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EDITORIAL

Is topical therapy a way forward in osteoarthritis?

Osteoarthritis is a major public health problem. In the last decade there have been few significant advances in the therapy of this prevalent condition. Indeed, many trials have reported negative results and the area has been a therapeutic wasteland in comparison to dramatic advances in other areas of rheumatology. These failures include biologic therapies commonly used for rheumatoid arthritis, bone-directed therapy, antimalarials, statins, vitamin D, glucosamine and fish oil. At the same time, safety issues have become more paramount with nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and narcotics. There have been some promising results for moderate dose prednisolone,[1] different injectable corticosteroid preparations,[2] curcumin[3] and methotrexate.[4] The effect sizes with these therapies have generally been small to moderate, so there is a major unmet need. The anti-nerve growth factor therapies had a major benefit in terms of pain[5] and there was much excitement. However, these therapies improved pain so much that they increased the rate of joint replacement possibly by causing functional neuropathic joints. As a result, the development program has largely been suspended on these agents.

NSAID gels have been used fairly effectively for osteoarthritis for many years since the original trial by Altman et al.[6] The effect size based on an Osteoarthritis Research Society International review was moderate and actually significantly greater than oral NSAIDs for knee osteoarthritis as well as being quite safe.[7] In this issue of the journal, Tomatsu and colleagues[8] report on a new large trial of a different method of delivery of an old therapy for osteoarthritis. The agent was a novel plaster delivery of flurbiprofen. After a 2 week period of therapy with celecoxib (presumably to identity NSAID responders), they did a 2-week multicenter open label randomized trial with blinded assessors. This was designed as a non-inferiority trial which is important for inferences that can be made from this trial. The key result is that non-inferiority was met for this new agent. There were also results suggesting superiority. Unfortunately, the authors did not prespecify this in the analysis plan as has been commonly done in other rheumatology trials when non-inferiority is met.[9] While there is a reasonable rationale for why this agent may be superior, all of these results must be considered *post hoc* analyses. The primary outcome was pain on arising from a chair. Contrary to the authors' assertion, this measure has not been fully validated as an outcome measure in osteoarthritis. It has face and content validity but other measures of validity have not been evaluated. It is thus hard to interpret the magnitude of benefit and the pain effect had not plateaued after 14 days, suggesting there may be a greater effect over time. As expected, the therapy was very safe. Overall, I would welcome this novel therapy as an option in my osteoarthritis patients.

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REVIEW

Consensus statements for evaluation and nonpharmacological Management of Psoriatic Arthritis in UAE

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Abstract

Objective: Psoriatic arthritis (PsA), a chronic inflammatory arthropathy, is often underdiagnosed in Middle Eastern countries, substantially impacting the treatment of affected individuals. This article aims to highlight current unmet clinical needs and provide consensus recommendations for region-specific evaluation methods and nonpharmacological therapies in the United Arab Emirates (UAE).

Method: An extensive literature review was conducted, focusing especially on global and regional guidelines for the evaluation and treatment of PsA. These form the basis of the consensus statements formulated. Additionally, an expert panel of key opinion leaders from the UAE reviewed these guidelines and available literature at an advisory board meeting to identify unmet needs, bridge clinical gaps in the UAE, and develop consensus statements for the evaluation and treatment of PsA.

Result: The consensus statements were developed based on overarching principles for the management of PsA, evaluation of patients with PsA, and nonpharmacological approaches for the management of PsA. The overarching principles included adopting a targeted, multidisciplinary approach, along with collaboration between rheumatologists and dermatologists in cases of clinically significant skin involvement. The panel also highlighted the value of composite disease severity measures for characterizing clinical manifestations of PsA. In terms of nonpharmacological management approaches, lifestyle modification (comprising dietary change, exercise, and cessation of smoking) and psychotherapy were recommended.

Conclusion: The consensus statements will aid healthcare professionals in clinical decision-making in the context of PsA.

KEYWORDS
assessment tools, guidelines, nonpharmacological approach, overarching principles, psoriatic arthritis, severity

1 | INTRODUCTION

Psoriatic arthritis (PsA), an autoimmune disorder characterized by chronic inflammation of the skin and joints, affects approximately 2%-3% of the general population.[1] The global prevalence of PsA varies by geographic region and ranges from 0.001% to 0.42%,[2–4] whereas the prevalence of PsA is 0.01%-0.3% in Middle Eastern countries.[5,6] Evidence of nail dystrophy, scalp lesions, intragluteal and/or perianal lesions, involvement of three or more sites, male sex, and family history of PsA[7–9] are risk factors for the development of PsA in patients with psoriasis. Approximately 20% of patients diagnosed with PsA may develop a more aggressive form of arthritis, resulting in joint damage.[4] Studies have shown that in many patients, PsA may progress to erosive disease in as little as 2 years after onset.[10]

Beyond musculoskeletal and skin manifestations, PsA is associated with comorbidities that contribute to the disease burden substantially. The most frequently associated comorbidities include cardiovascular disease, obesity, type 2 diabetes mellitus, metabolic syndrome, hyperlipidemia, hypertension, nonalcoholic fatty liver disease, hyperuricemia, gout, Crohn disease, and depression.[11–15] Studies have reported that more than 50% of patients diagnosed with PsA are affected by at least one comorbidity. Comorbidities impact disease activity, physical functioning, and the quality of life of patients with PsA and, therefore, are an important consideration in treatment decision-making.[16]

A key aspect of PsA treatment is understanding the classification criteria and outcome measures used to assess disease activity. Psoriatic arthritis is different from other forms of chronic inflammatory arthritis in terms of its complex clinical presentation. Therefore, it is important for clinicians and rheumatologists to use appropriate classification criteria in clinical practice to optimize care for patients with PsA. Currently, ClASsification criteria for Psoriatic Arthritis (CASPAR) are widely used for recruitment in randomized clinical trials and longitudinal observational studies, and are validated in primary healthcare settings. However, the criteria require the healthcare practitioner to differentiate inflammatory arthritis from other nonspecific aches and pains in tendons and joints, which would pose a challenge for practitioners other than rheumatologists. For this reason, classification criteria that can better define the inflammatory musculoskeletal disease component are required. Furthermore, there are several validated outcome measures defining low, medium, and high disease activity. However, there is no consensus on the use of any specific outcome measure to assess disease activity and evaluate treatment response in patients with PsA.[17]

Therapeutic decisions in PsA are guided by a patient-centric approach in collaboration with dermatologists, primarily aimed at addressing disease activity, comorbidities, structural damage, and patient-reported outcomes.[18,19] Considering the heterogeneity in the clinical manifestations of PsA, it is important to ensure standardized treatment practices to assist practising physicians; rheumatologists, and dermatologists. Dermatologists and rheumatologists should collaborate and coordinate their efforts to achieve optimal care for patients with PsA. Treatment recommendations developed by members of the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have been widely adopted in clinical practice.[20,21] Apart from pharmacological therapies, nonpharmacological approaches such as lifestyle modification—including overcoming obesity, smoking cessation, reduction in alcohol intake, and low-impact physical exercises—are beneficial in the context of PsA.[22–25]

The objectives of this article are to address the gaps in clinical practice recommendations for the assessment of PsA severity and nonpharmacological therapeutic approaches for the treatment of PsA to assist practising physicians in the United Arab Emirates (UAE).

2 | MATERIALS AND METHODS

Six experts from the Emirates Society for Rheumatology representing different healthcare sectors of the UAE set up advisory board meetings to develop the consensus guidelines. The panel reviewed international and regional guidelines to determine clinical gaps in the evaluation of patients with PsA, as well as nonpharmacological approaches for the management of PsA. This would facilitate the development of consensus statements positioned around the identified gaps for the UAE.

2.1 | Targeted literature review

An extensive literature review was conducted considering unmet needs in clinical practice in the UAE. The current international and regional guidelines were reviewed by the panel of experts, and comparisons were made with the American College of Rheumatology/National Psoriasis Foundation Guideline (ACR/NPF) for the Treatment of Psoriatic Arthritis 2018, EULAR 2019, GRAPPA 2015, and the 2014 Saudi Practical Guidelines on the Biologic Treatment of Psoriasis.[20,21,26,27]

Based on a review of international and regional guidelines, consensus statements were developed for the following categories—overarching principles, evaluation of patients with PsA, and management of PsA using nonpharmacological approaches. Additionally, overarching principles from the GRAPPA 2020 treatment recommendations were adapted based on regional and cultural specifications for the UAE.[28] Key findings from the review were presented to the advisory board as statements from the expert panel. The prime objectives were:

1. To review similarities/differences between various international and regional guidelines for PsA treatment.
2. To identify and discuss gaps and unmet needs in current clinical practice for the evaluation and nonpharmacological management of PsA in the UAE.

The consensus statements were generated following the first advisory board meeting; the statements were authenticated and confirmed during the second advisory board meeting. The final statements formulated were then approved by all the members of the panel and put forth as recommendations.

The consensus statements have been presented in two separate parts. The present article, which is the first part, focuses on overarching principles, evaluation of PsA, and nonpharmacological treatment options for PsA. The second part covers consensus statements related to the pharmacological management of PsA (dosing and administration recommendations, treatment recommendations for PsA domains, and consensus statements on efficacy and safety profiles of nonbiological and biological therapies), monitoring requirements for therapies, and management of comorbidities.

3 | RESULTS

3.1 | Overarching principles

Based on current international guidelines, the following principles have been proposed for the management of PsA:

1. For the treatment of PsA, clinicians should adapt to both the treat-to-target and multidisciplinary approaches.
2. In patients with active PsA, using the treat-to-target strategy is recommended, where treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular assessment of disease activity and appropriate adjustment of therapy.
3. Rheumatologists should primarily care for the musculoskeletal manifestations of patients with PsA.
4. In the presence of clinically significant skin involvement, a rheumatologist and a dermatologist should collaborate in the diagnosis and management.
5. Treatment should aim to offer the best care and must be based on shared decision-making between the patient and rheumatologist, considering disease factors (activity, previous treatment, structural damage, comorbidities), treatment factors (safety and efficacy), and patient factors (access and preference).

3.2 | Evaluation of patients with psoriatic arthritis

The 2009 GRAPPA recommendations state that patients can be stratified into "mild," "moderate," and "severe" categories for each of the clinical manifestations of PsA (peripheral arthritis, skin disease, spinal disease, enthesitis, and dactylitis).[29] However, it was understood that patients may present with different levels of disease activity and clinical manifestations, and therefore, the 2015 updated GRAPPA statements removed these rigid categorizations and designed treatment approaches based on the disease activity, prognostic factors, comorbidities, and local access to therapies for the individual domains of PsA, namely peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, uveitis, and inflammatory bowel disease.[20,21]

The expert panel acknowledged the value of composite disease severity measures for characterizing the clinical manifestations of PsA. The Psoriatic ArthritiS Disease Activity Score (PASDAS) is a widely adopted weighted index measure that incorporates evaluator and patient assessments of visual analogue scale (VAS) scores, tender and swollen joint counts, dactylitis, enthesitis, health-related quality of life, and C-reactive protein levels. The Disease Activity for Psoriatic Arthritis (DAPSA) is a composite activity measure adapted from the disease activity index for the assessment of reactive arthritis (DAREA).[30] The DAPSA has been clinically validated[31] and performs well on arthritis domains,[32,33] but was found to be less powerful than the Composite Psoriatic Disease Activity Index (CPDAI) for the other clinical domains of PsA.[33,34] The CPDAI is a composite measure that includes assessments for six domains of PsA: peripheral arthritis, functional disability, skin, dactylitis, enthesitis, and spinal manifestations.[35] Unlike DAPSA, the CPDAI composite measure evaluates the extent of disease activity, as well as the effect of a particular domain on physical function and health-related quality of life, which includes the mental, emotional, and social functioning domains.[36] Overall, the PASDAS has been shown to perform better than the DAPSA and CPDAI measures, specifically for estimating high and low disease activity.[33,37,38] The expert panel urges that the PASDAS scoring assessment should be performed by a trained healthcare professional (trained nurse or rheumatology fellow), because rheumatologists do not routinely use this instrument.

For assessment of peripheral joint involvement, the Psoriatic Arthritis Response Criteria (PsARC) is an easy instrument that can be used in clinical practice. The PsARC evaluates tender and swollen joint scores, and physician's and patient's global assessment of disease activity.[39] The PsARC was able to distinguish between outcomes in the treated and placebo groups in several trials.[40–42] PsARC is no longer part of the Outcome Measures in Rheumatology Clinical Trials core domain set, but some insurance companies in the UAE mandate it for approval of immunosuppressive therapy.

The Minimal Disease Activity (MDA) scoring instrument is a clinically validated, reliable indicator of the state of disease activity at a given point. The MDA aids in the assessment of the treatment target.[43,44] The MDA consists of seven outcome measures, including evaluation of tender joints, swollen joints, Psoriasis Area and Severity Index (PASI) or body surface area (BSA) patient pain VAS, Patient Global Assessment, Health Assessment Questionnaire (HAQ), and tender entheseal points. The MDA is achieved when five out of seven criteria are met. The MDA can be widely adopted in the routine rheumatology clinic, owing to the ease of evaluating the individual component measures and the absence of blood tests.[45] Very low disease activity (VLDA), a modified MDA, has been developed and validated in recent studies. It represents the most stringent target for remission in PsA. The VLDA state is achieved when seven out of seven criteria are met.[46]

TABLE 1 Components in calculation of disease activity measures in PsA[40,52–55]

Components	DAPSA	CPDAI	PASDAS	MDA	PsARC	ASDAS
Clinical assessment						
Tender joint count	68	68	68	68	68	
Swollen joint count	66	66	66	66	66	
PASI		X	X	X		
Enthesitis (LEI)		X	X			
Dactylitis count		X	X			
VAS physician			X		X	
Physician Global						X
Patient questionnaire						
VAS global	X		X	X	X	X
VAS skin						
VAS joints						
VAS pain				X		
Back pain						X
HAQ		X		X		
DLQI		X				
BASDAI		X				X
ASQoL		X				
SF-36 PCS			X			
PsAQoL						
ASAS partial remission						X
Laboratory assessment						
CRP	X		X			X
ESR						X

Note: Consistent use of scoring method for assessment is important in clinical practice.

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CPDAI, Composite Psoriatic Disease Activity Index; CRP, C-reactive protein; DAPSA, Disease Activity index for PSoriatic Arthritis; DAS28, Disease Activity Score 28; DLQI, Dermatology Life Quality Index; ESR, erythrocyte sedimentation rate; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PASDAS, Psoriatic ArthritiS Disease Activity Score; PASI, Psoriasis Area and Severity Index; PsAQoL, Psoriatic Arthritis-specific Quality of Life; PsA, psoriatic arthritis; PsARC: Psoriatic Arthritis Response Criteria; SF-36 PCS, Short Form 36 Physical Component Scale; VAS, visual analogue scale.

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a recently developed composite disease activity score endorsed by the Assessment of SpondyloArthritis International Society (ASAS). The preferred version selected by the ASAS is the ASDAS-C-reactive protein, and the alternative is the ASDAS-erythrocyte sedimentation rate. The ASDAS score correlated well with disease activity and showed good discriminative power, in terms of both physician and patient global assessments of disease severity.[47,48] The expert panel recognized the lack of validation of ASDAS in patients with PsA and axial involvement. However, the panel suggests that in such cases, the ASDAS be used.[49,50]

Considering the paucity of information on the diagnostic instruments for the screening of patients with PsA, severity assessment of PsA should be performed on a case-to-case basis[26] and should account for the following factors: involvement of joints and damage based on imaging modalities, loss of physical function, impact on quality of life, and patient-reported outcomes. Patient-reported outcomes used for PsA, including the Short Form-12/36, Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scales, are used to capture disease activity, pain, physical function, fatigue, and productivity, among others.[51]

The expert panel acknowledged the pivotal role of rheumatologists in the care of patients with PsA and agreed that, for this reason, stratification of disease severity should primarily be based on rheumatological assessment.[20] Severe PsA should be established in accordance with the ACR/NPF criteria: poor prognostic factors (erosive disease, dactylitis, elevated levels of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein attributable to PsA), long-term damage that interferes with function (eg joint

TABLE 2 Consensus statements on assessing disease activity in PsA

1. Assessment of PsA requires consideration of major disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, nail disease, uveitis, and inflammatory bowel disease.
2. Instruments that could be considered for measuring activity in patients with PsA include: PASDAS and DAPSA scores, the PsARC, MDA score, and the ASDAS.
PsARC is an easy instrument that can be considered for assessment of disease activity in patients with PsA in clinical practice. Although PsARC is no longer part of the OMERACT core domain set, some insurance companies mandate it for approval of immunosuppressive therapy.
MDA score can be considered a valid and reliable instrument for the assessment of disease activity state and treatment target in patients with PsA.
The ASDAS score can be considered in the assessment of PsA with axial involvement, despite the lack of validation studies.
A combination of two or three of the most preferred instruments can be used to assess disease activity, and the practitioner should have the option to choose an instrument based on patient characteristics and disease involvement.
Stratification of disease activity should be assessed considering one or more of the following parameters:
Involvement of joints
Damage on imaging modalities
Loss of physical function
Quality of life impact
Patient-reported outcomes (eg SF-12/36, HAQ-DI, FACIT-F scale)
Axial involvement
For stratification of disease activity of PsA, only rheumatological assessment instruments should be considered.
Severe PsA disease includes the presence of one or more of the following (ACR/NPF):
Poor prognostic factors (erosive disease, dactylitis, extensive skin disease)
Long-term damage that interferes with function (eg joint deformities)
Highly active disease that causes major impairment to quality of life
Rapidly progressive disease
3. Regular assessment of the following is recommended:
Pain
Functional limitation
Quality of life and
Structural damage (eg X-ray, ultrasound, MRI)
4. Assessment and timely referral of comorbidities and related conditions, such as metabolic syndrome, obesity, cardiovascular disease, psychiatric disease, fibromyalgia, fatty liver disease, malignancies, chronic infections (eg hepatitis B virus/hepatitis C virus), and bone health, is recommended.

Abbreviations: ACR, American College of Rheumatology; ASDAS, Ankylosing Spondylitis Disease Activity Score; DAPSA, Disease Activity in Psoriatic Arthritis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MDA, minimal disease activity; MRI, magnetic resonance imaging; NPF, National Psoriasis Foundation; OMERACT, Outcome Measures in Rheumatology Clinical Trials; PASDAS, Psoriatic Disease Activity Score; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; QoL, quality of life; SF-12/36, Short Form-12/36.

deformities), and highly active disease that causes major impairment to quality of life and rapidly progressive disease.[26]

The important disease activity measures routinely used in clinical practice are provided in Table 1, along with their respective components. Consensus statements on assessing PsA disease severity are presented in Table 2.

3.3 | Nonpharmacological therapies

It is known that comorbid medical conditions and lifestyle factors (such as obesity, smoking, alcohol intake) and environmental triggers are risk factors for the development of PsA.[23,56,57] Patients with obesity and PsA are likely to experience chronic inflammation and have more severe disease activity when compared with patients with a normal body mass index. Obesity is an independent risk factor for PsA, but it is also true that patients with obesity have poorer outcomes and response to pharmacological therapies.[22,58] Although the evidence is limited to draw definitive conclusions,[59] weight-loss interventions can be particularly effective in improving disease activity in this population.[60,61] These patients may directly benefit from the use of a hypocaloric diet plan, either alone or in combination with aerobic physical exercise.[62] There is evidence that intermittent fasting, such as the circadian system of fasting observed during Ramadan, is associated with improved disease activity in patients with PsA, regardless of the pharmacological therapy they receive.[63]

In accordance with the recommendations of the ACR/NPF,[26] the expert panel agreed that any form of physical exercise is preferable

TABLE 3 Consensus recommendations for use of nonpharmacological therapies for psoriatic arthritis (PsA)

Recommendations
Diet
Patients with PsA should be provided dietary counseing
Intermittent fasting can have beneficial effects on PsA disease activity, including PsA-related disorders, such as enthesitis and dactylitis, regardless of the implicated drug therapy
In patients with overweight and obesity, weight loss should be emphasized
Limited intake of alcohol should be encouraged
Exercise
In patients with PsA, some form or combination of physical therapy, exercise, occupational therapy, acupuncture, and massage therapy should be considered
Low-impact exercises such as yoga, tai chi, and swimming should be encouraged
High-impact exercises such as running can be considered in patients who have no contraindication to these exercises
Smoking
Smoking (cigarettes and tobacco) cessation should be emphasized
Psychotherapy
Psychotherapy should be considered for patients with PsA, as depression is prevalent in these patients

to none in patients with active PsA.[25] Despite limited evidence, physical exercise has been shown to improve cardiorespiratory function and health-related quality of life in patients with active PsA.[64] Patients with active PsA may also benefit from the use of nonpharmacological interventions such as physical exercise, occupational therapy, massage therapy, and acupuncture.[65] The expert panel opined that low-impact physical exercises, such as tai chi, swimming, and yoga, should be encouraged in patients who cannot tolerate high-impact exercises such as running.

Despite the fact that there have been few studies examining the effect of smoking on treatment outcomes in PsA patients,[66] it is well established that smoking is strongly linked to radiographic progression and poor prognosis in rheumatoid arthritis (RA).[67–70] Smoking cessation is associated with lower disease activity and improved cardiovascular outcomes in patients with RA.[24] Therefore, in accordance with ACR/NPF, smoking cessation (cigarettes or tobacco) is recommended in patients with PsA.[26]

A significantly high proportion of patients with PsA report poor quality of life, depressive symptoms, anxiety, mood disturbances, and changes in sleep quality.[71–73] It has been reported that higher disease activity and pain scores are correlated with the presence of a comorbid mental condition.[74] Psychological interventions, therefore, are an important part of the multidisciplinary care plan for the management of PsA. Although studies are lacking for PsA, psychological interventions such as cognitive behavioral therapy, biofeedback, counseling, mindfulness, relaxation (eg tai chi and yoga), and patient education have been shown to have a positive effect on the physical and psychological distress associated with RA.[75]

Considering the value of these interventions in improving quality of life, which can ultimately have a positive impact on disease outcomes, the expert panel recommends the use of psychotherapy in the routine clinical management of PsA. Consensus recommendations for the use of nonpharmacological therapies for PsA are presented in Table 3.

4 | CONCLUSION

The present consensus statements are in agreement with established global guidelines on the different aspects of PsA, especially highlighting the evaluation of PsA and nonpharmacological therapies for PsA. These consensus statements can assist healthcare professionals in the UAE to effectively evaluate and treat patients with PsA.

AUTHOR CONTRIBUTIONS

KAA had a substantive role in drafting the final manuscript. The authors are fully responsible for all the content and editorial decisions; the authors involved themselves at all stages of manuscript development and approved the final version.

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CONFLICT OF INTEREST

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REVIEW

Association between genetic polymorphisms and osteoarthritis development. Overview of systematic reviews

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Abstract

Objective: To identify, critically evaluate and synthesize the evidence obtained from systematic reviews on the association between genetic polymorphisms and osteoarthritis (OA) development.

Methods: Considering gene polymorphisms associated with OA susceptibility (risk or protection), a comprehensive search was conducted in the following databases, without date or language restrictions: MEDLINE, via Pubmed; Embase, via Elsevier; Cochrane Database of Systematic Reviews, via Wiley; Biblioteca Virtual em Saúde. Gray literature was also searched through the OpenGrey database. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) was used to assess the methodological quality of the included systematic reviews.

Results: We included 14 systematic reviews of case-control studies comparing individuals with a radiographic diagnosis of all OA types and healthy controls, all submitted to the genetic examination of different polymorphisms in candidate genes. Meta-analyses showed a protective effect against knee and hand OA associated with *GDF-5* gene (odds ratio [OR] 0.90, 95% confidence interval (CI) 0.85-0.95), and knee OA with *ESRα* gene (OR 0.63, 95% CI 1.26-1.97). *SMAD3* gene was associated with knee and hip OA risk (OR 1.21. 95% CI 1.07-1.38) and *MMP-1* gene was associated with temporomandibular OA (OR 1.58. 95% CI 1.26-1.97).

Conclusion: Based on low-quality to critically-low-quality systematic reviews, some gene polymorphisms seem to be associated with risk or protection for OA. Further high-quality studies are needed to validate these hypotheses, contribute to disease understanding, and possibly help the decision-making related to early diagnosis and treatment options for OA. PROSPERO register CRD42021234231.

KEYWORDS
evidence-based medicine, genetic polymorphisms, osteoarthritis, systematic review

1 | INTRODUCTION

Osteoarthritis (OA) is one of the most common degenerative joint diseases, affecting around 300 million people and leading to a socioeconomic burden worldwide.[1–3] The Osteoarthritis Research Society International has defined OA as a progressive joint disorder characterized by cellular stress and extracellular matrix degradation, which activates an inadequate pro-inflammatory repair response. These conditions cause cartilage degradation, bone remodeling, intraarticular inflammation, joint space loss, and osteophyte development, leading to pain, stiffness, and decreased range of motion.[2,4,5]

The etiopathogenesis of OA is multifactorial; both intrinsic and extrinsic factors are considered etiologic, including lifestyle, environmental, aging, hormonal, and genetic factors. Many studies have sought to unravel the risk factors to OA, and the association of genetic polymorphism has recently attracted attention. However, it remains a challenge to find unanimous biomarkers that could help with the early diagnosis and targeted therapy for OA patients.[6]

Recent systematic reviews have assessed observational studies that addressed polymorphisms in numerous candidate genes, searching for an association that could indicate susceptibility to risk or protection in OA development. In addition, some of these polymorphisms may be specific to OA subtypes (hip, knee, or hand) and ethnic groups.[7–9] Although the importance of some genes in OA pathogenesis is relatively well established, the association of polymorphisms with susceptibility to OA was not consistent because of the heterogeneity and complexity of this disease.

Therefore, given the growing interest of clinicians and researchers in polymorphisms associated with OA and the large number of systematic reviews published so far, it is necessary to synthesize this information to facilitate the access and dissemination of knowledge, as well as to assess the methodological quality of these reviews to quantify confidence in the evidence for the support of decision-making. This overview aims to identify and critically synthesize the evidence obtained from systematic reviews regarding the association between genetic polymorphisms and OA development.

2 | MATERIALS AND METHODS

This overview of systematic reviews will follow the methodological recommendations of the Cochrane Manual for Systematic Reviews of Interventions[10] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11] with adjustments compatible with the overview items. The protocol of this overview was registered in the PROSPERO platform under the number CRD42021234231.

2.1 | Eligibility criteria

2.1.1 | Type of study

We included systematic reviews (with or without meta-analysis) assessing the association between any polymorphism and OA development. Protocols of systematic reviews, reviews withdrawn from the Cochrane Library, or reviews published as preprint were not considered.

2.1.2 | Type of participants

Adults (over 18 years) diagnosed with OA located in any joint.

2.1.3 | Type of exposure

Any polymorphism in recurrent genes that could be associated with OA development. Systematic reviews, including primary studies investigating serum gene polymorphism analysis, were not considered.

2.1.4 | Outcomes of interest

Type of gene polymorphism associated with susceptibility of OA (risk or protection), as reported by the included systematic reviews.

2.2 | Search strategy

A comprehensive and sensitive search was conducted in the following electronic databases, without date or language restrictions:

- Medical Literature Analysis and Retrieval System Online (MEDLINE), via Pubmed;
- Excerpta Medica Database (Embase), via Elsevier;
- Cochrane Database of Systematic Reviews, via Wiley;
- Biblioteca Virtual em Saúde.

The gray literature was also searched through the OpenGrey database (http://www.opengrey.eu/). In addition, the reference lists of relevant studies were hand-searched. The complete search strategies for each database are presented in Appendix S1.

2.3 | Study selection and data extraction

References identified in the search were selected by two independent reviewers using the Rayyan online platform.[12] The reviewers analyzed the titles and abstracts, and the studies with the potential of eligibility were assessed by reading the full text and classified as included or excluded. A third reviewer solved any divergences.

Two reviewers conducted, independently, the data extraction of the included systematic reviews using a standardized collection addressing: participants' characteristics, sample size, sex, age, body

mass index, subgroup analysis, gene polymorphism, OA anatomical site, data synthesis, methodological quality assessment, and funding sources.

2.4 | Methodological quality of the included systematic reviews

Two authors independently assessed the methodological quality of the included systematic reviews using the AMSTAR-2 tool (Assessing the Methodological Quality of Systematic Reviews).[13] AMSTAR-2 is composed of 16 items, and its assessment categorizes the overall quality of the systematic reviews as critically low (more than one critical failure), low (a critical failure), moderate (more than one non-critical failure) and high (none or non-critical failure). The certainty level was generated through the checklist available on the AMSTAR-2 website (http://amstar.ca/Amstar_Checklist.php). Disagreements were solved by consensus with a third author.

2.5 | Data synthesis

The results of the included systematic reviews were summarized narratively. In addition, when more than one systematic review analyzed the same gene polymorphism related to the exact OA anatomical location, we presented the results of the most recent review of higher methodological quality, intending to avoid the overlap and duplication of effect estimates.

3 | RESULTS

3.1 | Search results

Search results retrieved 155 records. After removing 24 duplicates, 131 studies were screened by title and abstracts, of which 19 were considered eligible and were analyzed in full text. Four systematic reviews were excluded because they: (a) did not include only OA patients,[14] (b) conducted serum analysis,[15,16] and (c) was not a systematic review.[17] One study was found only in Chinese and was considered as awaiting classification.[18] Hence, 14 systematic reviews were included (Figure 1).

3.2 | Characteristics of included systematic reviews

The main characteristics of the 14 included systematic reviews are presented in Table 1.

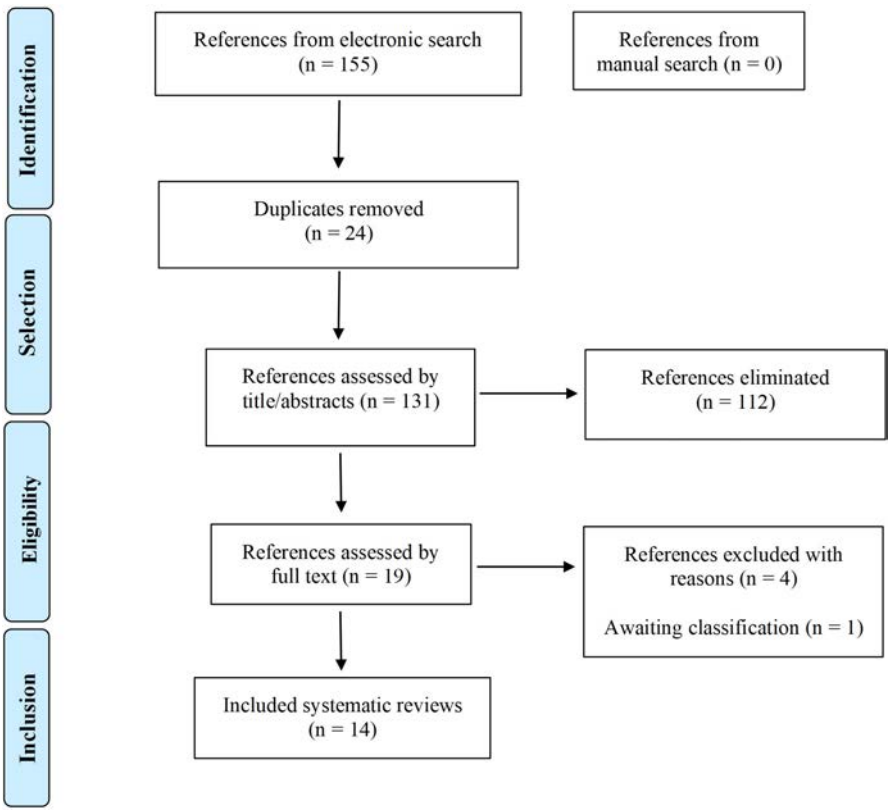

FIGURE 1 Flowchart of the study selection process

3.3 | Methodological quality of the included systematic reviews

The methodological quality of the included systematic reviews was classified as low to critically low according to the AMSTAR-2, with only one considered low quality. None of the included systematic reviews presented the protocol registration, and most of them conducted a limited search, with language and date restrictions. The detailed classification for each study is presented in Appendix S2.

3.4 | Data synthesis

The results obtained from the meta-analyses performed in the included systematic reviews are detailed in Table 2. The association between specific gene polymorphisms and OA susceptibility (risk or protection) was presented considering the allele genetic model. In summary, when assessing the overall population, the estimated effects showed:

(i) No association between:

- *ASPN gene (D-repeat* alleles polymorphisms) and knee, hip or hand OA;
- *MMP-1* gene (rs1799750 polymorphism) and knee OA;
- *CALM 1 gene* (rs12885713 polymorphism) and knee or hip OA;
- *ESRα gene* (rs2234693/rs9340799 polymorphisms) and knee OA;
- *GDF-5* gene (rs143383 polymorphism) and hip OA;
- *VDR* gene (rs731236, rs1544410, rs22285709 and rs7975232 polymorphisms) and overall OA.

(ii) Protective effect between:

- *GDF-5* gene (rs143383 polymorphism—C vs T allele) and knee or hand OA;
- *ESRα* gene (rs2228480 polymorphism/*Btg*I—A vs G allele) and knee OA.

(iii) Risk of OA between:

- *SMAD3* gene (rs12901499 polymorphism —G vs A allele) and knee or hip OA;
- *MMP-1 gene* (rs1799750 polymorphism—MMP-1-1607 1G > 2G) and temporomandibular joint OA.

The included systematic reviews also assessed subgroup analysis by ethnicity. There was no association between analyzed gene polymorphisms and OA development, except for (a) the protective effect of the *GDF*-5 (rs143383), *ESRα* (rs9340799), and *VRD* (rs731236 and rs22285709) polymorphisms against all OA types in Asian and Caucasian subgroups; (b) risk of all OA types regarding *ASPN D16* polymorphism in Caucasian and Latin American subgroups; and (c) risk of all OA types regarding *SMAD3* polymorphism (rs12901499) in Asian and Caucasian subgroups, and *VRD* (rs7975232) in Asian subgroup. The estimates of effect for each ethnicity subgroup analysis presented by systematic reviews are presented in detail in Appendix S3.

4 | DISCUSSION

The association between genetic polymorphism and OA development has been considered a possible contributor to managing people diagnosed or presenting risk factors for OA, so many candidate gene polymorphisms have been described as susceptible to risk or protection for this condition. This overview identified 14 systematic reviews throughout a comprehensive literature search, classified as methodologically low to critically low according to the AMSTAR-2. The allelic models have been analyzed to define allelic/genotypic combinations maximizing environment-phenotype association; however, in this review, the allele model was considered more relevant to correlate the results and conclusion with the association of risk or protection genetic polymorphisms and OA. The results showed a protective effect between polymorphisms in *GDF-5* (rs143383) and *ESRα* (rs2228480) genes and knee and hand OA. Knee and hip OA risk was observed in *SMAD3* polymorphism (rs12901499) and temporomandibular OA was associated with *MMP-1* gene polymorphism (rs1799750). There were no associations between *ASPN*, *MMP-1*, *CALM 1*, and *VDR* genes and knee, hip, or hand OA. It is worth mentioning that more than one systematic review investigated the effects of the same polymorphisms (*GDF-5*, *ASPN*, and *ESRα* genes), and although we had planned to present the results of the most recent and higher methodological quality review, the findings were consistent between all of them.

Nevertheless, these estimated associations are considered uncertain given the poor methodological quality of the systematic reviews and the lack of numerical data in some of the analyses. In addition, none of the studies reported the PROSPERO protocol registry, the search strategies were not fully presented by most of the reviews, and the certainty of the evidence using the GRADE approach was evaluated by only one review. Also, it is noteworthy that all systematic reviews classified the primary included studies as case-control; however, their methodology is compatible with a cross-sectional design because the exposure and outcome assessments, ie the genotype-based study and the radiographic image, were conducted once and at the same time.

Another point to be discussed is the possible influence of some confounder factors in the results, including individual aspects related to OA development, such as age, sex, obesity, lifestyle, sources of control, and other environmental factors. Substantial diversity was found between primary studies in most of the meta-analyses presented in the included systematic reviews, and the impact of these confounders could explain it. Subgroup analysis was conducted considering separate data by ethnicity, and there was no association between all analyzed gene polymorphisms and OA regarding the Caucasian, Asian and African populations, except

TABLE 1 Characteristics of the included systematic reviews

Study/year	Included studies	Participants	Gene/Polymorphism number or name	Methodological quality assessment of the primary studies	Certainty of evidence assessment (GRADE)	Funding sources
Aghili 2018[19]	n = 17 case-control studies	n = 7424 cases/11 310 controls Mean age NR Knee OA	*GDF-5*/ rs143383	Not assessed	Not assessed	NR
Ahrar 2019[20]	n = 25 case-control studies	n = 7144 cases/8468 controls Mean age NR Knee OA	*ESR1*/ rs2234693 and rs9340799	Not assessed	Not assessed	NR
Hong 2018[21]	n = 10 (6 case-control studies and 4 cohort)	n = 5093 cases/5699 controls Mean age NR Knee and hip OA	*SMAD3*/ rs12901499	Newcastle-Ottawa Scale (moderate to high quality—score>6)	Not assessed	Zhejiang Province Natural Science Foundation (LQ18H060001), Zhejiang Province medical and health project (2018269731), Zhejiang Province Chinese medicine project (2015ZB028)
Jia 2021[8]	n = 14 case-control studies	n = 5524 cases/10 000 controls Mean age NR Knee OA	*GDF-5*/ rs143383	Newcastle-Ottawa Scale (moderate to high quality—score > 6)	GRADE (low certainty evidence)	National Natural Science Foundation of China (81802151); Natural Science Foundation of Shandong Province (ZR2019MH012), postdoctoral Science foundation of China (2018 M642616), Qingdao Applied basic Research Youth Project (19–6-2-55-cg)
Lee 2009[22]	n = 10 case-control studies	n = 1591 cases/1781 controls Mean age between 56.3 and 70 years Hand, lumbar spine, hip, and knee OA	*VDR*/ rs731236, rs1544410 and rs7975232	Not assessed	Not assessed	NR
Li 2020[23]	n = 18 case-control studies	n = 2983 cases/4177 controls Mean age NR Knee, hip, hand, and spine OA	*VDR*/ rs731236, rs1544410, rs22285709 and rs7975232	Newcastle-Ottawa Scale (moderate to high quality—score>6)	Not assessed	No funding sources
Liu 2014[24]	n = 8 case-controls studies	n = 1626 cases/2024 Controls Mean age NR Knee, hip, hand, and spine OA	*VDR*/ rs731236, rs1544410 and rs7975232	Newcastle-Ottawa scale (moderate to high quality—score>6)	Not assessed	National Natural Science Foundation of China.

(Continues)

TABLE 1 (Continued)

Study/year	Included studies	Participants	Gene/Polymorphism number or name	Methodological quality assessment of the primary studies	Certainty of evidence assessment (GRADE)	Funding sources
Liu 2019[25]	n = 7 case-control studies	n = 1245 cases/1230 controls Age between 16 and 75 years knee and TMJ OA	*MMP-1*/ rs1799750	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	No funding sources
Shi 2018[26]	n = 5 case-control studies	n = 2183 cases/2654 controls Mean age NR Knee and hip OA	*CALM 1*/ rs12885713	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	National Natural Science Foundation of China (grant 81472106)
Sobhan 2017[27]	n = 11 (10 case-control and 1 cohort)	n = 4610 cases/3621 controls Mean age NR Knee OA	*ASPN*/ D-repeat alleles	Not assessed	Not assessed	NR
Wang 2017[9]	n = 12 case-control studies	n = 5190 cases/5167 controls Mean age NR Knee, hip, and hand OA	*ASPN*/ D-repeat alleles	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	Science and Technology foundation of Anhui province (grants 1301043051)
Yazdi 2017[28]	n = 22 case-control studies	n = 6575 cases/7459 controls Mean age NR Knee OA	*ESRα*/ rs2234693 rs9340799 rs2228480	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	No funding sources
Yin 2017[29]	n = 14 case-control studies	n = 19 973 cases/33 537 controls Mean age NR Knee, hip, and hand OA	*GDF-5*/ rs143383	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	No funding sources
Zhu 2014[30]	n = 13 case-control studies	n = 2104 OA patients and 2939 controls Mean age between 22 and 65.8 years Knee, hip, hand, and spine OA	*VDR*/ rs731236, rs1544410, rs22285709 and rs7975232	Newcastle-Ottawa Scale (moderate to high quality—score >6)	Not assessed	NR

Abbreviations: *ASPN*, asporin gene; *CALM 1*, calmodulin 1 gene; *ESR1*, estrogen receptor-1 gene; *ESRα*, rstrogen receptor α gene; *GDF-5*, growth differentiation factor 5; *MMP-1*, matrix metalloproteinase-1; n, number of participants; TMJ, temporomandibular joint; *VDR*, vitamin D receptor.

TABLE 2 Main results of the included systematic reviews regarding the association between gene polymorphisms and OA susceptibility (risk or protection), considering the allele genetic model

Gene polymorphism	Main results (overall population)	Included SR
GDF-5 (rs143383)	*No association* between polymorphism and hip OA (OR 0.88, 95% CI 0.76 to 1.01; studies NR; n = N; $P = 0.00$; I^2 = NR) *Protective effect* (C vs T allele) against hand OA (OR 0.90, 95% CI 0.85 to 0.95; studies NR; n = NR; $P = 0.06$; I^2 = NR)	Yin 2017
	Protective effect (C vs T allele) against knee OA (OR 0.79, 95% CI 0.73 to 0.87; 13 studies; n = 2949 cases/6398 controls; $P < 0.001$; I^2 = 54%, low certainty evidence (GRADE)	Jia 2021
ASPN D-repeat alleles	ASPN D14 vs other alleles *No association* between polymorphism and knee OA (OR 1.30, 95% CI 1.00 to 1.70; 11 studies; n = 4610 cases/3621 controls; $P = 0.32$; I^2 = 77%) ASPN D13 vs other alleles *No association* between polymorphism and knee OA (OR 0.93, 95% CI 0.82 to 1.06; 11 studies; n = 4610 cases/3621 controls; $P = 0.32$; I^2 = 77%) ASPN D13 vs D14 *No association* between polymorphism and knee OA (OR 1.10, 95% CI 0.90 to 1.36; 11 studies; n = 4610 cases/3621 controls; $P = 0.32$; I^2 = 61%)	Sobhan 2017
	ASPN D13 allele polymorphism *No association* with OA (OR 0.97, 95% CI 0.88 to 1.07; 12 studies; n = 5190 cases/5167 controls; $P = 0.52$; I^2 = 56%) ASPN D14 allele polymorphism *No association* with OA (OR 1.14, 95% CI 0.95 to 1.38; 12 studies; n = 5190 cases/5167 controls; $P = 0.16$; I^2 = 75%) ASPN D15 allele polymorphism *No association* with OA (OR 1.02, 95% CI 0.94 to 1.10; 12 studies; n = 5190 cases/5167 controls; $P = 0.70$; I^2 = 14%) ASPN D16 allele polymorphism *No association* with OA (OR 1.09, 95% CI 0.98 to 1.22; 12 studies; n = 5190 cases/5167 controls; $P = 0.11$; I^2 = 49%)	Wang 2017
SMAD3 rs12901499	*Risk* of knee/hip OA (G vs A allele) (OR 1.21, 95% CI 1.07 to 1.38; 10 studies; n = 5093 cases/5699 controls; $P = 0.003$; I^2 = 75%)	Hong 2018
MMP-1 rs1799750	*No association* between polymorphism and knee OA (OR 1.12, 95% CI 0.72 to 1.76; 5 studies; n = NR; P = NR; I^2 = 89%) *Risk* of TMJ OA (MMP-1-1607 1G > 2G) (OR 1.58, 95% CI 1.26 to 1.97; 2 studies; n = NR; $P < 0.01$; I^2 = 0%)	Liu 2020
CALM 1 rs12885713	*No association* between polymorphism and knee/hip OA (OR 1.11, 95% CI 0.97 to 1.27; 5 studies; n = 2183 cases/2654 controls; $P = 0.12$; I^2 = 0%)	Shi 2018
ESRα/ESR1 rs2234693 (PvuII T > C) rs9340799 (XbaI A > G) rs2228480 (BtgI G > A)	rs2234693 (*Pvu*II C > T) *No association* between polymorphism and knee OA (OR 0.95, 95% CI 0.89 to 1.02; 11 studies; n = NR; $P = 0.21$; I^2 = 24%) rs9340799 (*Xba*I A > G) *No association* between polymorphism and knee OA (OR 1.22, 95% CI 0.89 to 1.67; 8 studies; n = NR; $P = 0.20$; I^2 = 86%) rs2228480 (*Btg*I G > A) *Protective effect* (A vs G allele) against knee OA (OR 0.63, 95% CI 0.51 to 0.79; 3 studies; n = NR; $P < 0.001$; I^2 = 32%)	Yazdi 2017
	rs2234693 (*Pvu*II C > T) *No association* with knee OA (OR 1.06, 95% CI 0.92 to 1.23; 14 studies; n = 4084 cases/4993 controls; $P = 0.38$; I^2 = 78%) rs9340799 (*Xba*I A > G) *No association* with knee OA (OR 0.95, 95% CI 0.70 to 1.18; 11 studies; n = 3060 cases/3475 controls; $P = 0.50$; I^2 = 87%)	Ahrar 2019

(Continues)

TABLE 2 (Continued)

Gene polymorphism	Main results (overall population)	Included SR
VRD rs731236 (TaqI) (TaqI) rs1544410 (BsmI) (BsmI) rs22285709 (FokI) rs7975232 (ApaI) (ApaI)	rs731236 (*Taq*I) *No association* with OA (OR 0.87, 95% CI 0.74 to 1.02; 14 studies; n = NR; $P = 0.08$; $I^2 = 46.5\%$) rs1544410 (*Bsm*I) *No association* with OA (OR 1.06, 95% CI 0.92 to 1.21; 8 studies; n = NR; $P = 0.35$; $I^2 = 10\%$) rs7975232 (*Apa*I) *No association* with OA (OR 1.10, 95% CI 0.95 to 1.27; 10 studies; n = NR; $P = 0.43$; I^2 = NR) rs22285709 (*Fok*I) *No association* with OA (OR 0.71, 95% CI 0.50 to 1.00; 6 studies; n = NR; $P = 0.05$; $I^2 = 31\%$)	Li 2020

Abbreviations: 95% CI, 95% confidence interval; *ASPN*, asporin gene; *CALM 1*, calmodulin 1 gene; *ESRα*, estrogen receptor α gene; *MMP-1*, matrix metalloproteinase-1; n, number of participants; NR, not reported; OA, osteoarthritis; OR, odds ratio; SR, systematic review; TMJ, temporomandibular joint; *VRD*, vitamin D receptor.

for the protective effect of the *GDF-5* polymorphism (rs143383), which was also associated with the protection against OA in the overall population.

GDF-5 polymorphism is one of the most investigated polymorphisms to be associated with OA. This gene seems to play a role in the development, maintenance, and repair of cartilage and bone, and mutations in its coding gene can lead to musculoskeletal diseases. The association between T-allele polymorphism (rs143383) in the *GDF-5* gene and all types of OA risk have been investigated, but this association is still controversial. On the other hand, the C allele of *GDF-5* (rs143383) seems to be associated with protection against knee OA and/or hand OA. Also, the results showed that the allele C (or genotype CC) of the *GDF-5* polymorphism (rs143383) protected against knee OA occurrence in Caucasian, Asian, and African populations.[8,29,31]

The estrogen receptor α (ESRα) gene regulates cellular signal pathways in vivo and bone mass in skeletal systems. Moreover, human ESRα, a member of the nuclear receptor superfamily of ligand-activated transcription factors that regulates gene expression and function, is one of the critical mediators of hormonal response in estrogen-sensitive tissues.[28] Hence, the included studies suggested that the BtgI G > A (rs2228480) polymorphism in the *ESRα* gene was significantly associated with a decreased knee OA risk in the overall population. However, considering the other assessed polymorphisms *Pvu*II C > T (rs2234693) and *Xba*I A > G (rs9340799), the results suggested no association with knee OA.[28]

The SMAD family member 3 (*SMAD3*) gene plays a critical role in joint homeostasis. In the nucleus, SMAD3 regulates target gene transcription and produces the phenotype in cartilage.[21] Considering the risk to OA, this study suggested a significant association between *SMAD3* polymorphism (rs12901499) in the overall population, demonstrating that the G variant in this polymorphism increased the risk of knee and hip OA.[21]

Matrix metalloproteinase-1 (MMP-1) can degrade collagen fibers in the extracellular matrix of articular cartilage and plays an important role in the pathogenesis of OA because the expression of *MMP-1* in OA chondrocytes is higher than that in normal chondrocytes.[25] Regarding the *MMP-1-1607* 1G > 2G polymorphism (rs1799750), this study revealed a significant correlation with OA susceptibility in the temporomandibular joint.[25]

Another overview of systematic reviews published in 2016 summarized the single nucleotide polymorphisms (SNPs) linked to OA susceptibility. Over 50 SNPs from different genes seem to be associated with either hip OA, knee OA, or both, including results on *GDF-5* (rs143383), *SMAD3* (rs12901499), and *ESRα* (rs9340799) genes consistent with the present study.[6] Our overview updated the evidence by conducting a more comprehensive literature search to identify systematic reviews evaluating all types of genetic polymorphisms (SNP, deletion, insertion, and others) and analyzing the most investigated and relevant gene candidates for different types of OA.

Although some candidate genes or polymorphisms seem to contribute to playing roles in OA pathogenesis, the genetic factors responsible for the etiology of the disease remain unknown. Furthermore, a single gene polymorphism has only a moderate effect on OA development. Hence, polymorphisms in the other genes and environmental factors may influence the susceptibility and pathogenesis of OA.[19] Therefore, further studies with high-quality methodology are needed to validate these hypotheses and contribute to using this genetic information in understanding the disease pathogenesis and possibly helping the decision-making related to early diagnosis and treatment options for OA.

AUTHOR CONTRIBUTIONS

AAB contributed to conceptualization, methodology, resources, and software. MESC contributed to conceptualization, methodology, supervision, and validation. MCSPC supervised the study and contributed to validation;,visualization, and writing the original draft. RR contributed to methodology, data curation, investigation, and to writing/preparing the original draft. RLP contributed to methodology, resources, software, and data curation. GRC contributed to resources, software, and data curation. ALCM contributed to conceptualization, methodology, project administration, and validation. All authors contributed to the writing—review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

COVID-19 outcomes among rheumatic disease patients in Kuwait: Data from the COVID-19 Global Rheumatology Alliance (C19-GRA) physician registry

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Abstract

Purpose: We aimed to assess the characteristics of inflammatory rheumatic disease (IRD) patients in Kuwait diagnosed with COVID-19 and the factors linked with hospitalization, complications, and mortality.

Methods: Data of IRD patients from Kuwait diagnosed with COVID-19 between March 2020 and March 2021, submitted to the COVID-19 Global Rheumatology Alliance physician-reported registry, were included in our analysis. Data on patients' age, gender, smoking, diagnosis, IRD activity, and other comorbidities were collected. Statistical Package for the Social Sciences (SPSS), version 25, was used for statistical analysis.

Results: A total of 52 patients were included, with a mean age of 55 years (±14). The majority of patients were ≤65 years (77%), female (77%), non-smokers (80.8%), and diagnosed with rheumatoid arthritis (67.0%). Of the included patients, 19.2%, 9.6%, and 7.7% reported having methotrexate monotherapy, antimalarials monotherapy, and interleukin-6 inhibitors monotherapy immediately before COVID-19, respectively. Most of the included patients (92.3%) were either in remission or had minimal/low disease activity, while others (7.7%) had moderate disease activity. Forty-three patients (82.7%) were hospitalized, while 11 patients (25.6%) required ventilation (invasive or non-invasive). Ten of the ventilated patients (90.9%) received glucocorticoids as part of the local protocol to treat severe COVID symptoms, and 4 patients (7.69%) died. The duration till symptom-free ranged between 0 to 30 days, with a mean value of 10 days (±6.5).

Conclusion: The current study provides timely real-world evidence regarding characteristics and potential risk factors linked to poor COVID-19-related outcomes in the IRD population in Kuwait.

KEYWORDS
anti-rheumatic drugs, COVID-19, Global Rheumatology Alliance, Kuwait, rheumatic disease

1 | INTRODUCTION

There is insufficient reliable data to guide our knowledge of outcomes in patients with inflammatory rheumatic diseases (IRD) or those who are immunosuppressed after SARS-CoV-2 infection, leading to uncertainty about chronic disease treatment in such patients.[1-3] Previous literature has highlighted the uncertainty if individuals with IRD fall into a susceptible, higher-risk group for being infected with SARS-CoV-2 and have poor outcomes.[4-6] Compared to people without IRD, IRD patients appear to have similar or slightly worse results.[5,7] However, crucial illness-related confounding variables (eg, disease activity or therapies) have not been previously discussed.

COVID-19 and its subsequent complications have been treated with medications typically used to treat IRD, raising issues regarding the influence of these therapies on SARS-CoV-2 infection outcomes.[8-10] Previous literature had even suggested continuing immunomodulatory or immunosuppressive medication in order to control IRD activity, avoid the progression of the disease, and avoid joint/organ damage caused by chronic inflammation.[11] Even during a pandemic, the withdrawal of effective medicines should be supported by scientific data.

In March 2020, a worldwide network of rheumatologists, data scientists, as well as patients, created a COVID-19 physician-reported case registry to collect more comprehensive data related to IRD patients infected with SARS-CoV-2.[12,13] Analyzing the collected data showed that older age, as well as comorbidities, were linked to hospitalization and severe COVID-19 outcome compared to the findings in the general population.[4,14,15]

The current study aimed to assess the clinical characteristics of IRD patients in Kuwait diagnosed with COVID-19 from the data submitted to the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry. Moreover, we investigated the factors linked with hospitalization, complications, and mortality among these patients.

2 | METHODS

2.1 | Study population and data source

In the current study, we included patients from Kuwait who entered the registry as of March 2020. The detailed C19-GRA physician-reported registry has been previously described.[12,16,17] The data collected was multicenter, with Jaber Alahmed Alsabah Hospital being the source of most cases as the major COVID-19 center in Kuwait.

The included patients were IRD patients with a COVID-19 diagnosis. The diagnosis of COVID-19 was reported by the physicians, whether it was diagnosed by polymerase chain reaction (PCR) test, metagenomic analysis, computed tomography imaging, laboratory investigations, or preliminary clinical diagnosis based on the clinical manifestations. Data on patients' age, gender, the status of smoking, medications prior to COVID-19 diagnosis, IRD activity, and other comorbidities were captured. Moreover, we collected laboratory findings and COVID-19-related data in terms of the time of diagnosis, clinical manifestations, treatment, admission to the hospital, and the maximum level of care received.

2.2 | Medications prior to COVID-19

The medications before COVID-19 diagnosis were categorized as follows:

1. conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs): antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, and tacrolimus
2. biologic DMARDs (bDMARDs): abatacept, belimumab, CD-20 inhibitors, interleukin (IL)-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, tumor necrosis factor inhibitors (anti-TNF), and
3. targeted synthetic DMARDs (tsDMARDs), namely Janus kinase (JAK) inhibitors.

The physicians reported the duration from the onset of symptoms either until the resolution of the symptoms or death.

2.3 | Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) for Windows, version 25, was used. Continuous variables are reported as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. While dichotomous data are reported as frequency and percentage (%).

3 | RESULTS

3.1 | Demographic and clinical characteristics at the time of hospitalization

As of March 2021, a total of 52 Kuwaiti patients were included in the C19-GRA physician-reported registry. The mean age of the included patients was 55 years (SD = 14). Most of them were aged ≤65 years (n = 40, 77%), female (n = 40, 77%), Arab (n = 49, 94.2%), and never-smokers (n = 42, 80.8%). The most common primary rheumatology diagnosis was rheumatoid arthritis (n = 35, 67.0%), followed by systemic lupus erythematosus (n = 6, 12.0%). Twenty-eight patients (54%) were hypertensive, while 19 patients (37%) had diabetes. Interstitial lung disease was reported in 6 patients (12%), and obstructive lung disease was reported in 4 patients (8%).

TABLE 1 Patient demographic and clinical characteristics (N = 52)

Characteristic	Study cohort
Age	55 ± 14
Aged ≤65 y	40 (77%)
Aged >65 y	12 (23%)
Gender	
Female	40 (77%)
Male	12 (23%)
Race/ethnic origin	
Arab	49 (94.2%)
Non-Arab	3 (5.8%)
Smoking status	
Former smoker	1 (1.9%)
Never smoked	42 (80.8%)
Unknown smoking status	9 (17.3%)
Primary rheumatology diagnosis	
Rheumatoid arthritis	35 (67.0%)
Systemic lupus erythematosus	6 (12.0%)
Behçet's	2 (3.8%)
Inflammatory myopathy	2 (3.8%)
Sarcoidosis	2 (3.8%)
Antineutrophil cytoplasmic antibody-associated vasculitis	1 (1.9%)
Autoinflammatory syndrome (including tumor necrosis factor-associated periodic syndrome, cryopyrin-associated periodic syndrome, familial Mediterranean fever)	1 (1.9%)
Axial spondylarthritis (including ankylosing spondylitis)	1 (1.9%)
Immunoglobulin G4-related disease	1 (1.9%)
Mixed connective tissue disease	1 (1.9%)
Psoriatic arthritis	1 (1.9%)
Immune-modulating medications immediately before COVID-19 onset	
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) monotherapy	25 (48.1%)
Biologic DMARDs (bDMARDs) monotherapy	12 (23.1%)
Targeted synthetic DMARDs (tsDMARDs) monotherapy	2 (3.8%)
csDMARDs plus bDMARDs	7 (13.5%)
csDMARDs plus tsDMARDs	3 (5.8%)
Azathioprine / 6-mercaptopurine plus colchicine	1 (1.9%)
None	2 (3.8%)
Glucocorticoids at time of COVID-19 symptom onset	
Yes	7 (13%)
No	44 (85%)
Unknown	1 (1.9%)
Rheumatic activity	
Remission	26 (50%)
Minimal or low disease activity	22 (42%)
Moderate disease activity	4 (7.7%)
Comorbidities	
Hypertension	28 (54%)
Diabetes	19 (37%)
Interstitial lung disease	6 (12%)
Obstructive lung disease	4 (8%)
Chronic renal insufficiency or end-stage renal disease	3 (6%)
Obesity, body mass index ≥ 30	2 (4%)
Cardiovascular disease	2 (4%)
Others[a]	8 (15%)

Note: Continuous data are reported as mean ± SD; dichotomous data are reported as number and percentage (%).

[a]Includes other lung diseases, morbid obesity (BMI ≥ 40), cardiovascular disease (coronary artery disease, congestive heart failure), cerebrovascular disease, pulmonary hypertension, cancer, organ transplant recipient, immunoreactions, inflammatory bowel disease, liver disease, chronic neurological or neuromuscular disease, trisomy 21, psychiatric condition (eg, schizophrenia, bipolar disorder), macrophage activation syndrome (prior to COVID-19 diagnosis), psoriasis, pregnancy, post-partum (<6 weeks), or unknown.

Ten patients (19.2%) reported having methotrexate monotherapy before COVID-19 onset, while antimalarials monotherapy and IL-6 inhibitors monotherapy were reported in 5 patients (9.6%) and 4 patients (7.7%), respectively, Table S1. Of the participants, 44 patients (85%) reported no use of glucocorticoids at the time of COVID-19 symptom onset. The rheumatic disease activity was classified into remission, minimal/low disease activity, and moderate disease activity. Most of the included patients were either in remission or had minimal/low disease activity (n = 48, 92.3%), while only 4 patients (7.7%) had moderate disease activity. Of the included patients, only 2 (3.85%) received the COVID-19 vaccine, 12 patients did not, while vaccination status was unknown for the majority of patients (n = 38; 73.08%). The demographic and clinical characteristics of the study participants are shown in Table 1. Figure 1 shows the flowchart of the included patients. The most common COVID-19 symptoms at the time of presentation were cough (60%), fever (54%), and shortness of breath (48%), as shown in Figure S1. The majority of the included patients (n = 40, 76.9%) showed an absence of leukopenia (defined as white blood cells [WBCs] <5000/mm^3). The laboratory investigations for the included patients are shown in Table S2.

Table 2 shows the clinical characteristics of the included patients at the time of hospitalization. Of the included patients, 43 (82.7%)

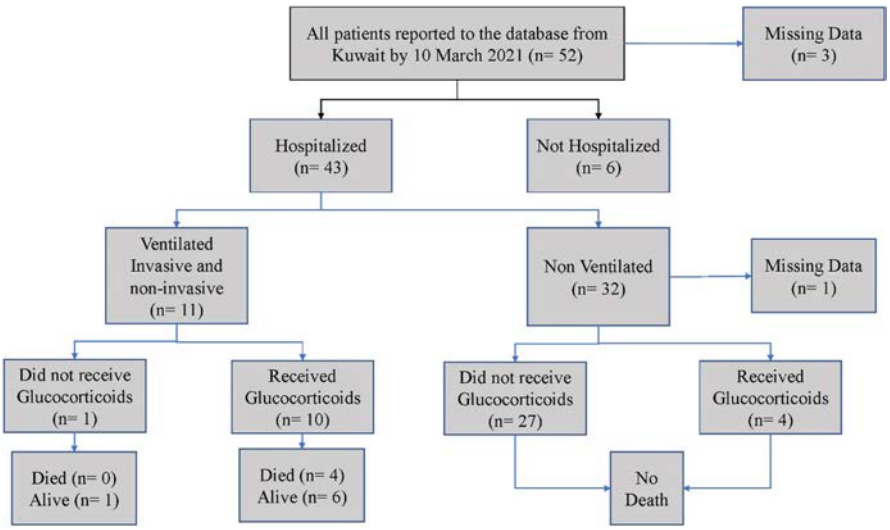

FIGURE 1 Flow diagram of the included patients

were hospitalized, and 6 (11.5%) were not hospitalized. Only 7 patients (13%) reported using glucocorticoids at the time of COVID-19 symptom onset. Nineteen patients (44.2%) did not require supplemental oxygen, while 13 patients (30.2%) required supplemental oxygen. Eleven patients (25.6%) required ventilation, either invasive or non-invasive. Of the 11 ventilated patients, 10 patients received glucocorticoids as part of the local protocol to treat severe COVID symptoms, and 4 patients (7.69%) died. In contrast, none of the non-ventilated patients have died. Adult respiratory distress syndrome was reported in 8 patients (15%), while sepsis was reported in 4 patients (7.7%). Regarding COVID-19 management, only supportive care was used for 25 patients (48.1%), and glucocorticoids were administered to 18 patients (34.6%).

3.2 | IRD patients with COVID-19 stratified by ventilation status

Based on the ventilation status, IRD patients diagnosed with COVID-19 were classified into 2 groups: non-ventilated and ventilated patients. Most of the 32 non-ventilated patients were ≤65 years (n = 24, 75.0%), female (n = 26, 81.25%), Arab (n = 30, 93.75%), never smoked (n = 27, 84.38%), non-diabetic (n = 21, 65.63%), hypertensive (n = 18, 56.25%), and did not receive glucocorticoids at time of COVID-19 symptom onset (n = 28, 87.50%). Moreover, most of the 11 ventilated patients were ≤65 years (n = 8), female (n = 10), Arab (n = 11), never smoked (n = 10), non-diabetic (n = 6), hypertensive (n = 7), and did not receive glucocorticoids at time of COVID-19 symptom onset (n = 9) (Table 3).

Among the non-ventilated patients, methotrexate monotherapy, csDMARDs (other than methotrexate), and biologics monotherapy were reported in 6 patients (18.75%), 7 patients (21.88%), and 9 patients (28.13%), respectively. Methotrexate plus other csDMARDs and biologics plus methotrexate combinations were reported in 3 patients (9.38%) and 5 patients (15.63%), respectively. On the other hand, methotrexate monotherapy, as well as methotrexate plus other csDMARDs and biologics plus methotrexate combinations, were reported in none of the ventilated patients. csDMARDs (other than methotrexate) and biologics monotherapy were reported in 6 patients (54.55%) and 5 patients (45.45%), respectively.

3.3 | IRD patients with COVID-19 stratified by COVID-19 complications

The demographic characteristics and the immune-modulating medications stratified by COVID-19 complications are shown in Table 4. The majority of IRD patients diagnosed with COVID-19 reported no known complications (n = 44). Of them, 32 patients were female, 34 patients aged ≤65 years, and 39 patients did not receive glucocorticoids at COVID-19 symptom onset. COVID-19-related complications were reported only in 8 patients. Out of the 8 patients (15.4%) who experienced COVID-19 complications, 6 were not on glucocorticoids (including prednisone, methylprednisolone) at the time of COVID-19 symptom onset. Among the patients with COVID-19-related complications, methotrexate monotherapy, csDMARDs (other than methotrexate), and biologics monotherapy were reported in 10 patients (22.7%), 11 patients (25.0%), and 12 patients (27.3%), respectively. Methotrexate plus other csDMARDs and biologics plus methotrexate combinations were reported in 3 patients (6.8%) and 5 patients (11.4%), respectively. On the other hand, methotrexate monotherapy, as well as methotrexate plus other csDMARDs and biologics plus methotrexate combinations, were reported in none of the patients with no known complications. csDMARDs (other than methotrexate) and biologics monotherapy were reported in half of them (n = 4, 50.0%).

3.4 | IRD patients with COVID-19 stratified by COVID-19-related mortality

Of the 52 included patients, only 4 patients (7.69%) died. The 4 patients were females aged ≤65 years. None of the patients who

TABLE 2 Patients' clinical characteristics during hospitalization (N = 52)

Characteristic	Study cohort
Hospitalization	
Yes	43 (82.7%)
No	6 (11.5%)
Glucocorticoids at time of COVID-19 symptom onset	
Yes	7 (13%)
No	44 (85%)
Duration till symptoms free (n = 33)	
Mean (±SD), d	10 (±6.5)
Range	0-30
Maximum care level during hospitalization (n = 43)	
Did not require supplemental oxygen	19 (44.2%)
Required supplemental oxygen	13 (30.2%)
Required non-invasive ventilation or high flow oxygen devices	3 (7.0%)
Required invasive mechanical ventilation or extracorporeal membrane oxygenation	8 (18.6%)
Complications	
No known complications	44 (85%)
Adult respiratory distress syndrome	8 (15%)
Sepsis	4 (7.7%)
Secondary infection	1 (1.9%)
Cytokine storm	1 (1.9%)
Other serious complications[a]	5 (9.6%)
Death	
Yes	4 (7.69%)
COVID-19 treatment	
Supportive care only	25 (48.1%)
Glucocorticoids	18 (34.6%)
Lopinavir /ritonavir	2 (4.0%)
Lopinavir /ritonavir and glucocorticoids	1 (1.9%)
Lopinavir /ritonavir and glucocorticoids and other	1 (1.9%)
Meronem and glucocorticoids	1 (1.9%)
Remdesivir and glucocorticoids	1 (1.9%)
Antimalarials	1 (1.9%)
Interleukin-1b inhibitors	1 (1.9%)
Colchicine	1 (1.9%)

Note: Continuous data are reported as mean ± SD; dichotomous data are reported as number and percentage (%). NB: hospitalization status is missing for 3 patients; Glucocorticoids status at time of COVID-19 symptom onset is unknown in 1 patient.

[a]Includes kidney failure/injury required dialysis, kidney failure/injury on dialysis, or pneumothorax.

received glucocorticoids (including prednisone, methylprednisolone) at COVID-19 symptom onset have died. Table 5 shows the demographic characteristics and the immune-modulating medications stratified by COVID-19 mortality. Among the patients who lived, methotrexate monotherapy, csDMARDs (other than methotrexate), and biologics monotherapy were reported in 10 patients (20.8%), 13 patients (27.1%), and 14 patients (29.2%), respectively. Methotrexate plus other csDMARDs and biologics plus methotrexate combinations were reported in 3 patients (6.2%) and 5 patients (10.4%), respectively. On the other hand, methotrexate monotherapy, as well as methotrexate plus other csDMARDs and biologics plus methotrexate combinations, were reported in none of the patients who died. Of the 4 deceased patients, mycophenolate mofetil/mycophenolic acid monotherapy was reported in only 1 patient, while CD-20 inhibitors (rituximab within the last 12 months) were reported in 3 patients.

3.5 | Days of hospitalization

The duration till symptom-free ranged between 0 to 30 days, with a mean value of 10 days (SD = 6.5). The detailed descriptive analysis of the days of hospitalization of the included patients is shown in Table S3.

4 | DISCUSSION

The COVID-19 pandemic undoubtedly influences the therapeutic approach to rheumatic diseases, whose infectious risk is considerably higher than the general population due to an overall immune system impairment characteristic of autoimmune diseases associated with the iatrogenic effect of corticosteroids as well as immunosuppressive drugs. Notably, numerous rheumatic medications, such as hydroxychloroquine, JAK, and IL-6 inhibitors, are being investigated to prevent and/or manage COVID-19 and its consequences.[8-10] A worldwide network of rheumatologists, scientists, and patients created a physician-reported case registry of patients with IRD confirmed with COVID-19 diagnosis to fill this knowledge shortfall.[16,17]

Kuwait's population is 4.67 million people as of 2021, with 1.85 million Kuwaitis and 2.8 million foreigners from more than 100 countries. Between March 2020 and March 2021, 230 596 COVID-19 cases have been reported by the Ministry of Health of Kuwait.

Earlier, a prevalence phase of a study on data of patients with rheumatic diseases conducted by Al-Awadhi et al on adult Kuwaitis[38] showed that 2057 people were classified as "sufferers", with a prevalence of musculoskeletal (MSK) pain of 26.8%. Male-to-female ratio was 1:1.9, and the mean age was higher in men than in women (47.5 years vs 44.4 years). A follow-up study[39] on the participants who had no MSK pain reported a new onset of MSK pain, with a prevalence of 6.6%. Of the 220 respondents, rheumatic conditions were reported in 29 patients (18 female and 11 male), with a male-to-female ratio of 1:1.6. The most frequent rheumatic condition was soft-tissue rheumatism (n = 17).

Most of our study participants were female. This is consistent with the predominance of autoimmune diseases in females. Similar

TABLE 3 Demographic and disease characteristics of individuals with rheumatic disease diagnosed with COVID-19 stratified by the ventilation status

	Non-ventilated		Ventilated	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Age				
≤65 y	24	75.00	8	72.73
>65 y	8	25.00	3	27.27
Gender				
Female	26	81.25	10	90.91
Male	6	18.75	1	9.09
Race/ethnic origin				
Non-Arab	2	6.25	0	0.00
Arab	30	93.75	11	100.00
Smoking status				
Former smoker	0	0.00	0	0.00
Never smoked	27	84.38	10	90.91
Unknown	5	15.63	1	9.09
Glucocorticoids at time of COVID-19 symptom onset				
No	28	87.50	9	81.82
Yes	4	12.50	2	18.18
Methotrexate monotherapy				
No	25	78.13	11	100.00
Yes	6	18.75	0	0.00
Missing	1	3.13	0	0.00
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (other than methotrexate)				
No	24	75.00	5	45.45
Yes	7	21.88	6	54.55
Missing	1	3.13	0	0.00
Methotrexate plus other csDMARDs				
No	28	87.50	11	100.00
Yes	3	9.38	0	0.00
Missing	1	3.13	0	0.00
Biologic DMARDs (bDMARDs) / targeted synthetic DMARDs (tsDMARDs) monotherapy				
No	22	68.75	6	54.55
Yes	9	28.13	5	45.45
Missing	1	3.13	0	0.00
bDMARDs/tsDMARDs plus methotrexate				
No	25	78.13	11	100.00
Yes	5	15.63	0	0.00
Missing	2	6.25	0	0.00
Interstitial lung disease				
No	28	87.50	10	90.91
Yes	4	12.50	1	9.09
Obstructive lung disease				
No	30	93.75	9	81.82
Yes	2	6.25	2	18.18

TABLE 3 (Continued)

	Non-ventilated		Ventilated	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Diabetes				
No	21	65.63	6	54.55
Yes	11	34.38	5	45.45
Hypertension				
No	14	43.75	4	36.36
Yes	18	56.25	7	63.64

Note: NB: ventilation status is missing in 9 patients; dichotomous data are reported as number and percentage (%).

findings were reported in previous studies that assessed the impact of the COVID-19 pandemic on IRD patients.[18,19] However, some literature reported a relative male predominance among IRD patients with severe SARS-CoV-2 infection.[20,21]

As reported by the Jaber Hospital electronic medical registry, the total number of hospitalized patients with COVID-19 in the same time period as our data collection was 13 825. A recent comparative study[22] revealed that, compared with matched comparators, IRD patients had a higher risk of hospitalization (relative risk [RR] = 1.14) and intensive care unit (ICU) admission (RR = 1.32), but not mechanical ventilation or death (RR = 1.05 and 1.08). The risks were reduced when the model was broadened to include comorbidities as well as healthcare utilization.

Of the included patients, 82.7% were hospitalized, 25.6% required either invasive or non-invasive ventilation, 15.4% had complications, and 4 female patients died. These findings reflect the increased rate of worse COVID-19-related outcomes, requiring ventilation, and death among females. Previous literature has reported contrary results. In the report by Hasseli et al, a total of 104 patients (63 female and 40 male) with IRD diagnosed with COVID-19 were included. The authors documented an overall hospitalization rate of 32%; the proportion of male patients who required hospitalization was higher, even though both genders were roughly evenly represented. In their study, out of the hospitalized patients, 39% required either non-invasive or invasive ventilation, and death was documented for 6 patients (3 female and 3 male).[20]

A previous comparative cohort study[19] conducted on 52 IRD patients and 104 non-rheumatic disease comparators showed a lower hospitalization rate among IRD patients diagnosed with COVID-19 (n = 23, 44%). This percentage was similar to the proportion of hospitalized patients from the non-rheumatic disease group (40%, $P = .50$). In their study, ICU admission and mechanical ventilation were required for 11 IRD patients (48%) compared with 7 (18%) non-rheumatic disease comparators (odds ratio = 3.11, 95% confidence interval = 1.07 to 9.05), and the mortality rate was comparable between the 2 groups (6% of IRD patients vs 4% of non-rheumatic disease comparators, $P = .69$).

Another prospective case series was conducted by Haberman et al[23] involving patients with immune-mediated inflammatory diseases. When proven or strongly suspected COVID-19 infection emerged, the included patients received anti-cytokine biologics monotherapy, immunomodulatory medications, or both. Fourteen patients (16%) were hospitalized. Compared with the hospitalized patients, the ambulatory patients (for whom hospitalization was not warranted) showed a higher percentage of being on biologics or JAK inhibitors at baseline (76% vs 50%). The overall hospitalization rate among individuals who had been on these therapies for a long time was 11%, and the multivariate analysis showed that patients with immune-mediated inflammatory disorders who needed hospitalization used more oral glucocorticoids (29% vs 6%), hydroxychloroquine (21% vs 7%), and methotrexate (43% vs 15%) than the ambulatory patients. When their analysis was limited to individuals with proven SARS-Cov-2 infection based on PCR testing, these findings remained consistent, and of the 14 hospitalized patients, 1 patient died while the other patient had high levels of IL-6 and required mechanical ventilation. None of the 2 patients received long-term biologic therapy. Gianfrancesco et al (2020)[14] showed that older age and comorbidities (such as diabetes mellitus, hypertension, cardiovascular disorders, etc) were associated with a higher risk of COVID-19 hospitalization. This is supported by previous literature.[24-26] As regards JAK inhibitors, Sparks et al (2021)[27] documented that when compared to RA patients who used anti-TNF therapies, RA patients who received rituximab or JAK inhibitors at the time of COVID-19 infection were more likely to have poor COVID-19 outcomes that ranged from hospitalization to death. The majority of patients with IRD are treated regularly with glucocorticoids, csDMARDs, and b/tsDMARDs. Some of the therapies used to manage IRD patients have been suggested to be useful in treating SARS-CoV-2 infection, while others may have negative side effects comparable to those seen in rituximab-treated patients.[28] Glucocorticoids, in particular, raise the risk of severe infection in a dose-dependent way. Data from the C19-GRA registry showed that a daily dose of glucocorticoids of ≥10 mg is linked to a greater risk of hospitalization.[14] The use of DMARDs has been linked to the development of infectious problems; the majority of these infections are bacterial, although some viral infections, such as herpes zoster, can affect the course of numerous anti-rheumatic treatments.[29,30]

TABLE 4 Demographic and disease characteristics of rheumatic disease patients diagnosed with COVID-19 stratified by the COVID-19 complications

	No COVID-19 complications		COVID-19 complications	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Age				
≤65 y	34	77.3	6	75.0
>65 y	10	22.7	2	25.0
Gender				
Female	32	72.7	8	100.0
Male	12	27.3	0	0.0
Race/ethnic origin				
Non-Arab	3	6.8	0	0.0
Arab	41	93.2	8	100.0
Smoking status				
Former smoker	1	2.3	0	0.0
Never smoked	35	79.5	7	87.5
Unknown	8	18.2	1	12.5
Glucocorticoids at time of COVID-19 symptom onset				
No	39	88.6	6	75.0
Yes	5	11.4	2	25.0
Methotrexate monotherapy				
No	32	72.7	8	100.0
Yes	10	22.7	0	0.0
Missing	2	4.5	0	0.0
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (other than methotrexate)				
No	31	70.5	4	50.0
Yes	11	25.0	4	50.0
Missing	2	4.5	0	0.0
Methotrexate plus other csDMARDs				
No	39	88.6	8	100.0
Yes	3	6.8	0	0.0
Missing	2	4.5	0	0.0
Biologic DMARDs (bDMARDs) / targeted synthetic DMARDs (tsDMARDs) monotherapy				
No	30	68.2	4	50.0
Yes	12	27.3	4	50.0
Missing	2	4.5	0	0.0
bDMARDs/tsDMARDs plus methotrexate				
No	36	81.8	8	100.0
Yes	5	11.4	0	0.0
Missing	3	6.8	0	0.0
Interstitial lung disease				
No	39	88.6	7	87.5
Yes	5	11.4	1	12.5
Obstructive lung disease				
No	42	95.5	6	75.0
Yes	2	4.5	2	25.0

TABLE 4 (Continued)

	No COVID-19 complications		COVID-19 complications	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Diabetes				
No	30	68.2	3	37.5
Yes	14	31.8	5	62.5
Hypertension				
No	21	47.7	3	37.5
Yes	23	52.3	5	62.5

Note: Dichotomous data are reported as number and percentage (%).

Gianfrancesco et al[14] documented that high prednisone dosages (more than 10 mg/d) were linked to a higher risk of COVID-19 hospitalization, while no link between previous NSAID or antimalarial usage and COVID-19 hospitalization was found. Moreover, the authors stated that biologic or tsDMARDs monotherapy was linked to decreased hospitalization risk, primarily driven by anti-TNF therapies. Previously, Richter et al (2016)[31] documented that TNF inhibitors are linked to a higher risk of severe infections in the early stages of treatment, but as they become much more effective, the risk reduces due to improved functional ability and reduced glucocorticoids usage. Interestingly, a recent study conducted by Izadi et al (2021)[32] on 6077 patients from 74 countries showed that, when compared to other frequently prescribed immunomodulatory management regimens, TNF inhibitor monotherapy was linked with a reduced risk of unfavorable COVID-19 outcomes in individuals with immune-mediated inflammatory diseases.

None of the patients who received glucocorticoids (including prednisone and methylprednisolone) at COVID-19 symptom onset have died in the current study. Previous literature has documented that mycophenolate mofetil and rituximab were significantly linked with worse outcomes after SARS-CoV-2 infection;[33,34] this is in line with our findings. Previous data from the GRA registry showed that, compared to methotrexate monotherapy, rituximab, sulfasalazine, immunosuppressants (including mycophenolate), and not receiving any DMARD were linked with a greater risk of death. Other csDMARDs/bDMARDs were not linked to death from COVID-19.[35] Rituximab attaches to CD-20 on B-cell surfaces, depleting this cell type and interfering with antibody production. As a result, B-cell depletion may impair antiviral immunity, including the production of anti-SARS-CoV-2 antibodies. Of the included patients, 5 received CD-20 inhibitors (3 patients used it as monotherapy, 1 patient used CD-20 inhibitors plus antimalarials, and 1 patient used CD-20 inhibitors plus mycophenolate mofetil). Three of the patients who used CD-20 inhibitors as monotherapy have died (3 out of the 4 reported mortality cases). Such an increased risk of mortality is a finding that warrants further investigation.

Data from the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) documented that 595 309 people in Kuwait were vaccinated during the same period of our study. The Ministry of Health of Kuwait revealed that as of 3 July 2021, 1 452 148 and 923 307 people had received 1 dose and 2 doses of COVID-19 vaccines, respectively, since the campaign began on 27 December 2020. In the current study, the status of the COVID-19 vaccine was unknown for most patients (n = 38; 73.08%). Only 2 patients (3.85%) were vaccinated, and 12 patients were not vaccinated. A recent study from the C19-GRA Vaccine Survey[36] assessed perception regarding the COVID-19 vaccine. Of 7005 respondents, 574 respondents (39.4%) reported being unsure or unwilling to receive a vaccine. Almost all of those unsure or unwilling cited worries regarding side effects, safety, and the fast development and deployment of COVID-19 vaccinations in clinical practice. Despite this, over half of the respondents reported they were pro-vaccine, while many others expressed varying degrees of apprehension: 98.5% of the unsure respondents and 66.9% of unwilling respondents mentioned that they would be more inclined to get vaccinated if a rheumatologist recommended it, and additional outcomes data are available.[36] Compared with the general population, systemic IRD patients vaccinated for COVID-19 showed comparable adverse events.[37] To boost vaccine efficacy, most patients were willing to temporarily discontinue receiving DMARDs. The low incidence of rheumatoid arthritis flare-ups necessitating treatment was reassuring (less than 5%).[37] This underlines the value of developing effective educational initiatives to boost the acceptance of the COVID-19 vaccine in Kuwait.

The available data highlights the vital relevance of vaccine safety and effectiveness concerns for IRD patients, which have persisted despite widespread vaccination. Educational initiatives aimed at increasing awareness and confidence in vaccines and the potential advantages of vaccination and combating the propagation of misleading information should be designed by Kuwaiti health authorities.

To our knowledge, this is the first study that assesses the sociodemographic characteristics and investigates the factors linked with hospitalization, complications, and death among IRD patients in Kuwait with a confirmed diagnosis of COVID-19. The main limitation of our study was the relatively small sample size of the included patients, and most of our study participants were from Jaber Alahmed Hospital. Because only individuals with severe symptoms are tested for COVID-19 in many countries, the C19-GRA registry has certain drawbacks that include a potential selection bias toward

TABLE 5 Demographic and disease characteristics of rheumatic disease patients diagnosed with COVID-19 stratified by COVID-19 mortality

	Alive	Deceased
	Frequency (%)	Frequency (%)
Age		
≤65 y	36.0 (75.0%)	4.0 (100.0%)
>65 y	12.0 (25.0%)	0.0 (0.0%)
Gender		
Female	36.0 (75.0%)	4.0 (100.0%)
Male	12.0 (25.0%)	0.0 (0.0%)
Race/ethnic origin		
Non-Arab	3.0 (6.2%)	0.0 (0.0%)
Arab	45.0 (93.8%)	4.0 (100.0%)
Smoking status		
Former smoker	1.0 (2.1%)	0.0 (0.0%)
Never smoked	39.0 (81.2%)	3.0 (75.0%)
Unknown	8.0 (16.7%)	1.0 (25.0%)
Glucocorticoids at time of COVID-19 symptom onset		
No	42.0 (87.5%)	3.0 (75.0%)
Yes	6.0 (12.5%)	1.0 (25.0%)
Methotrexate monotherapy		
No	36.0 (75.0%)	4.0 (100.0%)
Yes	10.0 (20.8%)	0.0 (0.0%)
Missing	2.0 (4.2%)	0.0 (0.0%)
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (other than methotrexate)		
No	33.0 (68.8%)	2.0 (50.0%)
Yes	13.0 (27.1%)	2.0 (50.0%)
Missing	2.0 (4.2%)	0.0 (0.0%)
Methotrexate plus other csDMARDs		
No	43.0 (89.6%)	4.0 (100.0%)
Yes	3.0 (6.2%)	0.0 (0.0%)
Missing	2.0 (4.2%)	0.0 (0.0%)
Biologic DMARDs (bDMARDs) / targeted synthetic DMARDs (tsDMARDs) monotherapy		
No	32.0 (66.7%)	2.0 (50.0%)
Yes	14.0 (29.2%)	2.0 (50.0%)
Missing	2.0 (4.2%)	0.0 (0.0%)
bDMARDs/tsDMARDs plus methotrexate		
No	40.0 (83.3%)	4.0 (100.0%)
Yes	5.0 (10.4%)	0.0 (0.0%)
Missing	3.0 (6.2%)	0.0 (0.0%)
Interstitial lung disease		
No	42.0 (87.5%)	4.0 (100.0%)
Yes	6.0 (12.5%)	0.0 (0.0%)
Obstructive lung disease		
No	44.0 (91.7%)	4.0 (100.0%)
Yes	4.0 (8.3%)	0.0 (0.0%)
Diabetes		
No	30.0 (62.5%)	3.0 (75.0%)
Yes	18.0 (37.5%)	1.0 (25.0%)
Hypertension		
No	21.0 (43.8%)	3.0 (75.0%)
Yes	27.0 (56.2%)	1.0 (25.0%)

more severe cases. Moreover, the included rheumatologists who reported cases were under marked stress to offer front-line medical treatment to all COVID-19 patients; thus, they may have been unable to submit cases or reported them late. We recommend that future clinical trials with larger sample sizes should address the association of different anti-rheumatic medications with COVID-19-related outcomes among IRD patients.

5 | CONCLUSIONS

Due to the fast gathering of data during the COVID-19 pandemic, very early characterization and distribution of information about COVID-19 in patients with IRD have been possible. Moreover, we could examine how sociodemographic and IRD characteristics, therapies used before COVID-19 diagnosis, and medications were given after diagnosis affect the severity of COVID-19 outcomes. The current study's findings would provide timely real-world evidence where considerable gaps in the literature exist, providing physicians with information on the treatment options for IRD patients diagnosed with COVID-19 and a better knowledge of potential risk factors linked to poor COVID-19-related outcomes in the IRD population.

AUTHOR CONTRIBUTIONS

Fatemah Abutiban wrote the manuscript with input from all authors. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

All authors declare no conflict of interests.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Rituximab on lung, skin, and joint involvement in patients with systemic sclerosis: A case series study and review of the literature

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Abstract

Objectives: To evaluate the effectiveness of rituximab (RTX) in systemic sclerosis (SSc) patients.

Methods: Data were collected from patient charts before and after RTX administration for 1 year of follow-up time. An updated review of the literature was also done.

Results: Of 8 patients enrolled (mean age: 62.4 years; mean disease duration: 16.7 years), 2 patients with pulmonary arterial hypertension (PAH) died after the first RTX cycle. The follow-up data of the remaining 6 patients were evaluated. There was a significant improvement in arthritis of Disease Activity Score of 28 joints – C-reactive protein and Clinical Disease Activity Index compared with baseline. The median change in modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), and carbon monoxide diffusing capacity between baseline and 12 months were similar. Lung involvement was detected in 5/6 of survivor patients, FVC was improved in 2/5, worsened in 1/5, and remained stable in 2/5 at the end of 1 year. Among the 5 diffuse cutaneous SSc patients, none of the patients' mRSS deteriorated by more than 5 points, while one patient's mRSS improved by greater than 5 points.

Conclusion: This study suggests that RTX is effective for arthritis in patients with SSc. Also, the effectiveness of RTX in skin and lung involvement of SSc was predominantly toward stable disease or improvement. Despite the long disease duration, the presence of patients who showed improvement in skin and lung involvement after RTX treatment suggests the need to investigate predictors of RTX response.

KEYWORDS
anti-CD20, review, rituximab, scleroderma, systemic sclerosis

1 | INTRODUCTION

There is a significant unmet need for effective treatment options for systemic sclerosis (SSc) because of the complexity of pathogenesis, including vasculopathy, dysregulation of innate and adaptive immunity and fibrosis. Until now, no treatment has yet proven to stop the fibrosing process of the disease and nonspecific immunosuppressive drugs including methotrexate for skin involvement, cyclophosphamide, mycophenolate mofetil (MMF) or azathioprine for lung involvement are used in treatment.[1] But these drugs have not enough capacity to prevent disease progression. New promising agents targeting fibrotic and inflammatory pathways, lymphocytes, cell-cell and

cell-extracellular membrane interactions, such as rituximab (RTX), tocilizumab, abatacept, pirfenidone, abituzumab, bortemozib, fresolimumab in SSc are under evaluation.[2,3] On the other hand, the evaluation of drug efficacy is challenging in SSc because of the rarity of the disease, heterogeneity of organ involvement, lack of well-assessed disease activity scale and possible spontaneous skin improvement.

Rituximab is a chimeric monoclonal antibody targeting cluster of differentiation 20 (CD20) antigen that is expressed on B-lymphocyte surfaces from pre-B-cell to the pre-plasma cell stage and has been used for non-Hodgkin lymphoma treatment since 1998. After randomized controlled clinical trials, RTX's first use in rheumatology was in patients with rheumatoid arthritis (RA) in 2007 as a consensus statement.[4] After RA, RTX was approved for antineutrophil cytoplasmic antibody-associated vasculitis.[5] Systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis and polymyositis, mixed cryoglobulinemia and immunoglobulin G4-related disease are other inflammatory rheumatic diseases for which RTX is used for treatment.[6-8] B-cell functional abnormalities were shown in both SSc patients and in animal models. Dysregulation of balance between CD19/CD22 regulating B-cell response, association between B-cell-activating factor and skin fibrosis, increase in production of pro-fibrotic cytokines with T-cell regulation by activated B-cells and altered homeostasis of B-cells in favor of decrease in numbers, but hyper-reactive memory B-cells were demonstrated in SSc patients and/or murine models.[9-13] In 2003 Whitfield et al demonstrated the upregulation of CD20 + B-lymphocytes in skin biopsies of SSc patients and in 2007 Lafyatis et al showed B-cell infiltrations in pulmonary tissue samples of SSc patients.[14,15] Furthermore, an association between progression in interstitial lung disease (ILD) and the percentage of CD19 positive cells in bronchoalveolar lavage fluid in SSc patients were reported.[16] RTX studies accelerated due to the encouraging results of these studies supporting the role of B-cells in the pathogenesis of SSc.

The primary endpoint of the majority of studies to date was to evaluate the effect of rituximab on lung and skin involvement in patients with early SSc. Only 4 of these studies reported the results of the effect of RTX on arthritis in SSc patients.[17-20] The aim of this study was to report the safety and efficacy of RTX treatment, including arthritis, in patients with long-standing SSc who were followed at our rheumatology department, and to provide a review of the literature.

2 | PATIENTS AND METHODS

We reviewed all medical records of SSc patients who had been treated with RTX followed at our university-based rheumatology unit. This study included 8 patients (5 female, 3 male) with SSc who fulfilled the new 2013 American College of Rheumatology / European League Against Rheumatism classification criteria.[21]

Baseline demographics, disease subset (limited or diffuse), disease duration, (the time period from first non-Raynaud's disease manifestation to RTX treatment), autoantibody status (anti-nuclear antibody [ANA], anti-cyclic citrullinated peptide antibody, anti-centromere antibody, anti-Scl70, -Sm, anti-ribonuclear protein, anti-Sjögren's syndrome B [SSB], -SSA, and -Jo1), current and previous medications, comorbidities, cutaneous and visceral organ involvement were obtained from medical records.

Standard pulmonary function tests (PFT), forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO) were recorded in all patients at baseline, 6th and 12th months. PFT parameters were expressed as a percentage of normal predicted values depending on age, gender and height, and DLCO corrected for hemoglobin concentration. Baseline and 12th month high-resolution computed tomographies (HRCTs) were evaluated by the same rheumatologist. For baseline HRCT, the time period between 3 months before and 1 month after the first RTX therapy were allowed. For the first year HRCT, the time period between 12 and 18 months after the first dose of RTX were allowed. The severity and extent of ILD were assessed by 4 different scoring methods. First scoring method was based on PFT and HRCT, and defined the extent of disease as severe and limited. According to this classification, patients with HRCT extent of lung disease >20% of the lung (independent of FVC) and those whose HRCT extent score of between 10%-20% with an FVC <70% predicted are classified as severe lung disease. Otherwise, patients with an HRCT extent score <10% and those with an HRCT extent score of between 10%-20% and an FVC ≥70% classifies as limited disease.[22] The second scoring method (Warrick's score) evaluates severity by giving increasingly high scores corresponding to increasingly severe disease abnormalities and extent by defining the total bronchopulmonary segments involved for each abnormality. Abnormalities in this score were ground-glass opacities (1 point), irregular pleural margin (2 points), septal or subpleural lines (3 points), honeycombing (4 points), and subpleural cyst (5 points). The sum of points ranging 0-15 was reported as the severity score. The extent was scored for each abnormality by giving 1 point for involvement of 1-3 lung segments, 2 points for 4-9 segments and 3 points to more than 10 segments (0-15 points).[23] The third scoring system which was developed by Wells et al estimates the extent of disease by calculating means of affected lung percentages at 5 different levels and evaluates the severity by rating the coarseness of reticulation at each 5 levels (0-15 points). Coarseness of reticulation were graded as ground-glass opacification alone (0 point), fine intralobular fibrosis (1 point), microcystic reticular pattern (2 point) and macrocystic reticular pattern (3 point).[24] The fourth scoring method which was developed by the Scleroderma Lung Study research group (SLS score) was based on evaluating ground-glass opacity, pulmonary fibrosis and honeycombing in 3 levels of the lung by giving increasing points for each 25% change.[25] Progression and improvement of ILD was defined as decrease and increase in either FVC/DLCO levels of ≥10%/≥15% from baseline, respectively. Changes in FVC/DLCO less than 10%/15% from baseline respectively were considered as stable disease.

Serial electrocardiograms and echocardiograms were performed every 6 months and were assessed for cardiac safety. Left ventricular ejection fraction and pulmonary arterial pressure evaluated in echocardiogram were recorded. The presence of pulmonary arterial hypertension (PAH) was defined according to the 2015 European Society of Cardiology and the European Respiratory Society

guideline.[26] Furthermore, the patients underwent the 6 minutes walking test. The included patients had neither any known fibrotic myocardial involvement nor coronary artery disease.

The pathological features of nailfold videocapillaroscopy were recorded from the patient charts including number of capillaries/mm, number of enlarged capillaries, giant capillaries, ramified capillaries and hemorrhages. All patients had a scleroderma pattern prior to RTX therapy. The changes in modified Rodnan Skin Score (mRSS), Disease Activity Score of 28 joints (DAS28) C-reactive protein (CRP) and Clinical Disease Activity Index (CDAI) were evaluated. mRSS and tender/swollen joint examinations were performed by the same experienced rheumatologist (HYT) blinded to therapy. The decision for RTX treatment was made by another experienced rheumatologist (MB).

Patients were treated 1 cycle of RTX every 6 months, in a total of 3 cycles. Each cycle included 1 g of intravenous (IV) RTX followed by a second infusion after 15 days. At each infusion 100 mg methylprednisolone was administered as premedication. Ongoing treatments including immunosuppressive ones, low-dose corticosteroids (less than 10 mg prednisolone or equivalent) and vasoactive drugs used for PAH were allowed during the period of RTX therapy.

Adverse events attributable to RTX were also evaluated. Infusion reactions and infections requiring hospitalization and/or intravenous antibiotics within 12 months after the RTX cycle were checked from records.

The study was performed according to the Declaration of Helsinki and approved by our hospital's Research Ethics Committee (EC No. 2019/09-06). Written informed consent was obtained from the patients/guardians who were still followed up and verbal consent from those who were lost to follow-up.

2.1 | Search strategy

We searched PubMed and Scopus databases for articles published between 2008 and 2021 using the keywords scleroderma, systemic sclerosis, rituximab, and anti-CD20. The authors had carefully reviewed about 1100 articles and relevant references. Observational studies and clinical trials were included and papers written in languages other than English, irrelevant articles, duplicates, case reports, case series including less than 5 patients were excluded. Twenty-five related articles to our current report are summarized in Table 1.

2.2 | Statistical analysis

Wilcoxon and Mann-Whitney *U* tests were used for the analysis of continuous variables of FVC and mRSS in related and unrelated samples, respectively. Values are expressed as median (interquartile range [IQR]). *P* values ≤.05 were considered statistically significant. Sensitivity analyses were performed assuming that the patients who died (patients 1 and 5) received RTX treatment at follow-up and that the measurement values of DAS28 CRP and CDAI did not change. And imputation of the median baseline DAS28 CRP and CDAI levels as baseline and last visit's scores were performed for the patient who did not have arthritis (patient 2). All the statistical analyses were performed using SPSS version 20.0.

3 | RESULTS

3.1 | Patient characteristics

Eight patients (5 female and 3 male), 5 of them with diffuse cutaneous SSc (dcSSc) and 3 of them with limited cutaneous SSc (lcSSc) receiving RTX were included. One patient with lcSSc had anti-SS-A antibody positivity but negative results for Sjögren's syndrome with repeated salivary gland biopsy twice. The mean age of the patients was 62.4 ± 6.9 years and mean disease duration was 16.7 ± 10.5 years. RTX was started with the indication of resistant arthritis in 7 of 8 patients. The indication was progressive skin involvement in 1 patient (patient 2). She received methotrexate thereafter cyclophosphamide and azathioprine for progressive skin involvement.[1] Table 2 summarizes the baseline demographic, clinical and laboratory data of the patients.

4 | CLINICAL EFFICACY

After RTX therapy, the patients showed a clear-cut improvement of articular manifestations of SSc. The DAS28-CRP and CDAI were improved in 5/5 patients with arthritis who survived. And the difference of DAS28-CRP and CDAI between before and after RTX therapy was statistically significant (Table 3). The results of sensitivity analyses were similar to those based on primary analysis (Table 3). Figures 1 and 2 represent the alterations in DAS28-CRP and CDAI for each patient during follow-up.

Skin thickening improved in 2, worsened in 2 and remained stable in 2 patients, respectively. In patients with progression of skin involvement, no increase in mRSS of more than 5 units or 25% was detected. The difference of mRSS between before and after RTX treatment was not statistically significant (Table 3).

According to the scoring method based on PFT and HRCT, 3 patients had severe and 4 patients had limited lung involvement. One patient had no lung involvement. Among the 5 patients with ILD who survived, 2 patients experienced improvement of FVC ≥10%, 2 patients' FVC remained stable and 1 patient experienced a decrease of FVC >10% at the end of 1 year. In 2 patients with clinically significant FVC improvement, none of the evaluated HRCT scores changed. Among 2 patients who were FVC stable, minimal progression was defined due to Warrick and Wells scores in 1 patient (Patient 4) and, improvement was defined due to Warrick, Wells and SLS scores in the other 1 (Patient 8). In the only patient with pulmonary progression during follow-up, only Warrick score could show progression among the 3 scores.

TABLE 1 Literature review on rituximab efficacy in systemic sclerosis patients

References	Type of study	No. of pts[a]	Infusion protocol[b] (cycle)	Disease duration mean (SD)
Lafyatis et al (2009)[41]	Prospective open-label noncomparative observational study	n = 15	2 (1)	Mean (range) 14.5 (9-18) mo
Daoussis et al (2010)[31]	Open-label, proof-of principle, RCT	n = 8 c = 6	1 (2)	6.87 (4.88) y
Bosello et al (2010)[42]	Open-label trial	n = 9	1 (1) in 2 patients 2 cycle	49 (73.1) mo
Daoussis et al (2012)[34]	Open-label trial	n = 8	1 (4)	6.87 (4.88) y
Smith et al (2013)[17]	Open-label therapeutic trial	n = 8	2 (2)	Median (range) 10 (8-34) mo
Moazedi-Fuerst et al (2014)[35]	Open case series	n = 5	4 (1 y)	Median (range) 3 (2-9) y
Jordan et al (EUSTAR) (2015)[37]	Retrospective nested case–control study	n = 9 (dcSSc + lcSSc)	2 (1)	Median (IQR) 6 (3-11) y Median (range) 5 (3-7) y
Bosello et al (2015)[18]	Prospective open-label noncomparative observational study	n = 20	2 (1), 8 patients ≥1 cycle	30.4 (35.6) mo
Giuggioli et al (2015)[19]	Case series study	n = 10 (dcSSc + lcSSc)	1 (1-5)	6.3 (2.7) y
Lepri et al (2016)[43]	Retrospective cohort study	n = 23 (dcSSc + lcSSc)	Cumulative mean dose 2.8 kg (at 1 y) 1.7 kg at 2 y	7.96 (7.65) y
Vilela et al (2016)[44]	Retrospective case series	n = 10	2 (1)	6.6 (4.3) y
Smith et al (2016)[45]	Open-label trial	n = 6	2 (2)	Median (range) 11 (5-22) mo
Melsens et al (2016)[46]	Open-label therapeutic trial	n = 14	2 (2)	Median (range) 10 (5-34 mo)
Boonstra et al (2017)[49]	Randomized double-blind, placebo-controlled trial (RTX vs placebo)	n = 8 c = 8 (dSSc + lSSc)	2 (2)	Median (IQR) 19.1 (17.6-24.4) mo
Daoussis et al (2017)[38]	Open-label non-RCT	n = 33 (dcSSc + lcSSc) c = 18	1 (≥2)	5.7 y (1-28)

Predicted FVC improvement (%)	P*,**,***	No. of pts	mRSS improvement	P*,**,***
At 6 mo +3.5 (89.2 vs 92.7)	ns*	n = 15	At 6 mo 20.6 vs 20.2	.8*
			At 12 mo 20.6 vs 21.1	.8*
At 12 mo +7.5 (68.1 vs 75.6) −4.3 (86 vs 81.7)	.002* .2** .002***	n = 8 c = 6	At 12 mo 13.5 vs 8.4 11.5 vs 9.7	<.001* .16** .06***
At the end of follow-up (16.7 ± 12.6 mo.) 91.6 vs 96.8	ns*	n = 9	At 6 mo 21.1 vs 12	.001*
At 24 mo +9 (68.1 vs 77.1)	<.0001*	n = 8	At 24 mo 13.5 vs 4.9	<.0001*
At 3/6/12/15/18 mo 92.8 vs 88.5/ 88.3/ 89.2/ 94.4/ 89.8	ns*	n = 8	At 3 mo 24.8 vs 19.4	<.01*
At 24 mo 92.8 vs 84.7	<0.05*		At 6/12/15/18 mo 24.8 vs 14.3/10.8/10.0/10.8/13.6	<0.0001*
At 6 mo 72 vs 82	<.008*	n = 5	At 12 mo 26.5 vs 11.8	<.001*
At 12 mo 72 vs 89	<.004*			
At 6 mo +0.7 (60.6 vs 61.3) mc: −4.8 (60.9 vs 56.1)	.5* mc: .02** **.01***	n = 46	At 7 mo 18.1 vs 14.4	<.001*
		n = 25 c = 25	At 6 mo 26.6 vs 20.3 25 vs 23	<.001* .1** .03***
At 12 mo +3.3 (87.4 vs 90.7)	.02*	n = 20	At 12 mo 22.4 vs 11.2	<.001*
Final follow up (48.5 ± 20.4 mo) +0.6 (87.4 vs 88)	ns*		Final follow up 22.4 vs 10.8	<.001*
		n = 10	At 6 mo 15.3 vs 11	.04*
		n = 5 (dSSc)	At 6 mo 25 vs 17.2	.02*
			At the last follow up 25 vs 19.6	.07*
At 12 mo (n = 21) 81 vs 89	.1*			
At 24 mo (n = 10) 81 vs 74.5	.06*			
At 6 mo 66.4 vs 71.2	.4*	n = 10	At 6 mo 20.9 vs 12.8	.003*
At 3/6/12 mo 99.7 vs 94.4/100.5/101.2	ns*	n = 6	At 3/6 /12 mo 24.8 vs 18.6/13.8/10.2	.03* <.001* <.001*
At 3/6/12 mo 95.7 vs 90.8/ 93.9/ 95.2	.48*	n = 14	At 3/6 /12 mo 24.8 vs 18.9/ 14.1/ 10.4	<.001*
At 12 mo (Δ FVC) +4.7 vs +0.3	.43***	n = 8 c = 8	At 12 mo (Δ mRSS) −3.6 vs −1.8	.95***
At 24 mo +4 vs −1.4	.65***		At 24 mo −5.3 vs −1.9	.95***
At 12 mo +2.4 (80.6 vs 83) −0.5 (77.7 vs 77.2)	.14* ns**	n = 33 c = 18	At 12 mo 14.7 vs 8.8 17.8 vs 15.8	<.001* .06** .002***
			At 24 mo 14.7 vs 5.9 17.8 vs 13.7	<.001* .03** .01***
At 24 mo +6.3 (80.6 vs 86.9) −0.1 (77.7 vs 77.6)	.04* ns** **.06***		At 36 mo 14.7 vs 4.5 17.8 vs 15.5	<.001* .04** .002***
At 7 y +11 (80.6 vs 91.6) −16.6 (77.7 vs 61.1)	.16* .001** .01***		At 48 mo 14.7 vs 5.4 17.8 vs 13.6	<.001* .02** .05***

(Continues)

TABLE 1 (Continued)

References	Type of study	No. of pts[a]	Infusion protocol[b] (cycle)	Disease duration mean (SD)
Sari et al (2017)[47]	Retrospective case series	n = 14 (dcSSc + lcSSc)	2, 3 (1-5)	Median (IQR) 9.1 (5.1-13.6) y
Sircar et al (2018)[32]	Open-label RCT (RTX vs CYC)	n = 30 c = 30	2 (2)	21.57 (8.49) mo
Melsens et al (2018)[48]	Open-label multicenter therapeutic trial	n = 17	2 (2)	Median (range) 10 (5-34) mo
Thiebaut et al (2018)[36]	Retrospective cohort study	n = 13 (dcSSc + lcSSc) c = 26 n = 7 n = 7 c = 14 n = 53 (dcSSc + lcSSc) n = 42	1 (2 pts) 2 (11 pts) Median 2 cycles (1,6)	Median (IQR) 12 (5-19) y c: 7 (5-9) y 40 pts from literature 72 (45-129) mo
Fraticelli et al (2018)[40]	Prospective case series study (RTX + MMF)	n = 15 (dcSSc + lcSSc)	1 (2) 2 (2)	Median 27 mo
Elhai et al (2019)[50]	Prospective cohort study	n:146 psmc:497 (dcSSc + lcSSc)	1 2 3	median (Q1-Q3) 5.2 (2-11.1) y
Ebata et al (2019)[39]	Retrospective case–control study (RTX vs CYC)	n = 9 c = 30	1 (3)	8.1(5.9) and 7.8 (3.2) y
Campochiaro et al (2020)[20]	Retrospective case series	n = 33 (dcSSc+lcSSc)	2 (1) 16 pts had previous 2 (1-8) cycles	9.8 (8.1) y
Narvaez et al (2020)[51]	Longitudinal retrospective observational study	n = 24 (dcSSc + lcSSc)	2 (at least 2 cycle) add on MMF	Median (Q1-Q3) 5 (2-8) y
Ebata et al (2021)[33]	Double-blind, investigator-initiated, randomized, placebo-controlled trial	n = 28 c = 26 (dcSSc + lcSSc)	1 (at least 1 cycle)	Median (range) 58.5 (0-268) and 52 (9-248) mo

Abbreviations: c, control; mc, matched control; psmc, propensity score matched controls; CYC, cyclophosphamide RTX, rituximab; RCT, randomized controlled trial; EUSTAR, European Scleroderma Trial and Research Group; ns, not statistically significant; FVC, forced vital capacity; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; IQR, interquartile range; mRSS, modified Rodnan Skin Score; MMF, mycophenolate mofetil.

Statistically significant ($p < .05$) in bold.

[a]Includes only patients with dcSSc unless otherwise specified

[b]Types of RTX protocol: Protocol 1: RTX 375 mg/m^2 weekly for 4 wk at baseline and every 6 mo. Protocol 2: RTX 1000 mg 2 doses at 0 and 2 wk apart every 6 mo. Protocol 3: RTX 500 mg on d 0 and d 14 every 6 mo. Protocal 4: RTX 500 mg on d 0 and d 14 every 3 mo.

*P value of comparing before and after RTX therapy in study population.; **P value of comparing before and after RTX therapy in control group.; ***P value of comparing change in therapy and control arms.

During 1 year follow-up of RTX therapy; it was observed that 4/6 patients experienced 1st degree atrioventricular block. Left ventricular ejection fraction, pulmonary arterial pressure and 6 minutes walking test results were not statistically different before and after therapy. Two lcSSc patients diagnosed with PAH for 4 and 2 years and with 2 high-risk factors[26] (6-minute walking distance <165 m and brain natriuretic peptide plasma level >300 ng/L) died after 1 cycle of RTX therapy. Both of these patients were in World Health Organization functional class III. One patient with new onset PAH at the start of RTX therapy had low risk for progression and PAH-stable during 1 year of RTX treatment.

Gastrointestinal involvement, including dysphagia, gastroesophageal reflux disease and diarrhea, was unchanged after RTX therapy. One patient had a history of renal crisis and was stable in terms of renal functions during RTX therapy.

Predicted FVC improvement (%)	P*,**,***	No. of pts	mRSS improvement	P*,**,***
At the end of follow up (median 15 mo) +5.5 (52.5 vs 58)	.06*	n = 14	At the end of follow up (median) 8 vs 6	.26*
6 mo +6.6 (61.3 vs 67.5) −1.2 (59.3 vs 58.1)	.002* .5** .003***	n = 30	At 6 mo −9.6 (21.7 vs 12.1) −5.5 (23.8 vs 18.3)	<.001* <.001** <.001***
At 24 mo +3 (93.5 vs 90.5)	.06*	n = 17	At 24 mo 25.5 vs 12.6	<.0001*
At 12 mo (median) 72 vs 85	.6*	n = 13 c = 26	At 12 mo (median) 13 vs 10	.5*
At last visit Δ: 4 vs −1.5	.23***		At last visit Δ: 0 vs 0	.09*
At 12 mo (median) 78 vs 83	.6*	n = 7	At 12 mo (median) 29 vs 18	.06*
At median 24 mo (IQR: 12; 46) (Δ) +12 vs −1.5	.003***	n = 7 c = 14	At last visit Δ: −5 vs −2	.07***
At 12 mo 71 vs 84	.001*	n = 53	At 6 mo (median) 18 vs 9	.007*
			At 12 mo 18 vs 13	.008*
			At last follow up 18 vs 10	.0002*
At 12 mo 71 vs 84	.0006*	n = 42	At 6 mo 24 vs 16	.01*
			At 12 mo 24 vs 13	.0001*
At 12 mo 82.4 vs 89.7	.009*		At 12 mo 17.6 vs 11.1	.004*
At 24 mo (Δ) +1.4 (76.3 vs 77.7) +1.6 (79.1 vs 80.7)	ns***	n = 74 psmc = 281 n:131 (mRSS > 10)	At 24 mo 22.1 vs 14.1 21.1 vs 16.2 At 24 mo 21.2 vs 13.4 20.4 vs 16.0	<.0001*** <.0001***
At 24 mo (Δ) +20.6 vs +1.1	<.05***	n = 9	At 24 mo 13.5 vs 5.8	<.05*
At 6 mo (n = 33) 85.5 vs 88.4	.07*	n = 33	At 6 mo 13.7 vs 11.1	.002*
(n = 11) 77.5 vs 81	.085*	n = 21	15.8 vs 12.2	.023*
At 12 mo (n = 24) (Δ) +8.8	.001*			
At 24 mo (n = 15) (Δ) +11.1	.003*			
At 24 mo (Δ) 0.09 vs −2.87	.044***	n = 28 c = 26	At 24 mo (Δ) −6.3 vs 2.14	<.0001***

5 | SAFETY AND TOLERABILITY

Infectious complications occurred in 2 patients. One patient (patient 2) developed cellulitis of the neck after 2.5 months of treatment and needed hospitalization and IV antibiotic treatment. Another patient (patient 8) required hospitalization and IV antibiotic treatment for pneumonia after 2 months of RTX. Both of the patients responded well after antibiotics and the next cycle of RTX was administered without delay. These infectious complications were considered probably unrelated to treatment because no neutropenia was observed on patient charts. But we do not have gamma globulin level data before and during the treatment of infection.

Two patients died during follow-up. One patient (patient 1) died 1 week after and the other (patient 5) died 4.5 months after the first cycle of therapy. Both patients had PAH and both had sudden

TABLE 2 Demographic, clinical, laboratory and radiologic data of patients before and after rituximab treatment

Patient	1	2	3	4	5	6	7	8
Age, y/Gender	67/M	63/F	64/F	53/M	53/F	62/F	63/F	74/M
Disease duration[a], y	14	16	14	6	9	22	40	13
SSc subset	Limited	Diffuse	Diffuse	Diffuse	Limited	Diffuse	Limited	Diffuse
Autoantibodies	SS-a	ANA, Scl-70	ANA, Scl-70	ANA, Scl-70	ANA, ACA	ANA, Scl-70	ANA	ANA
Rheumatoid factor	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Positive
Anti-CCP	Positive	Positive	Positive	Negative	Positive	Negative	Negative	Negative
Comorbidities	Parkinsonism, dementia	Psychosis, hypothyroidism, Op	HT, Op	No	Op	No	PBC	HT, CRF, latent HBV infection
Immunosuppressive treatment	SLZ, Cs	MTX, Cs	AZA, OHQ, Cs	MTX, Cs	MTX, Cs	AZA, OHQ, Cs	AZA, OHQ, Cs	Cs
PAH treatment	Bosentan	–	–	–	Bosentan, tadalafil, treprostinil	–	–	–
Clinical features (baseline/6th mo/12th mo)								
Skin								
mRSS	0	38/34/35	0/0/0	16/16/19	0	20/20/24	0/0/0	39/28/29
Digital lesions[b]	DPS	DU/u/u	–/–/–	DU/u/i	–	DU/u/u	DPS	DU/u/u
Lung								
Disease extent	Limited	Severe	Severe	Limited	Limited	Severe	No	Limited
Warrick's score (severity + extent)	10 + 7	9 + 7/9 + 7	10 + 8/10 + 9	6 + 5/6 + 6	5 + 4	9 + 7/9 + 7	0/0	5 + 4/5 + 3
Wells' score (extent–coarseness)	17%-5	22%-11 22%-11	36%-12 36%-12	6%-5 6%-6	8%-5	25%-11 25%-11	0 0	6%-5 4%-4
SLS score (total)	8	12/12	23/23	10/10	7	12/12	0/0	6/4
FVC (predicted %)	71	34/64/63	62/51/47	67/79/74	71	71/87/81	81/84/84	90/82/94
DLCO (predicted %)	30	40/57/61	35/30/29	55/55/61	23	51/54/54	81/75/77	41/35/42
Cardiac								
ECG change		+	–	+		–	+	+
LV involvement[c]	–	–/–/–	–/–/–	–/–/–	–	–/–/–	–/–/–	–/–/–
PAH	+	–/–/–	-/+/+	–/–/–	+	–/–/–		–/–/–
Mean PAP[d] (mm Hg)	27	–	27	–	38	–	–	–
SPAP (mm Hg)[e]	60	30/20/20	20/50/45	30/30/30	115	25/25/25	35/40/40	30/25/20
Musculoskeletal								
Arthritis	+	–	+/i/i	+/i/i	+	+/i/i	+/i/i	+/i/i

TABLE 2 (Continued)

Patient	1	2	3	4	5	6	7	8
Gastrointestinal								
Dysphagia	+	+/u/u	−/−/−	−/−/−	−	+/u/u	−/−/−	−/−/−
GERD	+	+/u/u	+/u/u	+/u/u	+	+/u/u	+/u/u	+/u/u
Diarrhea	−	−/−/−	−/−/−	+/u/u	−	−/−/−	−/−/−	−/−/−
Kidney								
Renal crisis	−	−/−/−	−/−/−	−/−/−	−	−/−/−	−/−/−	+/u/u
Cumulative results								
6 mo	−	i (L, S)	w (L), i (A)	i (A, L)	−	i (L, A)	i (A)	i (A, S)
12 mo	−	i (L, S)	w (L) i (A)	i (A), w (S)	−	i (L, A), w (S)	i (A)	i (A, S)

Abbreviations: A, arthritis; ACA, anti-centromere antibody; AIH, autoimmune hepatitis; AZA, azathioprine; CRF, chronic renal failure; Cs, corticosteroid; DPS, digital pitting scar; DU, digital ulcer; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; HT, hypertension; i/u/w, improved/unchanged/worsened (any change from baseline); L, lung; LV, left ventricle; OHQ, hydroxychloroquine; Op, osteoporosis; PAH, pulmonary artery hypertension; PAP, pulmonary artery pressure; PBC, primary biliary cirrhosis; S, skin; SLS, Scleroderma Lung Study; SLZ, sulphasalazine; SPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis.

[a]Disease duration from onset of first non-Raynaud's manifestation.

[b]Peripheral vascular involvement was defined as the presence of digital pitting scars or the presence of digital ulcers/gangrene.

[c]An ejection fraction less than 55% is defined as LV involvement.

[d]The mean PAP results from right heart cardiac catheterization (at the time of PAH diagnosis).

[e]Estimated SPAP values measured by echocardiography (right ventricle systolic pressure).

TABLE 3 Changes in clinical and laboratory parameters of the patients after treatment with rituximab and results of sensitivity analyses of DAS28 CRP and CDAI scores

	Before RTX	12th mo of follow up	*P*
Pulmonary function testing (n = 5)			
FVC, median (IQR)	69 (55-83.25)	77.5 (59-86.5)	0.25
DLCO, median (IQR)	46 (38.75-61.5)	57.5 (38.75-65)	0.53
ECHO evaluation (n = 6)			
PAP, median (IQR)	30 (23.75-31.25)	27.5 (20-41.25)	1
LVEF, median (IQR)	60 (57.5-61.25)	60 (60-60)	0.65
6MWT, median (IQR) (n = 6)	322 (180-332)	240 (165-348)	0.22
Skin (n = 6)			
mRSS, median (IQR)	18 (0-38.25)	21.5 (0-30.5)	0.85
Musculoskeletal involvement (n = 5), (n = 7)*, (n = 8)**			
DAS28 CRP, median (IQR)	4.97 (4.22-6.45)	3.95 (3.7-4.22)	**0.04**
	4.97 (4.10-7.46)*	3.98 (3.80-4.46)*	**0.04***
	4.97 (4.17-6.95)**	4.04 (3.84-4.84)**	**0.04****
CDAI, median (IQR)	39 (20-50)	16 (15-25.5)	**0.04**
	39 (19-57)*	18 (16-33)*	**0.04***
	39 (20.25-53.75)**	18.5 (16-37.5)**	**0.04****

Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; DLCO, diffusing capacity for carbon monoxide; ECHO, echocardiography; FVC, forced vital capacity; IQR, interquartile range; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan Skin Score; PAP, pulmonary artery pressure; 6MWT, 6-min walking test. Statistically significant ($p < .05$) in bold.

*The results of sensitivity analyses when analyses were done with patients who have died (patients 1 and 5) showing no improvement.;
**The results of sensitivity analyses when the median baseline value of DAS28 CRP and CDAI of 7 patients assumed as baseline and follow up values for patient 2.

cardiac death. The main cause of death is unknown since an autopsy was not performed.

No infusion-related complications were observed.

6 | DISCUSSION

This case series study of SSc patients with long disease duration seems to confirm the favorable effects of RTX therapy for arthritis. The effect of RTX on lung and skin involvement was in favor of stabilization or improvement. Also, risk assessment should be made in patients with PAH, and alternative therapies other than RTX might be considered in those with high risk of progression.

The frequency of synovitis defined by tender and swollen joints were reported as 16% of patients according to results of European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) registry.[27] There is no guideline in the management of arthritis in patients with SSc and the present treatment strategies are largely based on expert opinion which have been found effective in RA.[28] Although there are many studies investigating the effect of RTX on lung and skin findings of SSc patients, studies investigating its effect on arthritis are limited. In our patients, there was a statistically significant improvement in DAS28-CRP and CDAI after RTX therapy. But 5/5 patients reached only moderate disease activity after the 1st year of treatment. Smith et al reported statistically significant improvement in DAS during 2 years follow-up in early dcSSc patients.[17] Improvement of arthritis was reported in 4/4 patients with SSc reaching low or moderate disease activity after 6 months and, complete remission in 6/7 and stable disease in 1/7 patients at the end of follow-up of RTX therapy, respectively, in 2 studies.[18,19] A recent retrospective case series study evaluating efficacy of rituximab biosimilar (CT-P10) reported statistically significant improvement in DAS28 after RTX therapy.[20] All 5 studies, including our study, reported that RTX is effective in arthritis due to SSc. And results of the study NCT01748084 (RECOVER Trail) are pending about RTX therapy for SSc arthritis.

ILD is the most common pulmonary complication and a major cause of mortality accounting for 30% of SSc-associated deaths.[29,30] Favorable results of studies supporting the role of B-cells in the pathogenesis of SSc has encouraged clinical trials.[15,16] Two randomized controlled trials (RCT) in patients with dcSSc showed that 2 cycles of RTX were associated with a statistical but not clinically significant improvement in FVC as compared with the controls at 6 months and 12 months of therapy, although the disease durations and RTX protocol were different.[31,32] And a recent RCT in Japanese patients with dcSSc and lcSSc reported favorable results of RTX on lung involvement at 24 weeks follow-up.[33] The extension study of the first RCT involving 8 patients in the RTX arm showed a significant increase of FVC and DLCO at 2 years compared to baseline.[34] In another 3 studies in which only patients with dcSSc were evaluated (1 with selected patients from the literature), significant improvement of FVC was shown at 6 and 12 months of therapy compared to baseline.[18,35,36] In 1/2 non-RCTs in which patients with dcSSc and lcSSc were included, a significant improvement of FVC could be shown at 6 months of therapy.[37] And in the other study there was a tendency of improvement in FVC at 24 months compared with the control group, which could not reach statistical significance; a significant benefit was reported for the RTX group in FVC at 7 years of therapy.[38] In another non-randomized controlled study involving Japanese patients with dcSSc, change in FVC was statistically significant at 3 and 6 months and also clinically significant at 12 and 24 months of RTX compared to baseline, and clinically and statistically significant improvement were reported at 24 months of therapy compared to the cyclophosphamide (CYC) arm.[39] In a recent study evaluating the efficacy of combination therapy with RTX and MMF in patients with dcSSc and lcSSc, favorable results were reported in pulmonary involvement.[40] On the other hand, several open-label studies, a nested case–control study and non-RCTs

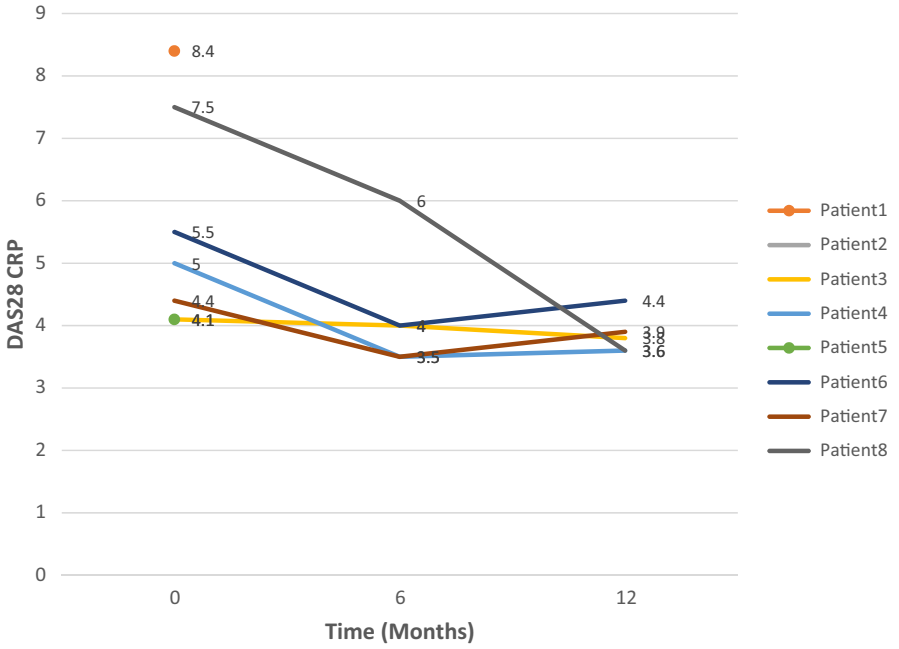

FIGURE 1 Alterations in Disease Activity Score of 28 joints – C-reactive protein (DAS28-CRP) of systemic sclerosis (SSc) patients during follow-up

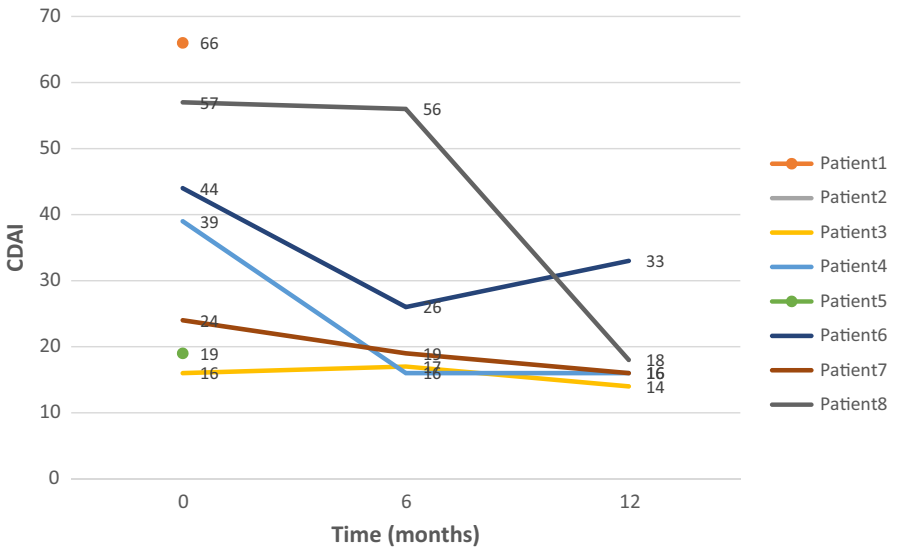

FIGURE 2 Alterations in Clinical Disease Activity Index (CDAI) of systemic sclerosis (SSc) patients during follow-up

including only dcSSc or dcSSc and lcSSc patients could not show a significant FVC change from baseline.[17-20,36-38,41-48] Additionally, 1 prospective cohort study (among propensity score matched patients treated or not with RTX) and 1 RCT including patients with dcSSc and lcSSc reported no significant difference between RTX and the control group.[49,50] In these studies the majority of them showed a tendency to improve FVC, the duration of disease ranged from 10 months to 12 years, and the follow-up period ranged from 6 months to 7 years. In a retrospective cohort study including literature patients, no change in FVC could be shown compared to baseline in study patients with median disease duration of 12 years, while a significant change in FVC was shown at 12 and 24 months when literature patients with a median disease duration of 6 years were added to the evaluation.[36] Recently, a retrospective study including SSc patients with a median disease duration of 5 years showed significant change in FVC at 12 and 24 months of RTX when added on to MMF.[51] Additionally, the results of the RECITAL trial, which is assessing the efficacy and safety of RTX versus CYC in 116 patients with ILD are pending.[52]

In our study, we had dcSSc and lcSSc patients, and an improvement trend was found which could not reach statistical significance. The mean disease duration exceeding 16 years may affect this result. We used 3 different scores (Warrick, Wells and SLS scores) for evaluating HRCT changes and Warrick's score was more precise than others in detecting progression. During the RTX treatment, an increase in FVC was observed in all of our patients except 1, regardless of whether it was clinically significant or not. Our only patient with progression in lung involvement during RTX therapy was the patient who already had the highest lung involvement score (patient 3). Conversely, a clinically significant improvement was observed in the patient with a longer disease duration but milder lung involvement scores (patient 6). This shows that the severity and extent of

lung involvement rather than the duration of disease can affect RTX response. Since no trails had standardized lung scoring, we compared the duration of the disease, which is an indirect indicator of the severity of the disease. If it is necessary to determine the window of opportunity for efficacy of RTX, it would be more appropriate to evaluate the radiologic extent rather than the duration of the disease.

Although evaluating RTX efficacy in skin involvement of SSc might be difficult because of possible spontaneous improvement, some uncontrolled or unadjusted studies suggested efficacy of RTX on skin involvement.[17-20,34-37,39,40,42,44-46,48] A recent large prospective cohort study and a recent RCT showed a high efficacy of RTX in skin fibrosis in RTX-treated patients compared with patients not treated with RTX.[33,50] However, a study including patients with early dcSSc (mean 14.5 months) and another study including patients with long-standing dcSSc and lcSSc (median 9.1 years) could not show significant improvement.[41,47] In addition, a small RCT in early SSc patients reported no improvement in skin score in RTX-treated patients compared to a placebo group.[49] Among 3 non-randomized controlled studies, while significant improvement was reported with RTX therapy compared to a control group in a study with mean/median disease duration of approximately 5 years, there was no significant improvement in a study with a median disease duration of 12 years.[36-38] Furthermore, among 2 RCTs of dcSSc, while the first study including patients with mean disease duration of 6.9 years showed no significant improvement in mRSS in RTX-treated patients compared to the control group, another study with mean disease duration of 22 months suggested that RTX is effective.[31,32] In our patients, the lack of improvement in skin fibrosis may be related to the long duration of the disease. From a different point of view, despite the long disease duration, none of our dcSSc patients had a worsening of more than 5 points in mRSS, which is the minimal clinically significant difference reported for dcSSc patients.[53] Also, an improvement of more than 5 points was achieved in 1 of our dcSSc patients after RTX therapy. From this point of view, long disease duration seems to be associated with stabilization in mRSS. The patient who showed improvement in mRSS suggests that other unknown factors may affect the RTX response despite the long disease duration.

The safety profile of RTX is one of the main concerns about its use in the treatment of SSc. RTX appears to have an acceptable safety profile based on the results of the studies on patients with SSc and/or RA.[37,54] Giuggioli et al reported progression of PAH in 3 patients during RTX treatment[19] and 2 of our patients with PAH died after 1 cycle of RTX treatment. Although PAH by itself increases the risk of early mortality in SSc, we do not know whether RTX has precipitated death or not in our 2 patients. A recent multicenter, double-blind, randomized, placebo-controlled trial including 57 SSc-PAH patients diagnosed within 5 years reported RTX as an effective and safe adjuvant treatment option.[55] Long disease duration, additional risk factors for mortality and non-cardiac causes may be the cause of mortality in our patients.

Our study has several limitations that need to be considered before definite judgment. Our study included low number of patients with lcSSc and dcSSc. Our patients had overlap diseases and had used additional immunosuppressive drugs. The mean disease duration of our patients was longer than the studies in the literature. We could not perform autopsy to reveal the cause of death in 2 patients.

In conclusion, RTX appears to be effective in SSc-associated arthritis as well as in RA. In terms of skin and lung involvement of SSc, the success rate of RTX seems to be higher in the mild severity/extent of lung involvement and early stage of skin involvement. Despite the long disease duration, the factors and markers affecting the treatment response in rituximab responders may be the subject of new studies.

AUTHOR CONTRIBUTIONS

All the authorship contributions were declared in line with the International Committee of Medical Journal Editors 4 criteria: HYT wrote the manuscript. BZ and GK searched the databases for review of the literature and read the selected articles and evaluated for eligibility. HYT, GK, FO and MB revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

All the authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Urate-lowering therapy for patients with gout on hemodialysis

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Abstract

Objective: Gout is the most common form of inflammatory arthritis and is caused by deposition of monosodium urate crystals resulting from a high burden of uric acid (UA). High UA burden also has been associated with increased morbidity and mortality in the general population and progression to chronic kidney disease. In persons with gout and end-stage renal disease (ESRD), prior studies suggest that UA levels decrease after initiation of hemodialysis (HD). We evaluated UA level and the use of urate-lowering therapies (ULTs) in patients with gout and ESRD on HD.

Methods: We performed a retrospective review of patients with gout and ESRD seen at a large urban public hospital (The MetroHealth System). We extracted data from the medical record (Epic) for patients diagnosed with gout and ESRD on HD. The main outcomes were the UA level and the use of ULTs before and after HD initiation.

Results: We identified 131 patients with gout on HD. Of these, 21 patients had crystal proven gout diagnosis, 10 of whom had data on UA level pre-HD and post-HD and were included in the analysis. For the total sample (N = 21), the mean age was 65 years, 7 were female and 20 were African American. Mean pre-HD and post-HD UA levels were 8.4 and 3.98 mg/dL respectively. Twenty-one patients were receiving ULT pre-HD, 11 discontinued post-HD.

Conclusion: Among patients with gout and ESRD, we observed a decrease in UA level associated with initiation of HD. For this group, discontinuation of ULTs may be appropriate.

KEYWORDS
end-stage renal disease on hemodialysis, gout arthritis, urate-lowering therapy

1 | INTRODUCTION

Gout is an inflammatory arthritis provoked by monosodium urate crystals (MSU) in joints and surrounding soft tissue.[1] It is associated with high serum uric acid (UA), defined as a level greater than 6.8 or 7.0 mg/dL.[2] In the USA, the prevalence of gout is estimated at 3.9% of adults (~8.3 million people) making it one of the most common inflammatory rheumatic diseases of adulthood.[2]

High serum UA levels have been linked to the development of new-onset chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the general population.[3] In patients on hemodialysis (HD) some studies have shown that increased serum UA levels are predictive of cardiovascular disease.[4,5] However, other studies have demonstrated that hyperuricemia in patients on HD has cardioprotective and mortality protective effects.[3,6] This is possibly due to the higher oxidative stress in ESRD patients compared to those with

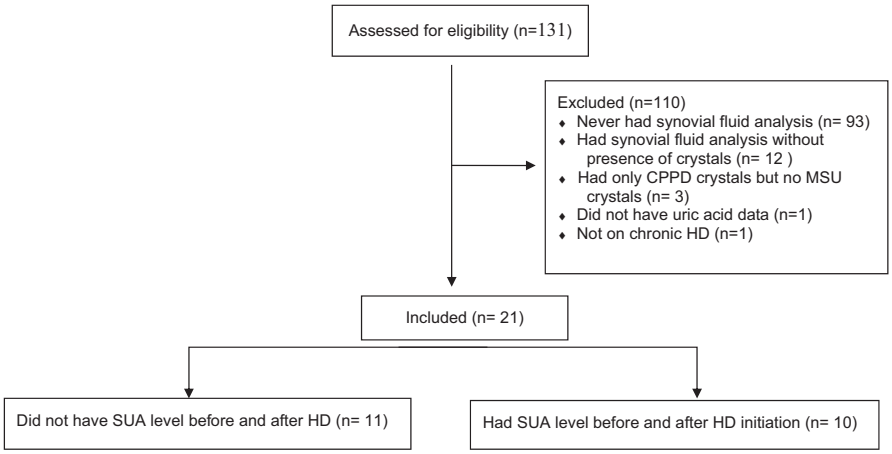

FIGURE 1 Consolidated Standards of Reporting Trials flow diagram. CPPD, calcium pyrophosphate crystals; HD, hemodialysis; MSU, monosodium urate crystals; SUA, serum uric acid

preserved renal function and the antioxidant effect of UA which is responsible for more than half of the antioxidant capacity of blood.[3]

According to the American College of Rheumatology (ACR) 2020 gout management guidelines, pharmacologic urate-lowering therapy (ULT) is recommended for patients with CKD stages 2-5, or ESRD with prior gout attacks and current hyperuricemia.[2] A treat-to-target approach is recommended by the European League Against Rheumatism (EULAR) with the goal to maintain serum UA levels at <6 mg/dL (360 μmol/L) and <5 mg/dL (300 μmol/L) in those with severe gout.[7] The EULAR recommendation includes both patients with preserved renal function as well as those with ESRD.

Studies have shown that in patients with ESRD, hemodialysis reduces gout attacks[4,8] and significantly reduces uric acid levels by almost 60% without additional ULT.[4,9] Studies also suggest that the duration of HD enhances the serum UA lowering effect. These data suggest that serum UA levels trend lower with increased time on HD. Therefore, we decided to investigate UA levels in patients with ESRD on HD and to evaluate whether patients on HD continue to require ULT.

2 | MATERIALS AND METHODS

2.1 | Inclusion and exclusion criteria

We performed an observational, retrospective cohort study at a large urban public hospital system. We obtained MetroHealth Medical Center institutional review board (IRB) approval (IRB20-00014).

Searching the Epic electronic medical record we identified all patients with an office visit between 1 January, 2018 and 1 January, 2020 who had a diagnosis of ESRD on HD (International Classification of Diseases 10 [ICD 10] codes N18.6, Z99.2) and gout (ICD10 codes M10-M10.09, M1A-M1A.9XX1, M10.9) on their problem list. We then manually reviewed the charts of all identified patients to verify the diagnoses and to identify those with a serum UA level recorded between 2000 and 2020. The initial search yielded 131 patients. We excluded patients without documented synovial fluid analysis or synovial fluid analysis without documented MSU crystals present. We also excluded patients who received HD for a short period for a specific indication and patients undergoing peritoneal dialysis. After exclusion of patients with missing data, the final sample consisted of 21 patients with ESRD on HD and at least 1 analysis of synovial fluid demonstrating presence of MSU crystals.

2.2 | Patient and public involvement

No patients were involved.

2.3 | Data collection

We collected baseline demographic and clinical data, including age, gender, race/ethnicity, HD start date, up to 4 serum UA levels, synovial fluid analyses for presence or absence of MSU crystals or other crystals, presence or absence of tophi, presence or absence of rheumatoid arthritis on the problem list, and any results for anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor (RF). We also identified all prescriptions for allopurinol, colchicine, pegloticase, and febuxostat.

The main study outcome was serum UA levels before and after initiation of HD and the use of ULT. The secondary outcome was racial and demographic disparities in our sample.

2.4 | Statistical analysis

This was a retrospective observational study. We report patient characteristics and outcomes as counts (%) for categorical variables and means (SD) for continuous variables. We calculated the mean UA level and 95% CI using a single-sample *t* test. We compared the serum UA level pre- and post-initiation of HD using a paired *t* test. We report the results as the mean difference with 95% CI.

3 | RESULTS

The initial search yielded 131 patients. After individually reviewing each chart to confirm the HD status and gout diagnosis

TABLE 1 Detailed data for the total sample

ID	Age	Gender	Race	HD	PD	NOE	MSU	CPPD	TOPHI	UACID	Losartan	Statin	RA	RF	CCP
1	72.00	Male	Black/African American	1	0	0	1	0	0	4.70	0	0	0	0	0
2	68.00	Female	Black/African American	1	0	0	1	0	0	9.0	0	1	0	0	0
3	87.00	Male	Black/African American	1	0	0	1	0	0	7.3	0	0	0	0	0
4	72.00	Male	Black/African American	1	0	0	1	0	1	1.6	0	1	0	0	0
5	48.00	Male	Black/African American	1	0	0	1	0	0	9.9	0	0	0	0	0
6	47.00	Female	Black/African American	1	0	0	1	0	0	3.1	0	1	0	0	0
7	43.00	Male	Black/African American	1	0	0	1	0	0	11.1	0	0	0	0	0
8	83.00	Female	Black/African American	1	0	0	1	0	0	3.5	0	0	0	0	0
9	63.00	Male	Black/African American	1	0	0	1	0	0	5.2	0	0	0	0	0
10	60.00	Male	Black/African American	1	0	0	1	0	0	7.4	0	0	0	0	0
11	70.00	Female	Black/African American	1	0	0	1	0	0	3.1	0	0	0	0	0
12	58.00	Male	Black/African American	1	0	0	1	0	0	7.9	0	0	0	0	0
13	71.00	Female	Black/African American	1	0	0	1	0	0	10.7	0	0	0	0	0
14	67.00	Male	White	1	0	0	1	0	0	4.3	0	1	0	0	0
15	84.00	Female	Black/African American	1	0	0	1	0	0	5.9	0	0	0	0	0
16	78.00	Male	Black/African American	1	0	0	1	1	0	5.8	0	1	0	0	0
17	45.00	Male	Black/African American	1	0	0	1	0	0	4.4	0	1	0	0	0
18	53.00	Male	Black/African American	1	0	0	1	0	0	6.6	0	0	0	0	0
19	69.00	Male	Black/African American	1	0	0	1	0	0	8.6	0	0	0	0	0

(Continues)

TABLE 1 (Continued)

ID	Age	Gender	Race	HD	PD	NOE	MSU	CPPD	TOPHI	UACID	Losartan	Statin	RA	RF	CCP
20	75.00	Female	Black/African American	1	0	0	1	0	1	3.3	0	0	1	1	0
21	44.00	Male	Black/African American	1	0	0	1	0	0	3.7	0	0	0	0	0
Total	n/a	n/a	n/a	21	0	0	21	1	2		0	5	1	1	0
Mean	64.62														

Note: General data for the total sample as explained in the text.

Abbreviations: CCP, anti-cyclic citrullinated peptide antibody; CPPD, calcium pyrophosphate crystals; HD, hemodialysis; MSU, monosodium urate crystals; NOE, not otherwise specified; PD, peritoneal dialysis; RA, rheumatoid arthritis; RF, rheumatoid factor; UACID, most recent uric acid level.

(defined by the presence of UA crystals in synovial fluid analysis), 22 patients were on HD and had a synovial fluid analysis demonstrating UA crystals. One patient had both MSU and calcium pyrophosphate crystals and 1 patient did not have any documented UA level. After exclusion of patients with missing data, the final sample consisted of 21 patients with ESRD on HD and at least 1 analysis of synovial fluid demonstrating presence of MSU crystals (Figure 1).

For the total of 21 patients, the mean age was 65 years, 7 were female, 14 were male, 20 African American and 1 White. Two patients had tophi documented on physical exam, 1 had rheumatoid arthritis with elevated RF. Allopurinol was prescribed to 19 patients pre-HD and was continued in 7/19 patients after they started HD; allopurinol was discontinued before HD initiation in 3/19 patients, within 1 year from HD initiation in 7/19 patients, and within 10 years from HD initiation in 2/19 patients. One patient was on febuxostat and one was on pegloticase, both were discontinued after initiation of HD. No one was on losartan and only 5/21 patients were placed on statin (Table 1).

From the total sample, 10 patients had an available serum UA level measured before and after initiation of HD; 8 were within 1 year of HD initiation, 1 within 3 years and 1 within 4 years of HD initiation (Table 2). Among those 10 patients, the mean age was 64 (SD 15), 4 were female and all were African American. The mean UA level before initiating HD was 8.43 mg/dL (95% CI 6.6-10.2) and the median was 8.2. The mean post-HD UA level was 3.98 mg/dL (95% CI 2.94-5.02) and median of 3.60 after HD was started (Table 1). Our analysis showed a statistically significant and clinically meaningful difference in UA before and after HD initiation, the mean UA difference (post-HD – pre-HD) was −4.45 mg/dL, (95% CI −6.49 to −2.41), $P = .008$.

4 | DISCUSSION

Hyperuricemia has been associated with adverse cardiovascular outcomes and increased morbidity and mortality in the general population.[10] However, in patients on HD, data on the effect of hyperuricemia have been controversial.[11] In patients on chronic HD, some studies including large retrospective studies have not shown an association between high serum UA level and cardiovascular mortality. Some have even shown an increased risk of all-cause mortality and cardiovascular mortality with lower serum UA and lower risk with elevated serum UA levels.[6,12-14] A 2-year prospective observational study of 261 hemodialysis patients from Tel Aviv University showed that lower serum UA is an independent risk factor for all-cause and cardiovascular mortality as well as future cardiovascular disease; for each 1 mg/dL increase in baseline serum UA, the hazard ratio of all-cause and cardiovascular death was 0.55 (95% CI 0.43-0.72 and 0.43-0.72 respectively).[17] Recently, Zawada et al showed a U-shaped pattern between serum UA and all-cause mortality with lowest risk at serum UA levels of 6.5 mg/dL (387 μmol/L).[15] In the chronic HD patient population, there is a paradoxical epidemiology

TABLE 2 UA levels before and after HD initiation

ID	Age	Gender	Race	Tophi	UA post-HD	UA pre-HD
1	72	Male	Black/African American	0	4.7	9.5
2	72	Male	Black/African American	1	1.6	11
3	47	Female	Black/African American	0	3.1	8.5
4	83	Female	Black/African American	0	3.5	4.4
5	70	Female	Black/African American	0	3.1	6.7
6	78	Male	Black/African American	0	5.8	9.1
7	45	Male	Black/African American	0	4.4	13.2
8	53	Male	Black/African American	0	6.6	7.9
9	75	Female	Black/African American	1	3.3	7.9
10	44	Male	Black/African American	0	3.7	6.1
Median					3.60	8.2
Mean	64				3.98	8.43
SD	15					
95% CI					2.94-5.02	6.6-10.2

Note: Data for uric acid level before and after HD initiation.

Abbreviations: CI, confidence Interval; HD, hemodialysis; UA, uric acid.

phenomenon where lower blood pressure, lower body mass index and lower serum low-density lipoprotein are correlated with unfavorable outcome, this suggests that there probably are other non-traditional cardiovascular risk factors and outcomes in this patient population.[11,18]

Gout is experienced in almost 20% of patients with CKD stage 3, compared to 5% of those with normal kidney function.[16] In a large analysis of 601 patients from 5 outpatient dialysis centers in Germany, investigators noted that the incidence of gout flares in patients on HD was only 3.6%, and hyperuricemia increased the risk by 17%.[11] However, another study by Yeo et al evaluated 216 patients on dialysis (HD and peritoneal dialysis), almost 25% of whom experienced gout, suggesting that HD alone is insufficient to achieve target UA mandating ULT and treat-to-target approach in this patient population.[16] Our results suggest that initiation of HD is associated with a decrease in UA levels in ESRD patients. Compared to current guideline recommendations to continue ULT, our results found that over 50% of patients on allopurinol at the start of HD had the medication stopped after they started HD. Patients on other ULT (eg, febuxostat or pegloticase) also had their medication stopped after initiation of HD.

We found poor monitoring of gout in our study patients, specifically a lack of serum UA monitoring after initiation of HD and continuation of the same dose of allopurinol contrary to recommended dosage post-HD.[10,19] In addition, we noticed that the diagnosis of gout often occurred without evidence of synovial fluid analysis. It is possible that gout flares continued despite a lower serum UA level post-dialysis. However, as we did not collect data on the frequency or severity of gout flares, we are not able to assess this hypothesis. Furthermore, some studies suggest that hyperuricemia has a cardioprotective effect in patients on HD, contrary to the general population, raising some concerns that very low UA levels may be harmful.[3,17]

One notable finding was the African American predominance in our sample (95%). While this may be unique to the patient population at our institution, other studies have suggested that African Americans tend to have higher prevalence of gout (5% compared to 4% Caucasians).[11,20] Future studies are necessary to confirm our results at other institutions.

Our study has some limitations that should be recognized. Our data come from a single site, which may affect generalizability. The sample size is small, and not all subjects had pre- and post-HD serum UA levels available. We did not collect information on gout symptoms, and we are not able to comment on the effect of serum UA levels or urate-lowering treatment on symptom burden. Our inclusion criteria may have missed some eligible subjects and we did not include patients with ESRD on peritoneal dialysis.

5 | CONCLUSION

Despite the study limitations, our data suggest that the management of gout in patients with ESRD and on dialysis requires further study. There is a need for improved monitoring of UA levels and assessment of the need for ULT among patients with gout and ESRD on hemodialysis. Because HD-treated patients often have multiple comorbidities, ULT contributes to polypharmacy and may influence drug interactions. Also, it highlights racial disparities with markedly increased gout risk in African American patients on HD. Further research on this topic may help to inform updated guidelines specifically for ULT in patients on dialysis. Improved collaboration between primary care providers, rheumatologists and nephrologists can help to ensure proper monitoring of these patients and to weigh the risk and benefits of continued ULT based on the serum UA level.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript.

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CONFLICT OF INTEREST

No conflict of interest.

ETHICS APPROVAL

MetroHealth Medical Center IRB approval IRB20-00014.

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ORIGINAL ARTICLE

Metabolic syndrome is associated with increased cardiovascular risk and disease damage in patients with Takayasu arteritis

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Abstract

Objective: Metabolic syndrome (MetS) is one of the preventable risk factors for cardiovascular disease (CVD). The aim of this study was to investigate the effect of MetS on CVD and cumulative organ damage in a multi-center, large cohort of patients with Takayasu arteritis (TAK).

Methods: This is a cross-sectional study involving 192 consecutive TAK patients from seven tertiary rheumatology centers in Turkey. Clinical data of TAK patients fulfilling the 1990 American College of Rheumatology classification criteria were collected from medical records. They were evaluated for risk factors of CVD, disease activity, damage, and MetS at their last visits.

Results: A total of 192 consecutive TAK patients were included in this study. One hundred and fifty-eight (82%) were female, the mean age was 43.3 ± 13 years, and mean disease duration was 13.5 ± 9.3 years. MetS was detected in 50 (26%) of the patients and CVD was detected in 28 (14.6%). The presence of MetS was detected as an independent risk factor for CVD ($P < 0.001$). In addition, the mean vasculitis damage index of the group with MetS was significantly higher than in the other patients (4.5 ± 3.3 vs 3.2 ± 2.2, respectively, $P = 0.004$).

Conclusion: The presence of MetS in TAK is associated with increased CVD and disease damage. Awareness and management of MetS can improve disease prognosis in patients with TAK.

KEYWORDS
cardiovascular disease, metabolic syndrome, Takayasu arteritis, vasculitis

1 | INTRODUCTION

Takayasu arteritis (TAK) that affects the aorta and its large branches is a chronic vasculitis with panmural inflammation, stenosis, occlusion, and aneurysm formation.[1] Most of the clinical findings are associated with arterial ischemia, and the frequency of hypertension, cardiac valve disease, and cardiovascular disease (CVD) increases as a result.[2] These involvements, which have a distinctive negative impact on TAK prognosis, are affected by CVD risk factors as well as disease activity.[3] Hence, taking the CVD risk factors into consideration is also important in therapeutic approaches.

Metabolic syndrome (MetS) is one of the preventable CVD risk factors. The prevalence of MetS in the general population varies according to age, gender, ethnicity, and geographic origin. Weight gain, aging, and sedentary life are associated with MetS in both high-income and low- and middle-income countries. Despite its close relationship with CVD there are limited studies on the frequency of MetS in systemic rheumatological diseases. The presence of MetS is a risk factor for disease damage in systemic lupus erythematosus (SLE), suggesting that it might also affect disease course and prognosis in inflammatory disorders [4].

Only one study has been encountered so far regarding the status of MetS in TAK.[5] The aim of this study was to investigate the effect of MetS on CVD and cumulative organ damage in a multi-center, large cohort of TAK patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a cross-sectional study involving 192 consecutive TAK patients from seven tertiary rheumatology centers in Turkey. Clinical data of TAK patients fulfilling the 1990 American College of Rheumatology classification criteria were collected from medical records.[6] They were evaluated for risk factors of CVD, disease activity, damage, and MetS at their last visits. Patients with insufficient data for the diagnosis of MetS, secondary rheumatic disease, and organ failure were excluded.

The study was approved by the Marmara University ethics committee (approval number: MAR-YÇ-2009-0230) and informed consent was obtained from all participants.

2.2 | Definitions

Radiological involvement was determined according to the Numano classification.[7] TAK disease activity and damage were evaluated by Kerr's criteria and vasculitis damage index (VDI), respectively.[8,9]

Cardiovascular disease was defined as documented coronary artery disease and/or cerebrovascular event including myocardial infarction and stroke.

MetS was defined based on the diagnostic criteria of the National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III).[10] Three or more of the following components are defined as MetS:

- Increased waist circumference (>102 cm for men, >88 cm for women)
- Hyperglycemia, fasting blood glucose ≥110 mg/dL, or have been diagnosed with diabetes and treated.
- Elevated triglycerides ≥150 mg/dL
- Low high-density lipoprotein (<40 mg/dL in men, <50 mg/dL in women)
- Hypertension. Arterial blood pressure ≥130 mm Hg/≥85 mm Hg or currently using an antihypertensive drug.

Waist circumference was measured at the end of a normal expiration, in a horizontal plane around the abdomen at the level of the iliac crest, parallel to the floor. Blood pressure was measured twice in rested patients.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS 21.0 (SPSS Statistics for Windows; IBM, Armonk, NY, USA). CVD and VDI between TAK patients with MetS (MetS + TAK) and without MetS (MetS – TAK) were analyzed. Kolmogorov-Smirnov test was used to check whether a continuous variable follows a normal distribution. Differences between continuous variables and categorical data were tested using the Student's *t* test or Mann-Whitney *U* test and χ^2 test. Those factors associated with MetS on univariate analyses at significance level $P < 0.2$ were tested with multivariate analysis using logistic regression. All analyses used a 5% two-sided significance level and results were expressed as odds ratio and 95% confidence interval.

3 | RESULTS

Ninety-five of the 287 registered patients were excluded from the study because of insufficient data for MetS. In all, 192 consecutive TAK patients were included in this study. One hundred and fifty-eight (82%) patients were female, the mean age was 43.3 ± 13 years, and mean disease duration was 13.5 ± 9.3 years. The most common radiological subtype was type V (49%). Immunosuppressive drug usage distribution of the patients was 141 (77%) for methotrexate, 87 (47%) for azathioprine, 49 (27%) for leflunomide, and 14 (8%) for cyclophosphamide. Forty-one (26%) of the patients used at least one biological disease-modifying drug. Tumor necrosis factor inhibitors were used by 40 patients, and 17 used tocilizumab. All of the patients were receiving corticosteroids, and immunosuppressive drugs were not used in only 6 (3%) of the patients.

MetS was detected in 50 (26%) of the patients and CVD was detected in 28 (14.6%). The most frequent criterion of MetS in TAK patients was hypertension (47%); abdominal obesity was second with presence in almost half of the patients (41%) (Table 1). Clinical characteristics of the patients according to their MetS and CVD status are shown in Table 2. The mean age and smoking rates of the TAK patients with MetS were higher than of those without MetS (50.3 ± 12.0 vs 40.8 ± 12.4 years, $P = 0.000$ and 41% vs 20%, respectively, $P = 0.007$). The mean VDI of the group with MetS was also significantly higher (4.5 ± 3.3 vs 3.2 ± 2.2, $P = 0.004$). As expected, the mean VDI was higher in the group with CVD (5.8 ± 2.7 vs 3.1 ± 2.3, $P = .000$).

Patients with TAK who had CVD were similar to the non-CVD group in terms of age, gender, disease duration, radiological type, and other clinical features. The smoking rate was also significantly higher in the TAK group with CVD (44% vs 22%, $P = 0.043$). The rate of active disease was found to be high in the group with MetS at the last visit (23% vs 10%, $P = 0.018$). There was no significant difference between the groups in terms of presenting symptoms and median number of relapses.

In the multivariable analysis shown in Table 3, the presence of MetS was detected as an independent risk factor for CVD ($P = 0.007$). In addition to MetS, cumulative prednisolone was also found to be an independent risk factor for CVD ($P = 0.037$).

4 | DISCUSSION

Although the rate of MetS in our TAK cohort (26%) was lower than the prevalence of MetS in the general population of Turkey, which was reported as 33% (38% in women, 27% in men),[11] we showed that MetS was associated with CVD. In addition, the VDI of TAK patients with MetS was found to be high.

At first glance, a lower rate of MetS in TAK patients compared with the general population may be surprising, because of glucocorticoid (GC) treatment in TAK, which may cause weight gain, hypertension, and hyperglycemia. However, control of disease activity by GC treatment, which may allow successful exercise and weight loss, as well as physician-patient awareness (diet, salt restriction, and use of statins), may be responsible for the low rates of MetS in our TAK cohort. Finally, the tendency for using lower doses of GC, supported by more frequent use of other conventional immunosuppressives, in Turkey might have affected our results. Indeed, only a few of our patients did not use immunosuppressive therapy. In the only study that can be compared with our data, the prevalence of MetS was found to be higher in Brazilian TAK patients compared with the general population. However, this finding was the result of an unbelievable low rate of MetS in the Brazilian general population (33.3% vs 8.5%).[5]

TABLE 1 Subsets of metabolic syndrome (MetS) in Takayasu arteritis (TAK) patients

Subset	n (%)
Hypertension	91 (47%)
Abdominal obesity	79 (41%)
Increased TG level	57 (30%)
Hyperglycemia	24 (12%)
Decrease HDL level	16 (8%)

Abbreviations: HDL, high-density lipoprotein; TG, triglyceride.

MetS frequency data also vary in other systemic inflammatory rheumatological diseases. In the meta-analysis of Zhang et al, MetS was reported more frequently in rheumatoid arthritis patients than in the normal population with increased mortality due to CVD.[12] In an antiphospholipid syndrome cohort, the prevalence of MetS (34.5%) was found to be similar to the general population,[13] whereas in antineutrophil cytoplasmic antibody-associated vasculitis an increased prevalence was present, which was associated with relapses.[14] The use of GC can be considered as a risk factor for MetS, affecting factors such as weight gain, hypertension, and hyperglycemia. However, disease activity, which may prevent weight gain or physician-patient awareness (higher exercise, use of statins etc), may be responsible for the low rates of MetS in our TAK population. Similarly, in another study from Turkey, Demir et al reported the prevalence of MetS in SLE patients as 19%, which, like our results, was also lower than in the general population.[4] Lower doses of GC are preferred in Turkey with high use of other conventional immunosuppressives.

Whether the use of biological agents apart from GC has an effect on MetS is another factor that needs to be clarified. It has been reported that the frequency of MetS in patients with ankylosing spondylitis who use biological drugs is higher than the group without the use of biologicals.[15] In our study, use of biological drugs was not found to be associated with MetS. However, the use of fewer biological drugs in TAK patients may be a confounding factor.

Although in previous studies MetS was shown to be an independent risk factor for CVD in patients with ankylosing spondylitis, SLE, and rheumatoid arthritis, to our knowledge, this is the first study reporting a similar finding in TAK.[4,12,15] CVD has an increased frequency in TAK and causes mortality.[3] In inflammatory rheumatic diseases, direct atherogenic effects of proinflammatory cytokines predispose the patients to CVD. Although GC show disturbance effects on metabolic pathways, they also reduce systemic inflammation and control disease activity, thereby having a dual effect on CVD.[16] In our study, high cumulative GC is also seen as a risk factor for CVD. Effective control of the disease using the lowest possible dose of GC reduces the risk of CVD. However, it is understood that the effect of MetS on CVD cannot be eliminated by controlling the use of GC. The management of MetS, as one of the general risk factors for CVD, is also important for reducing mortality and morbidity in TAK patients.

Apart from CVD, another factor that may be associated with mortality and morbidity is vascular disease damage. We have previously shown that higher damage scores were associated with higher cumulative GC doses in patients with TAK.[17,18] Our results in the present study showed that MetS was another factor affecting the vascular damage score in TAK. Similar to our results, Demir

TABLE 2 Clinical characteristics of Takayasu arteritis patients according to their metabolic syndrome and cardiovascular disease status

	MetS + TAK (n = 50)	MetS − TAK (n = 142)	*P*	CVD + TAK (n = 28)	CVD − TAK (n = 164)	*P*
Age (y), mean ± SD	50.3 ± 12.0	40.8 ± 12.4	**.000**	46.9 ± 12.3	42.7 ± 13	.103
Gender (female), n (%)	40 (80)	118 (83)	.668	21 (75)	137 (83)	.288
Smoking, n (%)	18 (41)	22 (20)	**.007**	11 (44)	29 (22)	**.024**
Disease duration (y), mean ± SD	13.4 ± 8.6	13.6 ± 9.6	.885	16.3 ± 10.9	13 ± 9	.147
Presenting symptoms, n (%)						
Fever	7 (15)	29 (22)	.407	3 (12)	33 (21)	.367
Weight loss	17 (36)	49 (37)	.513	8 (32)	58 (37)	.371
Extremity claudication	30 (62)	85 (63)	.464	15 (57)	99 (63)	.391
Pulseless	24 (62)	58 (56)	.106	14 (66)	68 (56)	.245 .094
Murmur	34 (72)	94 (71)	.493	21 (84)	107 (70)	
Smoking	18 (45)	22 (19)	**.008**	11 (44)	29 (22)	**.043**
Radiological type, n (%)						
I	12 (24)	39 (29)	.634	8 (30)	43 (27)	.709
II	9 (18)	2 (1.4)		3 (11)	31 (19)	
III	0	1 (0.7)		1 (4)	1 (0.6)	
IV	4 (0.8)	5 (0.3)		2 (7)	7 (4)	
V	24 (49)	66 (49)		13 (48)	77 (48	
Active disease in last visit n, (%)	11 (23)	13 (10)	**.018**	6 (24)	18 (11)	.084
Number of relapses, median (min-max)	0 (0-4)	0 (0-5)	.559	0 (0-5)	1 (0-4)	.489
CVaD, n (%)	7 (14)	25 (18)	.565	6 (22)	26 (16)	.643
Cumulative PRD (g), mean ± SD	9.5 ± 7.0	9.7 ± 8.7	.903	12.8 ± 11.2	9.2 ± 7.7	.202
Methotrexate, n (%)	37 (79)	104 (76)	.430	20 (77)	121 (77)	.596
Leflunomide, n (%)	13 (28)	36 (26)	.497	11 (42)	38 (24)	**.047**
Azathioprine, n (%)	21 (45)	66 (48)	.404	13 (50)	74 (47)	.464
Cyclophosphamide, n (%)	2 (4)	12 (8)	.255	1 (4)	13 (8)	.382
Biologic drug, n (%)	8 (19)	33 (28)	.307	7 (26)	34 (25)	.521
VDI, mean ± SD	4.5 ± 3.3	3.2 ± 2.2	**.004**	5.8 ± 2.7	3.1 ± 2.3	**.000**
VDI items, n (%)						
Musculoskeletal	17 (34)	26 (18)	.243	8 (29)	35 (21)	.290
Skin/mucous membranes	10 (20)	7 (5)	.108	4 (14)	13 (79)	.428
Ocular	13 (26)	33 (23)	.496	7 (25)	39 (24)	.579
ENT	1 (2)	0	.253	1 (4)	0	.176
Pulmonary	13 (26)	20 (14)	.375	7 (25)	26 (16)	.297
Cardiovascular	49 (98)	83 (58)	**.006**	23 (82)	109 (66)	.200
Peripheral vascular	50 (100)	118 (83)	.437	26 (93)	142 (87)	.384
Gastrointestinal	2 (4)	1 (7)	.444	1 (4)	2 (1)	.322
Renal	4 (8)	2 (1)	.156	2 (9)	4 (2)	.444 **.000**
Neuropsychiatric	7 (14)	16 (11)	.645	14 (50)	9 (5)	
Other	12 (38)	13 (9)	.068	1 (4)	24 (15)	.066

Abbreviations: CvaD, cardiac valve disease; CVD, cardiovascular disease; ENT, ear; nose, throat; MetS, metabolic syndrome; PRD, prednisolone; SD, standard deviation; TAK, Takayasu arteritis; VDI, Vasculitis Damage Index.

TABLE 3 Multivariable analysis for cardiovascular disease in Takayasu arteritis patients

	P	OR	95% CI
Smoking	.054	3.3	0.9-11.2
Metabolic syndrome	**.007**	4.9	1.5-15.6
Cumulative prednisolone	**.037**	1.1	1.0-1.1

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

et al found that presence of MetS was associated with higher SLE disease damage scores.[4] On the other hand, high VDI in TAK patients with CVD is an expected finding, because cardiovascular and neuropsychiatric items in the VDI overlap with CVD items. As a result, it is not possible to make further comments for these data in our study.

The main limitation of our study is its cross-sectional design with lack of baseline data of VDI and MetS. However, we think long disease duration in a sizeable patient cohort increases the validity of our results.

In conclusion, the frequency of MetS in patients with TAK was observed to be lower than the reported series for the general population of Turkey. However, the presence of MetS in TAK is associated with increased CVD and disease damage. When managing comorbidities such as hypertension, hyperlipidemia, and hyperglycemia during the follow up of TAK patients, improvement of waist circumference and high-density lipoprotein levels among other MetS components should be taken into consideration. Whether management of MetS positively affects the prognosis and the existence of links between MetS, CVD, and long-term damage require further studies in TAK patients.

CONFLICT OF INTEREST

Haner Direskeneli is an Editorial Board member of the journal and co-author of this article. He was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by members of the Editorial Board to minimize bias. All other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Polymorphism of protein tyrosine phosphatase non-receptor type 22 and protein arginine deiminase 4 gene among Ghanaian rheumatoid arthritis patients: A case–control study

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Abstract

Aim: Rheumatoid arthritis (RA) is an autoimmune disease which affects millions of lives globally characterized by chronic inflammation in the joints of the body. There is no known cause for RA; however, genetic predisposition has been associated with its occurrence. The association between genetic predisposition and RA has been reported largely among Caucasians and Asians. However, few studies with limited data have reported genome-wide association studies of RA in Africa, especially in Ghana. In addition, there is genetic heterogeneity that exists geographically among different populations. This study therefore investigated the association of protein arginine deiminase type 4 (PAD4) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) single nucleotide polymorphisms with susceptibility of RA among Ghanaians.

Methods: This case–control study included 75 RA patients and 75 healthy controls from the Komfo Anokye Teaching Hospital in Ghana. Validated questionnaires were used to obtain demographic data, and blood samples were collected and processed for DNA and polymerase chain reaction analysis. Statistical analysis was done using SPSS version 25.0.

Results: PTPN22 demonstrated a 100% minor allele frequency (GG) in both cases and healthy controls; however, an association could not be made for PTPN22 polymorphism with susceptibility of RA when comparing cases to controls. The homozygous minor allele (GG) of PAD4 was absent in the population.

Conclusion: PAD4 polymorphism was absent, while PTPN22 was present in the Ghanaian population. The association between PTPN22 (rs2476601) and PAD4 (rs2240340) with RA susceptibility could not be established, thus may not contribute as risk factors for RA in the Ghanaian population.

KEYWORDS
protein arginine deiminase type 4, protein tyrosine phosphatase non-receptor type 22, rheumatoid arthritis, single nucleotide polymorphism

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease which symmetrically affects the joints of the body.[1] RA has demonstrated global concern in Europe, Asia, and Africa with a prevalence between 0.5%-1%.[1,2] One study showed that RA is associated with mortality, comorbidities, and economic hardship. Moreover, it is reported that more RA patients with comorbidities die in a long-term observational study.[3] The increase in the deaths of comorbid RA patients has a long-term effect on the economic state of any country, as disability and death affect many lives.[1,3] Although the efforts rallied toward drug development against RA have been great, the high cost of these drugs consequently ravages victims and their families; additionally, several side effects of some of these drugs have caused patients to live with RA rather than being treated.[4] This is more critical in middle- and low-income countries with inadequate resources.[2] Over the years, collective efforts to address several side effects, high cost of drugs, and the prevention of severe RA have led to the investigation of genetic contributions to the development of RA.[5] Based on this scientific initiative, genome-wide association studies have shown that the protein tyrosine phosphatase non-receptor type 22 (PTPN22) and protein arginine deiminase type 4 (PAD4) genes contribute largely to RA.[6] Moreover, a study showed the hereditary of these susceptible genes is 60%, emphasizing their impact on RA development.[1] In RA, the PTPN22 gene enables auto-reactive T cells to escape clonal deletion during negative selection, while PAD4 gene contributes to RA by producing citrullinated proteins which become targets for anti-citrullinated autoantibodies.[7,8] It is reported that these putative RA-associated genes vary geographically and are highly prevalent among Caucasians and Asians.[1] Nonetheless, some studies have reported the lack of association of these genes in some populations. Studies done among Japanese, South African, and Egyptian populations have demonstrated a lack of association between the PTPN22 gene and RA. Similarly, the PAD4 gene has demonstrated an association with RA among some Asian populations; however, this gene is less common among Europeans.[9–11] The presence of genetic heterogenicity that exists geographically among different populations necessitates the need to investigate these genes among different populations. There is also a dearth of data on these RA-associated PTPN22 and PAD4 genes in Africa and particularly in Ghana, where data on PAD4 and PTPN22 associated with RA does not exist. Therefore, this study investigated the presence of PAD4 and PTPN22 genes among RA patients in the Ghanaian population.

2 | SUBJECTS AND METHODS

2.1 | Study design and site

This was a case–control study conducted at the Rheumatology Unit of the Komfo Anokye Teaching Hospital (KATH) from June, 2018 to September, 2020. KATH is the second largest hospital in Ghana, located in Kumasi, Ashanti region. Kumasi is a cosmopolitan town with a projected population of 4 780 380. KATH has 1200-bed capacity with a good geographical location and a perfect road network that makes it accessible to all parts of the country. This setting makes KATH a major referral center which serves 12 out of 16 regions in Ghana.

2.2 | Enrollment of study participants

A total of 150 consenting participants, 75 clinically diagnosed with RA from KATH, were selected as cases. All 75 participants were selected on the basis of meeting the American College of Rheumatology (ACR) 2010 RA criteria. The exclusion criteria were participants who had other autoimmune diseases and participants who failed to meet the ACR 2010. Seventy-five healthy blood donors with no cardiovascular complaints, chronic pain, or other inflammatory diseases were included as controls.

2.3 | Ethics approval and consent to participate

This study followed the provisions of the Declaration of Helsinki, and ethics approval was obtained from the institutional review board of KATH (KATH-IRB/AP/009A/20). Written informed consent was taken from all participants who decided to participate after the objectives of the study were explained. Responders were assured of the confidentiality of their information as they were only needed for research and academic purposes.

2.4 | Questionnaire administration, anthropometric measurements, and blood processing

Questionnaires were provided to collect sociodemographic data which included age, marital, gender, employment, and education status. Height was measured to the nearest 0.1 m using a measuring tape. Weight was measured to the nearest 0.1 kg using a calibrated beam scale. Body mass index (BMI) was calculated as (kg/m^2) = ($weight/height^2$). A total of 2 mL of venous blood was drawn from RA patients and healthy blood donors for DNA extraction.

2.5 | DNA extraction and single nucleotide polymorphism (SNP) analysis of PTPN22 and PAD4 using modified tetra primer amplification system – polymerase chain reaction (MTPA-PCR) assay

DNA was extracted from 2 mL whole blood using the Quick-DNA mini-prep kit, DNA quality was checked using 1% agarose gel electrophoresis and quantified using nanodrop spectrophotometry. The 2 SNPs PTPN22 (rs2476001), and PAD4 (rs2240340) were each amplified in a total reaction volume mixture of 25 μL using a MTPA-PCR technique. The reaction mixture consisted of forward and reverse

TABLE 1 Primer sequences for modified tetra primer amplification system – polymerase chain reaction-based amplification of SNPs of PAD4 and PTPN22 gene

SNPs	Chromosome	Allele	Primers	Primer sequence	BS
PAD4 (rs2240340)	Chr1	Major allele: A	FIP-G	ACAAGGAGATTTCTGAAATCCCATAAG	A-216
		Minor allele: G	RIP-A	CCTCACCAACCTCTCCTCTTCCT	G-163
			FOP	AACAGTTAACACGGAATACGGGG	
			ROP	GAACCTGTGTCTCCTCTGCAG	
PTPN22 (rs2476601)	Chr1	Major allele: A	FIP-G	AACCACAATAAATGATTCAGGTGTACG	G-396
		Minor allele: G	RIP-A	AATCCCCCCTCCACTTCCTGGAT	A-124
			FOP	AATTAAAGGCATGAGCCACCATTCC	
			ROP	CGATCTCCTGACCTTGTGCTC	

Abbreviation: BS, band sizes; Chr1, chromosome; FIP, forward inner primer; FOP, forward outer primer; PAD4, protein arginine deiminase type 4; PTPN22, protein tyrosine phosphatase non-receptor type 22; RIP, reverse inner primer; ROP, reverse outer primer; SNP, single nucleotide polymorphisms.

TABLE 2 Baseline characteristics of study participants

Variable	Total (N = 150)	Cases (N = 75)	Controls (N = 75)
Age, y			
<30	18 (12.0)	3 (2.0)	15 (10.0)
30–40	55 (36.7)	29 (19.3)	26 (17.3)
40–50	35 (23.3)	20 (13.3)	15 (10.0)
50–60	29 (19.3)	16 (10.7)	13 (8.7)
>60	13 (8.7)	7 (4.7)	6 (4.0)
Gender			
Male	10 (6.7)	5 (3.3)	5 (3.3)
Female	140 (93.3)	70 (46.7)	70 (46.7)
Body mass index			
<18.5	9 (6.0)	3 (4.0)	6 (8.0)
18.5–24.9	55 (36.7)	27 (36.0)	28 (37.3)
25–29.9	42 (28.0)	22 (29.3)	20 (26.7)
>30	44 (29.3)	23 (29.3)	21 (28.0)
Religion			
Christianity	131 (87.3)	68 (90.7)	63 (84.0)
Islamic	19 (12.7)	7 (9.3)	12 (16.0)
Education level			
Educated	122 (81.3)	65 (86.7)	57 (76.0)
Uneducated	28 (18.7)	10 (13.3)	18 (24.0)
Occupation			
Employed	88 (58.7)	46 (61.3)	42 (56.0)
Unemployed	62 (41.3)	29 (38.7)	33 (44.0)
Marital status			
Single	73 (48.7)	37 (49.3)	36 (48.0)
Married	68 (45.3)	33 (44.0)	35 (46.7)
Widowed	9 (6.0)	5 (6.7)	4 (5.3)

outer and inner primers, nuclease-free water, Taq polymerase, and genomic DNA. A volume of 5.0 μL of the amplicons was analyzed using 2% agarose gel. The primers, chromosome, primer sequences, the major and minor allele with their band sizes for each SNP is available in Table 1. The PCR initial denaturation temperature for both PTPN22 (rs2476601) and PAD4 (rs2240340) were 94°C, the annealing temperature at 30 cycles was 58.3°C for PTPN22 (rs2476601) and 62.4°C for PAD4 (rs2240340). The final extension cycle was 72°C for both PTPN22 (rs2476601) and PAD4 (rs2240340).

2.6 | Statistical analysis

All statistical analyses were performed using SPSS (version 25, IBM, Armonk, NY, USA). Results were expressed as means ± standard deviation (*SD*) for continuous variables, and frequency and percentages for categorical variables. The Chi-square was used to test for the association of PTPN22 (rs2476601), PAD4 (rs2240340) and RA susceptibility. The significance was described as Pearson *P* value with 95% confidence intervals (CIs); a *P* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of study participants

This case–control study consisted of 75 RA patients and 75 gender-matched healthy controls. Table 2 shows the baseline characteristics of the study population. Of the 150 participants included in the study, more than one-third were within the age of 30-40 years (36.7%) followed by 40-50 years (23.3%). The majority of participants were females (93.3%), had a normal BMI (36.7%), were Christians (87.3%), educated (81.3%), and were employed (58.7%).

3.2 | PTPN22 and PAD4 SNP distribution

PAD4 expressed a single allele band pattern representing the homozygous major allele (AA) with a band size of 216 bp, while that of PTPN22 expressed a single band representing a homozygous minor allele (GG) with a band size of 396 bp indicated in the gel photographs in Figures 1 and 2 respectively.

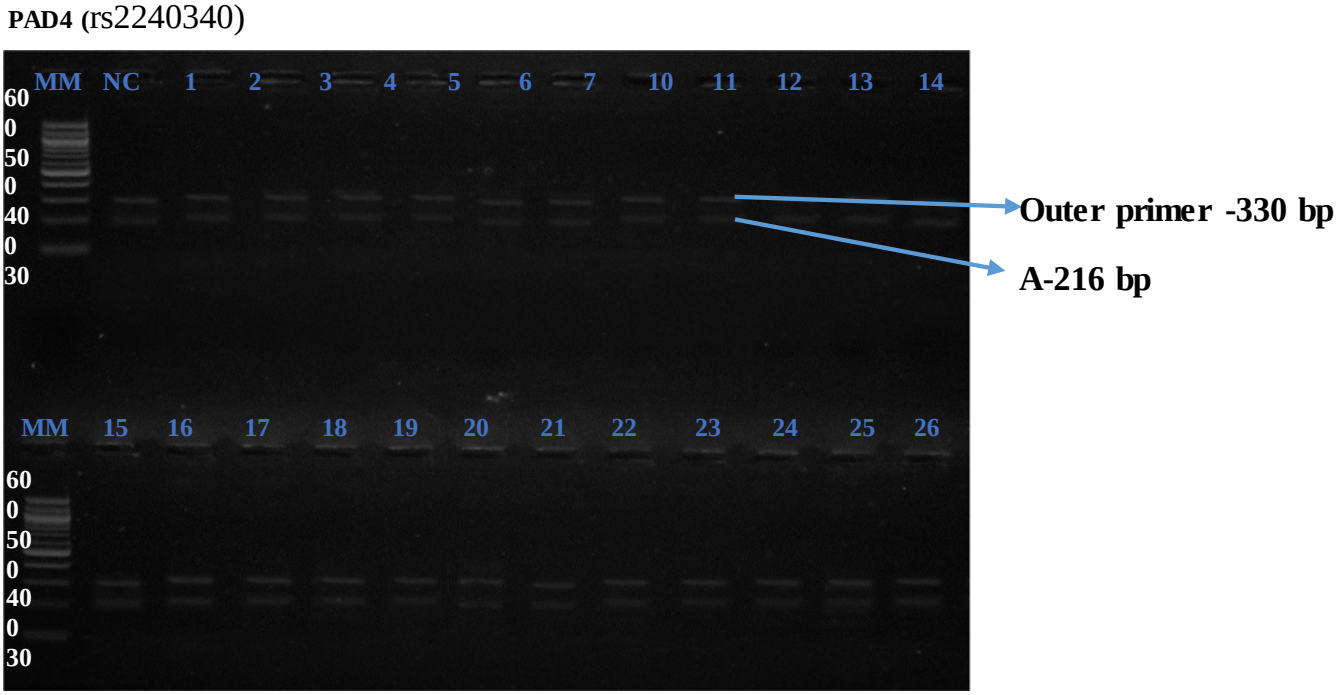

FIGURE 1 Protein arginine deiminase type 4 (PAD4) expressed a single allele band pattern representing the homozygous major allele (AA) with a band size of 216 bp

3.3 | Distribution of PTPN22 and PAD4 gene frequency in cases and controls

PTPN22 (rs2476601) had a minor allele (G) and gene (GG) frequency of 100%, but major allele (A) and gene (AA) frequencies were absent (0.0) in both cases and controls. PAD4 (Rs2240340) also showed a major allele (A) and gene (AA) frequency of 100%, but the minor (G) allele and gene (GG) frequency were absent (0.0) in both case and control groups (Table 3).

4 | DISCUSSION

This study investigated the presence of PAD4 and PTPN22 variants and their association with susceptibility of RA in the Ghanaian population. The only variant, that is, PAD4, expressed a 100% major allele frequency, while PTPN22 expressed 100% minor allele frequency among the study participants; however, the association could not be made with RA for each variant.

Non-human leukocyte antigen genes including PAD4 (rs2240340) and PTPN22 (rs2476601) have been reported to contribute independently to RA pathogenesis.[12,13] The contribution of these variants to RA largely depends on the presence or absence of minor alleles. However, the absence of these minor alleles is an indicator that its associated variant is normal in a given population, and thus, these variants would express major alleles. The minor allele frequency of PTPN22 (rs2476601) reported among Europeans and Asians is relatively high compared to African Americans and several sub-Saharan African countries.[14] In a European study, the minor allele frequency of PTPN22 among Europeans was 10% and 6% for African Americans.[15] A study by Viatte et al in 2018 reported the minor allele frequency of Africans to be below 2%. In contrast, the National Center for Biotechnology Information RefSNP reports of PTPN22 (rs2476601) show that few studies conducted expressed a minor allele frequency of 98% in some populations including Africans.[16] These findings were similar to this study, where the minor allele frequency of PTPN22 was 100% present in both RA patients and controls (Table 3). Genome-wide associative studies report that PAD4 is more associated with Asians than Caucasians, while there is a paucity of data from Africa.[17] The minor allele frequency of PAD4 varies in different populations. In a central Canadian study, a minor allele frequency of PAD4 in a North American native population was recorded as 49% in both RA patients and healthy controls.[8] These findings were contrary to our study findings, where the minor allele frequency of the PAD4 variant was absent in both RA cases and controls (Tables 3).

In a study by Jian et al, PTPN22 (rs2476601) showed an association with RA in a UK population but failed to show an association among Africans.[18] This indicates the heterogenicity that exists across different populations. This outcome was similar to this study, where an association could not be made between PTPN22 and RA susceptibility (Tables 3). PAD4 (rs2240340) is a gene with a strong association with RA, especially among Asians.[17] The role PAD4 plays in the pathogenesis of RA prompted researchers to investigate its association with the susceptibility of RA.[18,19] Jian et al in 2021 demonstrated a lack of association between PAD4

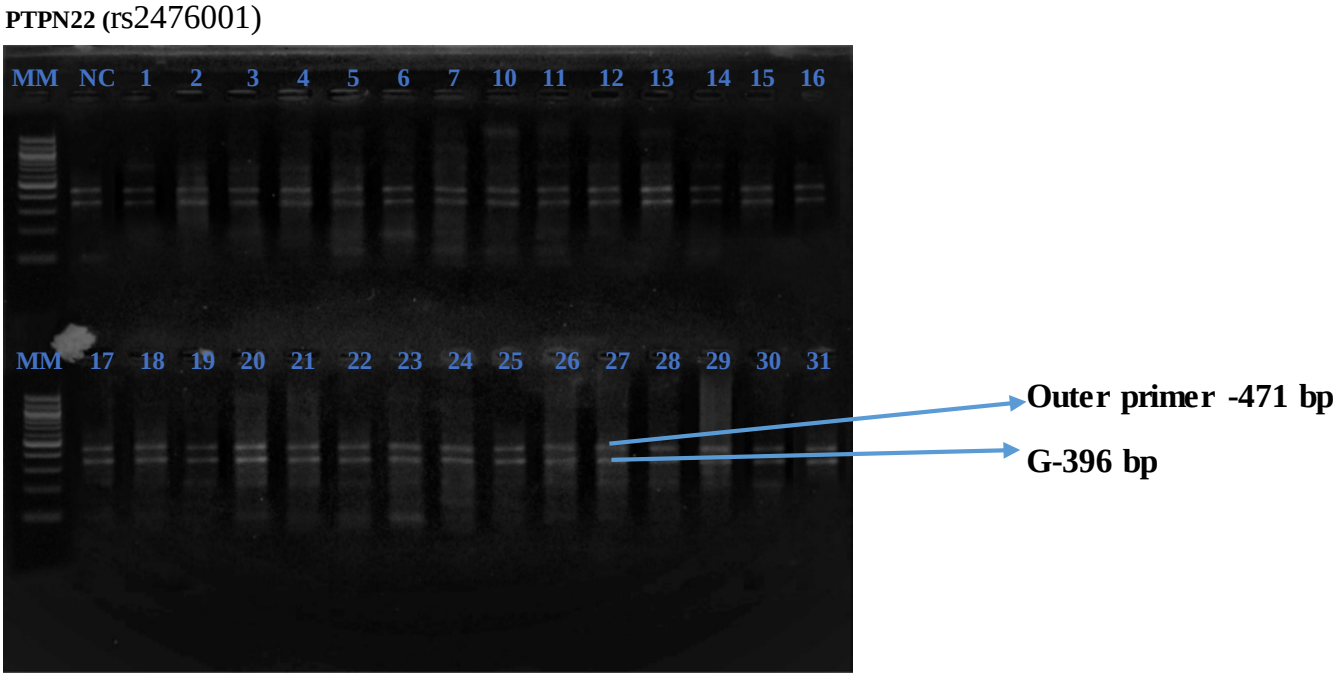

FIGURE 2 Protein tyrosine phosphatase non-receptor type 22 (PTPN22) expressed a single band representing a homozygous minor allele (GG) with a band size of 396 bp

TABLE 3 Distribution of PTPN22 and PAD4 gene frequency in cases and controls

SNPs	Controls (N = 75)			Cases (N = 75)			*P* value
	Total	Allele frequency		Total	Allele frequency		
		A	G		A	G	
		(Major allele)	(Minor allele)		(Major allele)	(Minor allele)	
PAD4 rs2240340							
Yes, major AA	75 (100.0)	75 (100.0)	0 (0.0)	75 (100.0)	75 (100.0)	0(0.0)	nc
No, minor GG	0 (0.0)			0 (0.0)			
Heterozygous AG	0 (0.0)			0 (0.0)			
PTPN22 rs2476601		A	G		A	G	
Yes, minor GG	75 (100.0)	0 (0.0)	75 (100.0)	75 (100)	0 (0.0)	75 (100.0)	nc
No, major AA	0 (0.0)			0 (0.0)			
Heterozygous AG	0 (0.0)			0 (0.0)			

Abbreviations: nc, not computed due to a constant variable; PAD4, protein arginine deiminase type 4; PTPN22, protein tyrosine phosphatase receptor type 22; SNPs, single nucleotide polymorphisms.

and RA susceptibility and severity in a UK population.[18] This finding was in agreement with the results of this study, where an association could not be made between PAD4 (rs220340) and RA susceptibility (Table 3).

In conclusion, PAD4 polymorphism was absent while PTPN22 was present in the Ghanaian population. The association between PTPN22 (rs2476601) and PAD4 (rs2240340) with RA susceptibility could not be established, thus may not contribute as risk factors for RA susceptibility in the Ghanaian population.

AUTHOR CONTRIBUTIONS

Conceptualization: Samuel Asamoah Sakyi, Andy Opoku Boateng, Ahenkorah Fondjo. Methodology: Samuel Asamoah Sakyi, Andy Opoku Boateng, Linda Ahenkorah Fondjo, Kwame Yeboah Mensah. Formal analysis and investigation: Andy Opoku Boateng, Linda Ahenkorah Fondjo, Steven Opoku, Ebenezer Senu, Tonnies Buckman, Joseph Entwi Sampson. Writing - original draft preparation: Andy Opoku Boateng, Samuel Asamoah Sakyi, Steven Opoku. Writing - review and editing: Andy Opoku Boateng, Samuel Asamoah Sakyi,

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CONFLICT OF INTEREST

The authors declare there are no competing interests relevant to this work.

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A single-center COVID-19 vaccine experience with CoronaVac and BNT162b2 in familial Mediterranean fever patients

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Abstract

Aim: To determine frequency of adverse events and attacks related to vaccination in recipients of CoronaVac and BNT162b2 in familial Mediterranean fever (FMF) patients, and to search whether history of prior COVID-19 or a booster dose increases occurrence of adverse events/attacks.

Methods: FMF patients were surveyed for administration of any COVID-19 vaccine and vaccine-related adverse events or FMF attacks. Demographic, clinical, vaccine-related data, history of COVID-19 infection before or after vaccination, adherence to FMF treatment during vaccination were collected.

Results: A total of 161 vaccinated FMF patients were included. Ninety-three patients out of 161 had reported suffering from an adverse event/attack after a vaccine dose. There were 54.7% of BNT162b2 recipients who reported any adverse event after any vaccine dose in comparison to 29.9% of CoronaVac recipients ($P < .001$). There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month after vaccination in comparison to 19.4% of CoronaVac recipients ($P = .653$). When patients with or without adverse event/attack were compared, no significant differences were observed in means of demographics, comorbid diseases, disease duration, total vaccine doses, or treatments adhered to for FMF. Rates of adverse events/attacks were similar between patients with and without prior COVID-19. In booster recipients, adverse events/attacks were most frequent after the booster dose.

Conclusions: A considerable number of FMF patients suffered from vaccine-related adverse events/attacks, particularly with BNT162b2. No serious events or mortalities due to vaccination were detected. Demographics, clinical characteristics and prior history of vaccination did not significantly affect these results. We observed an increased rate of adverse events/attacks with booster dose administration.

KEYWORDS
adverse events, COVID-19, familial Mediterranean fever, safety, vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has become the major global health problem since first human cases were reported in December, 2019 and despite the efforts, a curative treatment regimen is yet to exist except some promising results reporting decreased mortality and hospitalization rates with some antiviral and anti-inflammatory agents.[1] Hence, preventive measures have emerged, among which, vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) has been the foremost measure since vaccination is accepted to be the most effective strategy against infectious diseases.[2]

Several vaccines against SARS-CoV 2 have been developed by various countries and companies using different platforms such as inactivated vaccines, adenovirus vector vaccines and messenger ribonucleic acid (mRNA) vaccines.[3,4] In order to head off the rapidly spreading pandemic, these vaccines were put into use worldwide with emergency use authorizations, prior to completion of full procedures for approval, which raised some safety concerns alongside facilitation of vaccination, particularly for mRNA vaccines due to lack of any previous experience with any other disease. Likewise, the inactive vaccine CoronaVac (Sinovac) has been used since December, 2020 and BNT162b2 (Pfizer-BioNTech) since April, 2021 in our country.

Patients with autoimmune and auto-inflammatory rheumatic diseases compose a special population regarding the effects of COVID-19 vaccines due to presence of an already dysregulated immune system and long-term use of various immunosuppressant and anti-inflammatory agents. There have already been concerns for development of severe immune-mediated side effects such as myocarditis, multisystem inflammatory syndrome and Guillain-Barré syndrome related to COVID-19 vaccination, which means we should consider whether COVID-19 vaccination leads to disease flares or further adverse events in patients with rheumatic diseases.[5–9] Several studies have investigated vaccine safety in various rheumatic diseases with no significant safety signals; however, knowledge regarding familial Mediterranean fever (FMF) patients is still scarce.[10–14]

FMF is an auto-inflammatory disease characterized by mutations in *MEFV* gene encoding pyrin, which plays an important role as a part of the innate immune system in first defense against pathogens, as a recognizer of pathogen-associated proteins or "patterns".[15]Since pyrin-mediated inflammasome response is dysregulated and hyperreactive due to mutations in FMF patients, exposure to SARS-CoV 2 proteins via vaccination may potentially trigger inflammation, leading to attacks and/or increased rate of adverse events in FMF patients. Peet et al[16] reported no safety concerns for COVID-19 vaccines in 175 patients with auto-inflammatory diseases, only 13 of them being FMF patients. Haslak et al[17] reported an acceptable safety profile in children and young adults with auto-inflammatory diseases, the majority of whom were FMF patients. In a recent study, Shechtman et al[18] reported no increased safety signal after BNT162b2 in adult FMF patients with an increase in systemic adverse events after the second dose. However, comprehensive data regarding safety of different COVID-19 vaccine types, effects of a booster dose or history of COVID-19 infection prior to vaccination are still missing.

Effectiveness and safety of a booster dose following primary vaccination is another matter of debate. Primary vaccination is defined as completing the required series of doses for a single kind of vaccine, which differs according to type of vaccine. A booster dose, on the other hand, may also be required due to waning protective effects of primary vaccination and can be administered by another type of vaccine.[19] Although a booster dose is advocated for prolonged immunity, it further evokes safety issues regardless of being the same type with the primary vaccination or heterogeneous vaccination.[19]

In this single-center study, we investigated frequency of adverse events and attacks related to vaccination in recipients of CoronaVac and BNT162b2 comparatively in our FMF patients. Additionally, we also searched whether history of COVID-19 prior to vaccination or application of a booster dose increased occurrence of adverse events and/or FMF attacks.

2 | METHODS

This study was conducted as a single-center, cross-sectional study. Ethics approval was obtained by Ankara City Hospital ethics committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. An official permission was also obtained from the Ministry of Health.

FMF patients meeting Tel-Hashomer criteria[20] who had been followed in our clinic were reached via telephone numbers recorded in hospital records between October 1 and December 1, 2021 and surveyed for administration of any COVID-19 vaccine and vaccine-related adverse events or FMF attacks, upon verbal consent. Written consent could not be obtained due to study design. Patients younger than 18 years of age at the time of any vaccination and patients who did not want to participate were excluded.

Data regarding demographics, comorbidities, *MEFV* mutations and medical treatment administered for FMF were collected from hospital databases and confirmed during surveys. Presence of adverse events and/or FMF attacks after any vaccine dose was set as primary outcome and collected via telephone survey. Additionally, number of vaccine doses, types of vaccines (CoronaVac or BNT162b2), interval between adverse event/FMF attack and vaccine dose, history of COVID-19 infection before or after vaccination, adherence to FMF treatment during vaccination were also collected via telephone surveys. Primary vaccination was accepted as completed in presence of 2 consecutive vaccinations of the same kind. Booster vaccination is defined as any dose of any vaccine after completion of primary vaccination. Any adverse event or attack within 1 month after vaccine administration which was suspected to be related with vaccination by the patient was recorded in accordance

with the Vaccine Adverse Event Reporting System (VAERS).[21] Severity of adverse events was also accordingly assessed. A FMF attack was defined by patient feedback according to resemblance to a previously experienced attack.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) v22.0. Normality of continuous variables was evaluated with Kolmogorov–Smirnov test in addition to visual analyses with plots and histograms. Continuous variables are presented either with median (interquartile range [IQR] or min-max) or mean ± standard deviation (SD) and compared by Mann–Whitney-*U* or Student's *t* tests according to normality. Categorical variables are presented with numbers and percentages and compared by χ^2 test. *P* values <.05 were considered statistically significant for all analyses.

3 | RESULTS

Out of 464 FMF patients, 194 could be reached via telephone in which 30 were unvaccinated and 3 did not consent to enrolment. A total of 161 vaccinated FMF patients were included in the study. Among the remaining 270 patients, 2 were detected to be dead due to reasons unrelated to COVID-19 vaccination. Distribution of COVID-19 vaccines is presented in Figure 1. Demographics, clinical properties, FMF treatment agents are presented in Table 1. There were 96.3% of patients who adhered to FMF treatment during vaccination.

Two-hundred and thirteen doses of BNT162b2 and 140 doses of CoronaVac were administered to 161 patients (Table 2). There were 72.7% of patients who were ever vaccinated by BNT162b2 while 41.6% were by CoronaVac. Median (min-max) vaccine doses were 2 (1–4) in both groups. One hundred and forty-five patients completed primary vaccination, 54.0% with BNT162b2 while 36.0% were with CoronaVac. Thirty-seven patients had booster doses (14.9% BNT162b2, 8.7% of CoronaVac).

Among 117 patients who ever received BNT162b2, 64 (54.7%) reported any adverse event after any vaccine dose in comparison to 20 out of 67 (29.9%) who ever received CoronaVac (*P* < .001). Most common side effects were fever, malaise, local pain/arm pain and arthralgia in both groups. None of the patients reported headache after CoronaVac while 9.4% reported it after BNT162b2. None of the patients suffered from a severe adverse event, while a single patient developed palmoplantar pustular psoriasis with arthritis after a BNT162b2 dose, requiring hospitalization for optimal treatment. There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month of vaccination in comparison to 19.4% of CoronaVac recipients (*P* = .653). When attacks within a week of vaccination were taken into consideration, these frequencies reduced to 20.5% vs 16.4% (*P* = .496), respectively. The interval between vaccination and FMF attack was median (IQR) 7.0 (12.5) days in BNT162b2 recipients and 10.0 (13.5) days in CoronaVac recipients. Data regarding vaccine safety are presented in Table 2.

A total of 93 patients out of 161 reported suffering from an adverse event or FMF attack after a vaccine dose. When patients with or without adverse event/attack were compared, no significant differences were observed in means of demographics, comorbid diseases, disease duration, total vaccine doses and treatments adhered for FMF, except for an increased rate of canakinumab use in patients with adverse events/attacks nearly reaching statistical significance (7.5% vs 1.5%, *P* = .081) (Table 3).

Out of 145 patients who completed primary vaccination, 6 (4.1%) of them reported having COVID-19 at least 14 days after the last dose. COVID-19 infection was more frequent in patients with CoronaVac primary vaccination, without reaching statistical significance (7.0% vs 2.3%, *P* = .215). A total of 37 patients had a booster dose after primary vaccination (23 BNT162b2, 14 CoronaVac). A single patient in each group had COVID-19 after the booster dose (7.1% vs 4.3%, *P* = .715) (Table S1).

When 37 patients who received any booster dose after completion of primary vaccination with either vaccine types were investigated, 27% suffered from an adverse event or FMF attack after the first dose of vaccination, while this was 21.6% after the second dose and 32.4% after the booster dose (first dose vs second dose, *P* = .011; first dose vs booster dose, *P* = .029; second dose vs booster dose, *P* = .004).

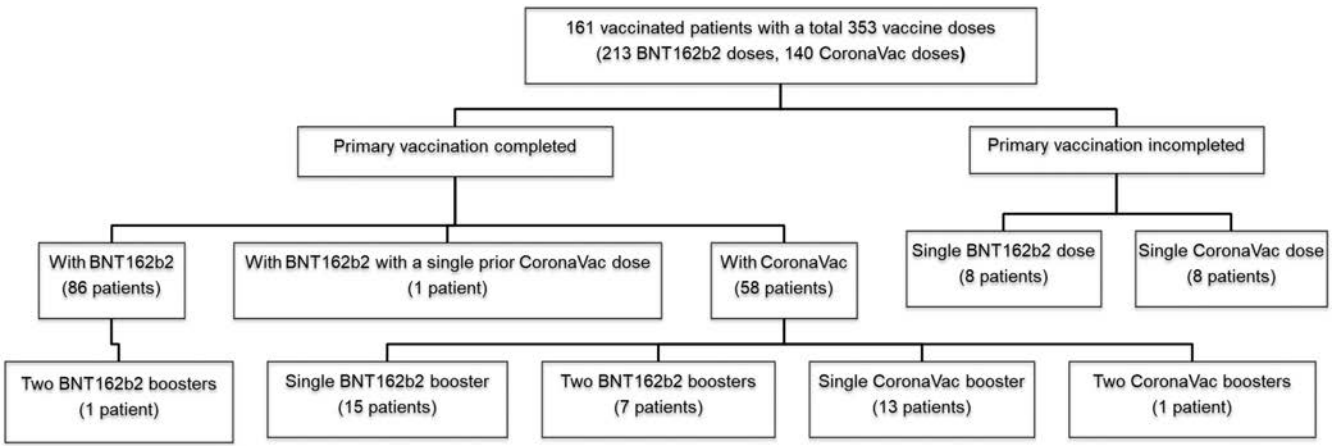

FIGURE 1 Distribution of vaccines among patients

TABLE 1 Demographics and clinical characteristics of FMF patients who were vaccinated for COVID-19

	N = 161
Age, y, mean ± SD	40.5 ± 11.7
Gender, female, n (%)	92 (57.1)
BMI, mean ± SD	25.9 ± 4.6
Active smokers, n (%)	54 (33.5)
Patients with ≥1 comorbidities, n (%)	83 (51.6)
Comorbidities, n (%)	
Hypertension	27 (16.8)
Diabetes mellitus	16 (9.9)
Chronic kidney disease	17 (10.6)
Coronary artery disease	6 (3.7)
Renal transplantation	3 (1.9)
Amyloidosis	15 (9.3)
Other	53 (32.7)
Time from diagnosis, y, median (min – max)	12.0 (1.0–50.0)
FMF attack characteristics, n (%)	
Abdominal pain	141 (87.6)
Fever	116 (72.0)
Pleuritic pain	83 (51.6)
Arthritis/arthralgia	47 (29.2)
Erysipelas-like erythema	9 (20.9)
Attack duration, d, mean ± SD	3.8 ± 1.8
MEFV mutations, n (%)[a]	
M694V heterozygous	20 (27.0)
M694V homozygous	16 (21.6)
E148Q heterozygous	7 (9.5)
M694V/M680I compound heterozygous	7 (9.5)
M694V/V726A compound heterozygous	6 (8.1)
M694V/E148Q compound heterozygous	5 (6.8)
M680I homozygous	3 (4.1)
V726A heterozygous	2 (2.7)
P369S/R408Q compound heterozygous	2 (2.7)
Others[b]	4 (5.6)
No mutations detected	2 (2.7)
Treatment agents, n (%)	
Colchicine	150 (93.2)
Anakinra	27 (16.8)
Canakinumab	8 (5.0)
TNFα inhibitors	4 (2.5)
Adherence to FMF drugs during vaccination, n (%)	155 (96.3)

Abbreviations: BMI, body mass index; FMF, familial Mediterranean fever; SD, standard deviation; TNFα, tumor necrosis factor alpha.

[a]Evaluated over 74 in whom results of *MEFV* gene analysis could be obtained.

[b]M680I heterozygous, G304R heterozygous, M680I/R761H compound heterozygous, M694V/V726Q/R202Q triple mutation each in single patient.

Thirty-nine patients had COVID-19 infection prior to completion of the primary vaccination. Of these, 61.5% suffered from an adverse reaction or FMF attack after any COVID-19 vaccine dose when compared to 56.6% of the patients without COVID-19 infection prior to vaccination ($P = .584$).

4 | DISCUSSION

Our results demonstrated that 93 out of 161 FMF patients (57.1%) had vaccine-related adverse events or FMF attacks after any dose of BNT162b2 or CoronaVac. The number of patients who reported adverse events after BNT162b2 was significantly higher. None of the patients had life-threatening, severe adverse events. There were 22.2% of BNT162b2 recipients who reported suffering from a FMF attack within 1 month after vaccine in comparison to 19.4% of CoronaVac recipients. Demographics, clinical features regarding FMF and history of COVID-19 prior to vaccination were not observed to be significantly related with the occurrence of adverse events/attacks. Significantly more patients reported adverse events/attacks after the booster dose when compared to primary vaccination doses. Rates of COVID-19 infection after primary vaccination and booster with BNT162b2 were observed to be lower despite not reaching statistical significance.

Several studies had investigated vaccine safety among patients with rheumatic diseases. Global Rheumatology Alliance reported that among 2860 subjects, 47.2% had any adverse event and 13.4% had any rheumatic disease flare.[13] Fan et al[14] reported 29.9% of patients had adverse events and 10.5% had disease flare. When studies regarding auto-inflammatory patients were investigated, Peet et al[16] reported adverse events in 51.4% of 138 vaccine administrations and disease flares in 18.8%, without any serious adverse event. In children and adults under the age of 21, Haslak et al[17] reported among 223 patients (comprising 123 FMF patients) 46.9% of non-biologic users and 39.5% of biologic users suffered from an adverse event. Severe events were reported in 2 patients. Disease flare within 1 month was reported 11.7% and 14.0% in these groups, respectively. Despite a relatively higher adverse event/attack rate in our study, we did not observe any life-threatening adverse events. Fatigue, headache, myalgia, arthralgia, fever and nausea-vomiting were the most common adverse events reported by Haslak et al.[17] Similarly, Peet et al[16] most commonly reported fatigue, myalgia, fever, headache and localized symptoms. Shechtman et al[18] evaluated BNT162b2 safety among 273 adult FMF patients, reporting 65.5% local and 26% systemic adverse events after the first dose and 60% local and 50.4% systemic adverse events after the second dose. The most common adverse events were local reaction/pain, fatigue, myalgia and fever. In our study, the total number of patients with any adverse event after any vaccine dose was 57.1%. Relatively lower incidence in our results may be due to the fact that 27.3% of our patients were only vaccinated by CoronaVac and our results demonstrated significantly fewer patients reported any side effect

TABLE 2 Adverse events and FMF attacks in vaccine recipients

	Total number of vaccinated patients = 161		
	BNT162b2	CoronaVac	*P*
Total vaccine doses, n	213	140	
Patients ever vaccinated with BNT162b2 and CoronaVac, n (%)	117 (72.7)	67 (41.6)	
Dose per patient, median (min-max)	2 (1–4)	2 (1–4)	
Patients with primary vaccination completed with BNT162b2 or CoronaVac, n (%)[a]	87 (54.0)	58 (36.0)	
Patients with a booster with BNT162b2 or CoronaVac, n (%)	23 (14.2)	14 (8.6)	
Patients vaccinated with BNT162b2 or CoronaVac alone, n (%)	94 (58.4)	44 (27.3)	
Patients with an adverse event after any dose of BNT162b2 or CoronaVac, n (%)[b]	64/117 (54.7)	20/67 (29.9)	**<.001**
Adverse events, n (%)[b]			
Fever	13 (11.1)	6 (9.0)	.644
Malaise	21 (17.9)	4 (6.0)	**.023**
Local pain/arm pain	17 (14.5)	4 (6.0)	.079
Arthralgia	19 (16.2)	4 (6.0)	**.043**
Myalgia	6 (5.1)	0 (0.0)	.059
Headache	11 (9.4)	0 (0.0)	**.010**
Nausea	6 (5.1)	1 (1.5)	.215
Vomiting	4 (3.4)	1 (1.5)	.439
Numbness	3 (2.6)	0 (0.0)	.186
Teeth pain	1 (0.9)	0 (0.0)	.448
Abdominal pain	5 (4.3)	1 (1.5)	.307
Hypotension	1 (0.9)	0 (0.0)	.448
Chest pain	1 (0.9)	0 (0.0)	.448
Flashes	1 (0.9)	0 (0.0)	.448
Backpain	2 (1.7)	0 (0.0)	.282
Weight loss	1 (0.9)	0 (0.0)	.448
Sore throat	1 (0.9)	0 (0.0)	.448
Dizziness	4 (3.4)	3 (4.5)	.718
Dyspnea	1 (0.9)	0 (0.0)	.448
Psoriasis	1 (0.9)	0 (0.0)	.448
Zona zoster	0 (0.0)	1 (1.5)	.185
Cough	0 (0.0)	1 (1.5)	.185
Diarrhea	0 (0.0)	1 (1.5)	.185
Patients with FMF attack within 1 mo after any dose of BNT162b2 or CoronaVac, n (%)[b]	26 (22.2)	13 (19.4)	.653
Attack within 1 wk, n (%)	15 (12.8)	6 (9.0)	.428
Attack within 2 wk, n (%)	20 (17.1)	9 (13.4)	.512
Attack within 3 wk, n (%)	24 (20.5)	11 (16.4)	.496
Time from vaccine dose to FMF attack, d, median (IQR)	7.0 (12.5)	10.0 (13.5)	.758

Abbreviations: FMF, familial Mediterranean fever; IQR, interquartile range.

[a] 9.9% of patients had only single dose of either vaccine.

[b] Over 117 ever vaccinated with BNT162b2 and 67 ever vaccinated with CoronaVac.

after any CoronaVac dose when compared to BNT162b2. Likewise, most common adverse events in our study were fever, malaise, local pain/arm pain and arthralgia. When FMF attacks were considered, we observed that 22.2% of BNT162b2 recipients and 19.4% of CoronaVac recipients reported suffering from a FMF attack within 1 month after any vaccine dose, which was similar to the results of the study of Shechtman et al,[18] who reported that approximately 19% of their patients had suffered from a FMF attack with 1 month after a BNT162b2 dose.

Polack et al[22] reported up to 83% local adverse events and up to 59% systemic events in 43 548 BNT162b2 recipients. As for CoronaVac, 0-28 day incidence of all adverse events were reported

TABLE 3 Clinical characteristics of patients with and without vaccine-related adverse events/attacks

	Total number of vaccinated patients = 161		
	With adverse events/attacks n = 93	Without adverse events/attacks n = 68	*P*
Age, y, mean ± SD	38.9 ± 12.4	41.9 ± 10.7	.113
Gender, female, n (%)	58 (62.4)	34 (50.0)	.117
BMI, mean ± SD	25.7 ± 4.9	26.1 ± 4.2	.681
Active smokers, n (%)	31 (33.3)	23 (33.8)	.948
Patients with ≥1 comorbidities, n (%)	46 (49.5)	37 (54.4)	.535
Comorbidities, n (%)			
Hypertension	12 (12.9)	15 (22.1)	.125
Diabetes mellitus	11 (11.8)	5 (7.4)	.349
Chronic kidney disease	11 (11.8)	6 (8.8)	.540
Coronary artery disease	2 (2.2)	4 (5.9)	.217
Renal transplantation	1 (1.1)	2 (2.9)	.387
Amyloidosis	9 (9.7)	8 (8.8)	.854
Time from diagnosis, y, median (min – max)	11.0 (1.0–41.0)	13.0 (2.0–50.0)	.121
Treatment agents, n (%)			
Colchicine	86 (92.5)	64 (94.1)	.683
Anakinra	16 (17.2)	11 (16.2)	.863
Canakinumab	7 (7.5)	1 (1.5)	.081
TNFα inhibitors	2 (2.2)	2 (2.9)	.750
Dose per patient, median (min-max)	2 (1–4)	2 (1–4)	.907

Abbreviations: BMI, body mass index; SD, standard deviation; TNFα, tumor necrosis factor alpha.

to be between 13%-22% varying on the vaccine dose.[23,24] Likewise, we observed that significantly more patients reported an adverse event after a dose of BNT162b2. Furthermore, Polack et al[22] also reported incidence of side effects was more frequent in younger patients. Fragoulis et al[10] demonstrated increased rates of adverse events in females and patients with chronic obstructive pulmonary disease among vaccine recipients with rheumatic diseases. Additionally, Li et al[25] indicated an increased rate of vaccine-related hospitalizations due to side effects in subjects with a history of COVID-19 infection prior to vaccination. Shechtman et al[18] reported adverse events and FMF attacks following vaccination were more common in FMF patients with higher disease activity and increased colchicine and canakinumab use. Similarly, in our study, patients with adverse events/FMF attacks had increased frequency of canakinumab use, nearly reaching statistical significance. When taken into consideration with results of Shechtman et al,[18] this finding may imply disease activity may actually be related to increased rates of vaccine-related adverse events/FMF attacks, since canakinumab is an agent selected in patients with high disease activity despite colchicine treatment. Our results did not imply any significant other relation between demographics, remaining clinical characteristics, history of prior COVID-19 infection and occurrence of adverse events/FMF attacks.

Thirty-seven patients in our study completed primary vaccination with at least 1 additional booster dose of either CoronaVac or BNT162b2. Among these, the number of patients with an adverse event/FMF attack after the second dose was significantly lower than the number of patients after the first dose, while the number of patients with an adverse event/FMF attack after the booster dose was significantly higher when compared to both first and second vaccine doses. Polack et al[22] revealed a decreased rate of local adverse events but increased rate of systemic events with the second dose of BNT162b2 when compared to the first dose. Haslak et al[17] reported a decrease in rate of overall adverse event occurrence with the second dose of BNT162b2 in patients with auto-inflammatory diseases. Shechtman et al[18] reported fewer local and more systemic side effects with the second BNT162b2 dose in FMF patients. In the study conducted by Aikawa et al,[26] in patients with rheumatic conditions who were administered 2 doses of CoronaVac, incidence of adverse events were lower after the second dose. As for booster dose administrations, several high-quality studies reported acceptable safety profiles both with homologous and heterologous boosters.[27–30] Regardless of the increased number of patients with adverse events/FMF attacks after the booster administration in our study, we did not observe any serious adverse event.

There are several limitations to our study to be mentioned. First, the small sample size, cross-sectional and single-center nature of the study hampers the power of our results and avoids general assumptions. Second, data regarding vaccine experience of our subjects collected via telephone survey and mainly based on subjects' self-reports and FMF attacks could not be confirmed by clinicians, which may have led to over-assumption of adverse events and FMF attacks. Another limitation is that the interval between vaccine doses was not evaluated, which may affect occurrence of vaccine-related adverse events/FMF attacks. Lastly, since this is a real-life study, vaccine types and doses administered to our patients were highly heterogeneous.

We observed a considerable number of FMF patients in our study suffering from vaccine-related adverse events and/or FMF attacks, particularly with BNT162b2. However, no serious events or mortalities due to vaccination were detected. Demographics, clinical characteristics and prior history of vaccination did not significantly affect these results. We observed an increased rate of adverse event/FMF attacks with booster dose administration. Larger, multi-center and longitudinal studies would further elucidate vaccine safety in FMF patients.

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CONFLICT OF INTEREST

Authors declare none.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Predictors of progression in rheumatoid arthritis-associated interstitial lung disease: A single-center retrospective study from China

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Abstract

Aim: Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis (RA) and is associated with high mortality, especially in progressive ILD. We aimed to identify predictors of disease progression in the early stages of ILD in a large sample of patients with RA.

Method: The medical records of 201 RA-ILD patients were retrospectively analyzed. According to changes in their pulmonary function tests, patients were divided into progressive disease and stable disease groups. Data were collected on clinical characteristics, laboratory findings, chest high-resolution computed tomography, and therapeutic agents. Univariate and multivariate analyses were performed to identify predictors of ILD progression.

Results: During a median follow up of 38 months, 105 (52.5%) patients were diagnosed with progressive ILD. These patients were mostly male, past or present smokers ($P = 0.028$, $P = 0.021$, respectively). Higher Health Assessment Questionnaire-Disability Index score and higher Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR) were observed in the ILD progression group ($P = 0.003$, $P < 0.001$, respectively). There were no significant differences in baseline respiratory symptoms, pulmonary function, or laboratory features. Multivariate analysis indicated that high DAS28-ESR, definite usual interstitial pneumonia pattern, fibrosis score, and less use of cyclophosphamide were independent risk factors for RA-ILD progression. Fifteen (7.46%) patients died during the follow up, and the most frequent cause of death was lung infection.

Conclusion: Our results suggested that high disease activity, definite usual interstitial pneumonia pattern, fibrosis score, and less use of cyclophosphamide at the onset of ILD may indicate the progression of ILD in RA patients.

KEYWORDS
high-resolution computed tomography, interstitial lung disease, predictors, progression, rheumatoid arthritis

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1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation of the synovial joints. Interstitial lung disease (ILD) is one of the most serious extra-articular manifestations and is considered to be the second cause of death after cardiovascular disease in patients with RA.[1] About 2%-10% of RA patients will develop clinically significant ILD.[2] A previous study has demonstrated that being male, old age, history of smoking, high titers of rheumatoid factor, elevated anti-cyclic citrullinated peptide (CCP) antibodies, longer duration of RA, and active articular RA are risk factors for the development of RA-ILD.[3] The pathogenesis of ILD in RA is unclear, and the treatment of RA-ILD is not standardized.

Interstitial lung disease in RA significantly reduces quality of life and increases mortality.[4,5] Previous studies exploring old age, usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT), high fibrosis score, and less exposure to rituximab were significantly associated with poor prognosis in patients with RA-ILD.[6–9] Many ILD subtypes, including RA-ILD, have a progressive phenotype and pulmonary function deterioration. In addition, progressive RA-ILD has a worse prognosis than the stable type, with a 5-year mortality of 55%, which is significantly higher than that of stable ILD (18.7%).[10] However, ILD progression is variable and tools to predict those at highest risk for disease progression are lacking.[11] Predicting ILD progression in RA patients remains a challenge for clinicians. Based on the intense relationship between ILD progression and high mortality, we should identify patients at high risk of ILD progression in the early stages of the disease.

To better understand the progression of patients with RA-ILD, we conducted a long-term retrospective single-center study. We collected clinical features, laboratory characteristics, and radiologic patterns and abnormal findings in RA patients at the time of ILD diagnosis. Moreover, we monitored changes in pulmonary function tests (PFTs) to identify patients with progressive ILD. The aim of the present study was to explore potential predictors of disease progression in the early stages of ILD development.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

A total of 248 patients with RA first diagnosed with ILD in the Department of Rheumatology and Immunology, the First Affiliated Hospital of Dalian Medical University between June 2014 and September 2019 were enrolled consecutively in this retrospective study. The inclusion criteria included: (a) age 16 years or older; (b) all patients who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria for RA; (c) patients who underwent lung HRCT at the time of ILD diagnosis;[12]; (d) patients had at least one follow-up visit to our center. The exclusion criteria were: (a) patients with other connective tissue diseases; (b) patients with infectious diseases, lung surgery, and other respiratory diseases; (c) other causes of ILD (idiopathic ILD, infectious pneumonia, drug or occupational-environmental exposures); (d) patients with incomplete primary data. RA-ILD was defined as a patient with both RA and ILD confirmed by HRCT according to the 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonia and the 2011 ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERJ/JRS/ALAT) consensus criteria for idiopathic pulmonary fibrosis (IPF), except for other causes of ILD (idiopathic ILD, infectious pneumonia, drug or occupational-environmental exposures). RA-ILD was diagnosed by multidisciplinary teams including an expert rheumatologist who confirmed RA and two experienced radiologists who confirmed ILD based on lung HRCT. Of the 523 RA patients who completed lung HRCT, 248 had RA-ILD. We excluded 47 patients, 38 with lack of baseline imaging data and follow-up PFTs, three with complications of other connective tissue diseases, and six with other causes of ILD. Patients were followed up for at least 1 year in this study. A total of 201 RA-ILD patients were finally included. Patients who repeated PFTs 1 year later from the baseline, were defined as progressive ILD if there was a relative decrease in forced vital capacity (FVC) of 15% of the predicted value or a decline in FVC of 10% combined with a decline in carbon monoxide diffusion capacity of 15% from the baseline PFTs. Patients who did not meet the criteria for progression were identified as stable ILD. ILD progression was defined as the previous definition of progression of systemic sclerosis-associated ILD.[13] All patients provided signed informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (approval number: PJ-KS-KY-2020-151).

The medical records of patients were obtained from the electronic medical record database. Demographics, clinical information, laboratory data, and treatments were extracted from the database. Patients' medical treatment referred to taking medication regularly for at least 3 months under the guidance of a physician. High titer positivity for rheumatoid factor and anti-CCP antibody was defined as a titer that was three times higher than normal. We assessed joint activity using the disease activity score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR). High disease activity or high DAS28-ESR was defined as a DAS28-ESR greater than 5.1.[14] Follow-up data were collected until September 2021 or death with a median follow up time of 38 months.

2.2 | HRCT scoring system and PFTs

All patients underwent high-resolution computed tomography (HRCT) scans at the initial stage of ILD diagnosis. HRCT examinations were performed using 1.0 mm thick collimations, and the entire two lungs were examined at 1 cm intervals during inspiration in the supine position. All HRCT images were independently reviewed by two experienced chest radiologists who had no knowledge of relevant clinical information. Based on the 2013

ATS/ERS classification of idiopathic interstitial pneumonia and the 2011 ATS/ERJ/JRS/ALAT consensus criteria for IPF, HRCT patterns were classified as follows (a): UIP; (b) possible UIP; (c) non-specific interstitial pneumonia (NSIP); (d) organizing pneumonia; (e) acute interstitial pneumonia; and (f) indeterminate.[15,16] Honeycombing (HC), ground-glass opacity (GGO), reticulation, interlobular septal thickening, and traction bronchiectasis on HRCT were defined according to Fleischner's recommendations.[17] Disagreement between the two radiologists after the evaluation was resolved through discussion. The extent of lung abnormalities was scored semi-quantitatively based on previous literature experience.[18] Both lungs were respectively divided into three zones, the whole six zones were chosen as follows (a) the upper zones at or superior to the left and right aortic arch; (b) the middle zones between the aortic arch and pulmonary veins; and (c) the lower zones at or below the pulmonary veins. The extent of HC, GGO, and reticulation was scored semi-quantitatively on a scale of 0 to 4 points as follows: 0 = absent; 1 = minor peripheral scattered changes; 2 = uniform peripheral or minor central changes; 3 = substantial peripheral changes deep into the lung parenchyma; 4 = very abundant peripheral and central changes. The total score for these three findings was up to 24 points. The extent of interlobular septal thickening and traction bronchiectasis was scored semi-quantitatively on a scale of 0 to 3 as follows: 0 = absent; 1 = single scattered changes; 2 = large single change or several minor changes; 3 = uniform or substantial changes. The total score of the above two findings was up to 18 points. The fibrosis score was defined as the sum of HC and reticulation. For each parenchymal finding, the scores of the six zones were summed.

Pulmonary function tests were acquired at the initial ILD diagnosis and the latest follow up. The follow-up duration was at least 1 year. The PFTs were performed in a sitting position with a patient at rest according to the current published guidelines.[19] PFT data included FVC, forced expiratory volume in 1 second, and carbon monoxide diffusion capacity. Results were expressed as a percentage of predicted values.

2.3 | Statistical analysis

Continuous variables were presented as means ± standard deviation or medians (interquartile range). Categorical variables were expressed as frequency (percentages). Student *t* test or Mann-Whitney *U* test was used to compare means or medians. The χ^2 test or Fisher exact test was used to compare proportions between groups. Predictors of ILD progression were analyzed by logistic regression and presented as odds ratios (OR) with their 95% confidence intervals (CI). Agreement between the two radiologists on HRCT pattern and radiologic findings was analyzed using the κ statistic test. A κ value of 0.41-0.60 was considered moderate agreement, and a κ value of 0.61-0.80 was considered good agreement. All statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

The demographics, clinical characteristics, laboratory features, PFTs, and baseline treatment of all patients are summarized in Table 1. Of 248 RA-ILD patients, 201 (83.9%) were finally identified during the follow-up period. The mean age at RA onset was 67 ± 10.8 years, and the median duration of ILD was 3.2 years. A total of 105 (52.2%) developed ILD progression. At the baseline visit, the progressive ILD group had more males, more past or present smokers, and higher DAS28-ESR scores and Health Assessment Questionnaire-Disability Index HAQ-DI scores compared with the stable ILD group (all $P < 0.005$). There were no differences in laboratory features, respiratory symptoms, or PFTs between patients with progressive ILD and those with stable ILD. Glucocorticoids were the most frequent therapeutic agent (68.7%). In all, 189 (94%) patients received conventional synthetic disease-modifying antirheumatic drugs. 24 (11.9%) patients received biologic agents. Of all drugs, only cyclophosphamide was used significantly more frequently in the ILD stable group ($P < 0.001$).

3.2 | The patterns and lung abnormalities on HRCT

Table 2 shows the HRCT pattern and the frequency of abnormal HRCT findings in patients with RA-ILD. Inter-observer agreement between radiologists for definite UIP, possible UIP, and NSIP patterns was moderate ($\kappa = 0.54$). 66 of 201 patients (32.8%) showed definite UIP on HRCT evaluation, followed by indeterminate (n = 46, 22.9%), NSIP (n = 45, 22.4%), and possible UIP (n = 38, 18.9%). Four patients (2.0%) were diagnosed with RA-organizing pneumonia. One patient (0.5%) with a previous normal HRCT and rapidly progressive dyspnea and bilateral GGO changes on HRCT was diagnosed with RA-acute interstitial pneumonia. Definite UIP (n = 50, 47.6%) and NSIP (n = 27, 28.1%) were the most common patterns in the progressive group and the most common pattern in the stable groups. Patients with progressive ILD had a significantly higher rate of definite UIP than the stable ILD patients (47.6% vs 16.7%, $P < 0.001$). Among the abnormal findings on HRCT, interlobular septal thickening (n = 170, 84.6%) was the most common among all patients. Moreover, HC was more found often in patients with progressive ILD (80.0% vs 31.3%, $P < 0.001$), whereas GGO was more common in patients with stable ILD (66.7% vs 51.4%, $P = 0.028$). There was no significant difference in the frequency of reticulation, interlobular septal thickening, and traction bronchiectasis between the two groups. In addition, the extent of lung abnormalities on initial HRCT is shown in Table 3. HC, reticulation, fibrosis score, and interlobular septal thickening were significantly more abundant in patients with progressive RA-ILD ($P < 0.001$, $P = 0.025$, $P < 0.001$, and $P = 0.015$, respectively), while GGO ($P = 0.015$) was more extensive in patients with stable ILD. The extent of traction bronchiectasis was not significantly different between the two groups.

TABLE 1 Characteristics of patients with progressive RA-ILD and stable RA-ILD

Characteristics	Total	Progressive ILD	Stable ILD	*P* value
Number	201	105 (52.2%)	96 (47.8%)	–
Demographics				
Age at RA onset	67 ± 10.8	68.94 ± 10.8	65.85 ± 10.7	0.061
Male	83 (41.3%)	51 (48.6%)	32 (33.3%)	0.028
Past or present smokers	55 (27.4%)	36 (34.3%)	19 (19.8%)	0.021
RA duration at ILD diagnosis, y	8 (4-16)	8 (5-15)	8.5 (4-18.5)	0.488
ILD duration, y	3.2 (2.5-4)	3.4 (2.6-4)	3 (2.3-4)	0.106
Clinical features				
HAQ-DI	0.75 (0.50-1.00)	0.75 (0.56-1.00)	0.63 (0.50-0.88)	0.003
DAS28-ESR	0.75 ± 0.5	5.3 ± 0.6	4.9 ± 0.8	<0.001
Respiratory symptoms				
None	112 (55.7%)	53 (50.5%)	59 (61.5%)	0.168
Shortness of breath	70 (34.8%)	42 (40%)	28 (29.2%)	
Dry cough	19 (9.5%)	10 (9.5%)	9 (9.4%)	
Laboratory features				
RF high titer positive	172 (85.6%)	79 (82.3%)	93 (88.6%)	0.206
Anti-CCP antibody high titer positive	185 (92%)	87 (90.6%)	98 (93.3%)	0.479
ESR, mm/h	34.9 ± 17.2	37 ± 17.6	32.6 ± 16.7	0.066
CRP, mg/L	7.8 (3.3-19.5)	8.9 (3.8-20.1)	6.2 (3.2-18.1)	0.064
Baseline pulmonary function tests				
FVC (% predicted)	88.8 ± 10.7	90.1 ± 12.5	87.7 ± 8.7	0.061
FEV1 (% predicted)	87.9 ± 11.9	89.3 ± 12.2	86.6 ± 11.7	0.055
DLCO (% predicted)	74.3 ± 9.7	73.4 ± 8.7	75.3 ± 10.8	0.055
Baseline treatment				
Glucocorticoids	138 (68.7%)	74 (70.5%)	64 (66.7%)	0.563
Cyclophosphamide	56 (28.9%)	16 (15.2%)	40 (41.7%)	<0.001
Leflunomide	88 (43.8%)	48 (45.7%)	40 (41.7%)	0.178
Methotrexate	12 (6%)	4 (3.8%)	8 (8.3%)	0.566
Iguratimod	16 (8%)	10 (9.5%)	6 (6.3%)	0.394
Azathioprine	3 (1.5%)	2 (1.9%)	1 (1%)	0.616
Hydroxychloroquine	5 (2.5%)	3 (2.9%)	2 (2.1%)	0.727
Biologic agents	24 (11.9%)	15 (14.3%)	9 (9.4%)	0.416

Note: Data are expressed as n (%), mean ± standard deviation, or median (interquartile range).
Abbreviations: CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score of 28 joints; DLCO, diffusion capacity of the lung for carbon monoxide; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire-Disability Index; ILD, interstitial lung disease; RA, rheumatoid arthritis; RF, rheumatoid factor.

3.3 | Multivariate logistic regression analysis of predictors of ILD progression

We chose significant factors in univariate analysis for further logistic regression to identify independent predictors of ILD progression, and the results are listed in Table 4. The multivariate logistic regression revealed that the baseline predictors of ILD progression were high DAS28-ESR (OR 1.883, 95% CI 1.065-3.329, $P = 0.029$), definite UIP (OR 3.625, 95% CI 1.134-11.589, $P = 0.030$), fibrosis score (OR 1.791; 95% CI 1.029-3.115;

TABLE 2 Comparison of ILD pattern and abnormal radiologic findings on HRCT among patients with progressive and stable RA-ILD

	Total	Progressive ILD	Stable ILD	*P* value
Number	201	105	96	–
Definite UIP	66 (32.8%)	50 (47.6%)	16 (16.7%)	<0.001
Possible UIP	38 (18.9%)	15 (14.3%)	23 (24.0%)	0.080
NSIP	45 (22.4%)	18 (17.1%)	27 (28.1%)	0.062
OP	4 (2.0%)	2 (1.9%)	2 (2.1%)	0.928
AIP	1 (0.5%)	0 (0)	1 (1.0%)	0.294
Indeterminate	46 (22.9%)	20 (19.0%)	26 (27.1%)	0.176
HC	114 (56.7%)	84 (80.0%)	30 (31.3%)	<0.001
Reticulation	147 (73.1%)	74 (70.5%)	73 (76%)	0.374
GGO	118 (58.7%)	54 (51.4%)	64 (66.7%)	0.028
Interlobular septal thickening	170 (84.6%)	91 (86.7%)	79 (82.3%)	0.391
Traction bronchiectasis	41 (20.4%)	22 (21.0%)	19 (19.8%)	0.838

Note: Data are expressed as n (%).

Abbreviations: AIP, acute interstitial pneumonia; GGO, ground-glass opacity; HC, honeycombing; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

TABLE 3 Comparison of scores of abnormal radiologic findings between progressive and stable RA-ILD patients

	Progressive ILD	Stable ILD	*P* value
Number	105	96	–
HC	4 (1-8)	0 (0-2)	<0.001
Reticulation	4 (0-10)	2 (1-4.75)	0.025
Fibrosis score	10 (7-14)	4 (2-6)	<0.001
GGO	1 (0-3.5)	2 (0-4.75)	0.015
Interlobular septal thickening	7 (3.5-12)	5 (1-8)	0.015
Traction bronchiectasis	0 (0-0)	0 (0-0)	–

Note: Data are expressed as median (interquartile range). The scores reflect the extent of different findings and are calculated by a semi-quantitative method summing the grade of the abnormal findings in the six evaluated zones.

Abbreviations: GGO, ground-glass opacity; HC, honeycombing; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; RA, rheumatoid arthritis.

$P = 0.039$), and less use of cyclophosphamide (OR 0.245, 95% CI 0.095-0.632, $P = 0.004$).

3.4 | The outcome of patients

Twenty-five of 201 (12.4%) patients died during the follow-up period. Of the patients who died, 12 had lung infections, four had acute exacerbations of ILD, four had malignancies, three had myocardial infarction, and two had unknown cause of death. Lung infections were the most common cause of death in patients with progressive ILD (62.5%). Compared with progressive ILD, malignancies had a higher incidence (33.3% vs 6.25%) and were the leading cause of death in patients with stable ILD. Of all deaths, 16 (64%) had ILD progression and 14 (56%) had a definite UIP pattern.

4 | DISCUSSION

The current retrospective study of 201 patients with RA-ILD suggested that high disease activity, definite UIP, fibrosis score, and less use of cyclophosphamide were predictors of ILD progression. We believe that this is the largest retrospective cohort study that combines the clinical features, different patterns, and abnormal findings on HRCT to analyze the predictors of ILD progression in RA patients.

Interstitial lung disease is frequently reported and related to poor prognosis in patients with RA.[4] In the present study, 52.2% of cases showed progression of ILD at a mean follow-up of 38 months, a result similar to previous studies.[10] Our findings revealed that male gender and tobacco exposure were related to progression of ILD, which is consistent with the previous studies.[5] Smoking may contribute to the production of anti-CCP antibodies and is believed to

TABLE 4 Multivariate logistic regression analysis for predictors of ILD progression in patients with RA-ILD

	OR (95% CI)	*P* value
Male	3.101 (0.970-9.912)	0.056
Past or present smokers	0.830 (0.223-3.095)	0.781
HAQ-DI	1.355 (0.627-2.926)	0.440
High DAS28-ESR	1.883 (1.065-3.329)	0.029
Definite UIP	3.625 (1.134-11.589)	0.030
HC	0.826 (0.482-1.413)	0.485
Reticulation	0.823 (0.480-1.412)	0.480
Fibrosis score	1.791 (1.029-3.115)	0.039
GGO	0.900 (0.787-1.028)	0.122
Interlobular septal thickening	0.971 (0.886-1.065)	0.534
Cyclophosphamide	0.245 (0.095-0.632)	0.004

Abbreviations: CI, confidence interval; DAS28-ESR, Disease Activity Score of 28 joints with erythrocyte sedimentation rate; GGO, ground-glass opacity; HAQ-DI, Health Assessment Questionnaire-Disability Index; HC, honeycombing; ILD, interstitial lung disease; OR, odds ratio; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

play a major role in the pathogenesis of RA-ILD. A recent systematic review hypothesized that the presence and higher titers of anti-CCP antibodies were significantly associated with an increased risk of RA-ILD. However, the quality of the evidence was rated as low or very low.[20] In the present study, comparing the progressive ILD group with the stable ILD group, there was no significant difference in the high titers of anti-CCP antibodies.

Several early studies investigated articular RA involvement and increased risk of RA-ILD.[21] Moreover, Sparks et al showed dynamically that for every unit increase in DAS28, the risk of RA-ILD increased by 35%.[3] Dixon et al reported that DAS28 at the time of RA-ILD diagnosis was a predictor of mortality after adjusting for potential confounding factors (including age, gender, calendar year, disease duration, HAQ score, steroid use, and methotrexate use) (hazard ratio 1.43, 95% CI 1.11-1.85).[22] Interestingly, we found that high disease activity at the onset of ILD was an independent risk factor for ILD progression. Articular joint involvement in RA reflects a continuous level of systemic inflammation.[4] Combined with our results, this suggested that systemic inflammation may contribute to the development and progression of RA-ILD.

HRCT patterns and radiologic findings play important roles in the prognosis of ILD.[23] HRCT is highly predictive of histopathologic UIP pattern with high specificity, and therefore this imaging technique may be a more practical and non-invasive method to assess the prognosis of RA-ILD compared with lung biopsy.[24] RA patients had the highest incidence of UIP pattern in both pathology and radiology.[25] Our results were in line with those of previous studies revealing that definite UIP pattern was the most frequent in RA patients. Many studies have identified that patients with a UIP pattern have worse survival than patients without UIP.[26,27] A meta-analysis enrolled 10 retrospective cohort studies showing that UIP pattern was associated with a high mortality risk rather than pulmonary physiology.[28] However, Solomon et al and Zheng et al revealed that pulmonary physiology, but not HRCT pattern, independently predicted progression and mortality.[29,30] The present study showed that definite UIP was an independent predictor of ILD progression, but there was no difference in baseline pulmonary function between the two groups. The reason for this conclusion may be that our patients underwent HRCT before an obvious decline in pulmonary function. In addition, several reports have suggested that the extent and severity of different imaging abnormalities were also associated with disease progression and prognosis in patients with RA-ILD.[31] Therefore, both the pattern and the extent of different radiologic abnormalities should be considered when assessing the prognosis of RA-ILD. We used a semi-quantitative scoring method to evaluate the extent of abnormal findings. This kind of scoring method has been confirmed to have a good correlation with computer-aided quantification.[32] In the present study, interlobular septal thickening was the most frequent finding in RA-ILD patients, and it is an important radiologic manifestation of ILD, which may predict fibrosis. The typical characteristics of UIP were reticular changes and HC in the subpleural sections of the lower lobes on HRCT, with fibrosis on histopathology.[33] The possible UIP on HRCT was characterized by the reticular pattern with traction bronchiectasis.[34] The only difference between definite UIP and possible UIP on HRCT is the presence of HC. In the univariate analysis, HC was more common in the progressive ILD group. Similarly, HC was more extensive than in stable ILD. The histologic features of NSIP were characterized by varying degrees of chronic inflammation or fibrosis, while the most frequent finding on HRCT was GGO with reticulation and little or no HC.[35] However, a subset of patients with NSIP showed progression to end-stage fibrosis. With a mixture of UIP and NSIP in pathologic findings, distinguishing UIP from NSIP based on HRCT is often challenging in clinical practice.[36] The fibrosis score accurately represents the extent of fibrosis and is easily calculated without distinguishing each parenchymal pattern, and it has been reported as an independent predictor of poor survival in systemic sclerosis-associated ILD and RA-ILD.[37] After adjusting for confounding factors, we found that definite UIP and fibrosis score, but not HC, reticulation, and NSIP, were independent risk factors for ILD progression.

Treatment options for RA-ILD are complicated by the potential pulmonary toxicity of many disease-modifying antirheumatic drugs and uncertain efficacy in pulmonary disease. To date, there are no treatment recommendations for RA-ILD.[38] In the present study, considering RA activity and ILD, glucocorticoids (68.7%) were the most widely used drugs. The inflammatory subtypes of RA-ILD, particularly NSIP and organizing pneumonia, may be responsive to steroids.[25] However, current data do not suggest that glucocorticoids can help improve the progression of ILD. There is some controversy regarding the treatment of RA-ILD with biologic agents, with some studies showing improvement and others showing development or progression of ILD.[39,40] A recent study showed that non-anti-tumor necrosis factor biologic agents were associated with slower progression of ILD secondary to RA.[41] In the present study, 11.9% of patients had received biologic agents, and we found no correlation

between the use of biologic agents and the progression of ILD, as were the cases with pirfenidone (10.4%). Cyclophosphamide has been used to treat many types of ILD, especially rapidly progressing ILD, and one study showed stabilization of lung function in fibrotic ILD.[42] The previous study demonstrated the improvement of dyspnea and quality of life, as well as the protection of decreased FVC, in individuals with worse fibrosis score after the use of cyclophosphamide compared with placebo.[43] Our multivariate analysis also showed that cyclophosphamide was an independent protective factor against ILD progression.

A total of 25 patients died during the follow-up period. Lung infection was the main cause of death in our cohort. Patients with RA-ILD were at increased risk of serious lung infection because of immunosuppressive therapy and abnormalities of the immune system.[44] In a large cohort of RA-ILD patients with a median follow up of 3.1 years, 29.8% developed serious infections requiring antimicrobial therapy and hospitalization. At the last follow up, 21% of deaths were directly attributable to infection.[45] Definite UIP was the main pattern in our patients who died. This finding was consistent with a previous study that demonstrated that patients with definite UIP pattern had worse survival than patients with other patterns.[26]

There are several limitations of the present study. First, it was a single-center retrospective study. Due to the nature of the study, there was selection bias when enrolling patients and the follow-up time varied between cases. Further multicenter prospective studies should be performed to confirm our conclusion. In addition, no further survival analysis was completed because there were too few events. Finally, a few patients in both groups used biologic agents, so it is necessary to further confirm their relationship with the ILD progression in RA patients in a large sample. However, the present study provides predictors of ILD progression, which could help clinicians to identify patients prone to progression earlier and improve the prognosis of RA-ILD.

In conclusion, the present study reveals that high DAS28-ESR, definite UIP on HRCT, and radiologic fibrosis score at the onset of ILD are independent risk factors for ILD progression in RA patients. Cyclophosphamide helps slow the ILD progression. The most frequent cause of death is lung infection and definite UIP is the main HRCT pattern in the patients who died.

AUTHOR CONTRIBUTIONS

Lei Liu: Patients recruitment, data collection and original draft preparation. Chunxiao Fang: Supervision, analysis and interpretation of data. Bo Sun and Ruyi Bao: Software and investigation & share in writing. Hongfeng Zhang: Design the work, writing - reviewing & editing.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Screening of behavioral disorders in children with hemophilia

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Abstract

Aim: To screen types of behavioral problems among children with hemophilia and their relation to the disease parameters.

Methods: Fifty boys, 6-18 years old, with moderate and sever hemophilia were subjected to: history taking, joint evaluation using the Hemophilia Joint Health Score, and behavioral assessment using the Child Behavioral Check List.

Results: Patients experienced different patterns of behavior disorder. Patients' age significantly correlated with anxious/depressed behavior, somatic complaints, social problems, aggressive behavior, internalizing behavior, and total behavior problems. Hemophilia severity significantly correlated with social problems, thought problems, aggressive behavior, internalizing behavior, externalizing behavior, and total behavior disorders. Affected joint number significantly correlated with withdrawn/depressed behavior, social problems, thought problems, aggressive behavior, internalizing behavior, and total behavior disorders. A high Hemophilia Joint Health Score of the target joints was significantly correlated with social problems, rule-breaking behavior, aggressive behavior, externalizing behavior, and total behavior disorders. Hemophilic arthropathy duration significantly correlated with somatic complaints, social problems, thought problems, attention problems, aggressive behavior, internalizing behavior, externalizing behavior, and total behavior problems.

Conclusion: Children with hemophilia had behavioral disorders. The most affected scale was aggressive behavior. The least affected scale was attention problems. Behavioral disorders in children with hemophilia are influenced by the age of the patient, the severity of the disease, the number of joints affected, the duration of hemophilic arthropathy, and the score of joint affected by Hemophilia Joint Health Score.

KEYWORDS
behavioral assessment, child behavioral check list, hemophilia joint health score, hemophilic arthropathy

1 | INTRODUCTION

Hemophilia is one of the commonest severe bleeding disorders in children and adolescents. The annual global survey of the World Federation of Hemophilia 2018 reported a worldwide incidence of hemophilia of 210454 distributed as 173711 hemophilia A and 34289 hemophilia B. They reported an incidence of hemophilia in Egypt of 6028 distributed as 4885 hemophilia A and 1143 hemophilia B.[1]

The severity of bleeding symptoms is related to the coagulant activity of the deficient factor. Therefore, hemophilia is divided into three clinical phenotypes (mild, moderate, and severe).[2]

In patients with hemophilia, 90% of all bleeding episodes occur into the joints. This affects most often the knees (>50% of all events), then the elbows, the ankles, the shoulder, then the wrists.[3]

Hemophilic arthropathy is a disabling immune-mediated arthritis caused by recurrent and chronic exposure of synovium and articular cartilage to the metabolized blood products.[4]

Children with hemophilia have a difficult life as they have to deal with chronic arthropathy, fatigue, and limb movement limitations. Some of the most serious concerns of both parents and healthcare workers are the emotional and behavioral problems in children with hemophilia, which become more complicated with increasing age and can affect their quality of life.[5]

Research has documented higher rates of school absenteeism in children with hemophilia than in other children.[6]

The aim of the present work was to screen types of behavioral problems among children with hemophilia and their relation to the disease parameters.

2 | PATIENTS AND METHODS

The study was conducted on 50 boys with moderate and severe hemophilia A or B attending the hematology outpatient clinic at Alexandria University Children's Hospital. Their age ranged from 6 to 18 years.

Patients with chronic illness, such as other hematological disorders rather than hemophilia, chronic renal diseases, chronic hepatic diseases, insulin-dependent diabetes mellitus, endocrine disorders, bronchial asthma, cystic fibrosis, and childhood malignancies were excluded.

The purpose of the study was explained to all participants' parents. Informed consent was taken from the parents of all children who were included in the study.

The study was approved by the Ethics committee of the Faculty of Medicine, University of Alexandria.

All patients included in the study underwent history-taking, joint evaluation, and behavioral assessment.

2.1 | History taking

The history taking included demographic data (age, gender, residence, and school grade), full history of hemophilia (age of diagnosis, type of hemophilia, severity, frequency of bleeding, site of bleeding, and response to conservative treatment and factor replacement therapy).

2.2 | Joint evaluation using Hemophilia Joint Health Score

The Hemophilia Joint Health Score (HJHS) version 2.1 is an eight-item tool that was developed to assess joint impairment of the six key index joints (both elbows, knees, and ankles) in hemophilia.[7,8] The eight items include swelling, the duration of swelling, muscle atrophy, flexion and extension loss, crepitus on motion, joint pain on motion, and strength.

The HJHS version 2.1 also incorporates: a global gait analysis as a ninth item. Maximum disease score for each joint is 20 with a possible total score of 120, plus a maximum of four for global gait. The global gait score assesses walking, hopping, running, and stair skills with scores of 0-4. In HJHS version 2.1 a higher score means worse joint health.

Joint evaluation was carried on the most affected and/ or the target joint, which was defined as "a joint in which recurrent bleeding has occurred four or more times in the past 6 months".[9]

2.3 | Behavioral assessment: using Child Behavioral Check List parents' form

The Child behavioral Check List (CBCL) (Parents' form) is a standardized 113-item informant-report questionnaire that parents fill out to describe the behavioral competency and behavioral problems in their children (ages 6-18 years).[10,11]

It is scored on a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often). The following syndrome scales are assessed: anxious/depressed, withdrawn/depressed, somatic complaints, thought problems, social problems, attention problems, aggressive behavior, rule-breaking behavior, and other problems. These scales are grouped into two higher scales—internalizing and externalizing.

Patients were divided according to age into two groups: group I (6-11 years) and group II (12-18 years) according to the boys-syndrome scales that interpret the check list.

2.4 | Statistical analysis of the data

Data were analyzed using IBM SPSS software package version 20.0 (IBM, Armonk, NY, USA). Qualitative data were described using numbers and percentages.[12] The Kolmogorov-Smirnov test was used to verify normality of distribution. Quantitative data were described using range (minimum and maximum), mean, median and standard deviation. Kruskal-Wallis test and Mann-Whitney test were used. The significance of the obtained results was judged at 5% level.

3 | RESULTS

3.1 | Demographic data

According to the CBCL/6-18 Profile for boys-syndrome scales; patients were divided into group I (included 30 patients [60%] aged between 6 and 11 years) and group II (included 20 patients [40%] aged 12-18 years). Among the studied patients, 74% had hemophilia A and 26% had hemophilia B.

3.2 | Clinical evaluation

Of the studied patients, 29 (58%) had moderate hemophilia and 21 (42%) had severe hemophilia. Polyarthropathy was presented in 30 (60%) patients and monoarthropathy was presented in 15 (30%) patients; five (10%) patients did not have affected joints. The duration of hemophilic arthropathies ranged between 0.0 and 15 years with mean ± standard deviation of 6.66 ± 3.84 years.

3.3 | Joint evaluation

Score of the target joint according to HJHS: ranged between 0.0-17.0 with mean ± standard deviation score of 9.02 ± 3.99.

3.4 | Child behavior check list parents' form

Distributions of the studied patients according to the CBCL score of different scales are summarized in Table 1.

Each scale was divided into three categories: disease, border line, and not ill (Table 2).

The most affected scale was aggressive behavior with 27 (54%) patients with disease, 1 (2%) patient borderline, and 22 (44%) patients not ill.

The least affected scale was attention problems; with 8 (16%) patients with disease, 2 (4%) patients borderline, and 40 (80%) patients not ill.

There was a positive statistically significant correlation between the age and the anxious/depressed behavior, somatic complaints, social problems, aggressive behavior, internalizing behavior, and total score ($P = .007$, $P = .002$, $P = .001$, $P = .037$, $P = .004$, and $P = .004$, respectively). Also a positive statistically significant correlation was found between the severity of hemophilia and social problems, thought problems, aggressive behavior, internalizing behavior, externalizing behavior, and total T score ($P = .025$, $P = .019$, $P = .003$, $P = .041$, $P = .001$, and $P = .001$, respectively; Table 3).

The number of joints affected had a positive statistically significant correlation with withdrawn/depressed behavior, thought problems, social problems, aggressive behavior, internalizing behavior, and the total T score ($P = .008$, $P = .008$, $P = .028$, $P = .020$, $P = .005$, and $P = .001$, respectively; Table 4).

There was a significant correlation between the high score of HJHS of the target joints and social problems, aggressive behavior, rule-breaking behavior, and externalizing behavior scores. Furthermore, long duration of hemophilic arthropathy had a statistically significant correlation with somatic complaints, social problems, thought problems, attention problems, aggressive behavior, Internalizing behavior, Externalizing behavior, and Total behavior scores (Table 5).

4 | DISCUSSION

Children with hemophilia are usually under chronic stress and consequently suffer from more difficulties with emotional well-being, that include slower self-perception and depressive symptomatology.[13] Parents of these children provide overprotective behavior towards them, which contributes to the development of chronic depression and anxiety in their children.[14]

Increased severity of the disease leads to frequent bleeding attacks, so more protective attitudes from the parents, which leads to less social and physical activity of patients compared with their peers, leading to social behavior problems, and thought problems that may be due to their feelings of inferiority compared with others. They also may feel anger towards others, leading to aggressive behavior towards them. We assumed that all of these changes lead to internalizing, externalizing, and total behavior problems.

To the best of our knowledge, the present study is one of the few to investigate behavioral disorders in children and adolescents with hemophilia.

TABLE 1 Distribution of the studied patients according to *T* score of different scales (n = 50)

Scale	*T* scores	Min.-Max.	Mean ± SD	Median (IQR)
Scale 1	Anxious/depressed behavior	50.0-83.0	67.52 ± 6.65	67.0 (63.0-72.0)
Scale 2	Withdrawn/depressed behavior	50.0-93.0	68.52 ± 8.37	68.0 (63.0-70.25)
Scale 3	Somatic complaints	50.0-85.0	66.68 ± 5.61	65.50 (64.0-70.0)
Scale 4	Social problems	50.0-87.0	63.76 ± 8.06	62.50 (58.0-69.0)
Scale 5	Thought problems	51.0-78.0	66.50 ± 5.69	66.50 (63.0-71.0)
Scale 6	Attention problems	52.0-75.0	63.14 ± 6.17	64.0 (58.50-69.0)
Scale 7	Rule-breaking behavior	52.0-80.0	67.36 ± 6.02	67.50 (63.0-72.0)
Scale 8	Aggressive behavior	52.0-96.0	67.62 ± 9.99	65.0 (61.0-72.25)
	Internalizing behavior (Scale 1 + scale 2 + scale 3)	52.0-85.0	69.86 ± 4.94	70.0 (67.75-73.0)
	Externalizing behavior (Scale 7 + scale 8)	55.0-80.0	68.10 ± 6.37	68.0 (63.0-73.0)
	Total	56.0-81.0	69.32 ± 5.36	70.0 (65.75-73.0)

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

TABLE 2 Distribution of the studied patients according to the CBCL score of different scales into clinical types (n = 50)

CBCL score	Disease		Border line		Not ill	
	n	%	n	%	n	%
Anxious/depressed behavior	21	42.0	14	28.0	15	30.0
Withdrawn/depressed behavior	19	38.0	19	38.0	12	24.0
Somatic complaints	15	30.0	10	20.0	25	50.0
Social problems	9	18.0	14	28.0	27	54.0
Thought problems	20	40.0	10	20.0	20	40.0
Attention problems	8	16.0	2	4.0	40	80.0
Rule-breaking behavior	22	44.0	13	26.0	15	30.0
Aggressive behavior	27	54.0	1	2.0	22	44.0
Internalizing behavior (Scale 1 + scale 2 + scale 3)	46	92.0	4	8.0	0	0.0
Externalizing behavior (Scale 7 + scale 8)	36	72.0	6	12.0	8	16.0
Total (all scales)	43	86.0	4	8.0	3	6.0

Abbreviation: CBCL, Child Behavioral Check List.

The present study gives evidence of the negative effect of hemophilia on emotions and behavior in patients with hemophilia. We highlighted the significance of studying the emotional and behavioral problems of this group, which may impact their quality of life.

In the present study, patients with polyarthropathy had more behavior problems than patients with monoarthropathy or those with no affected joints.

Patients with polyarthropathy suffered from depression, either withdrawn or anxious, that may be due to their multiple disabilities. Social problems can also be found as well as thought problems. This may be a result of them feeling that they are helpless and hopeless. Occurrence of aggressive problems could be explained as a defense mechanism to displace their deficit. These problems generally lead to internalization and total problems in their behavior.

It was found that high joint scores in HJHS, which result from joint damage, were significantly related to externalizing behavior problems as rule-breaking behavior—such as breaking the rules, cheating, lying, making mistakes without feeling guilt, and setting fires. Also patients had social problems that may be explained by lack of social activities compared with their peers. Aggressive behavior was also noted; it was suggested that this was a displaced behavior to compensate for disability. We suggested that all these changes can lead to total behavioral problems.

Internalizing, externalizing, and total scores were significantly related to duration of illness in the current study. This can be explained by the longer the duration of hemophilic arthropathy the more psychological burden due to the nature of the illness, its complications, and its treatment. These behavior problems are in the form of somatic complaints, which may be due to body aches and nightmares that lead to headache and feeling overtired. The longer the duration, the more deformed the joint, which leads to social problems. Thought and attention problems were also found. The long duration of hemophilic arthropathy also led to aggressive behavior against others.

Generally, the results of the present study showed that 43 (86%) children with hemophilia had clinically abnormal high CBCL total scores, which indicate the presence of behavioral problems in those children. Abnormal CBCL Internalization problem scores were present in 46 (92%) children, indicating symptoms of anxiety/depression, social withdrawal, and somatic complaints. Abnormal CBCL Externalization scores were present in 36 (72%) children with hemophilia, indicating rule-breaking behavior and aggressive behavior, which are clinically significant symptoms.

This matches the study by Firoozi[15] who compared children with hemophilia (n = 65) with healthy children (n = 65) in terms of cognitive, emotional, and behavioral problems. He found a significant difference between the two studied groups in average scores of internalization problems, externalization problems, and total behavior.

In contrast, Trzepacz et al[13] in their study showed no significant correlation between hemophilia and externalization problems compared with healthy children.

In the current study, 54% of patients showed aggressive behavior, which is the most affected behavior, this may be explained by displacement of their feelings, disability, and anger towards their illness. Regarding rule-breaking behavior, 44% of the patients were in the disease group and 26% were borderline; this is most probably multifactorial and may be due to family instability, physical victimization, and social problems. Forty per cent of the patients had thought problems, which may be due to their core belief that they are helpless.

These results were in agreement with those of Firoozi[15]and Trzepacz et al[13] who found a significant difference between the hemophilic and control groups in aggressive behavior, rule-breaking behavior, and thought problems.

In the present study, there was no significant relation between hemophilia and somatic complaints. Thirty per cent of patients had somatic complaints that may be suggested by body aches, which lead to difficulty sleeping, headaches and referred pain. Sixteen

TABLE 3 The correlation between *T* score of different behavior problems with patients' age and the severity of hemophilia (n = 50)

	Age (years)				Severity			
***T* score**	**6-11 (n = 30)**	**12-18 (n = 20)**	***U***	***P***	**Moderate (n = 29)**	**Severe (n = 21)**	***U***	***P***
Anxious/depressed								
Min.-max.	50.0-74.0	62.0-83.0			50.0-74.0	59.0-83.0		
Mean ± SD	65.27 ± 6.10	70.90 ± 6.09	163.5[a]	.007[a]	65.79 ± 6.23	69.90 ± 6.60	208.0	.056
Median	66.0	71.0			66.0	70.0		
Withdrawn/depressed								
Min.-max.	50.0-82.0	60.0-93.0			50.0-82.0	53.0-93.0		
Mean ± SD	66.80 ± 7.43	71.10 ± 9.20	251.000	.327	66.93 ± 7.16	70.71 ± 9.55	251.0	.288
Median	68.0	68.0			68.0	68.0		
Somatic complaints								
Min.-max.	50.0-73.0	62.0-85.0			50.0-75.0	61.0-85.0		
Mean ± SD	64.63 ± 4.17	69.75 ± 6.18	148.50[a]	.002[a]	65.48 ± 4.79	68.33 ± 6.34	239.5	.192
Median	64.0	69.0			64.0	67.0		
Social problems								
Min.-max.	50.0-74.0	53.0-87.0			50.0-74.0	53.0-87.0		
Mean ± SD	60.87 ± 6.48	68.10 ± 8.40	139.0[a]	.001[a]	61.28 ± 5.74	67.19 ± 9.58	191.0[a]	.025[a]
Median	60.0	66.5			61.0	66.0		
Thought problems								
Min.-max.	52.0-75.0	51.0-78.0			51.0-75.0	61.0-78.0		
Mean ± SD.	65.63 ± 5.28	67.80 ± 6.17	219.000	.107	64.90 ± 5.97	68.71 ± 4.54	185.5[a]	.019[a]
Median	66.0	68.50			64.0	70.0		
Attention problems								
Min.-max.	52.0-75.0	55.0-71.0			52.0-75.0	52.0-71.0		
Mean ± SD	62.53 ± 6.84	64.05 ± 5.04	262.500	.456	62.45 ± 6.36	64.10 ± 5.92	252.5	.305
Median	64.0	64.0			64.0	66.0		
Rule-breaking behavior								
Min.-max.	52.0-80.0	57.0-76.0			52.0-80.0	60.0-76.0		
Mean ± SD	67.13 ± 6.72	67.70 ± 4.93	291.000	.858	66.21 ± 6.62	68.95 ± 4.77	230.0	.142
Median	67.0	68.0			67.0	71.0		
Aggressive behavior								
Min.-max.	52.0-83.0	55.0-96.0			52.0-83.0	52.0-96.0		
Mean ± SD	65.23 ± 8.31	71.20 ± 11.38	195.0[a]	.037[a]	64.03 ± 7.19	72.57 ± 11.30	156.0[a]	.003[a]
Median	64.0	65.50			64.0	70.0		
Internalizing behavior								
Min.-max.	52.0-75.0	68.0-85.0			52.0-75.0	65.0-85.0		
Mean ± SD	68.17 ± 4.84	72.40 ± 3.98	156.0[a]	.004[a]	68.48 ± 4.79	71.76 ± 4.58	201.0[a]	.041[a]
Median	68.50	71.0			70.0	71.0		
Externalizing behavior								
Min.-max.	55.0-80.0	63.0-80.0			55.0-80.0	57.0-80.0		
Mean ± SD	66.70 ± 6.58	70.20 ± 5.57			65.72 ± 5.79	71.38 ± 5.76	139.5[a]	.001[a]
Median	68.0	68.0			67.0	72.0		
Total								
Min.-max.	56.0-75.0	65.0-81.0			56.0-75.0	61.0-81.0		
Mean ± SD	67.40 ± 5.22	72.20 ± 4.23	157.0[a]	.004[a]	67.24 ± 4.84	72.19 ± 4.76	134.5[a]	.001[a]
Median	68.0	70.50			69.0	71.0		

Note: U: Mann-Whitney test.

P: *P* value for comparing between the two categories.

Abbreviation: SD, standard deviation.

T score is a score on the chart to categorize patients into disease, borderline and not ill.

[a]Statistically significant at $P \leq .05$.

TABLE 4 The correlation between different behavior problems and the number of joints affected (n = 50)

	Number of joints affected				
T score	No joints affected (n = 5)	Monoarthropathy (n = 15)	Polyarthropathy (n = 30)	H	*P*
Anxious/depressed					
Min.-max.	50.0-70.0	51.0-74.0	59.0-83.0	7.356[a]	.025[a]
Mean ± SD	60.80 ± 7.66	65.47 ± 6.49	69.67 ± 5.61		
Median	59.0	66.0	69.50		
Sign. between groups	P_1 = .253, P_2 = .017[a], P_3 = .075				
Withdrawn/depressed					
Min.-max.	50.0-70.0	54.0-70.0	53.0-93.0	9.643[a]	.008[a]
Mean ± SD	59.60 ± 7.80	66.0 ± 4.19	71.27 ± 8.76		
Median	62.0	68.0	69.0		
Sign. between groups	P_1 = .173, P_2 = .006[a], P_3 = .047[a]				
Somatic complaints					
Min.-max.	61.0-68.0	50.0-79.0	61.0-85.0	4.147	.126
Mean ± SD	63.20 ± 2.95	66.33 ± 6.32	67.43 ± 5.48		
Median	62.0	67.0	67.0		
Social problems					
Min.-max.	50.0-65.0	53.0-70.0	53.0-87.0	9.609[a]	.008[a]
Mean ± SD	56.80 ± 5.89	60.80 ± 4.51	66.40 ± 8.67		
Median	56.0	60.0	66.50		
Sign. between groups	P_1 = .271, P_2 = .009[a], P_3 = .028[a]				
Thought problems					
Min.-max.	52.0-64.0	51.0-75.0	58.0-78.0	7.182[a]	.028[a]
Mean ± SD	60.0 ± 4.64	66.53 ± 6.48	67.57 ± 4.80		
Median	61.0	66.0	67.0		
Sign. between groups	P_1 = .028[a], P_2 = .007[a], P_3 = .609				
Attention problems					
Min.-max.	52.0-66.0	52.0-71.0	52.0-75.0	3.704	.157
Mean ± SD	58.60 ± 5.03	62.53 ± 6.46	64.20 ± 5.99		
Median	59.0	64.0	64.0		
Rule-breaking behavior					
Min.-max.	60.0-76.0	52.0-74.0	57.0-80.0	0.290	.865
Mean ± SD	66.60 ± 6.84	66.20 ± 7.09	68.07 ± 5.40		
Median	67.0	68.0	67.0		
Aggressive behavior					
Min.-max.	54.0-72.0	52.0-83.0	60.0-96.0	7.830[a]	.020[a]
Mean ± SD	61.20 ± 6.83	63.33 ± 8.79	70.83 ± 9.88		
Median	6.83	64.0	65.50		
Sign. between groups	P_1 = .491, P_2 = .030[a], P_3 = .028[a]				
Internalizing behavior					
Min.-max.	52.0-71.0	60.0-75.0	66.0-85.0	5.730[a]	.005[a]
Mean ± SD	63.20 ± 6.94	68.60 ± 4.26	71.60 ± 3.77		
Median	65.0	68.0	71.0		
Sign. between groups	P_1 = .131, P_2 = .003[a], P_3 = .042[a]				
Externalizing behavior					
Min.-max.	59.0-74.0	55.0-75.0	59.0-80.0	5.730	.057
Mean ± SD	63.60 ± 6.31	65.80 ± 6.65	70.0 ± 5.64		
Median	61.0	68.0	68.50		

TABLE 4 (Continued)

T score	Number of joints affected: No joints affected (n = 5)	Monoarthropathy (n = 15)	Polyarthropathy (n = 30)	H	P
Total					
Min.-max.	56.0-71.0	56.0-74.0	63.0-81.0	13.050[a]	.001[a]
Mean ± SD	62.60 ± 5.77	67.13 ± 4.72	71.53 ± 4.22		
Median	62.0	68.0	71.0		
Sign. between groups	P_1 = .274, P_2 = .003[a], P_3 = .007[a]				

Note: H: H for Kruskal-Wallis test, Pairwise comparison between each of two groups was done using post hoc test (Dunn's for multiple comparisons test).

P: *P* value for comparing between the two categories.

P_1: *P* value for comparing between No joints affected and Monoarthropathy.

P_2: *P* value for comparing between No joints affected and Polyarthropathy.

P_3: *P* value for comparing between Monoarthropathy and Polyarthropathy.

T score is a score on the chart to categorize patients into disease, borderline and not ill.

[a]Statistically significant at $P \leq .05$.

TABLE 5 The correlation between different behavior problems and each joint score (HJHS) and duration of hemophilic arthropathy

T score	HJHS score: r_s	HJHS score: P	Duration of hemophilic arthropathy (years): r_s	Duration of hemophilic arthropathy (years): P
Anxious/depressed	.223	.120	.224	.117
Withdrawn/depressed	.192	.182	.123	.396
Somatic complaints	.049	.736	.374[a]	.007
Social problems	.495[a]	<.001	.437[a]	.002
Thought problems	.234	.102	.294[a]	.038
Attention problems	.219	.126	.311[a]	.028
Rule-breaking behavior	.405[a]	.004	.237	.098
Aggressive behavior	.564[a]	<.001	.481[a]	<.001
Internalizing behavior	.255	.074	.334[a]	.018
Externalizing behavior	.592[a]	<.001	.459[a]	.001
Total	.553[a]	<.001	.522[a]	<.001

Note: r_s: Spearman coefficient.

Abbreviation: HJHS, hemophilia joint health score.

T score is a score on the chart to categorize patients into disease, borderline and not ill.

[a]Statistically significant at $P \leq .05$.

percent of patients have attention problems that may be explained on the basis that children are trying to pay more attention and doing well in school to compensate for their deficit in other fields. Eighteen percent of the patients had social problems that may result from the nature of chronic illness, which increases social sensitivity of the patients. Patients will also be concerned about the judgment of their peers, so they comply with normal social behavior of their community to avoid negative self-image. As a result, they suppress their feelings and accept norms more easily.

The aforementioned results were not in concordance with Firoozi,[15] who found significant differences between the hemophilic and control groups in attention and somatic complaints.

Regarding depression, 42% of the patients were anxious/depressed, and 28% were borderline, whereas 38% of the patients were withdrawn/depressed and 38% were borderline. This is in agreement with the study by Valentino et al,[16] who found that children with hemophilia more commonly showed symptoms of depression compared with healthy children. Also Rambod et al[17] demonstrated that 57.4% and 64.4% of the patients with hemophilia experienced depression and anxiety, respectively.

This work had some limitations. It was carried out on only 50 boys because we were restricted to number of patients attending the hematology outpatient clinic at Alexandria University Children's Hospital; also there is not much literature about behavioral problems

in children with hemophilia to be compared with the current study results. It seems that the psychiatric disorders of children with hemophilia receive less attention than routine hemophilia care, so it is proposed that attention should be shifted more towards psychiatric disorders.

5 | CONCLUSION

The present study gives evidence of the negative effect of hemophilia on emotions and behavior in patients with hemophilia.

Children with hemophilia had behavioral disorders. The most affected scale was aggressive behavior. The least affected scale was attention problems.

Behavioral disorders in children with hemophilia are influenced by the age of the patient, the severity of the disease, the number of joints affected, the duration of hemophilic arthropathy, and the score of joint affected on HJHS.

AUTHOR CONTRIBUTIONS

EEE revised the draft manuscript and contributed to the writing with the other authors. HGA conceived and designed the study, and performed the behavioral assessment of patients. HAH interpreted the results and revised the draft manuscript. MEA collected the data and prepared the tables. HMAG performed the joint evaluation using HJHS, analyzed the data, prepared the tables, and revised the draft manuscript.

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CONFLICT OF INTEREST

It was a non-funded study, so no conflict of interest exists.

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ORIGINAL ARTICLE

Meta-analysis confirmed genetic susceptibility conferred by multiple risk variants from CTLA4 and SERPINA1 in granulomatosis with polyangiitis

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Abstract

Background: Granulomatosis with polyangiitis (GPA) is a rare systemic autoimmune disease. Smaller sample size and complex nature of the disease pathogenesis has made it challenging to perform well-powered genetic investigations. We performed a systematic review based meta-analysis in GPA to investigate the genetic susceptibility conferred by non-human leukocyte antigen (non-HLA) candidate genes.

Methods: A systematic review was performed using web-based literature search and eligible studies were included following inclusion-exclusion criteria. Studies were evaluated for their quality of evidence and study outcome was assessed using the Newcastle-Ottawa Scale and Grades of Research, Assessment, Development and Evaluation tools. Reviewer's agreement was accessed through Cohen's κ value. Meta-analyses were performed using RevMan 5 tool. Meta-odds ratio (meta-OR) and Z test *P* value were evaluated to estimate the genetic susceptibility for each of the variants.

Results: Eighteen studies were found eligible and 7 genetic variants from only 4 genes, namely *CTLA4*, *PRTN3*, *SERPINA1* and *PTPN22* could be studied for meta-analysis. rs231775-G (49-G) (Meta-OR = 1.42 [1.14-1.76]; *P* = .001) of *CTLA4* and rs7151526-A (Meta-OR = 2.70 [1.51-4.85]; *P* = .0008) of *SERPINA1* were confirmed to be predisposing alleles, and rs5742909-C (318-C) (Meta-OR = 0.65 [0.44-0.97]; *P* =.03) of *CTLA4* was found to be protective for GPA. In concordance with the genetic association of rs7151526-A, serological marker for the same variant "Z" allele of *SERPINA1* was found to be predisposing (Meta-OR = 12.60 [5.01-31.68]; *P* < .00001) for GPA.

Conclusion: Genetic variants confirmed in this study play critical roles in T-cell mediated immune function and could be significantly implicated in GPA. Molecular pathology studies are warranted to confirm their role. These markers could be used for efficient patient classification and disease management.

KEYWORDS
genetic association, granulomatosis with polyangiitis, meta-analysis, susceptibility genes, systematic review

1 | INTRODUCTION

Granulomatosis with polyangiitis (GPA) formerly known as Wegener's granulomatosis (WG) is a type of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) and defined as a rare systemic complex disease of small or medium blood vessels with unknown and complex etiology.[1] Genetic association studies have identified 6 susceptibility human leukocyte antigen (HLA) loci (DP, DR, DQ, A, B, C) and 29 susceptibility non-HLA loci/genes in GPA but showed diverse predisposition in various ethnic groups.[2] Heritability of these genetic determinants associated with GPA is still illusive.

Several non-HLA candidate genes were studied to identify the susceptibility genetic variants associated with GPA. Beside HLA alleles, combinatorial presence of non-HLA risk alleles provides basis for clinical heterogeneity among subjects with GPA. Most of the genetic association studies in GPA include genetic variants from *PRTN3*, *SERPINA1*, *CTLA4* and *PTPN22*. *PRTN3* codes for proteinase 3 (PR3);[3,4] and *SERPINA1* coded alpha-1 anti-trypsin (A1AT) which inhibits PR3.[5] It was reported that variant rs62132293 (C > G) of *PRTN3* was associated with increased expression of PR3 in neutrophils.[6] Variant rs751526 in *SERPINA1* was reported as associated with altered levels of A1AT in GPA subjects.[7] Significant associations were found in *PTPN22*, which encodes a protein tyrosine phosphatase, regulating T and B-cell receptor-mediated cell activation[6,8] and *CTLA4*, which is involved in T cell activation.[9]

Recent studies on GPA revealed co-existence of GPA and rheumatoid arthritis (RA) due to the increased frequency of 620W functional variant of *PTPN22*.[10] Currently 4 genome-wide association studies (GWAS) have been reported on AAV where 3/4 studies provided substantial evidence for the association of HLA DP with GPA, and non-HLA susceptibility genes including *SERPINA1*, *PRTN3* and *PTPN22* with AAV.[11] The other 3 GWAS performed by Lyons et al, included 1683 GPA patients and 6858 controls and found association of *SERPINA1*, *PRTN3*, *ARHGAP18*, *MOSPD2* genes with GPA[3]; Xie et al reported *SEMA6A* as significant associated with GPA when compared with 987 GPA patients and 2731 controls,[12] and Merkel et al compared 1556 GPA patients and 4723 controls and identified *SERPINA1* and *PRTN3* as susceptibility genes.[6] One meta-analysis study found significant association for rs3087243 in *CTLA4* (odds ratio [OR] = 0.79 [0.70-0.89]; $P = 9.8 \times 10^{-5}$).[9]

Common genetic variants from *PRTN3* (rs62132295; A564G), *SERPINA1* (rs7151526), *CTLA4* (AT[86], rs3087243; CT[60], rs231775; +49A/G, and rs5742909; -318C/T) and *PTPN22* (rs2476601; R620W) have been studied in European, German, Swedish, Polish, Italian, French and Danish, Austrian, UK, Caucasian, American (USA), Australian and North Indian populations. A difference in distribution ($P = .009$) of the G allele of +49G/A, rs231775 between PR3-ANCA positive AAV subjects and healthy controls was reported.[13] Compared with controls, GPA had a significantly lower frequency of homozygosity for the shortest allele $(AT)_{86}$ (47.0% vs 69.9%; $P = .0005$) in an American population.[14] Although not consistently observed in candidate gene studies, the significant association of −1858 C/T, rs2476601 with GPA/MPA was reported in Caucasians but was not replicated among Indians.[6,15] An association of *PRTN3* promoter polymorphisms rs231775-G and A564G was observed in Germans, which was not replicated among European Americans.[16,17]

These genetic variants from *CTLA4*, *PRTN3*, *SERPINA1* and *PTPN22* have been studied in distinctly different ethnic populations and association heterogeneity was observed. These genetic associations are critical for better characterization of GPA. Being a rare disease, smaller study sample size was analyzed in most of the published literatures. Thus, further investigation is warranted to estimate their strength of association in larger sample size through meta-analysis. In this systematic review, case-control studies from all population groups were compared for the susceptibility of genetic (HLA and non-HLA) variants reported in GPA.

2 | METHODS

A study methodology was predesigned before carrying out this systematic review and meta-analysis considering the eligibility criteria, study preferences, means of extracting and evaluating data from studies as well as methods of quality assessment and statistical analysis.

2.1 | Data collection sources

Web-based search engines such as National Center for Biotechnology Information (PubMed/MEDLINE), SCOPUS and Web of Science were used to search and collect relevant literatures published up to July 2021. All the published peer-reviewed literature(s) on the genetics of GPA or WG were screened. ANCA-associated vasculitis is an umbrella term which consists of 3 different types of vasculitis such as GPA, EGPA (eosinophilic granulomatosis with polyangiitis), and MPA (microscopic polyangiitis). Therefore, a published literature search was conducted using specific key words such as "granulomatosis with polyangiitis and genetics", "Wegener's granulomatosis and genetics", to get all the relevant publications. Further additional literature(s) were collected from the cross references of already added studies.

2.2 | Selection criteria for the study

Stringent inclusion and exclusion criteria were followed while selecting eligible studies. Study inclusion criteria included: (a) case-control approach; (b) genetic association studies; (c) cases diagnosed as GPA, c-ANCA and/or PR3 serological criteria; (d) recruitment of healthy and ethnically matched controls; (e) studies showing discrete data only; and (f) full text available. No limitation on year of study or geographical location was considered. All the reports until July 2021

were considered. Studies were excluded if: (a) performed retrospectively; (b) MPO (myeloperoxidase) positive and/or p-ANCA antibody positive subjects were included as cases.

2.3 | Data extraction and critical appraisal of enclosed studies

Simple primary quantitative data on frequency of genotypes and alleles of susceptibility genes among GPA patients and healthy controls were considered. Data were extracted from the full text and supplementary information. For 2 studies, summary statistics were not available and also author contact information was not found. Standard checklists including risk of bias assessment in observational studies as proposed by the Cochrane handbook (https://training.cochrane.org/handbook) for conducting systematic reviews was used after data extraction and to review methodological quality and strength of association. The study conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (http://www.prisma-statement.org/).[18] The PRISMA statement can be seen in Table S1. Two authors (PB and SS) conducted study screening and data extraction independently, and ambiguity was resolved through mutual discussion.

2.4 | Quality assessment

To estimate the degree of agreement between reviewers, Cohen's kappa (κ) value was calculated. Values were categorized poor, slight, fair, moderate, substantial or almost perfect based on the % agreement and Cohen's κ score.[19] To calculate the effect of any particular study on the meta-analysis, outcome sensitivity analysis was carried out by deleting 1 study at a time from the pooled dataset. Significant changes in the heterogeneity (χ^2, P value and I^2 values) and meta-analyzed ORs (Meta-OR) were considered to determine the sensitivity. Publication biasness was estimated by evaluating the funnel plots. Publications were declared biased when they fell outside or generated asymmetric funnel plots. Studies were examined critically to exclude misfit studies. Assessment of quality (ie study participant selection, comparability, and outcome) of the eligible studies was done with the help of the Newcastle-Ottawa Scale (NOS) tool.[20] Studies were rated using stars within the range 0 (lowest) and 9 (highest), where studies were classified with low (stars 7-9), moderate (stars 4-6) and high (stars 0-3) risk of bias. Low risk studies were only chosen for the analysis.

Quality of evidence (QoE) for each of the outcomes was assessed by the Grades of Research, Assessment, Development and Evaluation (GRADE) tool by using GRADEpro. v.3.6.[21] Evidence was evaluated into 4 categories, namely high, moderate, low and very low based on the recommended criteria, such as study design, risk of bias, inconsistency, indirectness, imprecision and publication bias.

2.5 | Statistical analysis

RevMan (version 5.3.0, The Cochrane Collaboration) tool was used to perform statistical analyses. Individual studies with dichotomous outcome were used to calculate Meta-OR using the Mantel-Haenszel

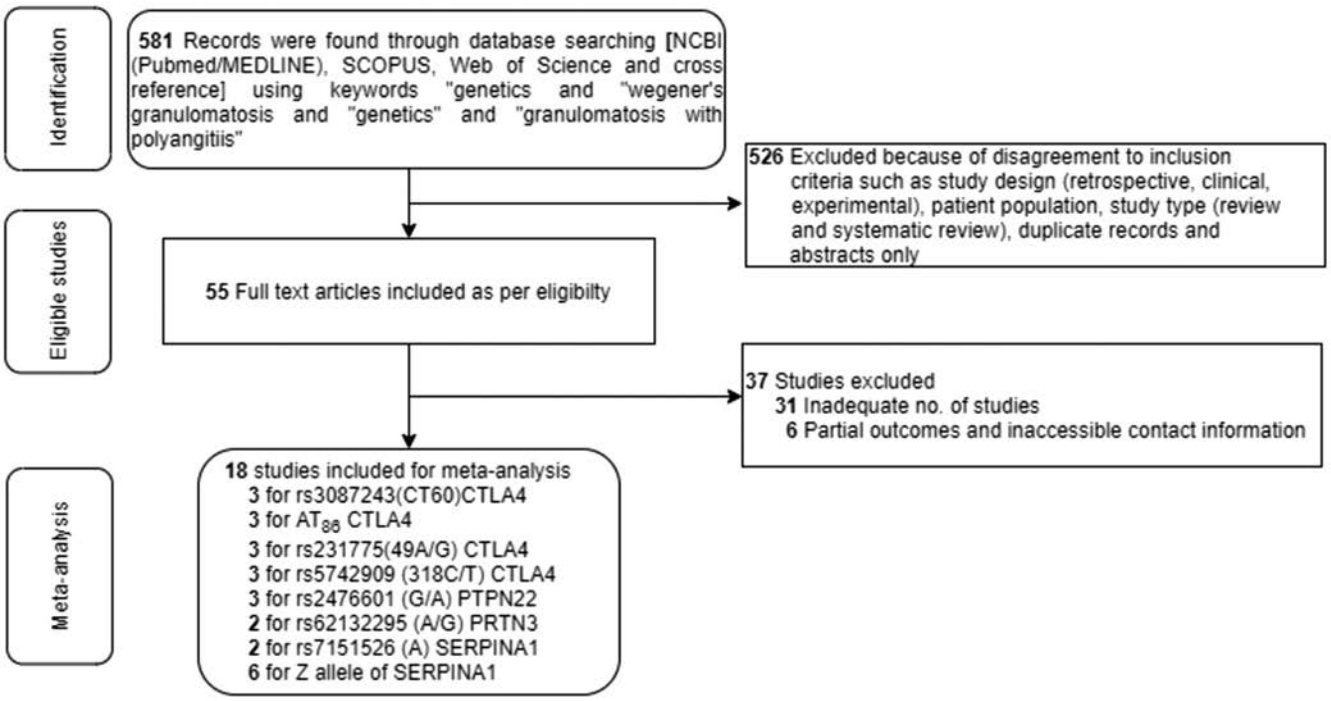

FIGURE 1 Flowchart representing the methodology for eligible study inclusion for the systematic review and meta-analysis

TABLE 1 Summary statistics of the genetic polymorphisms included in the meta-analysis and the quality of evidence as graded by the GRADE tool

Gene	Marker (allele)		Overall study comparison				
		Chr:position (hg38)	N	Total GPA	Total healthy controls	Ref allele Meta-odds ratio (95% CI)	I^2 (%) *P* value
CTLA4	rs3087243 (CT60) (G > A)	2:203874196	3	904	9633	A 0.79 (0.60-1.05)	65% (*P* = .10)
	$(AT)_{86}$	--	3	317	323	A 1.33 (0.61-2.90)	82% (*P* = .48)
	rs231775 (49 A > G)	2:203867991	3	536	1558	G 1.42 (1.14-1.76)	0% (*P* = .001)
	rs5742909 (318 C > T)	2:203867624	4	608	776	C 0.65 (0.44-0.97)	35% (*P* = .03)
PTPN22	rs2476601 (G > A)	1:113834946	3	15310	3342	A 1.17 (0.55-2.48)	88% (*P* = .69)
PRTN3	rs62132295 (A > G)	19:840448	2	186	278	G 1.15 (0.46-2.92)	82% (*P* = .76)
SERPINA1	rs7151526 (C > A)	14:94397299	2	200	200	A 2.70 (2.44-12.02)	0% (*P* = .0008)
SERPINA1	Z allele		6	1500	11400	Z 12.60 (5.01-31.68)	66% (*P* < .00001)

Note: Quality of evidence was accessed using 6 parameters. Quality of evidence was downgraded (by 1 or 2 depending on the severity) for the following: study design—randomized controlled trials are preferred over non-randomized/observational/case-control studies; risk of bias—downgraded for weak study design, shorter follow-up, and no matched case controls; inconsistency—downgraded for considerable heterogeneity, direction of effect, and lack of replication; indirectness—downgraded when population and diagnostic criteria varies; imprecision—wide confidence interval and optimal information size; publication bias—observation from funnel plots.

High quality: further research unlikely changes the study findings and effect estimates.

Moderate quality: further research is likely to change the study findings or the effect estimates.

Low quality: further research is very likely to have an impact on the confidence and effect estimates.

Very low quality: uncertain estimates.

Abbreviation: GPA, granulomatosis with polyangiitis.

(M-H) method with 95% confidence interval (CI). Level of significance was kept at 5% ($P \leq .05$) to test the association. While performing meta-analysis, pooled studies with $I^2 < 50\%$ and heterogeneity χ^2 *P* value > .05 were tested with a fixed effect model, while studies with $I^2 > 50\%$ and/or heterogeneity χ^2 *P* value < .05 were tested with a random effect (DerSimonian and Laird) model of association.[22]

3 | RESULTS

3.1 | Characteristic features of included studies

Initially, with web-based literature search with using defined key words, a total of 581 articles were retrieved. After reviewing abstracts and using stringent inclusion and exclusion criteria, 526 studies were excluded. Thirty-seven articles were excluded because of inadequate number of studies with the genetic variant and due to non-availability of summary statistics. Additionally, 6 studies were partially excluded (complete data were not available) due to unavailability of summary statistics and authors could not be contacted. Thus, a total of 18 articles having following genetic variants and serum typing information were included for meta-analysis (Figure 1): rs3087243 (CT60), $(AT)_{86}$, rs231775 (49A > G) and rs5742909 (318C > T) of *CTLA4*, rs2476601 (G > A) of *PTPN22*, rs62132295 (A > G) of *PRTN3* and rs7151526 (C > A) and "Z" allele of *SERPINA1*. Meta-analysis results along with their summary statistics are given in Table 1.

3.2 | Publication bias estimation and sensitivity analysis

Funnel plots were evaluated following application of appropriate statistical models, that is, fixed effect or random effect

Assessment of quality of evidence (GRADE tool)							
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence	Importance
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important
Non-randomized observational case-control	Not serious	Not serious	Not serious	Not serious	None	Low	Important

model. None of the studies were excluded based on funnel plot evaluation. Eighteen studies remained for meta-analysis given in Figure S1. Almost perfect agreement was observed between reviewers (Cohen's κ = 0.96; 98.28% agreement) regarding the inclusion and exclusion of eligible and ineligible studies from this systematic review.

3.3 | Quality of the studies included and risk of bias

All 18 studies were reported to have low risk (NOS = 7-8) of bias based on the assessment of QoE (Table S2). Through GRADE's approach, it was observed that none of the 18 studies raised risk of bias and the indirectness of the findings was not serious because of clear-cut diagnosis criteria and homogenous populations. Optimal information size was not made to increase precision. The QoE to eliminate any included study was low. Thus, all the studies were considered important and evaluated as low risk given in Table 1.

3.4 | Allelic association

A total of 18 studies were included in meta-analysis where allelic frequencies for every genetic marker were previously reported for subjects with GPA and healthy controls. Out of all, only 1 study was on an Indian (North India) population while the rest were on Caucasian populations or other Asian populations. Detailed information of study participants and allele frequencies are provided in Table S3. Pooled effect size for rs3087243 (CT60) G/A, $AT_{(86)}$, rs5742909 of *CTLA4*, rs62132295 of *PRTN3* and rs7151526 of *SERPINA1* in GPA

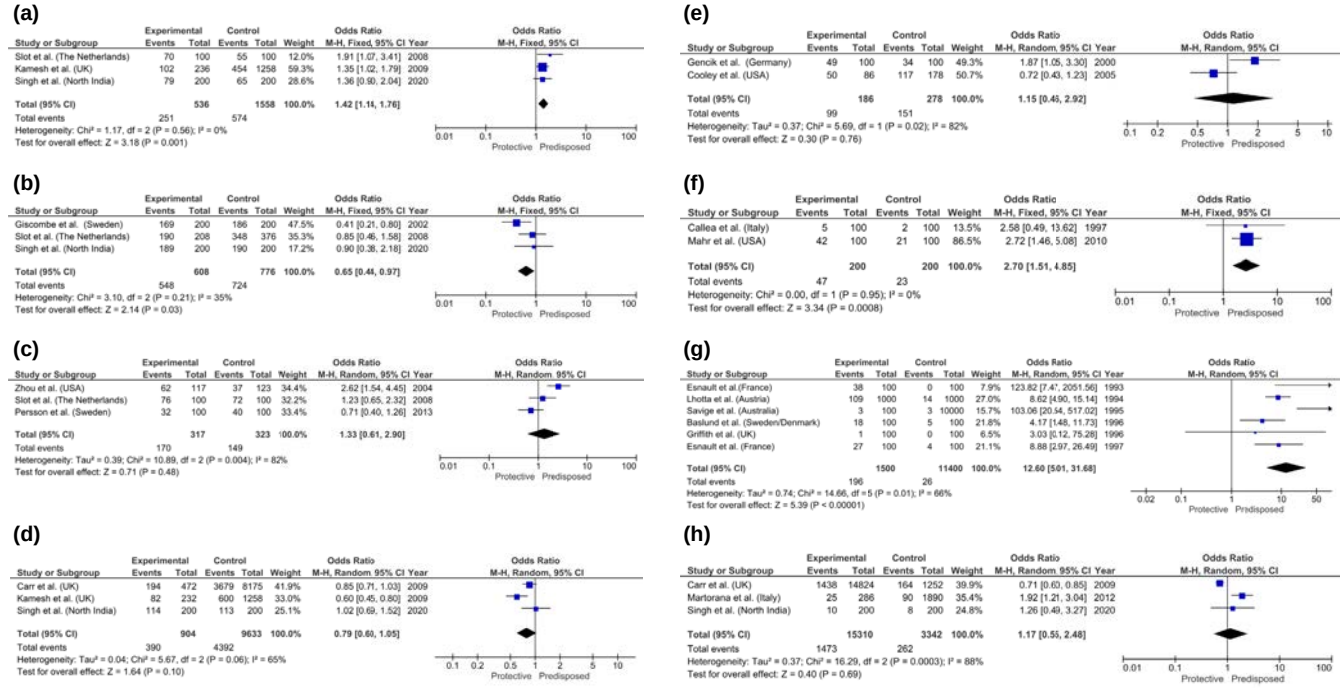

FIGURE 2 Forest plots to show the results of the meta-analysis of non-major histocompatibility complex genetic variants from *CTLA4*: (A) rs231775-G (49A/G); (B) rs5742909-C (318C/T); (C) $(AT)_{86}$; (D) rs3087243-A (CT60); from *PRTN3*: (E) rs62132295-G (A564G); from *SERPINA1*: (F) rs7151526-A; and (G) *SERPINA1*-Z allele; and from *PTPN22*: (H) rs2476601-A (R620W)

was performed with the random effect model. For rs231775 of *CTLA4* and rs2476601 of *PTPN22*, insignificant heterogeneity (χ^2 $P > .05$ and $I^2 < 50\%$) was seen and thus the fixed effect model was applied for study. *Z* test *P* values (ie Meta-*P* value) with less than .05 were considered as significant associations. Risk was determined based on the Meta-OR.

3.4.1 | CTLA4

A total of 7 studies[8,13–15,23–25] were included for *CTLA4*. G allele of 49A/G or rs231775 (Meta-OR = 1.42 [1.14-1.76]; $P = .001$) and $(AT)_{86}$ (Meta-OR = 1.33 [0.61-2.90]; $P = .48$) were identified as predisposing alleles in GPA, while 2 other alleles, namely C allele of 318C/T or rs5742909 (Meta-OR = 0.65 [0.44-0.97]; $P = .03$) and A allele of CT(60) or rs3087243 (Meta-OR = 0.79 [0.60-1.05]; $P = .10$) were identified as protective. Out of these, risk conferred by 49-G or rs231775-G and protection conferred by 318-C or rs5742909-C were found statistically significant (Figure 2A-D).

3.4.2 | PRTN3

Two studies were evaluated for *PRTN3*.[16,17] G allele of A564G or rs62132295 was identified to confer borderline risk (Meta-OR = 1.15 [0.46-2.92]; $P = .76$) for GPA. Observed Meta-*P* value was statistically insignificant (Figure 2E).

3.4.3 | SERPINA1

Two studies were evaluated for *SERPINA1*.[26,27] rs7151526-A (also known as Z allele) was identified as significantly associated with GPA ($P = .0008$). A allele of this marker was observed to provide high risk (Meta-OR = 2.70 [1.51-4.85]) for the disease (Figure 2F). In 6 additional serological studies, risk of Z allele was evaluated by analyzing the serum concentrations.[5,28–32] It was identified as predisposing with very high risk (Meta-OR = 12.60 [5.01-31.68]) for the disease with significant *P* value ($P < .00001$) (Figure 2G).

3.4.4 | PTPN22

Three studies were found eligible for the meta-analysis and were evaluated.[8,15,33] A allele of rs2476601 was identified to provide borderline risk (Meta-OR = 1.17 [0.55-2.48]; $P = .69$) with non-significant association (Figure 2H).

4 | DISCUSSION

In this study 2 genetic variants, namely rs231775-G (49G) of *CTLA4* (OR = 1.42) and rs7151526-A or Z allele of *SERPINA1* were identified to provide significant risk for GPA. Serological estimation of Z allele of *SERPINA1* was also found significantly associated and providing risk for GPA (OR = 12.60); rs5742909-C (318C) of *CTLA4* was

identified to exert a protective role on GPA (OR = 0.65), while association data from north Indians were evaluated for *CTLA4* variants, and only European data were available for *SERPINA1*. These polymorphisms from *CTLA4* and *SERPINA1* were previously identified in a number of other autoimmune and immune-mediated diseases (Figure S2).

CTLA4 majorly functions as a negative regulator of T cell responses. In this study G allele of rs231775 (49G) was identified as a predisposing allele. GG genotype of this variant causes alteration of alanine to threonine in the leader peptide, resulting in the down-regulation of *CTLA4* expression which leads to increased T cell activation and was also found to be significantly increased in patients with GPA as compared to the controls in the North Indian population.[15] rs231775-G (missense variant) also associated with alopecia areata (OR = 1.4) and autoimmune thyroid disease (OR = 1.18).[34,35] rs5742909-T (318 T) allele leads to higher promoter activity and thereby contributes in up-regulation of *CTLA4* and has been found associated with multiple sclerosis and esophageal cancer.[36,37] rs5742909-C was found to be protective in GPA. rs5742909-T allele is associated with up-regulated CTLA4 expression which leads to inhibition of increased immune activity.[38] Swedish GPA patients were found to be more often (31%) heterozygous for rs5742909 (−318C > T) compared to controls (14%) ($P < 0.05$). Homozygosity for "C" allele was frequently observed in healthy controls (86%) ($P < 0.05$).[23] A multicenter, double-blinded, placebo-controlled and randomized study with small sample size, earlier involvement of prednisone and other drugs, inclusion of only non-severe GPA cases, showed the efficacy of abatacept (CTLA4-IG) therapy where 90% of non-severe relapsing GPA patients with improvement, 80% reached remission and 70% achieved common closing and 73% of patients initially on prednisone were able to discontinue prednisone.[39] Further detailed investigation in the role of abatacept in GPA needs to be established.

SERPINA1 is a serine protease inhibitor which inhibits elastase, thrombin, trypsin, chymotrypsin, plasmin and plasminogen activator. Genetic variation in *SERPINA1* (rs7151526-A) also known as Z allele, results in deficiency of A1AT which acts as a reversible chymotrypsin inhibitor and elastase but does not inhibit trypsin. The main physiological function of *SERPINA1* is to protect the lower respiratory tract against proteolytic degradation by human leukocyte elastase. rs7151526 was reported associated with AAV (OR = 1.69) in an GWAS study on AAV.[3] Variants in *SERPINA1*, namely Pi*Z and Pi*S elicit potential effects on the clinical course of GPA. Serum anti-PR3 antibody levels were found to be higher in GPA patients with Pi*Z, Pi*S, or Pi*I variants than with the Pi*MM variant. Also, 7.8% of GPA patients carry heterozygous genotype Pi*MZ, Pi*MS and Pi*SZ and around 10% of those show occurrence of lung lesions.[40] In a study, it was reported that patients with at least 1 Z allele showed ear, nose and throat complications as compared to patients without any Z allele. Similarly, GPA patients with S allele displayed a higher frequency of pulmonary involvement than other GPA patients.[41]

Exact role of these genetic variants in GPA pathogenesis was not studied; however, their role in inflammation in general has been characterized. Therefore, these findings may be valuable for classification of GPA patients and would have prognostic value toward better disease management.

5 | CONCLUSION

There are limited evidence on genetic susceptibility in GPA. The present systematic review based meta-analysis included only 1 non-European study reported from India. Variants from *CTLA4* and *SERPINA1* were identified as major risk alleles and thus could be used for genomic constitution-based GPA classification for better disease management and to predict prognosis. The majority of the genetic studies and GWAS were done among Europeans. GPA is a rare disease and thus most of the high-throughput studies were done on AAV and not particularly focusing on GPA. To uncover the molecular pathogenesis, more genetic studies are warranted to investigate GPA in a bigger multi-ethnic cohort.

AUTHOR CONTRIBUTIONS

SS and UK conceptualized the study. SS designed the study and performed the initial literature search. PB and SS performed the systematic review. PK helped in statistical analysis. SS and PB performed the analysis and wrote the manuscript. PK and UK provided critical inputs. All the authors read the final manuscript and approved it for publication.

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CONFLICT OF INTEREST

None to declare.

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SUPPORTING INFORMATION

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

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Amrita Institute of Medical Sciences
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