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REVIEW

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Self-concept and body image of people living with lupus: A systematic review

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Abstract

Aim: To summarize existing evidence regarding body image in patients with systemic lupus erythematosus, with the following considerations: (a) the perceptions patients have of their body changes; (b) how patients cope with changes in their body; (c) and what their perceptions are of body changes.

Method: A systematic review of literature integrating quantitative and qualitative studies. We searched databases (PubMed, CINAHL, Embase, SCOPUS, the Web of Science, Medline, Medline Complete, and Academic Search Premier) and publications from 2010 to 2020 with "Systemic Lupus Erythematosus" AND "Self-Concept" OR "Body Image" AND "Woman" as medical subheading terms. The studies included were subjected to a thematic content analysis, which allowed subjective interpretation of data through a systematic classification process for coding themes or patterns.

Results: We identified 647 studies, of which 22 were analyzed in this study. Our results indicate that changes in the body image of people with lupus and their perception are issues that must be treated as characteristics of the disease; therefore, they need to receive the same attention as is given to physical disabilities and pain. The analysis identified 3 thematic categories: (a) depression and anxiety associated with body changes (hair loss, weight gain); (b) body image reflecting the disease; and (c) confrontations and interventions to promote acceptance and adaptation to the new image.

Conclusions: The dimensions of self-concept and body image are essential for assessing the quality of life of individuals with lupus. The formation of a adjusted self-concept can be managed by health professionals supporting these people.

KEYWORDS

body dissatisfaction, body image, self-concept, systematic review, systemic lupus erythematosus

1 | INTRODUCTION

Body image (BI) refers to the internal representation and perceptions of appearance and behavior and attitudes held by an individual.[1,2] The attitudinal dimensions of BI, which include the beliefs and values of the individual,[1,3] can be explored from many perspectives. The perceptual dimensions of BI are focused on the individual's precise judgments of their size, weight, and body shape.[1] Some aspects of BI are associated with efforts made to control or change appearance, adopt behaviors to avoid being judged by others,[1] and achieve a desired or idealized body.[1,4]

BI disorders can take many forms, including extreme dissatisfaction with appearance and compulsory checking and fear of judgment of appearance.[2] These disorders have been consistently associated with psychological consequences,[5] including depressive symptoms[6] and impaired self-esteem.[7] BI disturbance (BID) is defined as the distortion of perceptions or cognition related to body weight or shape.[8] BID plays an important role in anxiety/depression and reduces quality of life (QoL).[9,10]

BI reflects external appearance and is separate from self-concept, which refers to an individual's view of oneself as a person. In individuals with systemic lupus erythematosus (SLE), self-concept can remain positive, even when BI is negative.[11]

SLE is a multisystemic disease that can alter body appearance. Its rate of incidence is 9-240 cases/100 000 people and is prevalent in women in reproductive age (the female-to-male ratio is 9:1).[12,13] The disease has a different presentation in different individuals, with variable levels of severity.[14]

In general, clinical manifestations of SLE involve several organs, including the skin, kidneys, lungs, heart, and central nervous system. Affected organs and systems suffer from disease sequelae, and periods of remission may occur without clinical manifestations.[13,15] SLE manifestations include spots, flushing, and skin rashes, especially on the face, joint changes, hair loss, and weight gain,[13] which make the disease apparent and can cause changes in BI.

Therefore, this review focuses on the changes and adaptations that occur in the BI of people with SLE as primary interest and in their self-concept as secondary interest and is aimed at summarizing existing evidence regarding BI and self-concept in patients with SLE, with the following considerations: (1) the perceptions patients have of their body changes; (2) how patients cope with changes in their body; (3) and what their perceptions are of body changes. To fulfill these objectives, we will conduct an analysis of both quantitative and qualitative studies.

2 | METHODS

2.1 | Protocol and registration

This review was registered in PROSPERO, under number CRD42019126613. To design the study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used.[16]

2.2 | Inclusion criteria

2.2.1 | Types of patients and conditions

Adult patients (more than 18 years old) diagnosed with SLE, according to the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR),[17] were included in the study. The selected studies had to include self-concept and/or BI subjects.

2.2.2 | Types of outcomes

Outcomes are reported for the participants' experience or perception of the influence of SLE on their own persons: the patient's perception of their body; how they interpret and cope with their BI; what kind of symptoms are associated with how the patient feels; and how they see or conceptualize their self.

2.2.3 | Types of studies

Published peer-reviewed journal articles were considered in this review. Qualitative or quantitative designed observational studies (descriptive cross-sectional analyses, case-control analyses, and cohort analyses) and designed experimental studies (randomized and non-randomized) were included. There was no geographical restriction, and studies published in English, Spanish, French, or Portuguese were eligible. The articles were published between 2010 and 2020. We considered for inclusion studies focused on the issue of BI and those that made evident the relationship between BI and other issues, such as QoL as a primary interest, or even self-concept as a secondary interest. Methodological studies for instrument validation, case studies or case reports, and literature reviews were excluded.

2.3 | Search strategy

This systematic review asked the research question what the BI is of people living with lupus. A literature search was performed in February 2019 and updated in June 2020, and used the following electronic databases: US National Library of Medicine - National Institutes of Health (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica (Embase), SCOPUS, the Web of Science, Medline, Medline Complete, and Academic Search Premier. A manual search of lists of selected articles supplemented the electronic search. All studies selected were electronically available.

Two authors (LR and MSS) performed the search. The medical subheading (MeSH) terms used were "Systemic Lupus Erythematosus" AND "Self-Concept" OR "Body Image" AND "Woman".

2.4 | Study records

A database was created with the free software EndNote to manage the publications searched. For the exclusion process, the covidence.org tool for organizing systematic reviews (available at https://www.covidence.org) was used.

Two reviewers (LR and MSS) independently screened titles and abstracts. At the end of this selection phase, the 2 reviewers discussed cases of disagreement. If there was doubt about eligibility, the article was included until the full textual analysis phase. If doubt remained, a third reviewer (LMS) provided an opinion on the eligibility of the text. The search process is summarized in Figure 1.

2.5 | Bias assessment

Assessments of the quality of articles were based on checklists developed by Joanna Briggs Institute (JBI) for quasi-experimental, cross-sectional, and qualitative research,[18] available at The System for the Unified Management, Assessment and Review of Information (SUMMARI). Two authors (LR and MSS) performed the assessments. Disagreements were managed to reach consensus through analysis and discussion with a third author (LMS). The level of evidence provided by the studies was evaluated according to the JBI Model of Evidence Based Healthcare.[19]

2.6 | Data analysis

The studies were subjected to thematic content analysis, which allows data to be interpreted through a systematic classification process for coding themes or patterns.[18] To enable analysis of quantitative and qualitative studies, goal aggregation[20] was carried out using the following procedures: the high points of the qualitative studies were raised and themes were generated and codified,[18] and the variables in quantitative studies were transformed into similar themes and also codified.[20] The analysis culminated in a synthesis of the content, with construction of thematic categories for organization and presentation of the meta-aggregation material.[21]

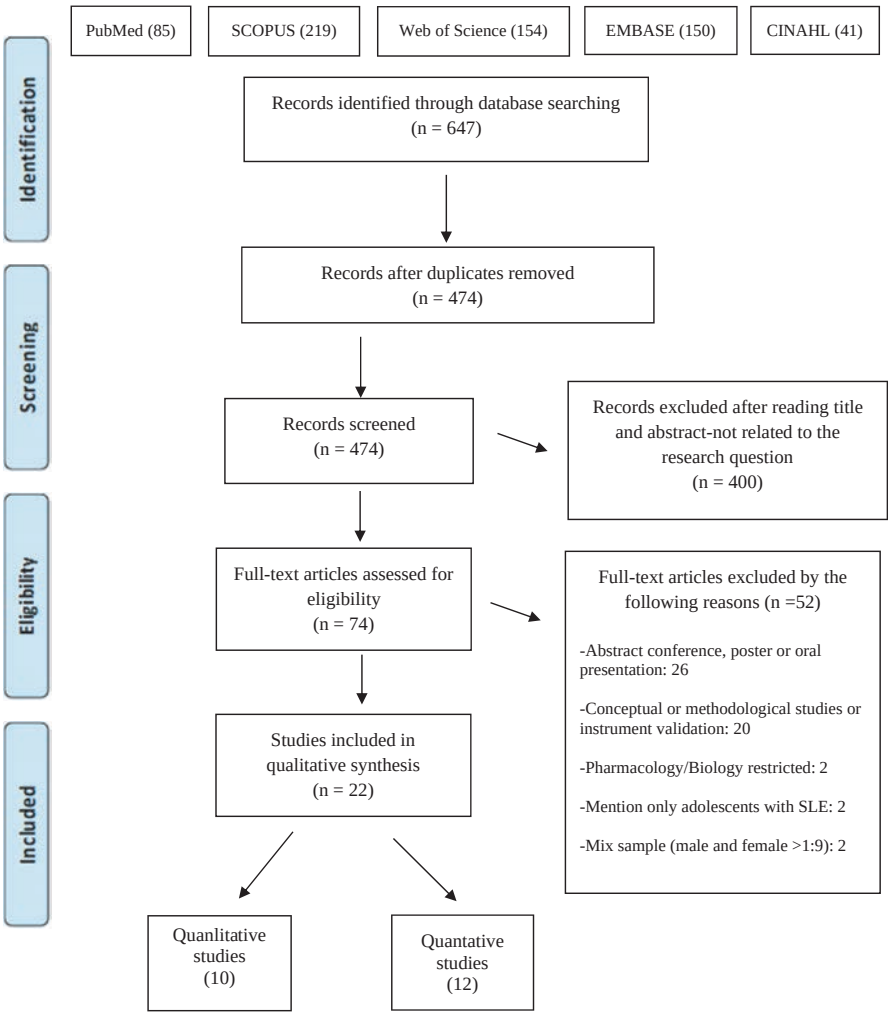

FIGURE 1 Study search flow diagram

3 | RESULTS

3.1 | Search results

Of the 647 articles identified, 173 were removed as duplicates. The inclusion and exclusion process included a peer review of the titles and abstracts of 474 articles, performed by 2 authors (LR and MSS), to identify studies that potentially met the inclusion criteria, followed by a full-text reading of 74 articles. Disagreements on the eligibility of articles were discussed with the third author (FGS) until consensus was reached. By consensus, 22 articles were finally selected for analysis. The flow chart in Figure 1 shows the studies included in the main analysis.

3.2 | Description of studies

Of the 22 studies, 15 were cross-sectional. Twelve studies had a quantitative approach, and 1 of them had a quasi-experimental design. The remaining 10 had a qualitative design. Figure 2 presents the main topics of the articles. These topics were always related to BI, either as a domain or as a question in a questionnaire or as an emerging theme in comments made by study participants. The results are for a total of 3394 participants. A large variation in sample size was observed, ranging between 6 and 1259 participants.

For the quantitative studies, the alpha coefficients of the applied instruments were .96 for the Body Image QoL Inventory (BIQLI),[22] .91 for the depression subscale of the Systemic Lupus Erythematosus Needs Questionnaire (SLENQ),[23,24] .73 for an adapted version of the Body Image Questionnaire,[10] and .93 for the Pain & Vitality domain and .94 for the BI domain of the LupusPRO questionnaire.[25] In studies that did not calculate Cronbach's alpha, evaluations from previous studies were reported.[26-30]

Quantitative studies carried out bivariate analyses using the following statistical tests: (a) Chi-squared test;[24,27-29,31] (b) Student's *t* test;[10,26,30,31] (c) one-way analysis of variance (ANOVA);[23,24] (d) Mann–Whitney *U* test;[27,28] and (e) correlations.[28,30] When indicated, non-parametric tests were applied.[28,29,31,32] Some studies also performed multivariate analyses.[10,24-27,30]

Qualitative studies examining the singularity of living experiences, the emerging cascading process, and the revelations of the participants[33] included 4 phenomenological studies,[11,34-36] 3 conceptual analysis studies based on focus groups,[37-39] and a content analysis of individual discourse in 3 studies.[40-42] The data interpretation process was supported by Dedoose software[43] in 1 case[38] and NVIVO software[44] in 2 cases,[40,42] whereas 7 cases did not clarify whether data were analyzed manually or with software.

Table 1 presents a summary of the structures of the 22 selected articles.

3.3 | Critical appraisal

In addition to the thematic analysis, articles were evaluated for methodological quality and the risk of bias separately by 2 authors (Figure 3). All studies met more than 70% of the criteria for methodological quality, which ranged between moderate and high. In the case of the level of evidence, 50% of the studies were at level 4b, 45.5% at level 3, and 4.5% at level 2c.

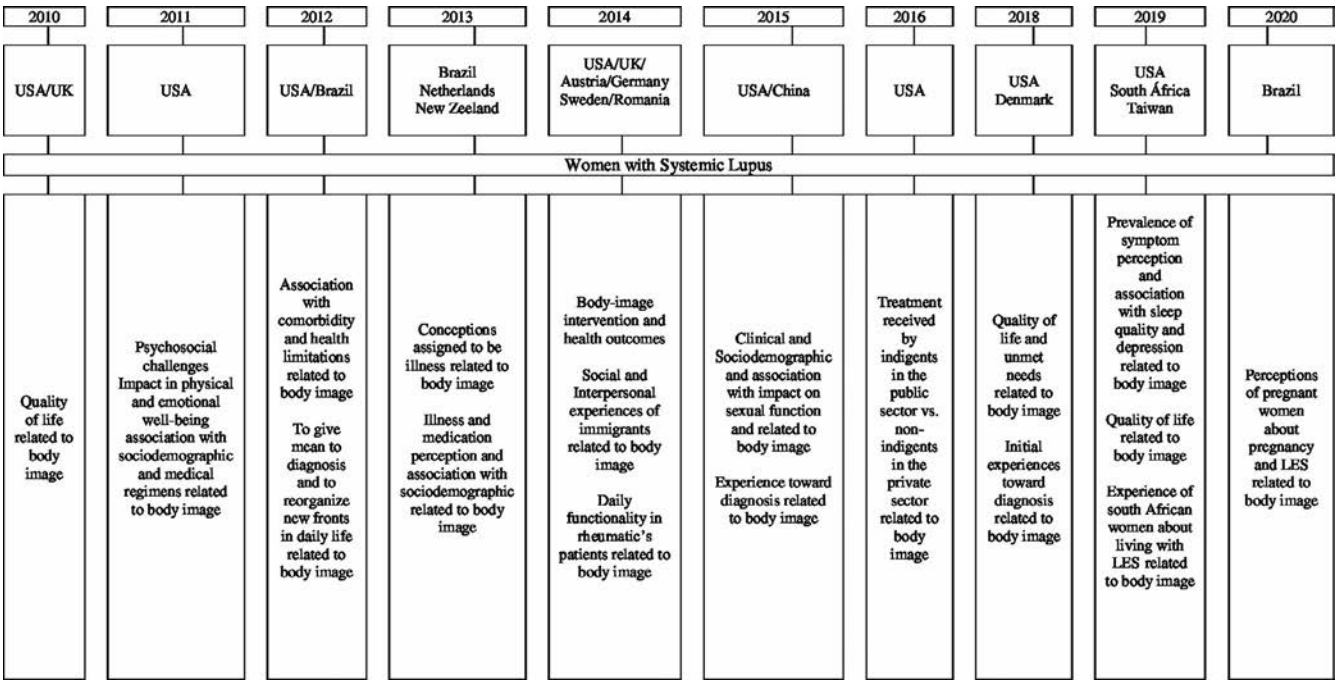

FIGURE 2 Publication in the last 10 years on various topics related to body image in the discussion of article

TABLE 1 Studies included in this review

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Auerback and Beckerman, 2011[23] USA	N = 378, 357 female; 13 male Age: 21-60 y	To identify and to clarify the unique psychosocial challenges for those living with SLE	Cross-sectional, descriptive & observational study Level 4b - SLENQ – Psychosocial needs and beliefs. Considering 3 subscales: depression, anxiety, social economic coping (SEC); - MHLOC – Multidimensional Health Locus of Control Scale: 2 subscales: chance and internal	Changes in the body have been associated with depression, as well as limitations with SLE and the side effects of treatment Changes in appearance were also associated with anxiety, as well as the feeling of injustice for being affected by the disease, anger because of SLE, perception of an uncertain future, side effects from treatment
Beckerman et al. 2011[24] USA	N = 378, 357 female; 13 male Age: 20-67 y	To identify psychosocial experiences To identify what ethnicities may be at risk for which psychosocial stressors	Cross-sectional Approach: quantitative study - Level 4b - SLENQ – Psychosocial needs and beliefs Considering 3 subscales: depression, anxiety, SEC MHLOC Scale: 2 subscales: chance and internal Side effects of medication	There were the following associations with changes in body image: changes in the body with depression; changes in appearance with the perception of the side effect of the medication (greater with the use of hydroxychloroquine and corticosteroids), hair loss with a higher degree of depression; weight gain with greater need for psychosocial care (for Hispanics); hair loss and muscle pain with feelings of depression and anxiety; hair loss with higher levels of anxiety
Beckermam, 2011[37] USA	N = 32, 29 female; 3 male Age: Under 35 y = 19; over 35 y = 13	The purpose was the further identification and clarification of unique psychosocial challenges for those living with SLE	Qualitative study Meaningfulness for qualitative studies Level 3 Focus group to explore, in an open way, how this disease affected women's lives, in a safe environment to talk about their shared and unique experiences Thematic content analysis was used	Body image, self-concept and the inability to function as before were related to feelings of depression. The reports are that the participants ceased to be who they were before the beginning of SLE
Chiang et al. 2019[26] Taiwan	N = 75, 67 female; 8 male Mean age 23.0 (range: 9.6-37.2)	Explore prevalence of symptoms perceived by SLE patients Develop groups of symptoms Examine the association of the load of each group of symptoms with sleep quality and depression	Descriptive correlational study Level 4b SSC (SLE Symptom Checklist) PSQI (Pittsburgh sleep quality) BDI (Beck Depression Inventory II) Demographic: treatment information; the medical impact; SFQ (Sexual Functioning Questionnaire); B-IPQ (Brief Illness Perception Questionnaire)	5 groups of symptoms prevailed: symptoms related to body image and circulatory problems, white fingers in the cold, hair loss and sensitivity to sunlight; symptoms related to weight gain: cheeks / face, more appetite and nightmares; symptoms related to pain and itching: aching joints, aching muscles, headache and itching; symptoms related to bruises and stomach complaints: spontaneous hematomas and stomach complaints; symptoms related to fatigue: fatigue, mood swings, loss of concentration, disturbed memory and skin vulnerability

(Continues)

TABLE 1 (Continued)

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Cordeiro and Andrade 2012[34] Brazil	N = 10 female = 100% Age >18 y	Understand the meaning attributed by women to the fact that they have a diagnosis of lupus	Qualitative study with phenomenology meaningfulness for qualitative studies Level 3 Face-to-face interview, with the following question: How do you feel, as a woman, to have a diagnosis of lupus?	Self-image has changes imposed by lupus, participants feel it in the relationship with family and in the development of activities daily Participants need care with clinical manifestations and psychological aspects of this pathology, helping them to develop a positive self-image, guiding them with self-care, control and prevention of possible complications
Daleboudt et al. 2013[30] The Netherlands New Zealand	N = 106 participants, female = 94.3%; male = 5.7% Mean age = 43.34 y (SD = 14.96)	Access the influence of SLE on sexual function Investigate the association between sexuality and perception of the disease and sociodemographic aspects Compare sexual functions of patients with SLE and other chronic diseases	Cross-sectional approach Quantitative study Level 4b PDSBE (Physical Disability and Sexual and Body Esteem scale) SFQ (Medical Impact Scale of the Sexual Functioning Questionnaire) B-IPQ (Brief Illness Perception Questionnaire)	The perception of changes in body image of patients was to experience negative effects of SLE on their sexual functioning, especially on their sexual and body esteem The perception of the disease was a more important predictor than the sociodemographic and clinical characteristics of sexual functioning The influence of SLE on sexual functioning appears to be disease-specific, unlike other chronic diseases
Gholizadeh et al. 2019[25] USA	N = 135 female 92.6%; male 7.4% Mean age: 48.54 (13.9)	Examined whether body image (specifically, body image-related quality of life) serves as a mediator of the relationship between pain and depressive symptoms among patients with SLE	Cross-sectional approach Quantitative study Level 4b LupusPRO Pain and Vitality LupusPRO Body Image HADS (Hospital anxiety and Depression Scale)	Body image related quality of life was a significant mediator in the relationship between pain and depressive symptoms
Hale et al. 2015[11] USA	N = 15; female = 14 (94%); male = 1 (6%) Ages ranged: 22 to 57 y	To understand experiences within a group of patients diagnosed with SLE	Cross-sectional approach Qualitative study Meaningfulness for qualitative studies Level 3 Qualitative mode of enquiry using semi-structured interviews with audio-records: (Q1: what body image and self-image meant to patients; Q2: how they cope about their medication's effects)	Women often refer to the appearance of women and compare themselves to other women Matter with skin, weight or functional problems Participants felt that, when more confident, they were less concerned with the external appearance, emphasizing their self-image Participants feel more prepared to address other people's comments or opinions when they receive interventions on psychosocial issues, such as social skills training

(Continues)

TABLE 1 (Continued)

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Jolly et al. 2010[28] USA	N = 185 patients; female = 174 (94%); male = 11 (6%) Mean age: 42.2 ± 14.5 y	To characterized US patients regarding demographic and LupusQoL-US	Cross-sectional approach Quantitative study Level 4b LupusQoL-US domains: Physical health, Pain, Planning, Intimate Relationships, Burden to others, Emotional health, Body image, and Fatigue	Alopecia correlated with body image, intimate relationships and pain Age was associated with body image domain Skin damage was associated with body image domain in LupusQoL
Jolly et al. 2012[22] USA	N = 165 participants Control group: 78 healthy (47.27%), experimental group: 87 SLE (52.72%) Age: 42.4 ± 13.1 for SLE and 38.7 ± 13.2 y for non-SLE subjects	To compare body image-related QoL (healthy and SLE patients) To determine associations: Body Image Quality of Life Inventory (BIQLI) and disease features, comorbid conditions and health-related QoL To determine the amount of variation in Health-related QoL (HRQoL) explained by disease activity, damage and body image	Cross-sectional approach Quantitative study Level 4b Body mass index BIQLI HRQoL SF-6D (functional status index; a variant of SF-36) EQ-5D (health status index)	Poor body image is a realistic problem that patients with SLE frequently face, and this needs to be addressed through focused on cutaneous disease activity, damage and depression Patients with SLE have significantly worse body image-related QoL than age-matched non-SLE controls Considering SLE patients, body image-related QoL has negative correlation with alopecia, irreversible cutaneous damage, depression Considering SLE patients, body image-related QoL was positive
Jolly et al. 2014[31] USA	N = 15 Intervention group: 10; control group: 5 Mean age = intervention group 43.2 (12.2), control group 44.4 (8.7)	Determine the feasibility and effectiveness of a novel body image intervention in improving body image - Determine health outcomes among women	Quasi-experimental study approach Quantitative study Level 2c BILS Body-image measures (Body Image in Lupus Scale) MBSRQ (Multidimensional Body Self-relations Questionnaire) Appearance Scale) Psychological health measures: (CES-D Center for Epidemiological Studies Depression; STAI State Trait Anxiety Index) QoL: (LupusPRO)	Major improvements in body image were seen after body image interventions Body image was modified in patients with SLE, improving psychological well-being and QoL, maintaining this improvement over time
Jolly et al. 2018[32] USA	N: 1259 patients with lupus nephritis (LN) Median age: 41.7 (13.5)	Describe HRQoL (lupus symptoms and medication; cognition; procreation; physical and emotional health; pain vitality; body image) and non-HRQoL (desire goals; social support; satisfaction care)	Cross-sectional approach Quantitative study Level 4b BILS body image measures: (Body Image in Lupus Scale; MBSRQ, Multidimensional Body Self-relations Questionnaire; Appearance Scale) Psychological Health Measures: (CES-D; STAI) QoL : (LupusPRO)	Patients with LN were younger had worse HRQoL and non-HRQoL Specific domains of HRQoL adversely affected include lupus symptoms, medications, procreation, emotional health, body image and desires goals Among patients with LN and active LN, lupus medications and procreation HRQoL are significantly adversely impacted, independent of their age, gender, ethnicity and country

(Continues)

TABLE 1 (Continued)

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Larsen et al. 2018[35] Denmark	N = 15 women Mean age = 45.6	To explore the experience of being diagnosed with SLE as an existential phenomenon	Cross-sectional approach Qualitative study Meaningfulness for qualitative studies Level 3 Semi-structured interview Van Manen's phenomenology of practice	About self-concept, receiving the diagnosis of lupus is an experience that suspends life, increasing uncertainties in the present and in the future, is to find yourself in a whirlwind of events, is to step on uneven ground and be at an inflection point with yourself and with others
Ogunsanya 2018[38]USA	N = 19, female = 18 (94.7%); male = 1 Mean age: 49 ± 14	To explore patients' views on how cutaneous lupus has affected their lives and the unmet needs with regard to SLE treatment and care	Qualitative study Meaningfulness for qualitative studies Level 3 Focus group discussion guide based on the themes Understanding the impact of SLE on patients' lives; Unmet needs in relation to treatment and care for SLE	Changes in appearance extrapolated the image and patients used several coping mechanisms, both positive and negative, to mitigate the effects of cutaneous lupus Several themes captured the burden of cutaneous lupus in patients; these ranged from disease sequelae and social effects to functioning
Phuti et al.2019[40] South Africa	N = 25 women Mean age: 30.9 y (range: 22-45)	To explore living experiences, perceptions and unmet needs of South African patients with SLE	Qualitative study Meaningfulness for qualitative studies Level 3 Individual in-depth interviews exploring their physical concerns, emotional health, sexual well-being and fertility	Changes in self-image have been associated with physical disfigurements resulting from lupus as alopecia, skin rashes and weight fluctuations induced by corticosteroids were a major concern. These changes were also associated with affected libido, leading to strained personal relationships
Rodrigues et al. 2020[42] Brazil	N = 26 pregnant women Mean age: 30 (SD 14.85)	To understand the meanings attributed to pregnancy by pregnant women with SLE during prenatal care	Qualitative study Meaningfulness for qualitative studies Level 3 Face-to-face interview with semi-structured script with open-ended questions with the following themes: feelings about being an SLE carrier, experience with carrying this disease while being pregnant, pregnancy monitoring, sexual behaviors after finding out about the illness and pregnancy, and daily life	Changes in self-concept and body image are associated with disease and the side effects of drugs used to control lupus, which can prevent pregnant women with lupus from identifying with themselves. This engenders psychological and social impacts activated by the visibility of the disease. Participants reported experiencing social isolation, sadness, and hopelessness because of their disease-related self-image
Rodriguez-Rivera et al 2016[29] USA	N = 98 patients disadvantaged = 40; private care = 58 Female = 94 (95.9%); male = 4 (4.1%) Mean age = 44.9 (SD 12)	To determine patient-reported outcomes measures To compare outcomes between public sector patients and private sector patients	Cross-sectional approach Quantitative study Level 4b LupusPRO HRQoL (8 domains; body image is 8th domain) Non-HRQoL (4 domains)	No significant differences were observed for the domains of body image Patients from the public sector reported better coping than the private group

(Continues)

TABLE 1 (Continued)

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Rutter and Kiemle 2014[36] UK	N = 6 female 100% Mean age = 42 (28-47)	To describe interpersonal experiences considering their ethnicity and cultural influences	Cross-sectional approach Qualitative study Meaningfulness for qualitative studies Level 3 Phenomenological interpretative analysis with semi-structured questions: (a) SLE diagnosis, physical effects, social function, sense of self, relationships, intimacy and the future	Body image and changes in the appearance of SLE medications were related to the feeling of helplessness. 5 themes arise: (a) SLE: complexities and ironies; (b) the power of SLE; (c) sense of personal responsibility; (d) essential relationships, qualities and consequences; (e) fighting in the public's view.
Shen et al. 2015[10] China	N = 352 participants (26 missing) 156 patients (SLE experimental group) 210 healthy (control group) Female = 142 patients (91%); 176 healthy (89.8%); male = 14 (9%); 20 healthy (10.2%) Mean age = 32.9 (±10.2) patients; 35.0 (±11.4) healthy	To examine the association between BID and sexual function	Cross-sectional approach Quantitative study Level 4b BID Body Image Disturbance (7 subscale) SAS Revised Self-Rating Anxiety Scale SDS Revised Self-Rating Depression Scale SF-36 QoL	In patients group, BID generally, has significant correlations with partner relationship; also BID generally, has significant correlations with sexual function. Patients have higher risk for anxiety than healthy group There were significant differences in sexual relationship impairment between patients and healthy, sexual partner relationships were disturbed by appearance-related concerns
Stamm et al. 2014[39] Austria	N = 229 patients (21 with SLE) Female = 20 (95%), male = 1 (5%) Age = 21-38 y	To compare and contrast the concepts of functioning in daily life in patients with different rheumatological conditions (multicentric 8 countries)	Cross-sectional approach Qualitative study Meaningfulness for qualitative studies level 3 focus group (3-8 people with SLE) interviews (6 open questions) supported by the who international classification of functioning, disability and health (ICF) (body functions and structures; activities and participation; environmental and personal factors)	Patients report: body image and appearance: changes in the body as a whole, but also specific parts (skin; weight loss) and attitudes of others (based on appearance): (1) positive attitudes recognized by family members, colleagues; (2) negative attitudes recognized by strangers, employers and society in general
Xavier et al. 2013[41] Brazil	N = 9 female patients (100%) Age = 21-38 y	To understand the conceptions attributed to the disease process	Cross-sectional approach Qualitative study Meaningfulness for qualitative studies Level 3 Semi-structured interviews (13 questions: life course from getting sick to the moment; patient perspective about treatment; describes the relationship with their doctor; how patient defines her pathology; how patient defines the association between her illness and the specific events in her life)	Body image and lupus as a unknown body: (a) negative feelings (strangeness, horror, anguish, shame); (b) the brand of a new image permanently/ chronically sick 5 themes: (a) the onset of the disease; (b) body and lupus; (c) treatment; (d) lupus and its causes; (e) the doctor's speech about lupus

(Continues)

TABLE 1 (Continued)

Study	Sample	Objective	Study design/ evidence level/ collection/ measures	Main results
Zhao, et al. 2018[27] China	N = 256 participants; 109 patients (experimental group), 128 healthy (control group) Missing 19 (9 patients; 10 healthy) Female = 101 patients (92.7%); 114 healthy (89.1%); male = 8 patients (7.3%); 14 healthy (10.9%) Mean age = 33 (SD 17) patients; 36.5 (SD 16.8) healthy	To investigate the relationship among psychological status, QoL, self-esteem, social support, BID To explore risk factors of BID	Cross-sectional approach Quantitative study Level 4b IDB (Body Image Disruption), 5 scales; IDB > 0.30 = disturbance HADS Rosenberg self-esteem SSRS (social support rating scale) HRQoL and LupusQoL	BDI higher in patients than in healthy ($P<.05$ in all 7 dimensions) LupusQoL in patients: body image the best score BID association with: personal health insurance, diabetes complication, appearance of new rash, depression, anxiety, self-esteem Risk factors for BID: appearance of new rash, high anxiety

3.4 | Thematic categories

Three thematic categories were created from the themes that emerged from the data to organize and present the meta-aggregation[20,21] performed during the analysis of the articles: (1) depression and anxiety associates with body changes (hair loss, weight gain); (2) BI reflecting the disease; and (3) confrontations and interventions to promote acceptance and adaptation to the new image.

Within each category, the results of the qualitative and quantitative studies are presented separately for didactic purposes. However, the complementarity of these studies is emphasized in the answer to the question that guides this review. Figure 4 shows the clustering of the studies.

3.4.1 | Depression and anxiety associates with body changes (hair loss, weight gain)

The disease causes body changes and the medications used to treat it cause significant discomfort.

BI, self-concept, and the use of SLE medications

SLE is commonly associated with hair loss and changes in appearance,[23,40] as well as psychosocial needs[37] and symptoms related to vasoconstriction.[26] Emotional and sexual life is disturbed,[10,29] and QoL suffers as a result of the disease.[22,24] In addition, problems with facial appearance and weight have a strong correlation with BI.[27,40]

QoL related to BI mediates the relationship between pain and depressive symptoms.[25]

Medications sometimes made participants feel worse than before treatment, and the discontinuation of treatment or non-adherence to medication due to side effects was not uncommon.[11]

The process of changes in BI brought about by SLE involves uncertainties, losses, and pain and is permeated by anguish.[41]

Visibility of disease and the judgment of others

Gender identity is often influenced by BI. Once an SLE patient compares themselves to stereotypes,[11] they experience a sense of lost identity[35] and withdraw from social interaction. A sense of having no autonomy in deciding how to get better may also emerge, and the patient may submit themself to their sick body.[36] Furthermore, body shame and low self-esteem can increase feelings of self-destruction.[27,35]

SLE patients felt they did not recognize themselves when looking in the mirror because they felt that the skin and hair damage altered their appearance, making the disease visible, and, therefore, making the situation more serious.[34]There is dissatisfaction related to BI due to the visibility of skin changes, such as scars, alopecia and depigmentation and weight gain (due to the use of steroids).[38]

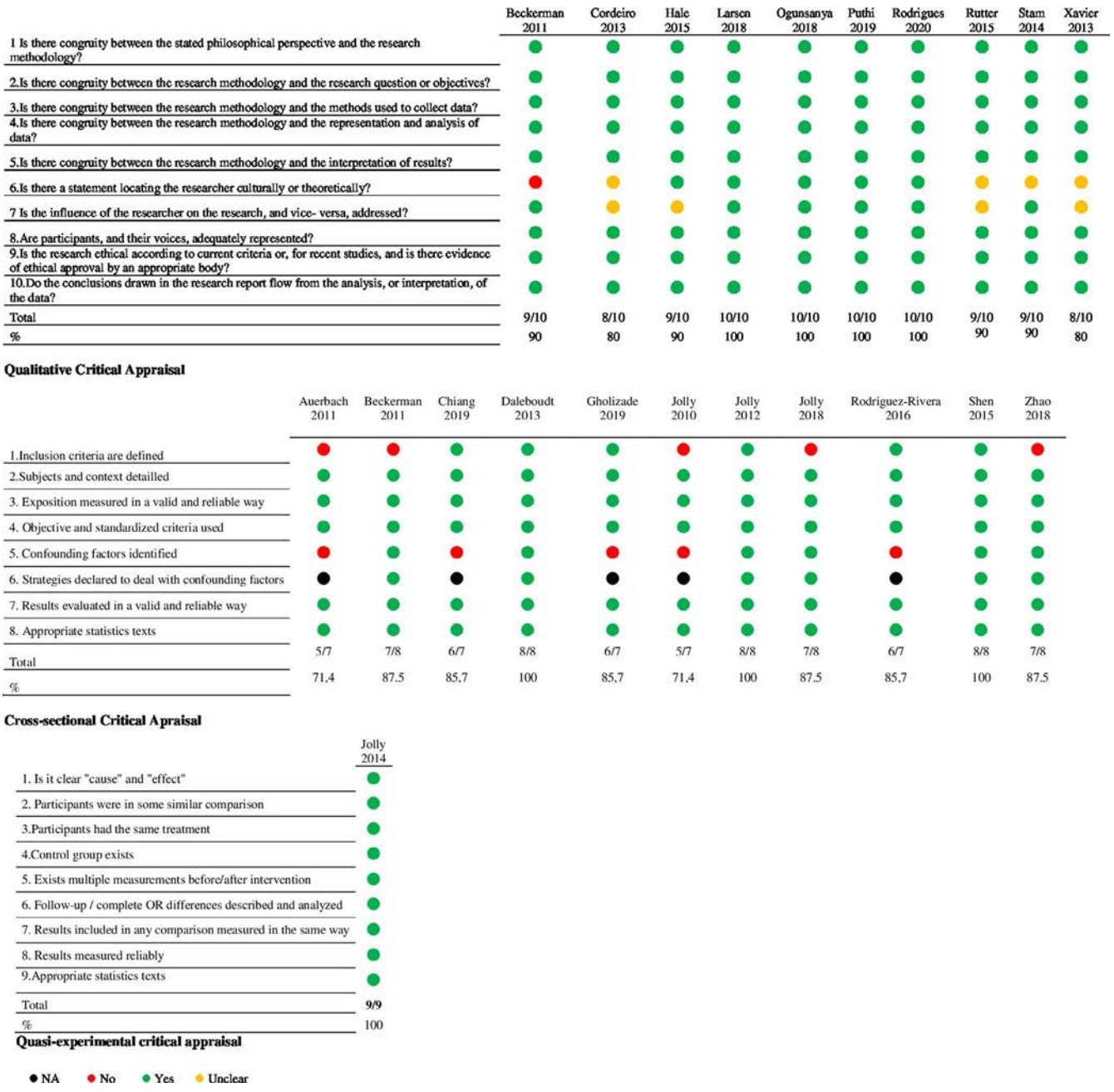

FIGURE 3 Quality appraisal of the included studies

3.4.2 | BI reflecting the disease

Appearance does not reflect who people with lupus nephritis are.[29,31] Ethnicity and other individual factors have an impact on the prevalence and severity of the disease, and may generate different feelings about BI in each person.[32] Many people with SLE use cosmetics to help their self-image,[31] a time-consuming and expensive process.[29]

Pain and swelling in the joints are common for these people, making them unable to participate in activities, which causes insecurity by altering their self-concept.[35] Pregnant women in the third trimester feel strange in their own bodies, often experiencing social isolation, sadness, and hopelessness related to this perception of their BI.[42]People expressed a desire to have the body they had before the onset of lupus symptoms.[38]

3.4.3 | Confrontations and interventions to promote acceptance of and adaptation to the new BI

Women with SLE experience major BID; 2 authors explore the relationship between the existence of lupus and BID,[10,27] and another highlights that women with SLE have a BI related with age but not with time of disease.[28] Confrontation with the new BI appears

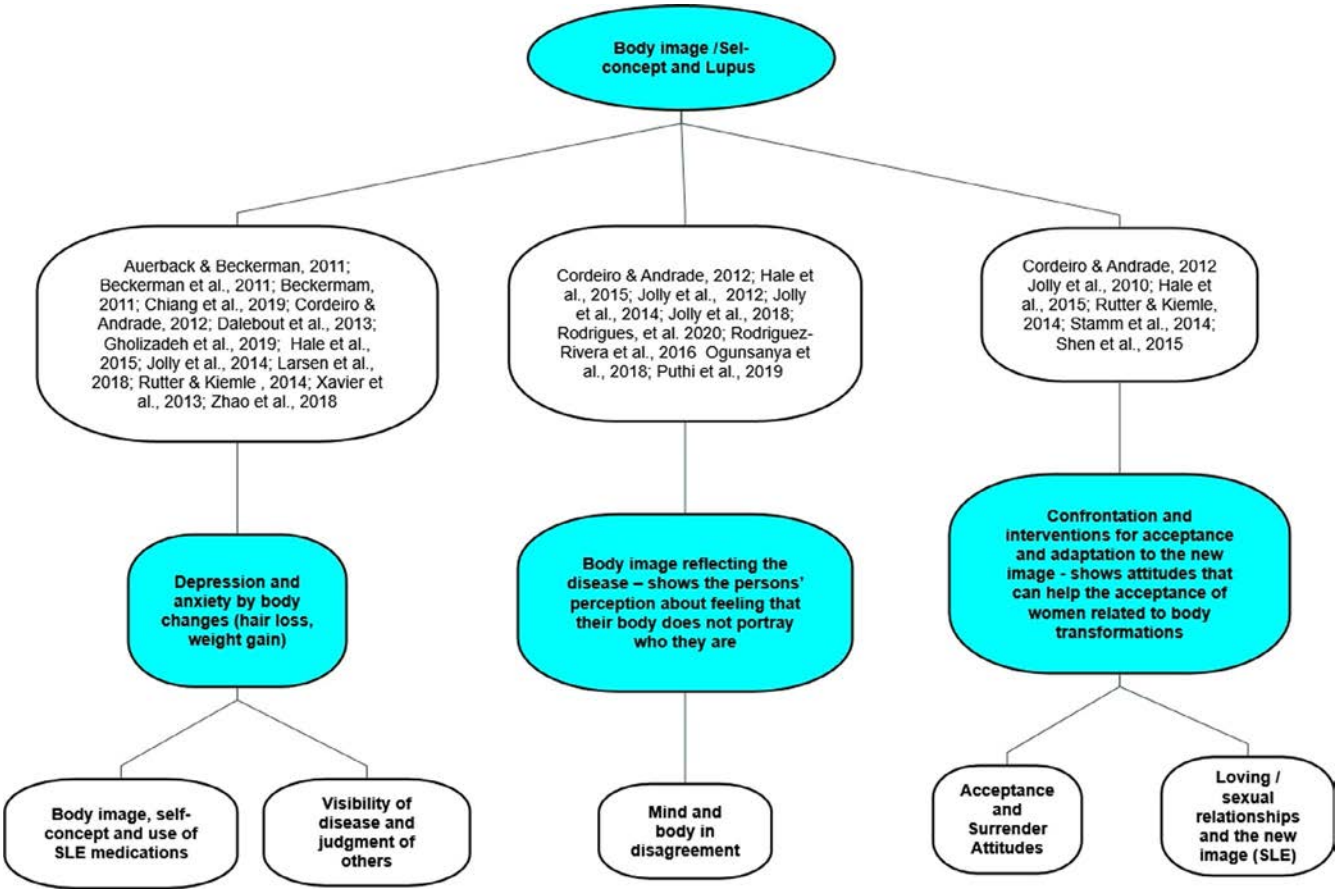

FIGURE 4 Clustering of included studies

to be relevant for the majority of SLE patients, and many change their lifestyles and attitudes to adapt to the disease and to their changing body.[32]

3.4.4 | Attitudes of acceptance and surrender

Acceptance of the disease, expressed as surrendered attitudes, suggests an internal lived experience.[35] Forms of communication such as irony, to better face the disease and remain unhurt, are common..[36] Better acceptance of oneself can be achieved by integrating into patient groups.[39]

3.4.5 | Loving/sexual relationships and acceptance of the changed body

Appearance-related concerns and sexual problems are associated[10] with SLE patients. Age, marital status, and BID are predictors of impairments between SLE patients and their partners, whereas BID scores and education are more closely associated with impairments in patients' sexual functioning.[10]

Unattractiveness is a major feeling reported by women with SLE, compared to those with other chronic diseases.[30] However, their emotions and feeling of coherence could explain the participants' perception of attractiveness.[30] Impaired sexual function, related to distress and deficiencies in the patient's social life, suggests a link between physical function and psychological function, which can contribute to sexual health and overall QoL.[10]

The female role in marriage intimacy, pertinent to most women, is often not fulfilled once BI issues are exacerbated.[36] A restricted life and the loss of experiences and relationships bring feelings of helplessness and small horizons.[36] These disease limitations significantly affect relationships.[10]

4 | DISCUSSION

4.1 | Considerations of study design and population representativeness

The results of this review are representative in terms of the SLE population. The 3394 participants in the studies came from 5 continents: Asia (Taiwan and China), Africa (South Africa), North and South America (USA and Brazil), Europe (Denmark, UK, Austria, Netherlands), and Oceania (New Zealand). Given the assessment of such a diverse population, it makes sense that BI, a burning problem among people with lupus, should be explored in different cultures.

4.2 | Considerations of measures of self-image

All instruments used in the studies included in this review are validated and widely used in research. However, we emphasize that while some instruments focused on BI,[10,22,27,31,32] others did not. Instead, they concentrated on issues such as QoL,[18,25,27-29] psychosocial needs,[23,24] quality of sleep, and sexual disfunction,[26,30] but used BI as a questionnaire domain to measure these factors; therefore, they provide information on BI for discussion, even if indirectly.

4.3 | Synthesis of research findings

Focusing on the changes and adaptations that occur in the BI of people with SLE (primary interest) and on their self-concept (secondary interest) (considering: [a] the perceptions that patients have of their bodily changes; [b] how patients deal with changes in their bodies; and (c) what are their perceptions of bodily changes), 3 thematic categories that were elaborated from the themes emerged from the data: (a) depression and anxiety caused by bodily changes (hair loss and weight gain); (b) BI reflecting the SLE, demonstrating the person's perception that their body does not portray who they are; and (c) coping and interventions for acceptance and adaptation to the new BI, indicating attitudes that can facilitate women's acceptance of bodily transformations.

The most reported and evaluated feelings associated with BI changes were depression,[22-27] anxiety,[10,23,24,27] social isolation,[42] anguish,[41] and helplessness.[36] These feelings can lead to illness if adequate support is not provided for coping with them, leading to aggravation of the condition of the person with SLE.[45] In addition, a feeling of loss and a lack of functionality related to the chronicity of the disease were reported.[39]

The condition of individuals with lupus is like that of chronic patients, and the limitations imposed can cause suffering, anguish, uncertainty, loss, and pain.[41] Despite having the same disease, with the same symptoms and even the same treatments (medication and dosage), each patient's experience of SLE is unique;[41] therefore, BI and self-concept can be altered by the conditions imposed by the disease, which may have an impact on sexual behavior[27] and personal relationships.[11]

Having and maintaining a positive attitude under disease conditions can be an actively difficult pursuit, and individuals with SLE must preserve their self-image despite the changes caused by the disease. Therefore, people with lupus report the use of "symbolic masks" to hide, such as keeping a smile on their face or appearing to be strong and cheerful, to meet the expectations of others, even if they are experiencing deep sadness[11] as a result of loss of identity,[34] which must be reconstructed.

People with lupus report a lack of support for the psychosocial aspects of the disease.[11] In the case of physical aspects, they feel that their bodies are no longer reliable compared to when they were healthy; thus, normal functioning becomes strange and activities of everyday life require great effort.[34]

4.4 | Limitations of primary studies

Although SLE most often affects women, some studies used mixed samples. Therefore, we chose to exclude studies that did not reflect the gender proportion indicated in the literature, which is 1 man to every 9 women with SLE.[12] From a gender perspective, studies should be designed to include only women or only men. However, we ensured that the studies considered in the review predominantly included female subjects; therefore, the themes identified here reflect the responses of women to BI and self-concept. The heterogeneity of the studies did not permit a deeper comparative analysis.

4.5 | Strengths of the systematic review

The present study provides a comprehensive explanation of the phenomena related to BI in SLE. As the participants of the selected studies were women, our review brings a gender perspective that may be different, given society's stereotypes of female BI.

4.6 | Implications for research

We argue that the effects of the psychosocial issues related to BI are essential considerations for health professionals when treating people with SLE.

Ongoing research examining the association of depression and anxiety with BID and SLE and potential associations with other mental disorders remains important.

The use of extensive questionnaires, which can identify different aspects of BI in people with SLE, and the addressing of cultural differences, nuances, and the meanings of each concept are also suggested. We recognize that there are limitations on the description of strategies or interventions that help to adapt to changes in BI of people with lupus; this is an important issue to focus on in research.

4.7 | Implications for clinical practice

The starting point for clinical practice is the consideration by health professionals of the effects of the disease and treatment on the external appearance of patients and recognition of the associations of BI with anxiety and depression. Likewise, professionals need to value the difficulties and psychosocial pressures faced by people with SLE that have an impact on the process of coping with the disease and changes in BI and self-concept. Professionals must value how existential experiences can result in a paradoxical and turbulent period after the individual is diagnosed with SLE. Orientation activities are the initial strategy to deal with this issue.

Knowledge and presentation of therapeutic options can prevent or limit adverse effects and ameliorate the negative impacts of BI on QoL. These options include: (a) the use of sunscreen; (b) early referral, screening, and treatment of active disease, thereby

limiting organ involvement and preventing impairment;[21,28] (c) training in the use of suitable cosmetics;[31] (d) early diagnosis, referral, and treatment of depression;[22,23,25] and (e) coping and self-esteem exercises.[31,34]

4.8 | Recommendations

We summarize 3 main recommendations for health professionals: (a) the need to value the importance of changes in BI and the self-concept of people with lupus, in the same way that their experience of pain and physical limitations is valued, since the literature exposes the impact of these changes; (b) the need to consider psychosocial problems and early screening for symptoms of illnesses due to depression, anxiety and relationship problems (eg, social isolation and helplessness) as the literature shows that they are associated with BI; and (c) the need to offer products, such as cosmetics, that can assist in coping with BI changes, since good results have been shown in a pilot study.

5 | CONCLUSION

Based on references available in databases, we believe to the best of our knowledge that our study is the first systematic review of BI and self-concept in people suffering from SLE. The most common changes reported were weight gain and changes in skin, hair, and joints, which impacted BI and functionality. The most reported feelings related to these changes were depression, anxiety, social isolation, helplessness, and anguish. Feelings of loss and lack of functionality were also related to the chronicity of the disease.

This study highlights the crucial importance of the dimensions of self-concept and BI for assessing QoL of individuals with lupus. These aspects can reveal the patient's relationship with SLE and how it can impact his/her life, particularly if these issues are not actively addressed by health professionals.

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CONFLICT OF INTEREST

None declared.

ETHICS APPROVAL

Formal ethicS approwval is not required for this type of study.

STATEMENT REGARDING INFORMED CONSENT

Formal consent is not required for this type of study.

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REFERENCES

1. Grogan S. Body image: Understanding body dissatisfaction in men, women and children. In: Grogan S, ed. *Body image: Understanding body dissatisfaction in men, women and children*, 3rd edn. New York: Routledge; 2017:250-xiv.
2. Jarry JL, Ip K. The effectiveness of stand-alone cognitive-behavioural therapy for body image: A meta-analysis. *Body Image*. 2005;2(4):317-331
3. Cash TF. Body image: past, present, and future. *Body Image*. 2004;1(1):1-5.
4. Tiggemann M. *Sociocultural perspectives on human appearance and body image. Body image: A handbook of science, practice, and prevention*, 2nd edn. New York: Guilford Press; 2011:12-19.
5. Watson B, Fuller-Tyszkiewicz M, Broadbent J, Skouteris H. The meaning of body image experiences during the perinatal period: A systematic review of the qualitative literature. *Body Image*. 2015;14:102-113.
6. Fuller-Tyszkiewicz M, Skouteris H, Watson BE, Hill B. Body dissatisfaction during pregnancy: a systematic review of cross-sectional and prospective correlates. *J Health Psychol*. 2013;18(11):1411-1421.
7. Davison TE, McCabe MP. Adolescent body image and psychosocial functioning. *J Soc Psychol*. 2006;146(1):15-30.
8. Dyer A, Borgmann E, Feldmann RE, et al. Body image disturbance in patients with borderline personality disorder: Impact of eating disorders and perceived childhood sexual abuse. *Body Image*. 2013;10(2):220-225.
9. Partridge KA, Robertson N. Body-image disturbance in adult dialysis patients. *Disabil Rehabil*. 2011;33(6):504-510.
10. Shen B, He Y, Chen H, et al. Body image disturbances have impact on the sexual problems in Chinese systemic lupus erythematosus patients. *J Immunol Res*. 2015;2015: 204513.
11. Hale ED, Radvanski DC, Hassett AL. The man-in-the-moon face: a qualitative study of body image, self-image and medication use in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2015;54(7):1220-1225.
12. Borella E, Lojacono A, Gatto M, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. *Immunol Res*. 2014;60(2–3):170-176.
13. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(8):2677-2686.
14. Pastore DEA, Costa ML, Parpinelli MA, Surita FG. A critical review on obstetric follow-up of women affected by systemic lupus erythematosus. *Rev Bras Ginecol Obstet*. 2018;40(04):209–24
15. La Paglia GMC, Leone MC, Lepri G, et al. One year in review 2017: systemic lupus erythematosus. *Clin Exp Rheumatol*. 2017;35(4):551-561.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
17. Aringer M, Costenbader K, Daikh D, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(9):1151.
18. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3(2):77-101.
19. Jordan Z, Lockwood C, Munn Z, Aromataris E. Redeveloping the JBI model of evidence based healthcare. *Int J Evid Based Healthc*. 2018;16(4):227-241.

20. Joanna Briggs Institute. *Reviewers' Manual: Methodology for JBI Mixed Methods Systematic Reviews. [Internet]*. Adelaide: JBI; 2014. Available from: http://joannabriggs.org/assets/docs/sumari/ReviewersManual_Mixed-Methods-Review-Methods-2014-ch1.pdf
21. Cardoso V, Trevisan I, Cicolella DA, Waterkemper R. Systematic review of mixed methods: method of research for the incorporation of evidence in nursing. *Texto Contexto Enferm* [Internet]. 2019;28:e20170279.
22. Jolly M, Pickard AS, Mikolaitis RA, et al. Body image in patients with systemic lupus erythematosus. *Int J Behav Med*. 2012;19(2):157-164.
23. Auerbach C, Beckerman N. What social workers in health care should know about lupus: A structural equation model. *Health Soc Work*. 2011;36(4):269-278.
24. Beckerman NL, Auerbach C, Blanco I. Psychosocial dimensions of SLE: implications for the health care team. *J Multidiscip Healthc*. 2011;4:63-72.
25. Gholizadeh S, Azizoddin DR, Mills SD, et al. Body image mediates the impact of pain on depressive symptoms in patients with systemic lupus erythematosus. *Lupus*. 2019;28(9):1148-1153.
26. Chiang YC, Huang JL, Wang CH, Lee HC, Lee MY, Hsiao YC. Symptom clustering in patients with childhood-onset systemic lupus erythematosus. *J Adv Nurs*. 2019;75(1):54-62.
27. Zhao Q, Chen H, Yan H, et al. The correlations of psychological status, quality of life, self-esteem, social support and body image disturbance in Chinese patients with Systemic Lupus Erythematosus. *Psychol Health Med*. 2018;23(7):779-787.
28. Jolly M, Pickard SA, Mikolaitis RA, Rodby RA, Sequeira W, Block JA. LupusQoL-US benchmarks for US patients with systemic lupus erythematosus. *J Rheumatol*. 2010;37(9):1828-1833.
29. Rodríguez-Rivera DV, Rodríguez-Navedo Y, Nieves-Plaza M, Vilá LM. Patient-reported outcome measures in a population of medically indigent patients with systemic lupus erythematosus in Puerto Rico. *SAGE Open Med*. 2016;4:2050312116670927.
30. Daleboudt GMN, Broadbent E, McQueen F, Kaptein AA. The impact of illness perceptions on sexual functioning in patients with systemic lupus erythematosus. *J Psychosom Res*. 2013;74(3):260-264.
31. Jolly M, Peters KF, Mikolaitis R, Evans-Raoul K, Block JA. Body image intervention to improve health outcomes in lupus: a pilot study. *J Clin Rheumatol*. 2014;20(8):403-410.
32. Jolly M, Toloza S, Goker B, et al. Disease-specific quality of life in patients with lupus nephritis. *Lupus*. 2018;27(2):257-264.
33. Grossoehme DH. Overview of qualitative research. *J Health Care Chaplain*. 2014;20(3):109-122.
34. Cordeiro SM, Andrade MBT. Ser mulher e ter lúpus [Being a female and having lupus] [Ser mujer y tener lúpus]. *Revista Enfermagem UERJ*; 2012;20(5): Número Especial 1. 2013 05/08/.
35. Larsen JL, Hall EOC, Jacobsen S, Birkelund R. Being in a standstill-of-life: women's experience of being diagnosed with systemic lupus erythematosus: a hermeneutic-phenomenological study. *Scand J Caring Sci*. 2018;32(2):654-662.
36. Rutter SJ, Kiemle G. Exploring the social and interpersonal experiences of South Asian women with a diagnosis of Systemic Lupus Erythematosus. *Psychol Health*. 2015;30(3):318-335.
37. Beckerman NL. Living with lupus: a qualitative report. *Soc Work Health Care*. 2011;50(4):330-343.
38. Ogunsanya ME, Brown CM, Lin D, Imarhia F, Maxey C, Chong BF. Understanding the disease burden and unmet needs among patients with cutaneous lupus erythematosus: A qualitative study. *Int J Womens Dermatol*. 2018;4(3):152-158.
39. Stamm T, Hieblinger R, Boström C, et al. Similar problem in the activities of daily living but different experience: a qualitative analysis in six rheumatic conditions and eight European countries. *Musculoskeletal Care*. 2014;12(1):22-33.
40. Phuti A, Schneider M, Makan K, Tikly M, Hodkinson B. Living with systemic lupus erythematosus in South Africa: a bitter pill to swallow. *Health Qual Life Outcomes*. 2019;17(1):65.
41. Xavier HV, Zanotti SV, Ribeiro MAT. Concepções atribuídas por mulheres ao processo de adoecimento por Lúpus. *Psicologia em Estudo*. 2013;18:223-233.
42. Rodrigues L, Alves VLP, Sim-Sim MMF, Surita FG. Perceptions of women with systemic lupus erythematosus undergoing high-risk prenatal care: A qualitative study. *Midwifery*. 2020;87:102715.
43. Dedoose Version 8.0.35. *Web Application for Managing, Analyzing, and Presenting Qualitative and Mixed Method Research Data*. Los Angeles: Socio Cultural Research Consultants, LLC; 2018.
44. Edhlund BM. *NVivo 10 essentials: your guide to the world's most powerful data analysis software*. Stallarholmen, Sweden: Form & Kunskap AB; 2012.
45. Zhang L, Fu T, Yin R, Zhang Q, Shen B. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. *BMC Psychiatry*. 2017;17(1):70.

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REVIEW

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Prevalence of obstructive sleep apnea among patients with rheumatoid arthritis and its association with age and body mass index: A systematic review and meta-analysis

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Abstract

Aim: The study aims to recognize the prevalence and possible risk factors of obstructive sleep apnea among individuals with rheumatoid arthritis (RA).

Methods: We searched PubMed, Scopus, EMBASE, and Google scholar for potential studies published before the October 30, 2020. The study characteristics, obstructive sleep apnea (OSA) events, and various types of rheumatic diseases were extracted, and the meta-analysis method was used to pool the estimates.

Results: We identified eight studies with 37 285 patients for this meta-analysis. The overall pooled prevalence of OSA was 29.8% (95% confidence interval [CI] 15.2-46.7; $I^2 = 99.6\%$) in the patients with RA. Age was higher in RA patients with OSA but this was not significant. Body mass index (BMI) was significantly associated with OSA in the RA population (standardized mean difference 1.08; $P = 0.044$). Assessment based on the Berlin Questionnaire© for Sleep Apnea resulted in a more precise estimate of OSA prevalence with reduced heterogeneity (prevalence 45.3%; 95% CI 37.4-53.3; $I^2 = 58.8\%$).

Conclusion: Prevalence of OSA among the RA cohort was 29.8% with significant heterogeneity. However, the prevalence was 45.3% when studies were restricted to the OSA diagnosis based on the Berlin questionnaire with very low heterogeneity. Higher BMI is the principal risk factor of OSA development in RA. Hence, controlling BMI could be a preventive strategy for OSA among RA patients.

KEYWORDS

meta-analysis, obstructive sleep apnea, rheumatoid arthritis, systematic review

1 | INTRODUCTION

In a number of rheumatic diseases akin to rheumatoid arthritis (RA)—osteoarthritis, systemic lupus erythematosus, Sjögren syndrome, fibromyalgia, juvenile idiopathic arthritis, systemic sclerosis, spondyloarthritis, and Behçet syndrome—sleep abnormalities comprising reduced sleep, sleep fragmentation, and insomnia have been recognized.[1] Sleep apnea is an under-recognized comorbidity among rheumatology patients and its presence may adversely affect the evaluation of rheumatic disease activity and treatment responses.[2]

Protocol registration number: CRD42020218713.

Obstructive sleep apnea (OSA) is increasingly recognized to be a significant public health issue.[3] OSA is a specific sleep disturbance that is characterized by recurring apneas (cessation of airflow for 10 seconds or longer) or hypopneas during sleep. Hypopneas may be defined as a 30% reduction in airflow for at least 10 seconds accompanied by a 4% reduction in oxygen saturation; an alternative definition of hypopnea is a reduction of airflow by 50% for 10 seconds or more with an associated 3% reduction in oxygen saturation.[4] OSA is defined by the American Academy of Sleep Medicine as repetitive episodes of upper airway obstruction occurring during sleep and usually associated with a reduction in oxygen saturation.[5] Obstructive apneas are defined as near-complete (>90%) cessations in airflow for more than 10 seconds during sleep, despite ventilatory effort, and hypopneas are generally defined as reductions in airflow by more than 30% with concurrent reductions in oxyhemoglobin saturation by at least 3% or arousals from sleep.[4] Collectively, the number of apneas and hypopneas per hour of sleep has been termed the apnea-hypopnea index (AHI), in which the presence of OSA is defined as an AHI of 5 or more events per hour. The AHI is also used to categorize disease severity; persons with an AHI of 5 to 15, 16 to 30, or more than 30 events per hour are considered to have mild, moderate, or severe OSA, respectively.[6]

Clinical features associated with OSA, particularly in men, include a history of apneic pauses during sleep as well as frequent and loud snoring.[7] The underlying pathophysiology of OSA involves the partial or complete collapse of the posterior oropharynx during sleep. Risk factors for OSA in adults include increasing age, obesity (body mass index [BMI] >30 kg/m^2), and larger neck circumference (>43 cm in men), although OSA can occur in individuals with none of these risk factors.[8] OSA is also associated with an increased risk of cardiovascular disease. Among a population-based cohort of more than 6000 participants (age >40 years), those with an AHI in the upper quartile (>11 events per hour) were more likely to have hypertension, stroke, coronary artery disease, or heart failure, even after adjustment for BMI and other cardiovascular risk factors.[9] A recent review shows that there is a substantial deficit in published research in OSA despite it being a highly prevalent condition leading to many adverse outcomes.[10]

Along with the other general risk factors such as increasing age, BMI, and neck circumference, rheumatic diseases are a particular risk for OSA.[7] In a mixed general rheumatology clinic population, which employed the Berlin questionnaire, 35.2% of 423 participants were classified as being at high risk for sleep apnea.[11] These reports indicate that a substantial proportion of patients with rheumatic disorders have co-existing sleep apnea or are at high risk for the same.[2] With the recognized increased prevalence of cardiovascular disease in rheumatological disorders, concurrent OSA is likely to further contribute to an increased mortality among this diagnostic class.[12,13]

This systematic review is aimed at recognizing the prevalence and risk factors of OSA among RA patients. Knowledge in this regard will help in the early detection and treatment of OSA in this rheumatic subgroup, which in turn will improve quality of life and reduce cardiovascular mortality.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategy

We followed the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] for conducting and reporting this study. Our protocol was registered on the prospective register of systematic reviews (PROSPERO) at the center for reviews and dissemination, University of York, UK under the registration number CRD42020218713. We conducted a systematic literature search using multiple electronic databases including PubMed, Scopus, and EMBASE until October 30, 2020. The Google Scholar database was also examined up to 10 pages to identify and retrieve relevant studies that were overlooked. In addition, references from review or other systematic review studies were cross-checked to retrieve any additional articles that were missed during the initial search. The search strategy was designed to retrieve all published articles that reported OSA and various types and forms of arthritis. We applied various combinations of Boolean operators by using the following keywords for our search: [("prevalence" OR "risk factors") AND ("obstructive sleep apnea" OR "OSA" OR "Pickwickian syndrome" OR "syndrome Z") AND "arthritis"]. Two authors (BT and MP) reviewed all articles to eliminate any duplicate studies. Studies with similar authors, the duration of data collection, and the location of the study were strictly matched to further identify any duplicated study/databases. All the duplicate studies were omitted from the analyses.

2.2 | Study selection

Studies were eligible for inclusion in our systematic review if they met the following criteria: (a) originally published in the English language; (b) contained information of cases with OSA OR high-risk/severe sleep apnea among RA cases; (c) included confirmed diagnosis of OSA; (d) conducted on human patients; and (e) published as an original investigation OR presented in a conference.

Studies lacking diagnostic information, involving patients not affected with RA, conducted on animals, those that were reviews, letters, or guidelines, and those that included sleep disorders other than sleep apnea were excluded from the analysis. In addition, any studies published as case reports or case series were also excluded from the analyses.

2.3 | Data extraction

The following relevant information on study characteristics were extracted from each study: name of the first author; year of publication; country where the study was conducted; study design; the total number of patients (total sample size); number of patients with and without OSA; disease (RA) duration; the average age in years with standard deviation or interquartile range (in total, among cases with and without OSA); the number of males and females (in total, among

cases with and without OSA); the average BMI with standard deviations or interquartile range (in total, among cases with and without OSA); and study-specific target population. All such information was extracted and recorded in an EXCEL datasheet by one author (BT) and verified by another author (MP).

2.4 | Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS) scale was used for critical appraisal of study quality.[15] Two authors (MP and PS) independently graded the quality of the included studies. Consensus discussions were carried out among all four authors to resolve any disagreements. The first eight items of MINORS were used in this study to assess the methodological quality of non-comparative studies. A score from 0 to 2 was given for each of the items according to whether the item-related attributes were reported in the included studies in addition to grading their adequacy—0, unreported; 1, reported but inadequate; or 2, reported and adequate). The total score assigned to each study was categorized according to Sundemo et al[16] for the quality assessment. The following were details of the possible scoring for non-comparative studies: 0-4, very low quality; 5-8, low quality; 9-12, fair quality; and 13-16, high quality.

2.5 | Statistical analysis

We estimated the pooled proportion with 95% confidence interval (CI) of OSA using a random-effects meta-analysis of proportions with the DerSimonian and Laird (D&L) method.[17,18] An a priori random-effects model was applied due to considerable heterogeneity across the studies. The pooled proportion with 95% CI of female patients was estimated and compared among the arthritis patients with and without OSA using the D&L method. We applied the Freeman-Tukey double arcsine method for computing a 95% CI for proportion estimation to obtain a reasonable range. The D&L method was also used to estimate the pooled weighted mean difference effect size and 95% CI for age and BMI between the patients with and without OSA. Heterogeneity was examined using the I^2 statistic.[19] An I^2 statistic with more than 75% suggests presence of high heterogeneity in the estimate across the studies.[19] All statistical analyses were conducted using STATA 15.1 (StataCorp, College Station, TX, USA). Possible sensitivity and subgroup analyses were performed to evaluate the reasons for heterogeneity and to identify factors associated with larger effect sizes.

3 | RESULTS

3.1 | Characteristics of included studies

We identified 94 unique records from the 136 searched documents from various electronic databases and manual searches. A total of 35 out of these 94 records were found to be eligible for full-text review, out of which a total of eight studies reported the burden of OSA among RA patients. These were found to be eligible for inclusion in our pooled analysis. A total of 27 studies were ineligible and were excluded for various reasons: not related with the study objective (13 studies), review articles (four studies), case series (six studies), and full texts unavailable (four studies). Figure 1 shows the search pattern and exclusion of articles with specific reasons at each step.

Out of the eight included and unique studies, three were conducted in the USA,[20-22] and the rest were conducted in Japan,[23] Saudi Arabia,[24] Taiwan,[25] Egypt,[26] and Brazil.[27]

These eight studies yielded a total of 585 patients with OSA among the total sample size of 37 285 patients with RA. The total reported number of women was 29 030 (78%). The range of reported age and BMI were 40.3-67.2 years and 23.8-32.1 kg/m^2, respectively. The reported range of the disease duration for these patients was from 6 to 23 years. Table 1 shows the summary of study characteristics of all the included studies.

3.2 | Quality synthesis of included studies

In our quality appraisal, we observed a high quality of conducting and reporting in all eight studies (Table 2).

3.3 | Proportion of OSA in patients with rheumatoid arthritis diseases

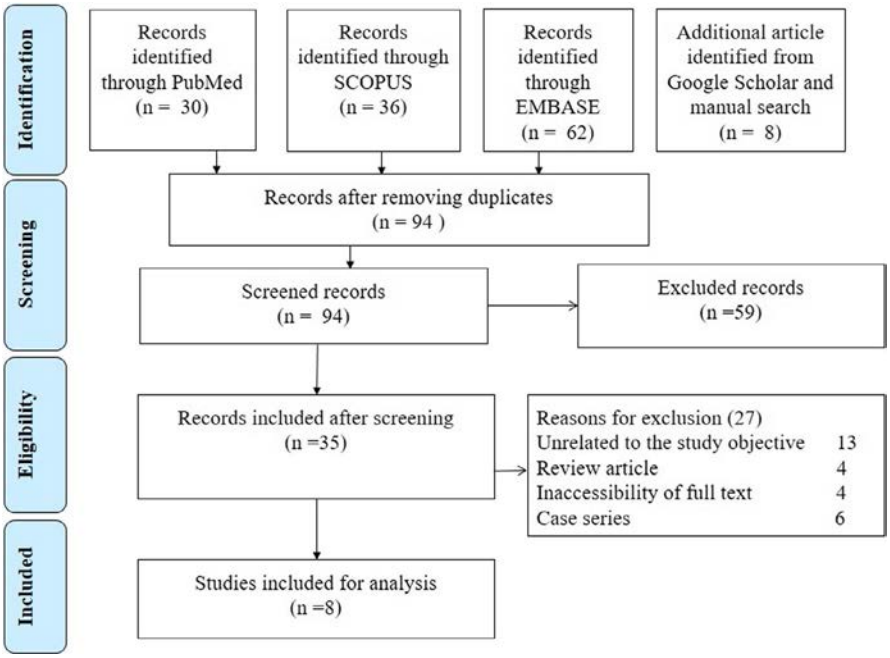
Utilizing random-effects meta-analysis, Figure 2 shows the pooled estimate of OSA prevalence among patients with RA. The OSA prevalence was observed as 29.8% (95% CI 15.2-46.7; $P < 0.001$). We found significant and substantial heterogeneity in the estimated OSA prevalence ($I^2 = 99.6\%$, $P \leq 0.001$).

Sensitivity analysis was performed on the basis of publication period and diagnostic criteria (Table 3). OSA prevalence was 79.3% (95% CI 60.3-92.0) in a single study by Shoda et al[23] in RA patients with occipitocervical lesions, which might be producing the significant observed heterogeneity. After excluding this study,[23] the OSA prevalence was reduced to 23.9% (95% CI 10.5-40.6) without any reduction in the heterogeneity measure ($I^2 = 99.6\%$, $P \leq 0.001$; Table 3). Sensitivity analysis based on the diagnostic criteria revealed that the OSA prevalence was 63.5% and 45.3% based on AIH criteria and the Berlin questionnaire, respectively. Assessment based on the Berlin questionnaire substantially reduced the study-level heterogeneity ($I^2 = 58.8\%$; $P = 0.10$).

3.4 | Association of demographic characteristics with OSA

The association of demographic characteristics with OSA prevalence is reported in Table 4. In random-effects meta-analysis of

FIGURE 1 PRISMA flow diagram



standardized mean difference (SMD), we found that the average age was higher among OSA patients in comparison to controls but this was not statistically significant (SMD 0.29; 95% CI −0.02 to 0.59; $P = 0.063$) in RA patients with minimal heterogeneity ($I^2 = 32.0\%$). BMI was significantly associated with OSA among the RA patients (SMD 1.08; 95% CI 0.3-2.12; $P < 0.044$; $I^2 = 92.3\%$) with substantial heterogeneity.

4 | DISCUSSION

This is the first review to systematically evaluate the prevalence of OSA in patients with various rheumatic diseases, especially RA. We observed that OSA was prevalent in 29.8% of patients with RA. Previous evidence claims that a maximum of 50% of RA patients can have OSA.[21] A previous nationwide population-based study (included in our meta-analysis) reported an increased rate of OSA in RA patients compared with non-RA patients.[25] Furthermore, patients with OSA have also been observed to have elevated levels of numerous inflammatory molecules including circulating acute-phase markers and pro-inflammatory cytokines.[28] Recently there has been a better understanding between the relationship of RA and OSA through major achievements in research. OSA has been found to be one of the major reasons for this increase in inflammatory factors caused by hypoxia and sleep disorder, which can further lead to aggravation of the chronic inflammatory responses recognized in RA.[29]

A high prevalence of OSA was reported in RA patients with occipitocervical lesions (79.3%), which further indicates that occipitocervical lesions are a risk factor for OSA in RA.[23] Several studies also reported that OSA was found to be common in RA patients with occipitocervical disease.[30,31] Previous evidence has advocated that destruction of the upper cervical spine by RA, resulting in potential compression of the medulla, may be a causative factor for OSA as well as for central sleep apnea.[32] Sleep apnea in patients with RA who have occipitocervical lesions (with upper cervical lesions) potentially improves when they undergo posterior fusion.[33]

Long-term systemic inflammatory responses exacerbate the inflammatory response of the synovial membrane as well and hence the clinical symptoms of RA. Apparently, improving sleep quality and reducing the levels of inflammatory factors can help to ease the clinical symptoms of RA and improve the patients' quality of life. The relationship between RA and OSA seems to be bidirectional. Uncontrolled RA results in anatomical changes leading to OSA, and OSA causes significant morbidity and mortality within this patient population. The identification and treatment of OSA in this population is crucial for improved health outcomes and management of disease burden. Immobility due to arthritic knees or hips may predispose to weight gain, which is a known risk factor for OSA. Therapies aimed at adequate disease control in RA leading to a reduced inflammatory state can impede OSA development and result in better sleep quality among RA patients.

In our meta-analysis, we observed that increasing age was promisingly associated with OSA in the RA population, though it was not statistically significant. This may be related to comorbidities like physical inactivity and obesity among elderly RA patients.

Our study found that BMI was significantly associated with OSA in RA. Consensus on the association between BMI and sleep quality is lacking in existing shreds of evidence. Further research on BMI and obesity phenotype-related findings is warranted to evaluate the OSA risk prediction in RA.

Additionally, we observed a high level of heterogeneity in the estimated prevalence of OSA. Different diagnostic criteria reported in different studies may be the cause of such high heterogeneity.

TABLE 1 Summary of the studies characteristics

Author	Country	Study design	Total sample size	OSA cases	Diagnostic criteria	Disease duration (years); mean (SD)	Female	Age (years); mean (SD)	BMI (in kg/m^2); mean (SD)
Shen et al 2016	Taiwan	Cohort	33 418	67	ICD-9-CM	NA	25 943	54.0 (13.9)	NA
Wilton et al 2018	USA	Cohort	792	97	Physician diagnosis paired with abnormal sleep study	14.8 (7.8)	556	55.9 (15.7)	27.7 (5.9)
Mustafa et al 2019	Saudi Arabia	Cross-sectional	101	37	Berlin questionnaire	7.8 (6.6)	96	48.7 (14.6)	32.1 (10.2)
Katz et al 2020	USA	Cross-sectional	2639	211	Physician diagnosis	23.0 (12.8)	2168	67.2 (11.4)	NA
Shoda et al 2009	Japan	Cross-sectional	29	23	AHI >5 events/hour	NA	26	NA	NA
Reading et al 2009	USA	Cross-sectional	164	82	Berlin questionnaire	NA	118	62.9 (12.2)	28.4 (5.5)
Fauda et al 2014	Egypt	Cross-sectional	30	14	AHI ≥5 events/hour	6 (2.8)	30	40.3(6.2)	23.8 (5.3)
Goes et al 2017	Brazil	Cross-sectional	112	54	Berlin questionnaire	NA	93	NA	27.5 (6.0)

Abbreviations: AHI, apnea and hypopnea index; BMI, body mass index; ICD-9-CM, the International Classification of Diseases, Ninth Revision, Clinical Modification; OSA, obstructive sleep apnea; SD, standard deviations; NA, not available.

TABLE 2 Quality appraisal of included studies according to MINORS assessment

	Criteria for non-comparative study								
Name of the first author	Clearly Stated aim	Inclusion of Consecutive patients	Prospective Collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to theaim of the study	Loss tofollow upless than 5%	ProspectiveCalculation ofthe study size	Total score
Shen et al 2016	2	2	0	2	2	2	2	2	14
Wilton et al2018	2	2	0	2	2	2	2	2	14
Mustafa et al2019	2	2	2	2	2	2	2	1	15
Katz et al 2020	2	2	0	2	2	2	2	2	14
Shoda et al 2009	2	2	2	2	2	2	2	0	14
Reading et al 2009	2	2	0	2	2	2	2	1	13
Fauda et al 2014	2	1	2	2	2	2	2	0	13
Goes et al 2017	2	0	2	2	2	2	2	0	12

FIGURE 2 Prevalence of obstructive sleep apnea in rheumatoid arthritis

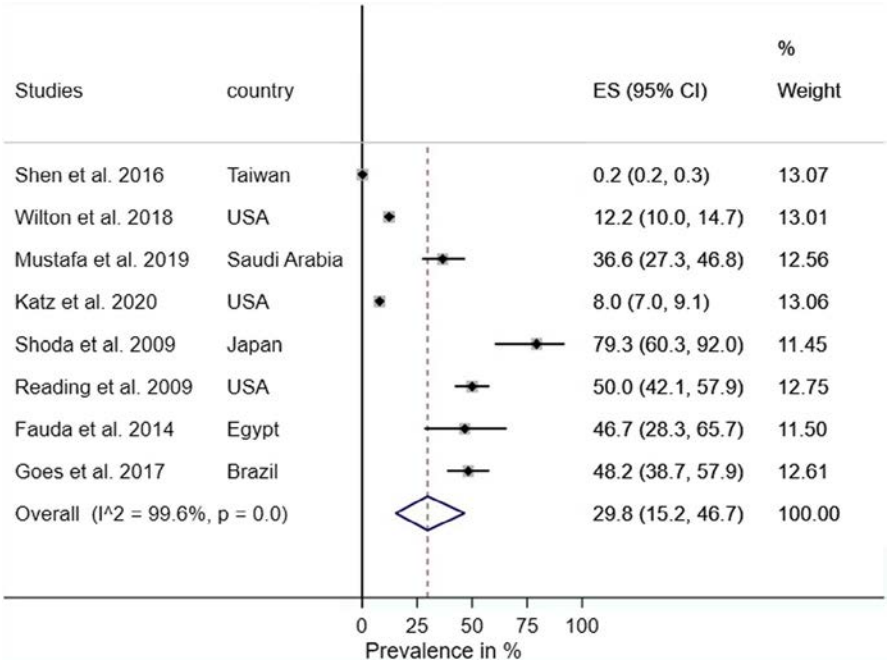


TABLE 3 Sensitivity analysis in obstructive sleep apnea prevalence estimation in patients with rheumatoid arthritis

	Rheumatoid arthritis			
Population	**N**	**Prevalence (95% CI)**	***P* value**	**I^2**
Age group				
≤60 years	4	18.0 (2.6-42.0)	<0.001	99.4%
>60 years	2	9.5 (8.5-10.7)	<0.001	ID
After excluding Shoda et al 2009[a]	7	23.9 (10.5-40.6)	<0.001	99.6%
Publication period				
Up to 2010	2	54.7(47.5-61.7)	<0.001	ID
After 2010	6	19.9 (7.8-35.7)	<0.001	99.6%
Diagnostic criteria				
AIH	2	63.5(50.5-75.5)	<0.001	ID
Berlin questionnaire	3	45.3 (37.4-53.3)	<0.001	58.8%
Other miscellaneous	3	5.2(0.03-17.8)	<0.001	ID

Abbreviations: AIH, apnea and hypopnea index; CI, confidence interval; ID, insufficient data.
I^2 is the percentage of variation in the obstructive sleep apnea prevalence across studies due to heterogeneity.
[a]Study population comprises rheumatoid arthritis patients with occipitocervical lesions.

Further, other study-level characteristics need to be explored for heterogeneity assessment.

4.1 | Strength and limitations

Our study has several strengths. First, it is, to date, the most comprehensive meta-analysis on the prevalence of OSA in the rheumatic disease population. Second, this meta-analysis is based on high-quality studies. Third, it is based on strict selection criteria to include various populations within RA.

Our study also has some limitations. We observed significant heterogeneity across the studies while pooling the prevalence estimates, which could be merely explained by either subgroup analyses or meta-regressions. Although we tried heterogeneity assessment by conducting sensitivity analysis, and observed the minimal heterogeneity based on the Berlin questionnaire criteria, other criteria may also cause the heterogeneity and require additional assessment. It is recommended to assess publication bias by statistical methods, however, current available methods, such as the funnel plot and the Egger regression test, are not considered useful tools in studies of proportions.[34] Moreover, tests for funnel plot asymmetry can

TABLE 4 Association of demographic characteristics of patients with obstructive sleep apnea

	Rheumatoid arthritis			
Characteristics	**N**	I^2	**Effect size (95% CI)**	***P* value**
Age (in years); SMD	4	32.0%	0.29 (−0.02 to 0.59)	0.063
BMI (kg/m^2); SMD	5	92.3%	1.08 (0.03-2.12)	0.044

Abbreviation: BMI, body mass index; CI, confidence interval; I^2, magnitude of heterogeneity variances; SMD, standardized mean difference.

be used in the presence of at least 10 studies included in a meta-analysis. For these reasons, such concerns must be addressed in future studies.

5 | CONCLUSION AND RECOMMENDATION

There is a high prevalence of OSA in patients with RA. Higher BMI is a principal risk factor of OSA whereas increasing age is promisingly associated with OSA in RA patients. These results support a high index of suspicion among patients with RA that may facilitate recognition of possible OSA. Utilization of a simple screening questionnaire for OSA may be of additional benefit. Referral to a dedicated sleep clinic for further diagnostic assessment and therapy as required would be appropriate. Treatment for co-existing OSA in patients with RA may prove beneficial in terms of future cardiovascular and respiratory morbidity, as well as potentially improving measures of inflammation, pain, and fatigue.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

BT and PP planned and designed the study; BT and MP contributed to study methods, and extracted and analyzed the data; MP and PS assessed and graded the methodological quality of included studies and wrote the study findings; BT and PP contributed to the discussion; all authors edited the manuscript for their intellectual input. All authors read and approved the final manuscript.

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REFERENCES

1. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev*. 2008;12(3):211-228.
2. Taylor-Gjevre RM, Gjevre JA, Nair B, Skomro R, Lim HJ. Hypersomnolence and sleep disorders in a rheumatic disease patient population. *J Clin Rheumatol*. 2010;16(6):255-261.
3. Leger D, Bayon V, Laaban JP, Philip P. Impact of sleep apnea on economics. *Sleep Med Rev*. 2012;16(5):455-462.
4. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep*. 2009;32(2):150-157.
5. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st edition. Westchester, IL: American Academy of Sleep Medicine, cop.; 2007.
6. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med*. 2019;380(15):1442-1449.
7. Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. *Thorax*. 1992;47(2):101-105.
8. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1(1):1–21.
9. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*. 2008;118(10):1080-1111.
10. Araslanova R, Paradis J, Rotenberg BW. Publication trends in obstructive sleep apnea: Evidence of need for more evidence. *World J Otorhinolaryngol Head Neck Surg*. 2017;3(2):72-78.
11. Senaratna CV, Perret JL, Matheson MC, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev*. 2017;36:116-124.
12. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med*. 2008;121(10 Suppl 1):S9-14.
13. Selim B, Won C, Yaggi HK. Cardiovascular consequences of sleep apnea. *Clin Chest Med*. 2010;31(2):203-220.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine*. 2009;6(7):e1000100.
15. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716.
16. Sundemo D, Hamrin Senorski E, Karlsson L, et al. Generalised joint hypermobility increases ACL injury risk and is associated with inferior outcome after ACL reconstruction: a systematic review. *BMJ Open Sport Exerc Med*. 2019;5(1):e000620.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
18. Pathak M, Dwivedi SN, Thakur B. Comparative role of various methods of estimating between study variance for meta-analysis using random effect method. *Clin Epidemiol Glob*. 2020;8(1):185-189.
19. Pathak M, Dwivedi SN, Deo SVS, Sreenivas V, Thakur B. Which is the preferred measure of heterogeneity in meta-analysis and why? A Revisit. *Biostat Biometrics Open Acc J*. 2017;1(1):1–7.

20. Katz P, Pedro S, Michaud K. Risk of Obstructive Sleep Apnea in Rheumatoid Arthritis [abstract]. *Arthritis Rheumatol*. 2018;70(suppl 10).
21. Reading SR, Crowson CS, Rodeheffer RJ, Fitz-Gibbon PD, Maradit-Kremers H, Gabriel SE. Do rheumatoid arthritis patients have a higher risk for sleep apnea? *J Rheumatol*. 2009;36(9):1869-1872.
22. Wilton KM, Matteson EL, Crowson CS. Risk of obstructive sleep apnea and its association with cardiovascular and noncardiac vascular risk in patients with rheumatoid arthritis: a population-based study. *J Rheumatol*. 2018;45(1):45-52.
23. Shoda N, Seichi A, Takeshita K, et al. Sleep apnea in rheumatoid arthritis patients with occipitocervical lesions: the prevalence and associated radiographic features. *Eur Spine J*. 2009;18(6):905-910.
24. Mustafa M, Bawazir Y, Merdad L, et al. Frequency of sleep disorders in patients with rheumatoid arthritis. *Open Access Rheumatol*. 2019;11:163-171.
25. Shen TC, Hang LW, Liang SJ, et al. Risk of obstructive sleep apnoea in patients with rheumatoid arthritis: a nationwide population-based retrospective cohort study. *BMJ Open*. 2016;6(11):e013151.
26. Fouda N, Dayem AA. Obstructive sleep apnea in patients with rheumatoid arthritis: correlation with disease activity and pulmonary function tests. *The Egyptian Rheumatologist*. 2014;36(4):165-171.
27. Goes ACJ, Reis LAB, Silva MBG, Kahlow BS, Skare TL. Rheumatoid arthritis and sleep quality. *Rev Bras Reumatol Engl Ed*. 2017;57(4):294-298.
28. Taylor-Gjevre RM, Nair BV, Gjevre JA. Obstructive sleep apnoea in relation to rheumatic disease. *Rheumatology (Oxford)*. 2013;52(1):15-21.
29. Almendros I, Khalyfa A, Trzepizur W, et al. Tumor cell malignant properties are enhanced by circulating exosomes in sleep apnea. *Chest*. 2016;150(5):1030-1041.
30. Long G, Hu Z, Jiao Z, et al. A radiologic parameter that could be applied in the development of sleep apnea in rheumatoid arthritis patients undergoing occipitocervical fusion. *J Orthop Sci*. 2021;26(4):521-527.
31. Shimizu M, Tachibana N, Hagasaka Y, Goto M. Obstructive sleep apnea in RA patients and effect of CPAP on RA activity [Abstract]. *Arthritis Rheum*. 2003;48(Suppl):S114–S114.
32. Pepin JL, Della Negra E, Grosclaude S, Billon C, Levy P. Sleep apnoea syndrome secondary to rheumatoid arthritis. *Thorax*. 1995;50(6):692-697.
33. Ataka H, Tanno T, Miyashita T, Isono S, Yamazaki M. Occipitocervical fusion has potential to improve sleep apnea in patients with rheumatoid arthritis and upper cervical lesions. *Spine*. 2010;35(19):E971-E975. https://doi.org/10.1097/BRS.0b013e3181c691df
34. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. 2018;23(2):60-63.

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ORIGINAL ARTICLE

Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib

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Abstract

Objectives: The aim of this study was to investigate hepatitis B virus (HBV) reactivation in patients with rheumatoid arthritis (RA) receiving tofacitinib.

Method: This was a retrospective study performed in a regional teaching hospital in southern Taiwan. During January 2017 and December 2020, patients with a clinician-confirmed diagnosis of RA using tofacitinib for at least 3 months were enrolled. Serum HBV DNA levels and serum alanine aminotransferase were followed up around every 3 to 6 months to assess HBV reactivation.

Results: A total of 98 patients with RA were enrolled, and eight were hepatitis B surface antigen positive (HBsAg+) (8.1%), 64 were HBsAg-negative (HBsAg−)/hepatitis B core antibody positive (HBcAb+) (65.3%). In the HBsAg+ patients, two patients received antiviral prophylaxis, and none of them had HBV reactivation or hepatitis flare-up. The HBV reactivation rate was 33.3% (2/6) in the HBsAg+ RA patient without antiviral prophylaxis. Among the HBsAg−/HBcAb+ patients, the HBV reactivation rate was 3.1% (2/64). The incidence rate of HBV reactivation was 153.8 per 1000 person-years for overall HBsAg+ patients and 250 per 1000 person-years after excluding patients receiving antiviral prophylaxis. The incidence rate was 11.2 per 1000 person-years for HBsAg−/HBcAb+ patients with RA receiving tofacitinib.

Conclusion: Tofacitinib could induce HBV reactivation in both HBsAg+ and HBsAg−/HBcAb+ RA patients. HBsAg+ patients receiving tofacitinib have a high incidence rate of HBV reactivation, which could be prevented by antiviral prophylaxis. Although the risk of reactivation is low in HBsAg−/HBcAb+ patients, closely monitoring HBV DNA and alanine aminotransferase should be suggested.

KEYWORDS

hepatitis B virus, reactivation, rheumatoid arthritis, tofacitinib

1 | INTRODUCTION

Hepatitis B virus (HBV) is a common viral infection in humans, and HBV infection is endemic in Taiwan.[1] Rheumatoid arthritis (RA) is characterized by chronic inflammation of the joints resulting in deformity and disability. Common medications for the treatment of RA include: (a) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); (b) biologic agents, such as tumor necrosis factor inhibitors, abatacept, rituximab, tocilizumab; and (c) targeted synthetic DMARDs, such as tofacitinib, baricitinib,

filgotinib, and upadacitinib.[2] In recent years, HBV reactivation has been a potentially life-threatening complication in RA patients, especially those receiving biologic agents.[3,4] Our previous study demonstrated that RA patients using biologic agents, such as rituximab or tocilizumab, might experience HBV reactivation leading to acute hepatitis, hyperbilirubinemia, and even death.[5,6]

Tofacitinib is a potent, selective Janus kinase (JAK) 1 and JAK3 inhibitor. It was initially approved for the treatment of RA, and thereafter for psoriatic arthritis and ulcerative colitis.[7] Recently, tofacitinib has been applied in patients with severe coronavirus disease 2019 pneumonia and led to a lower risk of death or respiratory failure.[8] Chen et al[9] reported two cases of HBV reactivation in four hepatitis B surface antigen positive (HbsAg+) patients with RA during tofacitinib treatment without prophylactic nucleotide analogs (NUCs). On the other hand, Serling-Boyd et al[10] reported no HBV reactivation events in eight HBV core antibody positive (HBcAb+) and HBsAg negative (HBsAg−) patients with RA during tofacitinib treatment. There is a need to clarify whether the use of tofacitinib would lead to HBV reactivation in HBsAg−/HBcAb+ patients with RA. The present study aimed to investigate the rate of HBV reactivation in HbsAg+ and HBsAg−/HBcAb+ patients with RA undergoing tofacitinib treatment.

2 | MATERIALS AND METHODS

The study was conducted in a regional teaching hospital in southern Taiwan between January 2017 and December 2020. The study protocol was approved by the institutional review board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10802021). The study was carried out in accordance with the Declaration of Helsinki.

2.1 | Patients

We retrospectively reviewed the medical records of RA patients who had received tofacitinib therapy between April 2015 and December 2020 in a regional teaching hospital in Taiwan. The inclusion criteria were as follows: (a) fulfilled the 2010 ACR/EULAR RA classification criteria;[11] (b) availability of HBsAg and HBcAb status at diagnosis; and (c) treated with tofacitinib for at least 3 months. Patients were excluded if they were less than 20 years of age or lacked the required data. In accordance with international guidelines, tofacitinib was administered at the standard oral form dose of 11 mg per day.[2]

2.2 | Follow up of the study population

Medical records of the patients were reviewed retrospectively. Clinical characteristics included serum markers of HBV (HBsAg, HBcAb, hepatitis B surface antibody [HBsAb], and HBV DNA), anti-hepatitis C virus antibody, liver biochemical parameters (serum aspartate aminotransferase and alanine aminotransferase [ALT]), co-morbidities, co-medications, and the occurrence of HBV reactivation were recorded. Patients were monitored for ALT and HBV DNA levels every 3-6 months, and HBsAg and HBV DNA tests were performed whenever clinically indicated. Detailed medical records were collected, including immunologic profiles, tofacitinib course, previous and concomitant DMARD therapy, and corticosteroid therapy.

Serum HBV DNA was measured using the cobas HBV test by Cobas 4800 system (Roche Diagnostics GmbH, Basel, Switzerland). HBsAg and HBsAb were measured using ARCHITECT HBsAg Qualitative II (analytical sensitivity 0.041 IU/mL to 0.049 IU/mL), and HBsAb assay (Abbott Laboratories, Chicago, IL, USA).

2.3 | Assessment of HBV reactivation and hepatitis flare-up

The primary endpoint of this HBV reactivation in HBsAg+/HBcAb+ patients was defined as one of the following: (a) >2 log (100-fold) increase in HBV DNA compared with the baseline level; (b) HBV DNA >3 log (1000) IU/mL in a patient with previously undetectable levels (given that HBV DNA levels fluctuate); or (c) an absolute level of HBV DNA >4 log (10 000) IU/mL if the baseline level was unavailable. For HBsAg−/HBcAb+ patients, HBV reactivation was defined as (a) HBV DNA is detectable or (b) reverse HBsAg seroconversion occurs (reappearance of HBsAg). A hepatitis flare-up is defined as an ALT level elevated at least three times that of baseline and more than 100 IU/L.[12]

2.4 | Statistical analysis

The data were analyzed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA). Categorical variables are reported as count and percentage, and continuous variables are presented as median and range.

3 | RESULTS

We collected 108 RA patients receiving tofacitinib, and 10 were excluded because of incomplete HBsAg or HBcAb data (n = 9), or receiving tofacitinib for less than 3 months (n = 1) (Figure 1). A total of 98 patients were enrolled; eight were HBsAg+ (8.1%) and 90 were HBsAg− (91.8%). In the HBsAg+ patients, two patients received antiviral prophylaxis, and none of them had HBV reactivation or hepatitis flare-up. The HBV reactivation rate was 33.3% (2/6) in the HBsAg+ RA patients without antiviral prophylaxis. Among the HBsAg− patients, 64 were HBsAg−/HBcAb+, and 26 were HBsAg−/HBcAb−. The HBV reactivation rate was 3.1% (2/64) in HBsAg−/HBcAb+ patients with RA.

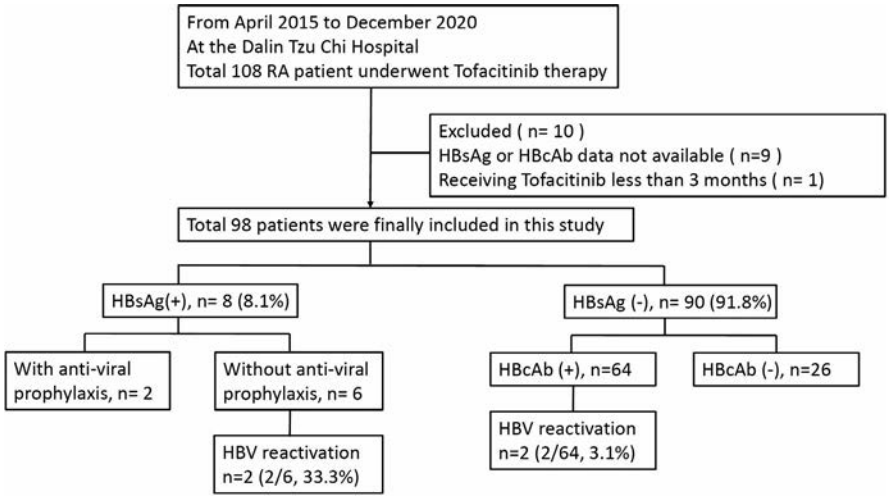

FIGURE 1 A flowchart for the rate of hepatitis B virus reactivation stratified by different HBV infection status in patients with rheumatoid arthritis treated with tofacitinib. Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; RA, rheumatoid arthritis

Clinical characteristics of the study participants are shown in Table 1. The study population had a median age of 61.5 years, and median disease follow-up time was 9.5 years. Tofacitinib was administered for a median 29.6 months (interquartile range 16.3-46.3). Fifty-six (57.1%) patients had HBsAb. Fifty-five (56.1%) patients had a history of non-tofacitinib biologic DMARD (bDMARD) treatment. Before using tofacitinib, most patients previously received tumor necrosis factor inhibitors (adalimumab, etanercept, and golimumab) (54 patients, 55.1%), or rituximab (12 patients, 12.2%). The characteristics of eight HBsAg+ patients are shown in Table 1. All patients were female, and none of them had concomitant hepatitis C virus infection. In the eight patients, five were in inactive phase, one was in immune-active phase, and the other two patients could not be classified because of missing data. HBV reactivation occurred in two of the six patients without antiviral prophylaxis (Figure 1). The baseline characteristics of the HBsAg−/HBcAb+ patients are shown in Table 1 and 43 (68.2%) patients were HBsAb+. The incidence rate of HBV reactivation was 153.8 per 1000 person-years for overall HBsAg+ patients and 250 per 1000 person-years after excluding patients receiving antiviral prophylaxis. The incidence rate was 11.2 per 1000 person-years for HBsAg−/HBcAb+ patients with RA receiving tofacitinib.

Clinical characteristics of the patients with HBV reactivation are shown in Table 2; case 1 and case 2 were HBsAg+ patients and case 3 and case 4 were HBsAg−/HBcAb+ patients. None of these four cases were receiving antiviral treatment because the status of HBV reactivation in our study did not meet the Taiwan's National Health Insurance criteria for NUCs payment at that time because these patients did not have persistently elevated serum ALT levels. Moreover, they could not afford the self-paid antiviral treatment. The clinical courses for these cases are shown in Figure 2. Case 1 was a 56-year-old woman, and her baseline HBV DNA was 28.8 IU/mL. After 56 months of tofacitinib treatment, she experienced HBV reactivation (HBV DNA: 3.96×10^6 IU/mL). She had transiently elevated ALT to 104 U/L. No acute liver decompensation was reported during the follow-up period (Figure 2A). Case 2 was a 38-year-old woman with HBV DNA level 2×10^3 IU/mL before using tofacitinib (Figure 2B). HBV DNA and ALT were followed up every 3 months. HBV reactivation was found (HBV DNA: 1.84×10^5 IU/mL) after using tofacitinib for 3 months. Eleven months after using tofacitinib, serum HBV DNA was elevated to 3.28×10^6 IU/mL, but no hepatitis was noted during the 1-year follow-up period. Case 3 was an 85-year-old man. His baseline HBV DNA was undetectable, and it was rechecked every 6 months. He had received tofacitinib for 4.7 years, and an elevated HBV DNA of 14 IU/mL with normal serum ALT was found after 57 months of tofacitinib treatment (Figure 2C). Case 4 was a 55-year-old woman whose HBV DNA was undetectable before using tofacitinib. HBV DNA was elevated to 79 IU/mL after 1 year of treatment with tofacitinib (Figure 2D). Both cases did not receive antiviral agents, and their HBV DNA became undetectable in the follow up; there was no hepatitis or liver decompensation during the entire 1-year follow-up period.

4 | DISCUSSION

Tofacitinib was the first clinically available first-generation JAK inhibitor available in Taiwan, but now there are several first-generation JAK inhibitors and even second-generation JAK inhibitors approved for the treatment of RA. In addition, the clinical indication for JAK inhibitors has increased, and tofacitinib is also approved for the treatment of psoriatic arthritis and ulcerative colitis.[13] JAK inhibitors have shown great potential for the treatment of many rheumatic diseases, including systemic lupus erythematosus, dermatomyositis, systemic sclerosis, Sjögren syndrome, plaque psoriasis, vasculitis, inflammatory bowel disease, and even coronavirus disease 2019, by suppressing the signaling pathways of multiple cytokines and eventually controlling the inflammation.[7,14] Therefore, it is crucial to understand the potential adverse effects of these JAK inhibitors, such as tofacitinib, in HBV reactivation.

Our previous studies evaluated the HBV reactivation risk in RA patients who received rituximab and tocilizumab.[5,6] In these two studies, around 7%-8% of the study population were HBsAg+ patients, and HBcAb+ patients accounted for 62%-65% of the study

TABLE 1 Clinical characteristics of the study participants

Characteristics	All (N = 98)	HBsAg+ (N = 8)	HBsAg−/HBcAb+ (N = 64)
Age, median (IQR)	61.5 (53.0-72.5)	57.7 (48.0-73.0)	63.0 (53.0-71.8)
Sex, female, n (%)	82 (83.7)	8 (100.0)	54 (84.4)
Duration of rheumatoid arthritis (years), median (IQR)	9.5 (5.5-14.6)	3.1 (1.8-6.7)	10.1 (6.9-15.0)
Duration of tofacitinib (months), median (IQR)	29.0 (15.1-45.6)	13.2 (4.2-30.8)	31.0 (20.2-47.9)
HBsAb positive, n (%)	56 (57.1)	1 (12.5)	43 (68.2)[a]
Anti-HCV positive, n (%)	9 (9.2)	0 (0.0)	7 (10.9)
Antirheumatic therapies before tofacitinib use, n (%)			
csDMARDs			
Methotrexate	67 (68.4)	4 (50.0)	45 (70.3)
Glucocorticoid (oral)	91 (92.9)	8 (100)	57 (89.1)
1-5 mg/day	64 (65.3)	5 (62.5)	43 (67.2)
6-10 mg/day	20 (20.24)	2 (25.0)	11 (17.2)
11-15 mg/day	7 (7.1)	1 (12.5)	3 (4.7)
Azathioprine	0 (0.0)	0 (0.0)	0 (0.0)
Cyclosporine	3 (3.1)	1 (12.5)	1 (1.6)
Leflunomide	25 (25.5)	1 (12.5)	17 (26.6)
Sulfasalazine	56 (57.1)	7 (87.5)	36 (65.2)
bDMARDs			
Abatacept	9 (9.2)	1 (25.0)	5 (7.8)
Adalimumab	17 (17.3)	0 (0.0)	11 (17.2)
Etanercept	28 (28.6)	2 (25.0)	21 (32.8)
Golimumab	9 (9.2)	2 (25.0)	5 (7.8)
Tocilizumab	9 (9.2)	0 (0.0)	6 (9.4)
Rituximab	12 (12.2)	1 (12.5)	5 (7.8)
Never used bDMARDs	43 (43.9)	4 (50.0)	26 (40.6)
Used one bDMARDs	36 (36.7)	2 (25.0)	27 (42.2)
Used two or more bDMARDs	19 (19.3)	2 (25.0)	11 (17.2)
HBV reactivation			
No. of patients	4	2	2
Person-years	249	13	178
Incidence rate/1000 person-years	16.1	153.8[b]	11.2

Abbreviations: Anti-HCV, anti-hepatitis C antibody; bDMARDs, biologic disease-modifying antirheumatic drug; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HBcAb, anti-hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; IQR, interquartile range.

[a]One patient has missing data.

[b]The incidence rate became 250 per 1000 person-years after excluding patients receiving antiviral prophylaxis.

population. In this study, the proportion of HBsAg+ was 8.1%, and the proportion of HBcAb+ was 65.3%. The prevalence of hepatitis infection and resolved infection in our study was compatible with that of the Taiwan general population.[15]

The risk of HBV reactivation is high among the HBsAg+ patients. Anti-CD20 monoclonal antibodies are the most notorious drugs for HBV reactivation, and the reactivation risks are very high (>30%).[3] The incidence of HBV reactivation by tumor necrosis factor inhibitors without antiviral prophylaxis was 15.6% in HBsAg+ patients.[3] There is a lack of large-scale studies regarding HBV reactivation in RA patients using tofacitinib. There is only one retrospective observational study in Taiwan, and this reported that two of four HBV carriers experienced reactivation.[4] Our study showed two of six (33.3%) HBsAg+ patients without antiviral prophylaxis experienced HBV reactivation. The two patients received antiviral prophylaxis and had no HBV reactivation. Both studies showed the high risk of HBV reactivation, and antiviral prophylaxis is recommended for HBsAg+ patients before tofacitinib therapy.

HBsAg−/HBcAb+ patients were at a lower risk of HBV reactivation than HBsAg+ patients.[3] Our study reported two

TABLE 2 Clinical features of patients with HBV reactivation

Variable	HBsAg+		HBsAg−/HBcAb+	
	Case 1	Case 2	Case 3	Case 4
Age/sex	56/female	38/female	85/male	53/female
Disease duration of rheumatoid arthritis (year)	8	2.1	6	16.3
Baseline DAS 28	6.26	6.27	6.34	5.85
DAS 28 on reactivation	3.1	2.8	3.2	3.53
Co-morbidities				
Diabetes	N	N	N	N
Hypertension	N	N	N	N
Dyslipidemia	Y	Y	Y	Y
Interferon-γ releasing assay	—	—	—	—
Duration of tofacitinib (till HBV reactivation) (months)	56	11	57	12
Tofacitinib dosage (mg/day)	11	11	11	11
HBsAb (mIU/mL)	—	—	27.46	73.72
HBeAg	—	NA	—	—
Anti-HBeAb	+	NA	NA	NA
Anti-HCV	—	—	—	—
HBsAg seroreversion	—	—	—	—
Baseline HBV DNA (IU/mL)	28.8	2010	0	0
HBV DNA (peak, IU/mL)	3 960 000	3 280 000	14	79
ALT (initial/peak, U/L)	39/104	35/65	28/31	30/33
Total bilirubin (peak, mg/dL)	0.6	0.6	0.4	NA
Prothrombin time prolonged	N	N	N	N
Ascites	N	N	N	N
Hepatic encephalopathy	N	N	N	N
Hepatitis flare-up	N	N	N	N
Treatment of HBV reactivation	N	N	N	N
Outcome	Alive & well	Alive & well	Alive & well	Alive & well
Antirheumatic therapy before tofacitinib				
bDMARDs (months)	N	N	N	N
csDMARDs (mg)	CyA, Pred HCQ	MTX, SAS, Pred	MTX, HCQ, Pred	MTX, LEF, Methylpred, HCQ
Concurrent immunosuppressants				
MTX (mg/week)	0	10	0	10
Prednisolone equivalent dose (mg/day)	5	5	0	5
csDMARDs (mg)	0	SAS	0	0

Abbreviations: ALT, alanine aminotransferase; bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CyA, cyclosporine; DAS28, disease activity score by 28 joints; HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCQ, hydroxychloroquine; HCV, hepatitis C virus; IU, international unit; LEF, leflunomide; Methylpred, methylprednisolone; MTX, methotrexate; N, not happened; NA, not applicable; Neg, negative; Pred, prednisolone; SAS, sulfasalazine; Y, happened.

(3.1%) cases of HBV reactivation during a median 31.3 months of tofacitinib treatment. Serling-Boyd et al[10] reported no HBV reactivation in eight tofacitinib-treated HBsAg−/HBcAb+ patients with median follow-up time 3.1 years. In a retrospective observational study in Taiwan, Chen et al[9] reported 75 HBsAg−/HBcAb+ patients without any HBV reactivation with a follow-up period less than 2 years. The clinical course of our HBsAg−/HBcAb+ patients with HBV reactivation was not clear, and most of them were receiving antiviral treatment after the reactivation of HBV.[16-19] HBV reactivation could also occur among HBsAg−/HBcAb+ RA patients treated with baricitinib (JAK1 and JAK2 inhibitor).[20] The evidence indicated that HBsAg−/HBcAb+ patients

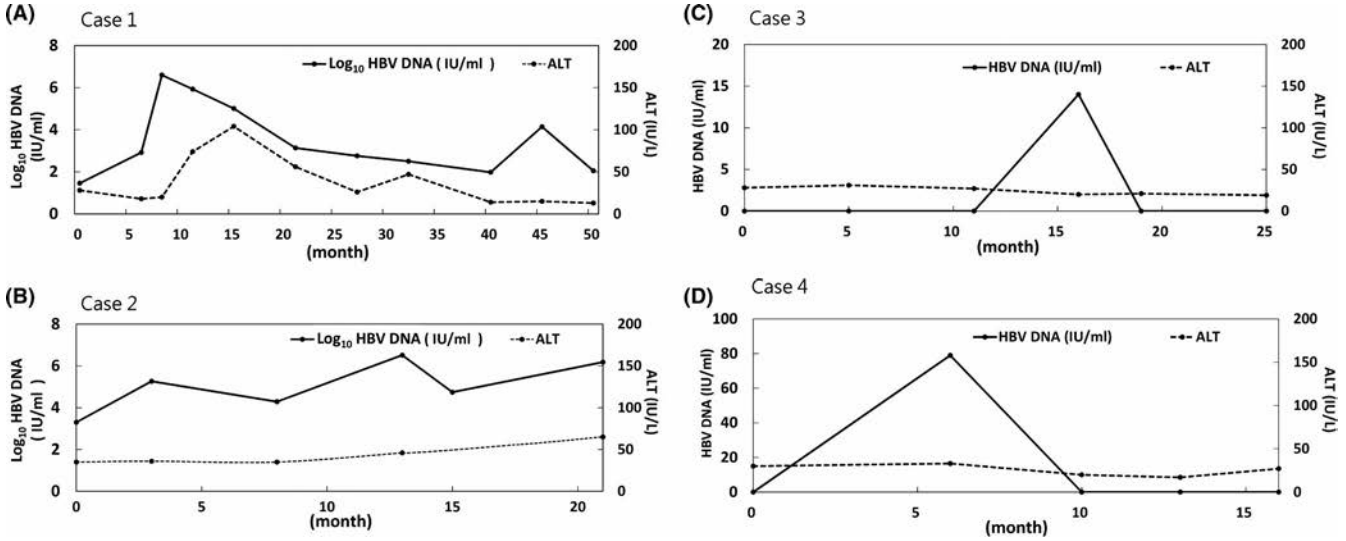

FIGURE 2 Time course of serum HBV DNA and alanine aminotransferase concentrations in four patients experiencing HBV reactivation. Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus

did have a lower risk of HBV reactivation under JAK inhibitors. We observed that the serum HBV DNA was low during HBV reactivation and the viral load fluctuated between undetectable and detectable in both cases without antiviral treatment. However, there were only two cases in our study. Physicians should carefully monitor these patients who still have a potential for HBsAg seroconversion.[6]

Four patients with HBV reactivation were treated with multiple drugs including DMARDs, steroids and tofacitinib. According to previous reports, conventional DMARDs such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine are relatively safe.[21,22] Long-term use of high doses of glucocorticoids (>20 mg/day for at least 4 weeks) is strongly associated with HBV reactivation in RA studies, resulting from their immunosuppressive activity and direct stimulation of HBV replication. In this cohort, most of our patients received a low dose (84/98, 85.7%; <10 mg/day). Three patients with HBV reactivation received prednisolone equivalent dose of 5 mg/day and one did not use glucocorticoids. Therefore, considering tofacitinib as the main drug for HBV reactivation seems reasonable. Some studies demonstrated that a history of bDMARD use was a risk factor of HBV reactivation. Schwaneck et al[23] showed an increased risk of HBV reactivation in patients who had received more than three different classes of bDMARDs. This finding was supported by Loras et al,[24] who reported treatment with more than two different immunosuppressants as an independent risk factor for HBV reactivation in patients with inflammatory bowel disease. In our study, 18% (13/72) of patients received more than two bDMARDs before tofacitinib therapy; however, four cases of HBV reactivation did not receive any bDMARDs before tofacitinib therapy. The HBV reactivation could have occurred during tofacitinib therapy in those patients who were naive for bDMARD treatment. In addition, the HBV reactivation could occur in HBsAb+ patients with RA. The reactivation case 3 and case 4 both have low positive HBsAb levels at 27.46 mIU/mL and 73.72 mIU/mL, respectively. These two patients had detectable HBsAb titers but were below 100 mIU/mL, and a low titer of HBsAb (<100 mIU/mL) might not have a protective effect for HBV reactivation.[25]

The four RA patients with HBV reactivation in our study were unable to fulfill the previous Taiwan's National Health Insurance criteria for NUCs payment. The criteria for (NUC) therapy of National Health Insurance of Taiwan include: (a) positivity of HBeAg for more than 3 months, with serum ALT more than five times the upper limit of normal (ULN); (b) positive HBeAg for more than 3 months with serum ALT more than twice the ULN in addition to HBV DNA more than 20 000 IU/mL; (c) negative HBeAg for more than 3 months with HBV DNA more than 2000 IU/mL and two episodes of ALT levels more than twice the ULN 3 months apart; (d) cirrhosis with evidence of portal hypertension, such as the presence of splenomegaly or gastro-esophageal varices, plus HBV DNA more than 2000 IU/mL. Case 1 showed high viral load but he did not have two episodes of ALT levels more than twice the ULN 3 months apart. The ALT levels of case 2 were more than twice the ULN. They could not afford self-paid antiviral treatment and were at increased risk of hepatitis, acute liver failure, or even death. Although the Taiwan's National Health Insurance criteria for NUCs payment have been adjusted recently, more information is needed to establish a consensus on prophylactic use of NUC in HBsAg−/HBcAb+ RA patients using potent immunosuppressive therapy.[26] In these four patients with HBV reactivation, we continued all the medication including tofacitinib, because the possibility of immune restoration after withdrawal of DMARDs might result in rapid, immune-mediated destruction of HBV-infected hepatocytes, leading to hepatitis.[27]

There are several limitations to this study. First, the case numbers of this study were relatively small—only four patients

had HBV reactivation with two for HBsAg+ patients and two for HBsAg−/HBcAb+ RA patients. We could not further analyze the risk factors for the reactivation of HBV. Second, this is a retrospective study and some data including HBeAg, HBeAb status, HBcAb levels, HBsAb levels were not available. Third, our data were collected from a regional teaching hospital in southern Taiwan, and many patients could not afford the self-paid antiviral prophylaxis treatment in this region, which might limit the generalization of our conclusions. Finally, HBV DNA was transiently detected in two HBsAg−/HBcAb+ patients. We might have failed to detect some HBV reactivation in HBsAg−/HBcAb+ patients.

5 | CONCLUSION

Tofacitinib could induce HBV reactivation in both HBsAg+ and HBsAg−/HBcAb+ RA patients, but no acute hepatitis flare-up was observed during the follow up. Because of the high risk of HBV reactivation for HBsAg+ patients, antiviral prophylaxis should be considered before tofacitinib therapy. The reactivation of HBV in HBsAg−/HBcAb+ patients appeared to involve the viral load fluctuating between undetectable and detectable. We suggest that HBV DNA and ALT should be closely monitored during tofacitinib treatment in HBsAg−/HBcAb+ RA patients.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization and data curation were by STW, CWT, CHT, KYH, MCL, and NSL. Formal analysis was by STW, CWH, and MCL. Funding was acquired by STW and MCL. Investigations were performed by CWT, MCL, and NSL. Methodology was by STW, CWT, and CWH. Project was administered by STW, CWT, and MCL. CWT and MCL supervised the study and reviewed and edited the article; STW wrote the original draft.

ETHICS APPROVAL

The institutional review board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10802021) provided ethical approval.

PATIENT AND PUBLIC INVOLVEMENT

This research was performed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding authors upon reasonable request.

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REFERENCES

1. Lin CL, Kao JH. Perspectives and control of hepatitis B virus infection in Taiwan. *J Formos Med Assoc*. 2015;114(10):901-909.
2. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-699.
3. Huang SC, Yang HC, Kao JH. Hepatitis B reactivation: diagnosis and management. *Expert Rev Gastroenterol Hepatol*. 2020;14(7):565-578.
4. Chen YM, Yang SS, Chen DY. Risk-stratified management strategies for HBV reactivation in RA patients receiving biological and targeted therapy: a narrative review. *J Microbiol Immunol Infect*. 2019;52(1):1-8.
5. Kuo MH, Tseng CW, Lee CH, et al. Moderate risk of hepatitis B virus reactivation in HBsAg-/HBcAb+ carriers receiving rituximab for rheumatoid arthritis. *Sci Rep*. 2020;10(1):2456.
6. Kuo MH, Tseng CW, Lu MC, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing tocilizumab-containing treatment. *Dig Dis Sci*. 2021;1-9. 10.1007/s10620-020-06725-1. Online ahead of print.
7. You H, Xu D, Zhao J, et al. JAK inhibitors: prospects in connective tissue diseases. *Clin Rev Allergy Immunol*. 2020;59(3):334-351.
8. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. 10.1056/NEJMoa2101643
9. Chen YM, Huang WN, Wu YD, et al. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study. *Ann Rheum Dis*. 2018;77(5):780-782.
10. Serling-Boyd N, Mohareb AM, Kim AY, et al. The use of tocilizumab and tofacitinib in patients with resolved hepatitis B infection: a case series. *Ann Rheum Dis*. 2021;80(2):274-276.
11. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581.
12. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599.
13. Coricello A, Mesiti F, Lupia A, et al. Inside perspective of the synthetic and computational toolbox of JAK inhibitors: recent updates. *Molecules*. 2020;25(15):3321.
14. Burrage DR, Koushesh S, Sofat N. Immunomodulatory drugs in the management of SARS-CoV-2. *Front Immunol*. 2020;11:1844.
15. Hu YC, Yeh CC, Chen RY, et al. Seroprevalence of hepatitis B virus in Taiwan 30 years after the commencement of the national vaccination program. *PeerJ*. 2018;6:e4297.
16. Lan JL, Chen YM, Hsieh TY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis*. 2011;70(10):1719-1725.
17. Nakamura J, Nagashima T, Nagatani K, et al. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis*. 2016;19(5):470-475.
18. Fukuda W, Hanyu T, Katayama M, et al. Incidence of hepatitis B virus reactivation in patients with resolved infection on

immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. *Ann Rheum Dis*. 2017;76(6):1051-1056.
19. Watanabe R, Igarashi T, Takahashi T, et al. Multidisciplinary approach to prevent de novo hepatitis b in patients with rheumatoid arthritis. *Tohoku J Exp Med*. 2020;252(2):133-141.
20. Harigai M, Winthrop K, Takeuchi T, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open*. 2020;6(1):e001095.
21. Choi J, Lim YS. Characteristics, prevention, and management of Hepatitis B Virus (HBV) reactivation in HBV-infected patients who require immunosuppressive therapy. *J Infect Dis*. 2017;216(Suppl_8):S778-S784.
22. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline onthe prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219.
23. Schwaneck EC, Krone M, Kreissl-Kemmer S, et al. Management of anti-HBc-positive patients with rheumatic diseases treated with disease-modifying antirheumatic drugs-a single-center analysis of 2054 patients. *Clin Rheumatol*. 2018;37(11):2963-2970.
24. Loras C, Gisbert JP, Mínguez M, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut*. 2010;59(10):1340-1346.
25. Tien YC, Yen HH, Li CF, et al. Changes in hepatitis B virus surface antibody titer and risk of hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients undergoing biologic therapy for rheumatic diseases: a prospective cohort study. *Arthritis Res Ther*. 2018;20(1):246.
26. Chien RN, Kao JH, Peng CY, et al. Taiwan consensus statement on the management of chronic hepatitis B. *J Formos Med Assoc*. 2019;118(1 Pt 1):7-38.
27. Mori S, Fujiyama S. Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. *World J Gastroenterol*. 2015;21(36):10274-10289.

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ORIGINAL ARTICLE

Idiopathic granulomatous mastitis associated with erythema nodosum may indicate a worse prognosis

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Abstract

Introduction: Idiopathic granulomatous mastitis (IGM) is a chronic inflammatory breast disease of unknown etiology, and erythema nodosum (EN) is a rare extramammary manifestation of this entity characterized by reddish, tender nodules of the lower legs. We aimed to investigate whether the association of IGM with EN has a role as a prognostic indicator. There are few case reports, and only 1 original article including 12 IGM patients with EN has been reported.

Methods: We present 43 women with IGM coexisting with EN and 43 with a diagnosis of IGM only, who were randomly selected from 610 patients for a control group. To the best of our knowledge, this paper comprises the first comparative study of the coexistence of IGM and EN to be reported in the literature.

Results: Our findings show that the association of IGM with EN indicates a more aggressive disease course. White blood cells, erythrocyte sedimentation rate, and C-reactive protein were significantly higher in the EN-positive group ($P < .05$). Arthralgia, breast feeding, fistula distribution and recurrence distributions were significantly higher in the EN-positive group ($P < .05$).

Conclusion: Since fistula distribution and recurrence rates were higher in EN-positive group, association of IGM with EN may be an indictor of a worse prognosis. The present study highlights the importance of dermatological care. All physicians should not neglect questioning breast complaints in patients with EN since EN may be caused by IGM.

KEYWORDS

breast, corticosteroids, erythema nodosum, idiopathic granulomatous mastitis, recurrence

1 | INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is an unusual benign and chronic inflammatory breast disease of unknown etiology that typically affects young women shortly after childbirth.[1,2] Despite being a benign entity, IGM simulates carcinoma of the breast both clinically and radiologically.[3] A firm breast lump associated with local inflammation of the overlying skin is generally the typical presentation of the disease. Patients may also have mastalgia, peau d'orange-like changes, cutaneous ulcerations, erythema, abscesses, skin fistulas, and nipple retraction[4] (Figure 1A). Demonstration of non-caseating granulomas histopathologically confined to breast lobules without history of trauma or foreign bodies is essential for definitive diagnosis.[5,6] Breast cancer, other granulomatous diseases and infectious etiologies should also be excluded. The etiology of IGM is unclear; however, an association between the disease and young women of

childbearing age has been shown. Additionally, autoimmune diseases, pregnancy, lactation, oral contraceptive drugs, breast trauma, and nicotine addiction have also been suggested to play a role.[7,8] Due to the unknown etiology and lack of prospective randomized studies and meta-analyses of prospective papers, the optimal treatment modality remains elusive.

Erythema nodosum (EN) is hypodermal septal inflammation associated with blood vessels and is characterized by reddish, tender nodules of the lower legs, typically the pretibial regions, which usually involute within a few weeks[9] (Figure 1B). Various infectious diseases can be associated with EN, and drugs, Behçet's disease, hematological malignities, tuberculosis, and sarcoidosis may be the underlying cause of EN.[10] Cribier et al.[9] showed that streptococcal infection was the major factor associated with EN, followed by sarcoidosis. Adams et al.[11] first described the relationship between IGM and EN in 1988. Similar to polyarthritis, EN is rarely seen in IGM patients as a systemic manifestation.

There are few case reports, and only 1 original article including 12 IGM patients with EN has been reported in Turkey.[12-16] Ringsted et al.[17] reported a case series consisted of 28 IGM patients with 5 (18%) patients with EN. Herein, we present 43 women with IGM coexisting with EN and 43 with a diagnosis of IGM only, who were randomly selected from 610 patients. To the best of our knowledge, this paper comprises the first comparative study of the coexistence of IGM and EN and is the largest series of IGM complicated with EN to be reported in the literature.

The goal of the present study was to determine the clinical and demographic characteristics of these patients and compare the 2 groups in terms of recurrence. Accordingly, we aimed to investigate whether the association of IGM with EN has a role as a prognostic indicator.

2 | METHODS

A total of 43 women with IGM coexisting with EN and 43 with a diagnosis of IGM only, who were selected randomly from 610 patients for a control group between January 2013 and January 2020 at Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, General Surgery Breast Outpatient Clinic were included in the present study. The data of the patients were reviewed retrospectively. Demographic characteristics of the patients, medical history, clinical findings (fever, arthritis, EN), local breast findings (pain, erythema, mass, fistula), lactation and pregnancy history, history of IGM, laboratory findings, microbiological examinations, imaging, and duration of therapy and the results were recorded.

2.1 | Design and subjects

This study was planned as a retrospective, comparative parallel arm study.

2.2 | Diagnosis of IGM and EN

After taking a careful history thorough physical examination, diagnosis of IGM was confirmed histologically by core needle or excisional biopsy in patients with first admission. Each specimen was analyzed using Gram, Erlich–Ziehl–Neelsen (EZN), periodic acid-Schiff, and hemotoxylin-eosin staining. In addition, following diagnosis, the purified protein derivative skin (PPD) and/or the QuantiFERON test were performed to exclude tuberculous mastitis. EN was diagnosed according to physical examination findings and no additional surgical procedure or interventions were applied to the EN group which may cause or increasing the rate of fistula formation. Both control and EN group patients had routine initial treatment. Thus, propensity score matching was not used, and randomization method was used for control group selection. The main motivation of the control selection method was to represent the IGM population with a selected control group.[18,19] Reddish, tender nodules of the lower legs, typically in the pretibial regions, were diagnosed as EN.[9] Reappearance of a breast lump or inflammatory skin signs such as ulcers or fistulas after complete remission of the disease is defined as the recurrence. Relapse is worsening of the disease during treatment or relapse of symptoms after completion of treatment.[20] Relapse was also defined as the recurrence of symptoms such as pain, mastitis, or abscess ≥3 months after treatment.[21] The criteria for remission tend to differ across many previous studies, and unfortunately, there is no complete standardization regarding this.[22-24] Postolova et al.[20] describes remission as complete resolution during treatment. In this study, complete elimination of inflammatory findings, fistulas not

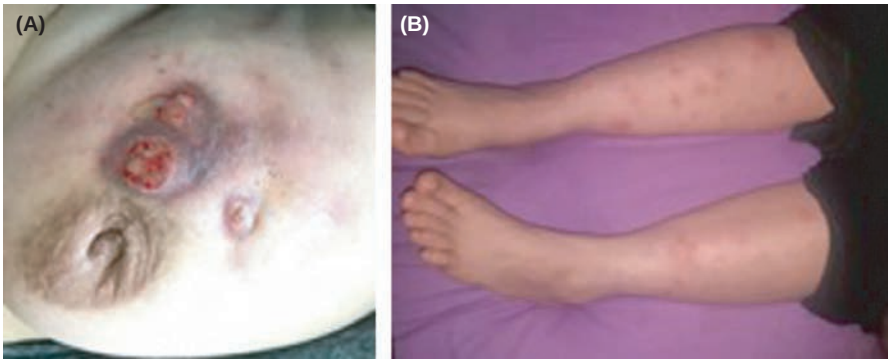

FIGURE 1 (A) Fistula formation. (B) A case of bilateral erythema nodosum (EN) in an idiopathic granulomatous mastitis (IGM) patient

being active, and fistula holes and/or skin erosions closing in the affected breast were defined as remission.

The patients who were at remission were free of disease after the treatment (during their average follow-up with the minimum time of 6 months) and without relapse.

2.3 | Inclusion and exclusion criteria

Women over 18 years of age with an inflammatory reaction (chronic lobulitis) disrupting the breast lobules and containing epithelioid histiocytes, lymphocytes, polymorphonuclear leukocytes, multinucleated Langhans-type giant cells, and plasma cells in the breast tissue and those with non-caseating granulomas in the breast lobules were included. Women histopathologically diagnosed with old or new breast cancer, any granulomatous disease (tuberculosis, fungal and parasitic infections, granulomatosis with polyangitiitis, foreign bodies), history of another malignancy, pregnant or breastfeeding, or receiving chemotherapy or radiotherapy, were excluded.

2.4 | Randomization and study groups

To reduce the effects of control group patient selection bias, control group patients were selected using a simple randomization protocol. Among all patients, those with EN were identified and treatment modalities in these patients were revealed. To eliminate bias, the same number of EN-negative patients as those with EN who used antibiotics, steroids, methotrexate, and expectant management were randomly selected from the general patient group. Twenty patients from the EN-negative general patient group who received corticosteroids were selected by simple random sampling to avoid bias to compare with 20 patients who received corticosteroids with EN. Seventeen patients from the EN-negative general patient group who received methotrexate were selected by simple random sampling to avoid bias to compare with 17 patients who received methotrexate with EN. Two patients from the EN-negative general patient group who received antibiotics were selected by simple random sampling to compare with 2 patients who received antibiotics with EN. Three patients from the EN-negative general patient group who were followed by expectant management were selected by simple random sampling to avoid bias to compare with 3 patients who were followed by expectant management with EN. Assessment of response to treatments, improvement in fistula and ulcerations, disappearance of palpable lesions, and regression of inflammatory findings were defined as complete clinical regression.

2.5 | Data

Demographic data, clinical findings, pathology, imaging, and treatment options were retrospectively collected from the patient medical records.

2.6 | Statistical methods

Nominal and ordinal parameters are described by frequency analysis and scale parameters by the mean and SD. The Kolmogorov–Smirnov test was used to assess normality of scale parameters, and the Chi-square test and Chi-square likelihood ratio were used to assess differences between ordinal or nominal parameters. Spearman's rho correlation and binary logistic regression were used for relational analysis. SPSS 17.0 for Windows was used at a 95% confidence interval (95% CI).

The protocol used in the present study was approved by the Ethics Committee of the Istanbul University-Cerrahpasa Medical School: 56388/22.04.2020.

3 | RESULTS

Some baseline characteristics of patients according to the assigned groups regarding the presence of EN are summarized in Table 1.

The mean age of the EN-negative group was significantly higher than that of the EN-positive group ($P < .05$). Fistula distribution was significantly higher in the EN-positive group ($P < .05$). Smoking was significantly higher in the EN-negative group ($P < .05$). There was no significant difference in birth region, location, the place of first application, antibiotic type, clinical history, family history, the presence of rheumatological disease, or abscess drainage parameters between the EN-positive and -negative groups ($P > .05$). Clinical findings of patients according to EN groups are given in Table 2.

The mean white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and mass dimension were significantly higher in the EN-positive group ($P < .05$). Arthralgia, breast feeding and recurrence distributions were significantly higher in the EN-positive group ($P < .05$) (Table 2). There was no significant difference in PPD, antinuclear antibodies (ANA), breast localization, bilateral, culture, trauma history, lactation, recurrence, first response to treatment, treatment duration or follow-up duration between the EN-positive and -negative groups ($P > .05$).

The number of patients with a mass in ultrasonography was significantly higher in the EN-positive group ($P < .05$). Collection and mastitis distributions were significantly higher in the EN-positive group ($P < .05$). However, there was no significant difference in other ultrasound (US) findings, symptoms or mammography findings between the EN-positive and -negative groups ($P > .05$) (Table 3).

Spearman's correlation results according to EN groups and the parameters with statistical significance are given in Table 4.

According to correlation analysis, there were significant positive correlations between the EN groups and age and smoking ($P < .05$). Negative correlations of EN with other parameters were also significant ($P < .05$).

There were no surgical treatments such as mastectomy or breast conserving surgery other than abscess drainage (Table 1).

TABLE 1 Baseline characteristics of patients according to EN groups

	Positive (n = 43)	Negative (n = 43)	*P*
Age, mean ± SD	30.21 ± 5.52	33.49 ± 5.27	.006[a]
The place of birth according to regions of Turkey, n (%)			
Black Sea	8 (18.6)	10 (23.3)	.487[b]
Marmara	6 (14.0)	8 (18.6)	
Eastern Anatolia	11 (25.6)	11 (25.6)	
Southeastern Anatolia	9 (20.9)	6 (14.0)	
Central Anatolia	5 (11.6)	3 (7.0)	
Mediterranean	4 (9.3)	2 (4.7)	
Location, n (%)			
Istanbul	39 (90.7)	43 (100.0)	.137[b]
Izmit	2 (4.7)		
Yalova	1 (2.3)		
Adapazari	1 (2.3)		
First application, n (%)			
Department	4 (9.3)	7 (16.3)	.333[c]
Other center	39 (90.7)	36 (83.7)	
Antibiotic type, n (%)			
None			.088[b]
Ampicillin sulbactam	4 (9.3)	11 (25.6)	
Amoxicillin clavulonic acid	13 (30.2)	6 (14.0)	
Cefuroxime axetil	18 (41.9)	19 (44.2)	
Ceftriaxone	2 (4.7)	1 (2.3)	
Ciprofloxacin + metronidazole	—	2 (4.7)	
Antibiotics duration, mean ± SD, d	24.12 ± 42.79	11.31 ± 7.79	.092[d]
Fistula, n (%)	21 (48.8)	5 (11.6)	.000[c]
Smoking, n (%)	1 (2.3)	6 (14.0)	.039[b]
History, n (%)			
None	38 (88.4)	40 (95.4)	.476[b]
DM	1 (2.3)	1 (2.3)	
Asthma	1 (2.3)	1 (2.3)	
Allergy	1 (2.3)	—	
Migraine	1 (2.3)	—	
Glaucoma	1 (2.3)	—	
Family history, n (%)			
None	40 (93.0)	39 (90.7)	.194[b]
First-degree relative	1 (2.3)	—	
Second-degree relative	1 (2.3)	4 (9.3)	
Third-degree relative	1 (2.3)		
Rheumatological diseases, n (%)			
None	40 (95.2)	43 (100.0)	.238[b]
ARF	1 (2.4)	—	
Behçet	1 (2.4)	—	
Abscess drainage, n (%)	25 (58.1)	19 (44.2)	.196[c]

Abbreviations: ARF, acute rheumatic fever; EN, erythema nodosum; DM, diabetes mellitus.

[a]Independent samples *t* test.

[b]Chi-square likelihood ratio.

[c]Chi-square test.

[d]Mann–Whitney *U* test.

4 | DISCUSSION

Although it has been nearly 50 years since IGM was first described by Kessler and Wolloch, its exact etiology remains unclear.[1] A diagnosis of IGM can be established by excluding other granulomatous diseases such as tuberculosis, sarcoidosis, or foreign body reactions. Some authors have speculated that the causes may include autoimmunity, oral contraceptive pills, smoking, breast trauma, pregnancy, and breastfeeding.[8,25-27]

Among these causes, the most common etiology in our patients was breastfeeding (76.7% in the EN-positive group and 48.8% in the EN-negative group; $P < .05$). Regarding the etiology, only smoking was significantly higher in the EN-negative group ($P < .05$).

EN is the most common type of panniculitis, which has an association with drugs, infections, sarcoidosis, tuberculosis, and even malignancies.[10] Bilateral pretibial subcutaneous regions are the typical localization of EN.[28] The coexistence of IGM with EN, granulomatosis with polyangitiiitis and lymphocytic alveolitis and polyarteritis nodosa can be seen.[29] In our series, the patients with IGM were complicated by only EN.

EN is an extramammary manifestation of granulomatous mastitis characterized by reddish, painful, tender nodules generally present on the extensor surface of the lower limbs.[9,10] Patients may also present with sudden onset of EN on their arms, associated with arthralgia, and bilateral swelling of the elbows, knees, and even ankles.[30] Our patients had pretibial lesions that appeared in conjunction with mastitis lesions (within 2 weeks before or after the mastitis). Pretibial lesions disappeared following treatment with steroids (0.5 mg/kg/d prednisolone) or methotrexate (15-20 mg/wk) for 2 weeks.

Due to the lack of prospective randomized studies and meta-analyses with a high level of evidence regarding the treatment strategies for IGM, there remains no commonly accepted approach to therapy. Several options have been recommended including anti-tuberculosis drugs, methotrexate, azathioprine, and surgical interventions such as drainage of the wound, wide local resection, and even mastectomy.[8,23,26,27,31-33] Altıntoprak et al.[23] also showed that topical steroids are effective in the treatment of IGM. Furthermore, Cetin et al.[34] performed a prospective study comparing topical, systemic, and combined (topical + systemic) steroid therapy with respect to their effectiveness in IGM, and concluded that the efficacy of topical treatment was similar to that of systemic and combined therapies. No intervention or medication, just expectant management (expectant management is following patients clinically and radiologically with regular intervals [1-3 months] for close monitoring of the patients, without giving surgical or medical treatment; considering the self-limiting situation arising from the nature of the disease, expectant management seems applicable and considered feasible[35]) with close follow-up, is also an effective alternative to aggressive treatments.[35,36] In the present study, 2 patients were treated with antibiotics, 20 with steroids (0.5 mg/kg/d prednisolone), 17 with methotrexate (15-20 mg/wk), and 3 patients were followed by expectant management (in each group).

There are a lack of data regarding the frequency, severity, and treatment response of IGM associated with EN; however, the frequency of EN among IGM patients was found to be 6.6% in a recently published study.[16] The frequency of coincidence was 7.05% in our study. Cetin et al.[16] found no statistically significant difference between IGM patients with and without EN regarding patient demographics, etiology, and clinical findings. In the present study, the mean age of the EN-negative group was significantly higher than that of the EN-positive group ($P < .05$). Cetin et al.[16] reported that presentation of IGM on physical examination (fistula formation, abscess, and ulceration) was similar; however, IGM was more severe in patients with EN since it presented more often as bilateral disease with diffuse involvement of the breast gland. We found that fistula distribution was significantly higher in the EN-positive group ($P < .05$). Smoking was significantly higher in the EN-negative group ($P < .05$). There was no significant difference in birth region, location, first application, antibiotic type, clinical history, family history, the presence of rheumatological disease or abscess drainage parameters between the EN-positive and -negative groups ($P > .05$).

EN, the most frequent clinicopathological variant of panniculitis, may be associated with a wide variety of diseases, such as infections, rheumatological diseases, and inflammatory bowel diseases.[37] EN is septal panniculitis with no vasculitis; the septa of subcutaneous fat are infiltrated by neutrophils during the early stage and lymphocytes and multinucleated giant cells are responsible for the late stage lesions.[37,38] Kunz et al.[38] found a correlation between "primed" polymorphonuclear neutrophils and CRP in patients with EN, and an association between the neutrophil levels and disease severity was also noted. In accordance with these studies, we found that the mean WBC, ESR, and CRP levels were significantly higher in the EN-positive group ($P < .05$). Arthralgia, breast feeding, and recurrence distributions were significantly higher in the EN-positive group ($P < .05$). Taking the recurrence rate as a poor prognostic factor, the IGM may show a worse course when coexisting with EN. Cetin et al.[16] also concluded that IGM in conjunction with EN was related to bilateral and aggressive involvement, which could be associated with an insufficient response to steroids.

In the present paper, we aimed to investigate whether the association of IGM with EN plays a role as a prognostic indicator; therefore, we considered the recurrence rate as a poor prognostic factor. Patients with EN had higher laboratory values (WBC, ESR, CRP) showing inflammatory parameters, and radiological findings (such as collection and mastitis) showing inflammation in the tissue. Additionally, fistula formation and mass size at presentation were significantly higher in the EN-positive group, again indicating a more severe clinical situation ($P < .05$). Arthralgia, a systematic finding, was also significantly higher in the EN-positive group. Based on this information, in patients with EN, the inflammation was more severe and an increased rate of recurrence was observed. EN may be encountered in patients with higher inflammatory parameters. As a result, association of IGM with EN may suggest a worse prognosis. Patients with EN can be followed more closely to check for disease recurrence.

TABLE 2 Clinical and laboratory findings of patients according to EN groups

	Erythema nodosum (n = 43)	No erythema nodosum (n = 43)	*P*
WBC, mean ± SD (μL)	9629.53 ± 2484.70	8339.53 ± 2387.38	.016[a]
ESR, mean ± SD (mm/h)	34.51 ± 20.80	19.02 ± 9.88	.000[b]
CRP, mean ± SD (mg/L)	26.00 ± 27.49	9.77 ± 10.44	.002[b]
PPD, mean ± SD (mm)	5.29 ± 6.49	6.53 ± 7.91	.637[b]
Mass dimension, mean ± SD (cm)	7.21 ± 3.50	5.81 ± 4.33	.018[b]
ANA, n (%)			
Negative	38 (88.4)	41 (95.3)	.214[c]
Positive	2 (4.7)	—	
Borderline	3 (7.0)	2 (4.7)	
Breast localization, n (%)			
Right	20 (46.5)	22 (51.2)	.238[c]
Left	21 (48.8)	21 (48.8)	
Bilateral	2 (4.7)	—	
Quadrant, n (%)			
Upper exterior	13 (30.2)	8 (18.6)	.042[c]
Lower exterior	4 (9.3)	11 (25.6)	
Upper interior	3 (7.0)	8 (18.6)	
Lower interior	3 (7.0)	4 (9.3)	
Retroareolar	2 (4.7)	4 (9.3)	
Two to 3 quadrants	12 (27.9)	7 (16.3)	
Whole breast	6 (14.0)	1 (2.3)	
Bilateral, n (%)			
Single-sided	41 (95.3)	43 (100.0)	.093[c]
Two-sided	2 (4.7)	—	
Microbiological evaluation, n (%)			
None	2 (4.7)	6 (14.0)	.258[c]
No microorganisms	39 (90.7)	35 (81.4)	
Corynebacterium spp.	1 (2.3)	2 (4.7)	
Klebsiella pneumoniae	1 (2.3)	—	
Arthralgia, n (%)	12 (27.9)	1 (2.3)	.001[c]
Trauma history, n (%)	2 (4.7)	4 (9.3)	.393[c]
Lactation, mean ± SD (mo)	24.07 ± 21.76	20.51 ± 19.52	.427[a]
Breast feeding, n (%)	33 (76.7)	21 (48.8)	.007[d]
Recurrence, n (%)			
No	28 (66.7)	37 (88.1)	.037[c]
Yes	9 (21.4)	2 (4.8)	
Lost to follow-up	5 (11.9)	3 (7.1)	
Treatment, n (%)			
Antibiotics	2 (4.8)	2 (4.8)	>.05
Steroids	20 (47.6)	20 (47.6)	
Methotrexate	17 (40.5)	17 (40.5)	
Expectant management	3 (7.1)	3 (7.1)	
First response to treatment, mean ± SD (d)	35.09 ± 27.76	36.77 ± 40.57	.432[b]
Treatment duration, mean ± SD (d)	154.97 ± 83.03	141.37 ± 91.99	.493[a]
Follow-up duration, mean ± SD (d)	984.47 ± 730.03	795.71 ± 491.30	.186[a]

Note: First response to treatment; the period when the diameter of the mass begins to decrease.

Abbreviations: ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PPD, purified protein derivative; WBC, white blood cell.

[a]Independent samples *t* test.

[b]Mann–Whitney *U* test.

[c]Chi-square likelihood ratio.

[d]Chi-square test.

TABLE 3 Symptoms, ultrasound (US) and mammography findings of patients according to EN groups

	Positive (n = 43)	Negative (n = 43)	*P*
Symptom duration, mean ± SD	121.63 ± 82.26	153.95 ± 135.13	.363[a]
Symptoms, n (%)			
Mass	41 (95.3)	32 (74.4)	.007[b]
Pain	31 (72.1)	29 (67.4)	.639[b]
Flux	16 (37.2)	9 (20.9)	.096[b]
Erythema	15 (34.9)	16 (37.2)	.822[b]
Fever	3 (7.0)	4 (9.3)	.693[b]
Nipple retraction	2 (4.7)	4 (9.3)	.393[b]
Breast discharge	1 (2.3)	—	.237[b]
US, n (%)			
Mass	11 (25.6)	9 (20.9)	.610[b]
Thickening	6 (14.0)	7 (16.3)	.763[b]
Collection	25 (58.1)	15 (34.9)	.031[b]
Mastitis	22 (51.2)	11 (25.6)	.015[b]
Lap	13 (30.2)	12 (27.9)	.812[b]
Edema	12 (27.9)	7 (16.3)	.194[b]
Normal	2 (4.7)	1 (2.3)	.553[c]
Other	1 (2.3)	4 (9.3)	.153[c]
Mammography, n (%)			
None	37 (90.2)	36 (83.7)	.159[c]
Increased density	1 (2.4)	3 (7.0)	
Focal asymmetry	—	2 (4.7)	
Mass	—	1 (2.3)	
Normal	1 (2.4)	1 (2.3)	
Other	2 (4.9)	—	

Abbreviations: EN, erythema nodosum; Lap, lymphadenopathy.
[a]Mann–Whitney *U* test.
[b]Chi-square test.
[c]Chi-square likelihood ratio.

To the best of our knowledge, this paper comprises the first comparative study of the coexistence of IGM and EN reported in the literature. Additionally, it is also the first original article which investigates the role of EN association as a prognostic factor in IGM. However, there are limitations to the present study. The retrospective design of the study unfortunately makes it more viable for a possible bias. Another limitation of the study is that the EN-positive group is not compared to our IGM population with 610 patients. Prospective controlled studies are therefore needed in order to confirm the current results.

TABLE 4 Spearman's correlation results according to erythema nodosum groups and the parameters with statistical significance

	R	*P*
Age	.328**	.002
Fistula	−.405**	.000
Smoking	.213*	.049
WBC	−.271*	.012
ESR	−.427**	.000
CRP	−.345**	.002
Quadrants	−.115	.292
Arthralgia	−.357**	.001
Breast feeding	−.289**	.007
Recurrence	−.243*	.026
Symptom mass	−.292**	.006
US collection	−.233*	.031
US mastitis	−.263*	.014

Note: *$P < .05$ **$P < .01$.
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; US, ultrasound; WBC, white blood cell.

5 | CONCLUSION

Although an infrequent association, IGM should be kept in mind for the differential diagnosis of EN. Granulomatous mastitis should also be considered as a possible etiological factor in EN. The present study highlights the importance of dermatological care. All physicians should not neglect questioning breast complaints in patients with EN since EN may be associated with IGM. This approach will prevent delay in the treatment of IGM. Since fistula distribution and recurrence rates were found to be higher in the EN-positive group, association of IGM with EN may be a poor prognostic factor.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

BPK, MV contributed to the conception, writing and proofreading of this manuscript. BM, SU contributed to the study design, and data interpretation. All authors read and approved the final manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

The study has been approved by Istanbul University-Cerrahpasa Faculty Of Medicine Ethics Board with number: 56388/22.04.2020.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study. Informed written consents are taken from the patients.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Kessler E, Wolloch Y. Granulomatous mastitis: a lesion clinically simulating carcinoma. *Am J Clin Pathol*. 1972;58(6):642-646.
2. Ozmen V, Canturk Z, Celik V, et al. *Breast Disease*. Federation of Breast Diseases Society, Gunes Medical Publishing; 2012:55-65.
3. Fazzio RT, Shah SS, Sandhu NP, et al. Idiopathic granulomatous mastitis: imaging update and review. *Insights Imaging*. 2016;7(4):531-539.
4. Kok KY, Telisinghe PU. Granulomatous mastitis: presentation, treatment and outcome in 43 patients. *Surgeon*. 2010;8(4):197-201.
5. Limaiem F, Korbi S, Tlili T, et al. Idiopathic granulomatous mastitis mimicking breast cancer: report of two cases. *Pathologica*. 2012;104(3):105-108.
6. Oran ES, Gurdal SO, Yankol Y, et al. Management of idiopathic granulomatous mastitis diagnosed by core biopsy: a retrospective multicenter study. *Breast J*. 2013;19(4):411-418.
7. Barreto DS, Sedgwick EL, Nagi CS, et al. Granulomatous mastitis: etiology, imaging, pathology, treatment, and clinical findings. *Breast Cancer Res Treat*. 2018;171(3):527-534.
8. Mizrakli T, Velidedeoglu M, Yemisen M, et al. Corticosteroid treatment in the management of idiopathic granulomatous mastitis to avoid unnecessary surgery. *Surg Today*. 2015;45(4):457-465.
9. Cribier B, Caille A, Heid E, et al. Erythema nodosum and associated diseases. A study of 129 cases. *Int J Dermatol*. 1998;37(9):667-672.
10. Koufakis T, Gabranis I. Erythema nodosum leads to the diagnosis of pulmonary tuberculosis. *Pan Afr Med J*. 2014;18:291.
11. Adams DH, Hubscher SG, Scott DG. Granulomatous mastitis–a rare cause of erythema nodosum. *Postgrad Med J*. 1987;63(741):581-582.
12. Alungal J, Abdulla MC, Narayan R. Idiopathic granulomatous mastitis with erythema nodosum and polyarthritis. *Reumatismo*. 2016;68(2):97-99.
13. Jacquin-Porretaz C, Devalland C, Delapparent T, et al. Idiopathic granulomatous mastitis associated with erythema nodosum. *Ann Dermatol Venereol*. 2019;146(8–9):571-576.
14. Fruchter R, Castilla C, Ng E, et al. Erythema nodosum in association with idiopathic granulomatous mastitis: a case series and review of the literature. *J Eur Acad Dermatol Venereol*. 2017;31(9):e391-e393.
15. Akin M, Karabacak H, Esendagli G, et al. Coexistence of idiopathic granulomatous mastitis and erythemanodosum: successful treatment with corticosteroids. *Turk J Med Sci*. 2017;47(5):1590-1592.
16. Cetin K, Sikar HE, Gulluoglu BM. Idiopathic granulomatous mastitis with erythema nodosum: is it a variant of clinical presentation indicating treatment resistance? A retrospective cohort study. *Breast J*. 2020;26(9):1645-1651.
17. Ringsted S, Friedman M. A rheumatologic approach to granulomatous mastitis: a case series and review of the literature. *Int J Rheum Dis*. 2021;24(4):526-532.
18. Baghbaninaghadehi F, Armijo-Olivo S, Woodhouse L. Fundamentals of randomization in clinical trial. *Int J Adv Nutr Health Sci*. 2016;4(1):174-187.
19. Kang M, Ragan BG, Park JH. Issues in outcomes research: an overview of randomization techniques for clinical trials. *J Athl Train*. 2008;43(2):215-221.
20. Postolova A, Troxell ML, Wapnir IL, Genovese MC. Methotrexate in the treatment of idiopathic granulomatous mastitis. *J Rheumatol*. 2020;47(6):924-927.
21. Kehribar DY, Duran TI, Polat AK, Ozgen M. Effectiveness of methotrexate in idiopathic granulomatous mastitis treatment. *Am J Med Sci*. 2020;360(5):560-565.
22. Pandey TS, Mackinnon JC, Bressler L, et al. Idiopathic granulomatous mastitis- a prospective study of 49 women and treatment outcomes with steroid therapy. *Breast J*. 2014;20:258-266.
23. Altintoprak F, Kivilcim T, Yalkin O, et al. Topical steroids are effective in the treatment of idiopathic granulomatous mastitis. *World J Surg*. 2015;39:2718-2723.
24. Sheybani F, Sarvghad M, Naderi HR, et al. Treatment for and clinical characteristics of granulomatous mastitis. *Obstet Gynecol*. 2015;125:801-807.
25. Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. *World J Clin Cases*. 2014;2(12):852-858.
26. Kaviani A, Vasigh M, Omranipour R, et al. Idiopathic granulomatous mastitis: Looking for the most effective therapy with the least side effects according to the severity of the disease in 374 patients in Iran. *Breast J*. 2019;25(4):672-677.
27. Azizi A, Prasath V, Canner J, et al. Idiopathic granulomatous mastitis: management and predictors of recurrence in 474 patients. *Breast J*. 2020;26(7):1358-1362.
28. White WL, Hitchcock MG. Diagnosis: erythema nodosum or not? *Semin Cutan Med Surg*. 1999;18(1):47-55.
29. Ocal K, Dag A, Turkmenoglu O, et al. Granulomatous mastitis: clinical, pathological features, and management. *Breast J*. 2010;16(2):176-182.
30. Nakamura Y, Yamaguchi M, Nakamura A, et al. Tender, red nodules and arthralgia in a young woman with mastitis. *Clin Exp Dermatol*. 2014;39(3):410-412.
31. Velidedeoglu M, Kilic F, Mete B, et al. Bilateral idiopathic granulomatous mastitis. *Asian J Surg*. 2016;39(1):12-20.
32. Hladik M, Schoeller T, Ensat F, et al. Idiopathic granulomatous mastitis: successful treatment by mastectomy and immediate breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2011;64(12):1604-1607.
33. Asoglu O, Ozmen V, Karanlik H, et al. Feasibility of surgical management in patients with granulomatous mastitis. *Breast J*. 2005;11(2):108-114.
34. Cetin K, Sikar HE, Goret NE, et al. Comparison of topical, systemic, and combined therapy with steroids on idiopathic granulomatous mastitis: a prospective randomized study. *World J Surg*. 2019;43(11):2865-2873.
35. Lai EC, Chan WC, Ma TK, et al. The role of conservative treatment in idiopathic granulomatous mastitis. *Breast J*. 2005;11(6):454-456.
36. Donn W, Rebbeck P, Wilson C, et al. Idiopathic granulomatous mastitis. A report of three cases and review of the literature. *Arch Pathol Lab Med*. 1994;118(8):822-825.
37. Requena L, Requena C. Erythema nodosum. *Dermatol Online J*. 2002;8(1):4.
38. Kunz M, Beutel S, Brocker E. Leucocyte activation in erythema nodosum. *Clin Exp Dermatol*. 1999;24(5):396-401.

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ORIGINAL ARTICLE

CTLA-4 polymorphisms in Thai patients with rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis

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Abstract

Aims: Studies on polymorphisms of the cytotoxic T lymphocytes associated antigen-4 (CTLA-4) genes in rheumatic disease patients are limited in Southeast Asia. This pilot study aimed to determine CTLA-4 polymorphisms in Thai patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), and correlate them with serology.

Method: One-hundred RA, 70 SLE and 50 SSc patients, and 99 healthy controls (HCs) were included in this study. Polymorphisms of the CTLA-4 gene at +49A/G, −318C/T, −1661A/G and −1722T/C loci were determined by polymerase chain reaction restriction fragment length polymorphism methods. Patient serum samples were determined as follows: RA (rheumatoid factor [RF] and anticyclic citrullinated peptide [anti-CCP]), SLE (antinuclear antibodies [ANA], anti-double-stranded DNA [anti-dsDNA], anti-Smith [anti-Sm], anti-ribonucleoprotein [anti-RNP], and anti-Sjögren's syndrome antigen A [SSA]), and SSc (ANA, anti-RNP, anti-SSA, anti-topoisomerase-1 [anti-Scl70], and anti-centromere antibodies [ACA]).

Results: Among the 4 loci studied (+49A/G, −318C/T, −1661A/G and −1722T/C) only the A allele frequency at the +49A/G was significantly higher in the RA patients than their HCs (47.25% vs 35.86%, $P = .029$, odds ratio [OR] 1.60; 95% CI 1.04-2.47). It also was significantly higher in the subgroup of RA patients with positive RF and anti-CCP than their HCs (47.50% vs 35.86%, $P = .020$, OR 1.62; 95% CI 1.06-2.47 and 48.89% vs 35.86%, $P = .012$, OR 1.71; 95% CI 1.11-2.64, respectively). No polymorphisms at these 4 loci were observed in SLE or SSc patients.

Conclusion: The A allele at +49A/G locus of the CTLA-4 gene was associated with RA in Thais.

KEYWORDS

CTLA-4 antigen, genetic loci, polymorphism

1 | INTRODUCTION

Cytotoxic T lymphocytes associated antigen-4 (CTLA-4) is a non-major histocompatibility complex (MHC) molecule, which expresses only on activated CD4+ and CD8+ T cells, and plays an important role by down-regulating T cells upon immune activation. Polymorphisms of the CTLA-4 gene have been shown to associate with many autoimmune diseases including autoimmune thyroid disease (Graves' disease and autoimmune thyroiditis), insulin-dependent diabetes mellitus (IDDM), Addison's disease, vitiligo, myasthenia gravis, multiple sclerosis, systemic rheumatic diseases (including rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]), Celiac disease, and so on.[1] Several loci have been involved in association with autoimmune disease; however, the +49A/G, −318C/T, −1661A/G, −1722T/C, and CT60A/G loci and the 3′ untranslated region (3′UTR) are among the common loci of interest studied.[2] RA, SLE and systemic sclerosis (SSc) are among the common rheumatic diseases studied.

Although polymorphisms of the CTLA-4 gene in patients with RA, SLE and SSc have been studied worldwide, the majority of them in Asia were reported from China,[3-5] Japan,[6-9] Korea,[10-12] Taiwan,[13,14] Iran[15,16] and India.[17,18] However, the results from these studies were inconsistent. Furthermore, studies from Southeast Asian countries were very limited.[19,20]

This pilot study aimed to determine the contribution of CTLA-4 polymorphisms at +49A/G, −318C/T, −1661A/G and −1722T/C loci and their susceptibility to RA, SLE and SSc in Thai patients, and also correlate them with the presence of serology.

2 | MATERIALS AND METHODS

Patients with RA, SLE and SSc, and followed up regularly at the Rheumatology Clinic in Chiang Mai University Hospital, were invited to join this study. They met the American Rheumatism Association 1987 revised criteria for the classification of RA,[21] the 1997 update of the American College of Rheumatology (ACR) revised criteria for the classification of SLE,[22] and the 1980 preliminary criteria for the classification of SSc (scleroderma) of the ACR,[23] respectively. SSc patients were classified further into either limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) as proposed by LeRoy et al.[24] Patients with overlapping autoimmune rheumatic diseases were excluded. Healthy controls (HCs) comprised medical personnel, who were unrelated to the patients, and had no symptoms or signs of any autoimmune rheumatic diseases.

Demographic data including age, gender and disease duration were obtained from all of the patients, whose blood samples and those from the HCs were collected on the day they entered the study. The blood samples were separated further for serum and DNA and kept at −20°C for analysis. Serum from the patients was determined as follows: RA (rheumatoid factor [RF] and anti-citrullinated peptide antibodies [anti-CCP]), SLE (antinuclear antibodies [ANA], anti-double-stranded DNA antibodies [anti-dsDNA], anti-Smith antibodies [anti-Sm], anti-ribonucleoprotein antibodies [anti-RNP] and anti-Sjögren's syndrome antigen A antibodies [anti-SSA]), and SSc (ANA, anti-topoisomerase-1 antibodies [anti-Scl70] and anti-centromere antibodies [ACA]).

RF was determined by nephelometry methods by using the N Latex RF kit and BN Prospec System (Siemens Healthcare Diagnostics Products GmbH). Anti-CCP was determined by enzyme-linked immunosorbent assay (ELISA) using an anti-CCP ELISA (immunoglobulin G [IgG]) test kit (Euroimmun). ANA was determined by indirect immunofluorescent (IIF) methods (IIFT mosaic: HEp-20-10/Liver [Monkey]; Euroimmun). Anti-dsDNA (anti-dsDNA-NcX IgG; Euroimmun), anti-Sm (anti-Sm IgG; Euroimmun), anti-RNP (anti-nRNP/Sm IgG; Euroimmun), anti-SSA (anti-SS-A IgG; Euroimmun), anti-topoisomerase I (anti-Scl-70 IgG; Euroimmun) and ACA (anti-centromeres IgG; Euroimmun) were determined by ELISA. Anti-cardiolipin antibodies (ACL), anti-β2 glycoprotein-1 antibodies, and lupus anticoagulant were not determined in this study.

The polymorphism at the position of the +49A/G locus was detected by the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method using specific oligonucleotide primers, 5′-GCT CTA CTT CCT GAA GAC CT-3′ and 5′-AGT CTC ACT CAC CTT TGC AG-3′, according to Donner et al.,[25] and the PCR product was digested using Bbv 1. The polymorphism at the position of the −318C/T locus in the promoter region was detected by the PCR-RFLP method using oligonucleotide primers, 5′-AAA TGA ATT GGA CTG GAT GGT-3′ and 5′-TTA CGA GAA AGG AAG CCG TG-3′, according to Deichmann et al.,[26] and the PCR product was digested using Mse I. The polymorphism at the position of −1661A/G and −1772T/C in the promoter region was detected by the PCR-RFLP method using the specific oligonucleotide primers, 5′-CTA AGA GCA TCC GCT TGC ACC T-3′ and 5′-TTG GTG TGA TGC ACA GAA GCC TTT T-3′, according to Hudson et al.,[27] and the PCR product was digested using Mse I and Bbv1 for −1661A/G and −1772T/C loci, respectively.

This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (no. 146/2547), and the Ethics Committee of the Faculty of Medicine, Tokyo University (no. 360). All of the participants gave their written informed consent before they entered the study.

2.1 | Statistical analysis

SPSS version 16.0 program was used for statistical analysis. Comparison of the genotype polymorphism between the patients and controls, and clinical manifestations and serologic abnormalities were determined by Chi-square or Fisher's exact test, where appropriate. Hardy-Weinberg equilibrium (HWE) was calculated by using the program available at https://www.had2know.com/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html. A P value of $<.05$ was considered statistically significant, and the odds ratios (OR) and 95% confidence intervals (95% CI) were determined.

3 | RESULTS

This study included 99 HCs, and 100 RA, 70 SLE and 50 SSc patients. Details of their characteristics and serology are shown in Table 1. Of the 99 HCs, 51 (51.52%) were female with a mean ± SD age of 45.59 ± 15.06 years.

Genotype frequency (GF), allele frequency (AF) and phenotype frequency (PF) of the polymorphisms of the CTLA-4 gene at the +49A/G, −318C/T, −1161A/G and −1722T/C loci among the HCs, RA, SLE and SSc patients are shown in Table 2. The allele distribution of each locus in the HCs was fitting statistically for the HWE with a *P* value of .906 for the +49A/G locus, .415 for the −318C/T locus, .918 for the −1661A/G locus and .555 for −1772T/C locus. The A AF at the +49A/G locus was significantly higher in the RA patients than in the HCs (47.50% vs 35.86%, *P* = .020, OR 1.62; 95% CI 1.06-2.47). It also was significantly higher in the RA patients who were RF and anti-CCP positive when compared with the HCs (47.25% vs 35.86%, *P* = .029, OR 1.60; 95% CI 1.04-2.47 and 48.89% vs 35.86%, *P* = .012, OR 1.71; 95% CI 1.11-2.64, respectively) (Table 3). However, these differences were not observed when comparing between patients who were RF or anti-CCP positive and their negative counterparts. There were no significant differences in the GF, AF and PF at the −318C/T, −1661A/G or −1722T/C loci between the RA patients and HCs.

There were no significant differences in GF, AF and PF at the +49A/G, −318C/T, −1661A/G and −1722T/C loci among the SLE patients, when compared with their HCs (Table 2). However, the SLE patients had a significantly higher TC GF at the −1722T/C locusin those who were anti-Sm positive than those being anti-Sm negative (80.00% vs 38.00%, *P* = .009, OR 6.53; 95% CI 1.71-30.05), and also those who were anti-SSA positive than those being anti-SSA negative (65.71% vs 34.29%, *P* = .048, OR 3.67; 95% CI 1.23-11.10). The T PF at −1772T/C was significantly higher in SLE patients with anti-Sm positivity than in those being anti-Sm negative (100% vs 74%, *P* = .028, OR 14.76; 95% CI 0.83-261.25) (Table 3). There were no significant differences in the GF, AF and PF when comparing between SLE patients who were antibody positive and those being negative (anti-dsDNA, anti-RNP, anti-Sm, or anti-SSA), or between those who were antibody positive and HCs in the other loci.

There were no significant differences in the GF, AF and PF at the +49A/G, −318C/T, −1661A/G and −1722T/C loci when comparing between the SSc patients and their HCs (Table 2), or between those with dsSSc and lcSSc. Also, there were no significant differences in the GF, AF and PF when comparing between SSc with positive antibodies (anti-Scl70, anti-RNP and anti-SSA) and either those with negative antibodies or their HCs.

4 | DISCUSSION

This study found that among the 4 CTLA-4 loci (+49/AG, −318C/T, −1661A/G and −1722T/C), only the A allele at the +49A/G locus was

TABLE 1 Demographics and serology among the patients studied

	HCs (N = 99)	RA (N = 100)	SLE (N = 70)	SSc (N = 50)
Age in y, mean ± SD	45.59 ± 15.06	52.28 ± 11.42	35.10 ± 11.34	48.72 ± 10.28
Gender, female, n (%)	51 (51.52)	93 (93.00)	69 (98.57)	45 (90.0)
Disease duration in y, mean ± SD		9.74 ± 7.27	7.09 ± 5.47	7.10 ± 5.36
SSc subtype, n (%)				
Diffuse				39 (78.00)
Limited				11 (22.00)
RF, n (%)		91 (91.00)		
Anti-CCP, n (%)		90 (90.00)		
ANA, n (%)			67 (95.71)	50 (100.00)
Anti-dsDNA, n (%)			53 (75.71)	
Anti-Sm, n (%)			20 (28.57)	
Anti-RNP, n (%)			31 (44.29)	16 (32.00)
Anti-SSA, n (%)			35 (50.00)	17 (34.00)
Anti-Scl70, n (%)			—	34 (68.00)
ACA, n (%)			—	1 (2.00)

Abbreviations: ACA, anti-centromere antibodies; ANA, antinuclear antibodies; anti-CCP, anti-citrullinated peptide antibodies; anti-dsDNA, anti-double stranded DNA antibodies; anti-RNP, anti-ribonucleoprotein antibodies; anti-Scl70, anti-topoisomerase-1 antibodies; anti-Sm, anti-Smith antibodies; HCs, healthy controls; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

TABLE 2 Genotype frequency, allele frequency and phenotype frequency of the CTLA-4 polymorphisms at +49A/G, −318C/T, −1661A/G and −1722T/C loci in patients with RA, SLE and SSc, and HCs

		HCs (N = 99)	RA (N = 100)		SLE (N = 70)		SSc (N = 50)	
		n (%)	n (%)	*P* value	n (%)	*P* value	n (%)	*P* value
+49A/G								
Genotype frequency	AA	13 (13.13)	26 (26.00)	.093	7 (10.00)	.633	8 (16.00)	.627
	AG	45 (45.45)	43 (43.00)	.776	37 (52.86)	.354	21 (42.00)	.729
	GG	41 (41.41)	31 (31.00)	.142	26 (37.14)	.633	21 (42.00)	1
Allele frequency	A	71 (35.86)	95 (47.50)	**.020**[b]	51 (36.43)	1	37 (37.00)	.899
	G	127 (64.14)	105 (52.50)		89 (63.57)		63 (63.00)	
Phenotype frequency	A	58 (58.59)	69 (69.00)	.142	44 (62.86)	.633	29 (58.00)	1
	G	86 (86.87)	74 (74.00)	.062	63 (90.00)	.633	42 (84.00)	.627
−318C/T								
Genotype frequency	CC	84 (84.85)	84 (84.00)	1	55 (78.57)	.313	37 (74.00)	.124[a]
	CT	15 (15.15)	15 (15.00)	1	13 (18.57)	.675	13 (26.00)	
	TT	0	1 (1.00)	1	2 (2.86)	.170	0	0
Allele frequency	C	183 (92.42)	183 (91.50)	.854	123 (87.86)	.188	87 (87.00)	.144
	T	15 (7.58)	17 (8.50)		17 (12.14)		13 (13.00)	
Phenotype frequency	C	99 (100.00)	99 (99.00)	1	68 (97.14)	.170	50 (100.00)	0
	T	15 (15.15)	16 (16.00)	1	15 (21.43)	.313	13 (26.00)	.124
−1661A/G								
Genotype frequency	AA	81 (81.82)	83 (83.00)	.854	54 (77.14)	.559	37 (74.00)	.290
	AG	17 (17.17)	15 (15.00)	.704	14 (20.00)	.689	12 (24.00)	.382
	GG	1 (1.01)	2 (2.00)	1	2 (2.86)	.570	1 (2.00)	1
Allele frequency	A	179 (90.40)	181 (90.50)	1	122 (87.14)	.379	86 (86.00)	.328
	G	19 (9.60)	19 (9.50)		18 (12.86)		14 (14.00)	
Phenotype frequency	A	98 (98.99)	98 (98.00)	1	122 (87.14)	.379	49 (98.00)	1
	G	18 (18.18)	17 (17.00)	.854	18 (12.86)	.379	13 (26.00)	.290
−1722T/C								
Genotype frequency	TT	28 (28.28)	28 (28.00)	1	22 (31.43)	.733	19 (38.00)	.264
	TC	52 (52.53)	61 (61.00)	.254	35 (50.00)	.757	25 (50.00)	.862
	CC	19 (19.19)	11 (11.00)	.117	13 (18.57)	1	6 (12.00)	.355
Allele frequency	T	108 (54.55)	117 (58.50)	.479	79 (56.43)	.740	63 (63.00)	.174
	C	90 (45.45)	83 (41.50)		61 (43.57)		37 (37.00)	
Phenotype frequency	T	80 (80.81)	89 (89.00)	.117	57 (81.43)	1	49 (98.00)	1
	C	71 (71.72)	72 (72.00)	1	48 (68.57)	.733	13 (26.00)	.290

Note: P value: compared between disease and HCs.

Abbreviations: HCs, healthy controls; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

[a]*P* value corrected by 2.

[b]Odds ratio [95%CI] = 1.62 [1.06-2.47].

Bold = significant p-value.

P values of each genotype frequency or phenotype frequency is corrected by 3 or 2, respectively.

significantly higher in the RA patients and HCs, indicating that it associated with RA. This association was observed also in RA patients with positive RF and anti-CCP. Unfortunately, this study could not find any polymorphisms at these 4 loci in association with SLE and SSc patients. However, in subgroup analysis, the TC genotype at the −1772T/C locus were significantly higher in SLE patients with anti-Sm positivity than in those who were anti-Sm negative, and the TC genotype also was significantly higher in SLE patients with anti-SSA positivity than in those who were anti-SSA negative.

Polymorphisms in several loci of the CTLA-4 gene in patients with RA have been determined in several ethnic groups, and the +49A/G was the most common locus studied (Table S1). However, the results of these studies were conflicting, not only those from the same country, but also those from meta-analysis. For example, a

TABLE 3 Genotype frequency, allele frequency and phenotype frequency of the CTLA-4 polymorphisms, which are significantly associated with serology at the +49/AG locus in patients with RA and −1722T/C locus in patients with SLE

RA		HCs (N = 99)	RA, RF+ (N = 91)	RA, RF− (N = 9)	*P* value (RA, RF+ vs RF−)	*P* value (RA, RF+ vs HCs)	RA, CCP+ (N = 90)	RA, CCP− (N = 10)	*P* value (RA, CCP+ vs CCP−)	*P* value (RA, CCP+ vs HCs)
+49A/G										
Genotype frequency	AA	13 (13.13)	24 (26.37)	2 (22.22)	1	.081	23 (25.56)	3 (30.00)	.717	.123
	AG	45 (45.45)	38 (41.76)	5 (55.56)	.493	.661	42 (46.67)	1 (10.00)	.120	.885
	GG	41 (41.41)	29 (31.87)	2 (22.22)	.717	.180	25 (27.78)	6 (60.00)	.066	.066
Allele frequency	A	71 (35.86)	86 (47.25)	9 (50.00)	1	**.029**[a]	88 (48.89)	7 (35.00)	.345	**.012**[c]
	G	127 (64.14)	96 (52.75)	9 (50.00)	1	**.029**[b]	92 (51.11)	13 (65.00)	.345	**.012**[d]
Phenotype frequency	A	58 (58.59)	62 (68.13)	7 (77.78)	.717	.180	65 (72.22)	4 (40.00)	.066	.066
	G	86 (86.87)	67 (73.63)	7 (77.78)	1	.054	67 (74.44)	7 (70.00)	.717	.082

SLE		HCs (N = 99)	SLE, Sm+ (N = 20)	SLE, Sm− (N = 50)	*P* value (SLE, Sm+ vs Sm−)	*P* value (SLE, Sm+ vs HCs)	SLE, SSA+ (N = 35)	SLE, SSA (N = 35)	*P* value (SLE, SSA+ vs SSA−)	*P* value (SLE, SSA+ vs HCs)
−1772T/C										
Genotype frequency	TT	28 (28.28)	4 (20.00)	18 (36.00)	.259	.584	8 (22.86)	14 (40.00)	.197	.659
	TC	52 (52.53)	16 (80.00)	19 (38.00)	**.009**[e]	.081	23 (65.71)	12 (34.29)	**.048**[g]	.235
	CC	19 (19.19)	0	13 (26.00)	**.042**[f]	.120	4 (11.43)	9 (25.71)	.218	.435
Allele frequency	T	108 (54.55)	24 (60.00)	55 (55.00)	.706	.602	39 (55.71)	40 (57.14)	1	.890
	C	90 (45.45)	16 (40.00)	45 (45.00)	.706	.602	31 (44.29)	30 (42.86)	1	.890
Phenotype frequency	T	80 (80.81)	20 (100.00)	37 (74.00)	**.028**[h]	.080				
	C	71 (71.72)	16 (80.00)	32 (64.00)	.259	.584				

Note: Data are expressed as n (%).

Abbreviations: −, negative; +, positive; CCP, anti-citrullinated peptide antibodies; HCs, healthy controls; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; Sm, anti-Smith antibodies; SSA, anti-Sjögren's syndrome antigen A antibodies.

[a]Odds ratio (OR) [95%CI] = 1.60 [1.04-2.47].

[b]OR [95%CI] = 0.62 [0.41-0.96].

[c]OR [95%CI] = 1.71 [1.11-2.64].

[d]OR [95%CI] = 0.58 [0.38-0.90].

[e]OR [95%CI] = 6.53 [1.71-30.05].

[f]OR [95%CI] = 0.068 [0.00-1.20].

[g]OR [95%CI] = 3.67 [1.23-11.10].

[h]OR [95%CI] = 14.76 [0.83-261.25].

Bold = significant p-value.

P values of each genotype frequency or phenotype frequency is corrected by 3 or 2, respectively.

study in Taiwan by Lee et al.[28] found that the G allele at the +49A/G locus was associated with their Chinese RA patients, but Liu et al.[13] from the same country could not confirm this finding. In China, a study by Liu et al.[5] found no polymorphisms at +49A/G in their RA patients, while a study by Tang et al.[29] found that the G allele at the +49A/G locus was associated with their RA patients. A meta-analysis performed in 2014 by Li et al.,[30] which included 16 studies, found that the G+ genotype at the +49A/G locus was associated with RA in the Asian but not Caucasian population; whereas the most recent meta-analysis in 2021 by Lui et al.,[31] which included 30 studies, found that the G allele was associated with decreased RA among Asian and Latin American ethnics, but not Caucasians or Africans. In other words, the A allele was associated with RA among Asians and Latin Americans. Also, the most recent meta-analysis by Liu et al.[31] found no association between the polymorphism at −318C/T and RA.

Polymorphisms of the CTAL-4 gene in patients with SLE and SSc have been studied widely also with inconclusive results (Tables S2 and S3). A similar discrepancy in findings on the CTLA-4 polymorphism also was found in SLE patients when Ahmed et al.[6] found that the G alleles and GG genotype at the +49A/G locus were associated with Japanese SLE, and this finding was not confirmed by Takeuchi et al.[32] However, it was found among 3 meta-analyses that involved the +49A/G, −318C/T, −1661A/G and −1772T/C loci; the G allele and G+ genotype at the +49A/G locus were associated with Asian but not Caucasian SLE,[33] and the T allele at the −1772T/C locus was associated with Asian SLE but not SLE of other ethnic groups,[34,35] whereas, no association between the CTLA-4 polymorphism and SLE was found at the −318C/T or −1661A/G locus.[35] No polymorphisms at the +49A/G locus in Thai SLE patients in this study were similar to those previously reported by Kimkong et al.[20] It was interesting that studies on polymorphisms of the CTLA-4 gene in SSc patients were far fewer than those on RA and SLE (Table S3). A meta-analysis by Song et al.,[36] which involved the above 4 loci, found that the T+ genotype of the −1722T/C locus associated with SSc patients.

The discrepancy in the results of the association between various loci of the CTLA-4 gene, including +49A/G, −1661A/G and −1722T/C in RA, SLE and SSc patients in these studies (Tables S1, S2 and S3), might not be explained solely by ethnic factors. Other factors including size of the population studied, genotyping methods,[30] the presence of other genetic factors (eg, shared epitopes or other genetic loci),[7,12,37,38] or other concomitant diseases that have genetic influence (eg, autoimmune thyroid disease and IDDM)[1,39] also might be involved. These factors were not identified or controlled in many previous reports that are similar to this study. We found that the A allele at the +49A/G locus was associated with increased risk of RA in Thai patients; or in other words, the G allele decreased that risk in this study, differing from many results in the aforementioned previous studies, which found that the G allele did associate with RA (Table S1). The finding that the A allele was associated with RA correlated with the study by Suppiah et al.[40] in a Northern Irish population, and the most recent meta-analysis by Lui et al.[31]

There were several limitations in this study. As it was a pilot study, the statistical power and sample size were not calculated at the beginning. However, retrospective calculation of the +49A/G locus in RA patients revealed a statistical power of 76%, which was slightly lower than the generally acceptable 80%, and the current sample size also was slightly lower than it should be. The statistical power was much lower and the sample size much smaller among the loci that did not show statistical significance in RA, as well as in SLE and SSc patients. Therefore, an association between the A allele at +49A/G in RA should be firm. Due to the reason above, therefore, the TC genotypes at the −1772T/C locus that were significantly higher in SLE patients with positive anti-Sm than in those without, and that the TC genotype at the same locus that also was significantly higher in SLE patients with positive anti-SSA than in those with negative anti-SSA, were difficult to conclude.

Another limitation was that the associations between genetic polymorphism and the clinical features or disease activity were not determined. Although an association between the +49A/G polymorphism and RA disease activity has been reported,[41] disease activity together with clinical manifestations or radiographic damage tends to change over time, depending on disease flare and treatment received. In contrast, the presence or absence of auto-antibodies is rather constant in making the association between them and a genetic marker quite firm. Lastly, the linkage disequilibrium was not determined, as the result might be inaccurate due to the small sample size. Furthermore, family study also is needed for correct estimation, but was not performed in this study. Nevertheless, the results from this pilot study could be useful for future studies in Thailand or other countries in Southeast Asia.

In conclusion, this study, with a limited number of cases and controls, found that the A allele at the +49A/G locus of the CTLA-4 gene was associated with Thai RA patients. Further studies with a larger sample size are needed to confirm this finding.

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CONFLICT OF INTEREST

The authors declare they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

WL: conception and design, acquisition of data, analysis, interpretation of data, and drafting and revising the manuscript. NK: acquiring the data, and critically revising the important intellectual content of the manuscript. AW: data analysis, interpretation of data and critically revising the important intellectual content of the manuscript. SK: conception and design, and critically revising the important intellectual content of the manuscript. FT: conception and design,

interpretation of data, and critically revising the important intellectual content of the manuscript. All of the authors approved the final version of the manuscript to be submitted for publication. Dr Louthrenoo had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data and analysis.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration as revised in Brazil (2013). The Ethics Committee of the Faculty of Medicine, Chiang Mai University (no. 146/2547). The Research Committee of the Faculty of Medicine, Tokyo University (no. 360).

INFORMED CONSENT

All of the participants provided written informed consent prior to entering this study.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

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REFERENCES

1. Kristiansen OP, Larsen ZM, Pociot F. CTLA-4 in autoimmune diseases–a general susceptibility gene to autoimmunity? *Genes Immun*. 2000;1:170-184.
2. Romo-Tena J, Gomez-Martin D, Alcocer-Varela J. CTLA-4 and autoimmunity: new insights into the dual regulator of tolerance. *Autoimmun Rev*. 2013;12:1171-1176.
3. Dong HR, Li HS, Wang SC, Balin QM, Chang PY. Association between PDCD1, CTLA4, and MECP2 gene polymorphisms and systemic lupus erythematosus in the Chinese Northern Han. *Genet Mol Res*. 2015;14:17567-17573.
4. Lei C, Dongqing Z, Yeqing S, et al. Association of the CTLA-4 gene with rheumatoid arthritis in Chinese Han population. *Eur J Hum Genet*. 2005;13:823-828.
5. Liu CP, Jiang JA, Wang T, et al. CTLA-4 and CD86 genetic variants and haplotypes in patients with rheumatoid arthritis in southeastern China. *Genet Mol Res*. 2013;12:1373-1382.
6. Ahmed S, Ihara K, Kanemitsu S, et al. Association of CTLA-4 but not CD28 gene polymorphisms with systemic lupus erythematosus in the Japanese population. *Rheumatology*. 2001;40:662-667.
7. Matsushita M, Tsuchiya N, Shiota M, et al. Lack of a strong association of CTLA-4 exon 1 polymorphism with the susceptibility to rheumatoid arthritis and systemic lupus erythematosus in Japanese: an association study using a novel variation screening method. *Tissue Antigens*. 1999;54:578-584.
8. Takeuchi F, Kawasugi K, Mori M, et al. The genetic contribution of CTLA-4 dimorphisms in promoter and exon 1 regions in Japanese patients with rheumatoid arthritis. *Scand J Rheumatol*. 2006;35:154-155.
9. Takeuchi F, Nakaue N, Kawasugi K, Mori M, Kuwata S, Tanimoto K. The CTLA-4 -1661A/G and -1772T/C dimorphisms in Japanese patients with systemic sclerosis. *Rheumatol Int*. 2007;27:785-787.
10. Lee YH, Choi SJ, Ji JD, Song GG. No association of polymorphisms of the CTLA-4 exon 1(+49) and promoter(-318) genes with rheumatoid arthritis in the Korean population. *Scand J Rheumatol*. 2002;31:266-270.
11. Lee YH, Kim YR, Ji JD, Sohn J, Song GG. Polymorphisms of the CTLA-4 exon 1 and promoter gene in systemic lupus erythematosus. *Lupus*. 2001;10:601-605.
12. Kim YO, Kim HJ, Kim SK, Chung JH, Hong SJ. Association of the CD28/CTLA4/ICOS polymorphisms with susceptibility to rheumatoid arthritis. *Clin Chem Lab Med*. 2010;48:345-353.
13. Liu MF, Wang CR, Chen PC, Lin TL. CTLA-4 gene polymorphism in promoter and exon-1 regions is not associated with Chinese patients with rheumatoid arthritis. *Clin Rheumatol*. 2004;23:180-181.
14. Liu MF, Wang CR, Lin LC, Wu CR. CTLA-4 gene polymorphism in promoter and exon-1 regions in Chinese patients with systemic lupus erythematosus. *Lupus*. 2001;10:647-649.
15. Almasi S, Erfani N, Mojtahedi Z, Rajaee A, Ghaderi A. Association of CTLA-4 gene promoter polymorphisms with systemic sclerosis in Iranian population. *Genes Immun*. 2006;7:401-406.
16. Rajaee A, Ebrahimi A, Ghiam AF, Kalantari T, Ghaderi A. Exon-1 polymorphism of ctla-4 gene is not associated with systemic sclerosis in Iranian patients. *Rheumatol Int*. 2006;26:687-692.
17. Devaraju P, Gulati R, Singh BK, Mithun CB, Negi VS. The CTLA4 +49 A/G (rs231775) polymorphism influences susceptibility to SLE in South Indian Tamils. *Tissue Antigens*. 2014;83:418-421.
18. Katkam SK, Kumaraswami K, Rupasree Y, Thishya K, Rajasekhar L, Kutala VK. Association of CTLA4 exon-1 polymorphism with the tumor necrosis factor-alpha in the risk of systemic lupus erythematosus among South Indians. *Hum Immunol*. 2016;77:158-164.
19. Chua KH, Puah SM, Chew CH, Tan SY, Lian LH. Study of the CTLA-4 gene polymorphisms in systemic lupus erythematosus (SLE) samples from Malaysia. *Ann Hum Biol*. 2010;37:274-280.
20. Kimkong I, Nakkuntod J, Sae-Ngow S, Snabboon T, Avihingsanon Y, Hirankarn N. Association between CTLA-4 polymorphisms and the susceptibility to systemic lupus erythematosus and Graves' disease in Thai population. *Asian Pac J Allergy Immunol*. 2011;29:229-235.
21. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31:315-324.
22. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.
23. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum*. 1980;23:581-590.
24. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15:202-205.
25. Donner H, Rau H, Walfish PG, et al. CTLA4 alanine-17 confers genetic susceptibility to Graves' disease and to type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 1997;82:143-146.
26. Deichmann K, Heinzmann A, Bruggenolte E, Forster J, Kuehr J. An Mse I RFLP in the human CTLA4 promotor. *Biochem Biophys Res Commun*. 1996;225:817-818.
27. Hudson LL, Rocca K, Song YW, Pandey JP. CTLA-4 gene polymorphisms in systemic lupus erythematosus: a highly significant association with a determinant in the promoter region. *Hum Genet*. 2002;111:452-455.
28. Lee CS, Lee YJ, Liu HF, et al. Association of CTLA4 gene A-G polymorphism with rheumatoid arthritis in Chinese. *Clin Rheumatol*. 2003;22:221-224.
29. Tang MJ, Zhou ZB. Association of the CTLA-4 +49A/G polymorphism with rheumatoid arthritis in Chinese Han population. *Mol Biol Rep*. 2013;40:2627-2631.

30. Li X, Zhang C, Zhang J, et al. Polymorphisms in the CTLA-4 gene and rheumatoid arthritis susceptibility: a meta-analysis. *J Clin Immunol*. 2012;32:530-539.
31. Liu W, Yang Z, Chen Y, et al. The association between CTLA-4, CD80/86, and CD28 gene polymorphisms and rheumatoid arthritis: an original study and meta-analysis. *Front Med*. 2021;8:598076.
32. Takeuchi F, Kawasugi K, Nabeta H, Mori M, Tanimoto K. CTLA-4 dimorphisms in Japanese patients with systemic lupus erythematosus. *Clin Exp Rheumatol*. 2003;21:527-528.
33. Chang WW, Zhang L, Yao YS, Su H. Association between CTLA-4 exon-1 +49A/G polymorphism and systemic lupus erythematosus: an updated analysis. *Mol Biol Rep*. 2012;39:9159-9165.
34. Zhu JM, Li BK, Chen GM, et al. CTLA-4 -1722T/C polymorphism and systemic lupus erythematosus susceptibility: a meta-analysis involving ten separate studies. *Immunol Invest*. 2013;42:91-105.
35. Zhu Y, Wang J, Feng X. CTLA-4 SNPs (CT60A/G, -1722T/C, -1661G/A, and -318C/T) and systemic lupus erythematosus: a meta-analysis. *Crit Rev Eukaryot Gene Expr*. 2014;24:89-100.
36. Song GG, Lee YH. The CTLA-4 and MCP-1 polymorphisms and susceptibility to systemic sclerosis: a meta-analysis. *Immunol Invest*. 2013;42:481-492.
37. Seidl C, Donner H, Fischer B, et al. CTLA4 codon 17 dimorphism in patients with rheumatoid arthritis. *Tissue Antigens*. 1998;51:62-66.
38. Torres B, Aguilar F, Franco E, et al. Association of the CT60 marker of the CTLA4 gene with systemic lupus erythematosus. *Arthritis Rheum*. 2004;50:2211-2215.
39. Benhatchi K, Jochmanová I, Habalová V, Wagnerová H, Lazúrová I. CTLA4 exon1 A49G polymorphism in Slovak patients with rheumatoid arthritis and Hashimoto thyroiditis—results and the review of the literature. *Clin Rheumatol*. 2011;30:1319-1324.
40. Suppiah V, O'Doherty C, Heggarty S, Patterson CC, Rooney M, Vandenbroeck K. The CTLA4+49A/G and CT60 polymorphisms and chronic inflammatory arthropathies in Northern Ireland. *Exp Mol Pathol*. 2006;80:141-146.
41. Luterek-Puszynska K, Malinowski D, Paradowska-Gorycka A, Safranow K, Pawlik A. CD28, CTLA-4 and CCL5 gene polymorphisms in patients with rheumatoid arthritis. *Clin Rheumatol*. 2017;36:1129-1135.

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

Non-gonococcal septic arthritis of native joints in Western Australia. A longitudinal population-based study of frequency, risk factors and outcome

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Abstract

Objective: To describe the incidence and long-term outcome of non-gonococcal septic arthritis (SA) in Western Australia (WA).

Methods: Newman criteria were applied to define culture-positive SA and suspected SA cases in the state-wide West Australian Rheumatic Diseases Epidemiological Registry with longitudinally linked health data for patients >16 years with a first diagnostic code of pyogenic arthritis (711.xx [ICD-9-CM] and M00.xx [ICD-10-AM]) between 1990-2010. Annual incidence rates/100 000 (AIR) and standardized (against WA population) mortality rates/1000 person-years (SMR) and outcomes during 10.1 years follow-up are reported.

Results: Among 2633 SA patients (68.6% male, age 47.4 years), 1146 (43.5%) had culture-positive SA. The overall AIR for culture-positive (1.6-6.3) and total SA cases (4.3-12.9) increased between 1990 and 2010 as did age at onset (39.5-54 years) and proportion of females (23-35.6%). Knees (33.6.%) were most frequently affected and 37.1% of cultures showed microorganisms other than Gram-positive cocci. Thirty-day rates for readmission and mortality were 25.4% and 3.2.%. During follow-up rates for serious infections (56.4%), osteoarthrosis (5.2%) and osteomyelitis (2.7%) were higher in culture-positive SA. SMR was increased for all SA patients but especially in those 17-40 years of age with culture-positive SA (24.2; 95% CI 2.3-261).

Conclusions: The incidence of SA in WA has risen steeply over 20 years. SA now occurs at higher age, affects females more often with over a third of cases caused by Gram-negative microorganisms. Not only culture-positive, but also suspected SA led to increased bone/joint complications, in-hospital and late mortality.

KEYWORDS
incidence, morbidity, mortality, septic arthritis

1 | INTRODUCTION

Septic arthritis (SA) is the broad term to describe the process of microorganisms entering and proliferating in the vascular synovium, that is prone to bacterial seeding due to the lack of a protective basement membrane.[1] SA following invasion by staphylococci and streptococci is regarded as the most frequent form of SA resulting from skin breaks, direct trauma, or intra-articular manipulation.[1,2] Seeding of Gram-negative bacteria following loss of gastrointestinal or urogenital mucosal integrity can also cause SA.[3] SA is a medical emergency as it can lead to rapid destruction of joints with poor functional outcome reported in up to 30% of patients but also because it associates with significant short-term mortality rate.[4-8] The worldwide incidence of SA is reportedly rising due to a combination of increased longevity, multi-comorbidity, iatrogenic complications and increasing use of immunomodulating therapies for chronic arthritis and other conditions over the last 25 years.[9-12] Based on the above, and the limited availability of comprehensive Australian data,[13,14] we investigated the frequency, underlying clinical characteristics and outcomes of incident SA of native joints in Western Australia (WA) for patients admitted to hospital for SA from 1990-2010, with follow-up extending to 2015.

2 | METHODS

This was a population-based retrospective observational study used routinely to collect state-wide administrative health data for patients with specific rheumatic diseases recorded in the Western Australian Rheumatic Disease Epidemiological Registry between 1980 and 2015 (WARDER). WARDER data were extracted and linked through the Western Australian Data Linkage System (WADLS) using probabilistic matching (based on a person's name, residential address, date of birth and gender) to link all health contacts over time for all people registered in the Hospital Morbidity Data Collection (HMDC), WA Cancer Registry, WA Mortality Registry or the Emergency Department Data Collection (EDDC) in WA (population 2.5 million).[15] A detailed description of the data linkage process across datasets is freely available (https://www.datalinkage-wa.org.au/dlb-services/linkage/).

Study cohort Patients with incident SA were identified by the first International Classification of Diseases code (Pyogenic arthritis; 711.xx [ICD-9-CM] and M00.xx [ICD-10-AM]; Table S2) in the HMDC and EDDC between 1 January 1990 and 31 December 2010. This study period allowed a minimum follow-up of 5 years. Notably and to facilitate comparison with most other studies on SA, we did not include patients with arthritis in ICD-classified other infectious and parasitic diseases such as gonococcal (M54), tuberculous (M01.1), Lyme's disease (M0.1.2), viral (M01.4-5), mycotic (M01.6) and parasitic (M01.8) joint infections. We also excluded all patients <16 years of age at incident record of SA and all patients with a diagnostic code for prosthetic joint infection (ICD-9-CM: 996.60-996.67; ICD-10-AM: T84.5-84.7, Y83, Y83.8 and E878.1; Table S2). In total 2691 patients were registered with a diagnostic code for SA, but we excluded 68 patients that were discharged from emergency department care with no further data available. For the remaining 2633 patients we applied Newman criteria to define culture-positive (Newman Grades A and B where an organism is isolated from the joint or elsewhere) and culture-negative cases (Newman grade C where no organism was isolated but there was strong suspicion based on clinical and/or synovial fluid and/or imaging findings).[7,16] We defined time-zero (T_0) as the date with a first SA diagnostic code but as this was not necessarily the first hospital contact, we implemented a lookback period defined as all observation time prior to T_0 in order to measure pre-existing comorbidity. Comorbidity was assessed according to the validated and prognostically important Charlson comorbidity index (CCI).[17,18] We also registered the occurrence of other serious infections across all hospital contacts defined as episodes leading to ED presentation and/or hospital admission resulting in an infectious disease code for 5 infectious disease categories (pneumonia, sepsis or bacteremia, urinary tract infection [UTI], skin and soft tissue infections) and opportunistic infections at any time point.[19,20]

Primary outcomes were annual incidence rates (AIR) per 100 000 population, risk of recurrence and post SA joint complications as well as all-cause mortality rates per 1000 person-years (MR) and survival estimates based on date of death in the WA Death Registry.

The Human Research Ethics Committee at the WA Department of Health (WADOH HREC # 2016.24) provided approval for this project.

2.1 | Statistical analyses

Descriptive statistics include median and interquartile range (IQR) for continuous variables compared by non-parametric methods (Kruskal-Wallis), categorical data described with a frequency and proportion and group comparisons tested with odds ratios (OR) and Fisher's exact test. AIRs for SA were calculated per 100 000 population with 95% CI derived from Poisson distribution. MR per 1000 person-years in patients with SA were compared with age (at death) and gender-matched categories from the general population by standardized mortality rate ratio (SMRR). Kaplan-Meier survival estimates up to date of death or study exit (1 July 2015) for subgroups were compared by log-rank testing and prognostic covariates analyzed hazard ratios (95% CI) from Cox regression. All analyses were performed using SPSS software v23.0 (IBM) and OpenEpi software with two-sided *P* values <.05 considered to be statistically significant.

3 | RESULTS

In total 2633 adults were admitted with a first diagnosis of SA between 1990 and 2010. Average overall AIR was 8.15/100 000 with a noteworthy rise from 4.39/100 000 in 1990 to 12.87/100 000 in 2010. AIR for culture-positive SA (43.1%) rose from 1.2 to

6.3/100 000 and for culture-negative SA (66.9%) from 3.2 to 6.6/100 000 (Figure 1A). There was no specific seasonal influence on SA occurrence regardless of Newman status (Figure 1B). SA was more predominant in males in both culture-positive and -negative groups while culture-positive patients were older at first SA admission (Table 1). Nearly a third of patients resided in rural areas of WA (34%) and Indigenous Australians (16.4%). The rising incidence rate coincided with an increase in age at diagnosis (from 45.1 to 55.6 years) and the proportion of female patients (23%-36%; Table S1).

Knees (33.6%) were the most frequently affected joints, with positive culture rates highest for shoulders and knees and lowest for ankles and hands (Figure 2). Staphylococci and streptococci were the main causative agents (62.8%) in cases where microorganisms were identified, but other micro-organism were found in over a third of culture-positive patients (Table 1). For 288 (10.9%) patients SA was the first registered hospital contact, but for the other patients lookback data available for an average 14.5 (±7.7) years revealed significant pre-existing morbidity with a high frequency of prior serious infections and underlying joint disease (Table 1). The average time spent in hospital for SA was 5 days (IQR 2-9) with longer length of stay in culture-positive patients. In total 44 (1.7%) mainly culture-positive patients required intensive care admission and 31-day mortality (3.2% overall) was significantly higher in culture-positive patients (6.2% vs 1%, $P < .001$; Table 1).

In total 365 patients (13.8%) were readmitted at least once within 30 days following discharge with a total of 416/716 readmissions (58.2%) coded as SA-related. Follow-up data beyond 30 days post-discharge were available for 2367 (92.8%) patients with a median follow-up of 121 months (IQR 71-185). SA recurrence beyond 30 days was rare (0.6%), but more frequent in culture-positive patients as was subsequent osteomyelitis (2.7%) with nearly half of cases diagnosed within the first year of follow-up (Table 2). Local complications such as ankylosis/dislocation and contractures were rare (0.15%) and subsequent diagnosis of crystals (1.6% vs 1.9%) and immune-mediated arthropathy (5.1% vs 4.0%) were equally

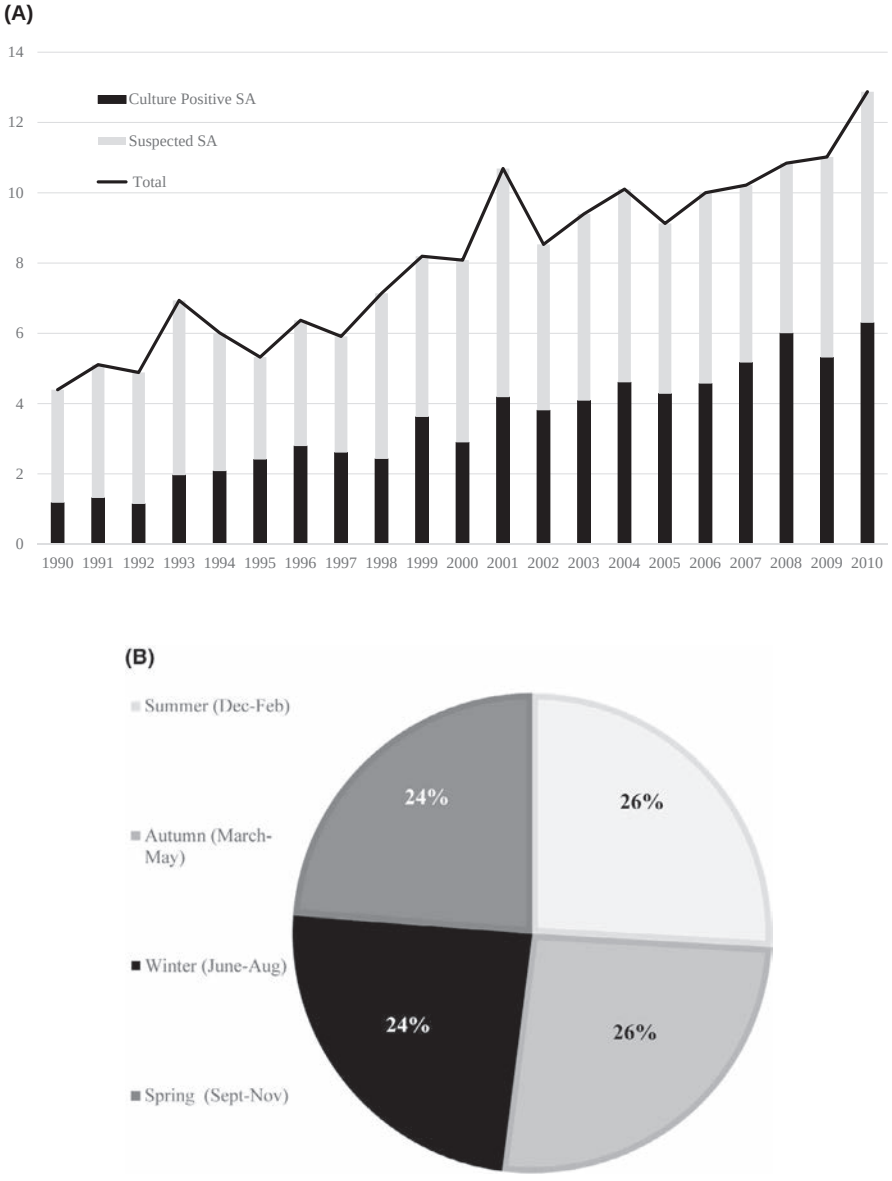

FIGURE 1 Annual incidence for native joint septic arthritis (SA) per 100 000 population >16 years of age in Western Australia over period 1990-2010 (A) and seasonal influence on hospital admission for SA (B)

TABLE 1 Demographic and clinical data at time of diagnosis of septic arthritis (SA). Figures represent median values (IQR) or numbers (%). *P* value for suspected vs culture-positive SA

	Total (*N* = 2633)	Suspected SA (*n* = 1497)	Culture-positive SA (*n* = 1136)	*P* value
Male	1771 (67.2)	996 (66.5)	775 (68.2)	NS
Median age (IQR)	49 (32-68)	47 (30-64)	54 (35-74)	<.05
Metropolitan area	1743 (66.2)	854 (57)	889 (68.2)	<.001
Rural area	890 (33.8)	663 (43)	247 (31.8)	
Indigenous background (%)	542 (20.6)	376 (25.1)	166 (14.6)	<.05
Micro-organism identified				
Staphylococci	–	–	549 (48.3)	
Streptococci	–	–	165 (14.5)	
Other	–	–	422 (37.1)	
Lookback period, y	14.7 (8.4-20.3)	13.9 (7.8-19.4)	15.1 (8.9-20.8)	.004
Underlying joint disease[a]	400 (15.1)	179 (12)	221 (19.5)	<.05
Serious infections	912 (34.6)	447 (29.8)	465 (40.9)	<.01
CCI score at SA diagnosis	1 (1-2)	1 (0-2)	1 (1-3)	<.01
CCI score=0	524 (22.4)	330 (25.3)	194 (18.7)	<.001
CCI score=1	875(37.4)	520 (39.8)	355 (34.2)	
CCI score=2	378 (15.8)	207 (15.8)	171 (16.5)	
CCI score=3	537 (22.9)	220 (17.6)	317 (30.6)	
Event <30 d prior to SA				
Joint aspiration	161 (6)	92 (6.5)	69 (6)	.23
Any infection	233 (8.8)	42 (2.9)	191 (16.8)	<.01
Sepsis	20 (0.7)	2 (0.1)	18 (1.6)	<.01
Admission outcome				
Length of stay, d	5 (2-9)	4 (2-7)	7 (3-14)	<.01
Admitted to ICU	11 (1.7)	3 (0.2)	41 (3.6)	<.01
Readmissions <31 d	671 (25.4)	304 (20.3)	367 (32.3)	<.01
Died <31 d	85 (3.2)	15 (1)	70 (6.2)	<.01

Note: Small numbers (*n* < 5) have been confidentialized due to Human Research Ethics Committee requirementsCCI, Charlson comorbidity index; ICU, intensive care unit.

Abbreviations: CCI, Charlson comorbidity index; ICU, intensive care unit.

[a]Includes patients with inflammatory and degenerative joint disease.

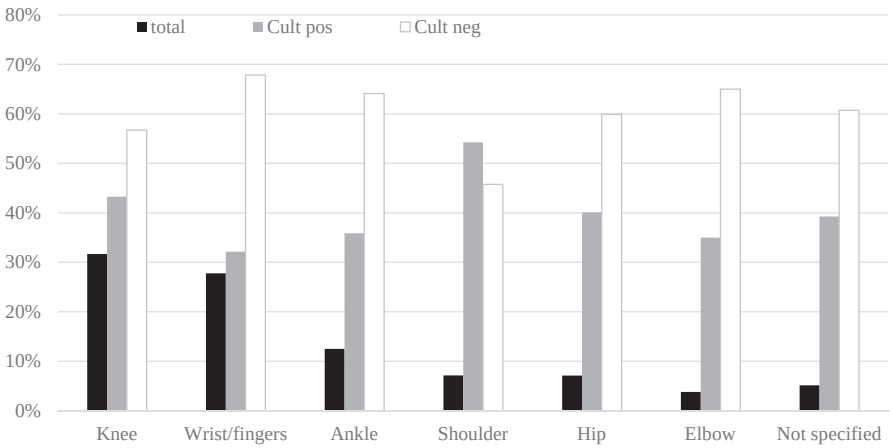

FIGURE 2 Distribution of joints affected by septic arthritis (SA) (percentage of total) and percentage of positive/negative cultures per affected joint

frequent in both subgroups. More patients with culture-positive SA received a new diagnosis of osteoarthrosis (7.3% vs 3.9%) but the need for subsequent joint replacement surgery (2.4% vs 1.8%) and joint aspiration (13.2% vs 14%) were similar in both subgroups. The rate of new other serious infections requiring admission was high (56.4% overall) coinciding with an increasing CCI score in both

TABLE 2 -erm complications in patients following septic arthritis (SA). Figures represent median values (IQR), frequency (% or rates [95% CI])

	Total (*N* = 2367)	Suspected SA (*n* = 1408)	Culture-positive SA (*n* = 959)	*P* value
Follow-up, mo	127 (73-197)	144 (78-212)	108 (64-168)	<.01
Male gender	1605 (67.8)	938 (66.7)	667 (69.6)	.14
Age last observation	61 (45-76)	60 (40-75)	62 (45-78)	<.01
New clinical diagnosis				
SA recurrence >30 d	15 (0.6)	<5 (0.2)	12 (1.3)	.003
Osteomyelitis	62 (2.7)	20 (1.4)	45 (4.7)	<.001
Contracture/ankylosis	<5 (0.1)	<5 (0.2)	<5 (0.1)	.8
Crystal arthropathy	42 (1.8)	27 (1.9)	15 (1.6)	.63
Osteoarthrosis	125 (5.2)	55 (3.9)	70 (7.3)	.01
Inflammatory rheumatic disease	105 (4.4)	56 (4.0)	49 (5.1)	.23
Peripheral fracture	27 (1.1)	18 (1.3)	9 (0.9)	.57
Procedure				
Subsequent joint aspiration	324 (13.7)	197 (14.0)	127 (13.2)	.63
Joint replacement surgery	49 (2.1)	26(1.8)	23 (2.4)	.59
Readmitted with serious illnessinfections	1336 (56.4)	762 (54.1)	574 (59.9)	.006
Pneumonia	584 (2407)	368 (26.1)	216 (22.5)	.05
Sepsis	217 (9.2)	110 (7.8)	107 (11.2)	.006
UTI	421 (17.8)	247 (17.5)	174 (18.1)	.71
Skin/soft tissue infections	104 (4.4)	67 (4.8)	37 (3.9)	.29
Staphylococcal infection	133 (5.6)	35 (2.5)	98 (10.2)	<.001
Streptococcal infection	56 (2.2)	16 (1.1)	40 (4.2)	<.001
CCI score at last observation	2 (1-5)	2 (1-4)	2 (1-5)	.02
CCI score =0	104 (4.4)	76 (5.4)	28 (2.9)	<.001
CCI score =1	769 (32.5)	471 (33.5)	298 (31.3)	
CCI score =2	493 (20.8)	279 (19.8)	214 (22.3)	
CCI score =3	1001 (42.3)	582 (41.3)	419 (43.7)	
Median ED visits	4 (1-11)	4 (1-13)	3 (1-9)	<.01
Median admissions	6.5 (3-13)	7 (3-14)	6 (3-12)	<.01
Non-survivors (%)	676 (28.6)	350 (24.9)	326 nn	<.01
Survival at 6 mo	97.2	98.2	95.7	<.01
Survival at 60 mo	85.2	87.8	81.4	

Abbreviations: CCI, Charlson comorbidity index; ED, emergency department; UTI, urinary tract infection.

subgroups, both more pronounced in patients with SA (Table 2 and Figure S1). Overall, the use of hospital resources (25 925 subsequent ED visits [median 6, IQR 3-14] and 44 024 admissions [median 7, IQR 3-15]) were substantial (Table 2). In total 676 patients died during follow-up with a higher proportion of deaths observed in culture-positive patients (34% vs 24.9%, $P < .001$). The overall 5- and 10-years survival estimates (84.5% and 75.1% respectively) were not different for the periods 1990-1999 and 2000-2010 ($P = .18$), but crude and age-adjusted survival rates were lower in culture-positive patients (Table 2 and Figure S2). Significant prognostic factors were increasing age (hazards ratio [HR] 1.064, CI 1.052-1.076, $P < .001$), female gender (HR1.064, CI 1.052-1.076, $P = .046$), higher CCI scores (HR 1.064, CI 1.052-1.076, $P < .001$) and not carrying private insurance (HR 1.777, CI 1.237-2.553, $P = .002$; Table S3). Compared with the general population, mortality rates were significantly higher in SA patients across all age and gender categories (Table 3). The highest SMRR was in culture-positive patients in the 16-40 age category (SMRR 24.2; CI 2.3-261). While there was a gradual decline of SMRR with aging in both subgroups, SMRR remained significantly elevated in all age categories for culture-positive patients.

TABLE 3 Age- and gender-specific mortality rates (MR) per 1000 person-years in patients with septic arthritis (SA) compared with age (at death) matched categories from the general population by standardized mortality rate ratio (SMRR) with 95% CI

Newman status	Age group	No.	Total deaths	Total person y	MR SA	MR gen. pop.[a]	SMRR
Culture-positive SA							
	16-40	165	27	1585	17.1 (11.2-24.8)	0.71 (0.2-50.3)	**24.2 (2.3-261)**
	40-59	294	59	3317	17.8 (13.5-22.9)	2.37 (1.6-3.7)	**7.1 (1.9-25.6)**
	>60	500	264	4602	57.4 (50.7-64.7)	25.57 (16.7-37.2)	**2.24 (1.5-3.4)**
	All	1408	350	9504	36.8 (33.1-40.8)	10.66 (5.2-19.1)	**3.45 (1.9-6.4)**
Suspected SA							
	16-40	236	14	2452	5.7 (3.2-9.6)	0.71 (0.2-50.3)	8.09 (0.7-87.2)
	40-59	484	61	6945	8.8 (6.7-11.3)	2.37 (1.6-3.7)	**3.70 (1.01-13.2)**
	>60	688	251	8471	29.6 (26.1-33.5)	25.57 (16.7-37.2)	1.15 (0.8-1.8)
	All	959	326	17 867	18.24 (16.3-20.1)	10.66 (5.2-19.1)	1.71 (0.9-3.2)
All							
	16-40	401	41	4037	10.2 (1.9-207)	0.71 (0.2-50.3)	**14.4 (1.4-149)**
	40-59	778	120	10 262	11.69 (9.7-13.9)	2.37 (1.6-3.7)	**4.93 (1.4-17-8)**
	>60	1188	515	13 072	39.4 (36.1-42.9)	25.57 (16.7-37.2)	**1.54 (1.04-2.9)**
	All	2397	676	27 371	24.7 (22.4-26.1)	10.66 (5.2-19.1)	**2.31 (1.3-4.2)**

[a]Based on WA death data from Australian Bureau of statistics in 2011.

4 | DISCUSSION

This study demonstrates that the incidence of native joint SA rose steeply between 1990 and 2010, both for culture-positive and suspected cases. While patients with culture-positive SA had more prior and subsequent comorbidity and higher mortality risk, patients with suspected SA were also at risk of bone and joint morbidity and increased mortality.

The overall AIR of 8.5/100 000 including suspected SA cases in this study was comparable to studies, that included Newman C status patients.[11,12] A UK study, which included pediatric cases and lacked microbiology data for 77% of cases, found an AIR of 7.8/100 000.[12] Despite variable case definitions (eg, inclusion of prosthetic joint infections), this increasing trend is seen across most studies.[11,12,21,22] The reasons behind this rise in SA cases are less clear. A contribution from increasing numbers of diagnostic and therapeutic joint procedures has been described,[9] while other studies suggest a role for aging populations with underlying organ-based comorbidities.[10,23] Our data confirm the role of comorbidity with SA being the first hospital contact ever in a minority of patients only (10.4%) and 80% of patients having already accrued some comorbidity at SA diagnosis associated with a high rate of prior serious infections. This broad comorbidity is in line with recent United States data [24,25] and shows that in most patients a complex interaction of comorbid conditions and infection risk underlies the development of SA. The proportion of Indigenous SA patients (16.4%) was high compared to the 4% population in WA identifying as Indigenous; this extends the increased risk of joint infections observed in children to the adult Indigenous population.[26,27] Pre-existing joint disease was present in 15% of patients, with a recent joint procedure contributing to around 6% of cases, which is considerably lower than the 13.4% iatrogenic rate in Iceland.[9] The clinical presentation of SA was unremarkable[9,21,22,28,29] as male preponderance is nearly universal in studies of SA while the comparatively low age at diagnosis (49 years) likely results from excluding patients with prosthetic joint infection.[30] Knees were the most frequently affected joint, and the relative high frequency of hand (wrist/small joints) SA is in line with some recent studies reporting 22%-31% frequencies of SA in the hands.[6,11] In culture-positive SA, Gram stain-positive cocci were found in 62% as in other studies[6,21,22] but with Gram-negative bacteria observed in about a third of cases, these should certainly be considered when initiating empirical antibiotic treatment.[29] While in-hospital mortality in this study was at the lower range (2%-10%) reported,[6,11,31] our results suggest that 1 in 10 patients require early readmission due to complications of SA. Importantly, our data also illustrate that intensive care unit admission, in-hospital mortality and early readmission were not rare in culture-negative, suspected SA. During long follow-up there was a low risk of SA recurrence limited to female patients,[7] which is surprising given that patients continued to accrue comorbidity and serious infections. A notable finding was the significant rate of late osteomyelitis (OM; 1 in 20 of culture-positive SA and one in 50 in suspected SA patients) usually within a year of SA diagnosis. OM is well recognized in children with SA where infection easily spreads across the growth plate,[32] although less so in adults.[1] These findings suggest that antibiotic therapy for SA may have been insufficient in some patients. We found a higher rate of newly diagnosed OA in culture-positive SA cases, suggesting more joint damage development following culture-positive SA. Subsequent rates for joint

aspirations (13.7%) and replacement (2.1%) and new onset of inflammatory joint disease were similar across groups and on the lower end of reported SA sequelae.[4,7] Rates for other bone/joint complications which are most likely managed on an ambulatory basis were low.[4,33] Compared with the general WA population, excess mortality was observed in patients with culture-positive SA across all age and gender categories, confirming the serious nature of SA. Five and 10 year survival were low for a cohort with a median age of 50 (IQR 33-78) years, while survival was similar across the first and second decade, suggesting that the longer-term impact of SA was stable over the study period. Finally, our study included a large comparator group of culture-negative SA patients. Small numbers of bacteria within the joint space, sample collection after starting antibiotics, poor plating technique, inability to obtain cultures in timely fashion, diagnostic uncertainty or mis-diagnosis (eg, copresence of crystal arthropathy) should all be considered as potential reasons for culture-negative SA.[31-34] Given the doubling of suspected SA cases and the similarities in pre-existing comorbidities and joints affected for culture-positive and suspected SA cases, it seems unlikely that the increase in culture-negative SA was solely due to more misdiagnoses. Importantly, our data show that suspected SA is not per se a benign condition with a 1% short-term mortality and increased SMRR in the age group 40-59 years. This supports recommendations that negative or absent microbiology testing in clinically suspected SA should not deter from initiating therapy.[1,29,34]

Limitations of this study need to be acknowledged. The inclusion of patients diagnosed with SA in the absence of positive cultures may be considered redundant but this methodology avoided the verification bias inherent in culture-positive series[34] and also provided a clinically relevant comparator group. We restricted inclusion to patients with the World Health Organization proposed ICD codes for pyogenic arthritis to improve compatibility with other studies, but this excluded some other forms of bacterial arthritis (Table S2). This study is based on ICD codes that reflect physician-based diagnoses reported in discharge summaries, which is a validated approach with a high positive predictive value.[22,25,35] However, ICD coding data do not allow study of clinical details such as laboratory findings, type and duration of antibiotic or other drug therapy or microbiological susceptibility. On the other hand, the large number of patients, the distinction between culture-positive and suspected SA and the inclusion of lookback as well as long-term follow-up data with validated endpoints lend considerable strength to these observations.

5 | CONCLUSIONS

A steep rise in incidence of native joint SA in WA over 20 years was linked to later age at diagnosis, increasing numbers of female patients and shifting spectrum of microorganisms. Given the impact of underlying comorbidity, SA incidence will likely continue to rise. Not only culture-positive, but also clinically suspected SA carries significant risks of bone and joint complications and death.

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CONFLICT OF INTEREST

None of the authors have competing interests to declare.

AUTHOR CONTRIBUTIONS

JCN, WR, HK, CI and DP developed the WARDER data set, JCN and WR performed data extraction and analysis. JCN wrote and all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The use of de-identified data in this study was approved by WA Health Human Research Ethics Committee and the Data Linkage Branch of WA with the restriction to confidentialize small numbers (WADOH HREC # 2016.24).

DATA AVAILABILITY STATEMENT

Linked data in WARDER data are the property of WA Health and can only be made available upon reasonable request to WA Health through the corresponding author.

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REFERENCES

1. Ross JJ. Septic arthritis of native joints. *Infect Dis Clin North Am*. 2017;31(2):203-218.
2. Ross K, Mehr J, Carothers B, et al. Outbreak of septic arthritis associated with intra-articular injections at an outpatient practice - New Jersey, 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66(29):777-779.
3. Goldenberg DL. Septic arthritis. *Lancet*. 1998;351(9097):197-202.
4. Lauper N, Davat M, Gjika E, et al. Native septic arthritis is not an immediate surgical emergency. *J Infect*. 2018;77(1):47-53.
5. Hassan AS, Rao A, Manadan AM, Block JA. Peripheral bacterial septic arthritis: review of diagnosis and management. *J Clin Rheumatol*. 2017;23(8):435-442.
6. Ferrand J, El Samad Y, Brunschweiler B, et al. Morbimortality in adult patients with septic arthritis: a three-year hospital-based study. *BMC Infect Dis*. 2016;16:239.
7. Kaandorp CJ, Krijnen P, Moens HJ, Habbema JD, van Schaardenburg D. The outcome of bacterial arthritis: a prospective community-based study. *Arthritis Rheum*. 1997;40(5):884-892.
8. Dadras M, Bohm C, Wallner C, et al. Long-term results of bacterial septic arthritis of the wrist. *J Plast Reconstr Aesthet Surg*. 2018;71(8):1138-1145.
9. Geirsson AJ, Statkevicius S, Vikingsson A. Septic arthritis in Iceland 1990–2002: increasing incidence due to iatrogenic infections. *Ann Rheum Dis*. 2008;67(5):638-643.

10. McBride S, Mowbray J, Caughey W, et al. Epidemiology, management, and outcomes of large and small native joint septic arthritis in adults. *Clin Infect Dis*. 2020;70(2):271-279.
11. Kennedy N, Chambers ST, Nolan I, et al. Native joint septic arthritis: epidemiology, clinical features, and microbiological causes in a New Zealand population. *J Rheumatol*. 2015;42(12):2392-2397.
12. Rutherford AI, Subesinghe S, Bharucha T, Ibrahim F, Kleymann A, Galloway JB. A population study of the reported incidence of native joint septic arthritis in the United Kingdom between 1998 and 2013. *Rheumatology*. 2016;55(12):2176-2180.
13. Gjika E, Beaulieu JY, Vakalopoulos K, et al. Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial. *Ann Rheum Dis*. 2019;78(8):1114-1121.
14. Matthews J, Bamal R, McLean A, Bindra R. Bacteriological profile of community-acquired musculoskeletal infections: a study from Queensland. *ANZ J Surg*. 2018;88(10):1061-1065.
15. Ognjenovic M, Raymond WD, Inderjeeth CA, Keen HI, Preen DB, Nossent JC. The risk and consequences of vertebral fracture in patients with ankylosing spondylitis: a population-based data linkage study. *J Rheumatol*. 2020;47(11):1629-1636.
16. Newman JH. Review of septic arthritis throughout the antibiotic era. *Ann Rheum Dis*. 1976;35(3):198-205.
17. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682.
18. Knox J, Hume S, Johnson D. Sternoclavicular septic arthritis caused by Neisseria elongata subspecies nitroreducens. *Pathology*. 2015;47(5):490-492.
19. Tektonidou MG, Wang Z, Dasgupta A, Ward MM. Burden of serious infections in adults with systemic lupus erythematosus: a national population-based study, 1996–2011. *Arthritis Care Res*. 2015;67(8):1078-1085.
20. Nossent JC, Raymond W, Keen H, Preen DB, Inderjeeth CA. Infection rates before and after diagnosis of IgA vasculitis in childhood: a population-wide study using non-exposed matched controls. *J Rheumatol*. 2020;47(3):424-430.
21. Kaandorp CJ, Dinant HJ, van de Laar MA, Moens HJ, Prins AP, Dijkmans BA. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. *Ann Rheum Dis*. 1997;56(8):470-475.
22. Huang YC, Ho CH, Lin YJ, et al. Site-specific mortality in native joint septic arthritis: a national population study. *Rheumatology*. 2020;59(12):3826-3833.
23. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet*. 2010;375(9717):846-855.
24. Singh JA, Yu S. Septic arthritis in emergency departments in the US: a national study of health care utilization and time trends. *Arthritis Care Res*. 2018;70(2):320-326.
25. Singh JA, Yu S. The burden of septic arthritis on the U.S. inpatient care: a national study. *PLoS One*. 2017;12(8):e0182577.
26. Nossent JC, Raymond WD, Keen HI, Inderjeeth CA. Septic arthritis in children: a longitudinal population-based study in Western Australia. *Rheumatol Ther*. 2021;8(2):877-888.
27. Nossent J, Raymond W, Keen H, Preen DB, Inderjeeth CA. Septic arthritis due to Neisseria gonorrhoea in Western Australia. *Internal Medicine Journal*. 2020. http://dx.doi.org/10.1111/imj.15169
28. Morgan DS, Fisher D, Merianos A, Currie BJ. An 18 year clinical review of septic arthritis from tropical Australia. *Epidemiol Infect*. 1996;117(3):423-428.
29. Gupta MN, Sturrock RD, Field M. Prospective comparative study of patients with culture proven and high suspicion of adult onset septic arthritis. *Ann Rheum Dis*. 2003;62(4):327-331.
30. Kaandorp CJ, Van Schaardenburg D, Krijnen P, Habbema JD, van de Laar MA. Risk factors for septic arthritis in patients with joint disease. A prospective study. *Arthritis Rheum*. 1995;38(12):1819-1825.
31. Vassallo C, Borg AA, Farrugia D, Mercieca C. The epidemiology and outcomes of septic arthritis in the Maltese islands: a hospital-based retrospective cohort study. *Mediterr J Rheumatol*. 2020;31(2):195-205.
32. Goergens ED, McEvoy A, Watson M, Barrett IR. Acute osteomyelitis and septic arthritis in children. *J Paediatr Child Health*. 2005;41(1–2):59-62.
33. Triki MA, Naouar N, Benzarti S, Kaziz H, Mouelhi T, Ayeche MLB. Septic arthritis of the wrist: about six cases. *Pan Afr Med J*. 2019;33:237.
34. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. *Acad Emerg Med*. 2011;18(8):781-796.
35. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol*. 2007;60(4):397-409.

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

An enquiry into the crippling gout affecting Pacific Islander and Māori men in Western Sydney

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Abstract

Aim: Despite the effectiveness and availability of urate-lowering therapies (ULT), we continue to see a number of advanced cases of tophaceous gout in the Pacific Islander and Māori population in Western Sydney. Although the high prevalence and increased severity of gout in this cohort has been well documented, there has been little qualitative research undertaken in Australia into the lived experience of this group of people. It is this gap in the research that our study aimed to address.

Methods: Participants were recruited from the rheumatology clinics at Westmead and Blacktown Hospitals. Those eligible to participate were Pacific Islander and Māori patients with tophaceous gout currently living in the Western Sydney Local Health District (WSLHD). Data collection took the form of 10 semi-structured interviews, which were subsequently transcribed verbatim. A thematic analysis of the data was then performed.

Results: Thematic analysis identified 6 key themes: lack of understanding of the disease and its potential effects; missed opportunities for intervention and disjointed care; chronic reliance upon corticosteroids; trivialization of gout as a nuisance illness; the substantial financial impact of chronic illness; and the all-consuming nature of severe gout.

Conclusion: The human cost of severe tophaceous gout in this cohort is immense. All 10 participants exemplified the disease's devastating social effects. We propose 4 key recommendations: improved education regarding diagnosis and management; immediate prescription of ULT at first presentation; a lower threshold for out-of-hospital rheumatologist referral; and improved follow-up through a nurse- and pharmacist-led collaborative gout management program.

KEYWORDS

chronic disease, gout, Māori, Pacific Islanders, qualitative study, tophi

1 | INTRODUCTION

1.1 | Context and rationale

Tophaceous gout is a preventable and curable disease when it is treated in a timely and appropriate manner.[1] Although effective and inexpensive urate-lowering therapies (ULT) have been available for over 50 years, we continue to see patients with poorly managed or untreated disease in the Western Sydney Local Health District (WSLHD).

The WSLHD is one of the state's fastest growing areas, encompassing 946 000 residents from diverse economic, social, and cultural backgrounds.[2] Almost half were born overseas and over half speak a language other than English at home.[2] Approximately 2% of residents self-identified as Pacific Islander or Māori in the 2016 census.[3]

The impetus for this qualitative study arose from the anecdotal observation that patients of Pacific Islander or Māori descent comprised a disproportionate number of those attending the Emergency Departments (ED) of Westmead and Blacktown Hospitals with severe tophaceous gout necessitating admission.

A literature search revealed that although the high prevalence and increased severity of gout in this population had been well-documented,[4-7] little research had looked into their lived experience. A recent Australian Capital Territory (ACT)[8] study had looked at factors contributing to acute flare-ups requiring admission, but did not address long-standing tophaceous disease. A number of studies in New Zealand (NZ)[7,9-11] and the United Kingdom (UK)[12,13] had highlighted gout's impact on such individuals and communities; however, no study had explored this in the Australian healthcare setting.

1.2 | Objectives

The objectives of this study were to:

1. address why and how, from each patient's perspective, their gout had become so debilitating
2. gain a deeper understanding of how each patient viewed their disease and the impact gout had on their lives, and
3. recommend possible strategies for remediation.

We used a 'grounded theory'[14] approach, aiming to form an initial inquiry into the lived experience of this particular cohort. Our findings might be confirmed in a larger study.

2 | METHODS

2.1 | Ethics approval

Approval was granted by the WSLHD Human Research Ethics Committee (HREC Ref: AU RED LNR/18/WMEAD/147). All participants gave prior written informed consent. Express permission was given for photographs to be taken and published. Cultural advice was kindly provided by 2 Pacific Islander general practitioners (GP) currently practicing in the WSLHD.

2.2 | Recruitment

Pacific Islander and Māori patients with advanced tophaceous gout were nominated by rheumatologists conducting clinics at Westmead and Blacktown. Patients were telephoned and offered an interview. Of 18 nominated, 10 men agreed to participate and consented to the protocol.

2.3 | Interviews

Data collection took the form of 10 semi-structured, 1-on-1 and face-to-face interviews. They were conducted by author 1, who had no prior involvement in the participants' care, using a combination of predetermined questions and open conversation. Half were conducted at Westmead Hospital and half at the participant's home – whichever was their preference. They ranged in length from 34 to 84 minutes (average 54 minutes). All were subsequently transcribed verbatim.

2.4 | Thematic analysis

We performed an inductive and iterative thematic analysis of the data. Author 1, using an open coding technique, coded the data manually. As themes emerged, they were explored with author 2 and Emeritus Professor Stephen Leeder.[1] Following the 10th interview theoretical saturation point was reached, with no new themes emerging in the previous 3 interviews and sufficient depth of data to suggest a small likelihood of new themes emerging in further interviews. The sample size of 10 was therefore considered sufficient for the purposes of this study, which is consistent with findings in qualitative methods literature.[15]

2.5 | Comprehensiveness of reporting

To ensure completeness and transparency of reporting, we used a modified version of the Consolidated Criteria for Reporting Qualitative Studies (COREQ).[16]

3 | RESULTS

3.1 | Demographics

Key demographic data for each study participant are presented in Table 1.

3.2 | Thematic analysis

Thematic analysis identified the following 6 key themes (summarized in Table 2).

3.2.1 | Lack of understanding of the disease and its potential effects

All participants commented on a lack of information provided by healthcare professionals early in their disease timeline and a lack

TABLE 1 Demographic data for each study participant

No.	Gender	Age (y)	Ethnic background	Employment status	FHx[a]	Age at diagnosis (y)	Disease duration (y)	ED presentation/ admission[b]
1	Male	62	Māori	Employed	Yes	32	30	No
2	Male	62	Samoan	Retired	No	32	30	Yes
3	Male	49	Samoan	Unemployed	Yes	26	23	Yes
4	Male	65	Cook Island	Retired	Yes	40	25	Yes
5	Male	71	Fijian	Retired	No	50	21	Yes
6	Male	59	Fijian	Retired	No	55	4	Yes
7	Male	35	Samoan	Unemployed	No	25	10	Yes
8	Male	38	Tongan	Employed	Yes	21	17	Yes
9	Male	26	Samoan	Unemployed	Yes	16	10	Yes
10	Male	32	Fijian	Employed	Yes	22	10	Yes

[a]Family history of gout.

[b]Emergency department presentation or hospital admission with gout as the primary cause.

TABLE 2 Key themes and illustrative quotes

Key themes	Illustrative quotes
1. Lack of understanding of the disease and its potential effects	'[The doctor] said just here, take these, you've got gout. Go take these, the inflammation will go down, and you'll be all right.' 'Never paid much attention to it. I just thought I'd pop a few of these, a few of those, and be okay.'
2. Missed opportunities for intervention and disjointed care	'They didn't tell me there was a specialist for gout. If they had told me about the rheumatologist, then I would have took it seriously.' '[It was] mainly a pig-headedness about what my body was trying to tell me. Just living, basically, in denial. I didn't want to know about it.'
3. Chronic reliance upon corticosteroids	'You shouldn't be taking this, but I'll give you this script.' 'I've just [been] seeing a GP, just getting pain killers… the doctor never said anything else.'
4. Trivialization of gout as a nuisance illness	'They're like, oh, I've got another drunk man. They call it the rich man's disease because they think that we live like kings and lazy, and then that's just what happens.'
5. The substantial financial impact of chronic illness on the patient and family	'Not even enough to buy a bread. For the past 2 something years I've been living here very, very tightly. Now I eat Nutri-Grain. Nutri-Grain for dinner, Nutri-Grain for breakfast, Nutri-Grain for a lot.'
6. The all-consuming nature of severe gout	'The worse thing ever man, gout. It's just taken over my life, I can't do anything. Basically, everything just broke down. It all started from the gout.' 'How much does gout affect my day-to-day life? 99.9%. I've got no life. Either in hospital or at home. I don't have a social life any more. Nothing.'

of clarity regarding their treatment. As one said, *'[the doctor] said just here, take these, you've got gout. Go take these, the inflammation will go down, and you'll be all right.'* This deficiency in information resulted in some only taking their allopurinol during flare-ups, rather than preventatively. When they realized that the allopurinol was ineffective for an acute attack, they reported stopping it altogether.

For one, this resulted in a 20-year period of managing his progressively worsening gout with symptomatic treatments alone. His severely deformed hands (Figure 1), with numerous large tophi, cause significant day-to-day morbidity. When asked why he thought that his gout had become so severe, he replied:

> 'It's just one of those things that of course you're young and bullet proof. But, if someone had set me down like [my new doctor] did, and just explained to me exactly what the situation is in lay terms. Man, if I'd have had that conversation 30 years ago, brilliant.'

Furthermore, 8 participants expressed that they had been unaware of how severe gout could become and so did not, initially, take it seriously. They perceived gout as an acute rather than a chronic illness, and so were mostly *'just looking for a quick fix'*. In the words of one, *'never paid much attention to it. I just thought I'd pop a few of these, a few of those, and be okay.'* Going forward, 7 believed that more needed to be done at the community level to ensure better understanding of gout and its potentially severe effects:

> 'They could have a program. I'd love to come speak at one of those programs. There should be something

FIGURE 1 Hands of a 62-y-old Māori man demonstrating extensive tophi. (Consent was obtained from the patient to publish this image)

> like that. Just to spread the word, it's serious. Gout is not a laughable [matter]… if you don't take care of it, look after it, it can ruin your life.'

3.2.2 | Missed opportunities for intervention and disjointed care

For 9 participants, a key barrier to gaining control over their illness was the lack of timely referral to a rheumatologist. Despite 1 participant's gout having been diagnosed 21 years earlier, he had never been so referred. His gout became progressively more severe, requiring frequent attendances to the ED. He commented on these missed opportunities for intervention, stating *'they didn't tell me there was a specialist for gout. If they had told me about the rheumatologist, then I would have took it seriously. I just thought the painkillers will fix it.'*

In a similar vein, 8 felt that their care had been disjointed; they experienced periods where they had, for both system and patient factors, been lost to follow-up. Most felt that their GPs did not see gout as important and many felt dismissed (see theme 4). However, the majority also volunteered their own culpability. Many reported they had been 'in denial' and had chosen to prioritize lifestyle over health. Some noted they had, at times, been reluctant to see their GP because they did not want to have to reduce their alcohol intake or alter their diet. One commented:

> '[It was] mainly a pig-headedness about what my body was trying to tell me. Just living, basically, in denial. I didn't want to know about it. I'll take the pills, I'll take the drugs and everything, and let it take care of itself. The one basic, main basic reason is that I just did not care enough about my condition to treat it properly. I liked my lifestyle.'

However, it is important to note that such often-advocated lifestyle changes have a limited evidence base.[17]

3.2.3 | Chronic reliance upon corticosteroids

Five participants had taken high-dose prednisone for extended periods and 3 were still taking it daily. A 35-year-old Samoan man reported taking up to 150 mg daily for 10 years. He sourced his prescriptions from 3 different GPs, who would say *'you shouldn't be taking this, but I'll give you this script.'* This over-prescription had disastrous consequences – in 2016 the participant suffered multiple osteoporotic vertebral fractures. He had been wheelchair-bound for 3 years at the time of interviewing.

Along with an over-prescription of corticosteroids, we also noted an *under*-prescription of ULT. Six participants reported that it was some years after their initial diagnosis that their GP first offered allopurinol. This is consistent with UK research demonstrating that the majority of patients had not been prescribed ULT even after 10 years.[18] One participant had been managing his worsening gout for 17 years with indomethacin alone, thinking that this was the only treatment available: *'I've just [been] seeing a GP, just getting pain killers… the doctor never said anything else.'* Now, aged 38, he has been told that his kidneys might be failing due to its excessive use. Given the availability and efficacy of modern ULT, this should have been preventable.

3.2.4 | Trivialization of gout as a nuisance illness

Seven participants felt that some individuals involved in their health care, particularly in primary care and ED, viewed gout as trivial, not warranting further investigation or special attention – as one described it, a *'nuisance illness'*.

One 26-year-old's gout had been diagnosed 10 years earlier – an unusually early onset. He had disabling gout in hands (Figure 2), knees and feet, and needed a wheelchair. In his earlier interactions with health care professionals, he felt as if he was being blamed for his illness: *'they're like, oh, I've got another drunk man. They call it the rich man's disease because they think that we live like kings and lazy, and then that's just what happens.'* As a result of this stereotyping, he was not afforded the support and treatment he needed and, at the age of 24, became bed-bound with chronic gout-related ulcers. It was only in the last 9 months, after his mother had actively sought a different specialist who recognized that his gout might be allopurinol-resistant and commenced him on an alternative medication (benzbromarone), that he has started to recover both physically and psychologically.

3.2.5 | The substantial financial impact of chronic illness on the patient and family

Chronic illness and disability can have damaging socio-economic effects on patients and their families.[19] All participants reported a substantial

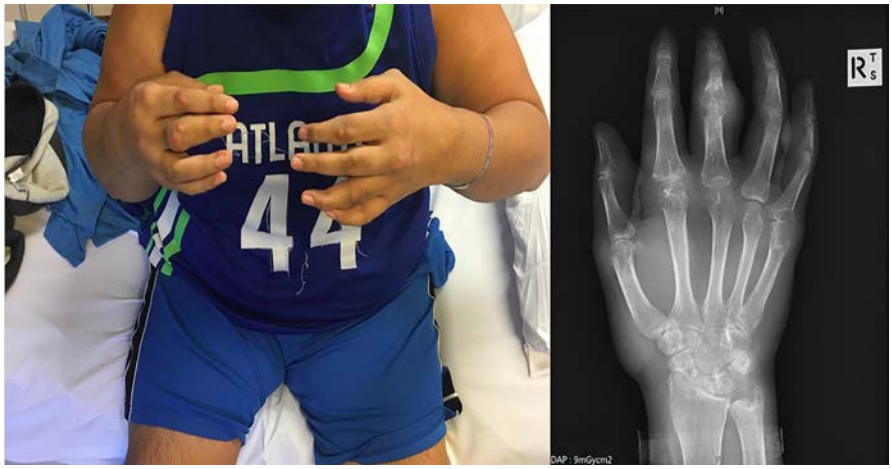

FIGURE 2 Hands of a 26-y-old Samoan man. X-rays demonstrate erosive changes in multiple joints and soft tissue swelling due to tophi. (Consent was obtained from the patient to publish this image)

impact on their financial situations. The severity of their gout forced 7 to stop work. One, unable to work due to his osteoporotic spinal fractures, relies on the Newstart allowance.[2] After rent and buying his necessary medications, he is left with $100 a week – in his own words:

> 'Not even enough to buy a bread. For the past 2 something years I've been living here very, very tightly. Now I eat Nutri-Grain. Nutri-Grain for dinner, Nutri-Grain for breakfast, Nutri-Grain for a lot.'

Chronic illness also affects patients' families. Following 8 years of poorly managed gout, the bed-bound aforementioned 26-year-old required such a high level of personal care that his mother had to give up full-time employment to look after him around-the-clock. The annual household income halved from $50 000 to $25 000, putting significant pressure on this already struggling family.

3.2.6 | The all-consuming nature of severe gout

A key theme emerging from previous qualitative studies of chronic illness centers on the struggle to balance one's life alongside one's illness management.[20] Our study confirmed this, with all 10 participants reporting that gout had greatly affected their ability to live the life they had envisioned. Seven reported having little or no social life due to their gout and 3 reported the disease as being the precipitating factor in the breakdown of a relationship. The following quotes from 2 interviews provide stark reminders of the devastating effect which chronic gout can have on an individual:

> 'The worse thing ever man, gout. It's just taken over my life, I can't do anything. Basically, everything just broke down. It all started from the gout.'

> 'How much does gout affect my day-to-day life? 99.9%. I've got no life. Either in hospital or at home. I don't have a social life any more. Nothing. Not what I used to have.'

Another major challenge of living with chronic illness is maintaining one's mental health.[21] One participant reported being depressed for many years, not wanting to leave the house and self-medicating with marijuana – *'and then it was like from there I just started to notice that I didn't really go out with people, or like my friends, I just cut them off because I was just too tired.'*

The osteoporotic patient also reported struggling with his mental health, finding it especially difficult because of the breakdown of his relationship. He spent almost all his time in his 3 × 3 m apartment, hardly ever seeing friends or family and unable, due to his spinal fractures, to get down the stairs:

> '23 hours a day. It's a prison. I got to get somebody to go do my shopping, or I starve… I nearly died a couple of times. There's one time I had an attack, for a week. I had nothing, no medication. I OD'ed on Panadol, I took a whole box of Panadol in a couple of hours.'

4 | DISCUSSION

Our first objective was to better understand why and how gout had become such a debilitating disease for these men. While the etiology is complex and multifactorial, our first 4 themes provided some level of insight. Similar themes were also noted in a recent ACT study.[8] A major barrier to effective management appears to be a lack of knowledge and understanding of gout, its treatment, and, when poorly controlled, its potentially severe long-term outcomes. This lack of knowledge was a key barrier emerging from qualitative studies in the UK[22] and New Zealand.[23] Due to this poor understanding and misperception of gout as largely an acute illness, it often requires a major adverse event for these patients to take their gout seriously. However, recognition of the potentially grave consequences of gout this late in

their disease timeline provides major challenges for both patients and their treating professionals.

Our second objective was to gain a deeper understanding of how these patients viewed their disease and what it was like to live with it. Previous studies demonstrated how chronically ill people need to make constant adjustments to their lives, juggling competing priorities, including the management of their condition.[20] What came through strongly, reflected in themes 5 and 6, was the immense human cost of gout. This human cost can be noted elsewhere in the literature - Tatlock et al describe pain as the defining symptom of gout, leading to a range of impacts on health-related quality of life, including impairment of physical function and sleep.[24] All 10 participants in our study provide excellent case examples of gout's crippling effects and the drastic changes it can impose on one's life. For many, gout had been the catalyst for a series of devastating outcomes and, given that these outcomes might have been avoided with effective control, this is now a source of immense frustration and regret.

Our final objective was to recommend strategies to help reduce this major disease burden. In response to the key deficits in patient care highlighted by our 6 themes, we propose 4 recommendations.

4.1 | Improved patient education and increased awareness of gout in this population group

As highlighted by theme 1, effective prevention will require greatly improved patient education, initially and continuing, particularly regarding the importance of adherence to ULT and the potential outcomes if gout is poorly controlled.

This information could come from GPs, but is likely to be more effective (see recommendation 4) coming from nurses[25] or pharmacists[26] as part of a wider gout management program. Australian work has suggested that community pharmacists have a particularly important role in the provision of education to gout sufferers and in monitoring medication adherence at the time of medication dispensing.[26] Two North American studies involving pharmacist-led interventions which used automated telephone technology[27] and telephone contact with provision of educational and dietary materials[28] also improved outcomes in gout patients.

Effective prevention would also be aided by increased awareness of gout in the wider Pacific Islander and Māori community, especially among the young. Some participants suggested that this could be achieved through seminars run either through the various Pacific Islander and Māori parishes or through established community groups, such as the Fiji Youth Initiative. Given the low health literacy in this population, educational interventions would need to be carefully designed and culturally appropriate.

4.2 | Immediate prescription of ULT at first presentation

Current Australian Therapeutic Guidelines state 'starting ULT has traditionally been delayed until the acute attack has resolved; however, starting ULT concurrently with treatment for the acute attack may be appropriate.'[29] As Pacific Islander and Māori individuals are more at risk of severe outcomes, prescription of ULT at first presentation should be strongly encouraged. As highlighted by theme 2, these patients are at risk of loss to follow-up and therefore the first presentation might be the only opportunity to commence ULT. However, early prescription must be combined at commencement with improved education about flare-ups. This should improve ULT adherence and minimize reliance on prednisone and symptomatic treatments. The potential benefits of this strategy are being recognized by clinicians and governing bodies, with starting ULT immediately during a flare-up now being a conditional recommendation[3] of the 2020 American College of Rheumatology (ACR) clinical guidelines.[30]

4.3 | A lower threshold for rheumatological referral in this population group

While gout can often be managed effectively without hospital involvement, Pacific Islander and Māori patients are at greater risk of tophaceous erosive joint disease and other adverse outcomes, as highlighted by themes 5 and 6. An early appointment with a rheumatologist is indicated.

Gout care in secondary or tertiary settings such as rheumatology clinics is not the single or ideal solution, and we must ensure that GPs and pharmacists involved in the care of gout patients are adequately trained in gout management.[31,32] However, a one-off initial appointment at a rheumatologist's consulting rooms for diagnosis and early formulation of a comprehensive management plan would likely be beneficial. While the effect of an earlier referral has not yet been investigated in the literature – perhaps a focus for future research – it is important to note that almost all our participants felt they would have benefited from this extra level of surveillance.

4.4 | Improved follow-up care through either a nurse-led or pharmacist-led gout program

In order to minimize the loss to follow-up we noted in our study, each patient needs more individualized and closely monitored management. Both pharmacist-led[27,28] and nurse-led[25] interventions have been shown to result in significant improvement in achieving the target serum urate levels.[33] Two programs in New Zealand, *Gout Stop*[34] and *Owning My Gout*,[35] have demonstrated that pharmacist-led collaborative programs can reduce the barriers to accessible treatment for Pacific Islander and Māori people and improve outcomes. A recent UK randomized trial demonstrated that gouty patients preferred nurse-led to GP-led care. It resulted in better knowledge, greater persistence on ULT, and fewer flare-ups.[36] Furthermore, this approach has also been shown to be cost-effective.[25] One potential advantage of a nurse-led program over a pharmacist-led program is that community nurses can visit patients' homes, which likely results in greater awareness of their social and economic circumstances,

more patient engagement with the program and a decreased loss to follow-up.[25]

4.5 | Study limitations

Aside from the small sample size, which has already been addressed in the methods section of this paper, a further limitation was participant recall bias regarding management. This potential confounder was more likely given the long duration of many participants' disease.

Another important limitation to address was the absence of female participants in our study. Because of the greatly increased prevalence of gout in men in general, a separate study of women, especially of post-menopausal women, is warranted.

Finally, it is important to note that as the study population comprised those of Pacific Islander and Māori ethnicity only, study findings are not necessarily generalizable to other gout populations.

5 | CONCLUSION

The initial focus of this research project was the financial cost to the public health system of severe tophaceous gout in this at-risk population group. However, what quickly became apparent was that the real cost, both financial and social, was not to the hospital but to the individuals, families and communities suffering the illness' long-term consequences. Because of our duty of care to alleviate this unnecessary suffering and to prevent such devastating effects, future research should focus on this area.

In order to address the deficits in patient care that were highlighted by our study results, we recommend a trial of a nurse- and pharmacist-led collaborative gout management program in the WSLHD targeting this particular high-risk group. Such a program could ensure greater knowledge of gout prevention and management, provide more individualized care, decrease loss to follow-up, and improve ULT adherence among Pacific Islander and Māori patients. This could help empower these individuals to take early ownership of their disease and ultimately prevent such devastating disease progression.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Western Sydney Local Health District (WSLHD) Human Research Ethics Committee.

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[2] Fortnightly payment of approximately $565 from the Australian Government. Available to those between the ages of 22 and 66 who are either looking for work or are sick or injured and cannot do their work for a short period of time. The name was changed from *Newstart* to *JobSeeker* in March 2020.

[3] The ACR guidelines state that 'conditional recommendations reflect scenarios for which the benefits and risks may be more closely balanced and/or low certainty of evidence or no data are available'.

REFERENCES

1. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in new perspective. *J Adv Res*. 2017;8:495-511.
2. Western Sydney Local Health District. About Us [homepage on the Internet]. NSW Government [cited 24 March 2020]. Available from: https://www.wslhd.health.nsw.gov.au/About-Us
3. Australian Bureau of Statistics. Census of population and housing 2016: Cultural diversity: Local Government Areas: Blacktown, Cumberland, Parramatta, The Hills Shire: Selected person characteristics: ANC1P ancestry first response [data online]. Available from: https://www.abs.gov.au/websitedbs/censushome.nsf/home/2016
4. Paul BJ, James R. Gout: an Asia-Pacific update. *Int J Rheum Dis*. 2017;20:407-416.
5. Winnard D, Wright C, Taylor WJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. *Rheumatology (Oxford)*. 2017;51:901-909.
6. Jackson G, Wright C, Thornley S, et al. Potential unmet need for gout diagnosis and treatment: capture-recapture analysis of a national administrative dataset. *Rheumatology (Oxford)*. 2012;51:1820-1824.
7. Dalbeth N, House ME, Horne A, et al. The experience and impact of gout in Māori and Pacific people: a prospective observational study. *Clin Rheumatol*. 2013;32:247-251.
8. Kong DCH, Sturgiss EA, Raj AKD, Fallon K. What factors contribute to uncontrolled gout and hospital admission? A qualitative study of inpatients and their primary care practitioners. *BMJ Open*. 2019;9(12):e033726
9. Te Karu L, Bryant L, Elley CR. Māori experiences and perceptions of gout and its treatment: a kaupapa Māori qualitative study. *J Prim Health Care*. 2013;5(3):214-222.
10. Lindsay K, et al. The experience and impact of living with gout: a study of men with chronic gout using a qualitative grounded theory approach. *J Clin Rheumatol*. 2011;17(1):1-6.
11. Dalbeth N, Petrie KJ, House M, et al. Illness perceptions in patients with gout and the relationship with progression of musculoskeletal disability. *Arthritis Care Res*. 2011;63(11):1605-1612.
12. Chandratre P, Mallen CD, Roddy E, et al. 'You want to get on with the rest of your life': a qualitative study of health-related quality of life in gout. *Clin Rheumatol*. 2016;35:1197-1205.

13. Liddle J. Mapping patients' experiences from initial symptoms to gout diagnosis: a qualitative exploration. *BMJ Open* [serial on the Internet] 2015 [cited 23 May 2020]; **5**. Available from: https://bmjopen.bmj.com/content/bmjopen/5/9/e008323.full.pdf
14. Glaser BG, Strauss AL. *The discovery of grounded theory: strategies for qualitative research*. Aldine Publishing; 1967.
15. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Method*. 2006;18:59-82.
16. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19:349-357.
17. Moi JHY, Sriranganathan MK, Edwards CJ, Buchinder R. Lifestyle interventions for chronic gout. *Coch Data Sys Rev*. 2013;5:10038.
18. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. *JAMA*. 2014;312(24):2684-2686.
19. Jeon YH, Essue B, Jan S, Wells R, Whitworth JA. Economic hardship associated with managing a chronic illness: a qualitative inquiry. *BMC Health Serv Res*. 2009;9:182-193.
20. Jeon YH, Jowsey T, Yen L, et al. Achieving a balanced life in the face of chronic illness. *Aust J Prim Health*. 2010;16:66-74.
21. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *MJA*. 2009;190(7):54-60.
22. Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a quantitative study. *Ann Rheum Dis*. 2012;71(9):1490-1495.
23. Horsburgh S, Norris P, Becket G, Arroll B, Crampton P, Cumming J. Allopurinol use in a New Zealand population: prevalence and adherence. *Rheumatol Int*. 2014;34(7):963-970.
24. Tatlock S, et al. What outcomes are important for gout patients? In depth qualitative research into the gout patient experience to determine optimal endpoints for evaluating therapeutic interventions. *Patient*. 2017;10(1):65-79.
25. Doherty M, Jenkins W, Richardson H, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet*. 2018;392:1403-1412.
26. Counsell AB, Nguyen AD, Baysari MT, et al. Exploring current and potential roles of Australian community pharmacists in gout management: a qualitative study. *BMC Family Practice*. 2018;19:54-61.
27. Mikuls TR. A pharmacist-led intervention to improve gout medication adherence and outcomes with urate lowering therapy: a site randomised trial. *Am J Med*. 2019;132(3):354-361.
28. Goldfien RD, Ng MS, Yip G, et al. Effectiveness of a pharmacist-based gout care management programme in a large integrated health plan: results from a pilot study. *BMJ Open*. 2014;4:e003627.
29. Long-term management of gout with urate-lowering therapy [homepage on the Internet]. Melbourne: Therapeutic Guidelines Ltd [updated December 2019; cited 23 March 2020]. Available from: https://tgldcdptgorgau
30. Fitzgeral JD, Dalbeth N, Mikuls T, et al. 2020 American College of rheumatology guidelines for the management of gout. *Arthritis Care Res (Hoboken)*. 2020;6:1-17.
31. Bavanendrakumar M, Robinson PC. Management of patients with gout and achievement of target serum urate levels at a tertiary rheumatology service in Australia. *Int Med J*. 2020;50(3):337-341.
32. Leonardo N, Lester S, Whittle S, Rischmueller M. Review of gout clinic in a tertiary hospital setting. *Int Med J*. 2020;50(1):117-120.
33. Fields TR, Batterman A. How can we improve disease education in people with Gout? *Curr Rheumatol Rep*. 2018;20(3):12-21.
34. Lawrence A, Scott S, Saparelli F, et al. Facilitating equitable prevention and management of gout for Māori in Northland, New Zealand, through a collaborative primary care approach. *J Prim Health Care*. 2019;11(2):117-127.
35. Phone D. Owning My Gout: a pharmacist-led collaborative gout management model at Counties Manukau DHB. *Int J Integr Care*. 2017;18(1):1-8.
36. Fuller A, Jenkins W, Doherty M, Abhishek A. Nurse-led care is preferred over GP-led care of gout and improves gout outcomes: results of Nottingham Gout Treatment Trial follow-up study. *Rheumatology*. 2020;59:575.

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ORIGINAL ARTICLE

Expanding the role of Australian community dietitians in gout management

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Abstract

Aim: Gout is a common form of inflammatory arthritis with suboptimal management. Management guidelines for gout highlight the importance of both pharmacological and non-pharmacological treatments. Dietitians can potentially assist in improving gout's associated dietary and lifestyle factors, and thereby play a role in improving its management. The aim of this study was to investigate perspectives of Australian community dietitians on whether their role in gout management could be expanded to improve management and treatment of gout.

Method: A snowballing recruitment strategy was used. Dietitians known to the research team were invited to participate and then they suggested further dietitians. Semi-structured interviews (one-on-one) were conducted with 16 dietitians. The focus was on their experiences of contributing to the management of gout, including any barriers and facilitators experienced. Interviews were transcribed verbatim and independently analyzed by 2 reviewers to identify themes.

Results: The main reported role of dietitians in gout management was providing patient education. An identified facilitator was dietitians' understanding of gout and its dietary management. Barriers included the emphasis placed on medications for treatment by clinicians and patients, consultation costs, limitations in the evidence for the efficacy of dietary changes and lack of specific training in gout for dietitians. Dietitians predominantly managed the other metabolic conditions commonly associated with gout.

Conclusion: Currently, the role dietitians play in gout management is limited. However, dietitians have the potential to take on larger roles in gout education and can also indirectly contribute by way of management of commonly associated comorbidities in gout patients.

KEYWORDS

diet, education, gout, nutritionists, patient care

1 | INTRODUCTION

Gout is the most common form of inflammatory arthritis, affecting approximately 2.9% of Australians.[1] Hyperuricemia, defined as serum uric acid (SUA) concentration >0.41 mmol/L,[2] is the leading cause of gout, which results in the deposition of monosodium urate crystals in joints and surrounding tissues.[2] Progressive crystal deposition is painful, debilitating and if left untreated, may cause irreversible joint damage.[3] The condition contributes to poor quality of life, decreased work productivity[4] and is associated with long-term metabolic comorbidities such as cardiovascular disease.[5]

Hyperuricemia and gout are associated with a range of lifestyle factors such as excessive consumption of purine-rich foods (including meat and seafood), alcohol (particularly beer and spirits) and sugar-sweetened beverages.[6] There are international guidelines which outline both pharmacological and non-pharmacological strategies for gout management.[7-9] Urate-lowering therapies (ULTs), such as allopurinol, are the main pharmacological treatments for gout. Non-pharmacological strategies include limiting dietary purine intake and weight loss for patients who are overweight or obese. Despite these guidelines and the availability of effective ULTs, knowledge of gout and drug adherence among people with gout remains low. People with gout demonstrate the lowest adherence to drug therapy when compared to patients with other chronic diseases.[10]

Current literature suggests the limited education patients receive, and thereby the deficit in patient knowledge, on the dietary and lifestyle factors associated with gout may contribute to the poorly controlled condition.[11] In a United States study, the vast majority of participants with gout were unaware of foods that may lead to a gout attack. Specifically, patients reported vegetables and chicken as triggers compared to high-purine foods, such as meat and seafood which are documented to precipitate gout attacks.[12] In Australia, accredited practicing dietitians play a role in chronic disease prevention and management by delivering counseling, education and support to patients to achieve dietary patterns that optimize health. Thus, dietitians could potentially fill knowledge gaps in gout education and provide individualized and holistic advice to patients with gout in accordance with management guidelines. Studies conducted in China and Finland have demonstrated the effectiveness of dietary counseling and lifestyle modification for the management of chronic diseases such as type 2 diabetes mellitus (T2DM) and heart disease. In a large randomized clinical trial, diet and lifestyle education as well as monthly follow-ups with dietitians were shown to be more effective than medication alone in preventing T2DM.[13] Similarly, studies exploring people living with gout experiences suggest a more personal and individualized approach to gout management may lead to better monitoring and patient outcomes.[14]

Few studies have examined the specific role of dietitians in the management of gout. The aim of this study was to explore the current role of Australian community dietitians in gout management and dietitians' views on whether their role could be expanded upon to improve treatment. We also aimed to identify any perceived facilitators or barriers to dietitians' involvement in the management and treatment of gout.

2 | METHODS

Ethics approval was obtained by University of New South Wales Human Research Ethics Application (Reference number 2014-7-10) prior to study commencement.

2.1 | Participants and recruitment

Australian community dietitians were recruited by contacting general practitioners (GP), who had participated in previous research conducted by the research group,[15] and asked to provide contact details of dietitians within their networks. Dietitians were then contacted via a letter of invitation to participate in the study. This was followed with a phone call 3 months post-distribution if dietitians failed to respond. A snowballing recruitment strategy was used, where participants were asked to provide contact details for other dietitians they thought would be interested in participating in the study.[16] Recruitment continued until thematic saturation was achieved (16 interviews).

2.2 | Data collection

Directly prior to each interview, the purpose of the study was explained to participants and written consent was obtained. One-on-one interviews, of approximately 20-30 minutes (average 26 minutes), were conducted. Participants were reimbursed with $50 gift cards for their time. Interviews were semi-structured and focused on participants' interactions with people living with gout and their experiences of managing gout. All interviews were conducted by one researcher with expertise in conducting qualitative interviews with clinicians (ABC). Interviews were audio-recorded, transcribed verbatim and de-identified to ensure confidentiality.

2.3 | Analysis

Analysis of transcripts was undertaken concurrently with conduction of interviews in order to determine when theme saturation occurred. Each transcript was analyzed by 2 independent reviewers with expertise in qualitative methods and gout (ABC, ADN) and themes were extracted using a general inductive approach (ie no a priori framework was used). After analysis of 5 transcripts, the reviewers convened to discuss emerging themes and developed a framework for the analysis of remaining transcripts and re-analysis of the first 5 transcripts.[17] Any discrepancies in coding were resolved via consensus. Discrepancies can arise in qualitative analysis when 2 reviewers independently analyze transcripts. Discrepancies

included coding of text under different themes/subthemes. When this occurred, the 2 reviewers convened to discuss why they coded the text under the specific theme/subtheme. This discussion led to resolution of all discrepancies. A third independent reviewer was not required in this study.

3 | RESULTS

Fourteen women and 2 men were recruited and had on average 12 years of experience (range = 2-30 years). Dietitians were either practicing in private practice (n = 13), government community health (n = 2) or both (n = 1). All dietitians were practicing in New South Wales, Australia and relatively distributed across 6 local health districts of Sydney, Australia (2 in South-eastern Sydney, 2 in Sydney, 4 in Nepean Blue Mountains, one in Northern Sydney, 2 in South-western Sydney and 5 in Western Sydney).

Emerging themes from dietitian responses were grouped into 3 categories: (a) dietitians' current role in gout management; (b) facilitators to dietitian current role and/or expansion of role; (c) barriers to dietitian current role and/or expansion of role. These are summarized in Table 1.

3.1 | Current role in gout management

Most dietitians reported they had a small role in gout management as it was a condition that was infrequently seen in their practice. A participant explained, "Definitely a smaller role when compared to, for instance, diabetes, high blood pressure, high cholesterol" (Dietitian #27). Nonetheless, dietitians described a typical gout patient as male, middle-aged to elderly, overweight and an alcohol drinker with various comorbidities such as diabetes, hyperlipidemia, hypertension and cardiovascular disease. Dietitians also reported that a high proportion of gout patients were taking medications for treatment of gout.

3.1.1 | Referrals

All dietitians reported most of their gout patients were referred to them from a GP. However, dietitians explained that gout patients were referred primarily for other comorbidities, in particular weight loss and diabetes, "Usually [gout's] probably a secondary or an underlying condition. It's not usually why they're referred to me" (#27). Consequently, gout was very rarely the primary focus of the consultation. Dietitians reported that gout was viewed as less important than other conditions within the consultation and by doctors and patients. A dietitian said "[Gout] would tend to be a sort of thing that might get talked about as a one off and maybe as just 5 minutes or so within another consult… It just seemed like a trifling… health issue" (#47).

3.1.2 | Advice and education

Dietitians explained they provided individualized and holistic advice with respect to diet and lifestyle. Diet advice for gout patients consisted of foods that should be limited such as high-purine foods, red meat, organ meats, fructose, seafood and vegemite. Additionally, low purine foods, vegetables and milk/dairy products were encouraged. Dietitians also mentioned limiting alcohol intake and increasing water consumption as part of their advice to gout patients. Lifestyle advice was reported to consist of encouraging basic levels of physical activity and losing weight if required.

Dietitians also described providing advice in the context of associated comorbidities such as diabetes and obesity, stating that dietary advice for these conditions can in turn help with gout. One dietitian stated, "Giving them a diet, it's not only going to help … one of their conditions, it's going to help all of them … a lot of the diets overlap with each other" (#27).

Most dietitians also reported providing written educational material to gout patients, most commonly sourced from the Dietitians Association of Australia or Arthritis Australia. One dietitian stated, "Everything that I give is always written down because no-one remembers things when they go home" (#46).

3.2 | Facilitators to current role or an expansion of role in gout management

3.2.1 | Good understanding of gout and its management

Most dietitians appeared to have a good understanding of the diet changes that are recommended for a patient with gout, and also demonstrated a good understanding of the impact of such foods on SUA concentrations. A dietitian said, "It's actually the purines in

TABLE 1 Summary of dietitian roles, and facilitators and barriers to involvement, in gout management

Current roles	Facilitators	Barriers
Referrals received from general practitioners infrequently for gout	Good understanding of gout and its management	Strong emphasis placed on medications in gout management
Provision of advice and education	Patient's positive attitude toward managing gout with diet and lifestyle	Lack of evidence for link between diet and gout
		Lack of training on gout for dietitians
		Cost of dietitian consultations

food that get converted into the uric acid or raise the uric acid levels" (#47).

3.2.2 | Patients' positive attitudes toward diet and lifestyle

Dietitians explained that some patients preferred managing their gout with lifestyle and diet changes, referring to medication as a "last resort" (#44). A dietitian said, "There's some people who you get who come in, they say 'I really don't want to try the medication. I want to try through diet first'" (#10) and another explained, "Generally medications is one that they don't like taking for the long term" (#12).

3.3 | Barriers to current role or an expansion of role in gout management

3.3.1 | Emphasis on medications in gout management

The majority of dietitians believed gout management is currently very pharmacologically focused. This was the most frequently reported barrier and why dietitians felt they played a small role in gout management. A dietitian said, "I really do see that medication is taking a higher role at the moment" (#40). Several dietitians disagreed with the emphasis on medications, with one stating, "Medication should always be the backup plan… diet and exercise should always be first" (#46). This emphasis on mediations was viewed to be the primary reason why "GPs don't refer" (#32). Furthermore, dietitians reported that GPs "don't realize that there are some dietary components that can be changed to reduce uric acid levels" (#18), and GPs "don't see the dietitians having a role in managing [gout]" (#47). In response, a number of dietitians reported that educating GPs would facilitate an expansion of dietitians' roles in gout management.

3.3.2 | Lack of evidence for link between diet and gout

Dietitians stated there was not enough evidence and research linking positive effects of managing diet on gout outcomes to justify a strong involvement of dietitians in gout management, and thus why gout was not a primary focus for dietitians. A dietitian said, "If there's some really good evidence that I should be giving dietary advice then I would, but I'm not aware of that evidence" (#47). Many dietitians stated that, "Some more research would be nice" (#24) and having more evidence would drive their involvement in gout management. One dietitian explained, "If I knew that there was a real course where diet alone could contribute and help with these people… Then there's a real drive to see those patients as well" (#40).

3.3.3 | Lack of training on gout for dietitians

The majority of dietitians reported a lack of training or continuing education for dietitians in gout. One dietitian said, "I don't think we get a lot of [training] at all… when I first started as a dietitian, I think when I heard someone come in with gout, it was like what?" (#40). A smaller number of dietitians explained the lack of continuing education on gout was likely to be because gout patients represented only a small proportion of their clients. A dietitian said, "I think, as you do get more patient referrals you might look into going to more conferences and web chats as well" (#18).

3.3.4 | Cost of dietitian consultations

A number of dietitians raised concerns surrounding the eligibility of gout patients for Medicare-covered dietitian consultations. One dietitian said, "They have to meet certain criteria, so I don't know if gout alone is enough of a condition to get that" (#32). Participants explained that patients who were specifically referred to dietitians for gout had to pay for their consultation and this stopped people from visiting a dietitian and also returning for multiple consultations. For example, "Wouldn't be all that easy to access a dietitian just for gout unless you're wealthy enough to be willing to pay… I think the cost would be a bit of a barrier" (#47).

4 | DISCUSSION

This was the first qualitative study to explore the views and role of Australian community dietitians in gout management. Our interviews revealed that the main role of dietitians is to provide individualized and holistic advice and education about diet and lifestyle to people with gout. Supporting this, participants demonstrated a good understanding of gout and its management, which could facilitate their further involvement in gout management. The primary barrier to dietitians currently being involved and broadening their role was identified to be the strong emphasis placed on medications and not diet in the management of gout.

Dietitians appear to play a limited role in gout management, primarily because they very rarely see patients for gout. Dietitians explained that this was likely due to multiple factors (eg cost), a key factor being the heavy emphasis on pharmacological gout management by doctors and guidelines. Guidelines for gout recommend long-term ULT, which has been shown to be extremely effective in lowering SUA concentrations in gout patients,[18,19] but guidelines also recommend patients with gout limit their consumption of high-purine foods, drink plenty of water and lose weight. Dietitians also believed that GPs' lack of awareness about diet and lifestyle in gout could be fueling this over-emphasis on pharmacological management.

The literature surrounding the importance and effect of dietary interventions in gout is still unclear. The advice currently provided by

dietitians to gout patients is in accordance with internationally published guidelines;[7,20,21] however, guidelines published in Australia and New Zealand suggest more general dietary recommendations for gout due the paucity of high-level evidence.[8] Although studies have successfully demonstrated the impact of diet and lifestyle on reducing the incidence of gout,[22,23] there is limited evidence on the impact of diet and lifestyle changes on gout outcomes in people with gout. Recent pilot studies suggest that dietitian-directed diet modification may lower SUA concentrations and gout flares in people with gout.[24,25] However, previous studies, not involving dietitians, have demonstrated that providing general dietary education compared with specific dietary recommendations for gout to people already on ULT does not affect SUA concentrations.[26] Such uncertainty surrounding diet interventions could, in part, also account for the reported lack of referrals from GPs to dietitians specifically for gout. Further, as expressed in the interviews, most dietitians themselves would like more robust evidence linking diet and improved gout outcomes before expanding their role in gout management.

Dietitians in our study described that they often managed gout in combination with other comorbidities, particularly obesity, diabetes and other cardiovascular risk factors, which are commonly associated with gout.[27-29] One study found that reducing the body mass index of gout patients through dietary modifications can lead to a reduction of SUA concentrations and gout attacks.[30] Another study demonstrated a graded relationship between weight loss and reduction in SUA concentrations in men with a high cardiovascular risk profile.[31] This could be a potential area where dietitians could indirectly improve the management of gout, as the typical gout patient was reported by dietitians in our study to be overweight, and weight loss was one of the primary reasons patients were reported to be referred to dietitians.[32,33] Furthermore, there is high prevalence of cardiometabolic comorbidities (eg cardiovascular disease, diabetes) in people living with gout, contributing to increased mortality risk.[34,35] Diet modifications are well-known to reduce cardiometabolic risk factors and recently have been demonstrated to also concurrently lower SUA concentrations, whereas similar benefits have not been shown with ULT.[36,37] Therefore, individualized and holistic dietary advice simultaneously targeting gout and cardiometabolic comorbidities could be an area where dietitians have a greater role. Increasing awareness of the association between obesity, cardiometabolic comorbidities and gout and the potential benefits of dietary modification, through education of dietitians and GPs, could lead to increases in the number and frequency of gout patients consulting with dietitians.

Studies have found that people with gout are very interested in diet information.[38,39] Furthermore, dietitians reported that people with gout often expressed a desire not to manage their gout with medications. Therefore, there is a potential role for dietitians to educate patients in this area, particularly people with a preference for non-pharmacological management. Dietitians demonstrated a good understanding of the diet and lifestyle aspects currently recommended for gout management and as such, would be capable of providing accurate information to people with gout. However, this good understanding was despite a reported lack of training received by dietitians in gout. Additionally, dietitians reported viewing gout with less importance than other conditions they commonly manage. This may suggest that a lack of training, combined with people with gout representing only a small proportion of their patients, is influencing their attitudes and focus rather than their knowledge.

There were several limitations to this study, including a reliance on self-reporting, and confirmation of the validity of dietitian claims through ethnography studies was not performed. As with all research involving voluntary recruitment methods, there can be an inherent selection bias in participants, as those who agree to the study may be more interested and/or knowledgeable in gout. However, undertaking continuous recruitment until thematic saturation is reached can alleviate some of this selection bias. Furthermore, Sydney is a large multi-cultural city with gout prevalence varying across different ethnic backgrounds. Although dietitians in this study practiced in a wide cross-section of local health districts across Sydney, there may be some differences in the advice provided by dietitians based on an individual's ethnic background with advice dependent on foods they are used to eating. This may also impact on the extent to which an individual's diet can be adapted for management of gout. Similarly, health literacy is variable across locations in Sydney and people with gout may not be receptive to dietary advice or seeing a dietitian if they do not understand the information provided. In addition, there are associated costs to seeing a dietitian in Australia, a concern raised by dietitians in this study. However, this factor is removed if a patient receives a referral to see the dietitian from their general practitioner.

In conclusion, this study explored the current and potential role of Australian community dietitians in gout management. Dietitians currently report playing a minor role in gout management. However, given that gout is becoming increasingly prevalent and international guidelines for dietary and lifestyle modifications for managing gout exist, dietitians could play a larger role in gout management in conjunction with pharmacological treatment. Particularly, as gout patients are largely multimorbid, dietitians could have an increasing role in the secondary holistic management of gout through treatment of associated metabolic comorbidities to indirectly manage gout, such as programs to improve weight loss and increase physical activity. Collaborations with GPs, the main carers of patients with gout, or with community pharmacists who dispense the medications for gout, is required. GPs can more regularly refer their patients with gout to a dietitian for a more holistic approach to gout management as gout guidelines suggest medications in conjunction with dietary and lifestyle modifications. Similarly, pharmacists can suggest to patients picking up their long-term gout or over-the-counter acute gout medications to ask their GPs about referral to a dietitian to expand their gout management.

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CONFLICT OF INTEREST

The authors declare they have no competing interests.

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REFERENCES

1. Ahmed F, Tscharke B, O'Brien J, et al. Wastewater-based estimation of the prevalence of gout in Australia. *Sci Total Environ*. 2020;715:136925.
2. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. *Nat Rev Dis Primers*. 2019;5(1):69.
3. Roddy E, Mallen CD, Doherty M. Gout. *BMJ*. 2013;347:f5648.
4. Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: results from a cross-sectional survey. *Health Qual Life Outcomes*. 2012;10:117.
5. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation*. 2007;116(8):894-900.
6. Li R, Yu K, Li C. Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. *Asia Pac J Clin Nutr*. 2018;27(6):1344-1356.
7. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care Res (Hoboken)*. 2020;72(6):744-760.
8. Graf SW, Whittle SL, Wechalekar MD, et al. Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative. *Int J Rheum Dis*. 2015;18(3):341-351.
9. Sivera F, Andres M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Ann Rheum Dis*. 2014;73(2):328-335.
10. Briesacher BA, Andrade SE, Fouayzi H, Chan A. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28(4):437-443.
11. Harrold LR, Mazor KM, Velten S, Ockene IS, Yood RA. Patients and providers view gout differently: a qualitative study. *Chronic Illn*. 2010;6(4):263-271.
12. Harrold LR, Mazor KM, Peterson D, Naz N, Firneno C, Yood RA. Patients' knowledge and beliefs concerning gout and its treatment: a population based study. *BMC Musculoskelet Disord*. 2012;13:180.
13. Wylie-Rosett J, Delahanty L. An integral role of the dietitian: implications of the Diabetes Prevention Program. *J Am Diet Assoc*. 2002;102(8):1065-1068.
14. Dalbeth N, Lindsay K. The patient's experience of gout: new insights to optimize management. *Curr Rheumatol Rep*. 2012;14(2):173-178.
15. Vaccher S, Kannangara DR, Baysari MT, et al. Barriers to care in gout: from prescriber to patient. *J Rheumatol*. 2016;43(1):144-149.
16. Noy C. Sampling knowledge: the hermeneutics of snowball sampling in qualitative research. *Int J Soc Res Methodol*. 2008;11(4):327-344.
17. Pope C, Ziebland S, Mays N. Qualitative research in health care: Analysing qualitative data. *BMJ*. 2000;320(7227):114-116.
18. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59(11):1540-1548.
19. Reinders MK, Haagsma C, Jansen TL, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann Rheum Dis*. 2009;68(6):892-897.
20. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology (Oxford)*. 2017;56(7):1056-1059.
21. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29-42.
22. Rai SK, Fung TT, Lu N, Keller SF, Curhan GC, Choi HK. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. *BMJ*. 2017;357.
23. McCormick N, Rai SK, Lu N, Yokose C, Curhan GC, Choi HK. Estimation of primary prevention of gout in men through modification of obesity and other key lifestyle factors. *JAMA Netw Open*. 2020;3(11):e2027421.
24. Juraschek SP, Miller ER 3rd, Wu B, et al. A randomized pilot study of DASH Patterned Groceries on Serum Urate in individuals with gout. *Nutrients*. 2021;13(2).
25. Singh JA, Green C, Morgan S, et al. A randomized internet-based pilot feasibility and planning study of cherry extract and diet modification in gout. *J Clin Rheumatol*. 2020;26(4):147-156.
26. Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. *Intern Med J*. 2015;45(2):189-194.
27. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med*. 2012;125(7):679-87.e1.
28. Lyu LC, Hsu CY, Yeh CY, Lee MS, Huang SH, Chen CL. A case-control study of the association of diet and obesity with gout in Taiwan. *Am J Clin Nutr*. 2003;78(4):690-701.
29. Williams PT. Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men. *Am J Clin Nutr*. 2008;87(5):1480-1487.
30. Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis*. 2000;59(7):539-543.
31. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. *Rheumatology (Oxford)*. 2010;49(12):2391-2399.
32. Seagle HM, Strain GW, Makris A, Reeves RS. Position of the American Dietetic Association: weight management. *J Am Diet Assoc*. 2009;109(2):330-346.
33. Lang A, Froelicher ES. Management of overweight and obesity in adults: behavioral intervention for long-term weight loss and maintenance. *Eur J Cardiovasc Nurs*. 2006;5(2):102-114.
34. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2007;57(1):109-115.
35. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med*. 2008;168(10):1104-1110.

36. Yokose C, McCormick N, Rai SK, et al. Effects of low-fat, mediterranean, or low-carbohydrate weight loss diets on serum urate and cardiometabolic risk factors: a secondary analysis of the Dietary Intervention Randomized Controlled Trial (DIRECT). *Diabetes Care*. 2020;43(11):2812-2820.
37. Yokose C, McCormick N, Choi HK. The role of diet in hyperuricemia and gout. *Curr Opin Rheumatol*. 2021;33(2):135-144.
38. Singh JA. Research priorities in gout: the patient perspective. *J Rheumatol*. 2014;41(3):615-616.
39. Chandratre P, Mallen CD, Roddy E, Liddle J, Richardson J. "You want to get on with the rest of your life": a qualitative study of health-related quality of life in gout. *Clin Rheumatol*. 2016;35(5):1197-1205.

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

Pain neuroscience education combined with usual treatment for fibromyalgia syndrome: A randomized controlled trial

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Abstract

Aim: The aim of this study was to investigate the effectiveness of pain neuroscience education (PNE) in addition to usual treatment in patients with fibromyalgia syndrome.

Methods: Forty patients were randomized into 2 groups. The experimental group underwent PNE sessions over 6 weeks in addition to pharmacological treatment, and the control group was given only pharmacological treatment. The primary outcome measure was functional status and the secondary outcome measures were widespread pain pressure threshold and kinesiophobia level. All assessments were conducted before the intervention and at the end of the 6th and 12th weeks by the same blinded researcher.

Results: The intervention group had significantly greater improvement than the control group in terms of the mean total scores in the Fibromyalgia Impact Questionnaire ($P = .001$) and the Tampa Scale of Kinesiophobia ($P = .001$) with large effect sizes. The intervention group also had significantly greater improvement in the pain pressure threshold values of the cervical ($P = .040$), thoracic ($P = .001$), lumbar ($P < .001$), elbow ($P = .005$) and calf ($P = .006$) regions with moderate-to-large effect sizes.

Conclusion: This study showed that the addition of 6-week PNE sessions to pharmacological treatment was successful in improving functional status, widespread pain pressure threshold, and level of kinesiophobia in patients with fibromyalgia syndrome during a 12-week follow-up period.

KEYWORDS

fibromyalgia, functional status, pain neuroscience education, pain pressure threshold, pharmacological treatment

1 | BACKGROUND

Fibromyalgia syndrome (FMS) is an important chronic condition seen in 2% to 5% of the general population, characterized by widespread pain and often accompanied by fatigue, cognitive problems, and sleep disturbances.[1] Although the etiology of FMS remains unclear, nociplastic pain has been reported as the most accepted mechanism in the pathophysiology of widespread pain experience and other symptoms related to FMS.[2,3] Different biologic factors may cause hyperexcitability of the central nervous system in patients with FMS.[4,5] In addition to such neurobiological factors, negative or maladaptive thoughts, emotions, cognitions, and catastrophizing and hypervigilance behaviors have been associated with FMS.[6]

There are multiple evidence-based treatment guidelines for fibromyalgia. Pharmacological treatments are widely used for this disease. The European Alliance of Associations for Rheumatology (EULAR) reported that among the many treatment modalities, the strongest evidence for the initial stage has been obtained from pharmacological treatments, exercise therapy, and patient education.[7] Furthermore, many patients diagnosed with fibromyalgia complain of widespread pain, but the underlying cause or mechanism is unknown. Patients who misunderstand pain mechanisms seem to describe pain as more threatening or dangerous due to damage or injury.[8-10] This perception results in lower pain tolerance, more destructive thoughts about pain, and fewer pain management strategies.[8] Therefore, patient education strategies providing up-to-date information about pain and pathophysiology of FMS are needed to be integrated into treatment.

Pain neuroscience education (PNE) is a recent patient education method which allows patients with any chronic pain conditions to understand and/or reconceptualize pain, thereby changing their negative beliefs and unfavorable attitudes about pain.[9,11] In PNE, patients are deeply informed about the neurophysiology of pain from a neuroscience perspective. Systematic reviews and meta-analyses have shown that PNE has a low-to-moderate effect on reducing pain, disability and psychological distress, as well as improving physical function, beliefs and attitudes of patients with chronic musculoskeletal pain.[11,12]

A limited number of studies examining the effectiveness of PNE as adjuvant therapy in patients with FMS have presented promising results but reported the need for further robust studies.[9,13,14] The aim of the current study was to investigate the effectiveness of PNE in addition to usual treatment in FMS.

2 | METHODS

2.1 | Study design

This was a single-center, prospective, assessor-blinded, randomized controlled trial study. Ethics approval was obtained from the Clinical Research Ethics Committee of Kutahya Health Sciences University (2019/05). The study was registered at ClinicalTrials.gov (NCT04050839). Data collection was performed between March 2019 and October 2020 at the Physical Therapy Department of the hospital. The Consolidated Standards of Reporting Trials (CONSORT) statements were considered to report the methods of this study.[15]

2.2 | Participants

2.2.1 | Recruitment and setting

Participants who directly presented to the Physical Therapy Department of Kutahya Health Sciences University Hospital during the study period with persistent and diffuse pain, were screened for eligibility by an independent physician (MAL). All the participants were informed in advance about the study procedure and signed consent forms.

2.2.2 | Inclusion criteria

Patients who met the following inclusion criteria were included in this study: (1) age ≥18 years; (2) meeting the 2010/2016 American College of Rheumatology diagnostic criteria for FMS; and (3) having Turkish as a native language.

2.2.3 | Exclusion criteria

Patients were excluded from the study if they: (1) had any severe mental or psychological disorder; (2) were illiterate; (3) had significant hearing and/or vision loss; and (4) refused to adhere to usual treatment.

2.3 | Procedure

Following the randomization of the patients into the 2 groups, a blinded researcher (FY) evaluated all the participants. Then, different researchers (IS and MAL) administered 6-week treatment programs to the participants. The blinded researcher (FY) re-evaluated all the participants at the end of 6 weeks and again at 12 weeks. The study arms were defined as follows: the intervention group which received PNE combined with usual treatment and the control group which received only usual treatment.

2.4 | Interventions

2.4.1 | PNE

PNE was applied as a face-to-face didactic educational model in groups of 4 to 5 people in a suitable training hall by a PNE-certificated researcher (IS). PNE sessions were adapted in accordance with previous studies and guidelines.[16,17] Briefly, the patients were given detailed information about the neurophysiology of chronic pain and its effects on FMS. In addition, the patients were encouraged to perform exercise and physical activity. Following each session, any patient questions were answered. The whole content of the educational sessions is shown in Figure 1. Throughout the program, graphics, pictures and various anecdotes were used to avoid technical terms and expressions. Previously prepared PowerPoint presentations were used during the educational sessions. Group PNE sessions were administered once a week for 6 weeks. A session lasted approximately 40-45 minutes.

FIGURE 1 Content of pain neuroscience education

Session 1	Welcome session. Definition of fibromyalgia and the goal of the educational program
Session 2	Etiology of fibromyalgia. Relations between pain mechanism and fibromyalgia symptoms
Session 3	Peripheral neuropathic pain, peripheral nerve sensitization, allodynia, central sensitization, and hyperalgesia
Session 4	Neuroplasticity, spreading pain, central sensitization, hyperalgesia, and allodynia
Session 5	Stress biology, immune response, emotional overload, fear, catastrophization, and their role in pain and other symptoms
Session 6	Coping with symptoms. Potential effects of education, physical activity, and medication

2.4.2 | Usual treatment

The patients in both the intervention and control groups were given usual treatment for FMS. In Turkey, the usual treatment for patients with FMS is mainly pharmacological therapy adjusted to the individual patient's symptomatic profile, often including antidepressants, membrane stabilizer agents, and opioid analgesics. Patients were asked not to change their medication regimen during the 12-week period.

2.5 | Outcome measurements

The patients' demographic data on age, height, body weight, body mass index, education level, and duration of symptoms were recorded. Their functional status, pain intensity, pain pressure threshold (PPT) and level of kinesiophobia were assessed at baseline, after treatment (at the end of 6 weeks), and at 12 weeks. In addition, the patients' compliance with the home exercise program was evaluated after treatment. The primary outcome measure was functional status, and the secondary outcomes measures were PPT and kinesiophobia level.

2.5.1 | Assessment of functional status

Functional status was evaluated using the Turkish version of the Fibromyalgia Impact Questionnaire (FIQ). The validity and reliability studies of this questionnaire were performed by Sarmer et al.[18] This scale measures several patient characteristics over the past week: physical functioning, work status (missed days of work and job difficulty), depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being. The total FIQ score ranges from 0 to 100 and higher scores indicate severe effects of FMS. The minimal clinical important difference (MCID) for FIQ was reported to be minimum 14% or 8.1-point improvement.[19]

2.5.2 | Assessment of PPT

PPT was evaluated with a Jtech digital algometer (Jtech Medical Industries, ZEVEX Company) according to the measurement protocol published elsewhere.[20] The PPT measurement was performed bilaterally over the spine (5 cm left and right of the spinous processes of C7, T8 and L3), over the belly of the extensor wrist muscles, over the middle phalanx of the second finger, and over the belly of the gastrocnemius muscles. The applied pressure force was gradually increased to 1 kg/s, and the patients were asked to verbally express the first change from the sense of pressure to the sense of pain, and the pressure force on the screen was recorded. Each measurement was repeated 3 times (PPT1, PPT2 and PPT3) at 10-second intervals, and data were recorded by taking the average of the last 2 measurements (PPT2 and PPT3). When there were no significant difference with reference to the side of the measurement, the side with a lower PPT was taken into account for data analysis.[21]

2.5.3 | Assessment of kinesiophobia

The Tampa Kinesophobia Scale (TSK) was used to evaluate the level of kinesiophobia. TSK is a 17-item self-reported questionnaire developed to measure the fear of motion/re-injury. The validity and reliability studies of TSK were performed by Yılmaz et al.[22] The scale includes injury/re-injury and fear avoidance parameters in work-related activities. The items are based on a 4-point Likert-type scale (1 = strongly disagree, 4 = strongly agree). The total TSK score ranges from 17 to 68, with a higher score indicating a high level of kinesiophobia. MCID for TSK was reported to be at least 4.5 points for patients with chronic musculoskeletal pain.[23]

2.6 | Sample size

A 2 × 2 repeated-measures analysis of variance (ANOVA) between-subject factor (intervention and control group) was used. The primary outcome measure was the FIQ score. Based on a previous study,[24] the effect size was large for FIQ (Cohen d = 0.95) for the time × group interaction. Using this effect size, 30 participants (15 participants in each group) were required to show statistically significant differences at 80% power and an α level of .05. At least 36 participants were aimed for, due to possible loss to follow-up of 20%.

2.7 | Randomization

Randomization was carried out by a different researcher (VK), who did not apply the intervention or evaluate the outcomes, using a computer program (SPSS. v.21; IBM). Concealment of allocation was obtained using opaque, sealed and stapled envelopes.

2.8 | Blinding

Different researchers performed all the assessments and treatments separately in this study. The assessor (FY) was blinded to group allocation during the assessments. The participants were also asked not to disclose any information about their treatment during the follow-up assessments.

2.9 | Statistical analysis

IBM SPSS version 21.0 (IBM) software package was used for data analysis. The normal distribution of data was assessed using the Kolmogorov–Smirnov or Shapiro–Wilk test. The independent-samples *t* test was used to compare continuous data between the intervention and control groups, and the Chi-square test was used to compare categorical data. Patient adherence to the home exercise program was compared between the groups using the *t* test. To analyze changes in functional status, PPT, and level of kinesiophobia between the groups, a mixed-model repeated-measures ANOVA was conducted. In the presence of group × time interactions, the main effects were examined using a Bonferroni correction. A *P* value of less than .05 was accepted for statistical significance. The partial eta-squared value (η^2) was considered as an effect size. η^2 values less than 0.01 indicate a small effect size, 0.06 indicate a moderate effect size, and values over 0.14 indicate a large effect size.[25] The mean differences within groups and reference MCID values given in the

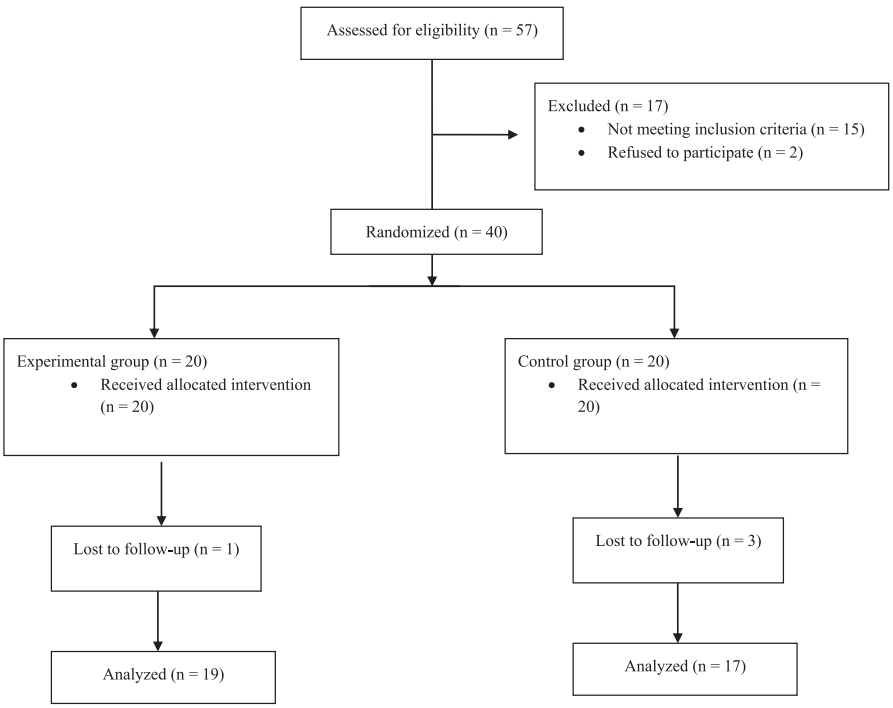

FIGURE 2 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study

literature were used for the interpretation of clinically meaningful effects.

3 | RESULTS

From the initial group of 40 participants, 4 were excluded because they did not comply with the follow-up assessment. The intervention group included 19 participants (mean age: 44.25 ± 7.87 years) and the control group included 17 participants (mean age: 41.44 ± 11.35 years; Figure 2). All the participants in both groups were female. There was no significant difference between the 2 groups in terms of age ($P = .900$), height ($P = .773$), body weight ($P = .831$), body mass index ($P = .315$), onset of pain ($P = .108$) or level of education ($P = .084$). Further, there was no significant between the 2 groups regarding the use of pharmacological agents. The demographic data are shown in Table 1. The baseline scores for pain intensity, functional status and kinesiophobia were similar, but PPT statistically significantly differed between the groups (Table 2).

3.1 | Primary outcome

From the baseline to the end of treatment, the FIQ score both statistically ($P < .001$) and clinically (>8.1 points) improved in the intervention group, whereas in the control group, only statistical improvement ($P < .001$) was observed and there was no significant

TABLE 1 Demographic characteristics of the study groups

	Intervention group (N = 19) Mean ± SD	Control group (N = 17) Mean ± SD	*P*
Age, y	44.25 ± 7.87	41.44 ± 11.35	.900
Height, cm	162.65 ± 6.46	161.50 ± 62.52	.773
Weight, kg	73.00 ± 10.04	70.72 ± 10.47	.831
BMI, kg/m^2	27.73 ± 4.51	27.07 ± 3.38	.315
Onset of pain, mo	90.70 ± 81.16	70.67 ± 63.08	.108
Education			
Primary school	11 (57.8%)	5 (27.8%)	.084
High school	4 (21.1%)	3 (16.7%)	
University	4 (21.1%)	10 (55.5%)	
Pharmacological treatment			
SSRIs	6 (31.6%)	7 (41.2%)	.549
SNRIs	5 (26.3%)	3 (17.6%)	.532
Membrane stabilizer agents	11 (57.9%)	9 (52.9%)	.765
Opioid analgesics	8 (42.1%)	7 (41.2%)	.955

Abbreviations: BMI, body mass index; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

TABLE 2 Outcome measures at baseline

Outcome measures	Intervention group (N = 19) Mean ± SD	Control group (N = 17) Mean ± SD	*P*
FIQ (0-100)	61.20 ± 12.39	53.45 ± 18.69	.147
NPRS (0-10)	7.20 ± 1.64	7.00 ± 1.49	.697
PPT cervical spine (kg/cm^2)	3.66 ± 0.63	5.44 ± 1.39	.000*
PPT thoracic spine (kg/cm^2)	4.26 ± 1.17	5.73 ± 1.23	.002*
PPT lumbar spine (kg/cm^2)	4.07 ± 1.10	5.55 ± 1.22	.000*
PPT elbow (kg/cm^2)	3.72 ± 0.75	4.92 ± 1.19	.001*
PPT hand (kg/cm^2)	3.75 ± 0.62	4.70 ± 1.36	.012*
PPT calf (kg/cm^2)	4.04 ± 0.81	6.19 ± 2.08	.000*
TKS (17-68)	41.60 ± 2.84	39.28 ± 5.65	.128

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; NPRS, numeric pain rating scale; PPT, pain pressure threshold; TKS, Tampa kinesiophobia scale.
*$P < .05$.

TABLE 3 Mean differences between the baseline, post-intervention and 12th-week follow-up within groups

	Intervention group mean difference (95% CI)	Control group mean difference (95% CI)
FIQ		
Baseline vs post-intervention	16.79 ± 12.49	5.82 ± 5.70
	(10.94-22.63)*	(2.99-8.66)*
Post-intervention vs 12th week	0.67 ± 4.66	−0.83 ± 2.84
	(−1.51-2.85)	(−2.25-0.58)
Baseline vs 12th week	17.45 ± 13.44	4.99 ± 4.15
	(11.63-23.74)*	(2.92-7.06)*
PPT cervical spine, kg/cm^2		
Baseline vs post-intervention	0.78 ± 0.75	0.30 ± 0.77
	(0.43-1.13)*	(−0.07-0.68)*
Post-intervention vs 12th week	0.05 ± 0.39	0.03 ± 0.33
	(−0.12-0.24)	(−0.19-0.14)
Baseline vs 12th week	0.84 ± 0.73	0.27 ± 0.82
	(0.49-1.17)*	(−0.14-0.68)
PPT thoracic spine, kg/cm^2		
Baseline vs post-intervention	1.72 ± 1.11	0.33 ± 1.24
	(1.20-2.24)*	(−0.28-0.95)
Post-intervention vs 12th week	0.03 ± 0.42	0.12 ± 0.44
	(−0.16-0.22)	(−0.09-0.34)
Baseline vs 12th week	1.75 ± 1.13	0.46 ± 1.30
	(1.22-2.28)*	(−0.19-1.10)
PPT lumbar spine, kg/cm^2		
Baseline vs post-intervention	2.05 ± 1.03	0.70 ± 1.38
	(1.57-2.53)*	(0.01-1.39)
Post-intervention vs 12th week	0.00 ± 0.28	0.16 ± 0.64
	(−0.12-0.12)	(−0.16-0.47)
Baseline vs 12th week	2.05 ± 1.09	0.54 ± 1.05
	(1.54-2.55)*	(0.02-1.06)*
PPT elbow, kg/cm^2		
Baseline vs post-intervention	0.91 ± 0.89	0.03 ± 0.80
	(0.49-1.33)*	(−0.43-0.37)
Post-intervention vs 12th week	0.31 ± 0.76	0.18 ± 0.31
	(−0.05-0.66)	(0.02-0.33)
Baseline vs 12th week	0.60 ± 1.11*	0.21 ± 0.93
	(0.08-1.12)	(−0.25-0.68)
PPT hand, kg/cm^2		
Baseline vs post-intervention	0.30 ± 0.42	0.05 ± 0.73
	(0.10-0.50)*	(−0.31-0.41)
Post-intervention vs 12th week	0.01 ± 0.20	0.00 ± 0.29
	(−0.08-0.11)	(−0.15-0.15)
Baseline vs 12th week	0.32 ± 0.42	0.05 ± 0.66
	(0.12-0.52)*	(−0.28-0.38)
PPT calf, kg/cm^2		

(Continues)

TABLE 3 (Continued)

	Intervention group mean difference (95% CI)	Control group mean difference (95% CI)
Baseline vs post-intervention	1.60 ± 1.42*	0.47 ± 1.39
	(0.94-2.27)	(−0.23-1.16)
Post-intervention vs 12th week	0.05 ± 0.36	-0.15 ± 0.47
	(−0.12-0.22)	(0.38-0.07)
Baseline vs 12th week	1.65 ± 1.28	0.31 ± 1.34
	(1.05-2.25)*	(−0.35-0.97)
TKS		
Baseline vs post-intervention	8.45 ± 3.50	2.22 ± 3.86
	(6.81-10.09)*	(0.30-4.14)*
Post-intervention vs 12th week	0.15 ± 2.28	0.28 ± 1.23
	(−0.91-1.26)	(−0.33-0.89)
Baseline vs 12th week	8.60 ± 4.26	2.50 ± 3.57
	(6.61-10.59)*	(0.73-4.27)*

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; PPT, pain pressure threshold; TKS, Tampa Kinesiophobia Scale.
*$P < .05$.

clinical improvement (<8.1 points). Similarly, the FIQ scores both statistically ($P < .001$) and clinically (>8.1 points) improved between the baseline and the 12th follow-up in the intervention group, whereas it improved statistically ($P < .001$) but not clinically (<8.1 points) in the control group. The clinical mean difference values are shown in Table 3. The intervention group had significantly greater improvement in the mean total score of FIQ ($P = .001$) and had a large effect size (Table 4).

3.2 | Secondary outcomes

In the intervention group, the PPT values of all the measured regions statistically improved ($P < .05$) after treatment compared to the baseline. Similarly, the PPT values statistically improved ($P < .05$) between the baseline and 12th follow-up measurements in this group. However, the control group had statistical improvement ($P < .05$) only in the cervical region from the baseline to the end of treatment and only in the lumbar region from the baseline to the 12th follow-up measurement (Table 3). Since there is no reported reference MCID for PPT in patients with FMS, only statistical meaningfulness was examined. The intervention group had significantly greater improvement than the control group in relation to the PPT values of all regions ($P \leq .05$) except the hand, and the effect sizes ranged from moderate to large (Table 4).

After treatment, the TSK score both statistically ($P < .001$) and clinically (>4.5 points) improved in the intervention group, whereas it improved statistically ($P < .001$) but not clinically (<4.5 points) in the control group. Similarly, the TSK score of the intervention group both statistically ($P < .001$) and clinically (>4.5 points) improved between the baseline and 12th week follow-up, whereas it improved statistically ($P < .001$) but not clinically (<4.5 points) in the control group (Table 3). Lastly, the intervention group had significantly greater improvement in the mean total score of TSK ($P = .001$) and had a large effect size (Table 4).

4 | DISCUSSION

The results of this study showed that PNE combined with usual treatment led to clinically significant improvement in functional status (17.5 points)[19] and level of kinesiophobia (8.6 points).[23] Moreover, the combination of PNE and usual treatment resulted in greater improvement in functional status, PPT in the majority of regions, and level of kinesiophobia compared to usual treatment only.

According to the results of this study, PNE combined with pharmacological treatment was associated with clinically significant improvement in functional status, whereas pharmacological treatment alone resulted in no clinical improvement in the 12-week follow-up period. Furthermore, the PNE + pharmacological treatment group showed greater improvement in functional status compared to pharmacological treatment alone. These results are similar to those of a previous study[24] comparing PNE combined with pharmacological treatment vs pharmacological treatment alone. In another study, a similar group structure was used in patients with migraine, and those who received PNE in addition to usual care were determined to have greater improvement than those only given usual care in terms of disability level and medication intake.[26] It can be stated that only pharmacological treatment for FMS or other chronic pain-related disorders may be insufficient for improving functional status or disability. Due to the lack of efficacy or tolerability problems, discontinuation or irregularities of medicine intake have been reported for patients with FMS.[27] Therefore, an educational intervention, such

TABLE 4 Changes in primary and secondary outcome measures after treatment

	Intervention group (N = 19) Mean ± SD	Control group (N = 17) Mean ± SD	Within-group comparison (*F*; *P*)	Partial eta-squared ES
FIQ (0-100)				
Baseline	61.20 ± 12.39	53.45 ± 18.69	12.16; .001*	0.252
Post-intervention	44.41 ± 18.08	47.63 ± 17.27		
12th week	43.74 ± 19.03	48.46 ± 17.62		
PPT cervical spine, kg/cm^2				
Baseline	3.66 ± 0.63	5.44 ± 1.39	3.99; .040*	0.100
Post-intervention	4.44 ± 0.88	5.75 ± 1.38		
12th week	4.50 ± 0.99	5.71 ± 1.125		
PPT thoracic spine, kg/cm^2				
Baseline	4.26 ± 1.17	5.73 ± 1.23	11.29; .001*	0.239
Post-intervention	5.99 ± 1.01	6.07 ± 1.29		
12th week	6.02 ± 0.97	6.10 ± 1.12		
PPT lumbar spine, kg/cm^2				
Baseline	4.07 ± 1.10	5.55 ± 1.22	13.83, 0.000*	0.277
Post-intervention	6.13 ± 1.12	6.25 ± 1.34		
12th week	6.13 ± 1.13	6.09 ± 1.25		
PPT elbow, kg/cm^2				
Baseline	3.72 ± 0.75	4.92 ± 1.19	6.93; .005*	0.161
Post-intervention	4.63 ± 0.88	4.89 ± 1.18		
12th week	4.32 ± 1.08	4.71 ± 1.13		
PPT hand, kg/cm^2				
Baseline	3.75 ± 0.62	4.70 ± 1.36	1.84; .180	0.049
Post-intervention	4.06 ± 0.50	4.75 ± 1.46		
12th week	4.07 ± 0.55	4.75 ± 1.45		
PPT calf, kg/cm^2				
Baseline	4.04 ± 0.81	6.19 ± 2.08	7.69; .006*	0.176
Post-intervention	5.65 ± 1.05	6.66 ± 2.26		
12th week	5.70 ± 0.85	6.08 ± 1.68		
TKS, 17-68				
Baseline	41.60 ± 2.84	39.28 ± 5.65	22.13; .000*	0.381
Post-intervention	33.15 ± 3.17	37.06 ± 6.78		
12th week	33.00 ± 3.95	36.78 ± 6.85		

Abbreviations: ES, effect size; FIQ, Fibromyalgia Impact Questionnaire; PPT, pain pressure threshold; TKS: Tampa Kinesiophobia Scale.
*$P < .05$.

as PNE could encourage regular medication intake in this patient group. Although patient adherence to medication intake was not evaluated in this study, the possible differences between the intervention and control groups in adherence to pharmacological treatment may be one of the reasons for the greater improvement observed in the former.

This study demonstrated that the addition of PNE to pharmacological treatment resulted in superior outcomes in all regions of PPT except the hand in the 12-week follow-up period. The significant difference between baseline PPT values in the intervention and control groups was felt not to be due to the randomization procedure because the baseline values of both groups were similar and not statistically different in primary outcome (FIQ) and other secondary outcome measures (TSK). However, Oosterwijck et al[10] reported no significant difference between PNE and conventional education including self-management coping strategies in PPT improvement in patients with FMS. This discrepancy may be related to differences in the setting of interventions and intensity of PNE between the 2 studies. Low widespread PPTs have been reported in the majority of patients with FMS, and

these findings have also been associated with the pain intensity and functional status of patients.[28] Therefore, the authors of the current study considered that the combination of PNE and pharmacological treatment could be a promising option to decrease widespread PPT and contribute to the improving functional status of patients with FMS.

The results of this study indicated that PNE in addition to pharmacological treatment was associated with clinically significant improvement in the level of kinesiophobia, whereas pharmacological treatment alone resulted in no clinical improvement in the 12-week follow-up period. Moreover, PNE added to pharmacological treatment was a more effective approach than pharmacological treatment alone in reducing kinesiophobia levels in patients with FMS. Similarly, in a previous study, a multimodal 12-week treatment including PNE was reported to achieve greater improvement than usual care alone in reducing kinesiophobia levels in patients with FMS.[29] These findings may be related to the content of PNE in the current study, since the PNE program included a specific session about the fear avoidance model proposed by Vlaeyen and Linton.[30] Future studies can examine whether PNE is an effective method to change patients' negative thoughts and beliefs using other scales, such as the Patient Catastrophizing Scale[31] and the Fear Avoidance Beliefs Questionnaire[32] in patients with FMS.

Either individual or group education can be preferred during PNE sessions. A previous study[33] compared the effectiveness of individualized neurophysiological pain education and group neurophysiological pain education in patients with chronic low back pain. As a result, it was reported that the group education setting was a cost-effective and less time-consuming method, but the effectiveness of treatment was lower than the individualized program. Due to the busy schedule of PNE-certificated clinicians, the group educational setting was selected in the current study, and the results showed that it had moderate-to-large effect size on functional status, PPT, and levels of kinesiophobia. This supports the view that group-based PNE can be used as an effective option, especially in busy clinics.

This study has certain limitations. First, the authors could not assess patient adherence to pharmacological treatment since the participants did not record medicine intake logs regularly. Therefore, the possible difference between the 2 groups in terms of adherence to medicine intake may have affected the results. Second, the sample size of the current study was smaller than previous studies. Lastly, the long-term effects of PNE in conjunction with pharmacological treatment are still not clear in patients with FMS.

5 | CONCLUSION

This study showed that the addition of 6-week group-based PNE sessions to pharmacological treatment can improve functional status, widespread PPT and levels of kinesiophobia in patients with FMS during a 12-week follow-up period. Further studies should investigate the long-term effects of this treatment option in patients with FMS.

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CONFLICT OF INTERESTS

The authors declare they have no conflict of interest.

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REFERENCES

1. Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep*. 2013;17(8):356. 10.1007/s11916-013-0356-5
2. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain*. 2007;8(11):893-901. 10.1016/j.jpain.2007.06.006
3. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Semin Arthritis Rheum*. 2014;44(1):68-75. 10.1016/j.semarthrit.2014.01.001
4. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*. 2005;114(1):295-302. 10.1016/j.pain.2004.12.032
5. De La Coba P, Bruehl S, Galvez-Sánchez CM, Del Paso GAR. Slowly repeated evoked pain as a marker of central sensitization in fibromyalgia: diagnostic accuracy and reliability in comparison with temporal summation of pain. *Psychosom Med*. 2018;80(6):573-580. 10.1097/PSY.0000000000000599
6. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26(4):465-473. 10.1007/s10067-006-0433-9
7. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76(2):318-328. 10.1136/annrheumdis-2016-209724
8. Jackson T, Pope L, Nagasaka T, Fritch A, Iezzi T, Chen H. The impact of threatening information about pain on coping and pain tolerance. *Br J Health Psychol*. 2005;10(3):441-451. 10.1348/135910705X27587
9. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(8):1153-1159. 10.1016/j.apmr.2010.04.020
10. van Oosterwijck J, Nijs J, Meeus M, et al. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: A pilot study. *J Rehabil Res Dev*. 2011;48(1):43-58. 10.1682/JRRD.2009.12.0206
11. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: a systematic review of the literature. *Physiother Theory Pract*. 2016;32(5):332-355. 10.1080/09593985.2016.1194646
12. Bulow K, Lindberg K, Vaegter HB, Juhl CB. Effectiveness of pain neurophysiology education on musculoskeletal pain: a systematic review and meta-analysis. *Pain Med*. 2021;22(4):891-904. 10.1093/pm/pnaa484
13. Amer-Cuenca JJ, Pecos-Martín D, Martínez-Merinero P, et al. How much is needed? Comparison of the effectiveness of different pain education dosages in patients with fibromyalgia. *Pain Med*. 2020;21(4):782-793. 10.1093/PM/PNZ069

14. Ceballos-Laita L, Mingo-Gómez MT, Navas-Cámara F, et al. Therapeutic exercise and pain neurophysiology education in female patients with fibromyalgia syndrome: a feasibility study. *J Clin Med*. 2020;9(11):3564. 10.3390/jcm9113564
15. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg*. 2012;10(1):28-55. 10.1016/j.ijsu.2011.10.001
16. Louw A, Nijs J, Puentedura EJ. A clinical perspective on a pain neuroscience education approach to manual therapy. *J Man Manip Ther*. 2017;25(3):160-168.:10.1080/10669817.2017.1323699
17. Eneberg-Boldon K, Schaack B, Joyce K. Pain neuroscience education as the foundation of interdisciplinary pain treatment. *Phys Med Rehabil Clin N Am*. 2020;31(4):541-551. 10.1016/j.pmr.2020.07.004
18. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Revised Fibromyalgia Impact Questionnaire. *Clin Rheumatol*. 2011;30(3):339-346. 10.1007/s10067-010-1546-8
19. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. *J Rheumatol*. 2009;36(6):1304-1311. 10.3899/jrheum.081090
20. Farasyn A, Meeusen R. The influence of non-specific low back pain on pressure pain thresholds and disability. *Eur J Pain*. 2005;9(4):375-381. 10.1016/j.ejpain.2004.09.005
21. Farasyn A, Meeusen R. Pressure pain thresholds in healthy subjects: influence of physical activity, history of lower back pain factors and the use of endermology as a placebo-like treatment. *J Bodyw Mov Ther*. 2003;7(1):53-61. 10.1016/S1360-8592(02)00050-5
22. Tunca Yilmaz Ö, Yakut Y, Uygur F, Uluğ N. Turkish version of the tampa scale for kinesiophobia and its test-retest reliability [Tampa kinezyofobi ölçeği'nin Türkçe versiyonu ve test-tekrar test güvenirliği]. *Fiz Rehabil*. 2011;22(1):44-49.
23. Pulles ANTD, Köke AJA, Strackke RP, Smeets RJEM. The responsiveness and interpretability of psychosocial patient-reported outcome measures in chronic musculoskeletal pain rehabilitation. *Eur J Pain*. 2020;24(1):134-144. 10.1002/ejp.1470
24. Barrenengoa-Cuadra MJ, Muñoa-Capron-Manieux M, Fernández-Luco M, et al. Effectiveness of a structured group intervention based on pain neuroscience education for patients with fibromyalgia in primary care: a multicentre randomized open-label controlled trial. *Eur J Pain*. 2021;25(5):1137-1149. 10.1002/ejp.1738
25. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Routledge; 1988. https://doi.org/10.4324/9780203771587
26. Aguirrezabal I, De San P, Román MS, et al. Effectiveness of a primary care-based group educational intervention in the management of patients with migraine: a randomized controlled trial. *Prim Heal Care Res Dev*. 2019;20:1-7. 10.1017/S1463423619000720
27. Häuser W, Walitt B, Fitzcharles MA, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. *Arthritis Res Ther*. 2014;16(1):1-10. 10.1186/ar4441
28. Castro-Sánchez AM, Matarán-Peñarrocha GA, López-Rodríguez MM, Lara-Palomo IC, Arendt-Nielsen L, Fernández-de-las-Peñas C. Gender differences in pain severity, disability, depression, and widespread pressure pain sensitivity in patients with fibromyalgia syndrome without comorbid conditions. *Pain Med*. 2012;13(12):1639-1647. 10.1111/j.1526-4637.2012.01523.x
29. Serrat M, Sanabria-Mazo JP, García-Troiteiro E, et al. Efficacy of a multicomponent intervention for fibromyalgia based on pain neuroscience education, exercise therapy, psychological support, and nature exposure (NAT-FM): study protocol of a randomized controlled trial. *Int J Environ Res Public Health*. 2020;17(2):634. 10.3390/ijerph17020634
30. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85(3):317-332. 10.1016/S0304-3959(99)00242-0
31. Ugurlu M, Ugurlu GK, Erten S, Caykoylu A. Validity of Turkish form of Pain Catastrophizing Scale and modeling of the relationship between pain-related disability with pain intensity, cognitive, and emotional factors. *Psychiatry Clin Psychopharmacol*. 2017;27(2):189-196. 10.1080/24750573.2017.1322672
32. Korkmaz N, Akinci A, Yörükan S, Selçuk Sürücü H, Saraçbaşi O, Özçakar L. Validation and reliability of the Turkish version of the fear avoidance beliefs questionnaire in patients with low back pain. *Eur J Phys Rehabil Med*. 2009;45(4):527-535.
33. Moseley GL. Joining forces – combining cognition-targeted motor control training with group or individual pain physiology education: a successful treatment for chronic low back pain. *J Man & Manip Ther*. 2003;11(2):88-94. 10.1179/106698103790826383

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ORIGINAL ARTICLE

Early combination of pulmonary vasodilators prevents chronic kidney disease progression in connective tissue disease-associated pulmonary hypertension

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Abstract

Aim: Pulmonary hypertension (PH) and chronic kidney disease (CKD) are interdependent for their development and exacerbation. We evaluated the effect of PH on CKD progression in patients with connective tissue disease (CTD)-associated PH.

Methods: We reviewed consecutive patients with CTD who were diagnosed with PH with right heart catheter (RHC) examinations in our hospital. Patients were divided into 2 groups according to the use of vasodilators: monotherapy or combination therapy. We further divided the patients with combination therapy into early and non-early combination groups. Early combination was defined as the addition of the second vasodilator within 1 month after starting the first drug. The clinical course of hemodynamics and CKD progression were compared.

Results: Thirty-eight patients were included in the analysis: 10 were treated with monotherapy and 28 with combination therapy (14 with early and 14 with non-early). At baseline, patients who received combination therapy had a significantly higher mean pulmonary arterial pressure with RHC and a higher right ventricular systolic pressure (RVSP) with echocardiography ($P = .04$) and showed a greater improvement in RVSP after treatment than those who underwent monotherapy. The incidence of CKD progression was significantly lower in patients who received combination therapy than in those who received monotherapy ($P = .05$). Among patients who received combination therapy, the early combination group had a lower incidence of CKD progression than the non-early combination group ($P = .03$).

Conclusions: Early combination therapy is associated with a lower incidence of CKD progression in patients with CTD-associated PH.

KEYWORDS

chronic kidney disease, connective tissue disease-associated pulmonary hypertension, mixed connective tissue disease, systemic lupus erythematosus, systemic sclerosis

1 | INTRODUCTION

Pulmonary hypertension (PH) is a rare but critical complication in patients with connective tissue disease (CTD).[1-5] The 1-year survival rate of patients with CTD-associated PH (CTD-PH) was 45% before the year 2000 when non-specific vasodilators were the sole treatment option. Over the past decade, several specific pulmonary vasodilators have been developed and significantly improved the survival of patients with CTD-PH.[3]

Chronic kidney disease (CKD) is another complication among patients with various CTDs. While the most frequent cause of CKD is CTD-associated renal involvement, CKD without clear renal involvement is also highly prevalent in CTDs.[6-9] Patients with systemic lupus erythematosus (SLE) without clear evidence of lupus nephritis have a higher risk of CKD than the age-adjusted general population.[10] Patients with systemic sclerosis (SSc) who have never experienced scleroderma renal crisis had a reduced glomerular filtration rate.[11] One of the causes of CKD in patients with CTD is PH due to its association with CKD; approximately 21% of patients with CKD experienced PH as a complication,[12] and 36% of patients with PH developed CKD.[13] PH is often progressive and associated with high morbidity and mortality in patients with established CKD compared to those without CKD,[12-15] as left ventricular (LV) hypertrophy and diastolic dysfunction complicated with CKD could lead to exacerbation of PH. Moreover, impaired hemodynamics due to PH can deteriorate renal blood flow, thereby affecting renal function.[13] These findings indicate that PH and CKD are interdependent for their development and exacerbation. However, little is known on the effect of the improvement of hemodynamics using recent specific pulmonary vasodilators on CKD progression.

Thus, the aim of this study was to evaluate the effect of PH on the prevention of CKD progression in patients with CTD-PH.

2 | MATERIALS AND METHODS

2.1 | Patients

We reviewed consecutive patients with SLE, mixed connective tissue disease (MCTD) and SSc based on each classification criteria,[16-18] who were diagnosed with PH using a right heart catheter (RHC) at the Keio University Hospital from 2000 to 2018. PH was defined as the mean pulmonary arterial pressure (mPAP) >20 mm Hg at rest with RHC, based on the criterion.[19] Pre-capillary PH (group 1) was defined as mPAP >20 mm Hg, pulmonary capillary wedged pressure (PCWP) <15 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood units (WU).[19] PH due to left heart disease (group 2) was defined as mPAP >20 mm Hg and PCWP >15 mm Hg.[19] PH due to lung disease (group 3) was defined as mPAP >20 mm Hg, PCWP <15 mm Hg, and PVR >3 WU with less than 70% of forced vital capacity.[20] This study was approved by the Ethics Committee of the Keio University School of Medicine, and the requirement for written informed consent was waived according to Japanese regulations.

2.2 | Data collection and definition

Demographic and clinical data, including the findings of RHC and echocardiography (UCG), were collected from the medical records of patients. Mitral inflow E- and A-wave velocities, E-wave deceleration time, and pulmonary venous reverse A-wave duration were used to categorize LV diastolic function into normal and grades I, II, and III diastolic dysfunction.[21] In monotherapy, one pulmonary vasodilator was used throughout the observation period, and in combination therapy, a combination of 2 or 3 pulmonary vasodilators during the same period. Early combination therapy was defined as the initiation of 2 or 3 pulmonary vasodilators within 1 month, and non-early combination therapy was defined when the second drug was added more than 1 month later. CKD progression was defined as the emergence of new CKD defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 on at least 2 occasions 90 days apart or a decline in eGFR category of the CKD guideline from baseline.[22] Therapeutic response of PH hemodynamics was defined as achieving either right ventricular systolic pressure (RVSP) $\leqq$ 38 mm Hg,[23] mean pulmonary arterial pressure (mPAP) $\leqq$ 20 mm Hg,[19] or cardiac index (CI) $\geqq$ 2.5 L/min/m^2.[24]

2.3 | Statistical analysis

Continuous variables are presented as a median and interquartile ranges (IQR). The differences between 2 groups were analyzed using the Mann-Whitney *U* test for non-parametric variables and the Chi-squared or Fisher's exact test for categorical variables. The survival rates were calculated using the Kaplan-Meier method with a significant difference tested with the log-rank test. Correlations between 2 continuous variables were analyzed using Spearman's rank correlation coefficient. A P value < .05 was deemed statistically significant. All statistical analyses were performed using GraphPad Prism version 7 (GraphPad).

3 | RESULTS

3.1 | Clinical characteristics

We identified 39 patients with CTD-PH. After excluding one patient who had chronic thromboembolic PH, 38 were included in the analysis: 8 with SLE (21.1%), 14 with MCTD (36.8%), and 16 with SSc (44.7%) with 1 overlapping with polymyositis. Among them, 10 (26.3%) underwent monotherapy, and 28 (73.7%) underwent combination therapy consisting of 14 early combination therapies and 14 non-early combination therapies. Three patients underwent 3 pulmonary vasodilators and were categorized under the early combination therapy group. The clinical features of PH diagnosis are shown in Table 1.

The median duration from CTD diagnosis to PH diagnosis was shorter in the combination therapy group than in the monotherapy group (0.0 years vs 14.0 years, P = .04). There was no significant

TABLE 1 Patients' baseline characteristics

	Monotherapy ($n = 10$)	Combination therapy			*P* Mono vs combi	*P* Early vs non-early
		All ($n = 28$)	Early ($n = 14$)	Non-early ($n = 14$)		
Age, y	57.0 (30.0-67.0)	55.0 (41.0-67.0)	51.0 (40.0-61.0)	57.0 (54.0-71.0)	.48	.57
Male : Female	1:9	0:28	0:14	0:14	.11	-
Duration from CTD diagnosis, y	14.0 (9.6-26.8)	0.0 (0.0-10.5)	0.0 (0.0-13.0)	0.0 (0.0-7.0)	.04	.78
Observation after PH diagnosis, y	7.5 (0.0-10.0)	5.5 (4.0-8.0)	4.0 (4.0-7.5)	6.0 (4.0-8.0)	.64	.74
Disease						
SLE (%)	4 (40.0)	4 (14.3)	3 (21.4)	1 (7.1)	.09	.28
MCTD (%)	4 (40.0)	10 (35.7)	5 (35.7)	5 (35.7)	.81	-
lcSSc (%)	2 (20.0)	12 (42.9)	5 (35.7)	7 (50.0)	.19	.45
dcSSc (%)	0 (0)	1 (3.6)	0 (0.0)	1 (7.1)	.47	.31
Overlap disease (SSc +PM) (%)	0 (0)	1 (3.6)	1 (7.1)	0 (0.0)	.47	.31
ANA positivity (%)	10 (100.0)	25 (100.0)	11 (100.0)	14 (100.0)	-	-
Anti-dsDNA (%)	2 (20.0)	6 (21.4)	3 (21.4)	3 (21.4)	.92	-
Anti-Sm (%)	5 (50.0)	8 (28.6)	5 (35.7)	3 (21.4)	.22	.41
Anti-U1RNP (%)	6 (60.0)	16 (57.1)	9 (64.3)	7 (50.0)	.87	.44
Anti-Topo1 (%)	0 (0.0)	2 (7.1)	1 (7.1)	1 (7.1)	.38	-
Anti-centromere (%)	2 (20.0)	11 (39.3)	3 (21.4)	8 (57.1)	.27	.05
Anti-SSA (%)	5 (50.0)	13 (46.4)	7 (50.0)	6 (42.8)	.85	.70
Hgb, g/dL	10.9 (10.9-13.2)	11.7 (11.3-13.3)	12.5 (11.4-13.8)	11.4 (10.0-12.7)	.46	.52
eGFR, mL/min/1.73 m^2	72.7 (46.3-77.6)	78.3 (59.2-92.5)	88.8 (59.9-101.5)	66.1 (60.1-81.9)	.58	.42
BNP, pg/mL	28.4 (17.1-78.7)	31.9 (15.1-33.8)	30.2 (25.1-80.6)	42.6 (34.3-124.7)	.50	.65
Hypertension, (%)	2 (20.0)	8 (28.6)	5 (35.7)	3 (21.4)	.69	.67
Diabetes mellitus, (%)	1 (10.0)	2 (7.1)	0 (0.0)	2 (14.3)	.99	.48
Interstitial lung disease (%)	4 (40.0)	9 (32.1)	6 (42.9)	3 (21.4)	.65	.22
%FVC (%)	81.2 (72.0-87.6)	86.9 (79.1-99.7)	84.8 (78.9-99.7)	88.8 (80.0-99.0)	.82	.88
WHO functional class						
II (%)	10 (100)	11 (39.3)	3 (21.4)	8 (57.1)	<.01	.05
III (%)	0 (0)	16 (57.1)	10 (71.4)	6 (42.9)	<.01	.12
IV (%)	0 (0)	1 (3.6)	1 (7.1)	0 (0.0)	.54	.31
Classification of PH						
Group 1 (%)	9 (90.0)	26 (92.3)	13 (92.9)	13 (92.9)	.77	-
Group 2 (%)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	.11	-
Group 3 (%)	0 (0.0)	2 (7.1)	1 (7.1)	1 (7.1)	.38	-
Steroid use (%)	4 (40.0)	16 (57.1)	9 (64.3)	7 (50.0)	.88	.45
Immunosuppressant use (%)	4 (40.0)	12 (42.9)	7 (50.0)	5 (35.7)	.88	.11
IVCY (%)	1 (10.0)	9 (32.1)	7 (50.0)	2 (14.3)	.17	.11
AZA (%)	1 (10.0)	8 (28.6)	5 (35.7)	3 (21.4)	.19	.40
MMF (%)	0 (0.0)	2 (7.1)	1 (7.1)	1 (7.1)	.38	-
TAC (%)	1 (10.0)	2 (7.1)	1 (7.1)	1 (7.1)	.77	-
CsA (%)	1 (10.0)	3 (10.7)	0 (0.0)	1 (7.1)	.94	.31
Pulmonary vasodilators						
Prostacyclin analogs[a] (%)	3 (30.0)	5 (17.9)	3 (21.4)	2 (14.3)	.41	.62

(Continues)

TABLE 1 (Continued)

	Monotherapy ($n = 10$)	Combination therapy			*P* Mono vs combi	*P* Early vs non-early
		All ($n = 28$)	Early ($n = 14$)	Non-early ($n = 14$)		
Endothelin receptor antagonists (%)	3 (30.0)	27 (96.4)	14 (100.0)	13 (92.9)	<.01	.31
Phosphodiesterase type 5 inhibitors (%)	4 (40.0)	24 (85.7)	11 (78.6)	12 (85.7)	<.01	.62
Prostacyclin receptor agonist (%)	0 (0.0)	3 (10.7)	3 (21.4)	0 (0.0)	.28	.07
Endothelin receptor antagonists + phosphodiesterase type 5 inhibitors (%)	-	20 (71.4)	8 (57.1)	12 (85.7)	-	.09
Endothelin receptor antagonists + prostacyclin analogs (%)	-	4 (14.3)	3 (21.4)	1 (7.1)	-	.28
Phosphodiesterase type 5 inhibitors + prostacyclin analogs[a] (%)	-	1 (3.6)	0 (0.0)	1 (7.1)	-	.31
Endothelin receptor antagonists + phosphodiesterase type 5 inhibitors + prostacyclin receptor agonist (%)	-	3 (10.7)	3 (21.4)	0 (0.0)	-	.07
RAAs inhibitor use (%)	0 (0.0)	2 (7.1)	1 (7.1)	1 (7.1)	.38	-
Diuretics use (%)	1 (10.0)	17 (60.7)	8 (57.1)	9 (64.3)	<.01	.69
Beta-blocker use (%)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	.58	-
Statin use (%)	3 (30.0)	7 (25.0)	3 (21.4)	4 (28.6)	.76	.67

Results show median (interquartile range) unless otherwise indicated.

Abbreviations: ANA, anti-nuclear antibody; AZA, azathioprine; BNP, brain natriuretic peptide; CsA, cyclosporine A; CTD, connective tissue disease; dcSSc, diffuse cutaneous systemic sclerosis; eGFR, estimated glomerular filtration rate; FVC, forced vital capacity; IVCY, intravenous cyclophosphamide; lcSSc, limited cutaneous systemic sclerosis; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PM, polymyositis; PSL, prednisolone; RAAS, renin-angiotensin-aldosterone system; SLE, systemic lupus erythematosus; TAC, tacrolimus.

[a]Oral beraprost sodium.

difference in prevalence of lupus nephritis among the 3 groups (monotherapy, 25.0% vs early combination, 33.3% vs non-early combination 0.0%, $P = .80$). The RVSP, mean mPAP, and PVR were higher in patients who received combination therapy (67.5 mm Hg vs 41.0 mm Hg, $P = .04$; 36.0 mm Hg vs 29.0 mm Hg, $P = .04$; and 7.9 WU vs 4.5 WU, $P = .03$) (Table 2).

A comparison between patients with early combination therapy and those with non-early combination therapy demonstrated that the mPAP in the early combination therapy group was higher than that in the non-early combination therapy group (51.0 mm Hg vs 33.0 mm Hg, $P = .03$).

3.2 | Serial change of echocardiography

Twenty-nine patients (7 in monotherapy, 12 in early combination therapy, and 10 in non-early combination therapy) underwent UCG 3 times. The mean interval from the first UCG (at PH diagnosis) to the second and the third UCG was 0.0, 11.0, and 24.0 months in monotherapy; 0.0, 7.5, and 21.5 months in early combination therapy; and 0.0, 9.0, and 25.0 months in non-early combination therapy, respectively (Figure S1A). All patients in the early combination therapy started 2 or 3 vasodilators before the second UCG, and all patients in the non-early combination therapy were treated with 1 vasodilator at the second UCG and with 2 vasodilators at the third UCG. Compared to the baseline UCG, the estimated RVSP at the third UCG was significantly reduced in early combination therapy (from 76.0 mm Hg to 38.0 mm Hg, $P = .01$) but not in monotherapy (from 41.0 mm Hg to 39.0 mm Hg, $P = .84$) and non-early combination therapy (from 67.0 mm Hg to 58.0 mm Hg, $P = .72$, Figure 1A). The proportion of patients with diastolic function grades II and III tended to decrease in early combination therapy but not in monotherapy and non-early combination therapy (Figure 1B). When we performed the same analysis in patients with SLE/MCTD and those with SSc separately, a similar trend was observed (Figure S2 and Figure S3).

3.3 | Serial change of RHC findings

We evaluated the findings of RHC in patients who underwent the second RHC within 2 years after the PH diagnosis (Figure S1B): 9 patients with monotherapy, 12 with early combination therapy, and 8

TABLE 2 Patients' baseline characteristics of echocardiography and right heart catheter

	Monotherapy ($n = 10$)	Combination therapy			*P* Mono vs combi	*P* Early vs non-early
		All ($n = 28$)	Early ($n = 14$)	Non-early ($n = 14$)		
Echocardiography						
RVSP, median (IQR) mm Hg	41.0 (31.0-45.0)	67.5 (55.1-83.0)	76.0 (56.0-92.0)	67.0 (54.0-74.0)	.04	.68
E, median (IQR) cm/s	54.8 (53.0-70.7)	57.0 (50.9-75.4)	54.0 (49.0-65.0)	74.8 (57.0-77.0)	.69	.27
E/A, median (IQR)	0.8 (0.8-1.1)	0.9 (0.7-1.0)	0.9 (0.7-0.9)	0.8 (0.8-0.9)	.88	.89
Septal-e', median (IQR) cm/s	6.1 (4.4-7.3)	6.8 (5.6-7.0)	6.9 (5.7-7.2)	6.7 (5.4-6.9)	.52	.78
Lateral-e', median (IQR) cm/s	7.5 (6.5-9.9)	10.6 (8.9-12.8)	12.4 (9.6-13.0)	9.9 (6.6-11.6)	.26	.36
E/e'	8.4 (7.5-12.2)	8.3 (7.8-9.8)	8.1 (7.3-8.5)	9.5 (8.2-11.6)	.46	.55
IVC, median (IQR) mm	1.3 (1.0-1.4)	1.5 (1.2-1.6)	1.4 (1.2-1.8)	1.5 (1.3-1.6)	.87	.85
LVMI, g/m^2	85.0 (67.5-90.6)	68.7 (57.6-79.0)	64.0 (48.0-75.2)	75.3 (68.7-81.1)	.42	.38
EF, median (IQR) %	71.4 (35.5-76.7)	74.3 (69.0-79.5)	75.4 (67.4-79.5)	71.2 (70.1-78.8)	.69	.58
LV diastolic disfunction grade						
Normal, *n* / tested number	2 / 8	5 / 23	3 / 12	2 / 11	.99	.62
Grade I, *n* / tested number	1 / 8	6 / 23	4 / 12	2 / 11	.64	.35
Grade II, *n* / tested number	3 / 8	9 / 23	5 / 12	4 / 11	.99	.69
Grade III, *n* / tested number	2 / 8	3 / 23	0 /12	3 / 11	.58	.07
Right heart catheter						
mPAP, median (IQR) mm Hg	29.0 (20.0-32.0)	36.0 (28.0-49.0)	51.0 (35.0-53.0)	33.0 (27.0-34.0)	.04	.03
PVR, median (IQR) Wood units	4.5 (3.3-5.1)	7.9 (6.0-11.0)	10.3 (6.1-18.5)	7.1 (5.5-8.3)	.03	.09
CI, median (IQR) L/min/m^2	2.3 (2.1-3.2)	2.3 (1.4-2.7)	1.9 (1.1-2.7)	2.4 (1.9-2.7)	.24	.19
PCWP, median (IQR) mm Hg	5.0 (3.0-8.0)	6.0 (3.0-8.0)	6.0 (6.0-8.0)	5.0 (3.0-6.0)	.69	.72

Abbreviations: A, atrial filling velocity; CI, cardiac index; E, early diastolic filling velocity; IVC, inferior vena cava; LVMI, left ventricular mass index; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedged pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure.

with non-early combination therapy. The improvement in mPAP was greater with combination therapy than with monotherapy although not significant ($P = .42$, Figure S4A), and CI significantly improved in combination therapy compared with monotherapy ($P = .03$, Figure S4B). This improvement in mPAP and CI was mainly due to the improvement in early combination therapy (Figure S4A and Figure S4B).

3.4 | CKD progression

CKD progression during the observation period occurred in 21 patients (55.2%); 15 (71.4%) patients had newly developed CKD and 6 (28.5%) had a decline in existing CKD. The mean observation period after PH diagnosis was not different between monotherapy and combination therapy (7.5 years vs 5.5 years, $P = .75$). CKD progression was observed more frequently in patients who received monotherapy than in those who received combination therapy (90.0% vs 42.8%, $P = .05$, Figure 2A). The incidence of CKD progression was significantly lower with early combination therapy than with non-early combination therapy (21.4% vs 64.3%, $P = .03$, Figure 2B). Furthermore, we excluded patients with CKD at baseline and compared the CKD-free survival (Figure S5). There was the same tendency for lower CKD progression rate in patients with combination therapy than monotherapy ($P = .08$) and early combination therapy than non-early combination therapy ($P = .09$). Although a long disease duration may be potentially associated with CKD progression, we found no correlation between eGFR change from baseline and disease duration ($r = 0.14$, $P = .41$) (Figure S6). We compared mean values of eGFR from the baseline to the end of follow-up (Figure S7A) and decline of eGFR category of CKD guidelines (Figure S7B). Patients with early combination therapy tended to have higher eGFR than patients with monotherapy and non-early combination therapy during the follow-up periods. We next found a significantly higher percentage of patients who experienced decline of eGFR category in monotherapy than early combination and non-early combination therapy ($P = .01$).

3.5 | Relationship between improvement in PH and CKD progression

We investigated the association between hemodynamic changes in PH and CKD progression. When we divided patients according to therapeutic response by RVSP, mPAP, and CI defined above, CKD progression was less frequent in patients who responded to PH

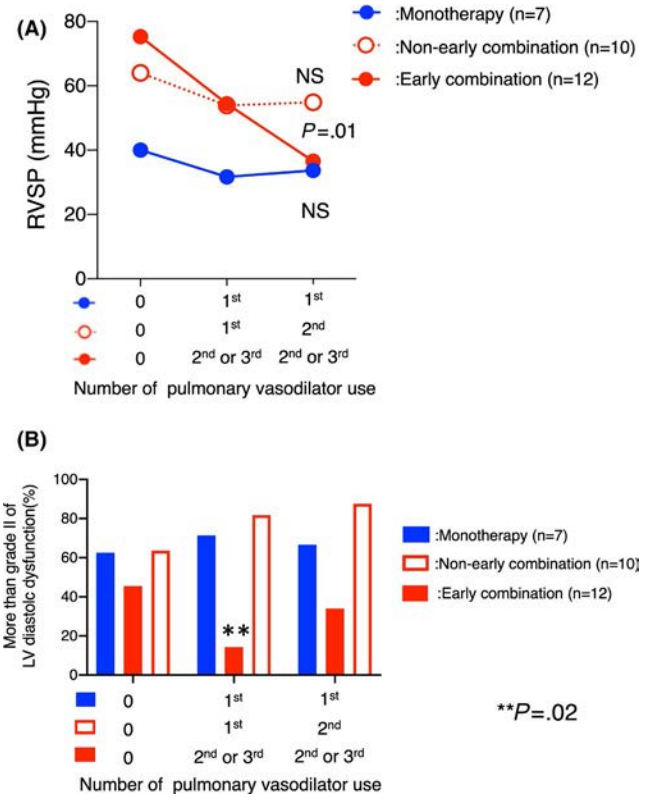

FIGURE 1 Serial change of echocardiography findings. Serial changes in right ventricular systolic pressure (RVSP) (A) and left ventricular diastolic dysfunction (B) were compared among patients receiving monotherapy, early combination therapy, and non-early combination therapy. LV, left ventricular; RVSP, right ventricular systolic pressure

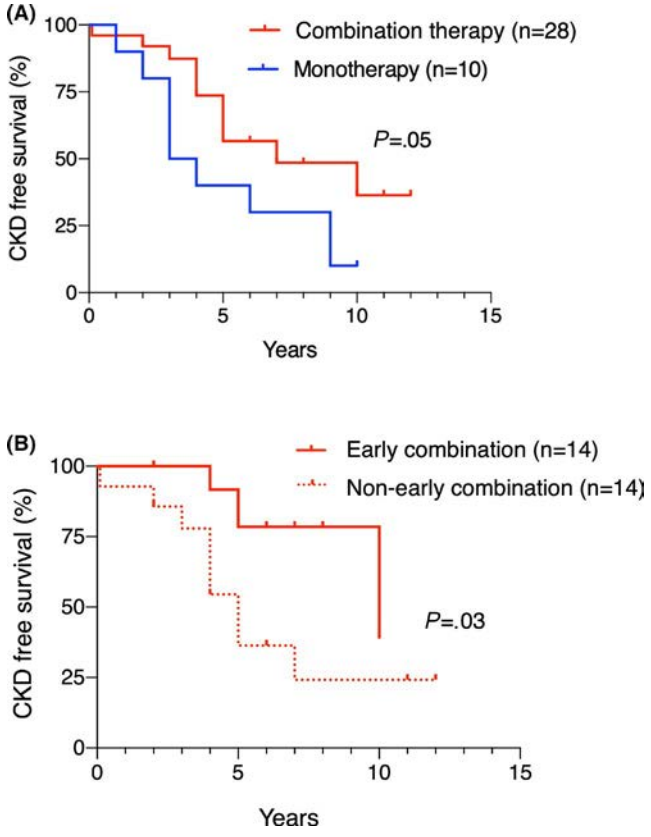

FIGURE 2 Chronic kidney disease (CKD)-free survival after the diagnosis of pulmonary hypertension is shown. CKD progression was observed in 9 patients (90.0%) in monotherapy and in 12 (42.8%) in combination therapy (A). In combination therapy, 3 (21.4%) patients in early combination therapy and 9 (64.3%) in non-early combination therapy had CKD progression (B)

therapy than in those who did not (20.0% vs 57.1%, $P = .03$; 12.5% vs 20.0%, $P = .62$; and 38.1% vs 83.3%, $P = .04$, respectively) (Figure 3).

4 | DISCUSSION

Our study revealed that CKD progression was frequent in patients with CTD-PH, but early improvement in PH with early combination therapy could decrease CKD progression. These findings support the simultaneous use of pulmonary vasodilators recommended for patients with WHO functional class more than II in the latest guidelines of PH for survival improvement, from the viewpoint of CKD management.

Our study demonstrated that 55.2% of CTD-PH patients experienced CKD progression during a median follow-up of 7.0 years, higher than 36% in non-CTD patients with PH.[13]

This can be ascribed to the predisposition of LV diastolic dysfunction in patients with CTD, causing low renal flow via low cardiac output. Even though a previous study investigating 299 patients with PH without CTD reported that grade II or III LV diastolic dysfunction was observed in only 13.7%,[25] more than half of our patients (56.7%) showed grade II or III LV diastolic dysfunction at PH

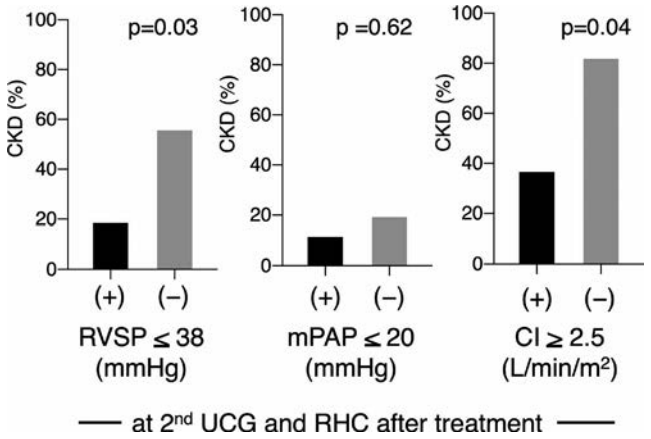

FIGURE 3 Association between PH hemodynamics and CKD progression. The association between PH hemodynamics and CKD progression was compared. The percentage of patients who achieved either less than 38 mm Hg of RVSP, 20 mm Hg of mPAP, or more than 2.5 L/min/m^2 of CI after treatment was compared between CKD progression (+) and CKD progression (-). CI, cardiac index; CKD, chronic kidney disease; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure

diagnosis. The decreased LV diastolic function in CTD is probably due to the underlying cardiac involvement of CTDs.[26-32] Recent studies have shown that a large part of the increase in pulmonary arterial pressure in patients with CTD-PH is attributed to impairment of the left ventricle.[33,34] Although we did not investigate the increase in post-capillary pressures on RHC at diagnosis, further analysis using exercise echocardiography or with the fluid challenge may reveal the underlying contribution of LV impairment in this study.

Our study revealed that CKD progression was associated with pulmonary vasodilators use and pulmonary hemodynamic change regardless of renoprotective drug use or underlying lupus nephritis. The treatment of PH has dramatically evolved over the last few years and has improved the survival of patients with PH. These treatments mainly target distinct vascular mediators involved in the pathogenesis of pulmonary arterial hypertension (PAH); endothelin, nitric oxide, and prostacyclin pathways.[35,36] The latest guidelines have recommended the initiation of combination therapy for patients with WHO functional classes II, III, and IV,[24] as early introduction of combination therapy contributes to reverse remodeling more efficiently than non-early introduction.[37] Several studies have reported the efficacy of up-front combination therapy to target 2 pathways simultaneously, thereby improving the clinical outcome of PH: death, hospitalization, and symptoms.[38,39] Furthermore, our study showed that early stabilization of PH hemodynamics could lower the incidence of CKD progression presumably through the improvement of cardiac output and renal perfusion. Another mechanism for the prominent effect on CKD progression of pulmonary vasodilator combination is their direct renoprotective effect. Endothelin receptor antagonists have been demonstrated to ameliorate or even reverse renal injury and fibrosis in experimental models of CKD.[40] Indeed, atrasentan, an endothelin receptor antagonist, showed a significant reduction in renal events in patients with type 2 diabetes in a phase 3 trial.[41] In addition, phosphodiesterase type 5 inhibitors have been shown to exert renoprotective action.[42] They have improved renal function and histopathological alterations in acute kidney injury through various mechanisms. The renoprotective effect of these agents may exert additional effects in preventing CKD progression in our study.

Our study has several limitations. First, this study was conducted retrospectively in a single center, with a short observation period and a small sample size. This could be generating a selection bias. Second, the interval of second or third RHC and UCG varied among patients, although these intervals were not significantly different among the treatment groups. Third, treatment strategies such as pulmonary vasodilators, glucocorticoids, and immunosuppressants, were determined at the discretion of the attending physicians, which may have influenced the results. Finally, many factors are potentially associated with CKD in patients with CTD, and other factors not related to pulmonary hemodynamics may influence the CKD progression in our study. Pulmonary hemodynamic improvement by using pulmonary vasodilators might be one of the important therapeutic interventions for decreasing CKD progression. Confirmation of our findings will require a multi-center prospective study.

In conclusion, early combination therapy can decrease the incidence of CKD progression in patients with CTD-PH. Careful monitoring of kidney function and PH-related symptoms is necessary to prevent both PH deterioration and CKD progression.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Chung L, Liu J, Parsons L, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest*. 2010;138:1383-1394.
2. Alharbi S, Ahmad Z, Bookman AA, et al. Epidemiology and survival of systemic sclerosis-systemic lupus erythematosus overlap syndrome. *J Rheumatol*. 2018;45:1406-1410.
3. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med*. 2009;179:151-157.
4. Hao YJ, Jiang X, Zhou W, et al. Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. *Eur Respir J*. 2014;44:963-972.
5. Qian J, Li M, Zhang X, et al. Long-term prognosis of patients with systemic lupus erythematosus-associated pulmonary arterial hypertension: CSTAR-PAH cohort study. *Eur Respir J*. 2019;53:1800081.
6. Sumida K, Molnar MZ, Potukuchi PK, et al. Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease. *Kidney Int*. 2018;93:1207-1216.
7. Hickson LJ, Crowson CS, Gabriel SE, McCarthy JT, Matteson EL. Development of reduced kidney function in rheumatoid arthritis. *Am J Kidney Dis*. 2014;63:206-213.
8. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038-2047.
9. Chrabaszcz M, Małyszko J, Sikora M, et al. Renal involvement in systemic sclerosis: An update. *Kidney Blood Press Res*. 2020;45:532-548.
10. Pokroy-Shapira E, Gelernter I, Molad Y. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. *Clin Rheumatol*. 2014;33:649-657.
11. Steen VD, Syzd A, Johnson JP, Greenberg A, Medsger TA Jr. Kidney disease other than renal crisis in patients with diffuse scleroderma. *J Rheumatol*. 2005;32:649-655.
12. Navaneethan SD, Roy J, Tao K, et al. Chronic renal insufficiency cohort investigators. Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. *J Am Soc Nephrol*. 2016;27:877-886.
13. Navaneethan SD, Wehbe E, Heresi GA, et al. Presence and outcomes of kidney disease in patients with pulmonary hypertension. *Clin J Am Soc Nephrol*. 2014;9:855-863.
14. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122:164-172.
15. Shah SJ. Pulmonary hypertension. *JAMA*. 2012;308:1366-1374.

16. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.
17. Tani C, Carli L, Vagnani S, et al. The diagnosis and classification of mixed connective tissue disease. *J Autoimmun*. 2014;48–49:46-49.
18. Masi AT, Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum*. 1980;23:581-590.
19. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913.
20. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53:1801914.
21. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107-133.
22. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int*. 2014;85:49-61.
23. Lafitte S, Pillois X, Reant P, et al. Estimation of pulmonary pressures and diagnosis of pulmonary hypertension by Doppler echocardiography: a retrospective comparison of routine echocardiography and invasive hemodynamics. *J Am Soc Echocardiogr*. 2013;26:457-463.
24. Galiè N, Humbert M, Vachiery JL, et al. ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.
25. Kirillova V, Garganeeva A, Sokolova L. Diastolic function of the left and right ventricles of the heart in outpatients with arterial hypertension. *Echocardiography*. 2020;37:1014-1020.
26. Park M, Hsu CY, Li Y, et al. Chronic Renal Insufficiency Cohort (CRIC) study group. associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*. 2012;23:1725-1734.
27. Iida H, Hanaoka H, Okada Y, et al. A low perfusion-metabolic mismatch in ^{99m} Tl and ^{123} I-BMIPP scintigraphy predicts poor prognosis in systemic sclerosis patients with asymptomatic cardiac involvement. *Int J Rheum Dis*. 2019;22:1008-1015.
28. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum*. 2000;43:2437-2444.
29. Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. *Circulation*. 1976;53:483-490.
30. Desai CS, Lee DC, Shah SJ. Systemic sclerosis and the heart: current diagnosis and management. *Curr Opin Rheumatol*. 2011;23:545-554.
31. Mizuno R, Fujimoto S, Saito Y, Nakamura S. Cardiac Raynaud's phenomenon induced by cold provocation as a predictor of long-term left ventricular dysfunction and remodelling in systemic sclerosis: 7-year follow-up study. *Eur J Heart Fail*. 2010;12:268-275.
32. Agoston G, Gargani L, Miglioranza MH, et al. A left atrial dysfunction detected by speckle tracking in patients with systemic sclerosis. *Cardiovasc Ultrasound*. 2014;12:30.
33. Sugiura A, Funabashi N, Ozawa K, Kobayashi Y. Left ventricular diastolic dysfunction and increased left ventricular mass index related to pulmonary hypertension in patients with systemic autoimmune disease without pericardial effusion. *Int J Cardiol*. 2016;220:268-272.
34. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J*. 2013;42:1083-1091.
35. Parikh V, Bhardwaj A, Nair A. Pharmacotherapy for pulmonary arterial hypertension. *J Thorac Dis*. 2019;11:S1767-1781.
36. Haarman MG, Lévy M, Roofthooft MTR, et al. Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension. *Eur Respir J*. 2020;57(1):2001120.
37. Akagi S, Matsubara H, Nakamura K, Ito H. Modern treatment to reduce pulmonary arterial pressure in pulmonary arterial hypertension. *J Cardiol*. 2018;72:466-472.
38. Lajoie AC, Bonnet S, Provencher S. Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges. *Pulm Circ*. 2017;7:312-325.
39. Kuwana M, Blair C, Takahashi T, Langley J, Coghlan JG. Initial combination therapy of ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) in the modified intention-to-treat population of the AMBITION study: post hoc analysis. *Ann Rheum Dis*. 2020;79:626-634.
40. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86:896-904.
41. Heerspink HJL, Parving HH, Andress DL, et al. SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393:1937-1947.
42. Georgiadis G, Zisis IE, Docea AO, et al. Current concepts on the reno-protective effects of phosphodiesterase 5 inhibitors in acute kidney injury: Systematic search and review. *J Clin Med*. 2020;9:1284.

SUPPORTING INFORMATION

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

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APLAR GRAND ROUND CASE

Multiple brain abscesses due to *Listeria monocytogenes* infection in a patient with systemic lupus erythematosus: A case report and literature review

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Abstract

Aim: To review the clinical features of systemic lupus erythematosus (SLE) complicated by central nervous system (CNS) infection due to *Listeria monocytogenes*.

Method: A patient with SLE receiving high-dose glucocorticoids combined with cyclophosphamide who developed multiple brain abscesses due to *Listeria* infection is described. The case is compared with known cases in a literature review.

Results: A review of the literature showed that CNS infections are rare bacterial complications of SLE, but they can be a significant cause of mortality, especially those due to *L. monocytogenes*. The most significant risk factor for listerial meningitis is a prior history of receiving immunosuppressive therapy. At-risk patients should avoid unpasteurized milk and soft cheeses along with deli-style, ready-to-eat prepared meats, particularly poultry products. The case we report is the fifth SLE patient with multiple brain abscesses due to *L. monocytogenes*, and the first to be discharged with no sequelae. Timely and accurate identification and treatment of CNS infections and neuropsychiatric lupus are very important for favorable disease prognosis.

Conclusion: Repeated blood culture is helpful for early diagnosis, and empirical anti-infective treatment that covers *L. monocytogenes* is recommended for SLE patients with risk factors when CNS infection occurs. A comprehensive assessment might be helpful to distinguish CNS infections from neuropsychiatric SLE. For severe infection, the dosage of steroids does not need to be reduced immediately but can be gradually adjusted based on the results of a comprehensive evaluation of the disease.

KEYWORDS

brain abscesses, central nervous system infections, *Listeria monocytogenes*, multiple, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a condition in which the immune system attacks healthy cells and tissues throughout the body, and infection is one of the most common causes of death in patients with SLE.[1] SLE patients are highly susceptible to infections as a result of disease-related immunological dysfunction itself or immunosuppressive treatments. A systematic review and meta-analysis showed that the pooled relative risks (RRs) for overall severe infection are significantly higher in patients with SLE than in the general

population/healthy controls (RR 2.96; 95% CI 1.28-6.83).[2] A retrospective analysis found that infection is the only factor affecting death after 10 years of disease evolution.[3] Infections are responsible for 30%~50% of morbidity and mortality in patients with SLE.[4,5] Central nervous system (CNS) infections are rare bacterial complications of SLE, but can be a significant cause of mortality.[6] Here, we report a case of *Listeria monocytogenes*-associated multiple brain abscesses in a patient with SLE.

2 | CASE REPORT

A 53-year-old female patient was diagnosed with SLE 2 months prior to admission on the basis of 1997 revised American College of Rheumatology criteria. The patient presented with polyarthritis, leukopenia (2.59×10^9/L), positivity for antinuclear antibodies (ANAs), anti-double-stranded DNA antibodies, hypocomplementemia (serum C3 level 23.6 mg/dL; serum C4 level 2.07 mg/dL) and proteinuria (915 g/24 h) at onset, resulting in a SLE Disease Activity Score (SLEDAI) of 11. She received 400 mg of cyclophosphamide (CYC) per week and 50 mg of prednisone daily. As the patient's condition improved, prednisone decreased at a rate of 5 mg per week from the 5th week. At the 9th week, the dosage of prednisone was gradually tapered to 30 mg/d combined with 400 mg of CYC per week (cumulative dose: 3.2 g).

The patient returned to our hospital on the date of admission with left upper limb weakness for 3 days and fever, headache (manifested as persistent dull pain), and lisp for 1 day. She did not experience nausea, diarrhea or vomiting. A physical examination showed that her body temperature was 39.1°C. She was fully conscious. Her pupils were irregular, with a left to right ratio of 5:2. The light reflex was slightly weakened in the left pupil and positive in the right pupil. There was no neck rigidity. Her muscle strength was grade III for the left upper limb and grade IV for the left lower limb. No positive meningeal irritation signs or pathological signs were found. A lumbar puncture was performed immediately after admission; the pressure was 130 mm H_2O, and routine and biochemical tests of the cerebrospinal fluid (CSF) appeared normal except for a slight increase in the CSF protein level (Table 1). Meanwhile, blood cultures were performed twice. CSF culture did not yield any bacterial colonies. The initial contrast-enhanced magnetic resonance imaging (MRI) brain scan showed multiple round lesions on the right frontal temporal lobe, bilateral basal ganglia, splenium of the corpus callosum, diencephalon, and mesencephalon, suggesting multiple brain abscesses (Figure 1). Initial empirical therapy with 3 g every 8 hours intravenous cefotaxime was administered. Background disease SLE evaluation revealed proteinuria, hypocomplementemia and alopecia, suggesting moderate activity (Table 1). The dosage of methylprednisolone was increased to 80 mg/d, and the use of CYC was discontinued. There was no significant change in the patient's condition. Three days later, *L. monocytogenes* infection was confirmed by 2 blood cultures. Investigation of the patient's history indicated that she had consumed contaminated pork. The patient was presumed to have multiple brain abscesses and bacteriemia due to *L. monocytogenes* infection. The therapy was changed to intravenous ampicillin (3 g every 6 hours) and trimethoprim-sulfamethoxazole (TMP-SMX) (2 g/d). Subsequently, the patient's body temperature decreased to normal, her headache disappeared, her speech recovered on the 7th day after admission, her pupils recovered to 3:3 on the 12th day, the light reflex was restored, and the muscle strength of the upper limbs recovered on the 19th day. Four weeks later, the methylprednisolone dosage was reduced to 40 mg/d.

TABLE 1 Laboratory data on admission

Items	Results	Reference values
Blood		
White blood cells	7.08	4.0-10.0 × 10^9/L
Neutrophils, %	78.3	40%-75%
Hemoglobin, g/L	101	120-160 g/L
Platelets	210	100-300 × 10^9/L
ANA antibody	1:800 homogeneous pattern	Negative
Anti-SS-A	+	Negative
Anti-SS-B	+	Negative
Anti-dsDNA	+	Negative
Quantitative Anti-dsDNA	0.8	<25 IU/mL
Anti-Sm	+	Negative
Complement C3	100	79-152 mg/dL
Complement C4	13.7	16-38 mg/dL
ESR	53	0-20 mm/h
CRP	5.57	0-0.8 mg/dL
Urine		
Protein	++	Negative
White blood cells	-	0-5/HP
Red blood cells	-	0-3/HP
Casts	-	negative
Urine total protein	783	<150 mg/24 h
Cerebrospinal fluid		
Pressure	130	mm H_2O
White blood cells	6	0-8 × 10^6/L
Red blood cells	4	0
Protein	0.61	0.2-0.4 g/L
Glucose	4.7	2.5-4.5 mmol/L
Chloride	125	119-130 mmol/L
ADA	0.8	<8 U/L
LDH	22	10-25 U/L
LAC	2.92	1-2.8 mmol/L
CRP	2.5	0.42-5.2 mg/L

Abbreviations: ADA, adenosine deaminase; ANA, antinuclear antibodies; Anti-dsDNA; anti-double-stranded DNA; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LAC, lactic acid; LDH, lactate dehydrogenase; SS-A, Sjögren's syndrome antigen A; SS-B, Sjögren's syndrome antigen B.

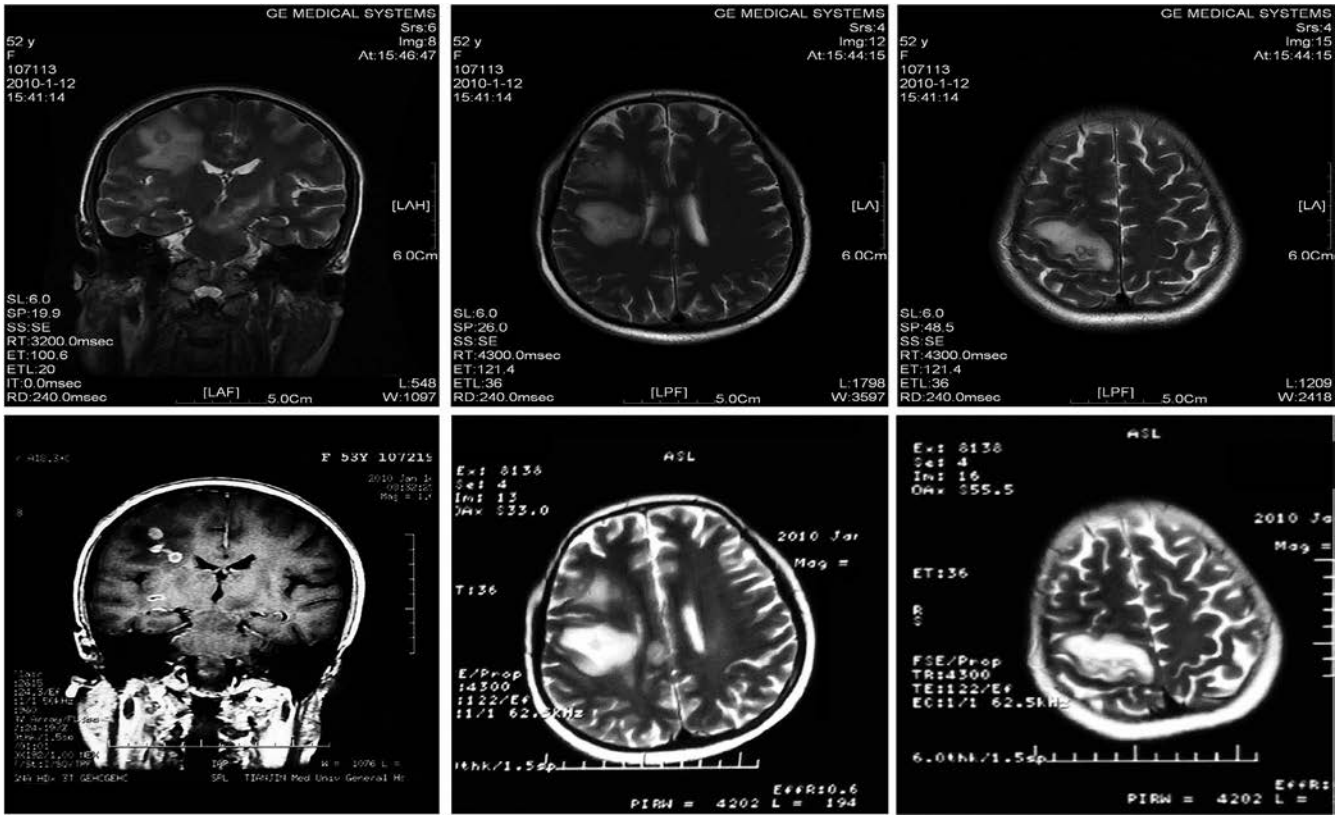

FIGURE 1 Multiple ring-like enhancements appeared in the right frontal lobe and basal ganglia before treatment

In the 5th week, the patient developed an allergic rash over her entire body. As drug-induced rash due to the use of different batches of ampicillin was diagnosed, ampicillin use was discontinued. Monotherapy with TMP-SMX was continued. The rash subsided at 3 weeks after discontinuation of ampicillin (the 8th week after admission). Thus, the original batch of ampicillin was used again after a negative dermal irritation test. However, the rash reoccurred. Ampicillin was withdrawn again, and meropenem (2 g every 8 hours) was administered. The dosage of methylprednisolone was reduced to 32 mg/d, and hydroxychloroquine (0.2 g/d) was administered for SLE starting in the 9th week. Repeated brain imaging studies were performed and suggested gradual improvement of the intracranial lesions (Figure 2). Meropenem and TMP-SMX were terminated at the 12th week. The total duration of antibiotic treatment was 12 weeks, including TMP-SMX for 12 weeks combined with ampicillin for more than 4 weeks and then meropenem for 4 weeks due to amoxicillin-induced delayed anaphylaxis. Then, the patient was discharged with no sequelae. She was in a stable condition with SLE at discharge: proteinuria decreased from 783 mg/24 h to 453 mg/24 h, serum complement rose to normal levels and alopecia improved. The use of methylprednisolone, *Tripterygium wilfordii* (a traditional Chinese medicine usually used to treat arthritis, rash and proteinuria) and hydroxychloroquine were recommended after discharge.

Six months after discharge, MRI revealed involution of the abscesses (Figure 3). Routine and biochemical tests of the CSF were normal. No bacterial colony was detected in the CSF culture. The overall condition of the patient was stable throughout the 10-year follow-up period without any recurrence of the brain abscesses (Figure 4) while undergoing treatment with low-dose methylprednisolone (8 mg/d), *T. wilfordii* and hydroxychloroquine. The patient's underlying SLE remained stable.

3 | LITERATURE REVIEW

We then performed a comprehensive review of the literature regarding SLE and *L. monocytogenes* published in English-language journals.

Listeria monocytogenes is an aerobic, Gram-positive, motile, nonspore-forming bacillus,[7] and *L. monocytogenes* infections have been linked to the consumption of contaminated food products. In patients with impaired cell-mediated immunity, such as SLE patients receiving corticosteroids and immunosuppressants, *L. monocytogenes* is an important pathogen that can cause life-threatening infections.[8-11]

To the best of our knowledge, since Dr Schulze et al[12] reported the first case of a patient with disseminated SLE who died due to *L. monocytogenes* infection in 1953, 52 cases have been reported in the English-language literature (Table 2).[4-7,12-33]

Meningoencephalitis is the most common manifestation in patients with SLE who develop *L. monocytogenes* infections; other

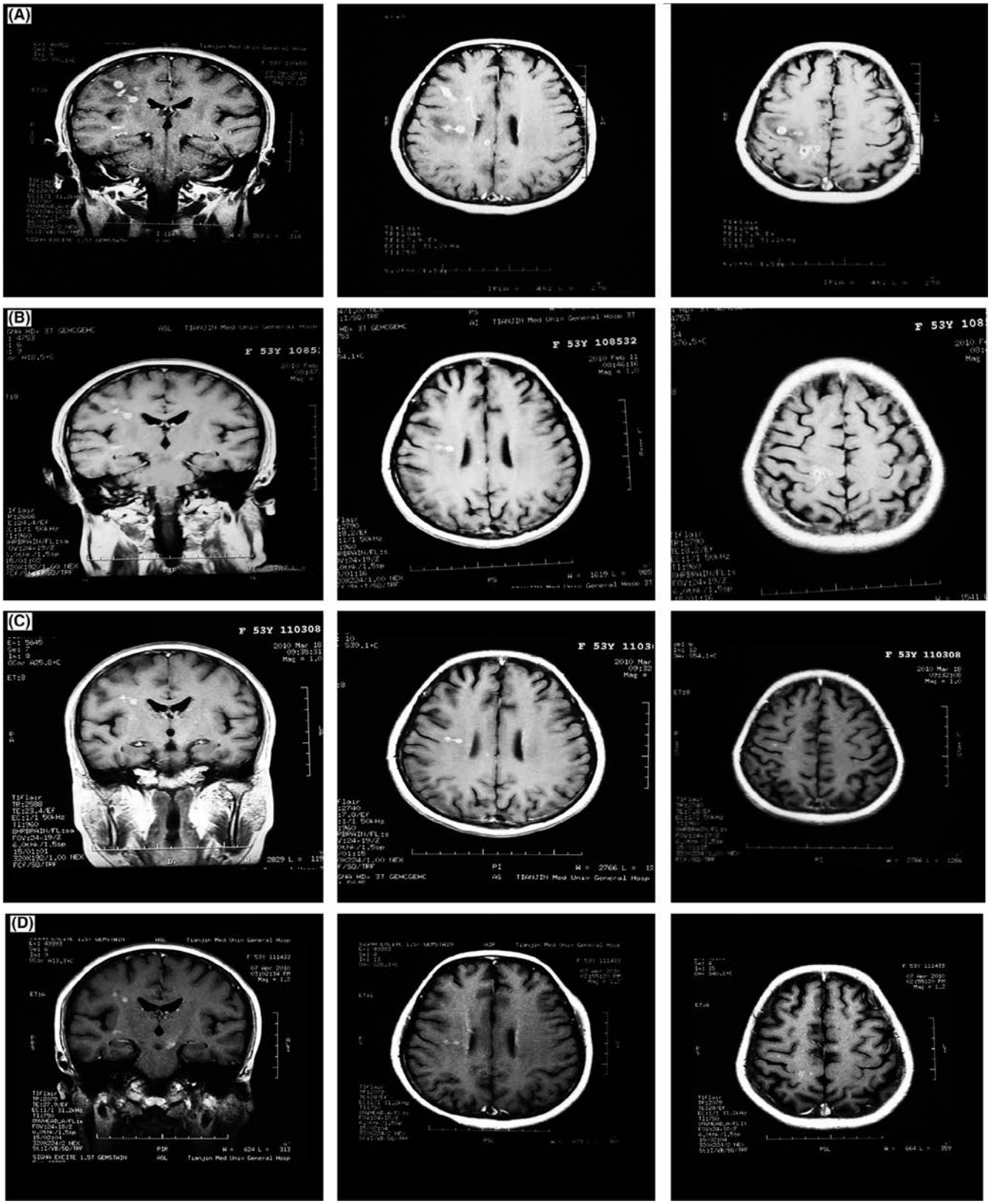

FIGURE 2 Magnetic resonance imaging (MRI) changes during treatment. A, MRI at the first week showed that the number and size of lesions had no significant change, and the ring wall was thicker than before. The swelling of the left cerebral foot was less. B, 4 wk after treatment. C, 8 wk after treatment. D, 12 wk after treatment. MRI at the 4th, 8th and the 12th week showed that the lesions in the right frontal lobe and left cerebral foot disappeared, and the right temporal lobe, basal ganglia, right stool and surrounding edema zone of corpus callosum gradually became smaller than before

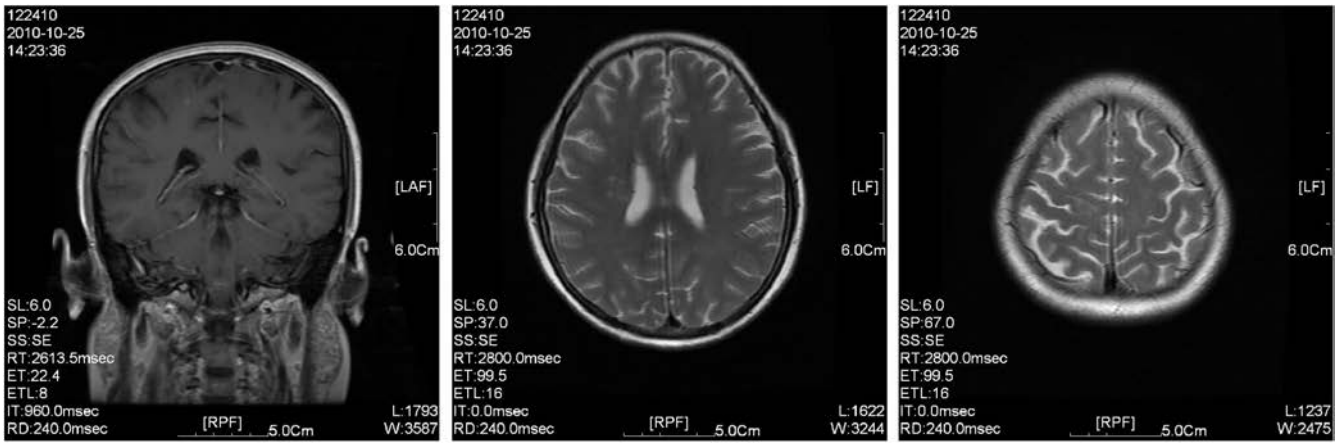

FIGURE 3 Patchy enhancement was shown in the right frontal lobe and basal ganglia. Compared with the previous examination, the magnitude and scope of the lesions were reduced

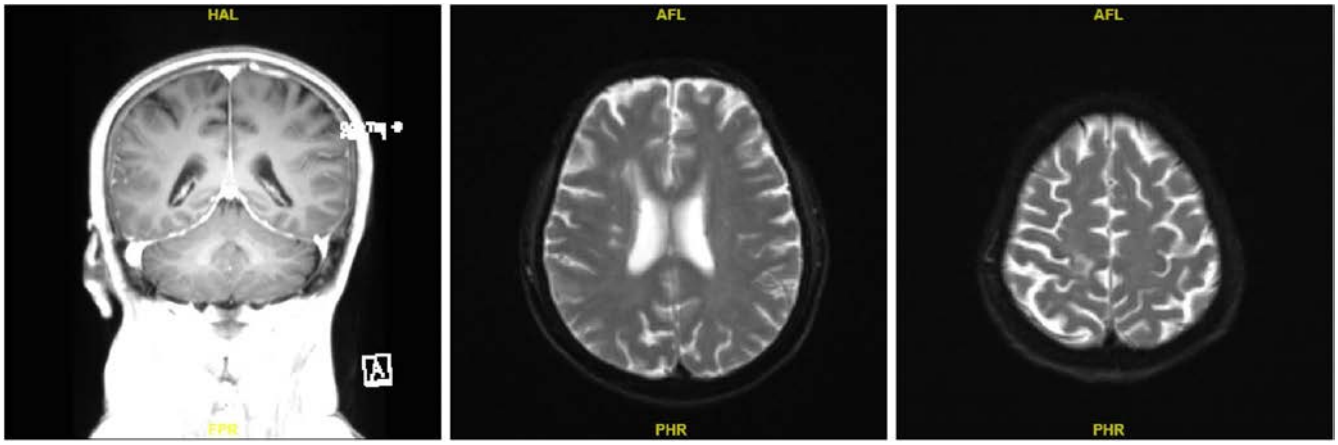

FIGURE 4 No enhancement was observed

manifestations included bacteremia, rhombencephalitis, liver abscesses, spleen abscesses, endocarditis, peritonitis, septic arthritis and brain abscesses. Brain abscesses due to *L monocytogenes* infection are rather rare in patients with SLE and are only present in 1%-10% of cases with neurolisteriosis.[9,34] As few as 6 cases have been reported, with 4 involving multiple brain abscesses (Table 3).[12,17,25,26,29,33]

Among the 52 cases reported in the literature, the treatment scheme of SLE at onset was provided for 32. Twenty-nine patients were receiving high to moderate doses of corticosteroids combined with/or immunosuppressants, including azathioprine, CYC, mofetil mycophenolate, methotrexate and cyclosporine.

Three of the 4 cases of multiple brain abscesses in SLE reported in the literature presented with positive culture results of CSF and/or positive blood culture, except 1 fatal case that was diagnosed by postmortem examination. This phenomenon is related to the pathogenic mechanism of the bacterium. Often the point of entry for *L. monocytogenes* is the gastrointestinal tract, followed by invasion of the mesenteric lymph nodes, entry into blood flow, and causes bacteremia.[7] Carried by blood flow, *L. monocytogenes* infects the CNS, where it adheres to the epithelial cells of the choroid plexus and induces the release of cytokines and chemotactic factors into the CSF, causing cerebral meningitis. In addition, *L. monocytogenes* penetrates capillary endothelial cells of the middle cerebral artery, inducing encephalitis and brain abscess.[35,36]

The associated mortality rate is high, and survivors usually have serious sequelae.[9] Regarding the prognosis of the 4 previously reported patients with multiple brain abscesses, 2 patients died soon after infection with *L. monocytogenes*, 1 patient survived with residual right facial hemiparesis and hypoalgesia on the left side of the body, and 1 patient survived with left hemiparesis and frontal lobe syndrome. The prognosis was also not universally satisfactory in the 2 patients with single brain abscesses: in 1 patient, the fever subsided, and computed tomography (CT) scans showed a decrease in the size of the right parietal lesion. However, the patient died due to concomitant hepatitis. The other patient survived without sequelae.

Clinical results were reported in the literature for 43 of the 52 SLE patients with *L. monocytogenes* infections; 16 patients died of *L. monocytogenes* infections, and 1 patient initially improved but then died of concomitant hepatitis. Twenty-three patients survived

TABLE 2 Characteristics of *Listeria monocytogenes* infection in patients with SLE published in English between 1953 and 2021

No.	Ref.	Age /Gender	Duration of SLE	SLE activity	Treatment for SLE	
					GC	IS
1	Schulze, M. L., et al 1953[12]	19/F	2 mo	Inactive	No	No
2	R. Rosengarten, et al 1959[13]	48/F	5 y	Inactive	Yes (no details)	NA
3	F O Finkelstein, et al 1976[14]	22/M	NA	Inactive	Steroids (high dose)	Yes
4	Perez HD, et al 1979[15]	46/F	2 y	Active	P 10 mg/d	No
5	RE Nieman., et al 1980[16]	31/M	37 d	Active	High-dose prednisone	No
6	Haykal H, et al 1987[17]	34/F	NA	NA	Standard immunosuppressive chemotherapy (no details)	
7	Fan YD, et al 1989[18]	27/F	10 y	Inactive	P 60 mg/d	AZA
8	Allais JM, et al 1989[19]	31/F	3 mo	Active	P 15 mg/d	No
9	V. Harisdangkul, et al 1992[20]	21/F	2 y	Active	P 20-6 mg/d IV MP pulses, 1 g/d for 3 d	No
10		52/F	1 y	Active	NA	No
11		25/F	6 y	Inactive	NA	NA
12	Kraus A, et al 1994[21]	25/F	3 y	Active	P 50 mg/d	NA
13		34/F	NA	Active	P 5omg/d	NA
14		29/F	NA	Active	P 100 mg/d	NA
15		20/F	NA	Inactive	None	NA
16		28/F	NA	Inactive	None	NA
17		60/F	8 y	Inactive	P 7.5 mg/d	NA
18		27/M	NA	Active	P 200 mg/d	NA
19	Jansen TL, et al 1998[22]	22/F	7 mo	NA	P 30 mg/d	MTX
20	Mylonakis E, et al 1998[23]	16/F	NA	NA	Yes (no details)	AZA, MTX
21	JJ Hung, et al 2005[5]	29/F	NA	4	NA	NA
22		24/F	NA	12	NA	NA
23		22/F	NA	10	NA	NA
24		22/M	NA	4	NA	NA
25-27	Yang CD, et al 2007[24]	3 cases of SLE were reported without more details				
28	Cone LA, et al 2008[25]	56/F	NA	NA	P (no details)	NA

Types of infection	Other special circumstances	Antibiotic(s) administered	Period of treatment	Outcome
Meningoencephalitis fulminant septicemia abscesses were present in the liver, spleen, adrenal glands, epicardium, superficial surfaces of the brain and spinal cord in postmortem examination	No	Streptomycin 0.5 g intramuscularly	2 d	Died
Meningitis, septicemia	No	Sulfadiazine chloromycetin	2 d	Died
Bacteriemia	Renal homograft from his father	NA	NA	Survived
Septicemia	No	NA	NA	Survived
Meningitis, bacteriemia	Intermittent IV	Ampi 1 g every 6 h	14 d	Survived
Meningitis, bacteriemia	A living renal allograft from an HLA-identical donor	Intravenous penicillin	4 wk	Fever subsided and CT scans showed a decrease in the size of the right parietal lesion; 1984. Died from hepatitis
Bacteriemia	At the 26th gestation week	Ampi	NA	Died
Peritonitis	PD	NA	NA	Survived
Bacteriemia	At the 16th gestation week	IV clindamycin 150 mg every 6 h	2 wk	Survived
Endocarditis	HD	NA	NA	Died
Peritonitis	CAPD	NA	NA	Survived
Bacteriemia	No	Ampi, amika	NA	Died
Bacteriemia	No	Ampi, amika	NA	Died
Meningitis, bacteriemia	No	Ampi	NA	Survived, died 1 month later of CNS hemorrhage
Meninges	HD	Ampi, amika, ceftr	NA	Died
Meninges	HD	Ampi, amika	NA	Survived
Meninges, bacteriemia	No	Penicillin, ceftr	NA	Survived
Meninges	No	Ampi, amika	NA	Died
Septic arthritis	No	Amoxicillin 1 g q6 h	22 d stopped due to allergic dermatitis	Survived
Meninges	No	Penicillin	14 d	Survived with neurologic residual (diplopia and facial weakness)
Meninges	No	NA	NA	Survived
Meninges	No	NA	NA	Died
Meningitis, bacteriemia	No	NA	NA	Died
Meninges	No	NA	NA	Survived
NA	No	NA	NA	NA
Meningitis, bacteriemia, single brain abscess	No	NA	NA	Survived

(Continues)

TABLE 2 (Continued)

No.	Ref.	Age /Gender	Duration of SLE	SLE activity	Treatment for SLE	
					GC	IS
29	Baizabal-Carvallo JF, et al 2009[26]	38/F	4 mo	NA	NA	NA
30-33		Four other cases of SLE were reported whose CSF culture obtained *Listeria monocytogenes*, without more details				
34	Lee MC, et al 2011[27]	32/F	5 y	Active	MP (no details)	MMF
35	McCaffrey LM, et al 2012[7]	57/M	2 y	Inactive	P 20 mg/d	NA
36	Wang HL, et al 2013[28]	56/F	NA	NA	P 30-40 mg/d	CYC 0.4/wk
37		23/F	NA	NA	P 50-80 mg/d	No
38		33/F	NA	NA	P 60 mg/d 2 courses of MP pulses	No
39		22/F	NA	NA	P 50-60 mg/d 2 courses of MP pulses	CsA/Dapsone/ MMF
40		18/F	NA	NA	No	No
41		53/F	NA	NA	P 30 mg/d	CYC 0.4/wk
42	Tobón GJ, et al 2013[29]	18/F	2 y	Inactive	P 0.5 mg/kg/d	AZA
43		27/F	3 y	Active	Pl (no details)	MMF
44		18/F	2 y	Inactive	P 0.5 mg/kg/d	MMF
45		5/F	3 y	NA	NA	NA
46		29/F	4 y	Inactive	P 10 mg/d	AZA 50 mg/d
47	Perić-Popadić A, et al 2013[6]	33/F	8 mo	Active	Pl 1 mg/kg/d → 30 mg/d	
48	Perini G, et al 2015[30]	16/F	2 y	Active	P 25 mg/d	MMF 2 g/d
49	Chen F, Hao F, et al 2017[31]	A retrospective medical records review was performed in female patients aimed to describe the characteristics of bacteremia in Chinese adults with SLE, and one of the 64 patients was identified as *L. monocytogenes* bacteremia without more details				
50	TY Shi, et al 2018[32]	47/F	5 y	Inactive	P 1 mg/kg/d	CsA 4 mg/kg/d
51	Morimoto, M., et al 2020[33]	41/F	3 y	Inactive	P 30 mg/d	No
52	Pereira MEVDC, et al 2020[34]	29/F	3 mo	Active	Intravenous pulse MP→p 1 mg/kg/d	MMF
53	The current case	53/F	1 mo	Active	40 mg/d	CYC 0.4/wk

Abbreviations: Amika, amikacin; Amin: ampicillin; AZA, azathioprine; CAPD, continuous ambulatory peritoneal dialysis; ceftr, ceftriaxone; CsA, cyclosporine A; CT, computed tomography; CYC, cyclophosphamide; GC, glucocorticoid; HD, hemodialysis; IS, immunosuppressant; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; MTX, methotrexate; NA, not available; P, prednisone; Pa, patient; PD, peritoneal dialysis; Pl, prednisolone; Ref, reference; SLE, systemic lupus erythematosus; TMP-SMX, trimethoprim-sulfamethoxazole.

Types of infection	Other special circumstances	Antibiotic(s) administered	Period of treatment	Outcome
Meningitis, multiple brain abscesses	No	Ampi + gentamicin for 2 wk TMP-SMX for 5 wk	12 wk	Survived with a residual right facial hemiparesis and hypoalgesia on the left side of the body
NA	No	NA	NA	NA
Meningitis, bacteriemia	No	Ampi 2 g every 8 h + gentamicin 100 mg	29 d	Died
Meningoencephalitis, bacteriemia	No	Ampi	6 wk	Survived
Bacteriemia sepsis, pneumonia	No	NA	NA	Died
Bacteriemia sepsis shock	No	NA	NA	Died
Bacteriemia	No	NA	NA	Died
Meningitis, bacteriemia	No	NA	NA	Survived
Meningitis, bacteriemia	No	NA	NA	Survived
Bacteriemia	No	NA	NA	Survived
Meningitis, bacteriemia	No	Ampi	NA	Survived
Meningitis, bacteriemia	No	Ampi	NA	Survived
Meningitis, bacteriemia	No	Ampi	NA	Survived
Bacteria, bacterial endocarditis	No	Ampi	NA	Survived
Bacteria	No	Ampi	NA	Survived
Meningoencephalitis together with encephalomalacia	No	NA	NA	NA
Bacteria, multiple brain abscesses	No	TMP-SMX +Ampi for 2 wk →TMP-SMX +meropenem 7 wk	9 wk	Survived with a left hemiparesis and a frontal syndrome characterized by reduction of verbal fluency and utilization behavior
Bacteria	No	NA		NA
Meningoencephalitis	No	Ampi + oral rifampicin 3wk→ oral TMP-SMX for 5 wk	8 wk	Survived
Bacteria	At the 35th gestation wk	Intravenous ampi (ABPC) 2 g 3 times a d	14 d	Survived
Meningitis, bacteria, multiple brain abscesses	No	Intravenous ampi	60 d	Died
Bacteria, multiple brain abscesses	No	Ampi 3 g every 6 h + TMP-SMX 2 g/d *more than 4 wk→TMP-SMX 2 g/d * 3 wk→meropenem 2 g every 8 h + TMP-SMX 2 g/d * 4 wk	12 wk	Survived

TABLE 3 Characteristics of 6 cases of listerial brain abscesses in patients with SLE published in English between 1953 and 2021 plus our patient

No.	Ref.	Age/ gender	Duration of SLE	SLE activity	Treatment for SLE
1	Schulze ML, et al 1953[12]	19/F	2 mo	Inactive	None
2	Haykal H, et al 1987[17]	34/F	NA	NA	Standard immunosuppressive chemotherapy
3	Cone LA, et al 2008[25]	56/F	NA	NA	Prednisone
4	Baizabal-Carvallo JF, et al 2009[26]	38/F	4 mo	NA	NA
5	Perini G, et al 2015[30]	16/F	2 y	Active	Prednisone 25mg/d + Plaquenil + MMF 2g/d
6	Pereira MEVDC, et al 2020[34]	29/F	3 mo	Active	Prednisone 1 mg/kg/d + MMF
7	Our patient	53/F	1 mo	Active	Prednisone 30 mg/d + CYC 0.4 g/wk

Abbreviations: CT, computed tomography; CSF, cerebrospinal fluid; CYC, cyclophosphamide; GC, glucocorticoid; IS, immunosuppressant; MMF, mycophenolate mofetil; MRI, magnetic resonance image; NA, not available; ND, not done; Ref, reference; SLE, systemic lupus erythematosus; TMP-SMX, trimethoprim-sulfamethoxazole.

without sequelae, and 3 patients survived with residual neurological sequelae.[23,26,29] The mortality rate in this group is as high as 37.2%. The prognosis is even worse in brain abscesses caused by *L. monocytogenes* infection with a mortality rate as high as 50%,[12,17,25,26,29,33] and this mortality is higher than in patients with nonlisterial abscesses.[37]The poor prognosis of SLE patients with *L. monocytogenes* infections suggests that more attention should be given to this topic in clinical practice.

4 | DISCUSSION

SLE is an autoimmune disease of unknown etiology involving a loss of immune tolerance of endogenous nuclear material, which leads to systemic autoimmunity that can damage various tissues and organs.[38] The incidence of CNS infections in patients with SLE is 0.54%~2.26%, and *L. monocytogenes* is among the top 3 pathogens causing CNS infections in SLE patients.[5,24]

In the present case, the patient had consumed pork that had been stored in a refrigerator for 2 weeks prior to the onset of symptoms, and this was considered to be the cause of disease. At-risk patients should avoid unpasteurized milk and soft cheeses along with deli-style, ready-to-eat prepared meats, particularly poultry products.[39] Leftover foods or ready-to-eat foods should be cooked until steaming hot.[39]

Based on general experience with listerial meningitis and the few cases of listerial abscesses reported, effective treatment relies on achieving an early diagnosis.[40] An early diagnosis depends on culture results, not only from CSF cultures but also from blood and tissue cultures.[9] The present patient had no meningeal irritation sign with apparent normal CSF cytology, chemistry and culture results except for a slight increase in the CSF protein level. Similar to Patient No. 5 in Table 3, it indicated that the patient had no meningitis. These findings are related to the pathogenic mechanism of the bacterium: *L. monocytogenes* can cause meningitis, encephalitis and/or brain abscess through blood flow, which also confirmed the importance of repeated blood culture for the diagnosis of *L. monocytogenes*

CT/MRI	Blood/CSF culture	Antibiotic treatment/duration	Outcomes
ND	+/+	Streptomycin 0.5 g intramuscularly/2 d	Died
CT showed an ill-defined superficial area of low attenuation in the left parietal lobe associated with faint curvilinear gyral enhancement	±	IV penicillin/4 wk	Fever subsided, and CT scans showed a decrease in the size of the right parietal lesion; however, the patient died due to hepatitis
MRI: frontal and occipital abscesses	+/+	NA/NA	Survived
MRI: multiple brain abscesses	NA/+	Ampicillin/12 wk combined with gentamicin for 2 wk and TMP-SMX for 5 wk	Survived with residual right facial hemiparesis and hypoalgesia on the left side of the body
MRI showed ring-enhancing lesions, some of which were hemorrhagic and interpreted as micro-abscesses appearing in the right frontal–parietal hemisphere, cerebellum and brainstem	∓	Sulfamethoxazole/trimethoprim (400/80 mg every 6 h). ampicillin/sulbactam (2/1 every 6 h) for 2 wk, then ampicillin/sulbactam was changed to meropenem (2 g every 8 h)/9 wk	Survived with left hemiparesis and frontal syndrome characterized by a reduction in verbal fluency and utilization behavior
MRI was performed with the T2 heavy echo turbo-spin technique. Expansive formation that was 3.0 × 3.0 × 3.5 cm in size was observed in the left frontal lobe, affecting mainly the upper and middle frontal gyres, with irregular contours, bordered by foci of hemosiderin deposits with an intense restriction on the inside diffusion. The findings were compatible with an abscess	+/+	Intravenous ampicillin/2 mo	Died
MRI showed multiple round lesions on the right frontal temporal lobe, bilateral basal ganglia, splenium of the corpus callosum, diencephalon, and mesencephalon, suggesting multiple brain abscesses	±	Ampicillin combined with TMP-SMX for 5 wk, then TMP-SMX monotherapy for 3 wk, and then meropenem combined with TMP-SMX for 4 wk	Survived with no sequelae

infection. To improve prognosis, early diagnosis is crucial, followed by timely treatment.[41] Early empirical therapy is essential for favorable outcomes of *Listeria* infection.[42] A retrospective case-control study indicated that delaying appropriate antibiotic therapy for more than 6 hours increased the risk of mortality by 2.78-fold.[43] Ampicillin is generally the preferred agent in the treatment of *L. monocytogenes* infections.[39] TMP-SMX is recommended for those allergic to penicillin.[37,39] The combination of ampicillin and TMP-SMX has previously been described as an effective treatment for CNS listeriosis.[39,44] In 1 retrospective series, therapy with TMP-SMX plus ampicillin was correlated with a lower failure rate and fewer neurologic sequelae than ampicillin combined with an aminoglycoside.[39] Imipenem and meropenem have also been used successfully to treat cases of listeriosis.[39] Although cephalosporins are often chosen as the first choice for the treatment of intracranial infections, they have limited activity against listeriae.[39] Consistent with these literature reports, our patient was successfully treated using a combination antibacterial therapy comprising ampicillin and TMP-SMX. A multicenter case-control study showed that the most significant risk factor for listerial meningitis was a prior history of receiving immunosuppressive therapy (odds ratio 8.12).[43] Accordingly, when treating SLE patients with high-risk factors with complicated meningitis or parenchymal infection, we recommend ampicillin as the preferred empirical treatment agent to cover *L. monocytogenes*.

No controlled trials have been conducted to establish a drug of choice or optimal duration of therapy for CNS listeriosis.[39] In cases of listerial brain abscess, surgical intervention may not be necessary.[39] An abscess size of more than 2.5 cm in diameter has been recommended as an indication for neurosurgical intervention,[45,46] and prolonged (6-8 weeks) intravenous antimicrobial therapy is based on culture results obtained at the time of the initial aspiration.[47] Patients with listerial brain abscesses should be treated for no less than 6 weeks and followed with repeated brain imaging studies.[39,45] The patient's clinical manifestation and repeated brain MRI imaging demonstrated that our patient responded well to intravenous ampicillin and oral TMP-SMX combined treatment; however, ampicillin treatment was terminated due to allergic reaction. After another attempt at ampicillin treatment

failed, we chose meropenem intravenous anti-infective therapy for another 4 weeks. At the same time, oral TMP-SMX treatment was continued. The total course of anti-infection therapy was 12 weeks, including 8 weeks of intravenous anti-infective therapy. The case we report here is the 5th SLE patient with multiple brain abscesses due to *L. monocytogenes*, and the 1st to be discharged with no sequelae after a long duration of antibiotic treatment. The patient remained well over the course of a 10-year follow-up period.

A challenge for the treatment of SLE with *L. monocytogenes* infection is that the symptoms of CNS infection may be similar to those of neuropsychiatric SLE (NPSLE), which increases the difficulty of diagnosis. CSF and imaging examinations cannot fully distinguish CNS infections from NPSLE. An evaluation of systemic SLE disease activity may be helpful. However, in the case series we reviewed, the proportions of patients with active and inactive SLE who developed *L. monocytogenes* infections were similar. Final diagnosis typically requires a comprehensive assessment based on the results of laboratory and imaging examinations.

Another challenge for the treatment of SLE with *L. monocytogenes* infection is that serious infections can trigger the development or exacerbation of SLE.[6] During a severe infection, basic treatment is very important to achieve a positive outcome. We adjusted the treatment dose based on the background of SLE in our patient while considering the severe infection by stopping treatment with CYC and increasing the dosage of methylprednisolone to 80 mg daily. Then, as her condition gradually improved, steroid treatment was tapered until the initial dose was resumed. A good outcome was obtained. Therefore, we suggest that in the case of a severe infection, the dose of steroids used to treat SLE does not need to be immediately reduced; instead, a gradual adjustment of the treatment after a full evaluation of the disease is appropriate.

In conclusion, to treat *L. monocytogenes* infections in patients with SLE, repeated blood culture is helpful for early diagnosis, and empirical anti-infective therapy that covers *L. monocytogenes* is recommended for SLE patients with *L. monocytogenes* infection risk factors. CSF and imaging examinations cannot fully distinguish CNS infections from NPSLE, and a thorough assessment might be helpful. For severe infection, the dosage of steroids does not need to be reduced immediately but can be gradually adjusted based on the results of a comprehensive evaluation of the disease.

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CONFLICT OF INTEREST

We declare no competing interests.

AUTHOR CONTRIBUTIONS

ZN collected the materials, provided important intellectual content, reviewed the literature and drafted the manuscript; SWW and DXY reviewed the literature; ZL contributed to interpreting the clinical materials; CM edited the language in the manuscript; WW designed the report and offered valuable suggestions for improving the manuscript; ZN wrote the paper.

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REFERENCES

1. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172:ITC81–ITC96.
2. Pego-Reigosa JM, Nicholson L, Pooley N, et al. The risk of infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis. *Rheumatology (Oxford)*. 2021;60:60-72.
3. Noel V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. *Ann Rheum Dis*. 2001;60:1141-1144.
4. Tobon GJ, Serna MJ, Canas CA. Listeria monocytogenes infection in patients with systemic lupus erythematosus. *Clin Rheumatol*. 2013;32(Suppl 1):S25-S27.
5. Hung JJ, Ou LS, Lee WI, Huang JL. Central nervous system infections in patients with systemic lupus erythematosus. *J Rheumatol*. 2005;32:40-43.
6. Peric-Popadic A, Bogic M, Tomic-Spiric V, et al. Acute meningoencephalitis in a patient with systemic lupus erythematosus. *Vojnosanit Pregl*. 2013;70:688-692.
7. McCaffrey LM, Petelin A, Cunha BA. Systemic lupus erythematosus (SLE) cerebritis versus Listeria monocytogenes meningoencephalitis in a patient with systemic lupus erythematosus on chronic corticosteroid therapy: the diagnostic importance of cerebrospinal fluid (CSF) of lactic acid levels. *Heart Lung*. 2012;41:394-397.
8. Al-Khatti AA, Al-Tawfiq JA. Listeria monocytogenes brain abscess in a patient with multiple myeloma. *J Infect Dev Ctries*. 2010;4:849-851.
9. Lorber B. Listeriosis. *Clin Infect Dis*. 1997;24:1-9. quiz 10–11.
10. Armstrong D, Wong B. Central nervous system infections in immunocompromised hosts. *Annu Rev Med*. 1982;33:293-308.
11. Buchner LH, Schneierson S. Clinical and laboratory aspects of Listeria monocytogenes infections. With a report of ten cases. *Am J Med*. 1968;45:904-921.
12. Schulze ML, Wahle GH Jr, White JB. Meningitis due to Listeria monocytogenes in a case of disseminated lupus erythematosus. *Am J Clin Pathol*. 1953;23:1028-1030.
13. Rosengarten R, Bourn JM. Listeria septicemia and meningitis in a case of lupus erythematosus. *Neurology*. 1959;9:704-706.
14. Finkelstein FO, Bastl C, Schiff M, Siegel NJ. Listeria sepsis immediately preceding renal transplant rejection. *JAMA*. 1976;235:844-845.
15. Perez HD, Andron RI, Goldstein IM. Infection in patients with systemic lupus erythematosus. Association with a serum inhibitor of complement-derived chemotactic activity. *Arthritis Rheum*. 1979;22:1326-1333.
16. Nieman RE, Lorber B. Listeriosis in adults: a changing pattern. Report of eight cases and review of the literature, 1968-1978. *Rev Infect Dis*. 1980;2:207-227.
17. Haykal H, Zamani A, Wang AM, Barsotti J. CT features of early Listeria monocytogenes cerebritis. *AJNR Am J Neuroradiol*. 1987;8:279-282.

18. Fan YD, Pastorek JG 2nd, Janney FA, Sanders CV. Listeriosis as an obstetric complication in an immunocompromised patient. *South Med J*. 1989;82:1044-1045.
19. Allais JM, Cavalieri SJ, Bierman MH, Clark RB. Listeria monocytogenes peritonitis in a patient on continuous ambulatory peritoneal dialysis. *Nebr Med J*. 1989;74:303-305.
20. Harisdangkul V, Songcharoen S, Lin AC. Listerial infections in patients with systemic lupus erythematosus. *South Med J*. 1992;85:957-960.
21. Kraus A, Cabral AR, Sifuentes-Osornio J, Alarcon-Segovia D. Listeriosis in patients with connective tissue diseases. *J Rheumatol*. 1994;21:635-638.
22. Jansen TL, van Heereveld HA, Laan RF, Barrera P, van de Putte LB. Septic arthritis with Listeria monocytogenes during low-dose methotrexate. *J Intern Med*. 1998;244:87-90.
23. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine (Baltimore)*. 1998;77:313-336.
24. Yang CD, Wang XD, Ye S, et al. Clinical features, prognostic and risk factors of central nervous system infections in patients with systemic lupus erythematosus. *Clin Rheumatol*. 2007;26:895-901.
25. Cone LA, Somero MS, Qureshi FJ, et al. Unusual infections due to Listeria monocytogenes in the Southern California Desert. *Int J Infect Dis*. 2008;12:578-581.
26. Baizabal-Carvallo JF, Delgadillo-Marquez G, Estanol B, Garcia-Ramos G. Clinical characteristics and outcomes of the meningitides in systemic lupus erythematosus. *Eur Neurol*. 2009;61:143-148.
27. Lee MC, Wu YK, Chen CH, Wu TW, Lee CH. Listeria monocytogenes meningitis in a young woman with systemic lupus erythematosus. *Rheumatol Int*. 2011;31:555-557.
28. Wang HL, Ghanem KG, Wang P, Yang S, Li TS. Listeriosis at a tertiary care hospital in Beijing, China: high prevalence of nonclustered healthcare-associated cases among adult patients. *Clin Infect Dis*. 2013;56:666-676.
29. Perini G, Pravettoni R, Farina E, Grande G, Contri P, Mariani C. Listeria brain abscesses during administration of mycophenolate mofetil for systemic lupus erythematosus: a case report. *Neurol Sci*. 2015;36:1019-1020.
30. Chen F, Hao F, Chen Q, et al. Bacteremia in female Chinese patients with systemic lupus erythematosus: a case-control study. *J Infect Dev Ctries*. 2017;11:393-398.
31. Shi TY, Zhang YF, Shi XH, et al. A rare case of meningoencephalitis by Listeria monocytogenes in systemic lupus erythematosus: case report and review. *Clin Rheumatol*. 2018;37:271-275.
32. Morimoto M, Fujikawa K, Ide S, et al. Systemic lupus erythematosus complicated with listeria monocytogenes infection in a pregnant woman. *Intern Med*. 2020;60(10):1627-1630. 10.2169/internalmedicine.5079-20
33. Pereira M, Gonzalez DE, Roberto FB, Foresto RD, Kirsztajn GM, Durao Junior MS. Listeria monocytogenes meningoencephalitis in a patient with systemic lupus erythematosus. *J Bras Nefrol*. 2020;42:375-379.
34. Simonsen AL, Shekhrajka N, Hertz FB, Helweg-Larsen J, Bengard Andersen A, Lebech AM. Listeria monocytogenes brain abscesses in a patient with disseminated non-small cellular lung cancer: MRI findings. *Diagnostics (Basel)*. 2021;11:1115.
35. Soares-Fernandes JP, Beleza P, Cerqueira JJ, et al. Simultaneous supratentorial and brainstem abscesses due to *Listeria monocytogenes*. *J Neuroradiol*. 2008;35:173-176.
36. Cone LA, Leung MM, Byrd RG, Annunziata GM, Lam RY, Herman BK. Multiple cerebral abscesses because of *Listeria monocytogenes*: three case reports and a literature review of supratentorial listerial brain abscess(es). *Surg Neurol*. 2003;59:320-328.
37. Frade HC, Pingili C, Nattanamai P. Multiple listeria abscesses in an immunocompetent patient. *Cureus*. 2020;12:e6642.
38. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. *Nat Rev Dis Primers*. 2020;6:7.
39. Clauss HE, Lorber B. Central nervous system infection with Listeria monocytogenes. *Curr Infect Dis Rep*. 2008;10:300-306.
40. Lechtenberg R, Sierra MF, Pringle GF, Shucart WA, Butt KM. Listeria monocytogenes: brain abscess or meningoencephalitis? *Neurology*. 1979;29:86-90.
41. Lan ZW, Xiao MJ, Guan YL, Zhan YJ, Tang XQ. Detection of Listeria monocytogenes in a patient with meningoencephalitis using next-generation sequencing: a case report. *BMC Infect Dis*. 2020;20:721.
42. Smiatacz T, Kowalik MM, Hlebowicz M. Prolonged dysphagia due to Listeria-rhombencephalitis with brainstem abscess and acute polyradiculoneuritis. *J Infect*. 2006;52:e165-167.
43. Lim S, Chung DR, Kim YS, et al. Predictive risk factors for Listeria monocytogenes meningitis compared to pneumococcal meningitis: a multicenter case-control study. *Infection*. 2017;45:67-74.
44. Merle-Melet M, Dossou-Gbete L, Maurer P, et al. Is amoxicillin-cotrimoxazole the most appropriate antibiotic regimen for listeria meningoencephalitis? Review of 22 cases and the literature. *J Infect*. 1996;33:79-85.
45. Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med*. 2014;371:447-456.
46. Campioli CC, Almeida NEC, O'Horo JC, et al. Bacterial brain abscess: an outline for diagnosis and management. *Am J Med*. 2021;134(10):1210-1217.e2. 10.1016/j.amjmed.2021.05.027
47. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis*. 1997;25:763-779. quiz 780–761.

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CORRESPONDENCE

Seropositive rheumatoid arthritis after vaccination against SARS-CoV-2 infection

Dear Editor,

Today a frequently asked question is: Can vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) trigger rheumatic and musculoskeletal diseases? Several cases of arthritis have been reported after vaccination against SARS-CoV-2.[1-4] A few articles have investigated the safety of SPUTNIK-V;[5] there is only our one case of arthritis reported after this vaccination.[1] In our *International Journal of Rheumatic Diseases* paper about arthritis after vaccination against SARS-CoV-2[1] we wrote: 'Several patients with rheumatic diseases, treated in the Medical Center of Joint Diseases (MCJD), developed transient flares after receiving the COVID-19 vaccine'. A possible association between rheumatoid arthritis (RA) and influenza vaccination was previously reported in a cohort study;[6] however, there were no cases of seropositive RA after SPUTNIK-V vaccination in the literature. A heterologous recombinant adenovirus-based vaccine, Gam-COVID-Vac (Sputnik V, Gamaleya National Research Centre for Epidemiology and Microbiology), showed a good safety profile and induced strong humoral and cellular immune responses.[5] We would like to present the first case of new-onset seropositive (for rheumatoid factor [RF] and anti-citrullinated protein antibodies [ACPA]) RA after a single dose of SPUTNIK-V vaccine.

We report the case of a 38-year-old Asian non-smoking woman with no history of chronic joint disease, infections, injuries, inflammatory back pain, morning stiffness, or joint swelling. The patient had no previous symptoms of SARS-CoV-2 infection; a serological anti-SARS-CoV-2 rapid test (COVID-19 IgG/IgM antibody test; Humasis,Germany) was negative. The patient received the first dose of the SPUTNIK-V vaccine on May 20, 2021 without developing a fever or adverse events. Twenty days later, pain and stiffness appeared in the left shoulder and 2 days later in the right shoulder, followed by swelling and pain in both knee joints. The patient used non-steroidal anti-inflammatory drugs. She did not visit a doctor nor did she receive the second dose of the vaccine. Two months after vaccination, pain and morning stiffness lasting more than 30 minutes appeared in the small joints of her hands and feet. On August 24, 2021, she underwent an examination at the Medical Centre of Joint Diseases in Shymkent (Kazakhstan). The patient presented morning stiffness for more than 2 hours and symmetric polyarthritis of the knees, feet, and hands. Testing showed a Disease Activity Score of 28 joints with a C-reactive protein (DAS28-CRP) level of 6.02. There were high levels of RF (170 IU/mL, normal range <18 IU/mL), erythrocyte sedimentation rate (39 mm/h), CRP (10 mg/L, normal <5 mg/L), and ACPA (157 U/mL, normal <20 U/mL). The anti-nuclear antibodY (ANA) screen-test and *Chlamydia* and *Ureaplasma* immunoenzyme tests were negative, and the levels of uric acid were normal (241 mmol/L). An immunoenzyme SARS-CoV-2 Spike IgG antibody test had a strongly positive result of 9.81 (0.80 negative, ≤0.80-1.10 borderline, ≥1.10 positive). The positivity coefficient was markedly high at 24.52. Hand X-rays did not show any lesions. Ultrasonography revealed moderate effusion in both knee joints and the metacarpophalangeal and proximal interphalangeal joints of both hands. According to the American College of Rheumatologists/European League Against Rheumatism (ACR/EULAR) classification criteria[7] early RA was diagnosed, and treatment with methotrexate (15 mg per week), non-steroidal anti-inflammatory drugs, and methylprednisolone (100 mg infusion daily for 3 days) was initiated. At the control examination (September 1, 2021) testing showed: CRP 1 mg/L, DAS28-CRP level 3.99, RF 231 IU/mL, and ACPA 314 U/mL.

Two variants of disease development may be considered: a flare of existing RA and a debut of de novo RA. Only two cases of flare RA after COVID-19 vaccination have been reported.[2,3] The first case, mentioned previously,[2] could be explained with the first variant, whereas the second case[3] most likely reflects the second option. In our case, RA pathogenesis could be due to either the first or the second possibility. Unfortunately, the patient was not tested for RF or ACPA before vaccination because she had no previous joint complaints. This woman may have had asymptomatic positive RA, and the COVID-19 vaccination triggered the flare. A rapid increasing of RF and ACPA is significant. We described the rapid growth of ACPA within a month from normal values (18 mg/L) to high values (104 U/mL)[8] in a case of RA that developed after SARS-CoV-2. It is likely that in this case, the vaccination might have been a trigger factor for the rapid onset of RA. It would be appropriate to conduct a genetic study of the patient, as French researchers did;[9] however, similar to other post-vaccine case reports, the causal correlation with RA was not formally established. Nonetheless, we assume that vaccination and SARS-CoV-2 might be trigger factors for

RA, though controlled studies are needed to prove this hypothesis. Analysis of the incidence of RA in different countries over the next 1-2 years is warranted; an increase in incidence in the next 2 years may prove our hypothesis.

KEYWORDS

rheumatoid arthritis, safety of vaccines, severe acute respiratory syndrome coronavirus 2 infection, SPUTNIK-V, vaccination severe acute respiratory syndrome coronavirus 2

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REFERENCES

1. Baimukhamedov C. Arthritis of the left elbow joint after vaccination against SARS-CoV-2 infection. *Int J Rheum Dis*. 2021;24(9):1218-1220. https://doi.org/10.1111/1756-185X.14202
2. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. *Lancet Rheumatol*. 2021;3:e469-e470. https://doi.org/10.1016/S2665-9913(21)00108-9
3. Magliulo D, Narayan S, Ue F, Boulougoura A, Badlissi F. Adult-onset Still's disease after mRNA COVID-19 vaccine. *Lancet Rheumatol*. 2021. 3(10):e680–e682. https://doi.org/10.1016/S2665-9913(21)00219-8
4. An QJ, Qin DA, Pei JX. Reactive arthritis after COVID-19 vaccination. *Hum Vaccin Immunother*. 2021;17:2954-2956. https://doi.org/10.1080/21645515.2021.1920274
5. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397:671-681. https://doi.org/10.1016/S0140-736(21)00234-8
6. Ray P, Black S, Shinefield H, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age. *Vaccine*. 2011;29:6592-6597. https://doi.org/10.1016/j.vaccine.2011.06.112
7. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581. https://doi.org/10.1002/art.27584
8. Baimukhamedov C, Barskova T, Matucci-Cerinic M. Arthritis after SARS-CoV-2 infection. *Lancet Rheumatol*. 2021;3(5):e324-e325. https://doi.org/10.1016/S2665-9913(21)00067-9
9. Perrot L, Hemon M, Busnel JM, et al. First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection. *Lancet Rheumatol*. 2021;3(1):e6-e8. https://doi.org/10.1016/S2665-9913(20)30396-9

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

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

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

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

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

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