in children with different forms of juvenile idiopathic arthritis. *Pediatr Allergy Immunol*. 2013;24:691-696.
49. Azzoni L, Anegon I, Calabretta B, Perussia B. Ligand binding to Fc gamma R induces c-myc-dependent apoptosis in IL-2-stimulated NK cells. *J Immunol*. 1995;154:491-499.

SUPPORTING INFORMATION

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

How to cite this article: Ichikawa T, Shimojima Y, Kishida D, Ueno K-I, Sekijima Y. The implication of interferon-γ-producing immunocompetent cells for evaluating disease activity and severity in adult-onset Still's disease. *Int J Rheum Dis*. 2021;24:1176–1185. https://doi.org/10.1111/1756-185X.14171

Received: 2 April 2021 | Revised: 6 June 2021 | Accepted: 14 June 2021

DOI: 10.1111/1756-185X.14172

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Prevalence and factors associated with low back pain in schoolchildren in Cameroon, sub-Saharan Africa

Fernando Kemta Lekpa[1,2,3] | Dominique Enyama[1,3,4] | Diomede Noukeu Njinkui[1,3,4] | Arielle Ngongang Chiedjio[2] | Sylvain Raoul Simeni Njonnou[1,3] | Christian Ngongang Ouankou[1,3,5] | Henry Namme Luma[2] | Simeon Pierre Choukem[1,2,3]

[1]Faculty of Medicine and Pharmaceutical Sciences, Department of Clinical Sciences, University of Dschang, Dschang, Cameroon

[2]Internal Medicine Department, Douala General Hospital, Douala, Cameroon

[3]Health and Human Development (2HD) Research Network, Douala, Cameroon

[4]Douala Gynaeco-obstetric and Pediatric Hospital, Douala, Cameroon

[5]Yaoundé University Teaching Hospital, Yaoundé, Cameroon

Correspondence
Fernando Kemta Lekpa, Faculty of Medicine and Pharmaceutical Sciences, Department of Internal Medicine and Specialties, University of Dschang. P.O. Box: 96 Dschang, Cameroon.
Email: fklekpa@yahoo.fr

Abstract

Background: Data on the prevalence and factors associated with low back pain (LBP) in schoolchildren are scarce in Africa, particularly in sub-Saharan Africa.

Objectives: To assess the prevalence and factors associated with LBP in schoolchildren in Cameroon.

Patients and methods: We performed a cross-sectional study in 10 randomly selected schools (public and private) in Douala, Cameroon. Using a self-administrated questionnaire, sociodemographic, usual physical activity, and clinical data were collected and all the schoolbags were weighted. Informed consent was obtained from the parents. Statistical significance was established at $P < .05$. Logistic regression was performed to identify factors associated with LBP.

Results: We included 1075 schoolchildren (543 boys, 50.5%). The prevalence of LBP was 12.3% (132 children: 81 girls and 51 boys). The mean age was 11 ± 1 years (range, 8-14 years). Body mass index was normal in 110 schoolchildren (83.4%). Sixteen schoolchildren had already met a physician for LBP. Among the factors evaluated, those associated with LBP were female gender, doing competitive sport, sitting position, and LBP in at least 1 parent. The mean weight of the schoolbags was 4.9 ± 1.9 kg. We had 99 children with LBP and a schoolbag weight ≥10% of their body weight. No association was found between the weight of schoolbag and LBP.

Conclusion: LBP is common in Cameroonian schoolchildren, where 12.3% suffer from it. The weight of schoolbags was not associated with LBP. However, female gender, competitive sport, sitting position, and parental history of LBP were significantly associated with its occurrence.

KEYWORDS

Cameroon, low back pain, prevalence, schoolbag, schoolchildren

1 | INTRODUCTION

Low back pain (LBP) is widely recognized as one of the most prevalent diseases of the musculoskeletal system and one of the most common causes of disability in developed countries.[1-3] LBP is generally considered to be a condition of adults and elderly people. It is also considered to be uncommon in children and adolescents and when it does occur at this age, it is thought to be of short duration. Recent data contradict this perception by showing that LBP may affect up to 37% of adolescents.[4] In addition, adolescents with persistent LBP during the previous year were 3.5 times more likely to have LBP in adulthood.[5]

Data are scarce in Africa, particularly in sub-Saharan Africa (SSA).[6-10] However, data on the prevalence of LBP in Africa negates any assumption that LBP prevalence is lower in the developing world than in developed countries.[6,7] The same is true for African children and adolescents where the mean LBP prevalence is around 11%.[6,7] Also, the factors associated with LBP in children and adolescents are age, female gender, trunk asymmetry, increased height, time spent watching television or using a computer, smoking, competitive sports, depression and emotional factors, history of spinal trauma, and family history of LBP.[3,7] Opinions differ on the role of schoolbags in the occurrence of LBP in schoolchildren.[8-21] Two systematic reviews agree there is no convincing evidence that certain aspects of schoolbag use increase the risk of LBP, subject to the methodological quality of the studies included in these reviews.[12,13]

To our knowledge, only 4 studies have been performed in SSA on back pain in children and adolescents.[8-11] These studies showed that back pain was common among school-age adolescents. They identified certain factors associated with back pain such as age, grade level, schoolbag weight, method of bag carriage, sitting position, prolonged sitting position, long duration of walking, presence of stairs at home, history of LBP and smoking in at least 1 parent and lumbar spine mobility.[8-11] No similar study has been conducted in Cameroon. Thus, we carried out this study intending to determine the prevalence of LBP in Cameroonian schoolchildren and to describe the associated factors. In contrast to previous studies that have assessed overall back pain, we deliberately chose to limit this study to LBP. Special attention will be paid to the relationship between LBP and schoolbag weight.

2 | PATIENTS AND METHODS

2.1 | Study design and sample

Between December 2015 and May 2016, we performed a survey of schoolchildren attending 10 public and private primary schools in the city of Douala in Cameroon. Douala is the economic capital of Cameroon with a cosmopolitan population with a catchment of 3 million inhabitants. The city of Douala is divided into 5 districts. From the list of registered primary schools obtained from the Cameroonian ministry of basic education, we randomly selected in each district 1 public school and 1 private school. Because of the absence of previous studies on LBP in children and adolescents in Cameroon and the varying numbers of schoolchildren in each class and school, particularly in public (≈76 per class) vs private school (≈30 per class), sampling was by convenience in each school by recruiting all schoolchildren in the selected classes. We chose schoolchildren in the upper primary category (classes 5 and 6) because we assumed they were most likely to provide reliable answers to the questions they would be asked.

2.2 | LBP assessment

This study was performed in accordance with the ethics of the Helsinki Declaration. It was approved by the local ethics committee (CEI--UD/291/12/2015/T). Informed and signed consent forms were obtained from parents. Schoolchildren were surveyed during free hours. In the absence of parents or guardians, schoolchildren completed a self-administrated, validated, and pretested questionnaire (Appendix 1) with the assistance of 1 of 2 trained interviewers for this survey.

We included in this study all schoolchildren with LBP defined as pain or discomfort in the area located between the lower margin of the 12th ribs to the lower gluteal folds with or without pain referred into 1 or both lower limbs that lasts for at least 1 day.[1] Prevalence estimates are based upon schoolchildren who reported experiencing LBP at least monthly for the last 3 months. The questionnaire assessed sociodemographic characteristics, anthropometric data, usual physical activity, self-reported by schoolchildren of personal and familial medical history (with a focus on the parental history of LBP), and location of LBP. Some suggested risk factors were screened, particularly the weight of schoolbags weighed during the screening. The weights of schoolchildren and schoolbags were measured with a mechanical calibrated scale. The weight of each schoolbag was compared with the weight of its owner. We have considered as normal of the schoolbag a weight <10% of the body weight of each child.[22] Regarding sitting position, schoolchildren had to choose among 4 figures representing different sitting positions in the classroom (Appendix 1).

2.3 | Data analysis

Data were analyzed using Epi Info 7.1.5 software (CDC). All variables that were significantly associated with LBP in bivariate analysis were included in a multiple logistic regression model to adjust the confounding effects. Statistical significance was established at $P < .05$.

3 | RESULTS

3.1 | Baseline characteristics of the study population

Among the 1137 schoolchildren surveyed, a total of 1075 were included (39 were absent and 23 refused to participate), giving a response rate of 94.5%. The gender ratio was 1.02 with boys (*n*

[%] = 543 [50.5%]) and girls (*n* [%] = 532 [49.5%]). Table 1 summarized the main characteristics of schoolchildren participating in this surveys, and those with LBP.

3.2 | Characteristics of schoolchildren with LBP

Among the schoolchildren surveyed, 132 (12.3%) reported having LBP monthly. There were more girls (*n* [%] = 81 [61.4%]) than boys (*n* [%] = 51 [38.6%]). The median age of these schoolchildren with LBP was 11 years (range, 8-14 years). The 10-12 years age group was the most affected by LBP, without any statistical difference with the other age groups. Schoolchildren with LBP aged 14 and over were exclusively male. Body mass index (BMI) was normal in 110 schoolchildren (83.4%) while 18 schoolchildren (13.6%) presented as overweight or obese. The course of LBP was more than 3 months in 120 of these schoolchildren (90.9%) (girls, *n* [%] = 73 [90.1%]; boys, *n* [%] = 47 [92.2%]).

Sixteen schoolchildren had already met a physician for LBP. Sick leave related to LBP was taken in the last 3 months by 2 schoolchildren. The main pain-relieving factors described by schoolchildren were physiotherapy (*n* [%] = 52 [39.4%]), supine position (*n* [%] = 36 [27.3%]), and painkillers (*n* [%] = 24 [18.2%]).

3.3 | Factors associated with LBP

We did not find any difference according to the BMI, the onset of LBP, the type of school attended (private or public), the educational level of the schoolchildren, the fact of being the oldest child of the family, the presence of stairs at home, and access to running and drinking water at home.

Factors associated with LBP in bivariate analysis were: age more than 10 years, female gender, history of LBP in at least 1 parent, practice of competitive sports, and bad sitting position on school benches (all $P < .05$). However, in multivariate analysis, only female gender (odds ratio [OR] = 1.73 [1.19-2.52]; $P = .004$), competitive sports (OR = 1.61 [1.03-2.53]; $P = .038$), parental history of LBP (OR = 3.01 [1.16-7.81]; $P = .024$), and bad sitting position (OR = 1.89 [1.07-3.33]; $P = .004$) were almost associated with LBP (Table 2).

TABLE 1 Baseline characteristics of schoolchildren experiencing low back pain

	Entire population (N = 1075)	Schoolchildren with low back pain (n = 132)	Schoolchildren without low back pain (n = 943)
	n (%)	n (%)	n (%)
Gender			
Male	543 (50.5)	51 (38.6)	492 (52.2)
Female	532 (49.5)	81 (61.4)	451 (47.8)
Body mass index, kg/m^2			
<18.5	24 (2.1)	4 (3.0)	20 (2.1)
18-25	928 (86.5)	110 (83.4)	818 (86.8)
>25	123 (11.4)	18 (13.6)	105 (11.1)
Oldest sibling	429 (39.9)	45 (34.1)	384 (65.9)
Type of school			
Public	640 (59.5)	53 (40.1)	587 (62.2)
Private	435 (40.5)	79 (59.9)	356 (37.8)
Educational level			
Grade 6	434 (40.4)	60 (45.4)	374 (39.7)
Grade 7	641 (59.6)	72 (54.6)	569 (60.3)
Parental history of low back pain			
No	580 (53.9)	44 (33.3)	536 (56.8)
At least 1 parent	495 (46.1)	88 (66.7)	407 (43.2)
House with stairs	313 (29.1)	45 (34.1)	268 (28.4)
Home water supply	774 (72.0)	90 (68.2)	684 (72.5)
Housework	978 (91.0)	119 (90.1)	859 (91.1)
Passive smoking	160 (14.9)	19 (14.4)	141 (15.0)
Physical incapacity	39 (3.6)	7 (5.3)	32 (3.4)
Competitive sports activity	191 (17.8)	102 (77.3)	89 (9.4)

TABLE 2 Factors associated with low back pain in schoolchildren

		Bivariate analysis			Multivariate analysis		
	n (%)	OR	95% CI	*P*	OR	95% CI	*P*
Age, y							
≤10	29 (21.9)	1 (ref.)	–	–	–	–	–
>10	103 (78.1)	1.15	1.07-1.28	.04	0.93	0.81-1.06	.25
Gender							
Boys	51 (38.4)	1 (ref.)	–	–	–	–	–
Girls	81 (61.6)	1.89	1.25-3.03	<.01	1.73	1.19-2.52	.004
Educational level							
Grade 6	60 (45.4)	1 (ref.)	–	–	–	–	–
Grade 7	72 (54.6)	0.94	0.83-1.05	.6	–	–	–
Oldest sibling							
Yes	45 (34.1)	0.88	0.76-1.02	.5	–	–	–
No	87 (65.9)	1 (ref.)	–	–	–	–	–
Type of house							
With stairs	49 (37.1)	1.17	0.95-1.37	.1	–	–	–
Without stairs	83 (62.9)	1 (ref.)	–	–	–	–	–
Body mass index, kg/m^2							
<18.5	4 (3.1)	1.92	0.78-2.21	.5	–	–	–
18.5-25	110 (83.3)	1 (ref.)	–	–	–	–	–
>25	18 (13.6)	0.83	0.67-1.12	.4			
Competitive sports							
No	102 (77.3)	1 (ref.)	–	–	–	–	–
Yes	30 (22.7)	2.28	1.25-3.28	<.001	1.61	1.03-2.53	.038
Parental low back pain							
No	44 (33.3)	1 (ref.)	–	–	–	–	–
Yes	88 (66.7)	4.99	1.64-8.19	<.001	3.01	1.16-7.81	.024
Weight of schoolbags							
≤10%	33 (25.0)	1 (ref.)	–	–	–	–	–
>10%	99 (75.0)	1.22	0.92-1.0	.09	–	–	–
Bad sitting posture							
No	64 (45.1)	2.33	1.04-4.51	.012	1.89	1.07-3.33	.004
Yes	69 (55.1)	1 (ref.)	–	–	–	–	–

Abbreviations: CI, confidence interval; OR, odds ratio; ref., reference.

3.4 | Relationship between schoolbags and LBP

The mean weight of schoolbags was 4.9 ± 1.9 kg. Of the 132 schoolchildren with LBP, 99 had schoolbags weighing ≥10% of their body weight. We did not find any relationship between LBP and the weight of the schoolbags, regardless of gender, BMI, duration of pain, type of school, distance from home to school, way of transportation from home to school, and age ($P > .05$).

4 | DISCUSSION

Almost 1 in 8 schoolchildren in Cameroon suffered from LBP at least monthly. LBP was more common in girls. Chronic LBP (pain that lasts over 3 months) was found in almost all children, with no difference based on gender. Surprisingly, only a minority of these schoolchildren had seen a physician for LBP. Only 2 children were absent from class because of LBP. This may reflect mild to moderate pain. In addition, to estimate the point prevalence of LBP in schoolchildren in our setting, our study showed that the factors significantly associated with LBP were female gender, competitive sports, family history of LBP, and bad sitting position in the classroom. Schoolbag weight was also not associated with LBP, whatever the different confounding factors evaluated.

The size of our sample is one of the main strengths of our study, although it could have gained statistical power with a larger sample. Moreover, it was performed in a cosmopolitan city in which inhabitants reflect baseline characteristics of SSAs ("Africa in miniature").

Also, interviewing schoolchildren in the absence of their parents would have led to a reduction in the potential influence that their parents could have on them by suggesting answers. However, our study has 5 main limitations. First, the uneven number of children per school led us to a convenience sample, rather than a representative sample in each school, randomly selected. This may limit the generalizability of the findings. However, our results are similar to those of previous studies.[13,15,18-20] Second, a clinical examination performed by a physician would have been ideal to provide a precise medical diagnosis for each schoolchild and provide greater qualitative data on the pain experience. It would have allowed us to find the other locations of the pain because somatic pain is very common in schoolchildren, more often coexisting than occurring in isolation.[4] Trained interviewers in this study made sure that the anatomical area shown by the schoolchildren matched the lumbar region. Thus, as pain is the main characteristic of LBP, this survey is sufficient to make accurate diagnoses of LBP.[1] Third, radiographic abnormalities were not also screened in this survey. However, the main radiographic abnormalities encountered in children are not correlated with clinical complaints from children.[12,15] Indeed, in a study performed on 3441 students aged from 9 to 15 years, lordosis and scoliosis did not correlate with LBP.[15] Fourth, we did not clearly appreciate the psychological aspects of the occurrence of LBP in children. This was indirectly assessed through social factors such as the means of travel to school, the performance of household and field work in the family, and the availability of water at home. However, we did not find a significant association between these factors and LBP. Thus, it would be interesting to carry out further studies to assess the clinical, radiological, and also psychological characteristics of LBP in children and adolescents in SSA. Fifth, it would have been interesting to follow these children in order to evaluate the evolution of their LBP into adulthood because persistent LBP in childhood would predispose to the occurrence of LBP in adulthood.[5,12,21] Indeed, a Danish twins study found adolescents with persistent LBP in the previous year had an OR of 3.5 for persistent LBP 8 years later.[5] However, we have not observed an increasing prevalence with age in our study as in a previous study.[15]

Furthermore, we have identified factors associated with LBP as previously described, including female gender, competitive sports, and parental history of LBP. Bad seating position on school benches is another factor identified in our study. This deserves to be evaluated in further studies. The schoolbag weight was not associated with LBP. The controversy is thus relaunched on the role of the schoolbag weight in the occurrence of LBP in schoolchildren. Indeed, the involvement of the schoolbag on LBP in schoolchildren is suggested in some studies,[8,9,11,16,17] but not found in several other studies.[13-15,18-20] Despite the methodological limitations of the studies included in the systematic reviews, we can cautiously state that schoolbag use does not appear to be a significant risk factor for LBP in schoolchildren.[13,14] The results concerning the way of schoolbag carrying (one-sided vs both shoulders) are also mitigated.[11,15,16,19] Carrying the schoolbag with 2 shoulders strap affects posture and gait less than carrying it on 1 shoulder.[21] Further, a change in the posture of the spine is observed as the schoolbag weight increases. However, the relationship with the development of scoliosis, lordosis or kyphosis, and schoolbag weight has not yet been demonstrated.[21] Then, to cause LBP, the schoolbag weight alone would not be sufficient but it would require the combination of some risk factors involved in the occurrence of LBP, including psychosocial factors.[3,8,9,12,20,21] Indeed, a systematic review found that the perception of heaviness or difficulty in carrying the schoolbag were associated with back pain and persistent symptoms.[14] Thus, it would be interesting to know through another study if reducing the weight of the schoolbag could have an impact on the occurrence of LBP, as suggested by some studies, even if it does not seem to be associated with LBP.[18,22]

Based on our data, and despite the limitations of the study, policymakers should consider LBP as a public health problem not only in adults, but also in children and adolescents.[6,7] Risk factors significantly associated with LBP,[3,12] especially those found in our study, should be integrated into the algorithms for the preventive and curative management of LBP. Emphasis should be placed on the proper attitudes for schoolchildren to adopt when sitting. Programs should be developed to teach children to sit up perfectly straight. Also, there is a need to standardize the type of classroom benches by choosing seats ergonomically designed. Based on our results and evidence from a systematic review,[13,14] no restrictions should be placed on schoolbag use. However, further studies with rigorous design should be carried out in order to appreciate aspects other than the weight of the schoolbag in schoolchildren, in particular the perception of heaviness[14] and the way of carrying the schoolbag.[11,15,16,19,21] Further, the implication of schoolchildren's age, height, bodyweight as well as the magnitude of scoliosis, kyphosis, and lordosis remains to be demonstrated.[3,15,17]

5 | CONCLUSION

LBP is common in school settings. It affects 12.3% of Cameroonian schoolchildren. Factors associated with LBP in this study were female gender, competitive sports, and parental history of LBP. The place of schoolbags remains unclear in the pathogenesis of LBP in schoolchildren. Our data add to existing evidence showing that schoolbag use does not increase the risk of LBP. Preventive measures must be taken early in childhood to prevent LBP in schoolchildren and its persistence into adulthood. Appropriate strategies must be adapted to the factors associated with LBP in schoolchildren. Our findings support the need for further research to improve the understanding of LBP in schoolchildren.

ACKNOWLEDGEMENTS

The authors are grateful to the schoolchildren and their families who participated in this survey as well as to the school staff.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Design and implementation of the research: FKL and ANC. Analysis of the results: FKL, DE, DNJ, ANC, SPC. Writing of the manuscript: FKL, DE, DNJ, ANC, SRSN, CON, FK, HNL, SPC. Manuscript revision for intellectual content: FKL, DE, DNJ, ANC, SRSN, CON, FK, HNL, SPC. All authors approved the final version of the manuscript.

ETHICS APPROVAL

This study was carried out following the ethical principles of the Helsinki Declaration. It was approved by the local ethics committee (CEI-UD/291/12/2015/T). Informed and signed consent forms were obtained from parents.

ORCID

Fernando Kemta Lekpa https://orcid.org/0000-0001-7592-5049

REFERENCES

1. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(6):968-974.
2. Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. *J Spinal Disord*. 2000;13(3):205-217.
3. Balagué F, Troussier B, Salminen JJ. Non-specific low back pain in children and adolescents: risk factors. *Eur Spine J*. 1999;8(6):429-438.
4. Swain MS, Henschke N, Kamper SJ, Gobina I, Ottová-Jordan V, Maher CG. An international survey of pain in adolescents. *BMC Public Health*. 2014;13(14):447.
5. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? a prospective study of a young population. *BMC Musculoskelet Disord*. 2006;16(7):29.
6. Louw QA, Morris LD, Grimmer-Somers K. The prevalence of low back pain in Africa: a systematic review. *BMC Musculoskelet Disord*. 2007;8:105.
7. Morris LD, Daniels KJ, Ganguli B, Louw QA. An update on the prevalence of low back pain in Africa: a systematic review and meta-analyses. *BMC Musculoskelet Disord*. 2018;19(1):196.
8. Houngbedji GM, Alagnide E, Niama D, Akpogan F, Kpadonou TG. The back pain in adolescents schooled in the town of Cotonou [Abstract]. *Ann Phys Rehabil Med*. 2016;59:e96. https://www.infona.pl//resource/bwmeta1.element.elsevier-9ef9586a-5609-3655-ac01-c92535bf0019
9. Ayanniyi O, Mbada CE, Muolokwu CA. Prevalence and profile of back pain in Nigerian adolescents. *Med Princ Pract Int J Kuwait Univ Health Sci Cent*. 2011;20(4):368-373.
10. Tiendrebeogo WJZ, Ouédraogo S, Yago ISE, et al. Low back pain among primary school children: prevalence and risk factors. a cross-sectional study in Ouagadougou (Burkina Faso). *J Rheumatol Res*. 2020;2(2):98-106.
11. Mwaka ES, Munabi IG, Buwembo W, Kukkiriza J, Ochieng J. Musculoskeletal pain and school bag use: a cross-sectional study among Ugandan pupils. *BMC Res Notes*. 2014;9(7):222. https://doi.org/10.1186/1756-0500-7-222
12. Roth-Isigkeit A, Schwarzenberger J, Baumeier W, Meier T, Lindig M, Schmucker P. Risk factors for back pain in children and adolescents. *Schmerz Berl Ger*. 2005;19(6):535-543.
13. Calvo-Muñoz I, Kovacs FM, Roqué M, Seco-Calvo J. The association between the weight of schoolbags and low back pain among schoolchildren: a systematic review, meta-analysis and individual patient data meta-analysis. *Eur J Pain Lond Engl*. 2020;24(1):91-109.
14. Yamato TP, Maher CG, Traeger AC, Wiliams CM, Kamper SJ. Do schoolbags cause back pain in children and adolescents? a systematic review. *Br J Sports Med*. 2018;52(19):1241-1245.
15. Korovessis P, Koureas G, Papazisis Z. Correlation between backpack weight and way of carrying, sagittal and frontal spinal curvatures, athletic activity, and dorsal and low back pain in schoolchildren and adolescents. *J Spinal Disord Tech*. 2004;17(1):33-40.
16. Skaggs DL, Early SD, D'Ambra P, Tolo VT, Kay RM. Back pain and backpacks in school children. *J Pediatr Orthop*. 2006;26(3):358-363.
17. Sheir-Neiss GI, Kruse RW, Rahman T, Jacobson LP, Pelli JA. The association of backpack use and back pain in adolescents. *Spine*. 2003;28(9):922-930.
18. Dianat I, Sorkhi N, Pourhossein A, Alipour A, Asghari-Jafarabadi M. Neck, shoulder and low back pain in secondary schoolchildren in relation to schoolbag carriage: should the recommended weight limits be gender-specific? *Appl Ergon*. 2014;45(3):437-442.
19. Assiri A, Mahfouz AA, Awadalla NJ, Abolyazid AY, Shalaby M. Back pain and schoolbags among adolescents in Abha City, Southwestern Saudi Arabia. *Int J Environ Res Public Health*. 2019;17(1):5.
20. van Gent C, Dols JJCM, de Rover CM, Hira Sing RA, de Vet HCW. The weight of schoolbags and the occurrence of neck, shoulder, and back pain in young adolescents. *Spine*. 2003;28(9):916-921.
21. Cottalorda J, Bourelle S, Gautheron V, Kohler R. Backpack and spinal disease: myth or reality? *Rev Chir Orthop Reparatrice Appar Mot*. 2004;90(3):207-214.
22. Dockrell S, Simms C, Blake C. Schoolbag weight limit: can it be defined? *J Sch Health*. 2013;83(5):368-377.

SUPPORTING INFORMATION

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

How to cite this article: Kemta Lekpa F, Enyama D, Noukeu Njinkui D, et al. Prevalence and factors associated with low back pain in schoolchildren in Cameroon, sub-Saharan Africa. *Int J Rheum Dis*. 2021;24:1186–1191. https://doi.org/10.1111/1756-185X.14172

Received: 26 March 2021 | Revised: 5 June 2021 | Accepted: 7 July 2021

DOI: 10.1111/1756-185X.14182

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

The relationship between common variants in the *DPEP1* gene and the susceptibility and clinical severity of osteoarthritis

Ziqi Zhang[1] | Yufeng Mei[2] | Min Feng[3] | Chunsheng Wang[1] | Pei Yang[1] | Run Tian[1]

[1]Department of Bone and Joint Surgery, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[2]Department of Rheumatology and Immune Joint Surgery, Honghui Hospital, Xi'an, China

[3]Department of Orthopedics, Shaanxi Provincial People's Hospital, Xi'an, China

Correspondence
Ziqi Zhang, Department of Bone and Joint Surgery, the Second Affiliated Hospital of Xi'an Jiaotong University, 257 Xiwu Road, Xi'an, 710004, China.
Email: ziqizhangdr@163.com

Funding information
Major Research Development Program of Shaanxi Province, Grant/Award Number: 2021SF-165

Abstract

Aim: Previous studies have provided evidence linking the *DPEP1* gene to the risk of osteoarthritis (OA) in Europeans. In this study, we aimed to examine the relationship between *DPEP1* gene and the susceptibility and clinical severity of OA in a Chinese Han population.

Methods: This study comprised two independent samples. For the discovery stage, 1022 patients with knee OA and 1864 controls were recruited. Fourteen tag single nucleotide polymorphisms (SNPs) covering the *DPEP1* gene were selected and genotyped. Associated SNPs in the discovery data set were subsequently genotyped in the replication data set consisting of 826 hip OA cases and 1662 controls. Both genotypic and allelic genetic associations were tested. The relationship of significant SNPs to the expression of *DPEP1* and its neighboring genes was examined using the GTEx database.

Results: A nonsynonymous SNP, rs1126464, was determined to be associated with the disease status of OA in both the discovery and replication stages (odds ratio [OR] 0.75, 95% confidence interval [95% CI] 0.68-0.82, $P = 7.16 \times 10^{-11}$). This SNP was further characterized as being significantly related to a higher Kellgren-Lawrence grade in OA patients (OR 0.64, 95% CI 0.55-0.74, $P = 2.53 \times 10^{-9}$). According to the GTEx data, SNP rs1126464 was significantly related to the gene expression of 15 genes in multiple types of human tissues.

Conclusion: We reported a common DNA variant in the *DPEP1* gene that contributes to the risk of OA, providing additional evidence that the *DPEP1* gene plays a significant role in the pathological mechanisms of OA.

KEYWORDS

case-control study, *DPEP1* gene, osteoarthritis, single nucleotide polymorphism

1 | INTRODUCTION

Osteoarthritis (OA) is the most common form of chronic joint degeneration and is characterized by destruction of articular cartilage and bone remodeling.[1,2] OA can occur in all joint tissues, primarily causing pain and disabilities in the knee, hip, and hand.[3] Affecting approximately 40% of elderly individuals aged over 70 years,[4] OA places high social and economic burdens on society. In the UK alone, there are more than 10 million OA patients, and the direct annual cost for treating this disease is approximately 14.8 billion GBP.[5] OA is co-regulated by environmental and genetic factors.[6] However, the genetic underpinnings of the susceptibility

to, development of, and therapeutic targets in OA remain to be elucidated.

As a protease that hydrolyzes a variety of dipeptides, dipeptidase 1 has been indicated to play a key role in the metabolism of glutathione and its conjugates in the kidney.[1] Dysregulation of dipeptidase 1 has been implicated in many diseases, including hypertension,[7] esophageal[8] and colorectal cancer,[9] as well as OA.[10] *DPEP1*, the gene encoding dipeptidase 1, is located on chromosome 16. Accumulating evidence indicates that the *DPEP1* gene plays an important role in the pathophysiology of OA. Expression of the *DPEP1* gene was found to be lower in OA samples than in non-OA samples in rodents by combining transcriptomics studies of murine OA models.[11] The single nucleotide polymorphism (SNP) rs1126464, a missense variant in the *DPEP1* gene, has been demonstrated to have a posterior probability of causality of 0.89 for OA through analyzing UK Biobank data.[1] To target *DPEP1*, cilastatin, an inhibitor of DPEP1, is approved for use in combination with imipenem (an antibiotic medicine for OA) to avoid the influence of dehydropeptidase and further extend its antibacterial effect.[12] Hence, the *DPEP1* gene has become a promising candidate target for treatment and prognosis prediction in OA. Further experimental evidence or causal roles of *DPEP1* in the susceptibility to and therapeutic effects in OA are required to obtain a comprehensive view. To date, it is not clear whether the same or similar association signals will be confirmed in non-European populations. For this reason, we performed the candidate gene association study to detect the correlation of *DPEP1* gene with the susceptibility and severity of OA in a Chinese Han population.

2 | MATERIALS AND METHODS

2.1 | Study participants

In the present study, we implemented a two-stage strategy. In the discovery stage, we recruited 1022 patients with knee OA and 1864 controls from the Second Affiliated Hospital of Xi'an Jiaotong University. Significantly associated SNPs identified in the discovery data set were subsequently genotyped in the validation stage, in which another independent sample consisting of 826 hip OA cases and 1662 controls was collected from the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an Honghui Hospital and Shaanxi Provincial People's Hospital (all in Xi'an city). The OA was diagnosed based on American College of Rheumatology guidelines. The Kellgren-Lawrence (KL) scores of OA patients included in the present study were more than 1. There were no signs or symptoms of joint disease in all OA cases. Those who suffered from abnormal bone development, inflammatory arthritis (regardless of the cause), and severe organic diseases were excluded. Additionally, to avoid potential population stratification in the study, study participants who had immigration history within three generations were not included in the present study. Demographic and clinical information was collected from study participants using a questionnaire. All participants signed informed consent forms, and the study proposal was approved by the ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University.

TABLE 1 Demographic and clinical characteristics of the study participants

	Discovery stage				Replication stage			
Variables	KOA cases (N = 1022)	Controls (N = 1864)	Statistics	*P* value	HOA cases (N = 826)	Controls (N = 1662)	Statistics	*P* value
Age, years	61.0 ± 7.1	61.2 ± 7.3	$t = -0.67$	0.50	61.9 ± 7.6	61.7 ± 7.5	$t = 0.77$	0.44
BMI, kg/m^2	26.0 ± 1.4	26.1 ± 1.5	$t = -1.73$	0.08	25.7 ± 1.5	25.6 ± 1.7	$t = 1.50$	0.13
Gender (%)								
Male	487 (48)	888 (48)	$\chi^2 = 0.00$	1.00	393 (48)	791 (48)	$\chi^2 = 0.00$	1.00
Female	535 (52)	976 (52)			433 (52)	871 (52)		
Smoking (%)								
Yes	240 (23)	435 (23)	$\chi^2 = 0.002$	0.97	168 (20)	340 (20)	$\chi^2 = 0.00$	0.99
No	782 (77)	1429 (77)			658 (80)	1322 (80)		
Alcohol (%)								
Yes	296 (29)	540 (29)	$\chi^2 = 0.00$	1.00	264 (32)	523 (31)	$\chi^2 = 0.04$	0.84
No	726 (71)	1324 (71)			562 (68)	1139 (69)		
KL (%)								
KL-2	374 (37)	–			289 (35)	–		
KL-3	334 (33)	–			280 (34)	–		
KL-4	314 (30)	–	–	–	257 (31)	–	–	–

Note: Age and BMI are presented as mean ± standard deviation.

Abbreviations: BMI, body mass index; KL, Kellgren and Lawrence classification system.

2.2 | SNP selection and genotyping

To capture the maximum information while minimizing the experimental cost, we have selected tag SNPs of the *DPEP1* gene region for genotyping. A total of 87 SNPs in *DPEP1* with minor allele frequency of at least 0.05 were extracted. Then we obtained tag SNPs from this candidate SNP set ($r^2 \geq 0.6$). Finally, an SNP set comprising 14 tag SNPs were selected and genotyped. Genetic information of these SNPs is summarized in Table S1. Genomic DNA was extracted from the peripheral blood samples collected from participants. Tiangen DNA extraction kits (TIANGEN Biotech (Beijing) Co.,Ltd., Beijing, China) were utilized and the experiments were performed based on the manufacturer's protocol. The Sequenom MassARRAY (Sequenom Inc., San Diego, CA, USA) platform was used for SNP genotyping. To control the experiment quality, technicians were blinded to the case-control labels.[13,14] In addition, 5% of the study samples were replicated for SNP genotyping. The genotype calls were successfully replicated for all of these samples.

2.3 | Statistical analysis

Power analyses were performed using the Genetic Association Study power calculator (https://csg.sph.umich.edu/abecasis/gas_power_calculator/). Parameters chosen for power analyses are summarized in Table S2. The sample size level of the present study could achieve more than 97% statistical power for detecting an SNP with effect size of 1.3 (Figure S1). Clinical and demographic characteristics were compared between OA cases and controls in both discovery and replication samples. For categorical variables χ^2 tests were performed. For continuous variables Student's *t* tests were performed. Tests for Hardy-Weinberg equilibrium were performed in samples of controls. The χ^2 tests were performed to compare the difference between observed and expected counts of genotypes. Genetic associations were tested between genotypes and disease status of the study participants. Genotypic and allelic analyses were implemented for each genotyped SNP to investigate the imbalanced distribution of genotypes and alleles in patients with OA and controls. In addition, haplotype-based association was also examined between haplotypes within linkage disequilibrium (LD) blocks and disease status. LD blocks were constructed based on data from the discovery stage. Furthermore, we have conducted association analysis between KL grade and SNPs significantly associated with OA status. This analysis enables us to investigate the connection between clinical severity of OA and relevant SNPs. In the discovery stage, to control multiple comparisons, Bonferroni correction was applied. We used 0.004 (0.05/14) as the threshold of *P* values for SNP genetic association analysis in the discovery stage. Plink was used for genetic association analyses.[15] LD structure was visualized using Haploview.[16] Locus zoom was used to construct regional association plots.[17]

2.4 | Bioinformatic analysis

To further investigate the functional consequences of the significant hits, two types of bioinformatic tools were used. We first examined the relationship of the significant SNPs and expression for *DPEP1* and its neighboring genes using the database of Genotype-Tissue Expression (GTEx).[18] In addition, for nonsynonymous variants, the bioinformatic tools Polyphen2[19] and SIFT[20] were subsequently used to predict the biological functions of the DNA variants on the protein encoded by *DPEP1*.

3 | RESULTS

3.1 | Demographic and clinical features of the study participants

A total of 1022 patients with knee OA and 1864 healthy controls were enrolled in the discovery stage. Another sample consisting of 826 patients with hip OA and 1662 healthy controls was recruited as a replication sample. No significant differences were identified for any of the demographic and clinical variables, including BMI, gender, age, smoking and alcohol habits, in the samples of both stages (Table 1 and Table S3).

3.2 | Genetic association between DPEP1 and risk of OA

All 14 genotyped SNPs in the discovery stage were in Hardy-Weinberg equilibrium (Table S1). In the discovery stage, only one nonsynonymous SNP, rs1126464, was determined to achieve significance in association with the risk of OA (Figure 1, Table S4). This SNP was subsequently genotyped and analyzed in the samples of the replication stage, and this association signal was still significant (Table 2). In general, the C allele of rs1126464 was found to be associated with the decreasing risk of OA (odds ratio [OR] 0.75, 95% confidence interval [95% CI] 0.68-0.82; Table 2). Patterns of dosage-dependent response were identified. The OR of the CC genotype versus GG was 0.5 (95% CI 0.40-0.62), and the OR of the CG genotype versus GG was 0.81 (95% CI 0.72-0.91) (Table 2). Four two-SNP LD blocks were constructed (Figure S2). Association analyses based on haplotypes were performed within each LD block (rs409170-rs117817715, rs78021403-rs258341, rs62068714-rs74966740, and rs908951-rs61217159). No significant haplotypes were identified within these LD blocks (Table S5).

3.3 | Association between SNP rs1126464 and clinical severity of OA

Similar to the results of genetic association, we also identified a significant signal between the clinical severity of OA and the genotypes of SNP rs1126464 (Table 3). The C allele of rs1126464 was

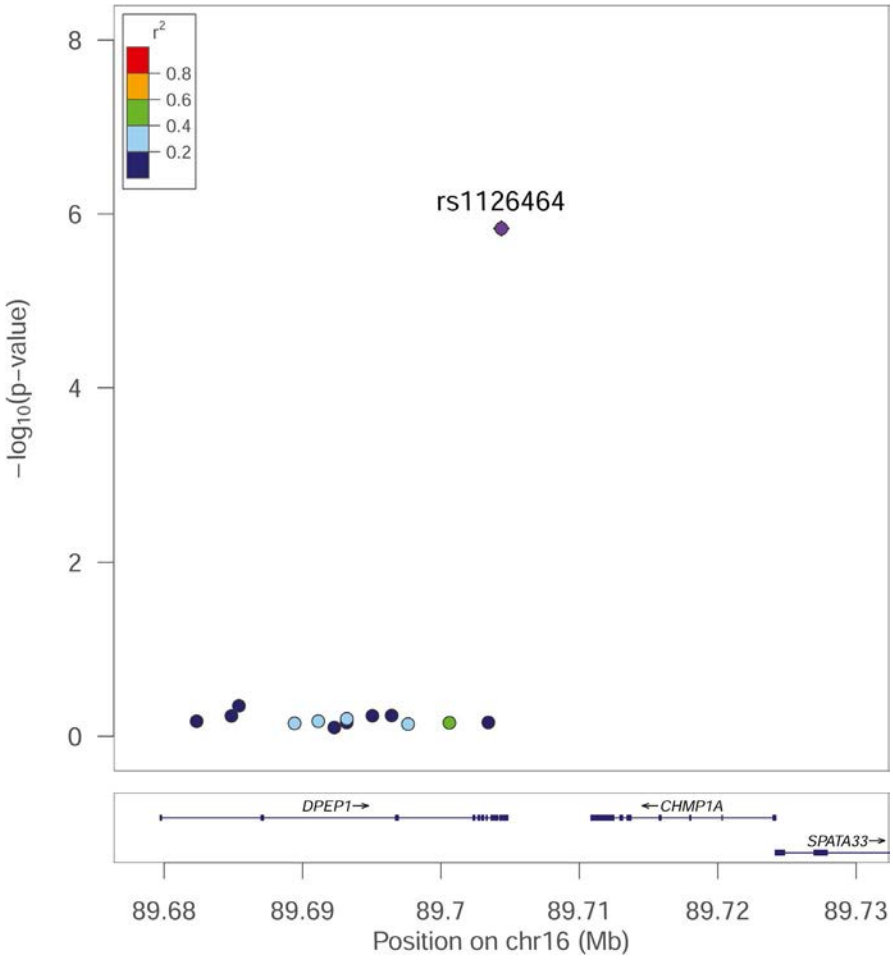


FIGURE 1 Regional association plots for the genetic association of genotyped single nucleotide polymorphisms with osteoarthritis (OA) susceptibility in the discovery data set

significantly correlated with a lower KL score (OR 0.64, 95% CI 0.55-0.74). A dose-dependent pattern could also be observed in the results of genotypic analyses. The OR value for genotypes CC versus GG was 0.39 (95% CI 0.27-0.57), and for genotypes CG versus GG was 0.62 (95% CI 0.51-0.76).

3.4 | Functional consequences of SNP rs1126464

Based on data obtained from the GTEx database, SNP rs1126464 was significantly associated with 15 genes in multiple human tissues. Notably, the *DPEP1* gene was not on this 15-gene list (Figure 2, Table S6). The SNP rs1126464 was not related to the gene expression level of *DPEP1* (Table S7). In addition, both Polyphen2 and SIFT showed that SNP rs1126464 had very limited functional consequences in variants of the protein encoded by *DPEP1* (Figure S3). Polyphen2 rated this SNP as "benign", and SIFT rated this SNP as "tolerated".

4 | DISCUSSION

In this study, we investigated the relationship between the risk of OA and genetic polymorphisms of gene *DPEP1* in a large sample from a Han Chinese population. We first replicated the significant hit, SNP rs1126464, identified based on meta-analysis using UK Biobank data. Our results indicated that the C allele of SNP rs1126464 was related to a decreased risk of OA, and the direction of effect was the same in a study performed by Tachmazidou et al[1] using UK Biobank data in which the G allele of rs1126464 was reported to be significantly associated with an increased prevalence of OA. The size of the effect for rs1126464 found in the present study was greater than that observed in the study based on UK Biobank data. As the UK Biobank data were primarily obtained from European populations, this divergence could be caused by the different structures of LD for the *DPEP1* gene region and minor allele frequency of SNP rs1126464 in different populations. In addition to replicating the results of a previous study, we went one step further by examining the relationship between genotypes of rs1126464 and the clinical severity of OA for cases. Our findings indicated that the C allele of rs1126464 was related to a lower KL grade. In other words, OA patients carrying the C allele generally had milder symptoms than G allele carriers. Given that it is difficult to draw solid conclusions only from SNP results,[21-25] this finding should be confirmed by more supportive evidence to facilitate the treatment of OA and guide personalized medicine for diagnosis and treatment of this disease in the future.

SNP rs1126464 is a missense variant and changes one amino acid in the protein encoded by *DEPE1*. Previous GWA studies have

TABLE 2 Genetic association between the single nucleotide polymorphism rs1126464 and disease status of osteoarthritis

	Genotypic analysis						Allelic analysis					
Stage	Genotypes	Cases	Controls	OR [95% CI]	χ^2	*P* value	Alleles	Cases	Controls	OR [95% CI]	χ^2	*P* value
Discovery stage	CC	69 (7)	216 (12)	0.50 [0.37-0.67]	24.34	5.17×10^{-6}					23.19	1.47×10^{-6}
	CG	417 (41)	809 (43)	0.81 [0.69-0.95]			C	555 (27)	1241 (33)	0.75 [0.66-0.84]		
	GG	536 (52)	839 (45)	—			G	1489 (73)	2487 (67)	—		
Replication stage	CC	55 (7)	191 (11)	0.50 [0.36-0.69]	20.3	3.90×10^{-5}					19.26	1.14×10^{-5}
	CG	339 (41)	725 (44)	0.81 [0.68-0.96]			C	449 (27)	1107 (33)	0.75 [0.66-0.85]		
	GG	432 (52)	746 (45)	—			G	1203 (73)	2217 (67)	—		
Combined set	CC	124 (7)	407 (12)	0.50 [0.40-0.62]	44.67	2.00×10^{-10}					42.48	7.16×10^{-11}
	CG	756 (41)	1534 (44)	0.81 [0.72-0.91]			C	1004 (27)	2348 (33)	0.75 [0.68-0.82]		
	GG	968 (52)	1585 (44)	—			G	2692 (73)	4704 (67)	—		

Note: Threshold of *P* values applied in discovery stage was 0.05/14 ≈ 0.004. Values are given as number (%) unless otherwise stated.

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 Genetic association between the single nucleotide polymorphism rs1126464 and severity of osteoarthritis

Genotypic analysis						Allelic analysis					
	Severity						Severity				
Genotypes	KL-3/4	KL-2	OR [95% CI]	χ^2	*P* value	Alleles	KL-3/4	KL-2	OR [95% CI]	χ^2	*P* value
CC	59 (5)	65 (10)	0.39 [0.27-0.57]								
CG	448 (38)	308 (46)	0.62 [0.51-0.76]			C	566 (24)	438 (33)	0.64 [0.55-0.74]		
GG	678 (57)	290 (44)	—	37.26	8.10×10^{-9}	G	1804 (76)	888 (67)	—	35.52	2.53×10^{-9}

Note: Values are given as number (%) unless otherwise stated.

Abbreviations: CI, confidence interval; OR, odds ratio.

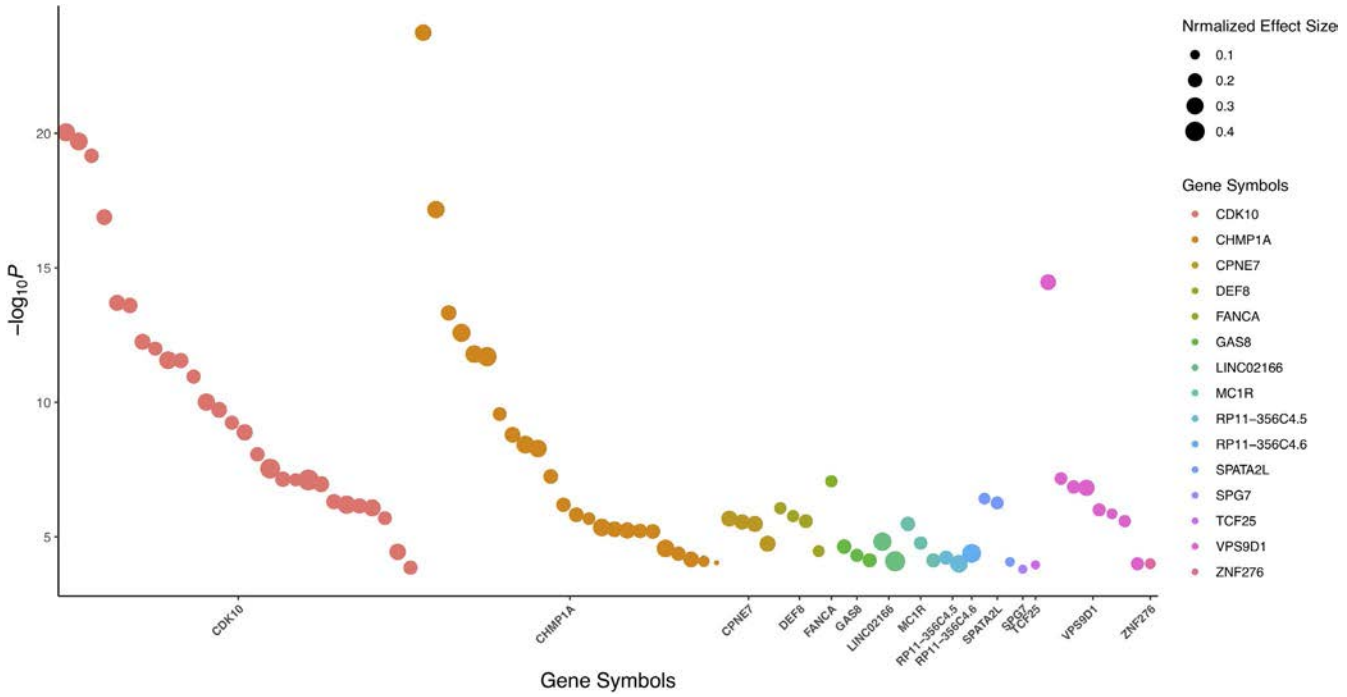


FIGURE 2 Significant association signals between single nucleotide polymorphism rs1126464 and gene expression level for 15 loci in multiple types of human tissues

linked SNP rs1126464 to multiple human traits and disorders including human height,[26] obesity-related traits,[27] blood pressure,[28] and hypertension.[7] Nevertheless, the results of bioinformatic analysis indicated that this change in one amino acid might have very limited functional significance in proteins. This DNA variant seems to be neutral for *DEPE1*, despite its location in the exonic region. On the other hand, data from the GTEx database also show no evidence that this SNP is an expression quantitative trait locus for gene *DEPE1*. Although a previous study mapped this SNP to *DEPE1* according to its physical position, it appears that this SNP could not be functionally mapped to this gene. Notably, GTEx data indicated that although SNP rs1126464 was not related to the gene expression of *DEPE1*, it was significantly associated with 15 surrounding genes. This finding strongly suggests that SNP rs1126464 could be functionally mapped to genes other than *DEPE1* and that these 15 genes could serve as candidate loci that contribute to the risk of OA. Nevertheless, it is necessary for us to be careful in presenting and interpreting the results based on publicly available databases. Although the GTEx project included 48 types of human tissues, the target tissue of OA, cartilage, was not included. Therefore, it is difficult for us to investigate the functional significance of this SNP to the pathological mechanisms of OA based solely on GTEx data. Studies on biological functions are still required to elucidate the pathological mechanisms governing the effect of SNP rs1126464 on the risk of OA.

Although it is beyond the scope of the present study, it is still necessary for us to briefly introduce the function of the candidate loci. Among the 15 genes to which SNP rs1126464 could be functionally mapped, three of them are of particular interest, including *CDK10* and *CHMP1A*. These two genes were significantly affected by SNP rs1126464 in a wide variety of human tissues. The *CDK10* gene encodes a type of cyclin-dependent kinase (CDK) that binds to cyclins to form active holoenzymes. This kinase was indicated to plays a significant role in the modulation of the eukaryotic cell cycle.[29] CHMP/Chmp family are comprised of proteins which formed components of a protein complex involved in the formation of endocytic multivesicular bodies and the degradation of surface receptor proteins.[30] The gene *CHMP1A* could encode a protein belonging to the CHMP/Chmp protein family. Both *CDK10* and *CHMP1A* have been reported to be related to several human diseases and traits, including melanoma,[31] height,[32] blood pressure,[7] sugar intake,[33] and cortical thickness.[34] However, to date, no evidence has connected these loci with OA and its related disorders. It would be informative if future studies could investigate the biological functions of both genes based on model animals.

A potential limitation of the present study is that in the discovery stage we have recruited individuals with knee OA in the discovery stage but patients with hip OA in the replication stage. Although some genes have been shown to be specific for OA, OA onset at different locations in general has a shared genetic basis.[35,36] More importantly, the study conducted with UK Biobank data identified SNP rs1126464 based on mixed OA patients, with OA at different sites. Hence, the influence of different types of OA in the discovery and replication stages might be limited. In addition, population stratification might have potential confounding effects on the results of genetic association. Unfortunately, as the present study only focused on two candidate genes and genotyped a small number of SNPs, it

is very difficult for us to implement some commonly used statistical methods (such as genomic control) to adjust for the population stratification. Nevertheless, during the present study's enrollment process, we limited our samples by excluding individuals with immigration history within three generations. This strategy would restrict the genetic heterogeneity of our study participants and therefore could, at least partly, control the population stratification.

5 | CONCLUSION

In the present study, a genetic polymorphism site physically mapped to the *DPEP1* gene was identified as being related to the risk of OA. This association signal was discovered and replicated in two independent samples from Chinese Han populations. In addition, the same SNP was correlated with the clinical severity of disease in OA patients.

ACKNOWLEDGEMENTS

This work was financially supported by the Major Research Development Program of Shaanxi Province (No. 2021SF-165). We would like to thank all participants for their support of this study and their cooperation in the collection of their peripheral blood samples and clinical information.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

ZZ conceived and designed the study, and carried out candidate SNP selection and statistical analyses. ZZ, YM, MF, CW, PY, and RT conducted participant screening. ZZ, YM, and MF contributed to the collection and preparation of DNA samples. ZZ wrote the paper.

ORCID

Ziqi Zhang https://orcid.org/0000-0003-1112-5231

REFERENCES

1. Tachmazidou I, Hatzikotoulas K, Southam L, et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat Genet*. 2019;51(2):230-236.
2. Reynard LN. Analysis of genetics and DNA methylation in osteoarthritis: what have we learnt about the disease? *Semin Cell Dev Biol*. 2017;62:57-66.
3. Aspden RM, Saunders FR. Osteoarthritis as an organ disease: from the cradle to the grave. *Eur Cells Mater*. 2019;37:74-87.
4. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196.
5. Hiligsmann M, Cooper C, Arden N, et al. Health economics in the field of osteoarthritis: an Expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheu*. 2013;43(3):303-313.
6. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol*. 2018;30(2):160-167.
7. Liu CY, Kraja AT, Smith JA, et al. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet*. 2016;48(10):1162-1170.
8. Wang JF, Xie X, Sun YR. Time series expression pattern of key genes reveals the molecular process of esophageal cancer. *Bioscience Rep*. 2020;40(2):BSR20191985.
9. Eisenach PA, Soeth E, Roder C, et al. Dipeptidase 1 (DPEP1) is a marker for the transition from low-grade to high-grade intraepithelial neoplasia and an adverse prognostic factor in colorectal cancer. *Brit J Cancer*. 2013;109(3):694-703.
10. Tuerlings M, van Hoolwerff M, Houtman E, et al. RNA sequencing reveals interacting key determinants of osteoarthritis acting in subchondral bone and articular cartilage: identification of IL11 and CHADL as attractive treatment targets. *Arthritis Rheumatol*. 2020;73(5):789-799.
11. Miller RE, Lu YZ, Tortorella MD, Malfait AM. Genetically engineered mouse models reveal the importance of proteases as osteoarthritis drug targets. *Curr Rheumatol Rep*. 2013;15(8):350.
12. Keynan S, Hooper NM, Felici A, Amicosante G, Turner AJ. The renal membrane dipeptidase (dehydropeptidase I) inhibitor, cilastatin, inhibits the bacterial metallo-beta-lactamase enzyme CphA. *Antimicrob Agents Chemother*. 1995;39(7):1629-1631.
13. Guan F, Zhang B, Yan T, et al. MIR137 gene and target gene CACNA1C of miR-137 contribute to schizophrenia susceptibility in Han Chinese. *Schizophr Res*. 2014;152:97-104.
14. Guan F, Zhang C, Wei S, et al. Association of PDE4B polymorphisms and schizophrenia in Northwestern Han Chinese. *Hum Genet*. 2012;131:1047-1056.
15. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*. 2015;4:7.
16. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005;21(2):263-265.
17. Pruim RJ, Welch RP, Sanna S, et al. LocusZoom: regional visualization of genome-wide association scan results. *Bioinformatics*. 2010;26(18):2336-2337.
18. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;7(4):248-249.
19. Vaser R, Adusumalli S, Leng SN, Sikic M, Ng PC. SIFT missense predictions for genomes. *Nat Protoc*. 2016;11(1):1-9.
20. Lonsdale J, Thomas J, Salvatore M, et al. The Genotype-Tissue Expression (GTEx) project. *Nat Genet*. 2013;45(6):580-585.
21. Guan F, Zhang T, Han W, et al. Relationship of SNAP25 variants with schizophrenia and antipsychotic-induced weight change in large-scale schizophrenia patients. *Schizophr Res*. 2020;215:250-255.
22. Zhang TX, Zhu L, Ni T, et al. Voltage-gated calcium channel activity and complex related genes and schizophrenia: a systematic investigation based on Han Chinese population. *J Psychiatr Res*. 2018;106:99-105.
23. Han W, Zhang TX, Ni T, et al. Relationship of common variants in CHRNA5 with early-onset schizophrenia and executive function. *Schizophr Res*. 2018;206:407-412.
24. Guan F, Ni T, Han W, et al. Evaluation of the relationships of the WBP1L gene with schizophrenia and the general psychopathology scale based on a case-control study. *Am J Med Genet B Neuropsychiatr Genet*. 2020;183:164-171.
25. Zhang B, Chang L, Lan X, et al. Genome-wide definition of selective sweeps reveals molecular evidence of trait-driven domestication among elite goat (Capra species) breeds for the production of dairy, cashmere, and meat. *Gigascience*. 2018;7(12):giy105.
26. Akiyama M, Ishigaki K, Sakaue S, et al. Characterizing rare and low-frequency height-associated variants in the Japanese population. *Nat Commun*. 2019;10(1):4393.

27. Zhu Z, Guo Y, Shi H, et al. Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank. *J Allergy Clin Immunol*. 2020;145(2):537-549.
28. Giri A, Hellwege JN, Keaton JM, et al. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet*. 2019;51(1):51-62.
29. Windpassinger C, Piard J, Bonnard C, et al. CDK10 mutations in humans and mice cause severe growth retardation, spine malformations, and developmental delays. *Am J Hum Genet*. 2017;101(3):391-403.
30. Tsang HTH, Connell JW, Brown SE, Thompson A, Reid E, Sanderson CM. A systematic analysis of human CHMP protein interactions: additional MIT domain-containing proteins bind to multiple components of the human ESCRT III complex. *Genomics*. 2006;88(3):333-346.
31. Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. *Nat Genet*. 2009;41(8):920-U85.
32. He MA, Xu M, Zhang B, et al. Meta-analysis of genome-wide association studies of adult height in East Asians identifies 17 novel loci. *Hum Mol Genet*. 2015;24(6):1791-800.
33. Hwang LD, Lin C, Gharahkhani P, et al. New insight into human sweet taste: a genome-wide association study of the perception and intake of sweet substances. *Am J Clin Nutr*. 2019;109(6):1724-1737.
34. van der Meer D, Frei O, Kaufmann T, et al. Understanding the genetic determinants of the brain with MOSTest. *Nat Commun*. 2020;11(1):3512.
35. Reynard LN, Barter MJ. Osteoarthritis year in review 2019: genetics, genomics and epigenetics. *Osteoarthr Cartilage*. 2020;28(3):275-84.
36. Reynard LN, Loughlin J. The genetics and functional analysis of primary osteoarthritis susceptibility. *Expert Rev Mol Med*. 2013;15:e2.

SUPPORTING INFORMATION

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

How to cite this article: Zhang Z, Mei Y, Feng M, Wang C, Yang P, Tian R. The relationship between common variants in the *DPEP1* gene and the susceptibility and clinical severity of osteoarthritis. *Int J Rheum Dis*. 2021;24:1192–1199. https://doi.org/10.1111/1756-185X.14182

Received: 26 April 2021 | Revised: 28 June 2021 | Accepted: 30 June 2021

DOI: 10.1111/1756-185X.14177

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial

Hazal Yakut[1] | Sevgi Özalevli[2] | Ridvan Aktan[3] | Aylin Özgen Alpaydın[4] | Ahmet Merih Birlik[5] | Gerçek Can[5]

[1]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Eskişehir Osmangazi University, Eskişehir, Turkey

[2]School of Physical Therapy and Rehabilitation, Dokuz Eylül University, Izmir, Turkey

[3]Department of Physiotherapy, Izmir University of Economics, Izmir, Turkey

[4]Department of Pulmonary disease, School of Medicine, Dokuz Eylül University, Izmir, Turkey

[5]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Dokuz Eylül University, Izmir, Turkey

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

Funding information
This research received a grant from the Dokuz Eylül University Scientific Research Projects (2019.KB.SAG.008) to obtain the portable digital spirometer (Pony FX; COSMED Inc.) and hand-held dynamometer (HHD, MicroFET2®; Hogan Health Industries, Inc.) used in the study.

Abstract

Aim: To compare the effects of supervised exercise and home exercise program in patients with systemic sclerosis (SSc).

Methods: Thirty-seven SSc patients were included. Patients with SSc were allocated into 2 groups as supervised and home exercise. Breathing, aerobic and resistance exercises were performed with a physiotherapist for 12 weeks in the supervised exercise group. Breathing, posture and aerobic exercises were given to the home exercise group as a home program for 12 weeks. All patients were assessed at baseline and 12 weeks later in terms of functional capacity, pulmonary functions, respiratory-peripheral muscle strength, dyspnea severity, health-related quality of life (HRQoL) and fatigue level.

Results: Significant improvements were observed in the functional capacity, measured by 6 minute walking test in the supervised exercise group (before = 376.21 ± 65.50, after = 518.78 ± 75.84 m) and home exercise group (before = 384.44 ± 68.14, after = 432.7 ± 70.8 m; ($P < .05$). Respiratory-peripheral muscle strength (with the exception of inspiratory muscle strength and upper limb strength in the home exercise group) and HRQoL were significantly increased and fatigue level was significantly decreased in the supervised exercise and home exercise groups ($P < .05$). However, pulmonary functions and dyspnea severity were significantly improved only in the supervised exercise group ($P < .05$). The supervised exercise program was found superior to the home exercise program for change in all parameters ($P < .05$).

Conclusion: This study suggests that exercise interventions should be applied in addition to the medical treatments of patients with SSc as supervised and home exercise programs play an important role in the functionality and health status of these patients.

KEYWORDS

dyspnea severity, exercise, health-related quality of life, pulmonary functions, systemic sclerosis

Clinical Trials Number: NCT04675502

1 | INTRODUCTION

Systemic sclerosis (SSc) is an uncommon chronic rheumatic disease that causes extensive microvascular damage, immune system activation and excessive collagen deposition in the skin and internal organs.[1] Raynaud's phenomenon and gastrointestinal involvement are the most common signs of disease besides skin fibrosis.[2] Cardiopulmonary involvement, 2 major complications of which are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), is the main cause of death from the disease.[3] Musculoskeletal damage in SSc occurs frequently with a prevalence of 24%-97% and is associated with significant widespread disability.[4] Due to all these involvements, patients with SSc have decreased muscle strength endurance and increased fatigue, rapid physical impairment (in terms of function, activity and participation) and a decrease in health-related quality of life (HRQoL).[5,6]

Non-pharmacological approaches including exercise programs have already shown improvement in pulmonary chronic diseases.[7] In addition, it has been stated that exercise programs can improve functional capacity and muscle function in rheumatic patients such as rheumatoid arthritis, inflammatory myositis and fibromyalgia.[8,9] However, the strength of evidence regarding the efficacy of exercise intervention in rehabilitation in SSc is restricted. Furthermore, despite the evidence of exercise, SSc patients may often avoid physical activity and exercise due to the anecdotal belief that exercise will exacerbate muscle inflammation or microvascular damage.[10] In fact, few studies have been conducted about the safety and effectiveness of exercise interventions in SSc.[11] However, there have been no studies investigating the role of a supervised exercise program consisting of breathing exercises, aerobic and resistance training in SSc.

Rehabilitation of SSc patients should be performed regularly and continuously at home as well as supervised programs in the hospital. However, home exercise programs are not very common in the rehabilitation treatment of SSc patients to date.[12-14] On the other hand, a few high-quality randomized controlled trials (RCT) of exercise practices in patients with SSc have been conducted. In these studies, the number of cases is low, the content of the exercise program given is unclear and patients included are generally with low disability level and no pulmonary involvement. To our knowledge, there is no study that has comprehensively evaluated and compared the effects of supervised exercise and home exercise programs in SSc patients. Thus, owing to lack of exercise recommendations for SSc patients, the aim of the present study is to compare the effects of a supervised exercise and home exercise program in patients with SSc.

2 | METHODS

2.1 | Participants

Thirty-seven patients who had a confirmed diagnosis of clinically definite SSc according to the American College of Rheumatology/European League Against Rheumatism[15] criteria by a rheumatologist, followed at a department of rheumatology between 2018 and 2021, participated in the study. This RCT was conducted at the outpatients' pulmonary rehabilitation clinic of Dokuz Eylül University Hospital.

2.1.1 | Inclusion criteria

The inclusion criteria were limited or diffuse SSc, being between the ages of 35-65 years, unchanged medication treatment for 3 months and volunteering to participate in the study.

2.1.2 | Exclusion criteria

Patients with SSc who had another neurological, musculoskeletal, visual, vestibular disorder, orthopedic surgery history involving spine and upper-lower limbs, using an assistive device for ambulation and inability to perform the test and exercise program, diagnosed with severe cognitive and/or psychiatric impairment, history of myositis and history of active tobacco use, were excluded.

The protocol for this RCT was approved by the Noninvasive Research Ethics Board of Dokuz Eylül University (Approval number: 2017/29-15) and was registered at ClinicalTrials.gov (NCT04675502). All participants were outpatients and gave their written informed consent to participate in the study before the recruitment started.

2.2 | Study design

This study was designed as a RCT. Patients were randomized by using a random numbers table with allocation stored in opaque sealed envelopes until completion of baseline assessment. A computer-generated list of random numbers was used and a randomization sequence was created by the Random Number Generator Pro v2.00 software (Segobit). Patients were randomized block design, into 2 groups, the supervised exercise group (SEG) or the home exercise group (HEG), by a single investigator blinded to patient identity (Figure 1). The researcher who was responsible for the randomization did not take part in data collection or data analysis. Measurements were done by unmasked assessors to the group allocation at baseline and immediately at the end of the exercise programs (ie, after 12 weeks).

2.3 | Intervention

In the light of the relevant literature, the exercise programs we created by examining the exercise programs applied especially to patients with rheumatic and respiratory diseases, and are described below.[16-18]

The SEG received the combined exercise training consisting of breathing, resistance and aerobic exercises under the supervision of

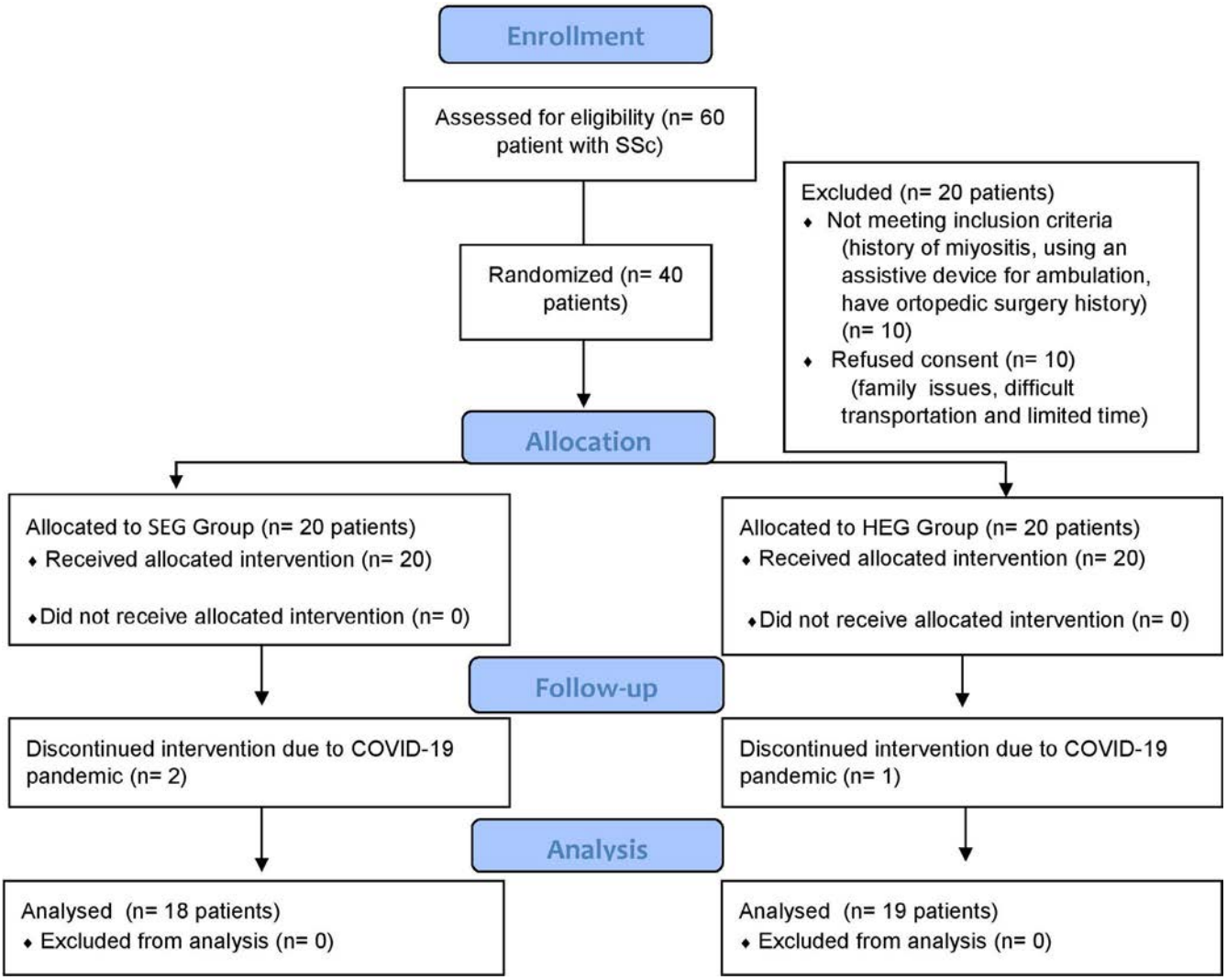


FIGURE 1 Flow diagram of the study

a physiotherapist twice per week for 12 weeks (in total 24 sessions). Each session lasted about 1 hour, with a warm-up session for the first 5 minutes and cool-down session for the last 5 minutes. Three to four repetitions, lasting 30 seconds of static active stretching and flexibility exercises for the large muscle groups of trunk and upper-lower extremities were performed as warm-up and cool-down exercises.

2.3.1 | Breathing exercises

Respiratory control was explained to the patients and "pursed-lip" breathing was shown. Thoracic expansion exercises and diaphragmatic breathing exercises were performed together with pursed-lip breathing. Also, at the end of inspiration, exercise of holding at maximum inspiration for 3 seconds was demonstrated to the patients. Breathing exercises were performed for 5-10 repetitions, 1 set and approximately 5-10 minutes.

2.3.2 | Resistance training

Resistance training included exercises for the main muscle groups: scapular adduction, bilateral shoulder flexion-hyperextension-abduction, knee extension, hip flexion, 4-way straight leg raises, squats, plunk, sit-ups. Body weight, free weights and elastic bands were used for resistance training exercises. One-Maximum Repetition (1 MT) method and modified Borg Rating of Perceived Exertion (RPE) Scale (0-10; 10 = maximum) were used to determine the intensity of the resistance training. Moderate/submaximal intensity resistance exercise training was performed at 50%-80% of 1 MT and 3-6 intensity according to RPE. Each exercise was performed with 8-12 repetitions/1 set and in about 15-20 minutes. Two minute rest periods were given between exercises. In SSc patients with PAH, especially the intensity of upper extremity training, was kept lower (40%-60% of 1 MT). Progression to greater resistance levels was implemented when the subject could perform 12 or more repetitions on the last training set for 2 consecutive workouts.

2.3.3 | Aerobic training

Aerobic training lasted approximately 30 minutes, including 20 minutes walking on the treadmill and 10 minutes pedaling on a bicycle ergometer. Heart rate reserve method and RPE were used to determine aerobic training intensity. Aerobic exercise training was performed at 40%-85% of heart rate reserve and 3-6 intensity according to RPE.

The patients in the HEG were instructed, in a session of about 1 hour, how to perform the exercise program at home by a physiotherapist. Then, they practiced the exercise program twice per week for 12 weeks at home. The HEG received the combined exercise training consisting of breathing and posture exercise and walking. The warm-up, cool-down and breathing exercises and their contents were the same with the SEG. Posture exercises consisting of bilateral shoulder flexion-abduction-circumduction, trunk rotation, knee extension and 4-way straight leg exercises were performed in 1 set of 8-12 repetitions. Then, they walked at a moderate/submaximal intensity (3-6 intensity according to RPE), at a constant speed for 20 minutes. RPE was explained to the patients for exercise intensity and added to exercise diaries. The patients were given a brochure containing the exercises in written and visual form and an exercise diary for exercise program follow-up. The patients were contacted by phone or email every 2 weeks and their exercise program was followed.

2.4 | Measurements

Demographic information (gender, age, body mass index), disease characteristics (disease duration, subtype of disease, comorbidities) and smoking history of all the patients were recorded. Then, primary and secondary outcomes were measured on the same day. The primary outcome was functional capacity measured by 6 minute walking test (6MWT). Secondary outcomes were pulmonary function, diffusion capacity, respiratory muscle strength, dyspnea severity, peripheral muscle strength, HRQoL and fatigue level. The patients were rested for 10 minutes between each assessment to prevent possible fatigue due to tests. Outcomes were assessed in the week prior to and the week following completion of the interventions.

2.4.1 | Functional capacity

The 6MWT was performed using the methodology specified by the American Thoracic Society (ATS) to determine the functional capacity. Heart rate, oxygen saturation and modified Borg scale assessing subjectively the degree of dyspnea and fatigue graded from 0 to 10, were collected at the beginning and at the end of the test. When the test was finished, total distance was recorded in meters. Each patient's predicted walking distance value was calculated by means of the equations formulated by Enrıght et al., as recommended by the ATS.[19]

2.4.2 | Pulmonary function and diffusion capacity

Pulmonary function test was measured with a portable digital spirometer (Pony FX; COSMED Inc.). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio and peak expiratory flow (PEF) were measured in accordance with the methods and criteria recommended by the ATS/European Respiratory Society (ERS).[20] All spirometric variables were expressed as a percentage of reference values.

Diffusion capacity of the lungs for carbon monoxide (DLCO) was measured with "single-breath holding method" technique with a rapid carbon monoxide and helium analyzer the HD CPL model computerized system (nSpire Health, Inc.) according to ATS/ERS standards.[21]

2.4.3 | Respiratory muscle strength

Respiratory muscle strength was measured with a portable digital spirometer (Pony FX; COSMED Inc.). Mouth pressure measurement, which is a noninvasive method, was used to evaluate respiratory muscle strength. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured as indicators of inspiratory and expiratory muscle strength, respectively, in accordance with the ATS/ERS. MIP was measured after a maximal expiratory maneuver (near residual volume), whereas MEP was measured after a maximal inspiratory maneuver (near total lung capacity).[22]

2.4.4 | Dyspnea severity

Modified Medical Research Council (mMRC) scale which consists of 5 statements that describe almost the entire range of dyspnea from none (Grade 0) to almost complete incapacity (Grade 4) was used to question the severity of dyspnea in the daily life activities of patients.[23]

2.4.5 | Peripheral muscle strength

To assess peripheral muscle strength, isometric knee extension strength and isometric handgrip strength were measured. Dominant side knee extensors (M. Quadriceps femoris) was evaluated with a hand-held dynamometer (HHD, MicroFET2®; Hogan Health Industries, Inc.) in kilograms. Patients were asked to continue the maximum isometric contraction for 5 seconds at the designated test position (in the seated position with 90° knee flexion, the lower leg on the ground). Dominant handgrip strength was evaluated with handgrip device (Jamar Hydraulic Hand Dynamometer) in a sitting position, shoulder adduction and neutral rotation, elbow 90° flexion, forearm mid rotation and support, wrist neutral. Peripheral muscle strength measurements were repeated 3 times, and the average of 3 measurement values was recorded.[24,25]

2.4.6 | HRQoL

Health Assessment Questionnaire Disability Index (HAQ-DI), Scleroderma Health Assessment Questionnaire (SHAQ) and Short Form-36 Quality of Life Questionnaire (SF-36) were used for HRQoL.

HAQ-DI evaluates disability, functionality and QoL in 8 functional areas of physical capacity. The SHAQ is created by adding the 5 SSc symptoms and signs to the HAQ-DI domain scores. High scores for both surveys indicate increased disability and worsening QoL.[26,27] SF-36, which measures the general HRQoL, consists of 36 questions grouped into 8 domains. A score ranging from 0 (the worst health status) to 100 (the best health status) is appointed for each domain. Domain scores can be summarized into a Physical Component Score (PCS) and Mental Component Score (MCS).[28]

2.4.7 | Fatigue level

Fatigue Impact Scale (FIS) was used for assessing fatigue level. It is a multi-dimensional 40-item questionnaire that collects information about the physical, cognitive and psychosocial dimensions of fatigue over the 4 weeks. High score indicates a high level of fatigue.[29]

2.5 | Statistical analysis

All data were analyzed using the program Statistical Package for Social Sciences (SPSS) Version 22.0 (SPSS Inc.). The normality of data and homogeneity of variance were examined via a Shapiro-Wilk test. Variables following normal distribution were summarized by mean and SD; the remaining variables were summarized as median (interquartile range [IQR]). Categorical variables were expressed as a percentage. Within and between-group differences were analyzed on a per-protocol basis. Comparison of variables across groups (SEG, HEG) was performed by using the Chi-squared test or Fisher's exact test for categorical variables, independent Student's *t* tests for parametric data and Mann-Whitney *U* tests for nonparametric data. Paired *t* test was used for normally distributed data and Wilcoxon rank-sum test was used for data that did not show normal distribution in the comparison of variables in the same group. Significance for the outcomes were set at a *P* value <.05.

The sample size was calculated based on an effect size of 0.98 to detect a difference of 54 m (standard deviation of 55 m)[19] on the 6MWT between the groups,[30] with a .05 α value and 85% power, using the G*Power program.[31] Thus, the minimum sample size required to detect a significant difference should be at least a total of 40 subjects (with 16 subjects in each group +4 subjects per group, considering dropouts).

3 | RESULTS

3.1 | Participants

Sixty patients with SSc were contacted from May 2018 to January 2021. Ten patients were not included in the study because they did not meet the inclusion criteria. Moreover, 10 patients declined to participate in the study due to reasons such as family issues, difficult transportation, and limited time. The 40 patients who satisfied the inclusion criteria where randomized and equally divided into the SEG (n = 20) and HEG (n = 20) groups. Two patients in SEG and 1 patient in HEG did not complete the study due to the COVID-19 pandemic. Finally, the data of 37 patients who completed the study were analyzed. Flowchart of the study is presented in Figure 1. The supervised exercise program and home exercise program were well-tolerated and no adverse or harmful events occurred during the study.

The demographic and clinic features of patients are given in Table 1, and there was no significant difference between groups ($P > .05$). There was no significant difference between SEG and HEG for the baseline pulmonary functions, diffusion capacity, respiratory muscle strength, dyspnea severity, functional capacity, peripheral muscle strength, HRQoL and fatigue level ($P > .05$, Table 2).

3.2 | Effects of exercise programs

Comparisons of changes from baseline to 12 weeks in the study outcomes across the study groups are presented in Tables 3 and 4.

After 12 weeks, within-group changes showed that 6MWT walking distance (m and %pred), FEV_1 %, FVC %, PEF %, DLCO %, MIP %, MEP %, knee extensor and handgrip strength significantly increased and mMRC score decreased in SEG ($P < .05$). On the other hand, 6MWT walking distance (m and %pred), MEP %, and knee extensor strength increased in HEG ($P < .05$), while FEV_1 %, FVC %, PEF %, DLCO %, MIP %, mMRC score and handgrip strength did not change ($P > .05$). There was a significant difference between the groups in favor of SEG in changes from baseline to 12 weeks in functional capacity, pulmonary function test parameters, diffusion capacity, respiratory muscle strength, dyspnea severity and peripheral muscle strength ($P < .05$) (Table 3). In addition, in terms of parameters such as heart rate, oxygen saturation, severity of dyspnea and fatigue level measured before and after 6MWT, there was a significant decrease in the severity of dyspnea and fatigue level after the test in the SEG ($P < .05$), while no change was observed in any parameter in the HEG ($P > .05$; these data are not presented in the tables).

Significant improvements were observed in the HAQ-DI score in the SEG and HEG ($P < .05$). The SEG had significantly decreased scores in all SHAQ subparameter scores ($P < .05$). Significant decreases were observed in the gastrointestinal problems, pulmonary problems, the severity of the overall disease and global assessment subparameter scores of the SHAQ ($P < .05$), while no significant changes were observed in the Raynaud's phenomenon and digital ulcers subparameter scores in the HEG ($P > .05$). SF-36 PCS and SF-36 MCS revealed significant increase in both groups ($P < .05$). Fatigue total score, physical, cognitive and psychosocial dimensions of fatigue scores were decreased in the SEG and HEG ($P < .05$). HRQoL and fatigue level changes were significantly greater in the SEG compared to HEG ($P < .001$) (Table 4).

TABLE 1 Demographic and clinical parameters of groups before the intervention

	Supervised exercise group	Home exercise group	*P*
Gender, female/male (%)	16 (84)/3 (16)	15 (83)/3 (17)	.942[a]
Age, y	51.21 ± 11.46	49.55 ± 8.14	.618[b]
Height, cm	161.36 ± 7.51	163.00 ± 7.54	.514[b]
Weight, kg	66.16 ± 11.59	75.05 ± 17.42	.175[b]
BMI, kg/m^2	24.85 ± 3.20	26.31 ± 5.59	.207[b]
Cigarette consumption, pack-y	10.00 (8.0-19.0)	12.00 (9.0-21.0)	.867[c]
Cigarette cessation, y	9.23 ± 2.24	10.42 ± 1.48	.446[b]
Disease duration, y	9.71 ± 4.93	8.61 ± 5.94	.249[b]
mRSS	9.30 (3.0-20.0)	9.10 (3.0-19.0)	.681[c]
Type of disease			
Limited SSc	15 (79)	16 (89)	.660[a]
Diffuse SSc	4 (21)	2 (11)	
Comorbidities, n (%)			
Pulmonary arterial hypertension	10 (53)	11 (61)	.666[a]
Interstitial lung disease	4 (21)	2 (11)	.660[a]
Arthralgia	10 (53)	8 (44)	.746[a]
Digital ulcers	5 (26)	3 (17)	.693[a]
Raynaud's phenomenon	17 (90)	15 (83)	.660[a]
Others, heart failure, diabetes, hypertension	5 (26)	4 (22)	.543[a]

Note: Data are expressed as mean ± SD, median (interquartile range) or n (%).

Abbreviations: BMI, body mass index; mRSS, modified Rodnan Skin Score; SSc, systemic sclerosis.

[a]Chi-squared test or Fisher's exact test.

[b]Independent Student's *t* tests.

[c]Mann-Whitney *U* tests.

4 | DISCUSSION

4.1 | Summary of results

Our study showed that a 12-week supervised exercise program and home exercise program were effective in SSc patients. Importantly, the supervised exercise program was superior to the home exercise program in improving functional capacity, pulmonary functions, respiratory muscle strength, dyspnea severity, peripheral muscle strength, HRQoL and fatigue level.

4.2 | Functional capacity

In our study, 6MWT walking distance and expected value percentage increased in both groups after exercise programs. Similarly, Oliveira et al.[10] reported a significant improvement in functional capacity in a group of 7 patients after an 8-week intensive aerobic exercise program of 40 minutes per session twice a week. In the study by Pinto et al.[32] similar results were obtained in 12 patients with SSc after a 12-week supervised exercise program consisting of aerobic and strengthening exercises. Contrary to the results of these studies, Alexanderson et al.[33] reported that 6MWT walking distance did not change after 8 weeks exercise program that included muscle endurance training and aerobic exercises. These differences in results may be due to differences in the type, duration and intensity of exercise training, tests used in measurements, and especially in the proportion of SSc patients with pulmonary involvement and high disability.

A change in 6MWT distance between 25 and 54 m in chronic obstructive pulmonary disease patients and 31 meters in ILD patients is considered to be of minimal clinical significance (MID).[19,34] In our study, the change in walking distance in both groups was greater than the minimal clinical significance value indicated in respiratory diseases with obstructive and restrictive patterns. Also, difference between the 2 groups of 94 m was similar to the MID reported for other diseases. These results showed that a supervised exercise program and home exercise program can improve exercise capacity in SSc patients, but that supervised exercise programs were more effective. Improvements were observed in the severity of dyspnea and fatigue among the 6MWT parameters in the SEG. We think that this result can be explained by the gains in the cardiopulmonary system (improvement in respiratory functions and increase in respiratory muscle strength) with a supervised exercise program. In the HEG, there was no significant change in perceived severity of dyspnea and leg fatigue, heart rate, and peripheral oxygen saturation. The 6MWT parameters were similar while the walking distance covered increased in the same period (longer walking distance) indicates that these parameters also improved in the HEG.

4.3 | Pulmonary functions and diffusion capacity

Similar to other studies, in our study, the baseline FEV_1%, FVC%, DLCO, PEF values of SSc patients in both groups were lower than the normal values (80% and above) and the FEV_1/FVC% ratio was found to be within normal limits.[35,36] FEV_1%, FVC%, PEF% and DLCO% values increased significantly after 12 weeks exercise program in the SEG. There was a minimal increase in respiratory parameters in the HEG, but this change was not significant. There are no studies investigating the effects of exercise programs on pulmonary functions in patients with SSc. However, studies on ILD and PAH, independent of SSc, have reported improvements in pulmonary functions and ventilation parameters of patients after pulmonary rehabilitation.[37] We think that pulmonary functions improved differently from the

TABLE 2 Supervised exercise group vs home exercise group: baseline outcome variables

Variables	Supervised exercise group	Home exercise group	*P*
Primary outcome			
Functional capacity			
6MWT walking distance, m	376.21 ± 65.50	384.44 ± 68.14	.743[a]
6MWT walking distance (% pred)	59.79 (48.25-67.10)	60.83 (56.03-65.30)	.715[b]
Secondary outcomes			
Pulmonary function			
FEV_1, % pred	75.94 ± 19.67	80.94 ± 18.88	.436[a]
FVC, % pred	77.10 ± 19.51	79.00 ± 19.80	.760[a]
FEV_1/FVC, %	82.95 ± 7.66	81.62 ± 6.11	.562[a]
PEF, % pred	74.21 ± 16.20	74.44 ± 16.68	.973[a]
DLCO, % pred	62.21 ± 14.72	65.83 ± 15.41	.570[a]
Respiratory muscle strength			
MIP, cmH_2O, % pred	61.15 ± 34.23	63.05 ± 35.73	.870[a]
MEP, cmH_2O, % pred	54.84 ± 26.31	61.88 ± 8.64	.356[a]
Dyspnea severity			
mMRC score	3.00 (2.0-3.0)	2.00 (2.0-3.0)	.202[b]
Peripheral muscle strength			
Knee extension strength, kg	6.43 ± 1.68	7.30 ± 1.86	.144[a]
Handgrip strength, kg	21.66 ± 5.77	24.04 ± 5.29	.234[a]
Health-related quality of life			
HAQ-DI	0.87 (0.5-1.5)	0.81 (0.5-1.5)	.951[b]
SHAQ-Raynaud's phenomenon VAS	1.40 (1.00-1.60)	1.00 (0.80-1.52)	.161[b]
SHAQ-digital ulcer VAS	0.80 (0.60-1.00)	0.60 (0.40-0.85)	.123[b]
SHAQ-digestive VAS	1.00 (0.60-1.40)	0.80 (0.40-1.00)	.214[b]
SHAQ-pulmonary VAS	1.20 (0.80-2.40)	1.00 (0.75-1.40)	.257[b]
SHAQ-overall disease severity VAS	1.20 (1.00-2.40)	1.20 (0.80-1.40)	.238[b]
SHAQ-global	0.91 (0.68-1.80)	0.90 (0.59-1.35)	.370[b]
SF-36 PCS	37.4 ± 12.33	43.7 ± 16.17	.323[a]
SF-36 MCS	40.57 ± 14.29	54.11 ± 15.84	.382[a]
Fatigue severity			
FIS total score	70.00 (48.00-99.00)	76.50 (40.50-100.00)	.891[b]
FIS cognitive score	12.00 (10.00-19.00)	14.00 (8.75-21.00)	.867[b]
FIS physical score	22.00 (17.00-30.00)	24.50 (13.75-30.50)	.976[b]
FIS psychosocial score	30.00 (23.00-56.00)	35.50 (16.50-49.25)	.952[b]

Note: Data are expressed as mean ± SD, median (interquartile range).

Abbreviations: 6MWT, 6-minute walking test; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FIS, Fatigue Impact Scale; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council; PEF, peak expiratory flow; SF-36 MCS, Short Form-36 Quality of Life Questionnaire Mental Component Score; SF-36 PCS, Short Form-36 Quality of Life Questionnaire Physical Component Score; SHAQ, Scleroderma Health Assessment Questionnaire; VAS, visual analog scale.

[a]Independent Student's *t* tests.

[b]Mann-Whitney *U* tests.

TABLE 3 Comparison of changes in clinical parameters of groups after the intervention

Variables	SEG			HEG			SEG	HEG	
	Before	After	*P*	Before	After	*P*	Change	Change	*P*
6MWT walking distance, m	376.21 ± 65.50	518.78 ± 75.84	**<.001**[c]	384.44 ± 68.14	432.7 ± 70.8	**.002**[c]	142.52 ± 39.25	48.33 ± 22.82	**<.001**[a]
6MWT walking distance, % pred	59.79 (48.25-67.10)	85.20 (69.86-90.34)	**<.001**[d]	60.83 (56.03-65.30)	67.37 (62.22-73.5)	**<.001**[d]	25.81 (11.11-30.83)	2.75 (2.14-15.49)	**<.001**[b]
FEV_1, % pred	75.94 ± 19.67	80.89 ± 18.92	**.011**[c]	80.94 ± 18.88	81.44 ± 18.27	.143[c]	4.94 ± 2.56	0.50 ± 0.18	**.019**[a]
FVC, % pred	77.10 ± 19.51	82.89 ± 19.01	**.004**[c]	79.00 ± 19.80	79.11 ± 17.46	.651[c]	5.78 ± 1.59	1.12 ± 0.02	**.003**[a]
FEV_1/FVC, %	82.95 ± 7.66	82.78 ± 6.77	.743[c]	81.62 ± 6.11	81.90 ± 6.52	.331[c]	0.37 ± 0.11	0.28 ± 0.10	.456[a]
DLCO, % pred	62.21 ± 14.72	66.73 ± 18.80	**.001**[c]	65.83 ± 15.41	65.88 ± 17.12	.914[c]	4.52 ± 1.02	0.59 ± 0.11	**.001**[a]
MIP, % pred	61.15 ± 34.23	83.21 ± 37.82	**<.001**[c]	63.05 ± 35.73	67.11 ± 37.26	.163[c]	24.05 ± 11.43	4.05 ± 2.78	**.001**[a]
MEP, % pred	54.84 ± 26.31	73.10 ± 29.32	**<.001**[c]	61.88 ± 8.64	65.50 ± 18.20	**.009**[c]	20.26 ± 13.48	3.61 ± 1.22	**.002**[a]
mMRC score	3.00 (2.0-3.0)	2.00 (1.00-2.00)	**<.001**[d]	2.00 (2.00-3.00)	2.00 (2.00-3.00)	.317[d]	-1.00 (-1.00--1.00)	-0.00 (-0.00--0.00)	**<.001**[b]
Knee extension strength, kg	6.43 ± 1.68	11.04 ± 1.92	**<.001**[c]	7.30 ± 1.86	7.90 ± 2.07	**.040**[c]	4.60 ± 1.70	0.59 ± 0.14	**<.001**[a]
Handgrip strength, kg	21.66 ± 5.77	25.14 ± 5.94	**<.001**[c]	24.04 ± 5.29	26.16 ± 6.49	.218[c]	3.47 ± 1.93	0.32 ± 0.18	**<.001**[a]

Note: Data are expressed as mean ± SD, median (interquartile range).

Abbreviations: 6MWT, 6-minute walking test; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HEG, home exercise group; MEP, Maximal expiratory pressure; MIP, Maximal inspiratory pressure; mMRC, modified Medical Research Council; PEF, peak expiratory flow; SEG, supervised exercise group.

[a]Independent Student's *t* tests.

[c]Paired Student's *t* tests.

[d]Wilcoxon test.

[b]Mann-Whitney *U* tests.

Level of significance was set at $P < .05$.

TABLE 4 Comparison of changes in health-related quality of life and fatigue level of groups after the intervention

	SEG			HEG			SEG	HEG	
Variables	**Before**	**After**	***P***	**Before**	**After**	***P***	**Change**	**Change**	***P***
HAQ-DI	0.87 (0.5-1.5)	0.37 (0.12-1.00)	**<.001**[a]	0.81 (0.5-1.5)	0.77 (0.37-1.47)	**.001**[d]	0.38 (0.25-0.87)	0.10 (0.02-0.12)	**<.001**[b]
SHAQ-Raynaud's phenomenon VAS	1.40 (1.00-1.60)	1.20 (0.80-1.40)	**<.001**[d]	1.00 (0.80-1.52)	1.00 (0.80-1.47)	.564[d]	0.20 (0.10-0.20)	0.00 (0.00-0.00)	**<.001**[b]
SHAQ-digital ulcer VAS	0.80 (0.60-1.00)	0.60 (0.50-1.00)	**.001**[d]	0.60 (0.40-0.85)	0.60 (0.40-0.85)	.100[d]	0.20 (0.20-0.40)	0.10 (0.00-0.10)	**<.001**[b]
SHAQ-digestive VAS	1.00 (0.60-1.40)	0.60 (0.40-1.10)	**<.001**[d]	0.80 (0.40-1.00)	0.70 (0.40-1.00)	**.001**[d]	0.20 (0.20-0.40)	0.10 (0.00-0.10)	**<.001**[b]
SHAQ-pulmonary VAS	1.20 (0.80-2.40)	1.00 (0.60-1.80)	**<.001**[d]	1.00 (0.75-1.40)	0.90 (0.67-1.30)	**.001**[d]	0.30 (0.20-0.30)	0.10 (0.75-0.20)	**<.001**[b]
SHAQ-overall disease severity VAS	1.20 (1.00-2.40)	1.00 (0.70-2.00)	**<.001**[d]	1.20 (0.80-1.40)	1.10 (0.77-1.40)	**.001**[d]	0.30 (0.20-0.40)	0.10 (0.00-0.10)	**<.001**[b]
SHAQ-global	0.91 (0.68-1.80)	0.56 (0.30-1.24)	**<.001**[d]	0.90 (0.59-1.35)	0.80 (0.50-1.25)	**.001**[d]	0.35 (0.29-0.54)	0.06 (0.00-0.10)	**<.001**[b]
SF-36 PCS	37.4 ± 12.33	71.47 ± 14.48	**<.001**[c]	43.7 ± 16.17	48.73 ± 17.34	**.001**[c]	34.01 ± 13.89	4.95 ± 2.38	**<.001**[a]
SF-36 MCS	40.57 ± 14.29	74.96 ± 11.74	**<.001**[c]	50.86 ± 14.40	54.11 ± 15.84	**.036**[c]	34.44 ± 12.46	5.81 ± 3.26	**<.001**[a]
FIS total score	70.00 (48.00-99.00)	25.00 (14.00-50.00)	**<.001**[d]	76.50 (40.50-100.00)	72.50 (37.00-91.25)	**.002**[d]	37.00 (25.00-44.00)	5.00 (3.00-8.25)	**<.001**[b]
FIS cognitive score	12.00 (10.00-19.00)	6.00 (4.00-14.00)	**<.001**[d]	14.00 (8.75-21.00)	11.50 (6.75-19.00)	**.026**[d]	6.00 (4.00-8.00)	2.50 (0.75-3.00)	**<.001**[b]
FIS physical score	22.00 (17.00-30.00)	7.00 (5.00-17.00)	**<.001**[d]	24.50 (13.75-30.50)	23.00 (14.25-27.25)	**.005**[d]	13.00 (8.00-16.00)	3.00 (2.00-4.25)	**<.001**[b]
FIS psychosocial score	30.00 (23.00-56.00)	12.00 (8.00-23.00)	**<.001**[d]	35.50 (16.50-49.25)	34.50 (15.00-42.00)	**.015**[d]	17.00 (9.00-22.00)	4.00 (0.00-5.25)	**<.001**[b]

Note: Data are expressed as mean ± SD, median (interquartile range).

Abbreviations: FIS, Fatigue Impact Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; HEG, home exercise group; SEG, supervised exercise group; SF-36 MCS, Short Form-36 Quality of Life Questionnaire Mental Component Score; SF-36 PCS, Short Form-36 Quality of Life Questionnaire Physical Component Score; SHAQ, Scleroderma Health Assessment Questionnaire; VAS, visual analog scale.

[a]Independent Student's *t* tests.

[b]Mann-Whitney *U* tests.

[c]Paired Student's *t* tests.

[d]Wilcoxon test.

Level of significance was set at $P < .05$.

other group due to the combined application of breathing, aerobic and resistance exercises in the SEG, and especially since the respiratory exercises could be performed more properly under supervision. The results suggest that supervised exercise program consisting of breathing, aerobic and resistance exercises can be used as a method to improve pulmonary functions and diffusion capacity in patients with SSc with or without pulmonary involvement.

4.4 | Respiratory muscle strength

In our study, in accordance with the literature, the expected % value of MIP and MEP in SSc patients in both groups was found to be lower than the stated normal values (80%).[38,39] A previous study stated that respiratory muscle weakness in SSc patients was associated with increased severity of dyspnea, decreased exercise capacity, and impaired QoL.[35] Therefore, there is a need for treatment strategies to improve respiratory muscle strength in this group. However, there are no studies evaluating the effects of exercises on respiratory muscle strength in SSc patients. After 12 weeks exercise programs, we observed significant improvements in MIP%, MEP% in the SEG; however, significant improvements were observed only in MEP% in the home exercised group. Also, the change in MEP% value was greater in the SEG. Previous studies stated that exercise programs applied in respiratory diseases positively support the inflammatory process, increase lung and chest wall compliance, and increase the endurance of type II fibers.[40] In our study, the improvement in respiratory muscle strength may have resulted from the gains of exercise programs on the cardiopulmonary and musculoskeletal system, similar to other respiratory diseases. However, studies that include the effectiveness of exercise programs on respiratory muscle strength and possible mechanisms of action in SSc patients are needed.

4.5 | Dyspnea severity

Similar to studies in respiratory diseases, the median value of the initial mMRC score of the SEG was 3 and the median value of the HEG was 2, which showed that both groups had a high perception of dyspnea in their daily living activities (cut-off value of mMRC score ≥2 points).[41] Impaired pulmonary functions and decreased respiratory muscle strength may have increased the perceived severity of dyspnea in this group. Exercise interventions in many respiratory diseases have shown to reduce the perception of dyspnea by improving respiratory muscle strength.[42] However, there is still no study examining the effect of exercise practices on perceived dyspnea severity in SSc. In our study after the exercise programs, the mMRC score decreased in the SEG, but no change was observed in the mMRC score in the HEG. It seems that the supervised exercise program was more effective to decrease dyspnea severity in SSc. In addition, the severity of dyspnea may not have changed because there was no increase in respiratory functions and inspiratory muscle strength in the HEG.

4.6 | Peripheral muscle strength

After the 12 weeks exercise programs, we observed significant improvements in knee extensor strength in both groups; however, significant improvements were observed in hand grip strength only in the supervised group. Also, lower limb strength improved more in SEG compared to HEG. Similarly, previous studies stated that exercise programs consisting of aerobic and strengthening exercises improve muscle strength and function, especially in the shoulder and hip groups in patients with SSc.[32,33] Although a special exercise program was not used to strengthen the hands in the supervised exercise program, grip strength increased at the end of 12 weeks. First, this result shows that the supervised exercise program had a direct effect on overall muscle strength, because grip strength is the predictor of global muscle strength. Second, this result can be explained as an indirect effect of upper extremity resistance training, since the grip strength is the expression of both the inner and outer muscles of the hand. In addition, although the home exercise program was suitable for developing lower extremity muscle strength, it was insufficient to develop upper extremity muscle strength. Therefore, we think that more specific resistance exercises should be added to home exercise programs to improve upper extremity functions. Peripheral muscle strength is associated with the level of functional independence in patients with SSc, so we think that in order to ensure the continuity of functional independence, supervised exercise programs, home exercise programs and physical activity recommendations should be added to the treatment strategies of patients.

4.7 | HRQoL

The HAQ-DI score, which reflects the disease-specific HRQoL and level of disability, decreased in both groups after exercise programs. In particular, patients in the SEG showed an improvement of HAQ-DI that was higher than the estimated MID for patients with SSc (−0.125 points).[30] After the exercise programs, significant decreases were observed in the digestive problems, respiratory problems, general disease severity domains and total score of SHAQ in both groups. However, significant improvement in Raynaud's phenomenon and digital ulcer domains of SHAQ were only observed in the SEG. This difference can be explained by the indirect effect of the home exercise program's inability to develop upper extremity muscle strength. Also, disease-related HRQoL improved more in SEG compared to HEG.

The SF-36 PCS and SF-36 MCS increased in both groups. SEG and HEG recorded an increase of PCS above the MID (2.25 points) and MCS above the MID (0.18) for patients with SSc.[30] The improvement seen in SF-36 PCS and MCS was higher in the SEG than in the HEG. These findings were consistent with the results of previous studies.[43,44] Besides the difference in the content of exercise programs, the difference can be attributed to this, as the supervised exercise program was more interactive with the physiotherapist during the exercise sessions. These results show that exercise programs in

SSc patients can increase motivation and social participation as well as functional and physical gains and thus can improve the mental and psychosocial health perceptions of the patients. We think that exercise programs are also effective in providing psychological adaptation and coping with the chronic and restrictive aspects of the disease in SSc patients. Our study strengthens the necessity of applying exercise programs more frequently as a treatment modality in the clinic in order to improve the HRQoL in patients with SSc.

4.8 | Fatigue level

Fatigue is very common in patients with SSc and is increasingly recognized as an important and limiting symptom. It has been stated that increased fatigue level in SSc is associated with a decrease in diffusing capacity, an increase in dyspnea severity, a decrease in peripheral-respiratory muscle strength and a deterioration in functional capacity.[45] In our study, cognitive, physical, psychosocial domains and total of fatigue scores decreased in both groups, but SEG was superior to HEG. In both groups, the highest decrease in fatigue subcategory scores was obtained in the level of psychosocial fatigue (17 points in the SEG, 4 units in the HEG). Also, this result draws attention to the importance of psychosocial gains as well as physical gains of exercise practices. Our study showed that the supervised exercise program and home exercise program were effective in fatigue management in SSc patients. The increase in pulmonary functions and respiratory muscle strength, decrease in the severity of dyspnea and increase in peripheral muscle strength may have been effective in reducing the level of fatigue. However, our study is the first study examining the effect of exercise programs on fatigue level in SSc patients. Therefore, long-term, prospective studies are needed to examine the effects of a supervised exercise program and home exercise program.

4.9 | Limitations and implications for future research

This study has several limitations. First, for ethical reasons, we could not include a third control group that did not receive any rehabilitation-type intervention. Second, blinding was not possible as 1 physical therapist was responsible for the treatments and evaluations. Third, data were collected 12 weeks before and after. Therefore, the results cannot provide any insight into the long-term effects of the supervised exercise program and the home exercise program. Fourth, because of the very low prevalence of this disease, we did not separate the results according to the type of disease (diffuse and limited) in the study sample. Fifth, we did not evaluate the motivation levels of the exercise programs. Finally, laboratory markers, radiographic imaging methods and cardiopulmonary exercise tests were not used in our study. This limited the demonstration of the effects of exercise at the cellular level in patients with SSc and a more comprehensive interpretation. Despite these limitations, to our knowledge, this is the first RCT to compare the effects of a supervised exercise program and home exercise program in patients with SSc. In addition, unlike the literature, the inclusion of SSc patients with different levels of lung involvement is another strength of the study. In this context, the results obtained from our study can guide studies that include supervised and home exercise programs in SSc patients to create a standard physiotherapy program. However, there is a need for more RCTs including exercise interventions.

5 | CONCLUSIONS

- Twelve weeks supervised exercise program and home exercise program were reliable and beneficial, overall resulting in improved functional capacity, respiratory muscle strength, knee extension muscle strength, disease-specific and general HRQoL and fatigue level.
- In addition to these effects, supervised exercise program provides significant improvements in respiratory functions, dyspnea severity and hand grip strength. However, the gains obtained with a supervised exercise program are higher than home exercise program.
- The results of this study underline the necessity and importance of exercise interventions in SSc patients. Nowadays considering the limited therapeutic possibilities in SSc, supervised exercise program and home exercise program should be added to pharmacological therapies in order to reduce functional limitations, increase the level of independence and improve HRQoL in patients with SSc.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HY, SÖ, RA, AÖA, AMB and GC. The first draft of the manuscript was written by HY and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

HUMAN AND ANIMAL RIGHTS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

ORCID

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

REFERENCES

1. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360(19):1989-2003. https://doi.org/10.1056/NEJMra0806188
2. Hinchcliff M, Varga J. Systemic sclerosis/Scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2010;78:961-968.
3. Mouthon L, Berezné A, Brauner M, Kambouchner M, Guillevin L, Valeyre D. Interstitial lung disease in systemic sclerosis. *Rev Mal Respir*. 2007;24:1-11. https://doi.org/10.1016/s0761-8425(07)92767-9
4. Morrisroe KB, Nikpour M, Proudman SM. Musculoskeletal manifestations of systemic sclerosis. *Rheum Dis Clin North Am*. 2015;41:507-518. https://doi.org/10.1016/j.rdc.2015.04.011
5. Almeida C, Almeida I, Vasconcelos C. Quality of life in systemic sclerosis. *Autoimmun Rev*. 2015;14:1087-1096. https://doi.org/10.1016/j.autrev.2015.07.012
6. Sandusky SB, McGuire L, Smith MT, Wigley FM, Haythornthwaite JA. Fatigue: an overlooked determinant of physical function in scleroderma. *Rheumatology*. 2009;48:165-169. https://doi.org/10.1093/rheumatology/ken455
7. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports*. 2006;1:3-63. https://doi.org/10.1111/j.1600-0838.2006.00520.x
8. De Jong Z, Vlieland TP. Safety of exercise in patients with rheumatoid arthiritis. *Curr Opin Rheumatol*. 2005;2:177-182. https://doi.org/10.1097/01.bor.0000151400.33899.88
9. Mannerkorpi K. Exercise in fibromyalgia. *Curr Opin Rheumatol*. 2005;17(2):190-194. https://doi.org/10.1097/01.bor.0000154202.56962.85
10. Oliveira NC, Sabbag LM, Pinto ALS, Borges CL, Lima FR. Aerobic exercise is safe and effective in systemic sclerosis. *Int J Sports Med*. 2009;30(10):728-732. https://doi.org/10.1055/s-0029-1224180
11. De Oliveira NC, Portes LA, Pettersson H, Alexanderson H, Bostrom C. Aerobic and resistance exercise in systemic sclerosis: state of the art. *Musculoskel Care*. 2017;15(4):316-323. https://doi.org/10.1002/msc.1185
12. Mugii N, Hamaguchi Y, Maddali-Bongi S. Clinical significance and usefulness of rehabilitation for systemic sclerosis. *J Scleroderma Relat Disord*. 2018;3:71-80.
13. Willems LM, Vriezekolk JE, Schouffoer AA, et al. Effectiveness of nonpharmacologic interventions in systemic sclerosis: a systematic review. *Arthritis Care Res*. 2015;67(10):1426-1439. https://doi.org/10.1002/acr.22595
14. Filippetti M, Cazzoletti L, Zamboni F, Ferrari P, Caimmi C, Smania N. Effect of a tailored home-based exercise program in patients with systemic sclerosis: a randomized controlled trial. *Scand J Med Sci Sports*. 2020;30(9):1675-1684. https://doi.org/10.1111/sms.13702
15. Van den Hoogen F, Khanna D, Fransen J, et al. Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheumatol*. 2013;72(11):1747-1755. https://doi.org/10.1136/annrheumdis-2013-204424
16. Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical therapy: a summary of systematic reviews. *Phys Ther*. 2005;85(11):1208-1223.
17. Riebe D, Franklin BA, Thompson PD, et al. Updating ACSM's recommendations for exercise preparticipation health screening. *Med Sci Sports Exerc*. 2015;47(11):2473-2479. https://doi.org/10.1249/MSS.0000000000000664
18. Holland AE, Hill CJ, Jones AY, McDonald CF. Breathing exercises for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;17(10):CD008250. https://doi.org/10.1002/14651858.CD008250.pub2
19. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117. https://doi.org/10.1164/ajrccm.166.1.at1102
20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. https://doi.org/10.1183/09031936.05.00034805
21. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir Soc*. 2005;26(4):720-735. https://doi.org/10.1183/09031936.05.00034905
22. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*. 2002;166:518-624. https://doi.org/10.1164/rccm.166.4.518
23. Richards JB. Calculated decisions: mMRC (Modified Medical Research Council) dyspnea scale. *Emerg Med Pract*. 2017;19(Suppl 10):1-2.
24. Deones VL, Wiley SC, Worrell T. Assessment of quadriceps muscle performance by a hand-held dynamometer and an isokinetic dynamometer. *J Orthop Sports Phys Ther*. 1994;20(6):296-301. https://doi.org/10.2519/jospt.1994.20.6.296
25. Haidar SG, Kumar D, Bassi RS, Deshmukh SC. Average versus maximum grip strength: which is more consistent? *J Hand Surg*. 2004;29:82-84. https://doi.org/10.1016/j.jhsb.2003.09.012
26. Pope J. Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). *Arthritis Care Res*. 2011;63(Suppl 11):S98-S111. https://doi.org/10.1002/acr.20598
27. Temiz Karadag D, Karakas F, Tekeoglu S, Yazici A, Isik CA. Validation of Turkish version of the Scleroderma Health Assessment Questionnaire. *Clin Rheumatol*. 2019;38(7):1917-1923. https://doi.org/10.1007/s10067-019-04494-5
28. Kocyigit H, Aydemir O, Fisek G, Olmez N, Memis A. Validity and reliability of Turkish version of Short form 36: a study of a patients with romatoid disorder. *J Drug Ther*. 1999;12:102-106.
29. Armutlu K, Keser I, Korkmaz N, et al. Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. *J Neurol Sci*. 2007;255:64-68. https://doi.org/10.1016/j.jns.2007.01.073
30. Sekhon S, Pope J, Baron M. The minimally important difference in clinical practice for patient-centered outcomes including health assessment questionnaire, fatigue, pain, sleep, global visual analog scale, and SF-36 in scleroderma. *J Rheumatol*. 2010;37:591-598. https://doi.org/10.3899/jrheum.090375
31. Chow SC, Shao J, Wang H. *Sample Size Calculations in Clinical Research*, 2nd edn. Boca Raton, FL: Chapman & Hall/Crc; 2008.
32. Pinto AL, Oliveira NC, Gualano B, et al. Efficacy and safety of concurrent training in systemic sclerosis. *J Strength Cond Res*. 2011;25(5):1423-1428. https://doi.org/10.1519/JSC.0b013e3181d6858b
33. Alexanderson H, Bergegård J, Björnådal L, Nordin A. Intensive aerobic and muscle endurance exercise in patients with systemic sclerosis: a pilot study. *BMC Res Notes*. 2014;7(7):86. https://doi.org/10.1186/1756-0500-7-86
34. Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. *Ther Adv Respir Dis*. 2017;11(2):115-128. https://doi.org/10.1177/1753465816676048

35. Kesikburun B, Köseoğlu BF, Şahin A, Turgay M, Doğan A, Öken AÖ. The effects of respiratory muscle weakness and pulmonary involvement on functional status, fatigue and health related quality of life in patients with systemic sclerosis. *Arch Rheumatol*. 2015;30(2):116-123.
36. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *Eur Respir Rev*. 2013;22(127):6-19. https://doi.org/10.1183/09059180.00005512
37. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev*. 2014;6(10):CD006322. https://doi.org/10.1002/14651858.CD006322.pub3
38. Lopes AJ, Justo AC, Ferreira AS, Guimaraes FS. Systemic sclerosis: association between physical function, handgrip strength and pulmonary function. *J Bodyw Mov Ther*. 2017;21(4):972-977. https://doi.org/10.1016/j.jbmt.2017.03.018
39. Lima TRL, Guimarães FS, Carvalho MN, Sousa TLM, Menezes SLS, Lopes AJ. Lower limb muscle strength is associated with functional performance and quality of life in patients with systemic sclerosis. *Braz J Phys Ther*. 2015;19(2):129-136. https://doi.org/10.1590/bjpt-rbf.2014.0084
40. Geddes EL, O'Brien K, Reid WD, Brooks D, Crowe J. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med*. 2008;102(12):1715-1729. https://doi.org/10.1016/j.rmed.2008.07.005
41. Baron M, Sutton E, Hudson M, et al. The relationship of dyspnea to function and quality of life in systemic sclerosis. *Ann Rheum Dis*. 2008;67(5):644-650. https://doi.org/10.1136/ard.2007.075721
42. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J*. 2011;37(2):416-425. https://doi.org/10.1183/09031936.00031810
43. Antonioli CM, Bua G, Frigè A, et al. An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility. *Clin Rheumatol*. 2009;28(2):159-165. https://doi.org/10.1007/s10067-008-1006-x
44. Maddali-Bongi S, Del Rosso A. Systemic sclerosis: rehabilitation as a tool to cope with disability. *Clin Exp Rheumatol*. 2016;100(5):162-169.
45. Yakut H, Özalevlİ S. Bİrlİk AM (2020) Fatigue and its relationship with disease-related factors in patients with systemic sclerosis: a cross-sectional study. *Turk J Med Sci*. 2020;51(2):530-539. https://doi.org/10.3906/sag-2005-314

How to cite this article: Yakut H, Özalevli S, Aktan R, Alpaydın A, Birlik A, Can G. Effects of supervised exercise program and home exercise program in patients with systemic sclerosis: A randomized controlled trial. *Int J Rheum Dis*. 2021;24:1200–1212. https://doi.org/10.1111/1756-185X.14177

Received: 13 May 2021 | Revised: 29 June 2021 | Accepted: 12 July 2021

DOI: 10.1111/1756-185X.14186

APLAR GRAND ROUND CASE

International Journal of Rheumatic Diseases

WILEY

Coexistence of Takayasu arteritis and chronic myeloid leukemia: Coincidental or paraneoplastic phenomenon?

Tuba Yuce Inel[1] | Aytac Gulcu[2] | Ali Karakas[1] | Elcin Erdogan Yucel[3] | Fatos Onen[1]

[1]Department of Rheumatology, Dokuz Eylul University School of Medicine, Izmir, Turkey

[2]Department of Radiology, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey

[3]Department of Hematology, Dokuz Eylul University School of Medicine, Izmir, Turkey

Correspondence
Tuba Yuce Inel, Dokuz Eylul Universitesi, Tip Fakultesi, Ic Hastaliklari ABD, Romatoloji BD, PK 35340, Balcova, Izmir, Turkey.
Email: dr.tubayuce@yahoo.com

Abstract

Vasculitis may rarely be seen in the course of myeloproliferative neoplasms (MPN). In vasculitis associated with hematological diseases, mostly small- and medium-vessel involvement is expected, aortitis is very rare. It is not exactly known whether large-vessel vasculitis associated with MPN is a paraneoplastic phenomenon or coincidental. We aimed to present an uncommon case diagnosed with chronic myeloid leukemia and Takayasu arteritis concurrently.

KEYWORDS

chronic myeloid leukemia, large-vessel vasculitis, myeloproliferative neoplasms, paraneoplastic phenomenon, Takayasu arteritis

1 | INTRODUCTION

Malignancy-associated vasculitis is uncommon and usually presents with cutaneous vascular involvement.[1] Systemic manifestations and large-vessel involvement are mostly seen in lymphoproliferative diseases.[2] However, vasculitis may be seen as a paraneoplastic phenomenon in myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN).[3-5] Small and medium vessels are mostly affected, aortic involvement is very rare. Herein, we present a female patient who presented with a transient ischemic attack and was concomitantly diagnosed with chronic myeloid leukemia (CML) and Takayasu arteritis.

2 | CASE REPORT

A 48-year-old woman was admitted to the hospital with a transient ischemic attack and thrombocytosis (2000 × 10^3/μL) was detected. The patient, who did not respond adequately to allopurinol,

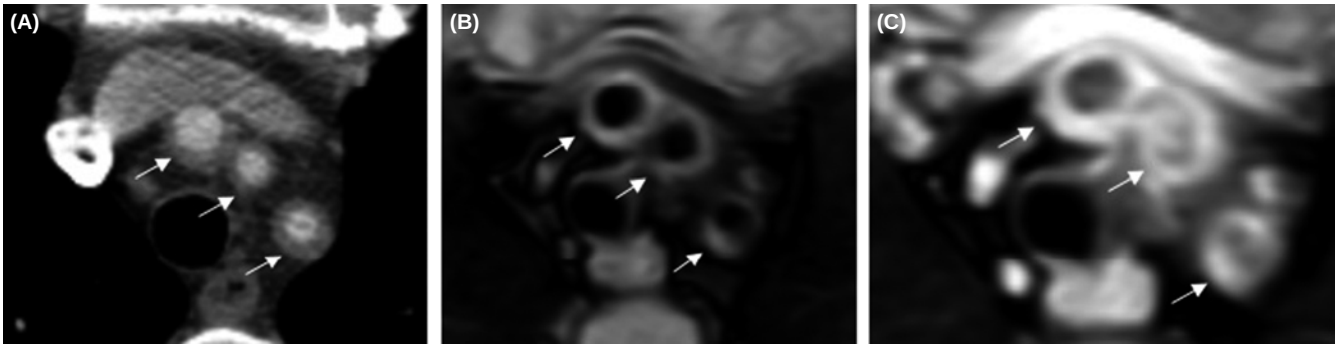


FIGURE 1 A, B, Computed tomography and magnetic resonance angiography, respectively, show increased wall thickness and luminal narrowing in the brachiocephalic, left common carotid, and subclavian arteries. C, Post-contrast series, all supra-aortic branches had circular enhancements

TABLE 1 Some reports of large-vessel vasculitis associated with malignant hematological disorders

	Age/Sex	Hematological disorders	Involved vessels	Rheumatological diagnosis	Treatments	Outcome
Donisan et al[7]	39/M	CML	Bilateral CCA, proximal LAD, celiac, proximal SMA	TA	Prednisone, methotrexate, imatinib	Improvement of symptoms
Fukumoto et al[13]	65/M	Indolent adult T-cell leukemia/lymphoma + PML	N/A	TA	Dexamethasone, mefloquin, mirtazapine	Died 6 months from onset
B'Chir Hamzaoui et al[14]	21/F	AML	Extracranial internal carotid (L), subclavian artery (L), axillary (L), abdominal infrarenal aorta	TA	Prednisone	Died 3 months from onset
Chandratilleke et al[15]	56/F	AML	Bilateral CCA, upper abdominal aorta, SMA	LVV	Prednisone, methotrexate, cytarabine, idarubicin, fludarabine	Died 8 months from onset
Cohen et al[16]	62/M	Transformation of MDS to AML	Subclavian (L), bilateral carotid, femoral, mesenteric arteries	TA	Prednisone, methotrexate, allogeneic bone marrow transplantation	Died 14 months from onset
Sasinowska et al[3]	68/F	CMML	Entire thoracic and abdominal aorta	LVV	Prednisone, hydroxyurea, leukapheresis, decitabine	Died 3 months from onset
Amberger et al[12]	50/F	Transformation of CMML to AML	Thoracic aorta, all supra-aortic branches	TA	Prednisolone, azathioprine, cyclophosphamide, cyclosporine, peripheral blood stem cell transplantation	Died 5 months from onset
This case	48/F	CML	Brachiocephalic, CCA (L), subclavian artery, bilateral axillary arteries	TA	Prednisolone, hydroxyurea, leukapheresis, imatinib	Improvement of symptoms

Abbreviations: AML, acute myeloid leukemia; CCA, common carotid artery; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; F, female; (L), Left; LAD, left anterior descending artery; LVV, large-vessel vasculitis; M, male; MDS, myelodysplastic syndrome; N/A, not available; PML, progressive multifocal leukoencephalopathy; SMA, superior mesenteric artery; TA, Takayasu arteritis.

hydroxyurea, and acetylsalicylic acid treatment, initiated considering essential thrombocythemia, was referred to our center for apheresis. Computed tomography performed for malignancy screening revealed a diffusely increased wall thickness in the aortic arch, supra-aortic main branches (Figure 1A), descending thoracic aorta and, although to a lesser extent, proximal abdominal aorta. Short segment stenosis not reaching 50% was observed in the proximal left subclavian artery. The patient was referred to the rheumatology department with a pre-diagnosis of vasculitis. She had complaints of headache, dizziness, loss of appetite, 8 kg weight loss in previous 6 months, arthralgia in the knees, intermittent arm claudication, and Raynaud phenomenon. Her comorbidities were asthma and migraine. She had a 30-pack per year smoking history. Her mother, sisters, and aunt had a diagnosis of rheumatoid arthritis. Laboratory findings revealed leukocytes 15 200/μL, hemoglobin 10.2 g/dL, platelets 2009 × 10^3/μL, C-reactive protein 24.4 mg/L, erythrocyte sedimentation rate 47 mm/h, anti-nuclear antibody-positive (1/320-1/1000 titer, speckled pattern), and extractable nuclear antibody- and anti-neutrophil cytoplasmic antibody-negative. *JAK2 V617F* mutation was negative. Bone marrow aspiration and biopsy were performed for the diagnosis of MPN. Bone marrow biopsy revealed hypercellularity with myeloid hyperplasia, an increase in megakaryocytes with minimal dysplasia and grade 3 reticulin fibrosis. Bone marrow aspiration demonstrated features of CML with the t(9;22) (q34;q11). She was diagnosed with CML and imatinib was initiated (Table 1).

Magnetic resonance angiography showed increased wall thickness and luminal narrowing in the brachiocephalic, left common carotid and subclavian arteries (Figure 1B), thin luminal calibration, and thickening of the wall in the bilateral axillary arteries. In the post-contrast series, all supra-aortic branches had circular enhancements in favor of activity (Figure 1C). In Doppler ultrasonography, concentric wall thickening and stenosis in the bilateral axillary artery were interpreted in favor of vasculitis, whereas stenosis in the common carotid artery and superior mesenteric artery was considered to be atherosclerotic. The patient was accepted as having Takayasu arteritis and methylprednisolone (0.5 mg/kg) was added to her treatment.

3 | DISCUSSION

Rheumatological symptoms usually develop later in the course of hematological disorders, but may rarely be the first presentation. Vasculitides can be seen as paraneoplastic in hematological disorders such as POEMS (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), non-Hodgkin lymphoma, and MDS, as well as secondary to hematopoietic stem-cell transplantation or other treatments.[6] However, considering that the current vascular lesions in this case developed slowly over time, large-vessel vasculitis (LVV) might be presumed to precede CML. Furthermore, it can be hypothesized that CML occurs in the LVV context as a result of the genetic tendency of the Philadelphia chromosome, which rejects the possibility of paraneoplastic phenomena and supports coincidental.

In the literature, cases of LVV have been reported in MDS/MPN, especially in patients with chronic myelomonocytic leukemia.[3,4] Although the mechanism of vasculitis secondary to MDS or MPN is not fully known, it is thought to be caused by deficiency in lymphocyte function, defective natural killer cells and phagocytic function, and dysregulated antigen presentation.[5] No cases were reported except for a patient using imatinib for CML who was diagnosed with Takayasu arteritis while investigating angina pectoris.[7] Treatment consists of steroids, and drugs specific to the underlying hematological disease. It has been shown that 87% of 26 chronic myelomonocytic leukemia patients who developed systemic inflammatory autoimmune disease responded to steroid monotherapy, but 40% of patients started second-line therapy for relapse or steroid dependence.[8] Steroid-sparing agents should be carefully selected in these patients because of the risk of interactions with tyrosine kinase inhibitors, and adverse effects such as cytopenia and hepatotoxicity. Imatinib has been shown to inhibit myointimal cell growth in temporal artery sections taken from patients with giant cell arteritis. It also inhibits platelet-derived growth factor, which is a potent vasoconstrictor, so it has a therapeutic potential to limit vascular occlusion and ischemic complications in LVV.[9] However, it should not be forgotten that tyrosine kinase inhibitors increase the risk of peripheral artery disease.[10,11] The emergence of the paraneoplastic process mimicking LVV worsens the prognosis of the underlying hematological malignancy.[12]

4 | CONCLUSION

Vasculitis can be seen in the course of MPN, but large-vessel involvement is extremely rare. It is not exactly known whether LVV associated with MPN is a paraneoplastic phenomenon or coincidental.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

INFORMED CONSENT

Written informed consent was obtained from the patient.

ORCID

Tuba Yuce Inel https://orcid.org/0000-0001-9026-9641

REFERENCES

1. Fain O, Hamidou M, Cacoub P, et al. Vasculitides associated with malignancies: analysis of sixty patients. *Arthritis Care Res*. 2007;57(8):1473-1480.
2. Wooten MD, Jasin HE. Vasculitis and lymph op roliferative diseases. *Semin Arthritis Rheum*. 1996;26(2):564-574. Elsevier.
3. Sasinowska S, Traisak P, McCormack M, Eid H. A rare case of paraneoplastic aortitis associated with chronic myelomonocytic leukemia. *Case Rep Hematol*. 2017;2017:1-3.
4. Park JK, Gelber AC, Zheng G, McDevitt MA, Gocke CD, Baer AN. Large-vessel vasculitis as an early manifestation of chronic myelomonocytic leukemia. *J Clin Oncol*. 2011;29(20):e601-e603.

5. Fleming S, Hellstr m-Lindberg E, Burbury K, Seymour JF. Paraneoplastic large vessel arteritis complicating myelodysplastic syndrome. *Leuk Lymphoma*. 2012;53(8):1613-1616.
6. Ravindran V, Anoop P. Rheumatologic manifestations of benign and malignant haematological disorders. *Clin Rheumatol*. 2011;30(9):1143-1149.
7. Donisan T, Balanescu DV, Mouhayar E, Tayar J, Iliescu C. Coronary lesions in Takayasu arteritis with chronic myelogenous leukemia-intravascular assessment with optical coherence tomography and fractional flow reserve. *Circ J*. 2018;83(1):245-246.
8. Grignano E, Mekinian A, Braun T, et al. Autoimmune and inflammatory diseases associated with chronic myelomonocytic leukemia: a series of 26 cases and literature review. *Leuk Res*. 2016;47:136-141.
9. Lozano E, Segarra M, García-Martínez A, Hernández-Rodríguez J, Cid MC. Imatinib mesylate inhibits in vitro and ex vivo biological responses related to vascular occlusion in giant cell arteritis. *Ann Rheum Dis*. 2008;67(11):1581-1588.
10. Hadzijusufovic E, Albrecht-Schgoer K, Huber K, et al. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia*. 2017;31(11):2388-2397.
11. Kim T, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia*. 2013;27(6):1316-1321.
12. Amberger C, Denzlinger C, Janzen J, Muller-Schimpfle M, Mohren M, Kotter I. Takayasu's arteritis secondary to myelodysplasia as a predictor of poor outcome: two case reports. *Clin Exp Rheumatol*. 2004;22(3):346-348.
13. Fukumoto S, Shiraishi H, Nakamichi K, Nakajima H, Saijyo M, Tsujino A. A case of progressive multifocal leukoencephalopathy with Takayasu arteritis and indolent adult T-cell lymphoma/leukemia. *Rinsho Shinkeigaku*. 2016;56(2):82-87.
14. B'Chir Hamzaoui S, Abdallah M, Baili L, et al. Takayasu's arteritis associated with acute myeloblastic leukemia. *J Mal Vasc*. 2006;31(5):280-283.
15. Chandratilleke D, Anantharajah A, Vicaretti M, Benson W, Berglund LJ. Migratory large vessel vasculitis preceding acute myeloid leukemia: a case report. *J Med Case Rep*. 2017;11(1):1-4.
16. Cohen MJ, Shyman A, Klein M, et al. Large vessel (Takayasu's) arteritis in a patient with myelodysplastic syndrome: is there a common pathogenesis? *Clin Lymphoma Myeloma Leuk*. 2011;11(1):60-63.

How to cite this article: Yuce Inel T, Gulcu A, Karakas A, Erdogan Yucel E, Onen F. Coexistence of Takayasu arteritis and chronic myeloid leukemia: Coincidental or paraneoplastic phenomenon? *Int J Rheum Dis*. 2021;24:1213–1216. https://doi.org/10.1111/1756-185X.14186

Received: 12 July 2021 | Accepted: 15 July 2021

DOI: 10.1111/1756-185X.14188

CORRESPONDENCE

International Journal of Rheumatic Diseases

WILEY

What is behind the elevated neutrophil to lymphocyte ratio in glucocorticoid-resistant polymyalgia rheumatica?

Dear Editor,

Owen and colleagues have pointed out that elevated neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) could predict glucocorticoid resistance among patients with polymyalgia rheumatica (PMR).[1] Many authors have described the association between these indices and the mortality of cancer patients.[2,3] Several authors have recently reported the association of these ratios with rheumatic diseases.[4] Following this trend, the article by Owen and colleagues would add insights into the utility of NLR and PLR in the field of rheumatology. However, there remains one question: what is behind the elevated NLR and PLR among these patients?

In their article, the difference of NLR and PLR values seems huge between the glucocorticoid-resistant group and the responsive group without log transformation. There is a possibility that inflammatory mechanisms other than PMR itself were present in some patients in the resistant group. For example, PMR can develop secondary to infectious diseases in some individuals.[5] In such situations, PMR can relapse after glucocorticoid administration unless the infection sources are controlled adequately. In other words, clarifying underlying diseases in patients with PMR seems essential to interpreting the results appropriately in this study.

KEYWORDS

neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, polymyalgia rheumatica

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

HI declares no conflict of interest.

AUTHOR CONTRIBUTION

HI conceptualized and wrote the whole article.

Hiroshi Ito

Division of Hospital Medicine, University of Tsukuba Hospital, Tsukuba, Japan

Correspondence

Dr Hiroshi Ito, Division of Hospital Medicine, University of Tsukuba Hospital, 2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576, Japan.

Email: itohirokan@yahoo.co.jp

ORCID

Hiroshi Ito https://orcid.org/0000-0002-9857-8614

REFERENCES

1. Owen CE, McMaster C, Liew DFL, Leung JL, Scott AM, Buchanan RRC. Neutrophil to lymphocyte ratio predicts glucocorticoid resistance in polymyalgia rheumatica. *Int J Rheum Dis*. 2021;24(1):56-62.
2. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106(6):dju124.
3. Li B, Zhou P, Liu Y, et al. Platelet-to-lymphocyte ratio in advanced cancer: review and meta-analysis. *Clin Chim Acta*. 2018;483:48-56.
4. Erre GL, Paliogiannis P, Castagna F, et al. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. *Eur J Clin Invest*. 2019;49(1):e13037.
5. Falsetti P, Conticini E, Acciai C, et al. Polymyalgia rheumatica following infective triggers or vaccinations: a different subset of disease? *Reumatologia*. 2020;58(2):76-80.

Received: 26 July 2021 | Revised: 28 July 2021 | Accepted: 28 July 2021

DOI: 10.1111/1756-185X.14202

International Journal of Rheumatic Diseases

WILEY

CORRESPONDENCE

Arthritis of the left elbow joint after vaccination against SARS-CoV-2 infection

The association between arthritis, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), and coronavirus disease-2019 (COVID-19) vaccination have been investigated and discussed in scientific literature. Several patients with rheumatic diseases, treated in the Medical Center of Joint Diseases (MCJD), developed transient flares after receiving the COVID-19 vaccine. The patient in this case report was a previously healthy man with an unremarkable medical history. He is also an author of this paper. This is the first documented case of arthritis after SPUTNIK-V vaccination without other possible causes of arthritis. The SPUTNIK-V vaccine (Gamaleya Research Institute) is a viral-vectored vaccine,[1] currently in production in Kazakhstan. The vaccination rate in Kazakhstan has increased with that of other countries. It is essential to discuss the various complications arising after vaccination.

1 | CASE PRESENTATION

The patient was B, a 58-year-old patient with no history of uncontrolled or chronic joint disease, infections, or injuries within the previous 3 months. He had no history of inflammatory back pain, morning stiffness, or joint swelling. The patient has had no history of active SARS-CoV-2 infection, and his COVID-19 polymerase chain reaction (PCR) and antibodies in March 2021 were negative. The patient underwent a complete clinical and laboratory examination on 21 April, 2021, before receiving the first dose of the COVID-19 vaccine. Aside from a mildly elevated total blood cholesterol, his examination results were unremarkable. His C-reactive protein (CRP) was normal (2.2 mg/L), and immunoglobulin G (IgG) and IgM antibodies to SARS-CoV-2 were negative. The patient received the first shot of the SPUTNIK-V vaccine on 22 April, 2021, without developing a fever or adverse events. The second shot was completed on 13 May, 2021. Then, mild discomfort in the left elbow joint was noted on 18 May, 2021. This was followed by pain upon movement without fever on 19 May. The following day, the patient reported joint swelling, worsening pain, and stiffness upon movement (Figure 1).

2 | INVESTIGATIONS

Ultrasonography revealed moderate effusion in the left elbow fossa and a small shoulder-elbow joint synovitis. No osteophytes were identified (Figure 2). Magnetic resonance imaging (Figure 3) confirmed the elbow joint arthritis, but mono-urate deposits were not detected. He had a moderately increased CRP of up to 14 mg/L (below 5 mg/L is normal) and erythrocyte sedimentation rate at 18 mm/h. Rheumatoid factor, anti-cyclic citrullinated peptides, and antistreptolysin O levels were normal. Chlamydia and urea plasma immunoenzyme tests were negative. He had a uric acid level of 341 mmol/L (428 mmol/L and less is normal), and sacroiliitis was not noted on pelvic radiography. The SARS-CoV-2 PCR was negative, while the immunoenzyme SARS-CoV-2 Spike IgG antibody test on 25 May had a borderline result of 1.07 (0.80 negative, ≤0.80-1.10 borderline, ≥1.10 positive). The positivity coefficient was 2.67.

3 | OUTCOME AND FOLLOW-UP

During the follow-up on 2 June, the SARS-CoV-2 Spike IgG was 2.68 with a positivity coefficient of 13.4. In addition, a significant increase in the post-vaccination antibodies was noted within 7 observation days. The patient underwent a joint puncture, and 7 mL of light-yellow liquid were obtained. Crystals were not detected on polarization microscopy. After excluding all other possible causes, the patient was diagnosed with "post-vaccination arthritis of the left elbow joint." The patient was treated with non-steroidal

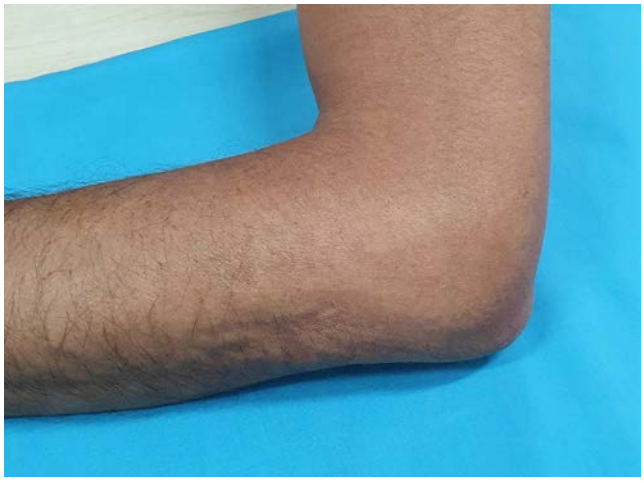


FIGURE 1 Arthritis of the left elbow joint

anti-inflammatory drugs, physiotherapy, and a single intra-articular injection of diprospan (0.5 mL). A repeat ultrasonography 1 week later revealed no arthritis. However, arthralgia on active motion was reported after 1 month.

4 | DISCUSSION

We report a confirmed case of arthritis of the left elbow joint 7 days after the second dose of the SPUTNIK-V SARS-CoV-2 vaccine. Following vaccination, a rapid increase in antibody titers was noted. The patient was a healthy 58-year-old man, and no other causes for the arthritis were identified. In the MCJD in the previous year, several unstable arthritis cases following COVID-19 infection and vaccination were reported. Arthralgia and arthritis have been reported after SARS-CoV-2 infection. Last March, a case of new-onset rheumatoid arthritis following COVID-19 infection was reported.[2] A rheumatoid arthritis flare was also reported recently in a patient who received the COVID-19 vaccine.[3] The articular complications caused by the different SARS-CoV-2 vaccines were compared,[4] but the Gam-COVID-Vac vaccine was not included. There have been no English reports describing arthritis after SPUTNIK-V vaccination. This is the first documented case of arthritis in a patient who received the SPUTNIK-V vaccine without other possible causes for arthritis. However, similar to other post-vaccine case reports, the causation was not formally established. In this case, all other possible reasons for the arthritis were evaluated. The number of patients experiencing joint manifestations after vaccination has increased with the vaccination rate. This report documented the first case of arthritis after vaccination in an otherwise intact joint.

The SPUTNIK-V vaccine is produced in Kazakhstan. While persons who received other vaccine types were not observed, joint manifestations can occur with any vaccine. Prospective studies and larger case series of patients undergoing vaccination are needed.

The patient provided informed consent, and is an author of this paper.

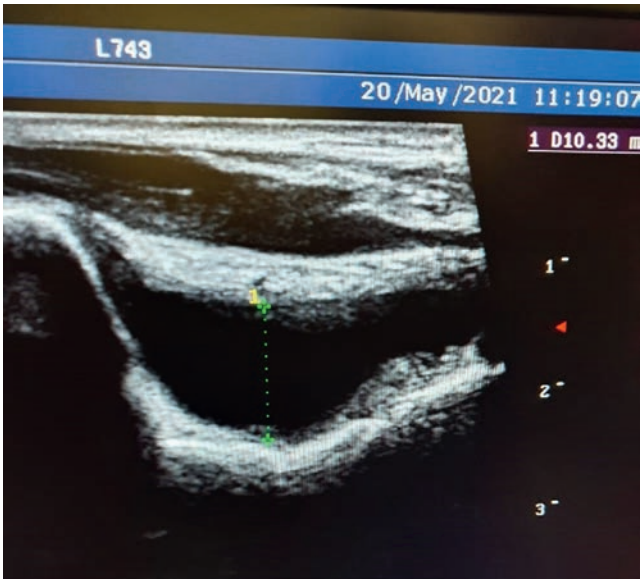


FIGURE 2 Ultrasonography of the left elbow joint revealing moderate effusion in the left elbow fossa

5 | LEARNING POINTS/TAKE HOME MESSAGES

1. Arthritis may be a complication of vaccination against SARS-CoV-2 infection.
2. The causation between vaccination and arthritis is difficult to establish.
3. In cases of arthritis after vaccination for the SARS-CoV-2 infection, all the possible causes for arthritis must be thoroughly investigated.

PATIENT'S PERSPECTIVE

The patient is an author of this paper. Further, he believes that this case may help educate doctors during the coronavirus disease-2019 pandemic.

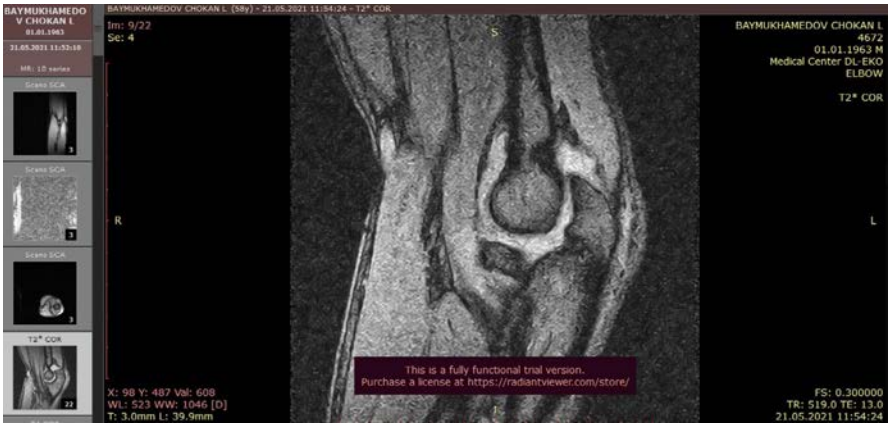


FIGURE 3 Magnetic resonance imaging showing elbow joint arthritis

KEYWORDS

arthritis, SARS-CoV-2 infection, SPUTNIK-V, vaccination against SARS-CoV-2 infection

Chokan Baimukhamedov

South Kazakhstan Medical Academy, Shymkent Medical Center of Joint Diseases, Shymkent, Kazakhstan

Correspondence

Chokan Baimukhamedov, South Kazakhstan Medical Academy, Shymkent Medical Center of Joint Diseases, Str. Sasbukaeva 32a, Postal Code 160013 Shymkent, South Kazakhstan, Kazakhstan.

Email: shocan@mail.ru

ORCID

Chokan Baimukhamedov https://orcid.org/0000-0003-3261-1036

REFERENCES

1. Won JH, Lee H. The current status of drug repositioning and vaccine developments for the COVID-19 pandemic. *Int J Mol Sci*. 2020;21:9775. doi:https://doi.org/10.3390/ijms21249775
2. Baimukhamedov C, Barskova T, Matucci-Cerinic M. Arthritis after SARS-CoV-2 infection. *Lancet Rheumatol*. 2021;3:e324-e325. doi:https://doi.org/10.1016/S2665-9913(21)00067-9
3. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. *Lancet Rheumatol*. 2021;3:e469-e470. doi:https://doi.org/10.1016/S2665-9913(21)00108
4. Boekel L, Kummer LY, van Dam KPJ, et al. Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. *Lancet Rheumatol*. 2021;3(8):e542-e545. doi:https://doi.org/10.1016/S2665-9913(21)00181-8

Received: 30 May 2021 | Revised: 20 July 2021 | Accepted: 31 July 2021

DOI: 10.1111/1756-185X.14204

International Journal of Rheumatic Diseases WILEY

CORRESPONDENCE

COVID-19 pneumonia can cause irreversible lung damage in dermatomyositis with pre-existing interstitial lung disease

We read the paper reported by Tam et al. in your journal with great interest.[1] They updated the guidelines of the Asia Pacific League of Associations for Rheumatology on the management of patients with rheumatic and musculoskeletal diseases during the coronavirus disease 2019 (COVID-19) pandemic based on the globally accumulated evidence. We would like to emphasize that there is still lack of data about pulmonary sequelae due to COVID-19 in patients with rheumatic and musculoskeletal diseases. Here we present our case of severe COVID-19 in dermatomyositis, in which chest computed tomography was examined before COVID-19 pneumonia, at the time of COVID-19 pneumonia, and at 4 months after surviving COVID-19 pneumonia.

A 69-year-old Asian man presented with fever and was positive for the reverse transcriptase polymerase chain reaction testing for SARS-CoV-2 (nasopharyngeal swab sample). He had a past history of smoking and anti-transcriptional intermediary factor (TFI)1γ-positive dermatomyositis complicated with interstitial lung disease (Figure 1A) and was receiving prednisolone (20 mg/d) and azathioprine (50 mg/d) at that time. Dermatomyositis was diagnosed 1 month earlier, based on the Bohan and Peter criteria: symmetrical weakness of limb-girdle muscles (manual muscle test of 3), positive evidence for typical myositis on muscle biopsy, elevation of serum creatine kinase (515 U/L, normal <248 U/L) and aldolase (7.5 U/L, normal <6.1 U/L), and heliotrope rash (Figure 1D-G). Anti-TIF1γ antibody was detected by enzyme-linked immunosorbent assay (126.0 index, normal <32 index), whereas anti-melanoma differentiation-associated gene-5 (MDA5), anti-aminoacyl tRNA synthetase (anti-ARS), and anti-Mi-2 antibodies were negative.

Arterial oxygen saturation of pulse oximetry was 85% at room air, and chest computed tomography performed at admission demonstrated newly emerging bilateral, non-segmental, diffuse ground glass opacities (Figure 1B). Serum ferritin was elevated (1736 ng/mL, normal <464 ng/mL). He was diagnosed with severe COVID-19 pneumonia and treated with a high-flow nasal canula, dexamethasone (6 mg for 10 days), and remdesivir (200 mg on day 1 followed by 100 mg on days 2-5). Fortunately, he survived and was discharged. Chest computed tomography at 4-month follow-up revealed residual ground glass opacities (Figure 1C). Pulmonary function test showed impaired lung diffusing capacity for carbon monoxide (26.8%) and poor 6-min walking test (320 m). The pulmonary sequelae due to COVID-19 resulted in significant decrease of his daily activities.

Our present case suggests that COVID-19 pneumonia can cause irreversible lung damage and critically affect the quality of life of patients with dermatomyositis with pre-existing interstitial lung disease. Recent studies have reported that half of the survivors of COVID-19 showed residual lung damage on chest computed tomography at 3-month follow-up.[2] Not only SARS-CoV but also MERS-CoV were reported to cause irreversible lung damage in survivors.[3] This nature of coronavirus is obviously distinct from other viruses such as influenza virus which usually show complete radiologic resolution of pneumonia after treatment.[2] How is COVID-19 pneumonia pathologically different from other virus-related pneumonias? What are the background factors that make COVID-19 pneumonia prone to irreversible interstitial lung disease? Are there any differences in the following background factors as a susceptibility for irreversible interstitial lung disease after COVID-19 pneumonia? (i) Presence or absence of pre-existing interstitial lung disease? (ii) Presence or absence of rheumatic and musculoskeletal diseases? (iii) Presence or absence of pre-existing interstitial lung disease with rheumatic and musculoskeletal diseases? There have been no reports to answer these questions.

Considering the similarities of lung lesions in anti-MDA5 antibody-positive dermatomyositis to COVID-19 pneumonia,[4] we suggest that viral infection may be one of the environmental factors that cause irreversible interstitial lung disease of dermatomyositis in susceptible individuals. Interestingly, MDA5 is involved in the recognition of viral RNAs including coronavirus and picornavirus, and plays a role for the production of interferons in response to those viruses.[5] Of note, SARS-CoV-2 induces MDA5-dependent interferon responses in lung cells.[6] Furthermore, a recent study has shown that anti-MDA5 antibody was positive in half of the patients with COVID-19 and the presence of anti-MDA5 antibody was associated with uncontrolled hyperinflammation and rapidly progressive interstitial lung disease.[7] Thus, viral infection may be the pathogenic cause of interstitial lung disease associated with dermatomyositis.

In any case, for the management of patients with rheumatic and musculoskeletal diseases during the COVID-19 pandemic, early dissemination of SARS-CoV-2 vaccines is desired to reduce the risk of severe COVID-19 pneumonia and to prevent irreversible lung damage in patients with rheumatic and musculoskeletal diseases.

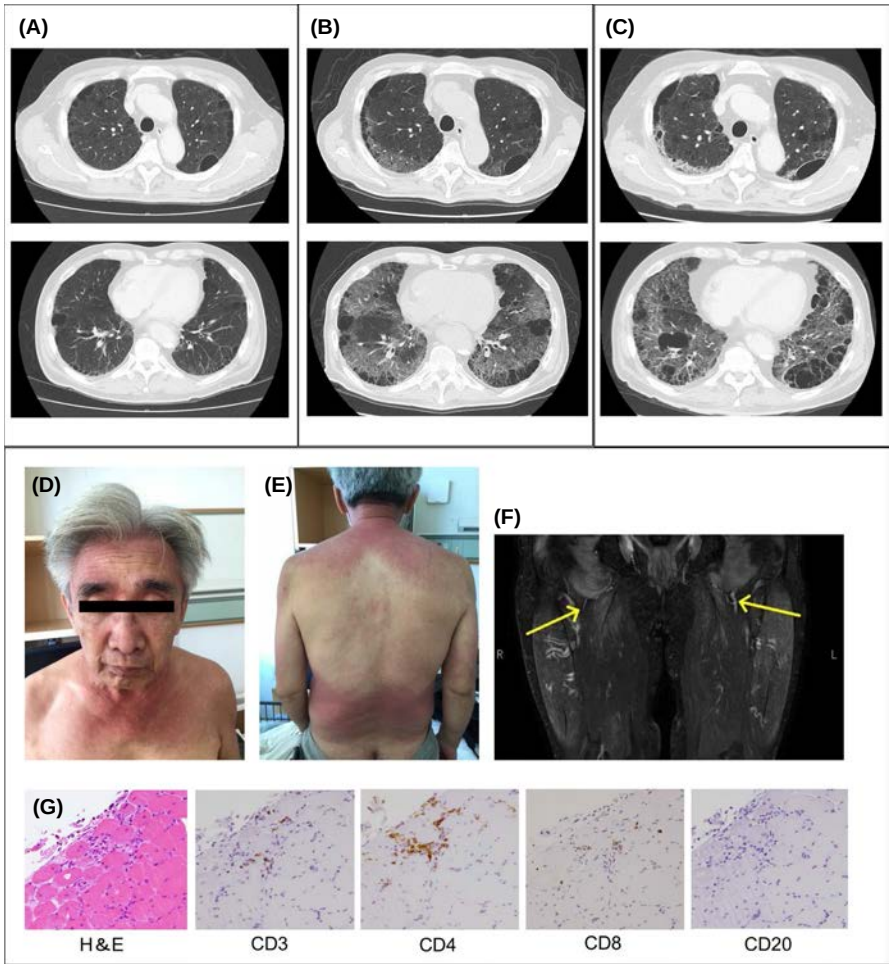


FIGURE 1 Chest computed tomography (CT) findings of COVID-19 pneumonia in a patient with dermatomyositis with pre-existing interstitial lung disease. (A) Chest CT performed before being affected with COVID-19 pneumonia shows multiple cysts in the upper lobe and honeycomb lung in the lower lobe. (B) Chest CT at the timing of COVID-19 pneumonia reveals newly emerging ground glass opacities in both lungs. (C) Chest CT at the 4-month follow-up after COVID-19 pneumonia demonstrates residual ground glass opacities and reticular fibrosis changes. (D) Heliotrope rash at diagnosis of dermatomyositis. (E) V-neck erythema and shawl sign at diagnosis of dermatomyositis. (F) High signal intensity of thighs on T2-weighted magnetic resonance imaging at diagnosis of dermatomyositis. (G) Muscle biopsy specimens of the right rectus femoris show CD4-positive T cell-dominant infiltration into the interstitium of muscle fibers at the margin of the muscle bundle. H&E, hematoxylin and eosin stain

PATIENT CONSENT FOR PUBLICATION

The authors obtained written informed consent from the patient.

KEYWORDS

COVID-19, dermatomyositis, interstitial lung disease, SARS-CoV-2

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

MA wrote the manuscript. SH and MA made the figure. SH, MA, TS, MHK, HT, KI, HO, and YO were responsible for the clinical care of the patient. MA and YO made critical revisions to the paper to enhance intellectual content. All authors read and approved the final manuscript.

Satoshi Hama[1]
Mitsuhiro Akiyama[1,2]
Tatsuya Shimada[1,2]
Misako Higashida-Konishi[1]
Hiroshi Takei[1,2]
Keisuke Izumi[1,2]
Hisaji Oshima[1]
Yutaka Okano[1]

[1]*Department of Connective Tissue Diseases, National Hospital Organization Tokyo Medical Center, Tokyo, Japan*
[2]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*

Correspondence
Mitsuhiro Akiyama, Department of Connective Tissue Diseases, National Hospital Organization Tokyo Medical Center, Tokyo 1528902, Japan; Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan.
Email: hhhirooo@hotmail.com

ORCID

Mitsuhiro Akiyama https://orcid.org/0000-0001-5075-8977
Misako Higashida-Konishi https://orcid.org/0000-0001-8712-3852
Keisuke Izumi https://orcid.org/0000-0001-8597-0759

REFERENCES

1. Tam LS, Tanaka Y, Handa R, et al. Updated APLAR consensus statements on care for patients with rheumatic diseases during the COVID-19 pandemic. *Int J Rheum Dis*. 2021;24(6):733-745. https://doi.org/10.1111/1756-185X.14124

2. So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. *BMC Pulm Med*. 2021;21:97.
3. Antonio GE, Wong KT, Hui DS, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology*. 2003;228:810-815.
4. Kondo Y, Kaneko Y, Takei H, et al. COVID-19 shares clinical features with anti-melanoma differentiation-associated protein 5 positive dermatomyositis and adult Still's disease. *Clin Exp Rheumatol*. 2021;39:631-638.
5. Xu L, Wang L, Lv C, Tan W. Anti-MDA-5-positive dermatomyositis associated rapidly progressive interstitial lung disease, a virus-triggered autoimmune-like symptom? *Rheumatology*. 2021:keab224. https://doi.org/10.1093/rheumatology/keab224
6. Rebendenne A, Valadão ALC, Tauziet M, et al. ARS-CoV-2 triggers an MDA-5-dependent interferon response which is unable to control replication in lung epithelial cells. *J Virol*. 2021;95:e02415-e2420.
7. Liu C, Wang Q, Wang Y, et al. Analysis of the correlation between Anti-Mda5 antibody and the severity of Covid-19: a retrospective study. *medRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.07.29.20164780v2

DOI: 10.1111/1756-185X.14193

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.