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REVIEW

Systemic lupus erythematosus increases risk of incident atrial fibrillation: A systematic review and meta-analysis

Yanlin Chen | Lu Fu | Sijia Pu | Yumei Xue

Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Correspondence
Yumei Xue, Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China.
Email: xymgdci@163.com

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Abstract

Background and Objectives: Patients with systemic lupus erythematosus (SLE) might have increased risk of atrial fibrillation (AF) as a result of initiating chronic and systematic inflammation. However, the prevalence of AF in patients with SLE have not been well quantified. The aim of this systematic review and meta-analysis was to collect and identify available clinical data to explore this possible correlation.

Methods: Articles were searched based on electronic databases (PubMed, Scopus, ScienceDirect, Cochrane Library, Web of Science). Review Manager 5.4 was used to perform meta-analysis of all selected studies and subgroup analyses (pooled separately by geographical distribution). Pooled risk ratio (RR) and 95% confidence intervals (95% CI) were calculated by random-effect model or fix-effect model.

Results: Six cohort studies were involved in this meta-analysis, including 311 844 participants, 78 134 cases of SLE and 347 883 non-SLE controls. Pooled studies indicated increased risk of AF development in patients with SLE compared to participants without SLE (I^2 = 96%, RR = 1.85; 95% CI: 1.23–2.79; P = .003). Four clinical trials including only European/ American populations were analyzed in subgroups. Heterogeneity analysis showed that I^2 = 9% and there was an increase in the risk of AF development in European/ American patients with SLE (RR = 1.79; 95% CI: 1.61–1.98; P < .001), while in 2 Korean studies, the heterogeneity was 98% and there was no correlation between AF and SLE (RR = 1.81, 95% CI: 0.39–8.43). Five clinical studies were involved in subgroup analysis after excluding the Beak study, with I^2 = 96% and they suggested that SLE increased the risk of AF development (RR = 2.13, 95% CI: 1.42–3.21, P = .002).

Conclusion: This meta-analysis suggested that SLE may be a risk factor for AF development and the results may vary with geographic distribution.

KEYWORDS
atrial fibrillation, epidemiology, heterogeneity, meta-analysis, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE or lupus) is a clinically heterogeneous disease with a variety of clinical presentations, such as rash, fatigue and arthritis. About 1 to 10 per 100 000 person-years have been diagnosed with new-onset SLE, with prevalence rate ranging from 0.3 to 241 per 100 000.[1] People of all ages can be affected; many studies have proven that women, especially

in their reproductive years, are more likely to develop SLE, with a ratio of 9:1, compared with men.[2] More importantly, SLE is a typical autoimmune rheumatic disease characterized by multisystem involvement, especially involving the cardiovascular system. According to previous studies, SLE might increase risk of cardiovascular disease via initiating systemic inflammation and immune response, such as coronary artery disease (CAD), conduction system disorder, heart failure and valvular disease.[3] Some antibodies in patients with SLE may target cardiomyocytes and cause myocarditis and arrythmias, such as circulating anti-Ro/SS-A antibodies.[4] Meanwhile, serum inflammatory factors such as interleukin (IL)-2, IL-6, tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) also play roles in increasing cardiovascular risk.[5,6] Studies of cardiovascular diseases in patients with SLE have concentrated mainly on CAD and heart failure, with little evidence illustrating the risk of atrial fibrillation (AF) in SLE compared with the general population.

AF is the most common arrhythmia. The incidence of AF increases with age, with less than 0.5% at 40–50 years, and 8%–10% in those older than 80 years.[7] Furthermore, AF is related to some cardiac and non-cardiac diseases, including CAD, hypertension, obesity, diabetes, heart failure and valvular-related heart disease. Although the pathophysiologic mechanisms of AF are complex, systemic inflammation has been implicated in the pathogenesis of AF.[8,9] Inflammation may fuel the atrial electrical and structural remodeling, which is the pathophysiological basis of AF. Meanwhile, in other inflammation-related diseases, such as rheumatoid arthritis (RA) and systemic sclerosis, many studies have indicated a risk factor for AF development compared with the general population.[10,11] SLE is characterized by triggering systemic inflammation, but there is sparse information about the relationship between SLE and AF. Due to the low numbers in individual cohort studies, a meta-analysis is firmly needed.

AF in patients with SLE have been reported in a little of the literature. It is necessary to analyze the risk of AF in SLE and how it differs by characteristics in comparison to the general population. Therefore, the objective of this study was to perform a comprehensive evaluation of the long-term risk of incident AF in cohort studies of patients with SLE. Here we conducted a meta-analysis and systematic review and hypothesized that the risk of AF would be increased in SLE compared to the general population.

2 | METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (refer to the PRISMA 2009 checklist in Table 1).[12] In addition, systemic review and meta-analysis were independently conducted by 2 investigators (Yanlin Chen and Lu Fu). And we mainly focused on human studies and English-language publications to answer the following research question. Is SLE a risk factor for developing AF?

2.1 | Study identification and search strategy

Two investigators separately screened published literature in Scopus (2005 to September 2021), PubMed (1948 to December 2021), ScienceDirect (1977 to April 2021), Cochrane Library (2017 to December 2021), and Web of Science (2004 to November 2021). Since the published articles that related to our topic were limited, the search terms and their combinations were searched in [All Fields]: (atrial fibrillation OR "AF") AND (systematic lupus erythematosus OR "systemic lupus erythematosus" OR "lupus" OR "SLE"). Meanwhile, when multiple literature reporting the same population were published, the most complete or recent one was used.

2.2 | Exclusion and inclusion criteria

According to different types of articles and population characteristics, 2 authors organized the excluded data in the following: (a) types of studies, case reports, commentaries, preclinical studies (in vitro and animal studies), reviews and so on; (b) medical history, patients had a history of AF/ flutter, ventricular arrythmias, heart failure, ischemic stroke/heart disease, or they had implanted cardioverter-defibrillator or pacemaker before SLE diagnosis; (c) ages, patients less than 18 years.

Additionally, evaluation of study eligibility was independently conducted by the 2 authors. The inclusion criteria were as follows: (a) patients were eligible to be included if they were diagnosed with SLE (according to diagnosis statements of the *International Classification of Diseases*) and without any history of cardiovascular disease that related to outcomes of interest before SLE was identified; (b) types of articles, clinical trials (especially for cohort studies including retrospective and prospective) or randomized controlled trials (RCTs); (c) complete clinical data were required. The detailed clinical characteristics of included studies are described in Table 2.

2.3 | Data extraction and collected outcomes of interest

This meta-analysis article yielded 308 studies; 259 articles were obtained after the duplicates were removed. Then 196 studies were excluded after screening their titles or abstracts, 54 were excluded for inappropriate article type. For the remaining studies, 3 were removed following the exclusion and inclusion criteria. Finally, 6 studies were assessed for eligibility (PRISMA flow diagram in Figure 1).

A standardized data abstraction form was used for collecting information needed in the meta-analysis. Details about the included publications were extracted as follows: (a) last name of the first author, year of publication; (b) country of study; (c) study design; (d) number of patients enrolled in the studies; (e) average time of follow-up; (f) number of patients with AF; (g) age of each study; (h) percentage of females in each research; (i) confounder adjusted in each study; and (j) quality score (shared in Table 2). To ensure the

TABLE 1 PRISMA 2009 Checklist for this systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	This report is identified as a systematic review and meta-analysis	1
Abstract			
Structured summary	2	The structured summary includes background; objectives; methods; results and conclusion	1
Introduction			
Rationale	3	Describe in the introduction.	2
Objectives	4	Stated in the introduction.	2
Methods			
Protocol and registration	5	The protocol is described in the Methods. Registration does not apply.	
Eligibility criteria	6	Specify study characteristics (eg length of follow-up) and report characteristics (eg years considered, language, publication status) is described in methods.	3–4
Information sources	7	Describe all information sources (eg databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (ie screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (eg piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (eg PICOS [Population, Intervention, Comparison, Outcomes and Study], funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Risk of bias in this meta-analysis was not noted in the study, because only 5 trials were included in this meta-analysis.	
Summary measures	13	State the principal summary measures (eg risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (eg study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Risk of bias in this meta-analysis was not noted in the study, because only 5 trials were included in this meta-analysis.	
Additional analysis	23	Give results of additional analyses, if done (eg sensitivity or subgroup analyses, meta-regression [see Item 16]).	6

(Continues)

TABLE 1 (Continued)

Section/topic	#	Checklist item	Reported on page #
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg healthcare providers, users, and policy makers).	6–8
Limitations	25	Discuss limitations at study and outcome level (eg risk of bias), and at review level (eg incomplete retrieval of identified research, reporting bias).	8–9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg supply of data), role of funders for the systematic review.	1

TABLE 2 Summary of main characteristics of included studies in this meta-analysis

Items	Barnado et al (2018)	Chen et al (2020)	Yafasova et al (2021)	Lim et al (2019)	Beak et al (2016)	Arkema et al (2017)
Country	USA	USA	Denmark	Korea	Korea	Sweden
Study design	Cohort study	Cohort study	Cohort study	Cohort study	Cohort study	Cohort study
Number of patients						
Sample size	6832	234 380	17 055	126 858	20 772	20 120
SLE	1097	46 876	3411	21 143	2217	3390
Controls	5735	187 504	17 055	105 715	18 555	16 730
Follow-up, y	9	2	8.5	8	6.8	10
Age, y	51 ± 17	41.5 ± 12.2	44.6 (31.9–57.0)	41.8 ± 13.13	42 ± 17	49.5 ± 17.6
Percentage of females	90.0	93.0	86.0	90.4	34.1	85
Number of patients with AF						
SLE	51	121	187	481	21	129
Controls	146	241	496	619	214	335
Confounder adjusted for	SLE cases age, gender, and race-matched controls	SLE cases age and gender-matched controls	SLE cases age, and comorbidity-matched controls	SLE cases age and gender-matched controls	SLE cases gender-matched control	SLE cases age and gender-matched controls
NOS values	7	8	8	7	6	7

Abbreviations: AF, atrial fibrillation; NOS, Newcastle-Ottawa Scale; SLE, systemic lupus erythematosus.

accuracy and reduce selection bias, data extraction and collection were completed independently by the 2 afore-mentioned investigators. Any discrepancy regarding the extraction data was resolved by referring to original studies or adjudication by the senior author (Yumei Xue).

2.4 | Quality assessment

Quality of observational studies was evaluated with Newcastle-Ottawa Scale (NOS),[13] which was assessed based on 3 factors: method of objects selection, comparability of the study groups, and outcomes of interest. Two reviewers (Yanlin Chen and Sijia Pu) evaluated the quality of the studies (low, high, unclear) by using Review Manager 5.4 and the risk of bias graph is shown in Figure 2. Studies given a score of 6 or more (NOS score rating of 0–9) were considered to be of high quality, as shown in Table 2.

2.5 | Statistical analysis

Meta-analysis was performed using Review Manager 5.4. Rational selection of odds ratio (OR) or risk ratio (RR) based on the study type (case–control study has the OR value, and cohort study has the RR value). The OR or RR value was used to compare dichotomous variables, and the result was reported with 95% confidence intervals

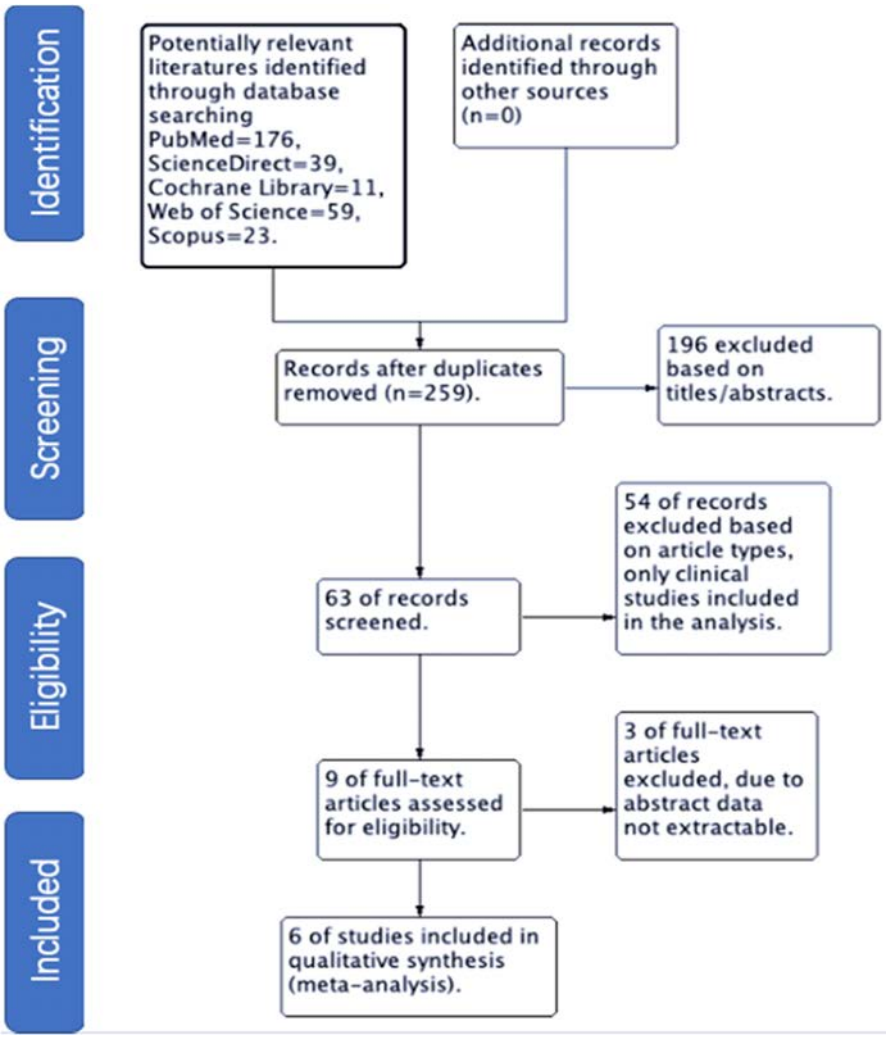

FIGURE 1 Flow diagram of search methodology and literature review process

(CI). Furthermore, statistical heterogeneity was assessed using the Chi-square test and I^2 values were calculated by Review Manager 5.4. I^2 is a value ranging from 0% to 100%, $I^2 < 25\%$ represents insignificant heterogeneity, $25\% \le I^2 < 50\%$ represents low heterogeneity, $50\% \le I^2 < 75\%$ represents moderate heterogeneity, $I^2 \ge 75\%$ represents high heterogeneity.[10] Consequently, when the I^2 value was more than 50%, a random-effect model would be required; otherwise, a fixed-effect model was used. Subgroup analysis was performed to reveal the factors that may explain heterogeneity between each study. Sensitivity analysis was conducted via excluding 1 study to assess if the individual studies affect the overall outcomes.

3 | RESULTS

3.1 | Characteristics of included studies

The characteristics of included studies are shown in Table 2. Six cohort studies were eligible for meta-analysis, which were identified using the predefined search and relied on exclusion and inclusion criteria. There were 4 studies from Europe and America (2 from USA, 1 from Denmark and another from Sweden) and 2 from Korea.[3,14–18]

Additionally, the 6 cohort studies included 311 844 participants, 78 134 cases of SLE and 347 883 non-SLE controls. Six eligible studies set a control group (non-SLE control), but the design of the control groups varied among the studies. In Barnado et al's[16] research, the SLE group was age, gender, and race-matched with control subjects; Chen et al[17] reported that patients with SLE (diagnosed 2007 to 2010, no history of cardiovascular disease) were age and gender-matched with non-SLE controls. In Yafasova et al's[15] study, SLE patients (from 1996–2018, no history of cardiovascular disease) were sex, gender, and comorbidity-matched with controls. Lim et al[3] reported that patients with SLE (database from 2008–2014, no history of cardiovascular disease) were age and gender-matched with controls. For Beak et al's[18] study, the SLE group was gender-matched with controls. Two included cohort studies also further investigated the difference in prognostic indictors of AF in patients with SLE. Lim et al[3] indicted the SLE patients who developed AF were more likely to have increased risk for mortality compared with the general population. Chen et al[17] investigated the incidence of hospitalization for AF in the SLE group compared to the general group and reported that AF hospitalization rate is twice as high in patients with SLE. The NOS values for all of the studies were more than 6, and were considered to be high quality.

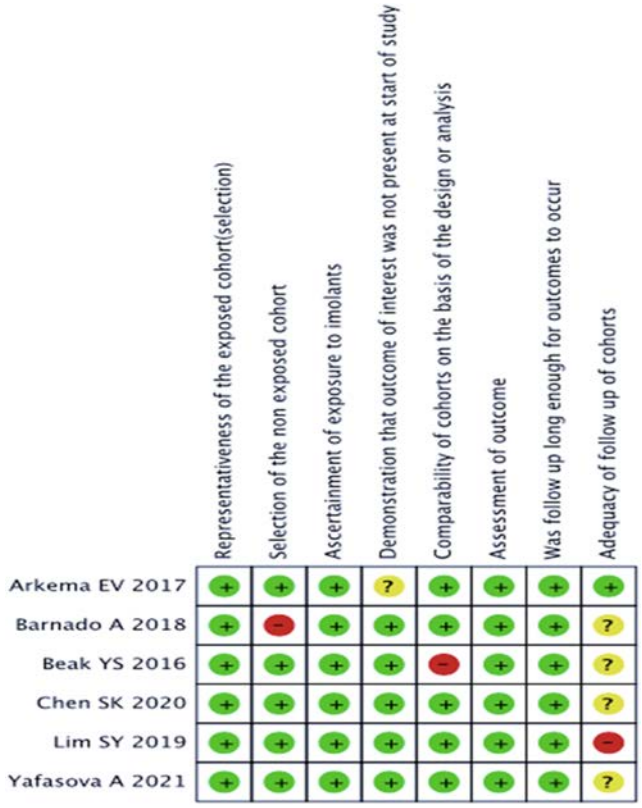

FIGURE 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

3.2 | Meta-analysis results

3.2.1 | Clinical outcome of AF in patients with SLE

Meta-analysis was performed to explore the incident AF in patients with SLE compared to participants without SLE. Since the 6 studies were cohort trials, RR values were used to determine the difference between SLE groups and controls. In meta-analysis results, the statistical heterogeneity was high with $I^2 = 96\%$ ($P < .001$), so a Mantel–Haenszel random-effect model was used to identify the relationship between the risk of AF and SLE. Among the SLE patients, 990 (1.15%) had AF and the prevalence of AF events were significantly higher in all SLE cohorts reviewed compared to controls ($P = .003$; in Figure 3A). Consequently, pooled data showed increased risk of development of prevalent AF in patients with SLE compared to participants without SLE (RR = 1.85; 95% CI: 1.23–2.79; $P = .003$).

3.2.2 | Subgroup analysis of the incident AF in patients with SLE

Patients with AF were pooled separately by geographical distribution. Four studies were from European/ American populations, including 278 387 participants, 54 774 cases of SLE and 223 613 non-SLE controls. The results for these populations reported that homogeneity with an $I^2 = 9\%$ ($P = .35$; shown in Figure 3B) and pooled data also indicated a statistically significant increased risk of AF in European/ American patients with SLE (RR = 1.79; 95% CI: 1.61–1.98; $P < .001$). However, in the remaining 2 Korean studies, including 147 630 participants, 23 360 cases of SLE and 124 270 non-SLE controls, as shown in Figure 3C, the statistical heterogeneity was $I^2 = 98\%$ ($P < .001$), and there was no correlation between AF and SLE (RR = 1.81; 95% CI: 0.39–8.43; $P = .45$). Furthermore, in Figure 3D, there were 5 studies, excluding Beak et al research, with statistical heterogeneity of $I^2 = 96\%$ ($P < 0.001$), which, for this subgroup analysis, showed that SLE increased the risk of AF development (RR = 2.13; 95% CI: 1.42–3.21; $P = .002$).

3.3 | Sensitivity analysis and publication bias evaluation

Among these 5 cohort studies, Beak et al research was a 1-center study, and the characteristics of its included population were not representative, so this study was excluded, and the final results (RR = 2.20; 95% CI = 1.33–3.62; $P = .0003$) showed stability (shown in Figure 3D).

However, publication bias in this meta-analysis was not noted in the study, because only 6 trials were included in this meta-analysis.

4 | DISCUSSION

4.1 | SLE tends to increase AF events and high heterogeneity may be induced by geographic distribution

SLE is an autoimmune disease that is associated with an increased risk of cardiovascular damage (accounts for 10%–15% of deaths in SLE[19]). Data to analyze the relationship between arrhythmias (especially AF) and SLE were limited and the results from available research were controversial. Therefore, a meta-analysis was required to estimate the risks for AF patients with SLE compared to the background population. Pooled data analysis indicated a strongly significant increased risk of incident AF among SLE patients with 85% excess risk compared with a background population without SLE.

In our study, the heterogeneity value was high, reaching 96%, which means the result may not be robust and credible. Therefore, subgroup analysis was required to identify sources of heterogeneity. Subgroup analysis was performed by geographic distribution and it was found that heterogeneity for Europe and America was very low with $I^2 = 9\%$; we observed approximately a 2-fold increased risk of AF in individuals with SLE compared to the background population. However, in Korea, the heterogeneity for these 2 studies was still high with $I^2 = 98\%$ and the results have shown that there was no relationship between SLE and AF. The Korean studies yielding such results might be due to Beak et al analyzing the clinical data from a tertiary hospital in Korea, so that a 1-center clinical study was not very representative. Therefore, this may explain why

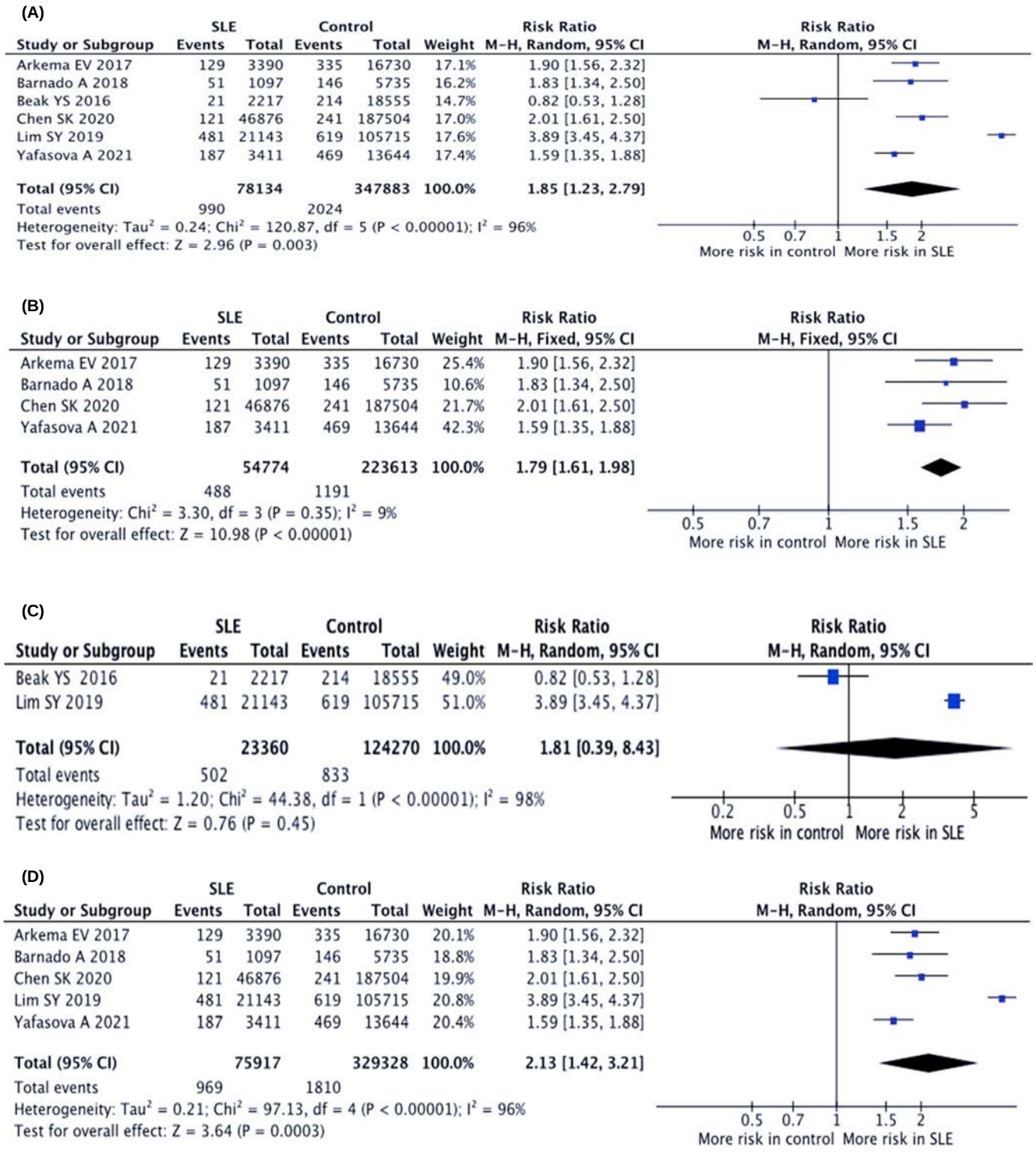

FIGURE 3 (A) Forest plot about risk of AF in patients with SLE compared to controls. (B) Forest plot about risk of AF in European/American patients with SLE compared to controls. (C) Forest plot about risk of AF in Korean patients with SLE compared to controls. (D) Forest plot about risk of AF which excluded the Beak et al study. SLE, systemic lupus erythematosus; AF, atrial fibrillation; M-H, Mantel–Haenszel random-effect model

subgroup analysis of these Korean populations had such high heterogeneity.[20] High heterogeneity values of meta-analysis may be due to differences in geographic distribution or inconsistent data selection. To further analyze the exact source of heterogeneity, data from the Beak study[20] was removed and a subgroup analysis for the remaining 5 cohort studies was conducted. The heterogeneity still exists ($I^2 = 96\%$), suggesting that the differences in geographic distribution itself, rather than the selection bias, was involved in causing heterogeneity. In a word, the prevalence of AF in SLE may be affected by differences in geographic distribution (Table 3 summarizes

these meta-analysis results). In Zulkifly et al's epidemiology study, an epidemiological investigation about the incidence of AF, they found that the prevalence of AF in Europe and the USA is about between 1%–4%, while in Asia it is much lower (0.49%–1.9%).[20] In O'Neal et al's[21] study, they indicated that AF is more prevalent in Blacks than Whites (White being the main ethnic group in Europe and the USA). Also, Al-adhoubi et al[22] reported that the incidence and prevalence of SLE may be attributed to geographic differences. Therefore, SLE may be a risk factor for AF development and the results may vary with geographic distribution.

Each cohort study was adjusted for age and gender. While enrolled cohort studies indicated that hypertension, diabetes were more susceptible for SLE, the results of studies may be biased easily by hypertension and diabetes. Three individual RRs from each enrolled cohort study were further subjected to sensitivity analysis, which adjusted for gender, age, hypertension, diabetes and indicated that SLE may be a risk factor for AF. RR for sensitivity analysis in Barnado et al was 1.46 (95% CI: 1.16–1.85); in Yafasova et al it was 1.59 (95% CI: 1.56–2.32); and in Lim et al it was 2.84 (95% CI: 2.50–3.23).[3,15–17] Therefore, according to sensitivity analysis of individual studies, SLE may be an independent risk factor for AF.

4.2 | Pathogenesis of AF in SLE

Although the pathogenesis of SLE-related AF has not been completely elucidated, previous studies have reported multiple mechanisms associated with the development of AF in SLE. It is well known that the underlying mechanisms of AF development are linked to structural and electrical remodeling.[23] Chronic inflammation from SLE may contribute to cardiovascular remodeling. Therefore, there are several possible mechanisms for SLE tending to increase AF development. According to the definition of SLE, it belongs to a chronic autoimmune disease; systemic inflammation may play a significant role in the pathogenesis of AF. Cardiac biopsies from patients with AF had found that inflammation infiltrated the atrial myocardium.[24,25] There are several key inflammatory markers: CRP, heat shock protein-27 (HSP27), IL-6, IL-8, TNF, which have been identified in patients with AF.[26] In clinical studies, SLE may induce systemic inflammation via elevating high levels of inflammatory markers, which damage the cardiovascular system leading to structural and electrical remodeling of the atrium, thus SLE may contribute to AF prevalence. Meanwhile, mast cells may also actively provoke atrial fibrosis by secreting platelet-derived growth factor (PDGF-A) and enhancing collagen expression and cell proliferation in patients with AF.[27] In SLE patients, a possible role of autoantibodies may also target the cardiovascular system, such as anti-Sjögren's syndrome-related antigen A and B (SSA, SSB), which may initiate cardiovascular remodeling.[28] It has been proposed that higher levels of these antibodies interact with L/T-type calcium channels and downregulate them, disturbing the intracellular calcium homeostasis and finally resulting in cardiomyocytes apoptosis.[29] Meanwhile, SSA antibodies against muscarinic acetylcholine receptor M3 cause a reduction in parasympathetic activity.[30] Several case reports indicate that AF in SLE may also be correlated with therapeutic agents, especially for methylprednisolone treatment; the possible mechanism of this may be caused by late potentials development and potassium efflux.[31] In addition, another lupus-treatment medication named hydroxychloroquine may also be considered a risk drug to develop AF, which has been discovered to be associated with cardiotoxicity.[32,33] Nevertheless, more scientific research is required to further investigate and identify the pathogenesis of the development of AF in SLE.

4.3 | Study strengths and limitations

Meta-analysis about specific autoimmune diseases and AF have been reported, such as AF in patients with RA or in patients with inflammatory bowel disease.[34,35] However, no meta-analysis has discussed the relationship between prevalence of AF with SLE. Consequently, this article is the first systematic review and meta-analysis to report SLE may be a risk factor for AF. Large sample sizes increase the study power in our meta-analysis and subgroup analysis has found major sources of heterogeneity. Sensitivity analysis has been performed and found that the final result was also stable (RR = 2.13, 95% CI = 1.42–3.21, $P = .0003$), which indicates the conclusion was reliable. However, we acknowledge some limitations in our study. The clinical data that we conducted in meta-analysis contained only 6 studies with high heterogeneity; publication bias

TABLE 3 The association between SLE and AF by different factors

		Test of association				Test of heterogeneity	
Stratified factors	No. of studies	RR	95% CI	*P*	Model	I^2 (%)	*P*
Area							
Overall	6	1.85	1.23–2.79	.003	Random	96	.000
Europe and the USA	4	1.79	1.61–1.98	.000	Fixed	9	.35
Asia (Korea)	2	1.81	0.39–8.43	.45	Random	98	.000
Excluded Beak et al study	5	2.13	1.42–3.21	.000	Random	96	.000

Abbreviations: AF, atrial fibrillation; RR, risk ratio; SLE, systemic lupus erythematosus.

could not be conducted. Clinical outcomes such as the mortality of AF patients with SLE, total hospital charges and hospital length of stay were not analyzed due to the limited publication information. Doubtless, further clinical trials are needed to understand the relationship between AF and SLE.

5 | CONLUSION

In summary, this meta-analysis suggested a statistically significant increased risk of AF prevalence among patients with SLE and this may vary with geographic distribution. Consequently, paying attention to AF screening during follow-up of SLE patients may be helpful for clinical prognosis. Future large-volume studies with extensive follow-up for SLE patients is firmly needed.

AUTHOR CONTRIBUTIONS

All authors participated in writing and editing of the manuscript (see article content for details).

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CONFLICT OF INTEREST

The authors declare the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ORCID

Yanlin Chen https://orcid.org/0000-0003-3597-3868

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REVIEW

Consensus statements for pharmacological management, monitoring of therapies, and comorbidity management of psoriatic arthritis in the United Arab Emirates

Khalid A. Alnaqbi[1,2] | Suad Hannawi[3,4] | Rajaie Namas[5] | Waleed Alshehhi[6] | Humeira Badsha[7] | Jamal Al-Saleh[8]

[1]Department of Rheumatology, Tawam Hospital, Al Ain, UAE

[2]College of Medicine and Health Sciences, UAE University, Al Ain, UAE

[3]Emirates Health Services (EHS), Dubai, UAE

[4]Ministry of Health and Prevention, Dubai, UAE

[5]Division of Rheumatology, Department of Internal Medicine, Cleveland Clinic Abu Dhabi, UAE

[6]Medcare Hospital, Dubai, UAE

[7]Dr. Humeira Badsha Medical Center, Dubai, UAE

[8]Dubai Hospital, Dubai, UAE

Correspondence
Khalid Alnaqbi, Department of Rheumatology, Tawam hospital, Al Ain, UAE.
Email: kalnaqbi@gmail.com

Funding information
Emirates Society for Rheumatology

Abstract

Objective: Psoriatic arthritis (PsA), a chronic inflammatory disease characterized by heterogeneous clinical manifestations, substantially impacts the quality of life of affected individuals. This article aims at developing consensus recommendations for the management of PsA and associated comorbidities and screening and monitoring requirements of PsA therapies in the United Arab Emirates (UAE) population.

Methods: An extensive review of present international and regional guidelines and publications on the pharmacological management, monitoring of therapies in the context of PsA was performed. Key findings from guidelines and literature were reviewed by a panel of experts from the UAE at several meetings to align with current clinical practices. Consensus statements were formulated based on collective agreement of the experts and members of Emirates Society for Rheumatology.

Results: The consensus recommendations were developed to aid practitioners in clinical decision-making with respect to dosage recommendations for pharmacological therapies for PsA, including conventional drugs, non-biologic, and biologic therapies. Consensus recommendations for therapeutic options for the treatment of PsA domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease, were developed. The panel emphasized the importance of monitoring PsA therapies and arrived at a consensus on monitoring requirements for PsA therapies. The expert panel proposed recommendations for the management of common comorbidities associated with PsA.

Conclusion: These consensus recommendations can guide physicians and healthcare professionals in the UAE in making proper treatment decisions, as well as efficiently managing comorbidities and monitoring therapies in patients with PsA.

KEYWORDS
biologics, comorbidities, disease-modifying drugs, domains, dosage, monitoring, pharmacological management, psoriatic arthritis, recommendations

1 | INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease occurring in about 30% of patients with psoriasis.[1] The global prevalence of PsA varies by geographic region and ranges from 0.001% to 0.42%, while the prevalence of PsA is 0.01% to 0.3% in Middle East countries.[2–6] Approximately 20% of patients diagnosed with PsA may develop a more aggressive form of arthritis resulting in joint damage.[4] In patients with PsA, quality of life (QoL) is substantially impacted consequent to stress, depression, mood changes, pain, and compromised physical functioning.[7,8]

Nearly all the current treatment recommendations for PsA are reflective of the treatment and disease landscape in developed countries, particularly Europe and the United States.[9–11] Currently, not much is known about the epidemiology and treatment practices specific to PsA in the Middle East. There are several local challenges that may not be adequately accounted for, in currently available treatment recommendations for PsA.[12]

Multiple factors necessitate national recommendations for the management of PsA specific to the United Arab Emirates (UAE), including wide variability in healthcare systems, patient access to advanced care, affordability of treatment, practicing rheumatologists trained in different countries and implementing different approaches to treatment, and ethnic diversities among patients from almost 200 countries in the UAE. Many of the newer approved therapies such as biological disease-modifying antirheumatic drugs (DMARDs) may not be accessible to patients who do not have insurance coverage, given their prohibitive cost. Other factors that preclude the implementation of global treatment recommendations in local clinical practice are lack of disease awareness among both patients and healthcare providers, shortage of healthcare resources, and lack of multidisciplinary healthcare clinics.[1]

The objectives of this article are to develop consensus statements for the pharmacological management of PsA and associated comorbidities and screening and monitoring requirements of PsA therapies, to assist practicing physicians in the UAE.

2 | METHODS

For the development of the consensus guidelines, 6 experts with international board certifications, and more than 15 years experience in rheumatology and an interest in psoriatic arthritis representing different healthcare sectors (government and private) of the UAE were chosen from the Emirates Society for Rheumatology and convened in several meetings.

A targeted literature review was conducted. Current international and local treatment guidelines for PsA were identified through an extensive literature search and reviewed by members of the panel to identify unmet needs in local treatment practices in the UAE. Regional guidelines were compared with the latest international guidelines from the American College of Rheumatology/National Psoriasis Foundation (ACR/NPF) Guideline for the Treatment of Psoriatic Arthritis 2018, European League Against Rheumatism (EULAR) 2019, The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2020 Update, GRAPPA 2015 (detailed), and 2014 Saudi Practical Guidelines on Biologic Treatment of Psoriasis.[9–11,13,14]

As of August 2021, there is a dearth for guidelines on management of PsA specific to the Arab region.

Based on a review of international and regional guidelines, consensus statements were developed focusing on pharmacological treatment options, screening and monitoring requirements for PsA therapies, and management of comorbidities associated with PsA. The results were discussed with all the members of Emirates Society of Rheumatology meeting to arrive at the final consensus statements. Key findings from the review were presented as statements.

The key objectives of the meetings were:

1. to critically review the available regional and international recommendations on the management of patients with PsA
2. to develop regional recommendations for effective management of PsA
3. to develop regional recommendations for screening and monitoring requirements for PsA therapies.

Several meetings were held to generate consensus statements regarding pharmacological management of psoriatic arthritis. The first expert panel meeting was conducted on September 23, 2020 and the meeting lasted for 2 hours. The second expert panel meeting was conducted on October 7, 2020 and the meeting lasted for 3 hours. The third expert panel meeting was held on December 16, 2020 and lasted for 2 hours. The fourth and fifth meetings were held in the presence of Emirates Society for Rheumatology members on December 18, 2020 and May 22, 2021 respectively; each meeting lasted for almost 2 hours. The final meeting was held on August 10, 2021 and lasted for 2 hours when the consensus statements were approved.

The consensus statements have been written in 2 separate papers. The first paper focuses on overarching principles, evaluation of PsA and non-pharmacological treatment options of PsA.[15] The present article, which is the second part covers consensus statements related to pharmacological management of PsA (dosing and administration recommendations, treatment recommendations for PsA domains and consensus statements on efficacy and safety profile of non-biologic and biologic therapies), screening and monitoring requirements for therapies and management of comorbidities.

3 | RESULTS AND DISCUSSION

3.1 | Pharmacological treatment options

GRAPPA recommendations (2015) are centered around major subdomains within PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease. In accordance with the

overarching principles outlined in the GRAPPA recommendations, the expert panel agreed that treatment selection should be based on shared decision-making between the physician and patient. The current treatment recommendations were developed to align with the core recommendations from GRAPPA.[9]

Pharmacological therapies for the management of PsA include:

- Symptomatic treatments: non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCCs)[9]
- DMARDs:
  - conventional synthetic DMARDs (csDMARDs): methotrexate, sulfasalazine, leflunomide[9]
  - targeted synthetic DMARDs (tsDMARDs): phosphodiesterase-4 inhibitor (PDE-4i) (apremilast), Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib).[9,10,16]
- Biologic DMARDs:
  - tumor necrosis factor inhibitors (TNFi): adalimumab, etanercept, infliximab, certolizumab pegol, golimumab[9]
  - interleukin-12/23 inhibitors (IL-12/23i): ustekinumab[9]
  - IL-23 inhibitors (IL-23i): guselkumab[17]
  - IL-17 inhibitors (IL-17i): secukinumab, ixekizumab[10]
  - cytotoxic T-lymphocyte-associated protein 4-immunoglobulin (CTLA4-Ig): abatacept[10]
  - upcoming therapies: filgotinib, risankizumab, brodalumab, bimekizumab, deucravacitinib.[18–22]

3.2 | Dosage and administration

The dosage recommendations for the pharmacological agents are shown in Table 1.

3.2.1 | NSAIDs

The expert panel urged that a thorough safety evaluation should precede the use of NSAIDs in patients with comorbid medical conditions (eg peptic ulcer disease, chronic kidney disease [CKD], cardiovascular disease [CVD]).

3.2.2 | GCCs

In the treatment of peripheral arthritis, GCC is recommended conditionally, and the lowest effective doses should be administered to reduce the risk of side effects.[9]

3.2.3 | csDMARDs

Conventional DMARDs are indicated for the treatment of moderate-to-severe PsA and in patients who have failed to respond to short-term NSAID therapy. Methotrexate has been shown to improve disease activity and health-related QoL in patients with PsA. Methotrexate has a broad therapeutic dose range (7.5–30 mg/wk) and different administration forms (oral, or subcutaneous).[23] Evidence suggests that monotherapy with methotrexate offers moderate improvement in joint and skin disease in patients with PsA, and doses >15 mg/wk are associated with greater clinical efficacy compared to lower doses.[24,25]

In patients with mild-to-moderate peripheral arthritis, use of sulfasalazine at a dose of 2–3 g/d may improve functional outcomes.[26,27]

Leflunomide monotherapy with a daily loading dose of 100 mg/d for 3 days, followed by 20 mg/d is effective in the management of patients with mild-to-moderate PsA.[28] In an ongoing randomized, placebo-controlled, double-blind trial, the effectiveness of combination therapy of methotrexate and leflunomide in the treatment of patients with PsA is being evaluated, and the outcomes of the study are expected to provide key information for treatment strategies in PsA.[29]

3.2.4 | tsDMARDs

Phosphodiesterase-4 inhibitors

Apremilast at a dose of 30 mg twice daily improves signs and symptoms and physical function in patients with active PsA.[30–33]

JAK inhibitors

The recommended dosage of upadacitinib, a selective JAK inhibitor, is 15 mg once daily orally in patients with active PsA, who have not adequately responded or are intolerant to 1 or more DMARDs.[16]

According to EULAR 2019 recommendations, tofacitinib should be administered after inadequate response or intolerance to at least 1 bDMARD, or in case bDMARDs are not considered appropriate (due to patient preference for oral therapy or adherence issues to injectable formulations).[10] The recommended dose of tofacitinib is 5 mg twice daily (immediate release) or 11 mg once daily (extended release) in combination with non-biologic DMARDs.[34]

3.2.5 | Biologic DMARDs

TNF inhibitors

TNFi agents approved by the US Food and Drug Administration (FDA) and other health authorities worldwide for PsA treatment include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. They are recommended for use in PsA after inadequate response to at least 1 synthetic DMARD, although they may also be used as initial therapy.[35] TNFi agents are recommended in peripheral arthritis, and are also the first choice of therapy in enthesitis, dactylitis, and nail psoriasis.[36]

The dosage recommendations for TNFi (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab) are shown in Table 1.

TABLE 1 Dosage recommendations for pharmacological therapies for PsA

Therapeutic class	Dosage	Route of administration
NSAIDs[a]		Oral and IM
GCCs[b]	Lowest effective dose	IM and IA
csDMARDs		
Methotrexate[23]	7.5–30 mg/wk	Oral, SC
Sulfasalazine[26,27]	2 to 3 g/d	Oral
Leflunomide[28]	Daily loading dose of 100 mg for 3 d followed by 20 mg/d	Oral
tsDMARDs		
Apremilast[30–33]	Apremilast 30mg twice daily (maintenance dose)	Oral
Tofacitinib[34]	5 mg twice daily (immediate release) or 11 mg once daily (extended release) in combination with non-biologic DMARDs	Oral
Upadacitinib[16]	15 mg once daily	Oral
TNFi[b]		
Adalimumab[107]	40 mg every 2 wks in patients with PsA with inadequate response to DMARDs	SC
Etanercept[108–110]	50 mg once weekly	SC
Infliximab[111,112]	5 mg/kg at 0, 2, 6 wks, and every 8 wks thereafter.	IV
Certolizumab pegol[113,114]	400 mg at wks 0, 2, 4 Maintenance dose: 200 mg every 2 wks, or 400 mg every 4 wks once clinical response is confirmed	SC
Golimumab[115]	SC: 50 mg monthly IV: 2 mg/kg over 30 min at Wks 0 and 4 (loading dose), thereafter every 8 wks (maintenance)	SC, IV
IL-12/23i[c]		
Ustekinumab[37]	45 mg or 90 mg (based on weight) at 0 and 4 wks, and every 12 wks thereafter	SC
IL-17i		
Secukinumab[116]	300 mg in patients with concomitant moderate-to- severe plaque psoriasis or who are TNFi inadequate responders at wks 0, 1, 2, 3 and 4 and every 4 wks thereafter. 150 mg in other patients at wks 0, 1, 3, 4 and every 4 wks thereafter and based on clinical response the dose can be increased to 300 mg.	SC
Ixekizumab[38,117]	160 mg followed by 80 mg every 2 or 4 wks in patients who previously had inadequate response to TNFi. For patients with arthritis and moderate-to-severe plaque psoriasis, using the dosing regimen for plaque psoriasis;160 mg SC at wk 0, then 80 mg SC at wks 2, 4, 6, 8, 10 and 12, then 80 mg SC every 4 wks, starting wk 16.	SC
IL-23i		
Guselkumab[40]	100 mg at wks 0 and 4, and every 8 wks thereafter (maintenance)	SC
(CTLA4-Ig) T-cell co-stimulation inhibitor		
Abatacept[43,118]	500 mg, 750 mg, or 1000 mg (based on weight range); following initial IV infusion, subsequent infusions should be administered at 2 and 4 wks and every 4 wks thereafter) 125 mg of abatacept injection should be administered SC once weekly	IV, SC

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTLA4-Ig, cytotoxic T-lymphocyte-associated antigen4-immunoglobulin; GCCs, glucocorticoids; IA, intra-articular; IL-17i, interleukin-17 inhibitor; IL-12/23i, interleukin-12/23 inhibitor; IL-23i, interleukin-23 inhibitor; IM, intramuscular; IV, intravenous; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; PDE-4i, phosphodiesterase-4 inhibitor (apremilast); SC, subcutaneous; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted systemic disease-modifying antirheumatic drug.

[a]Mentioning the doses of all available NSAIDs is beyond the scope of this paper.

[b]European League Against Rheumatism 2019 and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 guidelines recommend administering the lowest effective doses of GCC.

[c]Loading dosage might vary according to the severity of psoriasis and other domains of the disease.

IL-12/23 inhibitors

The IL-12/23 inhibitor ustekinumab has been recommended alongside other biologics such as TNFi and IL-17 inhibitors after DMARD therapy in patients with active PsA.[9,10] The recommended dose of ustekinumab is 45 mg or 90 mg (subcutaneous) at 0 and 4 weeks and every 12 weeks thereafter.[37]

IL-17 inhibitors

The recommended dose of IL-17i ixekizumab in patients with active PsA and inadequate response to TNFi agents is starting dose of 160 mg followed by 80 mg every 2 or 4 weeks for the safe and effective management of PsA.[38] IL-17 inhibitor secukinumab is administered subcutaneously at doses of 300 mg in patients with concomitant moderate-to-severe plaque psoriasis or who are TNFi inadequate responders at weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter. The loading dose can be 150 mg in other patients at weeks 0, 1, 3, 4 and every 4 weeks thereafter and based on clinical response the dose can be increased to 300 mg.[39]

IL-23 inhibitors

Guselkumab, a specific IL-23 inhibitor, has been recently approved for the treatment of PsA by the US FDA and European Medicines Agency (EMA).[17] The recommended dose of guselkumab is 100 mg at weeks 0 and 4, and every 8 weeks thereafter.[40] Risankizumab was not approved for PsA by the FDA and EMA when our consensus statements were drafted. However, the EMA and FDA approved it on November 22, 2021 and January 21, 2022 respectively for treatment of active psoriatic arthritis.[41,42]

CTLA4-Ig

Abatacept is a biologic agent that targets T-cell costimulatory signals selectively and is approved for the treatment of PsA patients with inadequate response to csDMARDs, excluding those with uncontrolled skin lesions and axial disease.[43]

3.2.6 | Biosimilars

In recent years, biosimilars of infliximab, etanercept, and adalimumab have been approved by regulatory bodies in Europe and the USA for the treatment of PsA. These agents have been approved for the treatment of PsA based on similar efficacy to the reference product in psoriasis and/or rheumatoid arthritis (RA), by the extrapolation principle.[44–46] Biosimilars are more cost-effective compared to biologics, and thereby represent a solution for better patient accessibility to therapy and reduction in associated healthcare costs.[47]

Consensus statements on dosage recommendations for non-biologic and biologic therapies are provided in Table 1.

3.3 | Treatment recommendations based on PsA domains

3.3.1 | Peripheral arthritis

In DMARD-naïve patients with peripheral arthritis, csDMARDs (methotrexate, sulfasalazine, and leflunomide), PDE-4i, IL-12/23i, IL-17i, IL-23i, JAKi, and TNFi are recommended therapeutic options.[9,11,33] In patients with monoarthritis or oligoarthritis accompanied by factors such as dactylitis or joint damage, the use of csDMARDs and intra-articular (IA) GCC should be considered.[9] In patients with polyarticular disease, csDMARDs should be considered either as first-line treatment or after a short course of NSAIDs. In patients with inadequate response to csDMARDs, TNFi, IL-12/23i, IL23i, IL17i, PDE-4i and JAKi are recommended therapeutic options.[9,10,34,48,49] In patients with inadequate response to 1 biologic treatment, switching to another biologic within the same drug class, or to a drug with a different mode of action, should be considered.[9,10] In all patients with peripheral arthritis, IA and systemic GCC are conditionally recommended at the lowest dosages and for a short duration.

3.3.2 | Axial disease

At the time of drafting consensus statements, there were no studies on management of psoriatic spondylitis. Therefore, management of this condition depends on current treatment modalities in ankylosing spondylitis. In patients with psoriatic spondylitis/axial disease who are biologic-naïve, NSAIDs, physiotherapy, simple analgesia, TNFi or IL-17i, JAKi are recommended therapeutic options. Tofacitinib was not approved for PsA by the FDA and EMA when the consensus statements were drafted. However, FDA and EMA approved it on November 18, 2021 and December 14, 2021 respectively for treatment of ankylosing spondylitis. Other therapeutic options such as sacroiliac joint GCC injections and bisphosphonates can be used, but with caution.[9,14,50–56]

3.3.3 | Enthesitis

For the management of PsA patients with enthesitis (inflammation at the sites of attachment of ligaments, tendons, and joint capsules to bone),[57] treatment with TNFi, IL-17i, IL-23i, IL-12/23i and JAKi are recommended therapeutic options. Other therapeutic options include NSAIDs, physiotherapy, methotrexate, CTLA4-Ig, and PDE-4i.[9,10,49,58–62]

3.3.4 | Dactylitis

The recommended therapies for the management of PsA patients with dactylitis include TNFi therapies (infliximab, adalimumab, golimumab, and certolizumab pegol), IL-17i, IL-12/23i, IL-23i, JAKi, and PDE-4i.[9,58,62,63] Other therapeutic options include NSAIDs, GCC injections, and methotrexate.[9]

3.3.5 | Nail disease

For the management of PsA patients with moderate-to-severe nail disease, TNFi, IL-17i, PDE-4i, IL-23i, IL-12/23i and acitretin are recommended therapeutic options.[9,10,64–67] Other options include

topical therapies, procedural therapies, csDMARDs (cyclosporine, leflunomide, and methotrexate).[9,68,69]

3.3.6 | Skin disease

The expert panel recommends the use of topical therapies, phototherapy, acitretin and csDMARDs (methotrexate, leflunomide, cyclosporine) as first-line therapeutic options, especially for PsA patients with milder skin disease.[9] TNFi, IL-17i, IL12/23i, IL-23i, JAKi and PDE-4i are recommended therapeutic options for treatment of PsA patients with significant skin involvement.[9] Furthermore, biologic agents such as IL-17i are preferred to TNFi, with or without topical treatments and DMARDs, in PsA patients with active psoriasis (≥3% of body surface area of skin involvement).[70] In accordance with GRAPPA 2015 recommendations, the expert panel recommends switching from one DMARD to another, or to biologic treatment, or from one biologic treatment to another.[9]

Consensus recommendations for the treatment of PsA domains were based on GRAPPA 2015, GRAPPA 2020, EULAR 2019 recommendations and literature review, and are presented in Table 2.

3.4 | Treatment response

Evaluating response to therapy in patients with PsA can be difficult due to its complex nature, which encompasses a multitude of clinical manifestations. To date, there is no standardized outcome measure for PsA.

In terms of efficacy and safety profile, experts agreed to adhere to the recommendations from guidelines, latest literature evidence and prescription label. Accordingly, consensus statements were developed for efficacy and safety of non-biologic and biologic therapies.

3.5 | Efficacy and safety profile of non-biologic pharmacological therapies

Consensus statements on efficacy/safety profile of non-biologic pharmacological therapies are detailed in Table 3

3.6 | Efficacy and safety profile of biologic pharmacological therapies

Consensus statements on the efficacy and safety of biologic pharmacological therapy are presented in Table 4.

3.7 | Treatment failure and switching therapy

The expert panel agreed that transitioning to alternative TNFi should be considered in PsA patients with primary or secondary failure of TNFi therapy. The response to alternative treatment should be assessed with the same criteria as those used for the first TNFi agent. Furthermore, possible consequences for control of skin disease should be considered and referral to a dermatologist also considered, if required.[11]

Similarly, switching within a class or between a class (bDMARD to tsDMARD) can also be considered in cases of primary or secondary failure of a bDMARD. However, it is more advisable to change class after a second failure within a given class.[11]

3.8 | Screening and monitoring requirements for PsA therapies

The expert panel suggested that before initiation of any systemic therapy, a practical approach should be adopted to monitor PsA patients based on medical history, physical examination, and tests (laboratory and imaging). The expert panel opined that monitoring of systemic therapies is crucial to maximize the benefits and minimize the risks associated with these drugs.

Owing to an increased risk of hepatotoxicity and renal toxicity associated with most systemic DMARDs, experts recommended monitoring tests including complete blood count, comprehensive liver function tests, renal function test, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum creatinine levels.

As most bDMARDs are immunomodulators, there is a high risk of serious infections, including tuberculosis, hepatitis, and human immunodeficiency virus (HIV). Therefore, it is important that patients are routinely screened for tuberculosis (QuantiFERON), hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV prior to initiating any biologic therapy.

Furthermore, patients should be assessed for their vaccination status before initiating any systemic therapy. Routine vaccination for pertussis and inactivated influenza, pneumococcal, and HBV is recommended in high-risk patients and in highly prevalent regions at baseline. Varicella-zoster antibody (IgG) test, especially in patients taking JAKi, should be conducted at baseline. Live vaccines should be avoided during treatment with biologics.

In accordance with the recommendations provided by the Saudi guideline and GRAPPA 2015 and evidence from the literature, the expert panel agreed upon consensus statements on screening and monitoring requirements for PsA therapies presented in Table 5.

3.9 | Management of comorbidities

Identifying comorbidities is critical to the optimal management and treatment of PsA. Common comorbidities in patients with PsA include CVD, obesity, metabolic syndrome, hypercholesterolemia, hypertension, diabetes mellitus, chronic kidney disease, malignancy, osteoporosis, non-alcoholic fatty liver disease (NAFLD), and depression. Moreover, some comorbidities such as inflammatory bowel disease (IBD) and ophthalmic disease (eg uveitis) might present as extra-articular manifestations of disease.

TABLE 2 Consensus recommendations for treatment of PsA domains

Domain	Recommended therapeutic options (strongly recommended)	Other therapeutic options (conditionally recommended)	To be avoided (strongly not recommended)
Peripheral arthritis DMARD-naïve[9,11,33]	• csDMARD • TNFi • PDE-4i • IL-12/23i • IL-17i • IL-23i • JAKi	• NSAIDs • GCCs (oral or IA) • CTLA-4 Ig	
• Peripheral arthritis DMARD inadequate response[9,10,34,48,49]	• TNFi • PDE-4i • IL-12/23i • IL-17i • IL-23i • JAKi	• NSAIDs • GCCs (oral or IA) • csDMARD • CTLA-4 Ig	
• Peripheral arthritis, inadequate response to biological treatment[9,54]	• TNFi • IL-17i • IL-12/23i • IL-23i • JAKi	• NSAID • GCC (oral and IA) • PDE-4i • CTLA-4 Ig	
• Axial PsA[9,50–52]	• NSAIDs and simple analgesia • Physiotherapy • TNFi • IL-17i • JAKi	• GCC injection for sacroiliac joints • Bisphosphonate	• csDMARD • IL-12/23i
• Enthesitis[9,10,49,58–62]	• TNFi • IL-17i • JAKi • IL-23i • IL-12/23i	• NSAIDs • physiotherapy • MTX • CTLA-4 Ig • PDE-4i	
• Dactylitis[9,54,58,62,63]	• TNFi • IL-17i • IL12/23i • IL-23i • JAKi • PDE-4i	• NSAIDs • GCCs injections • MTX • CTLA-4 Ig	
• Nail disease[9,10,64–66,68,69]	• TNFi • IL-17i • PDE-4i • IL-12/23i • IL-23i		
• Skin disease (plaque)[9,119–123]	• Topical therapies, phototherapy • Acitretin • csDMARDs (MTX, LEF, CSA) • TNFi • IL-12/23i • IL-17i • IL-23i • JAKi • PDE-4i		

Abbreviations: CSA, cyclosporine; CTLA-4 Ig, cytotoxic T lymphocyte-associated antigen-4 immunoglobulin; DMARD, disease-modifying antirheumatic drug; GCC, glucocorticoids; IA, intra-articular; IL-12/23i, interleukin-12/23 inhibitor; IL-17i, interleukin-17 inhibitor; IL-23i, interleukin-23 inhibitor; IV, intravenous; JAKi, Janus kinase inhibitor; LEF, leflunomide; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; PDE-4i phosphodiesterase-4 inhibitor (apremilast); SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.

3.9.1 | CVD

The risk of major adverse cardiovascular events has been found to be higher in patients with PsA not prescribed DMARDs compared to the general population or those with psoriasis only.[71,72] Based on clinical evidence and GRAPPA 2020 recommendations, JAKi, ustekinumab, IL-17i, IL-23i, abatacept could be considered as treatment options in management of PsA patients with comorbid CVD.[14,54,73–76]

GRAPPA recommends caution with the use of TNFi, glucocorticoids and NSAIDs in patients with congestive heart failure (CHF).[9]

3.9.2 | Obesity and metabolic syndrome

GRAPPA 2020 recommends that physicians should be cautious about prescribing glucocorticoids to patients with metabolic syndrome, and methotrexate to patients with obesity and metabolic syndrome.[14,54]

TABLE 3 Consensus statements on efficacy/safety profile of non-biologic pharmacological therapies

Symptomatic treatments

NSAIDs
- In PsA patients with peripheral arthritis, NSAID monotherapy without DMARDs should not exceed 1 mo if disease activity persists.[10]
- In the case of axial or entheseal involvement, NSAID therapy may be continued for up to 12 wks if relief has already been achieved after 4 wks.[10]
- Because of the potential for side effects (eg gastrointestinal complications, hepatic complications, allergic complications, cardiovascular complications and chronic kidney disease), NSAIDs should be used with caution.
- NSAIDs such as celecoxib are contraindicated in patients with hypersensitivity to celecoxib, patients with history of asthma, urticaria, or other allergic type of reactions after taking NSAIDs.
- NSAID use should be avoided during the perioperative period in the setting of coronary artery bypass surgery.

GCCs
- Systemic GCCs: may be associated with skin flares.
- Should be used with caution, especially when treatment is being tapered for the potential worsening of skin symptoms.
- Intra-articular injection of GCCs may rarely result in depigmentation.[124]

csDMARDs

Methotrexate
- Should be prescribed at an optimal dose of 25 mg per wk and with folate supplementation; if improvement does not exceed 50% of a composite measure for PsA within 3 mo or the treatment target is not reached within 6 mo, JAKi or bDMARD can be added to MTX treatment.
- Common adverse effects: gastrointestinal manifestations, hepatotoxicity, dizziness, photosensitivity.
- Should be used with caution in patients with impaired renal function, ascites pleural effusion and avoided in pregnant women due to its teratogenic effects.
- Other contraindications: liver disease, immunodeficiency syndrome, pre-existing blood dyscrasias and in patients with hypersensitivity to MTX.

Leflunomide
- Effective and safe in the management of PsA, particularly in reducing tenderness, pain, fatigue, dactylitis, and skin disease in patients with PsA.[125]
- Common adverse effects: diarrhea, nausea, headache, rash, respiratory infection, abnormal liver enzymes.
- Should be used with caution in patients with severe infections.
- Caution should be taken for its use in pregnant women and in patients with severe hepatic impairment.

TABLE 3 (Continued)

Sulfasalazine
- Shows greater improvement in patients with symmetrical polyarticular peripheral arthritis.
- Shows significant improvement in joint scores and reduction in disease activity as early as the 4th wk of treatment.[126]
- Well tolerated and safe in patients with PsA at a dose of 2.0 g/d.
- Patients with PsA who are known or suspected to have COVID-19, should continue using sulfasalazine.[127,128]
- Common adverse events: gastric upset, skin rashes, headache, and liver disorders.
- Should be used with caution in patients with severe allergy, bronchial asthma, and glucose-6-phosphate dehydrogenase deficiency (G6PD).
- Should be avoided in patients with intestinal or urinary obstruction, porphyria, and hypersensitivity to sulfasalazine.

tsDMARDs

Apremilast
- Effective in the treatment of biologic-naïve patients with PsA and has a tolerable safety profile.
- Most common adverse effects: diarrhea and nausea.
- Should be used with caution in PsA patients with depression.
- Does not require routine therapeutic monitoring.
- Safe and effective therapeutic option in the HIV-infected population with psoriatic arthritis.

Tofacitinib
- Safe and effective in the management of csDMARD-IR/ TNFi-naïve and TNFi-IR patients and is effective in PsA patients with enthesitis and dactylitis.
- Patients with recurrent deep-vein thrombosis and those at high risk of shingles infection should exercise caution.
- Has an acceptable safety profile with a low incidence of serious infections, malignancies, cardiovascular events, and gastrointestinal complications.

Upadacitinib
- Safe and effective in the management of patients with active PsA.
- Common adverse effects: upper respiratory tract infections, nausea, cough, and pyrexia.
- Patients with active and serious infections, malignancy, thrombosis, and gastrointestinal perforation should be treated with caution.

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; COVID-19, coronavirus disease-2019; GCC, glucocorticoids; HIV, human immunodeficiency virus; IR, inadequate response; JAKi, Janus kinase inhibitor; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; TNF, tumor necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

3.9.3 | Hypercholesterolemia

He expert panel emphasized the importance of lipid-lowering drugs and nutritionist referral in PsA patients with comorbid hypercholesterolemia. Evidence suggests that tofacitinib should be used with caution in PsA patients with comorbid hypercholesterolemia.[77]

TABLE 4 Consensus statements on efficacy/safety profile of biologic pharmacological therapy

TNFi

- Adalimumab at a dose of 40 mg (at baseline, wks 2 and 4, and every 4 wks thereafter), can significantly improve joint and skin manifestations and reduce radiographic progression in patients with active PsA, by achieving clinical response by 6 mo.[129,130]
- Etanercept (25 mg twice weekly) can significantly reduce the signs and symptoms of PsA and achieve clinical response by wk 12, with efficacy lasting from 48 wks to 2 y.[108,109]
- Infliximab, at a dose of 5 mg/kg (at wks 0, 2, and 6, and every 8 wks thereafter), significantly inhibits the progression of radiographic damage in patients with active PsA as early as 6 mo after starting treatment, and the beneficial effect continues through 1 y of treatment.[131]
- Infliximab at a dose of 5 mg/kg significantly improves the signs and symptoms of arthritis, psoriasis, dactylitis, and enthesitis in patients with active PsA resistant to DMARD therapy.[132,133]
- Certolizumab pegol (200 mg every 2 wks or 400 mg every 4 wks) provides rapid improvement in the signs and symptoms of PsA, including joints, skin, enthesitis, dactylitis, and nail disease. It can reduce the progression of structural damage for up to 2 y in PsA patients with/without prior TNFi exposure.[134,135]
- Golimumab (100 mg) also inhibits radiographic progression as early as 6 mo and is effective in maintaining clinical improvement for 5 y.[136]

- TNFi therapy should not be initiated or continued in the presence of serious active infection, but it can be restarted once the infection has clinically resolved.
- TNFi therapy should be used with caution in patients at high infection risk:
  - Active mycobacterial infection should be adequately treated before TNFi therapy is started.
  - HIV or HCV infection should not preclude treatment with TNFi therapy, although treatment should only be commenced in those with well-controlled disease and with appropriate monitoring under the care of a hepatologist or HIV specialist. Of note, etanercept has been shown to be safe in PsA patients with HCV.
  - TNFi therapy in those with chronic HBV should be approached with caution, given the potential risk of reactivation and fulminant hepatitis.
- TNFi therapy should be avoided in patients with a current or prior history of malignancy.
- Caution should be exercised in patients with serious infections and demyelinating diseases or systemic lupus erythematosus.

IL-12/23i

- Ustekinumab (SC) at a dose of 45 mg or 90 mg (weight-dependent) reduces the signs and symptoms of articular and dermatological manifestations in PsA patients with and without TNFi therapy exposure and is well tolerated through 16 wks of therapy.[137]
- Adverse effects of IL-12/23i: upper respiratory tract infections, nasopharyngitis, back pain, headache, injection-site reactions, myalgia, fatigue, and rarely severe infection and malignancy.
- Caution should be taken in patients with serious infections and malignancy.
- Ustekinumab is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of its excipients.

(Continues)

TABLE 4 (Continued)

IL-17i

- Secukinumab (SC) improves signs and symptoms in multiple clinical domains in patients with active PsA and is well tolerated through 5 y of therapy.[138]
- Secukinumab (150–300 mg) is well tolerated for long-term treatment.
- Ixekizumab is a highly effective treatment for active PsA patients, especially those previously exposed to csDMARDs and TNFi therapies.[38,139]
- Most common adverse effects associated IL-17i: upper respiratory tract infections and injection-site reactions.
- IL-17i should be used with caution in patients with concomitant IBD and severe infections.
- IL-17i are contraindicated in patients with serious allergic reactions to the molecule or its recipients.

IL-23i

- Guselkumab improves joint symptoms significantly, with more than one-third of patients achieving ACR50 by wk 24.[140]
- Guselkumab shows significant improvement in inhibition of radiographic progression of joint structural damage and resolving enthesitis, dactylitis in patients with active PsA at 24 wks.[140,141]
- Common adverse events of guselkumab: hypersensitivity reactions, including anaphylaxis and upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections.

CTLA4-Ig

- Abatacept can be effective in patients with PsA refractory to DMARDs.[49]
- Most common adverse effects associated with abatacept include headache, upper respiratory tract infection, nasopharyngitis, and nausea.

Abbreviations: ACR, American College of Rheumatology; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4-immunoglobulin; DMARD, disease-modifying antirheumatic drug; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IL-12/23i, interleukin-12/23 inhibitor; IL-17i, interleukin-17 inhibitor; IL-23i, interleukin-23 inhibitor; PsA, psoriatic arthritis; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.

3.9.4 | Hypertension

Statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II blockers are preferred treatment options in patients with PsA and hypertension.[9] Caution should be taken when prescribing NSAIDs, cyclo-oxygenase-2 (COX2) inhibitors, or prednisone, as they are associated with an increased risk of CVD.[9,78]

3.9.5 | Diabetes mellitus

The prevalence of type 2 diabetes mellitus in patients with PsA has been reported to be between 6.1% and 20.2% with a higher risk noted in women with more severe forms of PsA.[79] When selecting the treatment for PsA in such patients, most guidelines recommend taking caution with glucocorticoids and methotrexate, as they could worsen glycemic homeostasis and/or influence cardiovascular risk factors such as arterial hypertension.[9,11]

TABLE 5 Consensus statements on screening and monitoring requirements for PsA therapies

Recommendations
• Recommended laboratory tests prior to initiation of a biologic treatment include:[9,13] o Complete blood count: hemoglobin, hematocrit, white blood cell count, white blood cell differentiation, and platelet count o Comprehensive liver function tests: direct bilirubin, total bilirubin, ALP, ALT, and GGT o Renal function test • Other important tests include ESR, CRP, and serum creatinine.
• Screening for HIV, HBV, HCV, and tuberculosis (QuantiFERON preferable) should be strongly considered, in accordance with local guidelines and standards of medical practice before initiation of therapies that may potentially alter normal immune response.[9]
• Inclusion of varicella-zoster antibody (IgG) test, especially in patients taking JAKi, for baseline tests, should be considered.[142]
• Chest X-ray as a baseline monitoring test for all drugs should be strongly considered.
• A general screening questionnaire for malignancy should be considered on a case-by-case basis.
• Given the increased prevalence and incidence of CVD and diabetes among patients with PsA, regular screening is recommended (eg Framingham risk score or ASCVD for CVD risk assessment).[9]
• Screening for depression and anxiety among patients with PsA should also be considered.[9]
• Given the association of ophthalmic disease with spondylarthritis and an increased risk of IBD among patients with PsA, consideration of screening for eye disease and • Gastrointestinal disease is recommended as a part of the review of systems, as well as consideration of appropriate referral, as applicable.[9]
• Monitoring tests should be conducted every 1–3 mo during treatment and based on clinical judgment.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; GGT, G-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IgG, immunoglobulin G; JAKi, Janus kinase inhibitor; PsA, psoriatic arthritis.

3.9.6 | IBD

There is increased prevalence of IBD and subclinical bowel inflammation among patients with PsA.[80,81] Sulfasalazine, TNFi, and tofacitinib (only ulcerative colitis) are approved treatments for IBD. According to 2018 ACR/NPF guidelines, for patients with active PsA and concomitant active IBD who are DMARD-naïve, monoclonal TNFi are the preferred choice.[11] In patients who are contraindicated for TNFi, IL-12/23i can be prescribed. The use of NSAIDs and IL-17i should be avoided, as they may exacerbate IBD symptoms.[82,83] Interim analysis reports from a phase II study suggest that guselkumab could be effectively used in patients with Crohn's disease.[84] A long-term study on the efficacy of adalimumab in the treatment of patients with Crohn's disease with intolerance or inadequate response to infliximab reported sustained clinical remission and response with adalimumab maintenance therapy.[85]

3.9.7 | Uveitis

The management of concomitant uveitis in PsA patients varies depending on the severity of the disease and its impact on daily activities.[86] Both infliximab and adalimumab are effective treatment options;[87–89] certolizumab pegol/golimumab has shown moderate success, while etanercept has demonstrated only limited success.[90] Secukinumab showed promising results in phase II clinical trials; however, primary efficacy endpoint was not met in the phase III study.[91,92] The efficacy of IL-17i, IL-12/23i, and JAK/STAT (signal transducer and activator of transcription) inhibitors is currently under evaluation.[91,92]

3.9.8 | Depression

The prevalence of depression and anxiety among patients with PsA is 9% to 36% and 15% to 30%, respectively.[93,94] As both depression and anxiety may affect pain perception, QoL, and treatment outcomes; it is important to take appropriate screening measures and treatment decisions in such patients. Apremilast should be used with caution in patients with PsA and comorbid depression.[95]

3.9.9 | Hyperuricemia and gout

Hyperuricemia is common in patients with PsA, especially in those with longer CVD, metabolic syndrome, and disease duration.[96–98] It is therefore important to regularly monitor serum uric acid levels in patients with PsA.[97] Gout is an important differential diagnosis of PsA and, therefore, awareness about its increased incidence in this population is critical.[99]

3.9.10 | Hypothyroidism

Due to increased incident cases of hypothyroidism, thyroid dysfunction, positive antithyroid peroxidase antibodies (AbTPO), and appearance of a hypoechoic thyroid pattern in patients with PsA, especially women, it is important to evaluate AbTPO levels, thyroid function, and thyroid ultrasound, with regular follow-up visits.[100,101]

3.9.11 | Osteoporosis

Screening for osteoporosis in psoriatic patients is performed by measuring bone mineral density through dual-energy X-ray absorptiometry (DEXA) or assessing the Fracture Risk Assessment (FRAX) score. For management, specific guidelines should be followed for patients treated with chronic systemic glucocorticoids, as it may modify bone mineral density due to bone loss.[102]

3.9.12 | Malignancy

Given the potential risk of de novo or recurrent malignancy being associated with the use of TNFi, regular screening is recommended, especially in patients with a history of cancer.[9] In contrast, IL-17i, abatacept have a better safety profile for malignancy and are preferred treatment options in these patients.

3.9.13 | Fatty liver disease

Liver disease, particularly NAFLD, has an increased prevalence in patients with psoriasis and PsA.[103] Given the potential risk of liver damage with specific PsA treatments, regular monitoring of liver function abnormalities is deemed necessary. Liver biopsy should also be considered, based on the presence or absence of risk factors for hepatotoxicity and cumulative methotrexate dose.[9,11] Furthermore, caution should be taken when prescribing methotrexate, leflunomide, sulfasalazine, and NSAIDs in patients with established liver disease due to the increased risk of hepatotoxicity.

3.9.14 | Chronic kidney disease

Methotrexate should be avoided in patients with significant renal insufficiency or end-stage renal disease on hemodialysis, given that renal impairment is a major risk factor for developing methotrexate toxicity.[104] NSAIDs should also be avoided, given that they may increase the risk for acute kidney injury.[105]

TABLE 6 Consensus statements on management of comorbidities

Comorbid condition/s	Treatment options/referral/monitoring	Treatment requiring caution
Cardiovascular disease and congestive heart failure	JAKi, ustekinumab, IL-17i, IL-23i, abatacept[73–76]	NSAIDs, GCCs, TNFi (TNFi should be avoided in patients with severe CHF [NYHA class III and IV] and should be used with caution in patients with mild CHF [NYHA class I and II])[9,54,143,144]
Obesity and metabolic syndrome	Weight reduction, nutritionist referral, obesity/endocrine clinic referral	MTX, GCCs[9]
Hypercholesterolemia	Lipid-lowering agents, nutritionist referral	Tofacitinib[77]
Hypertension	Statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II blockers[9]	NSAIDs, GCCs[9]
Diabetes mellitus	Hypoglycemic medications	MTX, GCCs[9]
IBD	TNFi (excluding etanercept) for UC (tofacitinib, IL-12/23i) IL-23i[84]	IL-17i
Uveitis	TNFi (especially adalimumab and infliximab), MTX	NSAIDs, IL-17i[145]
Depression	Psychiatry referral	Apremilast
Hyperuricemia and gout	Monitoring serum uric acid levels Urate-lowering therapy if indicated	
Thyroid disease	Routine thyroid tests/endocrine referral	
Osteoporosis	Monitor with DEXA as indicated in non-PsA patients	GCCs
Malignancy	Oncology referral, IL-17i, abatacept	All biological agents
Fatty liver disease	GI referral Weight loss Dietician referral	NSAIDs, SSZ, MTX, LEF, tofacitinib[54]
Chronic kidney disease	Nephrologist referral	NSAIDs, MTX[54]
HBV	Ustekinumab GI referral, monitor HBV PCR (once a mo for first 3 mo and every 3 mo thereafter)[146]	NSAIDs, MTX, LEF, biologics (for carriers)[54]
HCV	GI referral, monitor HCV PCR (once in every 3-6 mo)[146]	NSAIDs, MTX, LEF, biologics (for carriers)[54]
Tuberculosis	IL-17i, abatacept, referral to respiratory or infectious disease specialist	TNFi especially infliximab

Abbreviations: CHF, congestive heart failure; DEXA, dual-energy X-ray absorptiometry; GCCs, glucocorticoids; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; IL-12/23i, interleukin-12/23 inhibitor; IL-17i, interleukin-17 inhibitor; IL-23i, interleukin-23 inhibitor; JAKi, Janus kinase inhibitor; LEF, leflunomide; MTX, methotrexate; NHYA, New York Heart Association; NSAIDs, non-steroidal anti-inflammatory drugs; PCR, polymerase chain reaction; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

3.9.15 | Serious infections

There is a high risk of serious infections, including tuberculosis, hepatitis, and HIV, associated with the use of certain PsA treatments—including TNFi.[9] Due to the low incidence of serious infections observed with IL-12/23i, IL-17i, and abatacept in comparison to TNFi, the former are preferred treatment options for PsA.[9]

Consensus statements on the management of comorbidities in patients with PsA are presented in Table 6.

3.9.16 | Immunization

Immunization status of the patient should be assessed. Routine vaccination for pertussis and inactivated influenza, pneumococcal, and HBV (in high-risk patients and in highly prevalent regions) should be performed at baseline.[9]

4 | CONCLUSION

The present consensus statements for the pharmacological management of PsA are in corroboration with established global guidelines on the different aspects of PsA, especially highlighting the management of PsA and associated comorbid conditions and monitoring of therapies in patients with PsA. There is a scarcity of such consensus-based statements in the Arab world. Furthermore, our consensus statements are aligned with the most recently published Saudi consensus recommendations.[106] Our detailed consensus recommendations can help physicians and healthcare professionals in the UAE to make informed treatment decisions, improvise treatment strategies, monitor therapies, as well as effectively manage comorbidities in patients with PsA.

AUTHOR CONTRIBUTIONS

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

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CONFLICT OF INTEREST

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ORCID

Khalid A. Alnaqbi https://orcid.org/0000-0001-5875-4663
Rajaie Namas https://orcid.org/0000-0003-0353-895X
Jamal Al-Saleh https://orcid.org/0000-0002-7569-003X

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The frequency of fibromyalgia in familial Mediterranean fever and its impact on the quality of life

Duygu Altıntas[1] | Meltem Alkan Melikoglu[2]

[1]Physical Medicine and Rehabilitation, Sivas State Hospital, Sivas, Turkey

[2]Rheumatology Division, Physical Medicine and Rehabilitation Department, Ataturk University School of Medicine, Erzurum, Turkey

Correspondence
Meltem Alkan Melikoglu, Rheumatology Division, Physical Medicine and Rehabilitation Department, Ataturk University School of Medicine, Erzurum, Turkey.
Email: mamelikoglu@gmail.com

Abstract

Background and aim: Concomitant fibromyalgia syndrome (FMS) has been known to be more frequent in patients with several rheumatic diseases. In this study, our aim was to investigate the prevalence of FMS in patients with familial Mediterranean fever (FMF), to analyze the possible factors related to this frequency, and to evaluate the impact of FMS on the functionality and quality of life (QoL) of the patients with FMF.

Patients and methods: One hundred cases with FMF and 100 controls were included to this case-control study. FMS coincidence was investigated in all participants according to revised 2016 classification criteria. Demographic features, FMF disease duration, FMF gene mutations, drugs used, attack frequency per year, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum fibrinogen levels were recorded. FMF disease severity was assessed by International Severity Scoring System for Familial Mediterranean Fever (ISSF). For the assessments of QoL and functioning, FMF-QoL, Short form 36 (SF-36), and Health Assessment Questionnaire-Disability Index (HAQ-DI) were used, and for the assessment of FMS impact, the fibromyalgia impact questionnaire (FIQ) were used.

Results: We found an FMS frequency of 33% in patients with FMF in our study using the current FMS classification criteria. This result was significantly higher than in age- and gender-similar controls (6% FMS frequency; $P < 0.05$). The number of woman patients and FMF disease duration were significantly higher in patients with FMF + FMS than in patients with only FMF ($P < 0.001$). There was no significant difference in ISSF scores, ESR, CRP, and fibrinogen levels, management regimens, and FMF gene mutation distributions between FMF + FMS and FMF groups. FMF attack frequency was reported as significantly higher in FMF + FMS patients than in others ($P < 0.000$). In spite of similar FMF-QoL scores, there were significant differences in HAQ-DI and SF-36 scores between groups ($P < 0.05$). Higher impact of FMS presented negative correlation with functioning and general health, and positive correlation with QoL in FMF + FMS ($P < 0.05$).

Conclusion: Concomitant FMS was a common clinical problem in patients with FMF regardless of the severity and characteristics of FMF. The FMS impact may affect function and QoL in patients of FMF. Considerations of the FMS component in the management of FMF may contribute to the holistic approach to FMF.

KEYWORDS
familial Mediterranean fever, fibromyalgia syndrome, functionality, quality of life

1 | INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread musculoskeletal pain frequently accompanied by sleep disturbances and fatigue.[1] The other symptoms of FMS such as joint stiffness, depression, anxiety, and cognitive dysfunction limit daily life, affect physical activity, and reduce the ability to cope with life.[2] It is a relatively common syndrome that can affect up to 7% of the general population.[3,4] Concomitant FMS has been known to be more frequent in patients with several rheumatic diseases. FMS has been reported in 14%-37% of patients with distinct rheumatic diseases such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, and Behçet disease.[1,5,6,7] Although the interactions between FMS and the more common rheumatic diseases such as rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus have been well studied, the relationship between FMS and relatively less frequent disorders such as autoinflammatory diseases is limited. The first group to be identified in this group of diseases was the periodic fever diseases, of which Familial Mediterranean fever (FMF) is the most common.[8] The studies investigating the prevalence of FMS in patients with FMF and the effects of this coincidence on FMF patients are limited in the literature. Previous studies on FMS in FMF used old FMS classification criteria and/or included a limited number of FMF cases.

In this study, our primary aims were to investigate the FMS frequency in patients with FMF, to analyze the possible factors related to this frequency and to evaluate the impact of FMS on the functionality and quality of life (QoL) of the patients with FMF.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This investigation was planned as a case-control study, conducted in accordance with the 1989 Declaration of Helsinki and approved by the Local Ethics Committee. Written informed consent was obtained from the participants. After calculating the sample size as 92 (80% power and 95% reliability), 100 consecutive cases with FMF and 100 individuals without any known diseases as controls were included for groups between October 2019 and April 2020.[9] Cases with FMF (diagnosed according to the Tel-Hashomer criteria, as revised by Livneh et al[10]) whose age ranges were between 18-65 years were included. Exclusion criteria were defined as any history of malignancy or any other rheumatic disease except FMS, any other chronic diseases, and diagnosis of amyloidosis and concomitant psychiatric drug administration.

The participants were screened for FMS and its coincidence was investigated in all participants according to revised 2016 FMS classification criteria.[11]

2.2 | Evaluations

For the clinical evaluations, demographic features including age and gender, and disease-related features including disease duration, FMF gene mutations, drugs used, and attack frequency per year were recorded. As laboratory evaluations erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP mg/L), and serum fibrinogen (mg/dL) levels of the patients with FMF were obtained by using standard laboratory methods.

FMF disease severity was assessed using the International Severity Scoring System for Familial Mediterranean Fever (ISSF). Total score may change from 0 to 10; severe, intermediate and mild disease are represented by scores of ≥6, 3-5, and ≤2, respectively.[12]

For the assessments of QoL and functioning in cases with FMF, FMF-QoL, Short form 36 (SF-36), and Health Assessment Questionnaire-Disability Index (HAQ-DI) were used. The FMF-QoL Scale includes 20 questions to evaluate the health status in relation to physical, social, recreational, psychological, and sleep impact factors.[13] Total score may change from 0 to 80 where a higher score represents poor QoL.[14]

The SF-36 has 36 items with eight subscales. The first four subscales evaluate physical functioning, role limitations—physical, bodily pain, and general health perception and the second four subscales evaluate the limitations due to emotional problems, vitality, mental health, and social functioning. For each subscale a score can range from 0 (the worst) to 100 (the best). As a widely used scale, it was validated to several languages one of which was Turkish.[15]

HAQ-DI evaluates the functional impairment of an individual and consists of 20 components in eight domains (dressing and grooming, arising, eating, walking, hygiene, grip, reach, and other common activities). The answers may differ from 0 to 3; no difficulty (0), with some difficulty (1), with much difficulty (2), unable to do (3). The HAQ-DI score can be between 0 and 3, with higher scores representing higher disability.[16,17] Scores of 0 to 1 are generally considered to represent mild to moderate difficulty, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[1]

The impact of FMS was evaluated by a fibromyalgia impact questionnaire (FIQ), which has been one of the most used questionnaires.[18] A total score of the scale can range between 0 and 100, higher scores indicate a more severe impact.

2.3 | Statistical analysis

Statistical analyses were performed using the SPSS for Windows 22 package program (Armonk, NY, USA). Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test normality. Mean ± standard deviation, median (minimum-maximum), numbers and percentages were used for general descriptive statistics. Mann-Whitney *U*, Student

t, χ^2, McNemar, and Fisher tests were evaluated for the comparison of continuous and nominal variables between groups. One-way analysis of variance and Kruskal-Wallis tests were also analyzed for further evaluations. Pearson's correlation and regression analysis was performed to assess the relation between fibromyalgia impact and QoL assessments. Statistical significance was set at *P* values less than 0.05.

3 | RESULTS

The demographic characteristics of the participants are shown in Table 1. The age and gender distributions were similar between cases with FMF and controls. FMS frequency was statistically higher in cases with FMF (33%) than age- and gender-similar controls (6%) ($P<0.05$).

Comparisons between FMF patients with or without FMS are shown in Table 2. Although there was no significant difference in age profiles between FMF cases with and without FMS, the number of woman patients was significantly higher in the FMF+FMS group ($P<0.000$).

In terms of FMF-related factors, FMF disease duration was significantly longer in cases with FMF+FMS than in cases with only FMF ($P<0.001$). Colchicine dose (minimum 0.5 mg/day, maximum 2 mg/day) and the number of cases with non-response to colchicine were similar between groups. The FMF gene mutations were homozygous, heterozygous, double heterozygous, and negative in 20%, 30%, 48%, and 2%, respectively, for all patients with FMF (the first three mutations were M694V heterozygous in 51 patients, V726A was heterozygous in 29 patients, and M694V was homozygous in 18 patients) and there was no significant difference in their distributions between the FMF and FMF+FMS groups. Attack frequency in the previous 6 months was reported as significantly higher in FMF+FMS patients than in patients with only FMF ($P<0.000$). There was no significant difference in ISSF scores, and in ESR, CRP, and fibrinogen levels between groups. FMF-QoL scores were not statistically different between patients with FMF+FMS and patients with only FMF. However, there were significant differences in the HAQ-DI and SF-36 scores between groups ($P<0.05$) (Table 2).

We also analyzed the correlation between FIQ and QoL assessments in patients with FMF+FMS. There were statistically significant correlations between FIQ and SF-36 physical functioning and general health subscales and FMF-QoL assessment ($P<0.05$, $r=-0{,}478$; $P<0.05$, $r=-0.469$ and $P<0.01$, $r=0.429$, respectively). The regression analysis also revealed that FIQ score had a significant effect on FMF-QoL ($P\leq 0.00$, $R=0.346$).

TABLE 1 Demographic features of the participants and FMS coincidence

	FMF patients (n = 100)	Controls (n = 100)	*P* value
Age (years)			
Mean ± SD (Min-max)	31.3 ± 11.2 (18-63)	33.1 ± 12.5 (19-65)	NS
Gender			
Male, n (%)	42 (42)	42 (42)	NS
Female, n (%)	58 (58)	58 (58)	
FMS; +, n (%)	33 (33)	6 (6)	**<0.05**
Female/male	(29/4)	(5/1)	**<0.05**
FMS; −, n (%)	67 (67)	94 (94)	**<0.05**

Abbreviations: FMF, familial Mediterranean fever; FMS, fibromyalgia syndrome; max, maximum; min, minimum; NS, not significant; SD, standard deviation.

4 | DISCUSSION

In this study we aimed to evaluate the FMS frequency in patients with FMF, to analyze the possible factors related to this co-existence and to evaluate the impact of FMS on QoL of the patients with FMF.

We found FMS frequency to be 33% in patients with FMF in our study using current FMS classification criteria. This result was significantly higher than age- and gender-similar controls, which had an FMS frequency of 6%. FMS has been reported to affect up to 7% of the general population and concomitant FMS has been reported in 14%-35% of the cases with several rheumatic diseases.[1] Few studies have investigated FMS comorbidity in patients with autoinflammatory diseases such as FMF, which is the most common. Cengiz et al found FMS frequency of 23.4% for an FMF group and 4.3% for the control group.[19] Haliloglu et al investigated FMS coincidence in a large group of patients with several rheumatic diseases and found an FMS frequency of 7.1% of 14 patients with FMF.[20] These different results may be related to the different FMS classification criteria used. Besides these limited number of studies directly investigating FMS in FMF, there have also been studies researched parameters that can be indirectly associated with FMS, such as fatigue, sleep quality, and depression, in these patients. Duruoz et al showed that scores presenting pain, fatigue, poor sleep quality, and depression in patients with FMF were significantly higher than in the control group.[21] Considering these data together, FMS seems to be an important co-existent clinical problem in patients with FMF.

In our study, although the age profile was similar between patients with FMF and patients with FMF+FMS, the number of woman patients was higher in the second group, as expected.

In terms of FMF disease-related factors, FMF disease duration was significantly longer in patients with FMF+FMS than in the others. FMS, a well-known to be concomitant with several chronic diseases, may also be expected to be accompanied by longer disease duration in patients with FMF. Although not directly FMS, fatigue, which is a common feature of FMS, was investigated in FMF by Duruoz et al and disease duration was found to be one of the most predictive clinical parameters contributing fatigue in these patients.[21] Our results may indicate that longer FMF disease duration is associated with higher FMS frequency in these patients.

TABLE 2 The comparisons between FMF patients with or without FMS

	FMF (n = 67)	FMF + FMS (n = 33)	*P* value
Age (years)	29.8 ± 10.2	34.1 ± 12.0	NS
Gender			
Female/male	29/38	29/4	<0.000
Female/male	(43.3/56.7)	(87.9/12.1)	
FMF disease duration (years)	10.6 ± 5.8	17.0 ± 9.0	<0.001
Cases with non-response to colchicine	4 (6)	2 (6)	NS
Attack frequency in last 6 months	0/6 1.8 ± 1.7	0/12 4.0 ± 3.1	<0.000
ISSF			
Mild	38 (74.5)	13 (25.5)	NS
Intermediate	27 (60)	18 (40)	
Severe	2 (50)	2 (50)	
ESR (mm/h)	14.5 ± 1.1 9 (1-74)	13.3 ± 9.4 13 (1-31)	NS
CRP (mg/L)	26.85 ± 6.34 3.28 (0.72-170)	9.75 ± 4.8 3.78 (3-82)	NS
Fibrinogen (mg/dL)	351 ± 119 330 (185-636)	337 ± 74 312 (211-501)	NS
FMF-QoL score	68.7 ± 19.4 (30-100)	68.4 ± 15.1 (31-95)	NS
HAQ-DI score	0.53 ± 1.16 (0-5.33)	2.23 ± 2.87 (0-12)	**<0.05**
SF-36 Physical functioning	77.9 ± 17.6 (20-100)	65.3 ± 2.7 (15-100)	**<0.05**
SF-36 Role-Physical	52.6 ± 39.4 (0-100)	38.6 ± 40.1 (0-100)	NS
SF-36 Role-Emotional	64.1 ± 41.6 (0-100)	31.3 ± 39.1 (0-100)	**<0.05**
SF-36 Vitality	52.9 ± 19.9 (5-95)	34.1 ± 19.7 (0-70)	**<0.05**
SF-36 Mental health	57 ± 18.1 (1-92)	42.9 ± 19.7 (0-80)	**<0.05**
SF-36 Social functioning	68.7 ± 21.7 (25-100)	51.7 ± 21.6 (13-100)	**<0.05**
SF-36 Bodily pain	67.3 ± 21.1 (10-100)	43.8 ± 19.5 (0-90)	**<0.05**
SF-36 General health	51.2 ± 22.9 (10-90)	35.8 ± 18 (0-85)	**<0.05**

Note: Values are given as number (percentage); mean ± standard deviation, minimum-maximum, or as median (minimum-maximum).

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, Familial Mediterranean fever; FMS, fibromyalgia syndrome; HAQ-DI, Health Assessment Questionnaire Disability Index; ISSF, International Severity Scoring System for Familial Mediterranean Fever; QoL, Quality of life; SF-36, Short form-36.

The distribution of FMF gene mutations in our cohort presented similar results to our general population.[22] In our study, there was no significant difference in MEFV gene distributions between the FMF and FMF + FMS groups. This was parallel to previous studies on FMS in FMF.[19] FMF gene distribution did not seem to be a factor related to FMS in our FMF patients.

In our study, the management regimens for FMF were similar and there was no significant difference in ISSF scores, or in ESR, CRP, and fibrinogen levels between FMF and FMF + FMS groups. Similarly, in a previous study investigating FMS in FMF, FMS was not associated with the severity of FMF.[19] On the other hand, the attack frequency reported by the patients was significantly higher in FMF + FMS cases

than in cases with only FMF. In spite of the similar disease profiles presented by similar mutations, treatment regimens, laboratory assessments, and ISSF scores between groups, the higher attack frequency reported by the patients with FMF + FMS might be the result of the subjective expression of symptoms. In addition, FMS itself or related features might be factors for this frequency. Supporting this consideration, in a previous study, Onat et al investigated the addition of selective serotonin reuptake inhibitors to the treatment of 11 colchicine-unresponsive patients (three of those patients also had FMS) and demonstrated that this regimen led to a reduce in attack frequency in these patients.[23]

A recent study that aimed to determine the prevalence of FMS in patients with FMF concluded that FMS can be seen in these patients and that patients with moderate and severe FMS symptoms have increased fatigue levels and decreased QoL.[24] In our study, FMF-QoL scores were not statistically different between patients with FMF + FMS and patients with only FMF. However, there were significant differences in functional assessments between these groups. Higher impact of FMS presented a negative correlation with functioning and general health, and a positive correlation with QoL in FMF + FMS. In a previous study, it was reported that co-existing FMS reduces the QoL in FMF, mainly determined by degree of depression and fatigue rather than the disease severity.[19]

The results of our study may have some limitations and strengths in some aspects. The main limitation of our study was the homogeneous profile of the cases. Our FMF cohort might not represent all the entire spectrum of patients with FMF because they were from a single tertiary center. However, using new classification criteria for FMS in a relatively large FMF population may be the strength of our study.

The results of our study demonstrated that FMS frequency was higher in patients with FMF than in controls with a co-existence of one-third of the patients with FMF. Female gender was predominant and FMF disease duration was longer in patients with FMF + FMS than in the other group. Although age profile, gene mutations, and severity of FMF were similar between patients with FMF + FMS and patients with only FMF, the attack frequency reported by the patients was significantly higher in the FMF + FMS group. There were significant differences in functional assessments between these groups and the higher impact of FMS seemed to negatively affect function and QoL of the patients with FMF.

In conclusion; concomitant FMS was a common clinical problem in patients with FMF regardless of the severity and characteristics of FMF. The FMS impact may affect function and QoL in patients of FMF. Considerations of the FMS component in the management of FMF may contribute to a holistic approach to FMF.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception, design and data collection. Material preparation and analysis were performed by MAM and DA. The first draft of the manuscript was written by MAM and all authors commented on previous versions of the manuscript. All co-authors are fully responsible for all aspects of the study and the final manuscript in line with the IJME four criteria.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Meltem Alkan Melikoglu https://orcid.org/0000-0001-7519-9470

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ORIGINAL ARTICLE

Common mineral nutrients in ankylosing spondylitis: A 2-sample Mendelian randomization study

Xiaoya Sun[1,2] | Yujie Deng[1,2] | Yubo Ma[1,2] | Ming Shao[1,2] | Man Ni[1,2] | Tao Zhang[1,2] | Xinqi Wang[1,2] | Shanshan Xu[1,2] | Yuting Chen[1,2] | Shengqian Xu[3] | Faming Pan[1,2]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China

[2]The Key Laboratory of Major Autoimmune Diseases, Anhui Medical University, Hefei, China

[3]Department of Rheumatism and Immunity, the First Affiliated Hospital of Anhui Medical University, Hefei, China

Correspondence
Faming Pan, Department of Epidemiology & Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, 230032, China.
Email: famingpan@ahmu.edu.cn

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Abstract

Objective: The causal relationship between common mineral nutrients and ankylosing spondylitis (AS) has not been studied. So this Mendelian randomization (MR) study aims to investigate the causal association of varying levels of calcium, zinc, copper, and selenium on AS.

Design: We selected 4 elements potentially associated with the onset and development of AS as exposure factors, single nucleotide polymorphisms (SNPs) as instrumental variables, and these SNPs are independent of each other($r^2 < 0.05$) and highly correlated with each of the 4 elements ($P < 5 \times 10^{-8}$). The 2-sample MR method takes Inverse-variance weighted (IVW) and MR-Egger as the main method and Simple mode (SM), Weighted median (WM^1), and Weighted mode (WM^2) as supplementary methods to evaluate the causal effect of mineral levels on AS.

Results: The IVW analysis does not provide convincing evidence to support a causal association between calcium (odds ratio [OR] = 1.000, 95% CI = 0.994, 1.005, $P = .875$), copper (OR = 1.000, 95% CI = 1.000, 1.001, $P = .533$) and selenium (OR = 0.999, 95% CI = 0.998, 1.000, $P = .229$) and AS. The IVW (OR = 1.001, 95% CI = 1.000, 1.002, $P = .029$) and WM^1 (OR = 1.001, 95% CI = 1.000, 1.002, $P = .011$) results of zinc show that per standard deviation increment in zinc is a suggestive association with risks of AS, and MR-Egger (OR = 1.004, 95% CI = 0.996, 1.013, $P = .265$) and other supplementary methods indicate that zinc is not causally associated with AS. All MR-Egger intercept parameters and MR Pleiotropy RESidual Sum and Outlier tests demonstrated the absence of horizontal pleiotropy.

Conclusions: This study does not provide convincing evidence to support a causal correlation between calcium, zinc, copper, and selenium with AS.

KEYWORDS
ankylosing spondylitis, calcium, Mendelian randomization, selenium, zinc

Xiaoya Sun and Yujie Deng contributed equally to this work and should be considered co-first author.

1 | INTRODUCTION

Ankylosing spondylitis (AS), an inflammatory disorder that in its extreme form can lead to the bony fusion of vertebral joints, is an uncommon but well-established cause of chronic back pain.[1] The etiology and pathogenesis of AS have not been clear. Studies suggest that it may be related to a variety of factors, including heredity, immunity, chronic infection, environmental influence, and their interactions.[2] Minerals are nutrients that are essential for the composition of human tissues and for the maintenance of normal physiological functions, and are the general term for inorganic substances in the body that play a vital role in metabolism.[3] It has been found that minerals may be involved in the pathology of AS.[4–8]

A previous study has found that metal triggers conformational reorientation of a self-peptide bound to a disease-associated human leukocyte antigen-B27 (HLA-B27) subtype and suggests that metals may have a role in triggering rheumatic diseases such as AS.[4] Inflammation and the progressive fusion calcification of axial joints are typical features of AS.[9] Patients with AS often have symptoms of low bone mass, which is related to the level of calcium. In addition, unbalanced calcium homeostasis may lead to inflammation, formation of new bone tissue, and bone loss in the progress of AS.[5] However, it is unknown whether calcium level is a protective factor or a risk factor for AS. Trace elements are a key factor in maintaining a healthy immune system. Copper and zinc are indispensable functional components of many enzymes and transcriptional regulatory proteins and play an important role in the biochemical process of the body.[10] Zinc is an essential trace element, which is involved in regulating innate and adaptive immune responses. The zinc-deficient innate immune system is characterized by reducing the chemotaxis of poly-morphonuclear cells (PMN) and phagocytosis with reduced nicotinamide adenine dinucleotide phosphate (NAPDH) production, thereby reducing the production of reactive oxygen species (ROS) for pathogen neutralization.[6] But in the excessive inflammatory response, ROS may aggravate local tissue damage and lead to chronic inflammation. In addition, zinc deficiency plays a role in inflammation, mainly improving inflammatory response and damage to host tissue. Zinc targets nuclear factor kappa B (NF-κB) involved in regulating pro-inflammatory response, and NF-κB is a transcription factor and a major regulator of pro-inflammatory response.[11] The zinc-containing proteins or enzymes associated with AS are matrix metalloproteinase (MMP),[12] endoplasmic reticulum aminopeptidase 1/2 (ERAP1/2),[13] and tumor necrosis factor alpha-induced protein 3 (TNFαIP3),[14] all of which have been the subject of more intense research in recent years. The zinc level may affect the occurrence and development of AS through some potential mechanisms. The above evidence shows that zinc is speculated to be one of the risk factors for AS. The largest contributor to copper in the plasma is ceruloplasmin (40%–70%).[15] One study pointed out that mean levels of serum copper and ceruloplasmin were raised significantly in AS.[7] A Wuhan-Zhuhai cohort study found a positive correlation between urinary copper and plasma C-reactive protein (CRP),[16] and CRP is usually used to indicate the degree of inflammation. Copper is a trace metal nutrient and excessive copper exposure can regulate the process of inflammation through various molecular and cellular signaling pathways, including the NF-κB pathway, the Janus kinase-signal transducer and activator of transcription pathway, and the nucleotide-binding and oligomerization domain (NOD)-like receptor protein 3 inflammasome.[17] These signaling pathways and inflammatory factors are also involved in the etiological mechanisms of AS.[18–20] Selenium is a necessary trace element for the human body. It is reported that selenium has antioxidant, anti-inflammatory, and intracellular signal transduction effects, and affects the differentiation, activation, and proliferation of immune cells.[8] In a related study, genetically predicted blood and toenail selenium levels were found to be negatively associated with the risk of systemic lupus erythematosus, but not with rheumatoid arthritis and inflammatory bowel disease.[21]

Several meta-analyses have expounded the correlation between serum zinc, copper, and selenium levels and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.[22–25] Serum mineral levels are modifiable and their levels can be changed through dietary modification or clinical intervention. Therefore, we decided to explore whether there is a causal relationship between mineral nutrients and another autoimmune disease, AS. After consulting a large amount of literature, we finally confirmed 4 elements: calcium, zinc, copper, and selenium.

Mendelian randomization (MR) is a design of integrating genomic data related to complex human traits and disease risk into traditional epidemiological study designs, drawing on individual genetic information to infer causal associations between risk factors (exposure) and disease risk (outcome).[26] Genetic variation replaces exposure to assess the causal relationship between exposure and disease. In traditional observational epidemiology, the association between exposure and outcome may be influenced by confounding factors and reverse causal associations, thus making its limitations in causal inference. MR can make up for the shortcomings of traditional methods.[27] In summary, we performed a 2-sample MR (TSMR) analysis to explore whether 4 elements (calcium, zinc, copper, and selenium) have a causal relationship with the risk of AS.

2 | MATERIALS AND METHODS

2.1 | Data sources

The single nucleotide polymorphisms (SNPs) highly related to exposure were strictly screened as the instrumental variables of our study. We collected instrumental variables of the minerals calcium, copper, zinc, and selenium. As for calcium, instrumental variables associated with serum calcium concentration were extracted from a large genome-wide association study (GWAS) data set,[28] which included 61 079 individuals of European ancestry. As for zinc and copper, genetic variation with erythrocyte concentrations of log-transformed standardized residuals of copper and zinc were taken from a GWAS (n = 2603) of twins and their families recruited in

Australia from the Queensland Institute of Medical Research.[29] As for selenium, SNPs associated with toenail and blood (TAB) selenium levels were obtained from a genome-wide meta-analysis, which included 4162 European descendants from 4 US cohorts.[30] The meta-analysis was adjusted for age, gender, smoking status, and study-specific covariates.[30] The GWAS database related to AS was obtained through the website (http://gwas.mrcieu.ac.uk/datasets), involving 337 159 European individuals (968 cases and 336 191 controls). The database was derived from Neale Laboratory in 2017.

2.2 | Study design

MR is required to satisfy 3 hypotheses: ① There is a strong correlation between instrumental variables and exposure; ② the selected instrumental variables and confounding factors were independent of each other; and ③ instrumental variables can affect the outcome only through exposure. The 3 hypotheses about the MR principle are shown in Figure 1.

To satisfy the first hypothesis of MR, we set $P<5\times10^{-8}$ at a genome-wide significance to ensure that instrumental variables are highly correlated with exposure.[31] We set the minor allele frequency (MAF) threshold for instrumental variables in exposure to 0.01. We chose the SNPs with linkage disequilibrium (LD) $r^2<0.05$ and clumping distance = 10000 kb to ensure instrumental variables are independent of each other, and effect alleles at different loci are randomly assigned. As for instrumental variables of serum calcium concentration, the SNP (rs1550532) of calcium was removed for being palindromic with intermediate allele frequencies. All selected SNPs can be found from the data of the outcome and there is no need to find the proxy SNPs. As for the second hypothesis of MR, we searched for some possible confounding factors, such as diet and environmental exposure,[32] and judged whether the SNPs we selected were related to confounding factors through the PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner) to further screen our instrumental variables. F statistics are usually used to assess the strength of correlation between instrumental variables and exposures. The formula of F statistic is $F=\frac{N-k-1}{k}\times\frac{R^2}{1-R^2}$. R^2 represents the degree of exposure explained by the selected SNPs, N is the sample size, and k represents the number of included SNPs. When calculating the F value of every single SNP, K is equal to 1. The calculation formula of R^2 of a single SNP is from Yarmolinsky et al.[31] $F>10$ is considered to have no weak instrument bias.[33] Finally, 4 mineral exposure factors of, zinc, copper, and selenium included 7, 3, 3, and 4 SNPs respectively as shown in Table 1. The characteristics of the selected SNPs for exposure are displayed in Table 1.

2.3 | Statistical analysis

We used Inverse-variance weighted (IVW) and MR-Egger as the main method and Simple mode (SM), Weighted median (WM^1), and Weighted mode (WM^2) as supplementary methods to evaluate the causal effect of mineral levels on AS. The odds ratios (OR) with 95% confidence intervals (95% CIs) were used to quantitatively describe the association between exposures and outcome. In addition, scatter plots of exposure and outcome were produced to observe the direction and magnitude of the effect of exposures on the outcome. The application of IVW can provide an accurate and comprehensive causal evaluation when each genetic variant satisfies the assumptions of a valid instrumental variable.[34] In MR-Egger regression, we consider the existence of intercept terms and use them to evaluate the potential horizontal pleiotropy.[35] If at least half of the SNPs were valid instrumental variables, SM, WM^1, and WM^2 as auxiliary methods were used to get an estimate of the causal effect.[36] To solve multiple testing, a Bonferroni-corrected P value of .0125 (ie, 0.05/4 putative risk factors) was considered significant, with a $.0125<P$ value $<.05$ being considered a suggestive association. Furthermore, the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test can find the outliers and further estimate horizontal pleiotropy biases.[37] However, this method is not available when the number of SNPs is less than 4. We next evaluated the robustness of our primary observation by applying the test of heterogeneity and Leave-one-out analysis. Further, we calculated statistical power via the website https://shiny.cnsgenomics.com/mRnd/. As MR study is generally limited by low statistical power,[38] we added a new MR model, Causal Analysis Using Summary Effect Estimates (CAUSE), which has the significant advantages of increasing statistical power and controlling for correlated horizontal

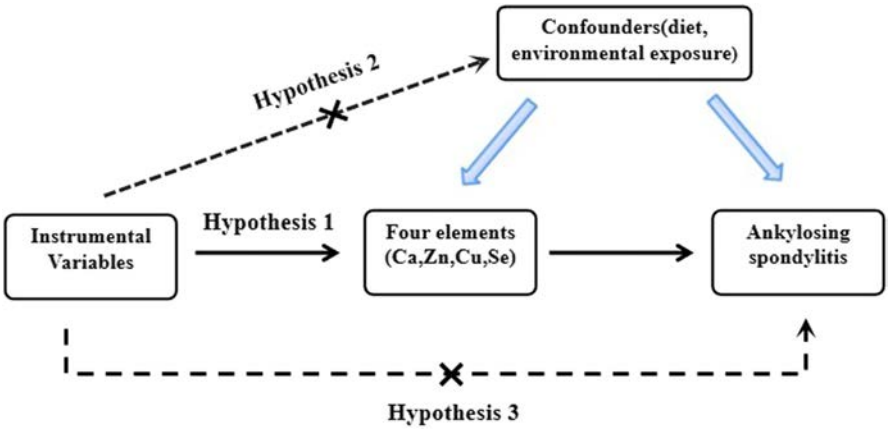

FIGURE 1 Schematic diagram of the 2-sample Mendelian randomization model

TABLE 1 Characteristics of the selected SNPs for exposures (calcium, zinc, copper, selenium)

Exposures	SNPs	CHR	Gene	EA/NEA	EAF	Association with exposure				
						β	SE	*P* value	F statistics[a]	
Calcium	rs10491003	10	GATA3	T/C	0.09	0.027	0.005	4.80E-09	315.1	>70.4
	rs1570669	20	CYP24A1	A/G	0.66	−0.018	0.003	9.10E-12	32.1	
	rs1801725	3	CASR	T/G	0.15	0.071	0.004	8.90E-86	29.2	
	rs7336933	13	DGKH; KIAA0564	A/G	0.15	−0.022	0.004	9.10E-10	36.0	
	rs7481584	11	CARS	A/G	0.30	−0.018	0.003	1.20E-10	30.2	
	rs780094	2	GCKR	T/C	0.42	0.017	0.003	1.30E-10	36.0	
	rs17711722	7	VKORC1L1T	T/C	0.47	0.021	0.003	2.80E-11	49.0	
Zinc	rs1532423	8	CA1	G/A	0.63	−0.178	0.026	6.40E-12	46.8	75.3
	rs11638477	15	C15orf39	T/G	0.44	0.223	0.028	1.01E-15	75.6	
	rs2120019	15	PPCDC	C/T	0.22	−0.287	0.033	1.55E-18	63.4	
Copper	rs1175550	1	SMIM1	G/A	0.21	0.198	0.032	5.03E-10	38.3	>45.6
	rs2769264	1	SELENBP1	G/T	0.17	0.313	0.034	2.63E-20	84.7	
	rs2769270	1	SELENBP1	A/G	0.17	−0.349	0.046	4.36E-14	57.5	
Selenium	rs1789953	21	CBSL	T/C	0.14	0.114	0.021	3.40E-08	29.5	41.4
	rs6586282	21	CBSL	C/T	0.83	0.113	0.019	3.96E-09	35.4	
	rs6859667	5	HOMER1	C/T	0.04	0.254	0.037	4.40E-12	47.1	
	rs921943	5	DMGDH	T/C	0.29	0.207	0.016	1.90E-39	167.3	

[a]The left column represents F statistics for single SNP and exposure, the right column represents F statistics for total SNPs and exposure.

Abbreviations: CHR, chromosome; EA, effect allele; EAF, effect allele frequency; NEA, non-effect allele; SE, standard error; SNP, single nucleotide polymorphism; β, estimate of the causal effect.

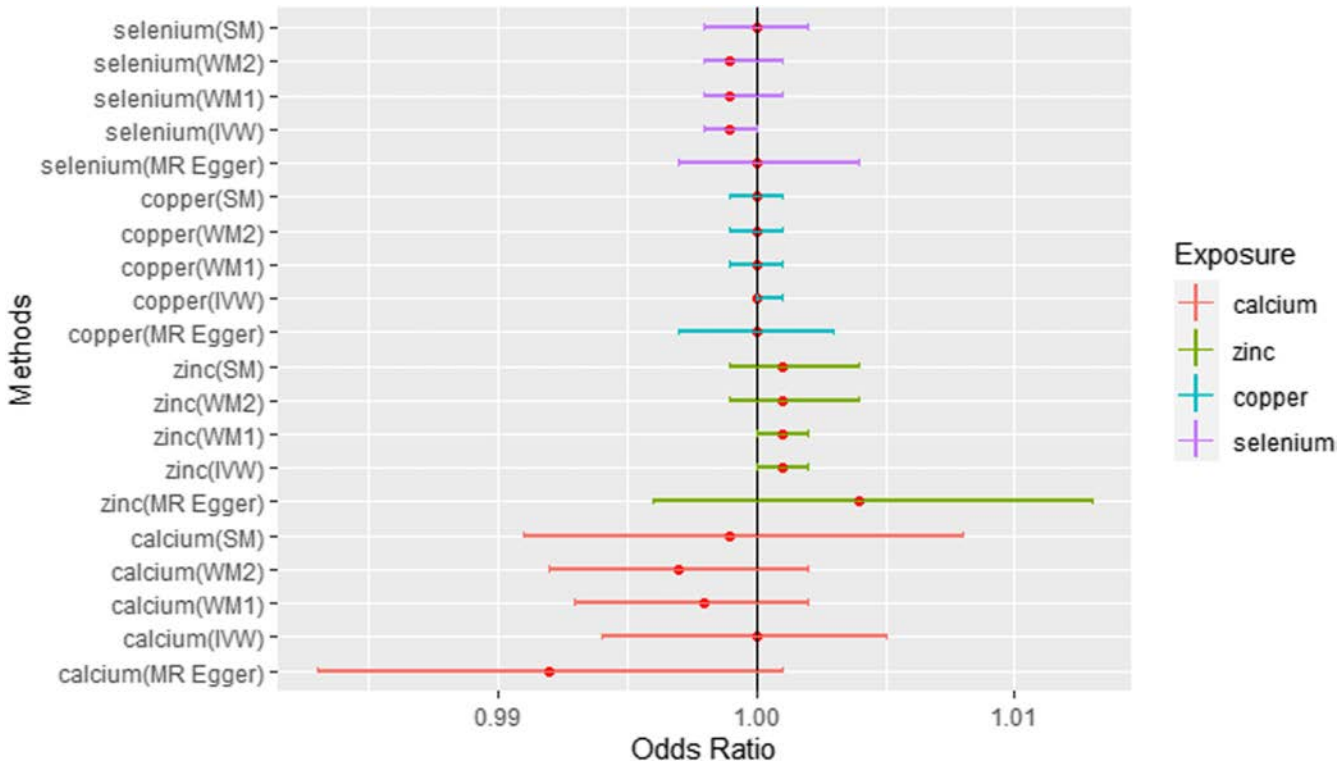

FIGURE 2 Forest plot summarized by 5 Mendelian randomization analysis methods

pleiotropy.[39] All statistical analyses were performed using R software (version 4.1.1, www.r-project.org). We conducted TSMR analysis by R packages "TwoSampleMR", "cause" and "MR-PRESSO".

3 | RESULTS

3.1 | Instrumental variables and statistical power

Finally, we screened a total of 17 SNPs as instrumental variables for our 4 exposure factors. Table 1 described the characteristics of the 17 SNPs and their association with 4 elements levels. SNPs for serum calcium, erythrocyte zinc, erythrocyte copper, and TAB selenium levels explained >0.8%, 8%, >5%, and 2.9% of the variance, respectively.[40–42] F-values were all greater than 10 and suggested that our instrumental variables were unlikely to suffer from weak instrument bias. The statistical power of the MR study of 4 exposures (calcium, zinc, copper, selenium) concentration and AS risk was 11%, 59%, 41% and 26%, respectively. Details are shown in Table S1.

3.2 | MR analysis results

3.2.1 | Calcium

The results of MR analysis of the 4 common mineral nutrients with the outcome AS are shown in Figure 2. The result of IVW fails to support a causal association between serum calcium and AS (OR = 1.000, 95% CI = 0.994, 1.005, P = .875). The increase of calcium level per genetically predicted 0.5 mg/dL (about 1 standard deviation [SD]) has no effect on AS (OR = 1.000). The MR-Egger method shows that there is no causal association between serum calcium and AS (OR = 0.992, 95% CI = 0.983, 1.001, P = .141). The remaining 3 auxiliary MR analysis methods do not support a causal link between serum calcium and AS (Table 2). The CAUSE method shows no causal relationship between serum calcium and AS (OR = 1.010, 95% CI = 0.942, 1.094, P = .806). The MR-Egger intercept parameter does not suggest evidence of directional pleiotropy (intercept = 2.547E-04, P = .110). The MR-PRESSO result shows that there were no outliers in instrumental variables, and once again proves that there is no horizontal pleiotropy (Table 2). There is no horizontal pleiotropy between instrumental variables and outcomes, and there is basically no heterogeneity between instrumental variables. From the Leave-one-out plot, we can see that the direction of the effect changes when rs1801725 is removed, but the 95% CI still includes the point where the effect estimate = 0 and does not have much effect on the results (Figure S3).

3.2.2 | Zinc

As shown in Table 2 and Figure 2, the IVW results indicate that zinc is a suggestive risk factor for AS (OR = 1.001, 95% CI = 1.000, 1.002, P = .029) and the MR-Egger result shows no causal association between zinc and AS (OR = 1.004, 95% CI = 0.996, 1.013, P = .265). The WM[1] result (OR = 1.001, 95% CI = 1.000, 1.002, P = .011) is significant and the effect values (OR) for all 5 results were greater than 1. The risk of AS increased by 0.001 with per SD increment in zinc level. The CAUSE method shows no causal relationship between zinc and AS (OR = 1.020, 95% CI = 0.914, 1.127, P = .695). The results of Cochran's Q statistics test show no heterogeneity between SNPs (Table 2). The MR-Egger intercept parameter (intercept = −7.759E-04, P = .327) shows there is no horizontal pleiotropy.

3.2.3 | Copper

As shown in Figure 2 and Table 2, all 5 methods indicate there was no causal correlation between copper and AS. The increase of copper level per SD has no effect on AS according to the IVW result (OR = 1.000, 95% CI = 1.000, 1.001, P = .533). The MR-Egger intercept parameter (intercept = 1.689E-04, P = .760) shows there is no horizontal pleiotropy. The CAUSE method suggests no causal relationship between copper and AS (OR = 1.568, 95% CI = 0.811, 3.158, P = .208). There is no heterogeneity between instrumental variables (Table 2).

3.2.4 | Selenium

As shown in Figure 2 and Table 2, all 5 methods indicate there is no causal correlation between TAB selenium and AS. The IVW result shows that the increase of selenium level per SD has a litter effect on AS at no statistical significance (OR = 0.999, 95%CI = 0.998, 1.000, P = .229). The CAUSE method indicates no causal relationship between TAB selenium and AS (OR = 0.995, 95% CI = 0.961, 1.030, P = .779). The MR-Egger intercept parameter (intercept = −1.206E-04, P = .728) and MR-PRESSO results show there are no outliers or horizontal pleiotropy (Table 2). There is no heterogeneity between instrumental variables.

4 | DISCUSSION

Despite much research, the etiological basis of AS has remained elusive. To gain insight into possible causal relationships, we applied the MR model to investigate the etiology of AS. Through the results of MR analysis, we can see there is no causal correlation between calcium, zinc, copper, or selenium with AS, and the results are reliable.

AS is characterized by inflammation and eventual calcification of the attachment points of the vertebral joints. Despite the tendency toward osteophytes, the increased risk of osteoporosis in AS may be based on chronic inflammation, lack of exercise, and malabsorption, and therefore calcium and vitamin D supplementation are often required.[5] Therefore, it is presumed that serum calcium levels are not associated with AS or that serum calcium changes only after

TABLE 2 MR analysis of the associations of 4 exposures (calcium, zinc, copper, selenium) with AS

						Test of heterogeneity		Intercept term			MR-PRESSO	
Exposure/outcome	Method	nSNP	OR	95% CI	*P* value	Q	*P* value	Intercept	SE	*P* value	Outliers	*P* value
Calcium/AS	MR-Egger	7	0.992	0.983–1.001	.141	6.929	.226	2.547E-04	1.313E-04	.110	N	.177
	IVW	7	1.000	0.994–1.005	.875	12.141	.059					
	WM[1]	7	0.998	0.993–1.002	.328							
	WM[2]	7	0.997	0.992–1.002	.260							
	SM	7	0.999	0.991–1.008	.882							
Zinc/AS	MR-Egger	3	1.004	0.996–1.013	.265	0.121	.728	−7.759E-04	4.377E-04	.327		
	IVW	3	1.001	1.000–1.002	.029	3.262	.196					
	WM[1]	3	1.001	1.000–1.002	.011							
	WM[2]	3	1.001	0.999–1.004	.148							
	SM	3	1.001	0.999–1.004	.172							
Copper/AS	MR-Egger	3	1.000	0.997–1.003	.848	0.128	.721	1.689E-04	4.269E-04	.760		
	IVW	3	1.000	1.000–1.001	.533	0.284	.868					
	WM[1]	3	1.000	0.999–1.001	.632							
	WM[2]	3	1.000	0.999–1.001	.763							
	SM	3	1.000	0.999–1.001	.706							
Selenium/AS	MR-Egger	4	1.000	0.997–1.004	.990	1.806	.405	−1.206E-04	3.018E-04	.728	N	.687
	IVW	4	0.999	0.998–1.000	.229	1.966	.579					
	WM[1]	4	0.999	0.998–1.001	.348							
	WM[2]	4	0.999	0.998–1.001	.445							
	SM	4	1.000	0.998–1.002	0\.890							

Abbreviations: AS, ankylosing spondylitis; CI, confidence interval; IVW, Inverse-variance weighted; MR, Mendelian randomization; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; N, No outliers; nSNP, number of SNPs; OR, odds ratio; SE, standard error; SNP, single nucleotide polymorphism; SM, Simple mode; WM[1], Weighted median; WM[2], Weighted mode.

the onset of AS. It is not the cause of AS. A previous meta-analysis study reported no significant association between serum calcium and AS,[43] which is consistent with our finding.

For the results of zinc and AS, the IVW method shows suggestive evidence that zinc is a risk factor for AS. The scatter plot of zinc and AS shows there may be a causal association between the 2 (Figure S2). However, the modest effect of the 3 zinc-associated SNPs on AS is weak and there is probably a false-positive result when the risk of AS increased by 0.001 per SD increases in genetically predicted zinc concentration. Based on the forest plot and Leave-one-out plot of zinc, we can infer that the weak positive result of zinc is driven by rs2120019 and its adjacent gene loci (Figure S1 and Figure S3). Therefore, we are not particularly convinced of the validity of associations between other SNPs and AS. The negative result of the CAUSE method confirms that zinc is not a risk factor for AS. From the article by Evans,[29] we can find that zinc and copper concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) on a Perkin-Elmer Elan 5000 mass spectrometer or a Varian Ultra-Mass. This means that the inorganic, organic and protein-bound forms are indistinguishable from each other and we cannot analyze their correlation in detail. Since the IVW method is uncorrected, the result is an unreliable method compared with MR-Egger. The negative result of the MR-Egger regression analysis contradicts our speculation, which may be explained by the fact that the level of zinc is not a precursor, but a consequence after the occurrence and development of AS.

As for copper and selenium, the results of the MR analysis show there is no causal association between blood copper and TAB selenium with AS, and the Leave-one-out method demonstrates that the results are robust. At present, there are few articles published about copper and selenium and AS.[7,44] According to our MR analysis results, copper and selenium are not the causes of AS. No single SNP was associated with AS, and the results of the 5 MR methods were consistent and reliable. There is a possible association between elemental copper and selenium, but not a causal association.

The present study is the first to explore the causal association between common mineral nutrients and AS using a MR design. Five MR statistical methods were applied to enhance the stability of our results. We used the CAUSE statistical method to validate our results and compensate for the lack of statistical power. Also, we used the MR-Egger intercept parameter and MR-PRESSO tests to detect abnormal SNPs as well as control horizontal pleiotropy bias. The advantages of SNPs as instrumental variables are manifested in several ways. First, alleles are randomly segregated from parents and then randomly passed on to offspring, suggesting that one trait is inherited independently of others and at random so that offspring genotypes are unlikely to be associated with environmental confounders in the population. Second, genotype distribution precedes acquired exposure in time and the association between genotype and disease is not influenced by reverse causality. Again, genotypes associated with exposure are usually associated from birth to adulthood, and thus attenuation due to error (regression dilution bias) can be avoided in causal inference. However, there are some limitations in this article. First, the populations we studied were not from the same race, including Europe and Oceania. When exposure factor and outcome are not of the same race, there may be confounding bias between exposure and outcome due to differences in race. Second, the lack of detailed demographic information prevented us from conducting subgroup analyses of gender, age, and so forth. Third, the number of SNPs as instrumental variables was small, which can explain only a limited causality. Fourth, the database of 4 common mineral nutrients contains too few people, so MR studies can be carried out on a larger scale or mineral nutrient levels in more human body parts in the future.

5 | CONCLUSION

In conclusion, our MR analysis does not provide convincing evidence to support a causal correlation between calcium, zinc, copper, and selenium and AS, and larger MR studies are needed to validate our conclusions.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Shanshan Xu https://orcid.org/0000-0002-8236-7687
Faming Pan https://orcid.org/0000-0003-4242-1025

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

Identification of symptom clusters in patients with ankylosing spondylitis

Wen Yang[1] | Li Rong[2] | Quan Xu[1] | Xiaoli Fu[1] | Xiaohong Deng[3] | Ailing Hu[3] | Yutong Jiang[1]

[1]Department of Rheumatology and Immunology, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[2]Department of Internal Medicine, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[3]Department of Nursing, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Correspondence
Ailing Hu, Department of Nursing, 2693 Kaichuang Avenue, Guangzhou 510000, Guangdong, China.
Email: h-ailing@163.com

Yutong Jiang, Department of Rheumatology and Immunology, 600 Tianhe Road, Guangzhou 510630, Guangdong, China.
Emails: ruo.v@163.com; jiangyt7@mail.sysu.edu.cn

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Abstract

Symptom cluster refers to a group of 3 or more related symptoms that occur together. Our objectives were to: (1) investigate the frequency, severity and gender difference of symptoms in patients with ankylosing spondylitis (AS); and (2) identify symptom clusters in AS patients. A cross-sectional questionnaire-based survey was conducted using the Patient Health Questionnaire Symptoms Group combined with self-designed variables. Demographic and symptom variables between male and female patients in terms of C-reactive protein (CRP) and *human leukocyte antigen* (*HLA*)-*B27* status were analyzed with 2-tailed independent *t* test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Symptom clusters were extracted and analyzed by principal component analysis. There were 122 AS patients included in the study. The most severe symptoms included severe back pain, extremity or joint pain, difficulty in breathing, constipation, intestine discomfort and diarrhea. Stomachache was more prevalent in male patients in which odds ratio was 4.60 (CI 1.59-12.97) ($P = .006$). Patients with *HLA-B27* negativity or a higher CRP value were more likely to have dry mouth. Four symptom clusters were classified, which explained 58.4% of the total variation. They were named as the gastrointestinal-cardiac cluster, the fatigue-sleep disturbance cluster, the headache-chest pain cluster, and the mouth-eye cluster. The symptoms appeared to cluster into 4 groups in AS patients, which should be noticed in clinical care.

KEYWORDS
ankylosing spondylitis, chronic disease, pain, symptom assessment, symptom cluster

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease which mainly involves the spine and sacroiliac joints, and in which the etiology remains unclear. The major clinical manifestations of AS include inflammatory back pain, morning stiffness, limited spinal activity, and even spinal deformity or ankylosis at the advanced stage.[1] The disease not only affects the joints and the spine but also presents with extra-articular manifestations, such as eye involvement and inflammatory bowel disease (IBD). Less commonly, AS patients may

experience cardiac diseases, pulmonary diseases, and bone metabolic disorder,[2] which implies the occurrence of multi-organ symptoms in AS patients. However, the lack of a specific symptom is closely related to delayed diagnosis and consecutive uncontrolled inflammation in AS patients.[3] The main objectives of treatment in AS are to relieve pain, stiffness and fatigue and to prevent structural damage. Therapy for AS includes education, exercise, physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) and biologic agents.[4]

The research of symptoms is particularly significant in patients with AS. First, symptoms, such as back pain, uveitis, skin rash, could guide patient to a rheumatic clinic for further testing and diagnosis. A delay of diagnosis could lead to physical disability, and that is why early diagnosis is crucial in the management of AS. Second, symptom assessment is largely applied in the evaluation of disease status of AS patients. Patient-reported outcomes (PRO), including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), are progressively used to track symptoms and to assess disease activity, quality of life, and even treatment effectiveness.[5,6] Third, a number of AS patients suffered from anxiety, depression and sleep disturbance,[7,8] which could potentially affect treatment effectiveness. Thus, exploring the symptom characteristics and strengthening the symptom management of AS patients is one of the focuses of clinical work.

AS is more prevalent in males, in which the ratio of male-to-female is around 2–3:1.[9] Studies concerning gender differences revealed that female AS patients had diverse disease manifestations due to altered immunological, hormonal and genetic responses. Further, a higher frequency of extra-articular manifestations in female patients, such as enthesitis, psoriasis and IBD, were noticed, whereas acute anterior uveitis is more likely to occur in male patients.[9] Evidently, a detailed comparison of more symptoms in males and females is worthy of attention.

Symptom cluster was first proposed in cancer by Dodd[10] in 2001, that is, a group of 3 or more related symptoms that occur together, and the symptoms within the group may not possess the same pathogenic mechanism. Kim[11] pointed out that regarding a symptom cluster as a unit, the comprehensive management of symptom clusters stays close to the concept of overall care, and meanwhile, the corresponding interventions can be more cost-effective. In recent years, scholars have extended the exploration of symptom clusters into some chronic diseases,[12] but not into AS. Being a chronic disease sharing the feature of chronic pain and mood disorders, like cancer, AS may possibly possess symptom clusters which need to be unveiled and evaluated.

AS patients at a late stage may have difficulty in going to the rheumatology clinic. Digital health facilitates long periods of disease management and health care to hard-to-reach populations predominantly by the assessment of symptoms.[13,14] As symptoms could affect the results of PRO, which in turn, influence doctors' judgment of disease status and treatment options,[4] the management of symptom clusters helps to improve the overall assessment of the condition.[11] The objectives of our study were: (1) to investigate the severity of symptoms in AS patients and compare the gender differences in the symptoms; and (2) to identify symptom clusters in AS patients.

2 | METHODS

2.1 | Patients

There were 122 patients with AS included in the rheumatology clinic of our hospital from October 2018 to February 2020. Inclusion criteria included: (1) patients met the modified New York Criteria;[15] and (2) patients were able to understand and complete the questionnaire. Exclusion criteria: patients with a history of malignancy or pregnancy. This study was conducted in compliance with the Helsinki Declaration to protect human subjects and was approved by the ethics committee of our hospital. All participants gave written informed consent before enrolment.

2.2 | Methods

A cross-sectional questionnaire-based survey was conducted. Research tools were employed in the study as follows.

1. General information questionnaire. The questionnaire included demographic data (including age, gender, marital status, occupation, etc) and disease-related variables, such as BASDAI and medication. BASDAI has a score of 0–10. A higher score indicates worse disease activity, which is frequently applied in clinical practice.[6]
2. Patient Health Questionnaire (PHQ)-15. It is a subscale of the PHQ. Kroenke et al showed that PHQ-15 has good reliability and validity and is suitable for screening self-rating scales for somatization disorders and assessing the severity of somatic symptoms.[16] The scale consists of 15 items, assessing the physical symptoms of the subjects within 1 month, which proves to be simple, operative, and effective. The 15 items were nausea, flatus or indigestion, constipation, intestinal discomfort or diarrhea, stomachache, dizziness, heart palpitation, sleep disturbance, feeling fatigue or listless, bursts of weakness, back pain, pain in the extremity or joint, difficulty in breathing, headache, chest pain, pain or other problems in sexual life. The items with positive symptoms are calculated with a total score of 0 to 15. Each symptom is judged by the frequency (0–2), in which 0 means "no", 1 indicating "a little" and 2 referring to "very much". Consequently, the total scores range from 0 to 30. The total scores of 0–4, 5–9, 10–14 and 15–30 correspond to slight, mild, moderate and severe sickness, respectively.
3. Self-designed variables. In terms of the specificity of symptoms in patients with AS, 5 supplementary items were added in this study, including dry mouth, oral ulcer, vision loss, itching and rash according to the extra-articular manifestations of AS.[17] Two well-trained researchers directed the patients to complete the above

questionnaire by explaining the purpose, significance and requirements of the study in detail. The questionnaire was collected by 2 researchers on the spot. The questionnaire survey process was conducted in about 20 minutes.

4. C-reactive protein (CRP) and *human leukocyte antigen* (*HLA*)-*B27* was acquired in the patients who agreed to have the tests. CRP was detected by using the automatic biochemical analyzer 7600 (Hitachi, Ltd, Japan). A CRP value over 6.0 mg/L is considered elevated. HLA-B27 was performed using Human Leukocyte Antigen B27 Gene Diagnostic Kit (PCR Fluorescence Probing, Jiangsu Mole, China).

2.3 | Statistical analysis

The Kolmogorov–Smirnov test was used to confirm the data distribution. A nonparametric test was employed for variables outside the normal distribution. First, participants within the normal distribution range were characterized with descriptive statistics, and data were described by rate, mean and standard deviation. Second, demographic and symptom differences in subgroups were detected by using 2-tailed independent *t* test, Mann-Whitney *U* test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Then symptom clusters were extracted and analyzed by principal component analysis (PCA). PCA can reduce data by projecting into lower dimensions termed principal components to summarize data with fewer components. It works as a valuable tool to recognize the main axes of variance and classify the crucial components in the dataset. The components with an eigenvalue higher than 1 were chosen, and each component accounted for more than 10% of the variance. The top factor score predicted the contribution of each symptom to independent factors.[18] The internal consistency and reliability of the clusters were measured using Cronbach's alpha. The Statistical Package for Social Sciences software version 21 was used for all data management and analysis. The level of significance was set at 2-sided $P < .05$.

3 | RESULTS

3.1 | Patient characteristics

A total of 122 patients including 99 males and 23 females were recruited from the inpatient department of our hospital. Descriptive statistics and disease characteristics are summarized in Table 1. The mean age of the participants was 29.6 ± 8.3 years. The mean disease duration was 4.8 ± 5.7 years. About 28.3% of male patients were smokers, while only one female patient (4.34%) was a smoker. The mean BASDAI scores were 3.01 ± 1.93 (0–9.2), and 27.9% of the patients had a BASDAI score of more than 4. The mean CRP was 16.13 ± 21.07 mg/L. There were 54 patients with *HLA-B27* positivity while 6 had *HLA-B27* negativity in the 60 patients who had undergone an *HLA-B27* test. There were 97 (79.5%) patients who were treated with biological agents. There were 45 (36.8%) who used NSAIDs; 34 (27.9%) were treated with sulfasalazine; 8 (6.6%) received traditional Chinese medicine (TCM); and 4 (3.3%) patients took glucocorticoids. Totally, 16.4% of the patients were treated with oral medications, and 4.1% of the participants did not receive any medication.

TABLE 1 Demographic and disease characteristics of the 122 participants

Variables	Results
Age, y	29.6 ± 8.3
Gender, male, %	81.1
Educational level, high school or above, %	83.6
Disease duration, y	4.8 ± 5.7
Disease manifestation, %	
• Axial involvement	91.0
• Peripheral involvement	51.6
• Uveitis	13.1
• Inflammatory bowel disease	4.1
• Psoriasis	0
Human leukocyte antigen-B27 positivity, %	89.3
CRP, mg/L	16.1 ± 21.1
BASDAI, 0–10	3.0 ± 1.9
Treatment, %	
• NSAIDs	36.8
• Biological therapy	79.5
• Sulfasalazine	27.9
• Glucocorticoids	3.3
• Traditional Chinese medicine	6.6
• Naïve to treatment	4.1

Note: The results are presented as mean ± standard deviation or percentage for continuous and categorical variables.
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity; CRP, C-reactive protein; NSAIDs, non-steroid anti-inflammatory drugs.

3.2 | Occurrence and severity of the symptoms

Among the 20 symptoms included in the questionnaire, the 5 most frequent symptoms presenting in AS patients were: extremity or joint pain (74.6%), back pain (73.8%), female dysmenorrhea (60.9% of female patients), feeling fatigued or listless (54.1%), constipation, intestinal discomfort and diarrhea (53.3%), and bursts of weakness (50%). The most severe symptoms included severe back pain, extremity or joint pain, difficulty in breathing, constipation, intestine discomfort, diarrhea, and over 15% of the patients had 1 or more severe symptoms (Figure 1). Noticeably, 6 patients having a disease duration from 3 to 13 years did not present with any of the symptoms. They were excluded from further symptom cluster analysis. Five of them treated with biologic agents displayed stable disease status, indicated by a BASDAI score of 0 to 1. The other case with a BASDAI score of 4.5, was diagnosed with AS 13 years ago. Presenting with lumbar kyphosis, this subject was receiving NSAIDs. The remaining

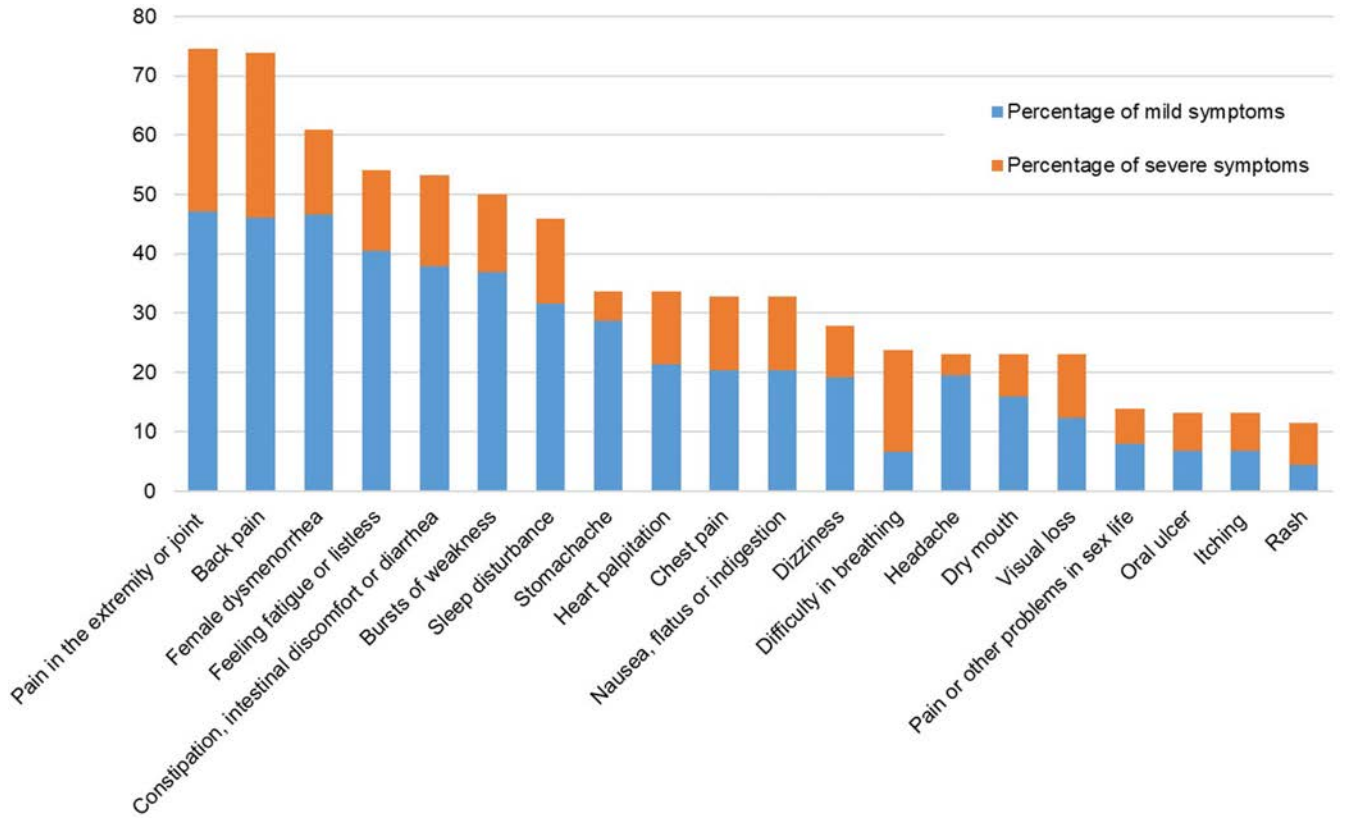

FIGURE 1 The proportion of various symptoms in ankylosing spondylitis patients. The percentage of 20 symptoms reported in the participants and the proportion of severe symptoms are shown in the figure.

116 patients with AS had a mean of 6.7 ± 4.5 symptoms, confirming that most patients with AS experienced multiple symptoms.

3.3 | Comparison of various symptoms between male and female patients

To explore if there were gender differences in symptoms, we compared age, disease duration and symptoms between males and female patients. We found that male patients had a mean age of 29.3 ± 7.6 years, while female patients had a mean age of 31.2 ± 10.9 years. There was no significant difference in age and BASDAI between the 2 groups. Fisher's exact and Chi-square analysis revealed that only stomachache was more prevalent in male patients; the odds ratio was 4.60 (CI 1.59 to 12.97) ($P = .006$). No difference was detected in other symptoms between male and female patients ($P > .05$).

3.4 | Comparisons of various symptoms between patients with different CRP values and *HLA-B27* status

We divided the patients into 2 groups according to CRP and *HLA-B27*. First, more patients with an elevated CRP value (>6.0 mg/L) presented with dry mouth, compared to those patients with a normal CRP value (≤6.0 mg/L) ($P = .021$). However, there was no significant difference in other variables between the 2 groups ($P > .05$). Second, we compared 2 groups with or without positive *HLA-B27* and found that patients with positive *HLA-B27* had more back pain ($P = .028$) but less dry mouth ($P = .0019$). Nevertheless, there was no significant difference in other variables between the 2 groups ($P > .05$), including CRP ($P = .081$).

3.5 | Symptom clusters in AS patients

To avoid the interference of relatively rare symptoms to the analysis, symptoms with the occurrence less than 20%, including pain or other problems in sexual life, oral ulcers, itching, and rash were excluded. Sex-specific symptoms such as dysmenorrhea was not counted as well. The remaining symptoms were included in the PCA. The sampling appropriateness value (Kaiser-Meyer-Olkin, KMO) of 0.869 by using the suitability test and Bartlett test indicated that it was suitable for further analysis ($P < .001$). We found there were 4 factors with an eigenvalue greater than 1, and the 4 symptom clusters explained 58.4% of the total variation. After rotating the maximum variance orthogonally, the covariance matrix was obtained (Table 2).

Four distinct symptom clusters were grouped and named as follows. (1) The gastrointestinal-cardiac cluster. It was characterized

by nausea, flatus, constipation, diarrhea, stomach pain, dizziness and heart palpitation. The contribution rate of variance within the group was 20.67% (Cronbach's α = .794). (2) The fatigue-sleep disturbance cluster. It was categorized by sleep disturbance, feeling fatigued or listless, bursts of weakness, back pain, pain in the extremities or joints and difficulty in breathing. The contribution rate of variance within the group was 17.94% (Cronbach's α = .782). (3) The headache-chest pain cluster. This cluster shared the symptoms of headache and chest pain, and its contribution rate of variance within the group was 10.342% (Cronbach's α = .496). (4) The mouth-eye cluster. Its features involved dry mouth and vision loss, and contribution of variance within the group was 9.41% (Cronbach's α = .467). Symptom clusters 1 and 2 with internal reliabilities of 0.794 and 0.782, showed better internal consistency than clusters 3 and 4.

4 | DISCUSSION

AS is a complex inflammatory disease which involves multiple sites and various symptoms. In our study, only 6 (4.9%) patients had no symptoms, possibly due to a long disease duration and high disease tolerance. Other patients presented with an average of 6.7 symptoms, showing that the majority of patients with AS experienced multiple symptoms. To our knowledge, this is the first study focusing on symptom clusters in patients with AS. Here, we identified 4 symptom clusters including the gastrointestinal-cardiac cluster, the fatigue-sleep disturbance cluster, the headache-chest pain cluster and the mouth-eye cluster.

The etiology of symptom clusters in AS remains unknown. Previous research has suggested that symptom clusters in cancer may share some mutual biological mechanisms, including pro-inflammatory cytokines.[19] As an inflammatory disease, AS has elevated levels of pro-inflammatory cytokines, altered immune cell distribution[20] and also concurs with pain, fatigue, sleep disturbance, and depression.[8] The possible mechanisms of the 4 symptom clusters were discussed based on the literature.

4.1 | The gastrointestinal-cardiac cluster

Symptoms of nausea, flatus or indigestion, constipation, diarrhea, intestinal discomfort, and stomach pain accounted for the majority of the first cluster. Islam et al pointed out that patients with AS have increased intestinal permeability and are prone to intestinal inflammation.[21] Microbes may participate in the pathogenesis and disease progression of AS through the intestine, not to mention the negative influence of long-term use of NSAIDs and disease-modifying antirheumatic drugs on the gastrointestinal system.[22] Further, AS patients with thoracolumbar kyphosis may experience reduced chest and abdominal volume, decreased gastric motility and digestive dysfunction.[23] We found that stomachache was more observed in male patients. As we know, NSAIDs, smoking and *Helicobacter pylori* (HP) infection are among well-known risk

TABLE 2 Rotated component matrix of the symptoms determined by the principal component analysis in patients with ankylosing spondylitis

	Components			
Symptoms	**Component 1**	**Component 2**	**Component 3**	**Component 4**
Nausea, flatus or indigestion	**0.738**[a]	0.193	0.086	0.180
Constipation, intestinal discomfort or diarrhea	**0.724**[a]	0.152	0.156	0.073
Stomachache	**0.650**[a]	0.046	0.163	0.302
Dizziness	**0.588**[a]	0.193	0.329	0.121
Heart palpitation	**0.581**[a]	**0.415**	0.000	0.178
Sleep disturbance	0.159	**0.712**[a]	0.116	0.091
Feeling fatigue or listless	**0.479**	**0.664**[a]	−0.050	0.014
Bursts of weakness	**0.498**	**0.617**[a]	−0.035	0.097
Back pain	−0.081	**0.609**[a]	**0.439**	0.077
Pain in the extremity or joint	0.138	**0.596**[a]	0.123	0.237
Difficulty in breathing	**0.425**	**0.463**[a]	0.318	−0.142
Headache	0.375	−0.019	**0.730**[a]	−0.069
Chest pain	0.090	0.266	**0.719**[a]	0.274
Visual loss	0.191	0.002	0.075	**0.789**[a]
Dry mouth	0.179	0.281	0.054	**0.659**[a]
Contribution of variance	20.674	17.936	10.342	9.406
Cronbach's α	.794	.782	.496	.467

[a]The factor with highest contribution score; an individual symptom with relatively large contribution to a component is considered to be part of that component. The values more than 0.4 are marked in bold.

factors for gastrointestinal diseases.[22] About 28.3% of male participants were smokers, which may increase the likelihood of gastrointestinal diseases. A further gastroscopy and HP test should be performed to confirm the reasons for stomachache. In addition, anemia is another outcome related to underlying systemic inflammation, including AS.[24] We previously reported that 13.0% of patients with spondyloarthritis had anemia,[2] which could lead to dizziness. Detailed examinations are required for prompt resolution of potentially life-threatening complications, especially those presenting with cardiac signs and the symptoms of palpitation, dizziness, dyspnea, syncope, fatigue and angina, as stressed by the American College of Rheumatology.[25]

4.2 | The fatigue-sleep disturbance cluster

AS is an inflammatory disease characterized by inflammatory back pain, referring to the feature that pain mainly manifests at rest and night, and relieved after movement. Literature has shown that sleep disturbance and fatigue are common complications which AS patients may experience.[2] Fatigue correlates with more severe low back pain, functional limitation, worse disease activity and poorer sleep quality.[26] Higher fatigue scores often suggest potential psychogenic problems, and the patients' description is “very tired”, that is, the sense of weakness. Medical staff should identify the interactions among symptoms in the fatigue-sleep disturbance symptom cluster and treat them as a whole.

4.3 | The headache-chest pain cluster

Our study showed that about 23% of patients suffered from headache and 32.8% had chest pain. The main type of headache in AS patients is cervicogenic headache. To maintain the balance and stability of the cervical vertebrae, the cervical muscles have to bear more stress.[27] This condition can consequently produce a sterile inflammatory response, leading to the release of inflammatory mediators and the occurrence of headache. Furthermore, the compression of the nerves due to cervical spine deformity can also lead to chest pain and other discomforts. The association between neck muscles and the myocardium was also unveiled by clone analysis.[28]

Chest pain is associated with banded chest pain caused by limited thoracic involvement. Further, chest pain is also a common symptom in patients with coronary heart disease. Studies have found that chronic inflammatory response in patients with AS may promote the progression of coronary arteriosclerosis. The prevalence of cardiovascular disease is significantly increased in AS.[2] A small number of patients with coronary heart disease could have headache as one of the main discomforts. Being aware of headache and chest pain in patients with AS enables early recognition and initiation of the appropriate treatment.

4.4 | The mouth-eye cluster

Dry mouth is one of the symptoms which AS patients easily ignore. It has been shown in the literature that the incidence of Sjögren's syndrome is increased in AS.[29] Loss of vision is mostly related to uveitis, which is one of the typical extra-articular manifestations in patients with AS. Studies have shown that the prevalence of uveitis is more than 10% in AS.[2] The main symptoms involve eye pain, congestion, photophobia, tearing, decreased vision and even blindness. In the current study, 23.0% of the patients reported visual loss, in which 57.1% had no confirmed uveitis, reflecting the fact that eye examination could be overlooked in AS patients. Surprisingly, patients with *HLA-B27* negativity or a higher CRP value tend to suffer more from dry mouth. The mouth-eye cluster provides instruction that the symptoms of dry mouth and eye discomfort could exist at the same time.

Strikingly, 60.9% of female patients had dysmenorrhea. Two cases of serious menstrual bleeding associated with use of tumor necrosis factor alpha blockers were described.[30] However, no other studies have reported similar findings. Dysmenorrhea in AS needs further exploration, especially in respect to the use of NSAIDS and biological agents.

Like other chronic diseases, AS requires long-term management. Symptom cluster management not only guides us to pay close attention to multiple symptoms that may be overlooked, but also helps the early diagnosis and a better evaluation of disease status, thus slowing disease progression. Adopting a symptom cluster approach can potentially improve symptom assessment and nursing care for patients. We believe that electronic self-report symptom screening mentioned in the study can be put into the agenda for new cases and the follow-up of AS patients, for example, in digital health apps. According to the 2021 European League Against Rheumatism recommendations for self-management strategies in patients with inflammatory arthritis, including AS, methods like digital healthcare are essential in supporting and optimizing self-management, which could result in improved patient experience of care and outcomes.[31] Prominently, further research is in need to recognize the influence of symptom clusters on quality of life, disease management and medical expenditure.

There were certain limitations in this study. First, this is a single-center cross-sectional study including only hospitalized patients, while a longitudinal study involving more participants will help to draw a more robust conclusion. Second, the number of symptoms included in this study was limited, therefore, some symptoms might be neglected during a comprehensive assessment of disease manifestations. Third, the number of patients using biologics was higher than the common rate, likely to mask some of the symptoms of AS patients. Last but not the least, a better correlation between symptom clusters and disease activity should be further explored.

To conclude, our study found that multiple symptoms of AS patients are not completely isolated, but appear as 4 symptom clusters. This finding could not only help us understand disease

manifestations, but also possibly enhance the management and care for patients with AS.

AUTHOR CONTRIBUTIONS

W.Y., A.H. and Y.J. designed the overall study with contributions from L.R. and Q.X. W.Y., X.F. and X.D. collected and analyzed data. W.Y. and Y.J. cowrote the paper. Y.J. and A.H. discussed and edited the paper.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

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

ORCID

Yutong Jiang https://orcid.org/0000-0001-6558-4201

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ORIGINAL ARTICLE

Rheumatoid arthritis and nutritional profile: A study in Brazilian females

João Gabriel Cavazzani Doubek[1] | Bárbara S. Kahlow[2] | Renato Nisihara[1] | Thelma L. Skare[1,2]

[1]Mackenzie Evangelical School of Medicine of Paraná, Curitiba, Brazil

[2]Rheumatology Unit, Hospital Universitário Evangélico Mackenzie, Curitiba, Brazil

Correspondence
Renato Nisihara, Mackenzie Evangelical School of Medicine of Paraná, Rua Padre Anchieta, 2770, Zip-Code 80730-000, Curitiba, Paraná, Brazil.
Emails: renatonisihara@gmail.com; renato.nisihara@fempar.edu.br

Abstract

Background: Patients with rheumatoid arthritis (RA) may have nutritional impairment. In RA, muscle loss is associated with an increase in fat tissue, and the patients may not have body mass index (BMI) alterations.

Aim: To study the nutritional status in a sample of patients with RA in Brazil through mini nutritional assessment (MNA) and electric bioimpedance and its relationship to BMI, functionality, disease activity, and treatment.

Methods: Seventy-one RA females were included. Chart review was used to obtain epidemiological, clinical, and treatment data. Patients answered the MNA and were submitted to electrical bioimpedance and anthropometric measurements. Disease activity was assessed through simple disease activity index (SDAI), clinical disease activity index (CDAI), and function, through health assessment questionnaire (HAQ).

Results: According to MNA, 23 (32.4%) patients were at risk for malnutrition and 1 (1.4%) was malnourished. MNA were associated with disease activity and function impairment (SDAI $P = .02$; CDAI $P = .02$, and HAQ $P = .002$) but not with used medications. According to BMI, 76% were overweight or obese. An increased percentage of body fat was found in 98.7% and a lower percentage of lean mass in 95.7%. Disease activity and function were not associated with the percentage of body fat of any used medications, with a lower percentage of body fat in those using abatacept ($P = .01$).

Conclusion: Almost one-third of patients had nutritional impairment according to MNA which was associated with disease activity and loss of function. Almost the whole sample had an increased percentage of fat mass and a diminished percentage of muscle mass that could not be linked with disease activity, function or used medications.

KEYWORDS
nutrition, obesity, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with profound repercussions on the patient's quality of life. Chronic pain, stiffness, fatigue, and disability bring isolation, unemployment, and economic losses, are some of the consequences of a long-term disease.[1] Furthermore, RA patients' survival may be reduced due to lung impairment,[2,3] infections, and cardiovascular diseases associated with accelerated atherosclerosis.[4] The nutrition of these patients is also affected, which may make the disease even more dangerous and kill more people.[1,5]

Cachexia in RA or rheumatoid cachexia is different from classic cachexia found in neoplastic diseases or in severe cardiac conditions. It is due to inadequate dietary consumption and is associated with weight loss. In RA, the muscle loss is somewhat compensated by an increase in body fat, so the body mass index (BMI) remains unaltered or even higher than before and it is called obese cachexia. It is thought to affect two-thirds of these patients[6] and has been linked to high inflammatory activity.[7] Increased production of pro-inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, and the presence of high levels of inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are found in this context.[7] Patients with RA have higher resting energy expenditure and muscle catabolism when compared to healthy controls.[6] Classic cachexia, with weight loss, is infrequent in RA and occurs only in 1%-13% of this population.[8–14]

The study of anthropometric parameters alone is not sufficient,[8,14] as may be shown in patients who are obese and have cachexia. Therefore, it is necessary to make use of other instruments, such as the determination of body composition and/or the mini nutritional assessment (MNA).[15]

MNA is considered to be a reliable method to evaluate nutritional status; it has been used mainly in elderly people, showing a sensitivity of 97.9% with a specificity of 100% in this population.[1] It has also been applied to study nutrition in RA.[1,8,14,15] Elkan et al[14] found that MNA had the highest sensitivity to identify undernourished individuals when comparing several tools used to evaluate nutrition in RA, and thus it should be used as a screening instrument in this setting. Nevertheless, although the sensitivity of this instrument in RA is estimated at 85%, the specificity of this method may be low (39%).[8] It is suggested that nutritional evaluation by MNA should be complemented with body mass measurements.[8]

In this study, we aimed to analyze the nutritional status in a sample of RA Brazilian patients through MNA and electric bioimpedance and its relationship to BMI, functionality, used treatment, and disease activity.

2 | METHODS

2.1 | Ethical issues

This study was approved by the local Committee of Ethics in Research under protocol number 4.023.752. All participants signed consent.

2.2 | Sample

A convenience sample of 71 female patients with RA was studied. It encompasses all patients that came for regular consultation in a single rheumatology unit from a tertiary hospital that cares for patients from the Public Health Service during the period of July, 2000 to July, 2021. Patients were invited to participate according to appointment order and willingness to participate.

2.3 | Inclusion and exclusion criteria

This study included 71 females with RA from a single rheumatology care unit from a university hospital that cares for patients from the Brazilian Public Health System. To be included, patients should fulfill at least 6 points from the RA American College of Rheumatology / European League Against Rheumatism classification criteria,[16] be older than 18 years of age, and have normal thyroid function.

Exclusion criteria consisted of pregnant patients, patients with any other inflammatory disease, current neoplastic and infectious diseases, untreated thyroid disease, malabsorption, severe cardiac insufficiency (New York Heart Association classification ≥3), severe renal failure (glomerular filtration rate ≤20 mL/min), chronic obstructive lung disease with emphysema, known eating disorders and individuals with pacemakers or metallic devices in the limbs that precluded the use of bioimpedance.

2.4 | Data collection

Thus included the following.

1. Epidemiological and clinical information: including age, auto-declared ethnic background, smoking, alcohol use, disease duration, presence of rheumatoid factor, nodules, and used treatment.
2. Disease activity and the patient's functionality: all patients had disease activity evaluated by SDAI (simple disease activity index) and CDAI (clinical disease activity index), ESR, CRP and functionality by HAQ (health assessment questionnaire).

CDAI was measured by the number of tender and swollen joints in 28 places, the patient's global disease activity (on a scale of 0-10) and the evaluator's global disease activity (on a scale of 0-10). The used CDAI cut-off values were: remission <2.8; low activity <10.2; moderate activity <22; high activity ≥22.[14] The SDAI was measured by the arithmetic sum of tender and swollen 28-joint count, the patient's and evaluator's global assessment (both from 0 to 10) and CRP in mg/dL. SDAI cut-off values were as follows: remission <3.3; low activity <11; moderate activity <26; high activity ≥26.[17]

The HAQ has questions about 20 specific activities that are assessed on a 4-point Likert scale where 0 = without difficulty,

1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do. The 20 activities are grouped into 8 functional categories, with each category given a single score equal to the maximum value of its component activities. The final value ranges from 0 (no impairment) to 3 (maximum impairment).[18]1. Nutritional status: this was evaluated by anthropometric measures, MNA, and body composition through electrical bioimpedance. Anthropometric evaluation included weight and height for BMI calculation, waist and hip circumference measurements for waist/hip ratio. BMI cut-offs for normal weight ($18.5 < BMI \leq 24.99\,kg/m^2$), overweight ($25 < BMI \leq 29.99\,kg/m^2$), and obesity ($\geq 30\,kg/m^2$) were considered.[19] Values until 88 cm for waist circumference and a ratio of 0.85 for abdominal/hip circumference were considered normal for females.[20]

The NMA comprises 18 questions, that contain a dietary questionnaire, subjective assessment (self-perception of health and nutrition), global assessment (questions related to lifestyle, medication, and morbidity), and anthropometric measurements (weight, height and weight loss). The maximum score is 30 points; values of >24 points indicate normal nutritional status from 23.5 to 17 refers to the risk of malnutrition; <17 points indicate malnutrition.[21,22]

Body composition was evaluated through electrical impedance analysis using a Bodystat 1500® device that measures fat percentage (%), fat mass (kg), lean mass percentage (%), lean mass (kg), body water percentage (%), body water mass (L), basal metabolism rate (kcal), estimated caloric need (kcal), and impedance at 50 Hz.

All questionnaires used were translated and validated in Portuguese.[18,23]

3 | RESULTS

Seventy-one women were included. The sample description is in Table 1. This table shows that the patients were mainly Caucasians, middle aged and non-smokers, in disease remission or mild disease activity. The most frequently used medications were methotrexate and leflunomide, followed by glucocorticoids and biologics.

Table 2 shows the studied parameters on nutritional evaluation. In this table, it is possible to observe that the majority of females were overweight or obese, with central obesity.

3.1 | Study of RA patients according to MNA

Patients with RA were divided into 2 groups and compared.

Group 1 included those undernourished (1/71) and those at malnutrition risk (23/71) and Group 2 included nourished individuals (n = 47) according to MNA. The results are in Table 3. This table shows that the nutritional profile got worse when there was a lot of disease and loss of function.

TABLE 1 Sample description: 71 rheumatoid arthritis women

Variable	N or central tendency
Mean age, SD, y	55.9 ± 10.5
Ethnic background	
Caucasian, n	46/71—64.8%
Afrodescendants, n	23/71—32.3%
Others, n	2/71—2.8%
Current smokers, n	9/71—12.6%
Exercising	
Median disease duration (IQR), y	8.0 (5.0-15.0)
Rheumatoid nodules, n	4/71—5.6%
Positive rheumatoid factor, n	45/71—63.3%
Treatment	
Antimalarial, n	7/71—9.8%
Methotrexate	44/71—61.9%
Leflunomide	43/71—60.5%
Biological	35/71—49.2%
Anti-tumor necrosis factor-α	13/71—18.3%
Anti-interleukin-6	10/71—14.0%
Abatacept	8/71—11.2%
Rituximab	4/71—5.6%
Tofacitinib	4/71—5.6%
Prednisone	37/71—52.1%
Median prednisone/d (IQR) mg	5.0 (5.0-10.0)
Median SDAI (IQR)	9.5 (3.0-18.5)
Remission, n	21/71—29.5%
Mild activity, n	17/71—23.9%
Moderate activity, n	24/71—33.8%
High activity, n	9/71—12.6%
Median CDAI (IQR)	8.2 (2.0-18.3)
Remission, n	19/71—26.7%
Mild activity, n	18/71—25.3%
Moderate activity, n	25/71—35.2%
High activity, n	9/71—12.6%)
Median ESR (IQR), mm	23.0 (12.0-55.2)
Median CRP (IQR), mg/dL	2.2 (0.6-7.3)
Mean hemoglobin (SD), g/dL	13.3 ± 1.1
Median HAQ (IQR)	1.1 (0.5-2.0)
Comorbidities	
Arterial hypertension	33/71—46.4%
Diabetes mellitus	14/71—19.7%
Dyslipidemia	46/71—64.7%

Abbreviations: CDAI, clinical disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, interquartile range; SD, standard deviation; SDAI, simple disease activity index.

TABLE 2 Description of nutritional parameters in 71 rheumatoid arthritis women

Mean body mass index (SD), kg/m^2	29.0 ± 4.7
Underweight	2/71—2.8%
Normal	15/71—21.1%
Overweight	24/71—33.8%
Obesity	30/71—42.2%
Mean abdominal circumference (SD), cm	97.9 ± 11.8
Patients above normal values, n	57/71—80.2%
Mean abdominal/hip circumference ratio, SD	0.92 ± 0.06
Patients above normal values, n	60/71—84.5%
Mean MNA, SD	24.4 ± 2.6
Undernourished, n	1/71—1.4%
At malnutrition risk, n	23/71—32.3%
Nourished, n	47/71—66.1%
Bioimpedance results	
Fat mass	
Mean fat mass, kg, SD	34.7 ± 10.8
Median % of fat mass (IQR)	47.4 (42.0-51.0)
Values above normal in % of body fat, n	70/71—98.5%
Lean mass	
Mean lean mass, kg, SD	38.4 ± 6.0
Median % of lean mass (IQR)	52.4 (48.3-57.4)
Values under normal in % of lean mass, n	68/71—95.7%
Median basal metabolism rate (IQR), kcal	1262 (1188-1761)
Mean basal metabolism rate/total mass (SD), kcal/kg	18.0 ± 2.4

Abbreviations: IQR, interquartile range; MNA, mini nutritional assessment; n, number; SD, standard deviation.

Association studies of Groups 1 and 2 by MNA with BMI, waist/hip circumference ratio, and all parameters from bioimpedance were all non-significant ($P > .05$).

3.2 | Nutritional evaluation by bioimpedance

The analysis of the main parameters of bioimpedance with disease activity is shown in Table 4, and no associations could be found. The study of the percentage of body fat according to used medications showed no associations (P = ns) except for abatacept, which had a mean value of 41.48% ± 8.65% in those using it vs 47.10% ± 5.86% in those not using it (P = .01). In addition, the study of waist/hip circumference ratio was not associated with used drugs but, again, with abatacept (using abatacept with a mean value of 0.88 ± 0.06 vs 0.92 ± 0.06 in those not using it; P = .04).

The correlation studies of the percentage of body fat and percentage of lean mass with HAQ were non-significant (P = ns).

4 | DISCUSSION

The assessment of the nutritional profile by MNA has shown that almost one-third of the presently studied sample had malnutrition or was at malnutrition risk. In this sample, the MNA scores were associated with disease inflammatory markers and loss of function. Presently, none of the commonly used medications is linked to changes in nutritional status measured by this tool. The analysis of our results suggested that, to achieve a better nutritional status, the important thing is to obtain inflammatory control of the disease regardless of the used medication. A study of 49 patients with RA from Sweden using MNA found a high proportion of malnourished individuals (76%), and confirmed the association between poor nutritional status with disease activity and loss of function.[14]

In terms of the bioimpedance body composition parameters studied, almost all patients in this sample had high fat mass and low lean mass, reflecting findings from other populations' studies.[14,15,24] In RA, muscle mass deterioration is credited to the elevation of pro-inflammatory cytokines that favor proteolysis through the ubiquitin–proteasome pathway and induce anabolic resistance in the muscles.[25] The tendency to gain fat mass is attributed to a decrease in physical activity associated with normal dietary intake, resulting in a positive energy balance. Loss of muscle mass may lead to deterioration of function, although joint inflammation and deformity may also play a role in this setting.[25] Surprisingly, some authors have linked an increase in body fat to improved outcomes in RA structural damage. Serum levels of adiponectin have been linked to low adiposity and radiographic damage in RA.[26] This cytokine, considered to be anti-inflammatory at systemic levels, may have pro-inflammatory properties in the joint milieu.[27] Another given explanation is that patients with a higher percentage of fat complain more frequently of pain and this results in higher disease activity scores and overtreatment by doctors.[28] Serum nerve growth factor is higher in obese people, and it is an important pain mediator that may explain why obese people feel pain more.[29]

Chronic use of low doses of prednisone for treatment could not be connected to either fat accumulation or increased waist/hip circumference ratio, or with malnutrition by MNA in this study. According to Huscher et al,[30] weight gain during glucocorticoid use was seen in patients treated with at least 5 mg of prednisone/d for at least 6 months. Westhovens et al[31] found an association of glucocorticoid use with central fat distribution, but Inaba et al,[32] studying patients with RA, did not. Furthermore, research on anti-TNF-α drugs in body composition has produced contradictory results. Serelis et al[33] could

TABLE 3 Comparison of epidemiological, clinical, treatment profiles, disease activity score and function according to nutritional status classified by mini nutritional assessment

	Group 1 (undernourished and at risk), N = 24	Group 2 (normal), N = 47	*P*
Mean age, SD, y	55.5 ± 10.6	56.1 ± 10.5	.83
Median disease duration (IQR), y	10.0 (6.0-16.5)	8.0 (5.0-15.0)	.41
Positive rheumatoid factor, n	15/24—62.5%	30/47—63.8%	.91
Smokers	3/24—12.5%	6/47—12.7%	.99
Median ESR (IQR), mm	35.0 (20.0-58.7)	29.5 (8.0-55.2)	.03
Median CRP (IQR), mg/dL	2.2 (0.71-11.1)	2.2 (0.6-7.0)	.71
Mean hemoglobin, SD, g/dL	13.3 ± 1.36	13.3 ± 1.0	.87
Treatment			
Antimalarials	1/24	6/47	.41
Methotrexate	18/24	26/46	.12
Leflunomide	12/24	31/47	.19
Biologics	14/24	21/47	.27
Tofacitinib	0	4/47	.99
Prednisone	14/24	23/47	.45
Median prednisone (IQR) mg/d	5 (5-10)	5 (5-10)	.49
SDAI	16.3 (4.5-25.1)	7.1 (2.3-17.8)	.02
CDAI	15.5 (4.5-24.2)	6.0 (1.0-16.0)	.02
HAQ	1.7 (0.90-2.2)	0.7 (0.5-1.7)	.002

Abbreviations: CDAI, clinical disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, interquartile range; SD, standard deviation; SDAI, simple disease activity index.

TABLE 4 Study of BMI and main bioimpedance parameters in relation to disease activity

Disease activity	Remission	Low	Moderate	High	*P*
SDAI, n	21	17	24	9	
Median % fat mass (IQR)	49.0 (42.2-53.1)	48.0 (44.1-53.2)	46.1 (41.1-49.9)	45.0 (39.1-20.0)	.27
Median % lean mass (IQR)	49.3 (46.7-55.3)	52.0 (46.7-55.8)	53.8 (50.3-58.7)	55.0 (50.0-61.4)	.11
Mean basal metabolism/kg, SD	17.7 ± 2.8	18.0 ± 2.3	18.3 ± 2.3	18.3 ± 1.8	.83
Median BMI (IQR) kg/m^2	29.4 (26.2-33.2)	28.1 (25.5-31.2)	29.1 (26.5-32.1)	26.9 (23.3-32,4)	.82
CDAI, n	19	18	25	8	
Median % fat mass (IQR)	49.0 (43.0-53.2)	48.6 (43.3-56.3)	46.3 (41.6-49.7)	44.5 (38.6-51.7)	.28
Median % lean mass (IQR)	50.0 (46.6-63.0)	51.4 (46.8-56.6)	53.7 (50.2-67.7)	55.5 (50.0-56.9)	.16
Mean Basal metabolism/kg, SD	17.8 ± 2.8	17.7 ± 2.4	18.5 ± 2.2	18.1 ± 1.9	.72
Mean BMI, SD, kg/m^2	28.7 ± 5.3	29.7 ± 5.3	28.6 ± 4.3	28.9 ± 4.3	.90

Abbreviations: BMI, body mass index; CDAI, clinical disease activity index; IQR, interquartile range; n, number; SD, standard deviation; SDAI, simple disease activity index.

not find changes in lean or fat mass in studying 19 patients with RA, but others found increases in fat mass and body weight with the use of this medication.[34–36] Etanercept is used to increase weight and lean mass.[37] Tocilizumab has also been linked to an increase in lean mass in at least 2 studies;[38,39] no studies on rituximab use affecting body composition in patients with RA were found. In this sample, no proven alterations in nutritional status or body composition with used medications, except abatacept, were found. Abatacept was linked to a lower percentage of body fat and a lower waist/hip circumference ratio, but not to MNA results. However, it is not possible to come to any conclusion since the number of patients using abatacept was quite small. More studies with larger samples are needed to confirm this finding.

Differences in the results from MNA and body composition have already been noted and credited to the fact that MNA may also evaluate general health and not only nutrition.[40] MNA also refers to

changes during the previous 3 months, which may be considered a short period of observation.[8]

Assessment of nutrition is important in patients with RA as obesity has strong positive associations with adverse cardiovascular risk factors such as hypercholesterolemia, diastolic hypertension, and high concentrations of CRP. Central obesity is associated with insulin resistance, arterial thickening and stiffening.[5]

This work is limited by its low number of patients and not having healthy controls for comparison. It included only women and patients using public health care services, who are usually those with low socio-economic status. Therefore, the present findings only apply to this population and cannot be generalized. Also, no study of vitamin shortage was performed. Another observation is about the use of MNA to evaluate nutritional status; this is only a screening tool and not diagnostic of malnutrition, and this should be taken into account in the interpretation of the results. However, it does show that nutritional status is altered in a large proportion of patients with RA in Brazil, and this issue should be addressed in their care.

In summary, nearly one-third of patients with RA were at nutritional risk by MNA, which associates undernutrition with disease activity and loss of function. Almost the whole sample had an increased percentage of fat mass and a diminished percentage of muscle mass that could not be associated with disease activity or function.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection were performed by JGCD and BSK. The data analysis and the first draft of the manuscript was done by TS and RN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

All authors declare there are no conflicts of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Committee of Ethics in Research from Evangelic Mackenzie School of Medicine under protocol number 4.023.752.

CONSENT TO PARTICIPATE

All participants signed an informed consent.

CONSENT FOR PUBLICATION

Yes.

TRANSPARENCY DECLARATION

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Renato Nisihara https://orcid.org/0000-0002-1234-8093
Thelma L. Skare https://orcid.org/0000-0002-7699-3542

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ORIGINAL ARTICLE

Aberrant messenger RNA expression in peripheral blood mononuclear cells is associated with gouty arthritis

Jiayan Shen[1] | Zhaohu Xie[1] | Yi Liu[1] | Ting Zhao[1] | Zhenming Li[1] | Yifei Ren[1] | Yujiang Xi[1] | Niqing Xiao[1] | Xiaoli Yang[1] | Shuiyan Shao[1] | Dongdong Qin[1] | Jiangyun Peng[2] | Zhaofu Li[1]

[1]Yunnan University of Chinese Medicine, Kunming, China

[2]The First Affiliated Hospital of Yunnan University of Chinese Medicine, Kunming, China

Correspondence
Zhaofu Li, Traditional Chinese Medicine/Rheumatology, Yunnan University of Chinese Medicine, Kunming, China.
Email: lzf0817@126.com

Jiangyun Peng, Traditional Chinese Medicine/Rheumatology, The First Affiliated Hospital of Yunnan University of Chinese Medicine, Kunming, China.
Email: pengjiangyun@126.com

Dongdong Qin, Neurobiology, Yunnan University of Chinese Medicine, Kunming, China.
Email: qindong108@163.com

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Abstract

Aim: Gouty arthritis (GA) is a type of self-limiting inflammatory arthritis caused by deposition of monosodium urate (MSU). This study aimed to analyze the expression variation of messenger RNAs (mRNAs) in GA patients and investigated the role of mRNAs in GA pathogenesis.

Methods: Five patients with acute GA (AGA), 5 with non-acute GA (NAGA), and 5 healthy controls (HC) were recruited to examine differential mRNA expression profiles in peripheral blood mononuclear cells (PBMCs) and explore whether mRNA is involved in the pathogenesis of AGA. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were used to study the biological functions of differentially expressed mRNA and the relationship between genes and signal pathways.

Results: Compared with HC, the AGA group had 1456 differentially expressed mRNAs, while the NAGA group had 437 differentially expressed mRNAs and compared with the NAGA group, 115 differentially expressed mRNAs were found in the AGA group. GO analysis showed that the differentially expressed mRNA in the AGA group was mainly enriched in processes related to leukocyte activation and immune response, while KEGG analysis showed that "*Staphylococcus aureus* infection" and "Cytokine-cytokine receptor interaction" are enriched in the up-regulated mRNAs in the AGA group.

Conclusion: This study identified genes and pathways that are differentially expressed during the onset of AGA, which might reveal part of the pathogenesis of the disease and provide clues to explaining the severe pain associated with disease onset and the rapid development of inflammatory response that subsides by itself.

KEYWORDS
acute gouty arthritis, inflammation, messenger RNA, pain, pathogenesis

Jiayan Shen and Zhaohu Xie contributed equally to this manuscript. And also co-first authors.

1 | INTRODUCTION

Gouty arthritis (GA) is a kind of inflammatory arthritis caused by monosodium urate (MSU) crystal deposition in patients with hyperuricemia.[1,2] Acute GA (AGA) is the most common first symptom of GA and if not treated actively, it will lead to bone metabolic disorder and bone destruction, which may eventually develop into joint injury and deformity.[3–5] Nuclear factor kappa-B (NF-κB) and NOD-like receptor protein 3 (NLRP3) are important components of the innate immune system which are closely associated with the inflammatory response[6] and AGA pathogenesis. In normal individuals, inactive NF-κB dimers exist in the cytoplasm.[7] MSU can lead to NF-κB entering the nucleus and being activated, which promotes the transcription and synthesis of a large number of pro-inflammatory cytokines that in turn trigger or aggravate AGA.[8,9] The NLRP3 receptor protein can also recognize MSU in tissues and is activated to form the NLRP3 inflammatory body that promotes the maturation and release of cytokines such as interleukin (IL)-1β and IL-18 which trigger or aggravate AGA.[10–12]

Elevated serum urate concentration (hyperuricemia) is the most critical risk factor for GA;[2] however, not all hyperuricemia causes AGA. Studies have shown that in patients with serum uric acid concentrations ≥10 mg/dL, only about 50% of patients develop AGA within 15 years.[13] Therefore, other factors unrelated to uric acid metabolism could play a role in the pathogenesis of AGA. Researchers have used genomics to reveal the relationship between AGA and healthy people and hyperuricemia based on candidate genes and pathways.[14,15]

It is well known that messenger RNA (mRNA) is transcribed from a strand of template DNA and carries genetic information that guides protein synthesis and participates in various biological processes, such as disease occurrence and development. Studies have shown that mRNA expression of certain cytokines is closely associated with the development and treatment of GA. For example, it is possible to predict the susceptibility to GA,[16–18] as well as the relationship between hyperuricemia and GA[19] and the potential side effects of therapeutic drugs.[20] Other studies have shown that the mRNA of cytokines can enhance inflammatory responses and promote the development of GA through the activations of different signaling pathways.[21–23] Therefore, we examined the differential mRNA expression profiles in peripheral blood mononuclear cells (PBMCs) of AGA patients, non-acute GA (NAGA) patients, and healthy controls (HC) to study whether mRNA is involved in AGA pathogenesis. We used Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis to define the biological functions of differentially expressed mRNAs and the relationship between genes and signal pathways.

2 | METHODS

2.1 | Participants and ethical statement

The study group consisted of patients with AGA, NAGA, and HCs (n = 5 for each group) who were recruited from the rheumatology center of the First Affiliated Hospital of Yunnan University of Chinese Medicine from February 2019 to July 2020. The diagnosis of GA followed the preliminary criteria published in the 1977 American College of Rheumatology classification criteria (n = 10).[24] Depending on whether the patients presented with onset symptoms at the joint,[25,26] those with GA were further divided into an AGA group (swelling, redness, stiffness, and severe pain in the last 2 weeks), and a NAGA group (no swelling, redness, stiffness, and severe pain occurred in the last 2 weeks). Physically health people who had no history of hyperuricemia, metabolic syndromes, or other chronic diseases were recruited as HCs. All participants fasted for at least 8 hours before blood sample collection.

This study was approved by the institutional ethics committee of Yunnan Provincial Traditional Medicine Hospital Ethics Committee (approval number: YJ 2019-006-01). Before the start of the study, all participants signed the informed consent form, and all protocols were conducted according to the International Conference on Harmonization.

2.2 | RNA isolation and quality control

The PBMCs were isolated using Ficoll-Hypaque density gradient centrifugation from total blood samples. Total RNA was extracted from the PBMC samples with TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. RNA quantity and purity were measured by NanoDrop ND-1000c and RNA integrity was assessed by Agilent 2100 Bioanalyzer. The RNA samples with RNA integrity numbers (RIN) >7.0 were selected and frozen in the refrigerator at −80°C until further analysis.

2.3 | Microarray analysis

The Arraystar Human mRNA Microarray V5.0 was used for mRNA microarray analysis, which was performed by Aksomics (Shanghai, China). After removing ribosomal RNA from the total RNA, mRNA was obtained. Then, the mRNA samples were transcribed into fluorescent complementary RNA (cRNA) with the Arraystar RNA Flash Labeling Kit and purified by RNeasy Mini Kit. The concentration and specific activity of the labeled cRNAs (pmol Cy3/μg cRNA) were measured with a NanoDrop ND-1000. It was 1 μg of the quantified cRNA samples that was added to the hybridization solution for hybridization at 60°C for 30 minutes, and then moved to the mRNA expression microarray slide. The slides were incubated in an Agilent hybrid oven at 65°C for 17 hours. The hybrid array was cleaned, fixed, and scanned with an Agilent DNA microarray scanner (Part No. g 2505c). The mRNAs with P values <.05 and fold changes >2 were identified and selected.

2.4 | GO and KEGG analysis

The GO knowledgebase provided a controlled vocabulary to characterize genes and their attributes. (http://www.geneontology.org).

The KEGG enrichment analysis (www. Genome.jp/kegg) was used to analyze pathways of differentially expressed mRNAs.

2.5 | Statistical analysis

Measurement data were expressed as the mean ± SD. Student's *t* tests were used to analyze the differential expression of the mRNAs in the microarray analysis. Agilent Feature Extraction software (version 11.0.1.1) was used to analyze acquired array images. Quantile normalization and subsequent data processing were performed using the GeneSpring GX v12.1 software package (Agilent Technologies). Note that *P* values <.05 were used to indicate statistical significance.

3 | RESULTS

3.1 | Characteristics of the study subjects

There were 15 participants in this study who were divided into 5 with AGA, 5 with NAGA, and 5 individuals used as HC. All participants were male. The duration of the disease was 4.90 ± 1.90 years in patients with AGA and 5.10 ± 2.12 years in patients with NAGA. Information about participants including their age, serum uric acid (UA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are shown in Table 1.

3.2 | Differentially expressed mRNAs associated with AGA

The mRNA samples from the 3 test groups were analyzed by expression profiling. The microarray data analysis showed that there were differences in mRNA expression between AGA, NAGA, and HC (Figure 1A-D). The result showed that there were significant differences in the expression of 1458 mRNAs in the AGA group compared with the HC group, of which 552 mRNAs were up-regulated and 906 mRNAs were down-regulated (Figure 1B). Moreover, of the 10 mRNAs that were most up-regulated and down-regulated in AGA patients compared with the HC group, *FBXL13* (17.319 fold-change) was the most up-regulated and *HLA-DRB5* (38.458 fold-change) was the most down-regulated (Figure 2A,B). There were significant differences in the expression of 437 mRNAs in the NAGA group, of which 51 mRNAs were up-regulated and 386 mRNAs were down-regulated (Figure 1C). We found that of the top 10 differentially expressed mRNAs the in NAGA group, *DEFA4* (6.183 fold-change) was the most up-regulated and *HLA-DRB5* (51.265 fold-change) was the most down-regulated mRNAs (Figure 2C,D). There were 115 mRNAs that were differentially expressed in the NAGA group, of which 36 mRNAs were up-regulated and 79 mRNAs were down-regulated when compared with patients in the AGA group (Figure 1D). Of the top 10 differentially regulated mRNAs in the NAGA group, *CXCR4* (3.125 fold-change) was the most up-regulated, and *TNFAIP6* (5.157 fold-change) was the most down-regulated compared with those in the AGA group (Figure 2E,F). Together, these results showed there were significant differences in the expression of mRNAs in the AGA group compared with the HC and NAGA groups.

3.3 | GO analysis of differentially expressed genes associated with AGA

Three domains in the differentially expressed transcripts were identified using GO database analysis. These included biological processes (BP), cellular components (CC), and molecular functions (MF). Compared with the HC group, the up-regulated mRNAs in the AGA group were abundant in "Myeloid leukocyte activation", "Myeloid cell activation involved in immune response", "Myeloid leukocyte mediated immunity", "Leukocyte degranulation" in the BP, "Integral component of plasma membrane" and "Intrinsic component of plasma membrane" in the CC; as well as "Signal transducer activity", "Molecular transducer activity", and "Signaling receptor activity" in the MF (Figure 3A-C). The down-regulated mRNAs in the AGA group were enriched in "Cellular nitrogen compound metabolic process", "Organic cyclic compound metabolic process" and "Cellular aromatic compound metabolic process" in the BP, "Intracellular", "Intracellular part" and "Organelle" in the CC, "Binding" and "Protein binding" in the MF (Figure 3D-F).

Compared with the NAGA group, the up-regulated mRNAs in the AGA group were abundant in "Cell activation",

TABLE 1 General information of participants in this study

Characteristics	HC (n = 5)	AGA (n = 5)	NAGA (n = 5)
Gender	Male	Male	Male
Age, mean ± SD, y	37.50 ± 19.09	39.33 ± 19.63	38.47 ± 18.74
Disease duration, y	-	4.90 ± 1.90	5.1 ± 2.12
UA, μmol/L	390.80 ± 15.66$^{\#}$	536.00 ± 61.56*	402.40 ± 35.95*$^{\#}$
ESR, mm/h	3.20 ± 1.48$^{\#}$	39.20 ± 10.71*	16.40 ± 5.18*$^{\#}$
CRP, mg/L	0.90 ± 0.96$^{\#}$	21.12 ± 9.79*	2.43 ± 0.47*$^{\#}$

Note: Compared with HC, *P < .05; compared with AGA, $^{\#}P$ < .05.

Abbreviations: AGA, acute gouty arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NAGA, non-acute gouty arthritis; HC, healthy controls; UA, uric acid.

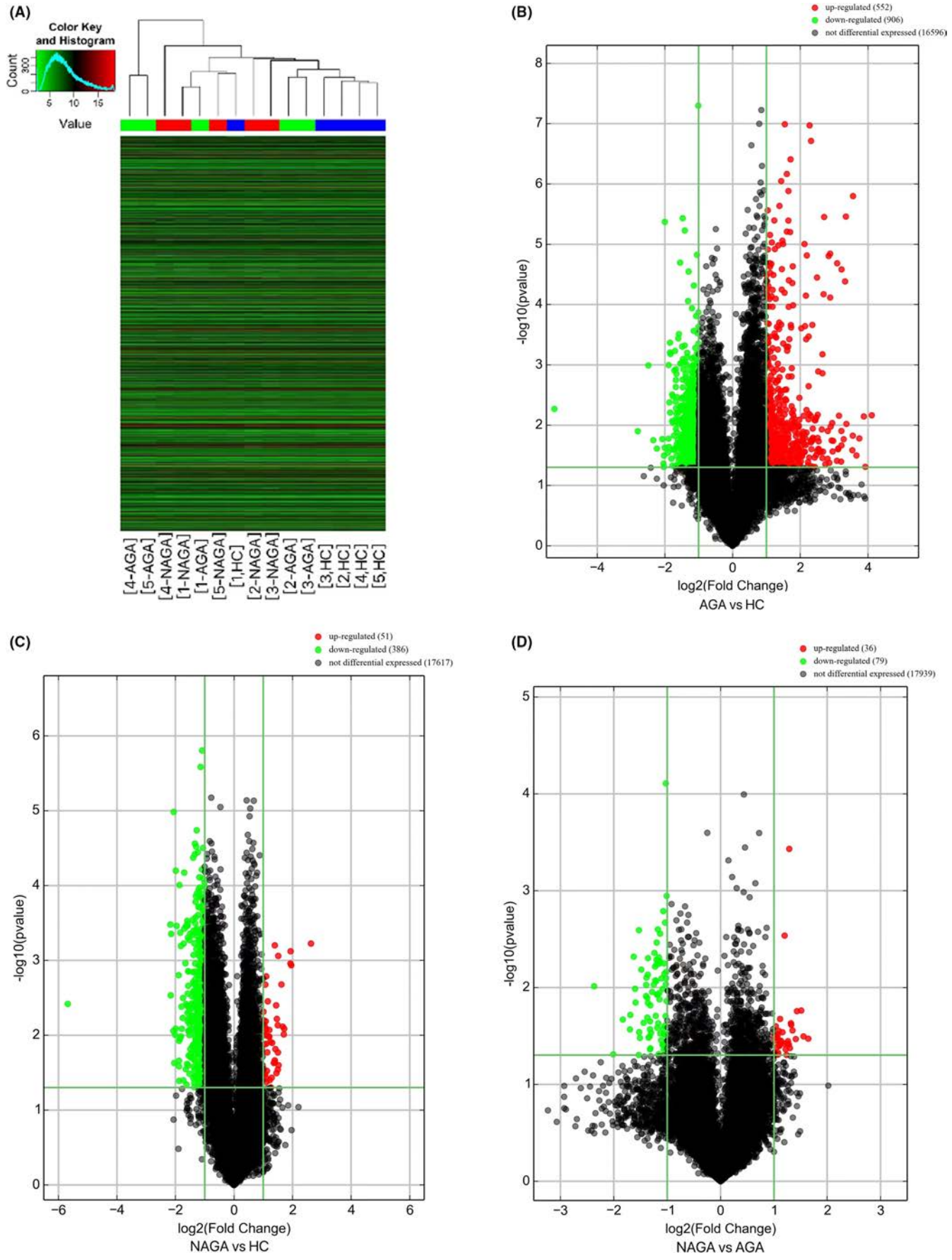

FIGURE 1 The hierarchical clustering and volcano map of differential messenger RNA expression. Red represents up-regulated genes and green represents down-regulated genes. AGA, acute gouty arthritis; NAGA, non-acute gouty arthritis; HC, healthy controls

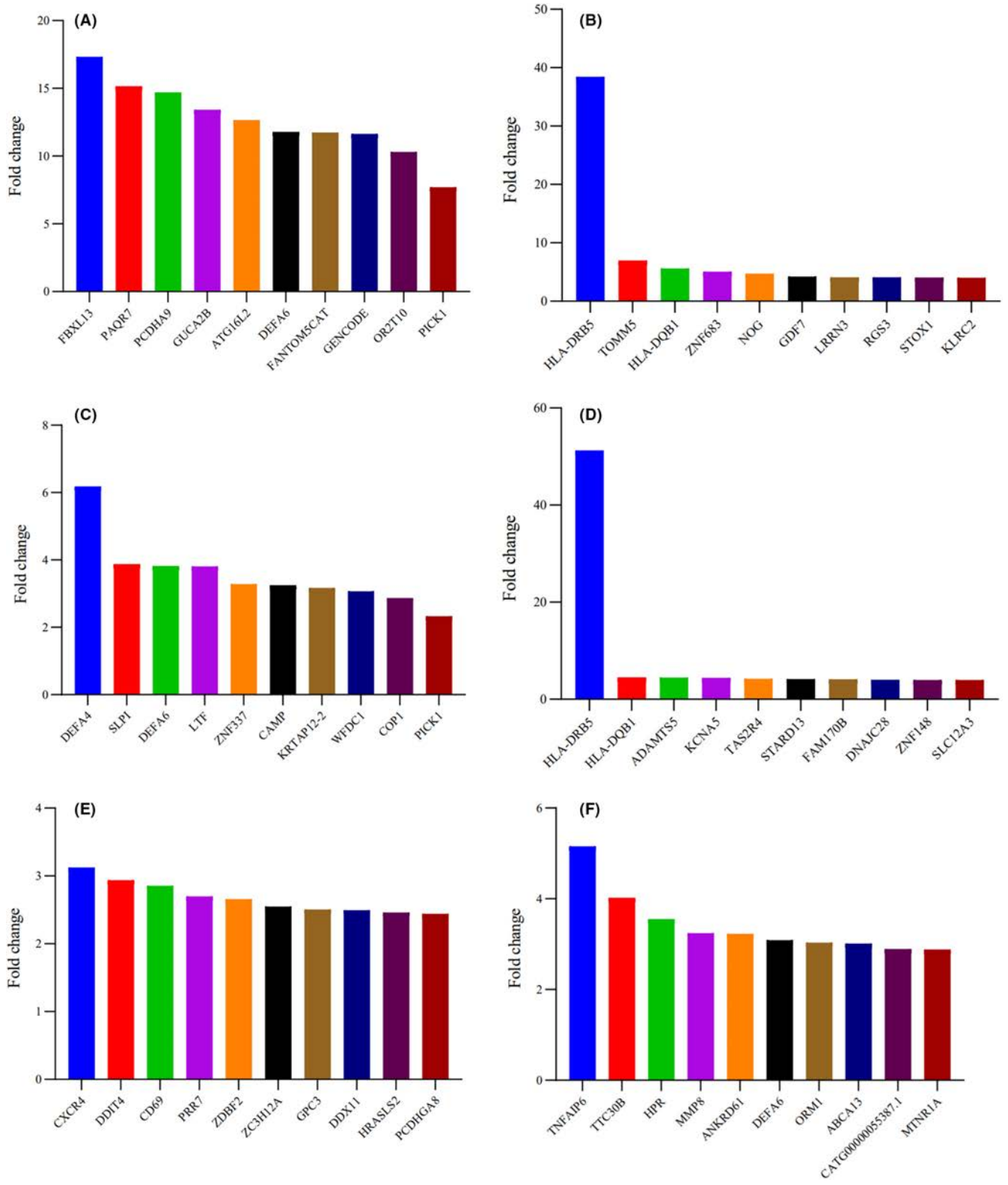

FIGURE 2 Differentially expressed messenger RNAs (mRNAs) associated with AGA pathogenesis. The top 10 up-regulated (A) and down-regulated (B) mRNAs between patients with AGA and HC, respectively. The top 10 up-regulated (C) and down-regulated (D) mRNAs between patients with NAGA and HC, respectively The top 10 up-regulated (E) and down-regulated (F) mRNAs between patients with NAGA and AGA, respectively. AGA, acute gouty arthritis; NAGA, non-acute gouty arthritis; HC, healthy controls

"Leukocyte activation" and "Immune effector process" in the BP, "Endomembrane system" and "Cytoplasmic vesicle part" in the CC, "Cytokine receptor binding", "Cytokine activity", "Calmodulin binding", and "Growth factor activity" in the MF (Figure 4A-C); while the down-regulated mRNAs in AGA group were abundant in "Multicellular organism development", "Anatomical structure

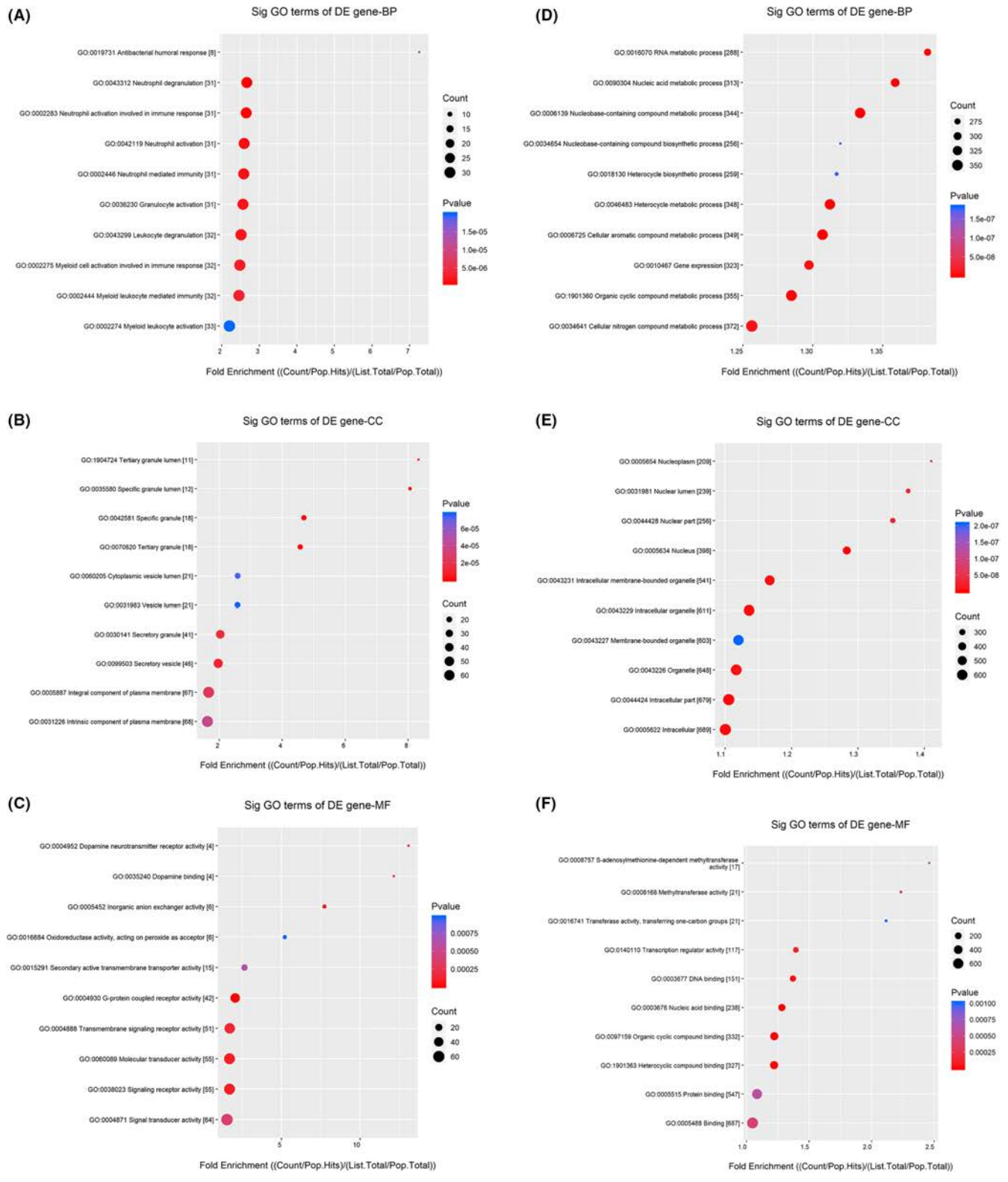

FIGURE 3 Gene Ontology (GO) analysis of differentially expressed messenger RNAs (mRNAs) in patients with AGA. The most enriched GO terms associated with up-regulated (A-C) and down-regulated (D-F) mRNAs in the AGA group compared with the HC group. AGA, acute gouty arthritis; NAGA, non-acute gouty arthritis; HC, healthy controls; BP, biological processes; CC, cellular components; MF, molecular functions

development" in the BP, "Membrane", "Membrane part", "Integral component of membrane" and "Intrinsic component of membrane" in the CC, "Ion binding", "Metal ion binding", and "Cation binding" in the MP (Figure 4D-F). These findings indicated that leukocyte and immune responses were activated and significantly up-regulated in the AGA group.

3.4 | KEGG pathway analysis of differentially expressed genes in AGA

The biological pathways related to differentially expressed mRNAs were evaluated using KEGG pathway analysis. When compared with the HC group, the most enriched networks of the up-regulated mRNAs in the AGA group were "Olfactory transduction", "Neuroactive ligand-receptor interaction", "Ras signaling pathway", and "*Staphylococcus aureus* infection" (Figure 5A). The most enriched networks of the down-regulated mRNAs in the AGA group were "Herpes simplex virus 1 infection", "Human T-cell leukemia virus 1 infection", "Cellular senescence", and "Antigen processing and presentation" (Figure 5B).

Compared with the NAGA group, there were no enriched pathways of the down-regulated mRNAs in the AGA group; however, the most enriched networks of the up-regulated mRNAs in the AGA group were "Cytokine-cytokine receptor interaction", "Signaling pathways regulating pluripotency of stem cells", "mTOR signaling pathway", and "Hippo signaling pathway" (Figure 5C). These results showed that "*Staphylococcus aureus* infection" and "Cytokine-cytokine receptor interaction" were the more enriched pathways in the AGA group of up-regulated mRNAs.

4 | DISCUSSION

Episodes of inflammation and severe pain are characteristics of AGA; therefore, current research on AGA has focused on what produces the inflammation[27,28] and has suggested that pain is part of the inflammatory response. However, the inflammatory response mainly occurs locally in the joints, while some patients mainly present with severe localized pain during AGA episodes without significant swelling and redness associated with inflammation. Therefore, it is particularly important to explore the inflammation and pain responses of AGA at the genetic level, which may contribute to developing new ideas and methods for the in-depth study of AGA pathogenesis.

Our results showed that leukocyte and immune responses were activated and significantly up-regulated in the AGA group compared to NAGA and HC groups, which is similar to the current understanding of AGA. KEGG analysis showed that "*Staphylococcus aureus* infection" and "Cytokine-cytokine receptor interaction" are enriched in the up-regulated mRNAs in the AGA group. In addition, *PICK1* was one of the significantly up-regulated mRNAs (Figure 2A, C), which may be an important component of pain induction in AGA.[29,30]

The high expression of these pathways and cytokines may be closely related to the pathogenesis of AGA. Therefore, we will discuss and analyze the specific functions of these pathways and cytokines within this current study to find the link between them and the pathogenesis of AGA and to provide some basis for developing additional treatments for AGA.

4.1 | Immune cell chemotaxis and AGA

The cytokines enriched in "Cytokine-cytokine receptor interaction" pathways include bone morphogenetic protein 2 (BMP2), C-C motif chemokine ligand 8 (CCL8), and chemokine (C-X-C-motif) ligand 1 (CXCL1). These factors, which are highly expressed during AGA pathogenesis, and have a strong chemotactic effect on certain immune cells. Chemokines are substances that attract immune cells to sites of biological activity, where they affect many BPs such as cell growth, angiogenesis, inflammation, and autoimmunity.[31]

CXCL1 is a member of the CXC chemokine subfamily that acts as a chemotactic agent for a variety of immune cells, especially chemotactic neutrophils or other non-hematopoietic cells, to recruit the cells to a site of injury or infection and plays an important role in regulating immune and inflammatory reactions. In the periphery, CXCL1 promotes the release of prostaglandins, resulting in increased sensitivity to pain and the stabilization of nociceptors through chemotactic neutrophils.[32–34] In addition, CXCL1 can also change K^+ currents by regulating the electrophysiological characteristics of the cell membrane, which is important in the activation of immune cells.[35] Additionally, CCL8, also known as MCP-2, HC14, SCYA8, or SCYA10, is one of the 4 subfamilies of chemokines.[36] It is chemotactic and activates many different types of immune cells, including monocytes, T cells, and natural killer cells and is related to inflammatory response through its binding to chemokine receptors on the surface of different cells, such as C-C motif chemokine receptor 1 (CCR1), CCR2, CCR3, and CCR5.[37] As a key signaling factor, CCL8 can induce Th2 cell differentiation under specific conditions so that they release Th2 cytokines like IL-4 and IL-5, which then trigger the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway.[38] The JAK-STAT pathway is a key step in the downstream signal transduction of inflammatory cytokines such as interferon (IFN) and interleukin.[39] In addition, CCL8 regulates the transcription of NF-κB and promotes the transcription and synthesis of many pro-inflammatory cytokines that trigger or aggravate AGA.[40]

Although BMP2 is not a chemokine, it plays an important role in the evolution of local inflammatory responses. Studies have reported that BMP2 can induce osteoblast differentiation and proliferation[41] and enhance cell migration and invasion.[42] BMP2 also plays a role in the treatment of inflammatory joint diseases by regulating the PI3K/AKT signaling pathway.[43,44] Therefore, our analysis suggests that the genes that encode BMP2, CXCL1, and CCL8 are enriched in the biological processes of AGA and may be relevant to its pathogenesis.

4.2 | *PICK1* can inhibit inflammation but exacerbate pain in AGA

Inflammatory pain can be caused by peripheral tissue damage and persistent inflammation and is characterized by abnormal pain and nociceptive hypersensitivity at a site of injury and adjacent tissues.[45,46] ESR and CRP are non-specific indicators that are used

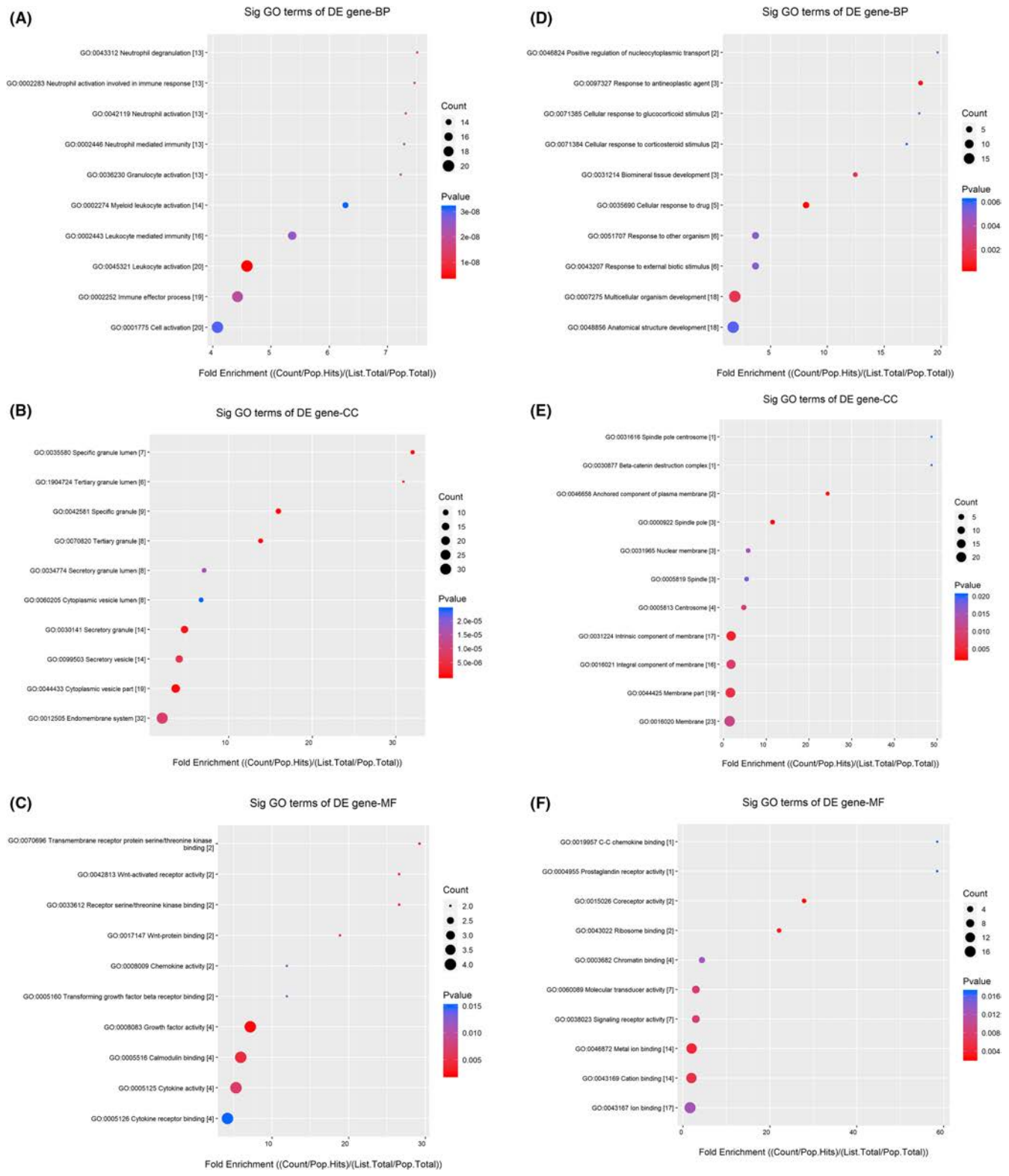

FIGURE 4 Gene Ontology (GO) analysis of differentially expressed messenger RNAs (mRNAs) in patients with AGA. The most enriched GO terms associated with up-regulated (A-C) and down-regulated (D-F) mRNAs in the AGA group when compared with the NAGA group. AGA, acute gouty arthritis; NAGA, non-acute gouty arthritis; HC, healthy controls; BP, biological processes; CC, cellular components; MF, molecular functions

clinically to evaluate the degree of inflammation and most commonly used as laboratory indicators of disease activity in patients with GA.[47] However, not all patients with AGA have elevated levels of ESR and CRP[48] and in some cases, clinical administration of anti-inflammatory and analgesic drugs is not effective in relieving pain symptoms. Therefore, it is extremely important to

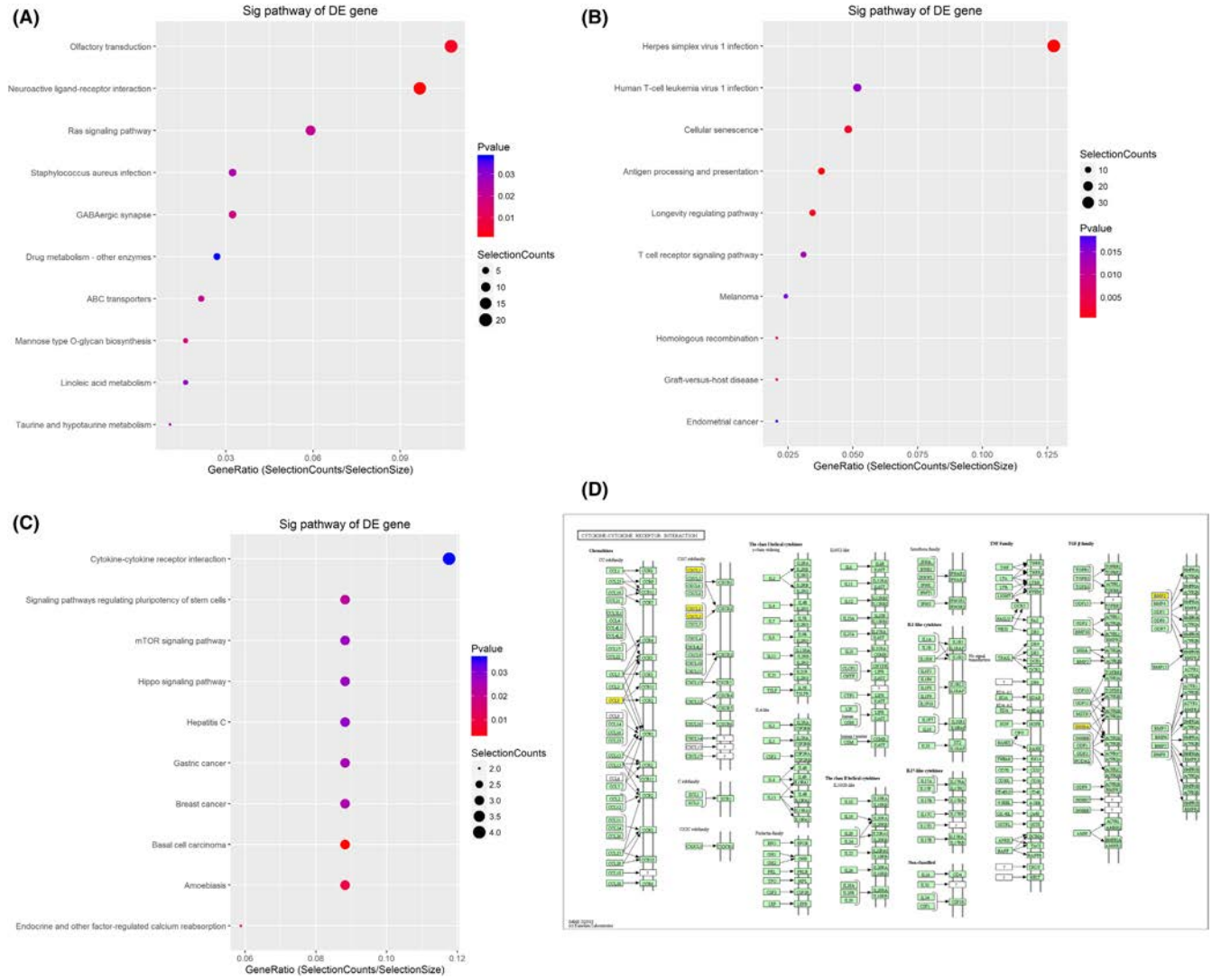

FIGURE 5 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of differentially expressed messenger RNAs (mRNAs) in AGA. The most enriched networks associated with mRNAs up-regulated (A) and down-regulated (B) in the AGA group compared with the HC group. The most enriched networks of the up-regulated mRNAs (C) in the AGA group compared with the NAGA group. A schematic of the gene category for the "Cytokine-cytokine receptor interaction" pathway (D). AGA, acute gouty arthritis; NAGA, non-acute gouty arthritis; HC, healthy controls

explore other possible mechanisms of patient pain to develop coping strategies.

PICK1 (Protein Interacting with C-kinase 1) is a scaffold protein that is widely distributed in various cells and tissues that participates in the occurrence and development of neuropathic and inflammatory pain, making it an attractive candidate target for pain treatment.[29] Indeed, *PICK1* was identified as a target for the treatment of inflammatory pain because its inhibition can effectively alleviate neuropathic and inflammatory pain and does not produce some of the side effects associated with current pain drugs, such as drowsiness, fatigue, apathy and addiction.[30] The PDZ domain of *PICK1* directly interacts with calcineurin B in osteoclast progenitor cells and promotes osteoclast differentiation through the activation of calcineurin nuclear factor of activated T-cells signaling, which may be an important component of bone destruction observed in patients with GA.[49]

While M1 macrophages release TNF-α, IL-1β, and other inflammatory cytokines to induce an inflammatory response, M2 macrophages can inhibit inflammation.[50,51] The inhibition or knockout of *PICK1* was reported to promote M1 macrophage polarization and inhibit M2 macrophage polarization.[52,53] Moreover, *PICK1* has a definite regulatory effect on PI3K/Akt pathway,[54] and deletion of this gene can lead to lysosomal damage and autophagy dysfunction and result in an increased inflammatory response.[55] In this study, we found that *PICK1* expression was significantly higher in the AGA group than the HC group, suggesting that the severe pain symptoms in patients with AGA may not be induced by the inflammation only. Perhaps because *PICK1* can aggravate pain in AGA but have a suppressive effect on inflammation, may partly explain why AGA attacks are more painful than in other inflammatory arthritis diseases such as ankylosing spondylitis and rheumatoid arthritis.

The results of this study showed that *PICK1* expression was significantly higher in the AGA group compared to the HC group. Therefore, we hypothesize that *PICK1* is closely related to the pathogenesis of AGA. *PICK1* not only aggravates pain in AGA, but also promotes the differentiation of osteoclasts, which leads to the bone destruction associated with AGA. Additionally, *PICK1* suppresses inflammation in AGA by regulating macrophage differentiation and promoting the autophagic process.

4.3 | "*Staphylococcus aureus* infection" pathway may suggest triggers of an AGA attack

Our results showed that the "*Staphylococcus aureus* infection" pathway was associated with one of the most abundant up-regulated mRNAs in the AGA group when compared with the HC group. Studies show that although rare, infectious arthritis and GA can copresent,[56,57] and bacteriological analyses have demonstrated the predominance of *Staphylococcus aureus*.[56] *Staphylococcus aureus* tolerates an acidic environment and induces Ca^{2+} overload when its invasion process is initiated on the surface of host cells, which eventually leads to necrotic cell death.[58–60] However, the effects of multiple forms of cell death, such as pyroptosis, apoptosis, necroptosis, and entotic cell death are involved in the pathogenesis of GA.[61] Therefore, these results may suggest that the "*Staphylococcus aureus* infection" pathway may induce AGA by causing cell death.

In conclusion, we systematically investigated the differential mRNA expression in PBMCs isolated from patients with GA and found that genes involved in leukocyte and immune responses were activated and significantly up-regulated in AGA compared to NAGA and HC. Also, the "*Staphylococcus aureus* infection" pathway and genes such as *BMP2*, *CXCL1*, *CCL8*, and *PICK1* were highly expressed in AGA. We suggest that high expression of these genes and their associated pathways may be related to the inflammation and severe pain observed in AGA pathology. Under the stimulation of pathogenic factors such as MSU, the body expresses and secretes chemotactic factors, such as CXCL1 and CCL8, which cause immune cells to converge toward the site of MSU deposition and induce inflammatory responses that can lead to an AGA attack, which is consistent with the inflammatory response in patients with AGA that is confined to specific joints. Moreover, the "*Staphylococcus aureus* infection" pathway may also induce AGA by causing cell death. We also found that *PICK1* inhibited inflammation but exacerbated pain symptoms, and CXCL1 not only increased sensitivity to pain, but stabilized nociceptors. This may partly explain the self-limiting inflammatory arthritis symptoms of GA and why pain symptoms are extremely severe during AGA attacks.

There were some limitations to this study. Although some pathways and genes were found to be highly expressed in AGA, the exploration of their correlation with the development of AGA was only preliminary due to insufficient blood samples that did not support additional validation of the results presented. In addition, only 5 patients were recruited for each group and therefore, the results from this small sample size could represent specific deviation. Future studies using larger sample sizes as well as additional animal and in vitro experiments will be required for validation.

AUTHOR CONTRIBUTIONS

JYS conducted the experiment and wrote the manuscript. ZHX designed the study. DDQ and ZHX revised the manuscript. JYP and ZFL conceived of and proposed the idea. YL, TZ, NQX, YFR,YJX and ZML recruited patients and collected information. SYS and XLY participated in data analysis. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare for authors.

ORCID

Zhaofu Li https://orcid.org/0000-0001-7414-3707

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ORIGINAL ARTICLE

Assessment of interclass and intraclass variability of specific lesions of sacroiliac magnetic resonance imaging

Zeynep Nilufer Tekin[1] | Cennet Sahin[2] | Tuna Demirbas[3] | Esen Kasapoglu[4]

[1]Department of Radiology, Goztepe Prof Dr Suleyman Yalcin City Hospital, Istanbul Medeniyet University, Istanbul, Türkiye

[2]Department of Radiology, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye

[3]Department of Radiology, Samsun Training and Research Hospital, University of Health Sciences, Samsun, Türkiye

[4]Division of Rheumatology, Department of Internal Medicine, Istanbul Medeniyet University Faculty of Medicine, Istanbul, Türkiye

Correspondence
Zeynep Nilufer Tekin, Department of Radiology, Goztepe Prof Dr Suleyman Yalcin City Hospital, Istanbul Medeniyet University, Dr. Erkin Street Kadikoy, Istanbul 34722, Türkiye.
Email: drnilufer@gmail.com

Abstract

Aim: Sacroiliac joint (SJ) imaging is the key point in the diagnosis of ankylosing spondylitis (AS). The curved anatomy of the SJ makes the interpretation of imaging difficult. The aim of this study is to evaluate the interclass and intraclass reliability of specific lesions (bone marrow edema [BME], joint space narrowing, erosions, effusion, ankylosis, bridging, sclerosis, fat deposition, and other additional pathologies) on SJ magnetic resonance imaging (MRI).

Method: In a total of 310 randomly chosen patients, 620 SJs were evaluated by three different radiologists with different radiology experiences of specialties other than musculoskeletal radiology.

Results: The agreement between readers for BME was fair to substantial, for active sacroiliitis was moderate to substantial, for sacroiliac narrowing was fair at best, for erosions was fair to moderate, for SJ sclerosis was none to slight, for chronic sacroiliitis was slight to fair, for degenerative sacroiliitis was none to slight, for normal SJ was slight, for SJ effusion was none to slight, and for fatty deposition was none. Intraclass correlation for readers 1 and 3 was usually good to excellent and for reader 2 was poor to fair.

Conclusion: This study was designed to assess the agreement between radiologists who were not familiar with SJ MRI. The agreement between readers was usually fair to substantial and even intraclass correlation was poor to fair for reader 2. Future studies can be designed for standardization and validation of each MRI lesion for better interpretation of SJ MRI.

KEYWORDS
observer agreement, reliability, sacroiliac imaging, sacroiliac magnetic resonance imaging, sacroiliitis

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a major subtype of spondyloarthritis (SpA) and one of the most common forms of inflammatory arthritis worldwide. Sacroiliitis is the hallmark of axial SpA (aSpA); if there is definite sacroiliitis on the plain sacroiliac joint (SJ) radiographs (PSJR), aSpA is classified as radiographic aSpA or AS; if there are no definite changes on PSJRs, aSpA is classified as nonradiographic aSpA (nraSpA).[1] Since SJ MRI was included in the SpondyloArthritis International Society nraSpA classification criteria in the absence of sacroiliitis on the radiograph PSJR, SJ MRI has been widely used.[2–4]

Although PSJR is the method of choice for detecting inflammatory changes on SJ because it is cheap and readily available, it is inadequate to detect early changes on SJ and it is difficult to interpret. Interobserver and intraobserver agreement is substantial. Detecting sacroiliitis with PSJR has modest sensitivity and specificity. Moreover, training of the readers does not improve either sensitivity or specificity.[5]

MRI is better than PSJR for detecting sacroiliitis especially with acute and early changes on the SJ. However, interobserver and intraobserver variability can be modest among trained readers, which may not be the case in daily, real life. This study was designed to assess the interobserver and intraobserver consensus of each SJ MRI finding among inexperienced radiologists on SJ MRI.

2 | MATERIALS AND METHODS

The study was approved by the local ethics committee (2018/0418). Informed patient consents were taken before the rereading of sacroiliac MRI examinations. All the patients were scanned with a General Electric (Chicago, IL, USA) 1.5 T Optima MR450W scanner using axial oblique T1-FSE (Fast spin echo), coronal oblique T1-FSE, coronal oblique STIR (short tau inversion recovery), axial oblique T2-FatSat (fat-saturated), axial oblique T1-FatSat, contrast-enhanced axial oblique T1-FatSat, and contrast-enhanced coronal oblique T1-FSE sequences. The SJ MRIs performed in the time period between 2015 and 2017 were reassessed retrospectively. Patients with clinically suspicious sacroileitis aged between 18 and 65 years were selected; producing 1900 SJ MRIs. Sample size was calculated as 306. Every first one was chosen of six MRI chosen randomly. A total of 310 patients with 620 SJs were reassessed by three different radiologists (ZNT, CS, TD) working in three different institutions, with different training careers, similar experience of radiology (15 years) and different specialties other than musculoskeletal radiology. MR images were evaluated for bone marrow edema (BME) defined as hyperintensity/inflammatory edema within the sacrum or ilium on contrast-enhanced T1-FatSat sequences and fluid-sensitive sequences, such as STIR or T2-FatSat,[6] joint space narrowing, presence and size of bone erosions (evaluated in its largest dimension as <5 mm, 5-10 mm, >10 mm), effusion, ankylosis, bridging, sclerosis, fat deposition, degeneration, and other pathologies (metastasis etc.) on sacral and iliac parts of the 620 SJs were reassessed. Bone marrow edema, narrowing and sclerosis on MRI were graded as 1 (poor/mild), 2 (moderate), or 3 (severe).

Active sacroiliitis was defined primarily as abnormal enhancement or edema on bone marrow and high signal intensity of erosions on STIR or T2-FatSat sequences. However, MRI findings suggestive of chronic disease were characterized by hypointensity on T1- and T2-weighted sequences, subchondral sclerosis, narrowing of the joint spaces, bridging, and ankylosis.

Readers were blinded for any clinical or laboratory data including imaging data.

2.1 | Statistics

SPSS 16 version (SPSS, Chicago, IL, USA) was used for Cronbach's α coefficient and the κ analysis for the assessment of inter-reader and intrareader variability, respectively. For the intraobserver variability, 50 patients were chosen randomly and reassessed after 6 months and the readers were blinded to the symptoms, diagnosis of the patients, and their own or each other's first assessments of the SJ MRIs; variability was rated as poor, fair, good, or excellent according to intraclass correlation coefficient (<0.5, 0.5-0.75, 0.76–0.9, >0.91, respectively).

3 | RESULTS

One hundred and five (34%) of the patients were male, mean age was 44 (18–65) years. Results of SJ MRI assessment of each reader are shown in Table 1. κ analysis for BME, joint space narrowing, erosions, acute/chronic and degenerative changes, effusion, bridging, ankylosis, sclerosis, and fat deposition detected in the right and left SJ MRI can be seen in Table 2. The agreement between readers for BME was fair to substantial, for active sacroiliitis was moderate to substantial, for sacroiliac narrowing was fair at best, for erosions was fair to moderate, for SJ sclerosis was none to slight, for chronic sacroiliitis was slight to fair, for degenerative sacroiliitis was none to slight, for normal SJ was slight, for SJ effusion was none to slight, and for fatty deposition was none at all. According to reader 3 there was no bridging on the SJs, the agreement was calculated as fair between reader 1 and 2 for bridging. We preferred to give two different κ values for right and left part of the SJ instead of 1 and found that although there was good agreement in the left iliac part of the SJ, it was poor in the right iliac part concerning BME (Table 2).

Intraclass correlation for each reader was usually good to excellent for readers 1 and 3. The lowest intraclass correlation was for left iliac BME for reader 1. For reader 2, intraclass correlation was poor to fair (Table 3).

When grading BME as poor, moderate, and severe, the agreement decreased to poor from fair. When sacroiliac narrowing was graded as mild, moderate, severe; there was no agreement at all for moderate narrowing, but there was poor agreement for mild and severe narrowing. Agreement between readers was no better when SJ sclerosis was graded as mild, moderate, severe. When grading erosions according to as <5 mm, 5-10 mm, >10 mm, κ test could not be calculated because the cells were empty in the cross-tabulation (data not shown).

4 | DISCUSSION

This study was designed to assess the agreement between radiologists who were not familiar with SJ MRI. Bone marrow edema, joint space narrowing, erosions, effusion, ankylosis, bridging, sclerosis, fat deposition, and other additional pathologies on sacral and iliac parts

TABLE 1 Assessment of sacroiliac MRI by each reader (310 patients, 620 sacroiliac joints)

	Reader 1	Reader 2	Reader 3
	n (%)	*n* (%)	*n* (%)
Sacral BME	84 (14%)	118 (19%)	66 (11%)
Grade 1	61 (10%)	98 (16%)	49(8%)
Grade 2	16 (3%)	14 (2%)	15 (2%)
Grade 3	7 (1%)	6 (1%)	2[a]
Iliac BME	90 (14%)	133 (22%)	72 (12%)
Grade 1	64 (10%)	106 (17%)	49 (8%)
Grade 2	15 (2%)	19 (3%)	20 (3%)
Grade 3	11(2%)	8 (1%)	3[a]
Active sacroiliitis	94 (15%)	156 (25%)	75 (12%)
SJ narrowing	78 (13%)	399 (65%)	25 (4%)
Grade 1	55 (9%)	270 (44%)	22 (4%)
Grade 2	14 (2%)	92(15%)	1[a]
Grade 3	9 (1%)	37 (6%)	2[a]
Erosion	92(15%)	171 (28%)	44 (7%)
<5 mm	74 (12%)	142 (23%)	34 (5%)
5-10 mm	15 (2%)	21 (3%)	10 (2%)
>10 mm	3[a]	8 (%1)	0[a]
Bridging	6[a]	197 (32%)	0[a]
Ankylosis	5[a]	21 (3%)	2[a]
SJ sclerosis	48 (8%)	411 (67%)	41(7%)
Grade 1	33 (5%)	329 (53%)	36 (6%)
Grade 2	11 (2%)	69(11%)	5[a]
Grade 3	4[a]	13 (2%)	0[a]
Chronic sacroiliitis	42 (7%)	305 (49%)	36 (6%)
Degenerative sacroiliitis	10 (1%)	266 (43%)	12 (2%)
Normal SJ	486 (79%)	94 (15%)	502 (81%)
SJ effusion	7 (1%)	23 (4%)	1[a]
Fatty changes of SJ	36 (6%)	92 (15%)	7 (1%)
Metastasis	4[a]	2[a]	3[a]

Abbreviations: BME, bone marrow edema; L, left; MRI, magnetic resonance imaging; R, right; SJ, sacroiliac joint.

[a]<%1.

TABLE 2 Kappa analysis between readers for sacroiliac MRI

	Reader 2	Reader 3
Reader 1		
R Sacral BME	0.57	0.7
L Sacral BME	0.58	0.79
R Iliac BME	0.54	0.35
L Iliac BME	0.59	0.76
R Active sacroiliitis	0.54	0.75
L Active sacroiliitis	0.55	0.76
R SJ narrowing	0.1	0.4
L SJ narrowing	0.09	0.4
R Erosion	0.3	0.5
L Erosion	0.22	0.38
R Bridging	0.4	NA[a]
L Bridging	0.42	NA[a]
R Ankylosis	0.0	0.0
L Ankylosis	0.0	0.0
R SJ sclerosis	0.07	0.47
L SJ sclerosis	0.05	0.4
R Chronic sacroiliitis	0.1	0.4
L Chronic sacroiliitis	0.08	0.4
R Degenerative sacroiliitis	0.0	0.18
L Degenerative sacroiliitis	0.0	0.1
R Normal SJ	0.04	0.1
L Normal SJ	0.04	0.65
R SJ effusion	0.0	NA[b]
L SJ effusion	0.8	0.0
R Fatty changes of SJ	0.3	0.3
L Fatty changes of SJ	0.0	0.0

Abbreviations: BME, bone marrow edema; L, left; MRI, magnetic resonance imaging; R, right; SJ, sacroiliac joint.

[a]NA: Not available because reader 3 detected no bridging.

[b]NA: Not available because reader 3 detected no SJ effusion.

of the 620 SJs were assessed by three different readers working in different institutions. Intraclass correlation for each reader was usually good to excellent for readers 1 and 3. The lowest intraclass correlation was for left iliac BME for reader 1. For reader 2, intraclass correlation was poor to fair.

Weber et al[2] showed the diagnostic utility of SJ MRI for detecting sacroiliitis. They found that agreement for the diagnosis of SpA was 85% in patients with inflammatory back pain and agreement for the absence of SpA was 92% and 95% in nonspecific back pain patients and in healthy controls, respectively. Reporting of the MRIs was after calibrating the reader using an MRI training set including standardized definitions of lesions, and poor reproducible lesions were excluded. Although concordance and discordance of the SpA diagnosis were studied, interclass or intraclass agreements between readers were not studied by Weber et al.[2]

Sacroiliac joint MRI is included in the SpondyloArthritis International Society aSpA classification criteria as an established tool. Therefore standardization is also of value.[3–5] Radiologists studying in the SpondyloArthritis International Society MRI working group and also in clinical studies involving SJ MRI are experienced and trained; however, expert radiologists may not be readily available in everyday life.

Rueda et al compared SJ MRI readings of a local radiologist, expert radiologist, and rheumatologist and found that interobserver agreements of SJ MRI readings were between fair and substantial, and also showed that a rheumatologist had a better performance in the interpretation of SJ MRI.[7] Our study compared readings of

TABLE 3 Kappa analysis between readers for sacroiliac MRI

	Reader 1	Reader 3
Reader 2		
R Sacral BME	0.5	0.4
L Sacral BME	0.2	0.5
R Iliac BME	0.55	0.4
L Iliac BME	0.27	0.5
R Active sacroiliitis	0.5	0.4
L Active sacroiliitis	0.5	0.5
R SJ narrowing	0.1	0.2
L SJ narrowing	0.9	0.04
R Erosion	0.3	0.2
L Erosion	0.2	0.15
R Bridging	0.0	NA[a]
L Bridging	0.4	NA[a]
R Ankylosis	0.0	0.1
L Ankylosis	0.2	0.14
R SJ sclerosis	0.36	0.7
L SJ sclerosis	0.5	0.06
R Chronic sacroiliitis	0.0	0.1
L Chronic sacroiliitis	0.8	0.09
R Degenerative sacroiliitis	0.0	0.03
L Degenerative sacroiliitis	0.0	0.02
R Normal SJ	0.9	0.06
L Normal SJ	0.0	0.05
R SJ effusion	0.0	NA[b]
L SJ effusion	0.00	0.0
R Fatty changes of SJ	0.0	0.09
L Fatty changes of SJ	0.0	0.0

Abbreviations: BME, bone marrow edema; L, left; MRI, magnetic resonance imaging; R, right; SJ, sacroiliac joint.

[a]NA: Not available because reader 3 detected no bridging.

[b]NA: Not available because reader 3 detected no SJ effusion.

radiologists working in different institutions with different experiences but who were not experts specifically on musculoskeletal radiology and found that interobserver agreement was poor in most of the parameters, including normal sacroiliac findings.

The κ values for sacroiliac erosions and BME on SJ MRIs were substantial between different readers in the study by Arnbak et al and Weber et al. Erosions, extended erosions, and backfill of excavated erosions were assessed and recorded according to standardized definitions.[8,9] We assessed erosions only according to size, which did not change the agreement between readers.

In the study by Weber et al comparing MRI-based classification, κ values for inter-reader agreement were 0.76 and 0.80 for two different inception cohorts. In this study the MRI criteria were prespecified by consensus among readers.[9] Weber et al evaluated BME, erosions, fatty infiltration, and ankylosis and concluded that erosions performed better than BME related to the false positivity. In our study, κ analysis for erosions was poor and fair at best, and showed differences between right and left SJs.

Bone marrow edema is considered to be the most diagnostic feature of active sacroiliitis. Although there are scoring systems like Berlin and SPARCC,[10] they are not widely used in daily practice. The κ values were fair between readers 1 and 2 and were fair for right SJ and good for left SJ between readers 1 and 3. These values were even inconsistent between right and left parts of SJs.

Jacquemin et al[11] found that the agreements between local and central readings and also between central readings on structural lesions like erosions, fatty lesions, and ankylosis of SJ MRI, were fair to moderate. Including fatty lesions increased the reliability. These findings were not compatible with our findings. In the study by Jacquemin et al, although central readers participated in a calibration session, local readers who were radiologists and rheumatologists did not participate in any training session.

Poddubnyy et al[12] investigated the performance of SJ MRI compared with PSJR for detection of chronic changes in patients with aSpA and also evaluated the inter-reader agreement between two experienced radiologists. They found that κ values were better in patients with AS than nraSpA; for erosions 0.59 versus 0.346, for sclerosis 0.409 versus 0.231, for joint space changes 0.476 versus 0.286, respectively. The low κ values in our study may be related to the high frequency of nraSpA patients, but we cannot reach any conclusions because this was out of the scope of the study.

Our study has limitations. Demographics, symptoms, laboratory findings other than SJ MRI, physical examination findings, and the clinical diagnosis of the patients were not included in the study. Specific criteria for reading and grading SJMRI were not used and there was no MRI training specified for musculoskeletal radiology before either the first or the second readings, but this was a preference for imitation of daily life.

5 | CONCLUSION

In this study we showed that interclass and intraclass agreements of one of the readers for SJ MRI readings were mostly poor. Taking SJ MRI into consideration as a diagnostic utility for SpA, standardization and validation of each MRI finding seems to be a need for reading SJ MRI. Sacroiliac lesions other than active sacroiliitis and vertebral inflammatory and structural changes related to SpA, when necessary, can be considered to improve both specificity and sensitivity of detecting sacroiliitis on SJ MRI and the existing scoring systems can be improved.

AUTHOR CONTRIBUTIONS

ZNT contributed to design, concept, planning, data collection, data analysis, manuscript writing, supervision, and editing. CS contributed to design, materials, data analysis, conduct, supervision, and editing. TD contributed to design, planning, conduct, data collection, and data analysis. EK contributed to design, concept, planning, conduct, supervision, manuscript writing, and editing.

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CONFLICT OF INTEREST

The authors report no declarations of interest.

ORCID

Zeynep Nilufer Tekin https://orcid.org/0000-0002-8209-0331
Cennet Sahin https://orcid.org/0000-0002-8695-327X
Tuna Demirbas https://orcid.org/0000-0003-0934-2640
Esen Kasapoglu https://orcid.org/0000-0002-5866-7153

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ORIGINAL ARTICLE

Non-radiographic axial spondyloarthritis in South America. Burden of disease and differential features with respect to ankylosing spondylitis at time of diagnosis. A comprehensive analysis with a focus on images

Rodrigo Garcia Salinas[1] | Rosario Jaldin Cespedes[1] | Ramiro Adrian Gomez[2] | Dario Aguerre[3] | Fernando Sommerfleck[4]

[1]Rheumatology Unit, Hospital Italiano La Plata, La Plata, Argentina

[2]Rheumatology Unit, Hospital Nacional Posadas, Buenos Aires, Argentina

[3]Radiology Department, Hospital Italiano de La Plata, La Plata, Argentina

[4]Rheumatology Unit, Sanatorio Mendez, PANLAR: SPA Study Group, Ciudad Autonoma de Buenos Aires, Argentina

Correspondence
Rodrigo García Salinas, Rheumatology Unit, Hospital Italiano de La Plata, 51 street, 1725, La Plata (1900), Buenos Aires Province, Argentina.
Email: gsalinasrodrigo@gmail.com

Abstract

Background: Non-radiographic axial spondyloarthritis (nr-axSpA) data from South America are scarce, especially regarding image features.

Objective

To estimate the frequency of nr-axSpA and ankylosing spondylitis (AS) in a cohort of Argentinian patients with chronic low back pain (LBP) and to analyze the difference between both, with focus on magnetic resonance imaging (MRI) lesions, at diagnosis.

Methods: Patients with LBP and a diagnosis of axSpA who participated in a reumacheck program were included. All patients with a suspicion of SpA were evaluated using blood analytics, HLA-B27, and images (MRI). Sociodemographic data, SpA features, diagnostic dela,y and clinimetrics were assessed by an operator who was blinded to the patient's test results. On MRI, the presence of SpA lesions was assessed and a concordance exercise was carried out between rheumatologists and radiologist.

Result: Of 198 LBP patients, 97 had axSpA, 54% of whom were nr-axSpA. A positive MRI was found in 50%. No difference in terms of disease activity, functional impact, laboratory or treatments between nr-axSpA and AS were found. Higher frequencies of male sex and chronic lesions on sacroiliac MRI were found in AS patients. In the logistic regression, an independent association with AS diagnosis was found: male (odds ratio [OR] 4.8), MRI fat replacement (OR 4.6), MRI sclerosis (OR 7.6), and diagnostic delay of more than 2 years (OR 10). The concordance between rheumatologists and radiologists was considered good to very good (κ 0.7-0.8).

Conclusion: The frequency of nr-axSpA was 54%. We found a higher frequency of being male, more SpA features, and a longer diagnostic delay in patients with AS. Patients with AS had more structural lesions, with a good concordance between rheumatologist and radiologist.

KEYWORDS
ankylosing spondylitis, HLA-B27, non-radiographic axial spondyloarthritis, sacroiliac MRI

1 | INTRODUCTION

The emergence of the concept of non-radiographic axial spondyloarthritis (nr-axSpA) has allowed rheumatologists to classify patients defined by axial spondyloarthritis without classic sacroiliitis on plain radiography, using HLA-B27 and magnetic resonance imaging (MRI).[1] This entity together with ankylosing spondylitis (AS) with New York criteria constitute the complete spectrum of axial spondyloarthritis (axSpA).[2]

There has been much debate about whether these are two separate diseases or different evolutionary stages of the same disease.[3,4] However, we currently know that many patients with nr-axSpA never progress to radiographic stages.[5] In contrast, many cohorts, especially from European countries, have shown that patients with non-radiographic forms can progress to radiographic stages, with male gender, presence of HLA-B27, and high levels of C-reactive protein as risk factors for progression. It has been proven that disease activity and functional impact are similar in nr-axSpA and AS, maintaining an equal burden of the disease regardless of the radiographic progression.[6,7]

Previous investigations have shown that the characteristics of patients with axSpA in Latin America differ from those of patients from North America or Europe from the genetic and phenotypic point of view, with a lower prevalence of HLA-B27 and greater peripheral involvement.[8–10] There are descriptions of axSpA cohorts in American countries, but no comparisons that would give us information regarding the similarities and differences between nr-axSpA and radiographic axSpA (r-axSpA), especially in terms of sacroiliac joint MRI image characteristics.

The objective of this study is to estimate the frequency of nr-axSpA and AS at the time of diagnosis in an Argentinian cohort of patients with chronic low back pain (LBP) beginning before 45 years of age; and to analyze the difference between nr-axSpA and AS with a focus on sacroiliac joint MRI lesions. We also tested the concordance in the reading of the MRI of the sacroiliac joints between rheumatologists and radiologists.

2 | MATERIALS AND METHODS

A single-center study, including consecutive patients 18 years or older admitted to the "Reuma-check" SpA program between August 2017 and July 2021 was carried out. The patients were admitted to the program if they had LBP without another explanatory cause with duration longer than 3 months and onset before 45 years old. They were evaluated by a trained nurse who included in the comprehensive circuit those who presented at least one SpA feature.

All patients underwent the following tests during the same day: clinical assessment—Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Health Assessment Questionnaire Disability Index (HAQ);[11–14] laboratory tests; and diagnostic images, including plain radiography (X-ray) and MRI of sacroiliac joints, and ultrasound of heel entheses. All the evaluators (clinician, laboratory, and images) were blinded to the results of the other studies. All the procedures and steps of the Reuma-check are detailed in the cited publication.[15] The indication for biological treatment was recorded at 1 year of follow up.

2.1 | Acquisition and reading of images (MRI and X-ray)

Magnetic resonance imaging of both sacroiliac joints without intravenous paramagnetic contrast was performed using a 1.5-T General Electric Signa Horizon LX machine (General Electric, Chicago, IL, USA). The orientation and thickness of the slices, the presence or absence of active inflammatory lesions (Short-TI inversion recovery) as bone marrow edema (osteitis), capsulitis, synovitis, and enthesitis, and chronic inflammatory lesions (T1) as sclerosis, erosions, fat deposition, and bony bridges/ankylosis were determined following the Spondyloarthritis International Society (ASAS) protocol. The presence of bone marrow edema (osteitis) was considered as a positive MRI. If there was only one signal of bone marrow edema (osteitis) per MRI slice, the lesion should be present on at least two consecutive slices. If there was more than one signal of bone marrow edema (osteitis) on a single slice, one slice was sufficient.[16,17]

The pelvic X-ray and MRI were read by two radiologists (with MRI-SI reading certification) and two rheumatologists (who did not belong to the center, but were also trained in MRI reading), blinded to the results of the patients' other tests or clinical data.

2.2 | Diagnosis of r-axSpA and nr-axSpA

All data, including clinical evaluation, were loaded into a system of electronic medical records. The diagnosis was made in all cases by the opinion of the same expert rheumatologist; in cases of diagnostic doubt, the opinion of a second expert rheumatologist was used for the final diagnosis of axSpA. Patients diagnosed as having axSpA with radiographic sacroiliac involvement according to the New York criteria were classified as AS.[18] In a second step, for patients with nr-axSpA, the admission arm was established according to the ASAS criteria (imaging arm by MRI, clinical by HLA-B27 or both).[19]

2.3 | Data analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as medians and interquartile ranges or as means and standard deviations depending on their distribution, and categorical variables were expressed as percentages. Comparisons were performed using parametric and nonparametric tests for continuous variables and the χ^2 test for categorical variables. A multivariate logistic regression analysis

using r-axSpA as the dependent variable, and clinical features, laboratory, and images as independent variables was also conducted. Concordance of qualitative readings of sacroiliac MRI lesions between rheumatologists and radiologists was evaluated, the presence or absence of the lesion was recorded dichotomously. The κ value was defined as: 0.2-0.4: Low; 0.4-0.6: Moderate; 0.6-0.8: Good; 0.8-1.0: Very good.

3 | RESULTS

3.1 | Patient characteristics

One hundred and ninety-eight patients with chronic LBP beginning before the age of 45 years, were included in the Reuma-check circuit (male, 49%; mean age, 47 years [±13 standard deviation] at the time of evaluation; the median duration of symptoms at diagnosis was 37 months [interquartile range 12-121]). A total of 97 patients were diagnosed as axSpA (48% 95% confidence interval [CI] 42-56) and their characteristics at the time of diagnosis are shown in Table 1.

3.2 | Frequency of nr-axSpA and entry criteria branch

Nearly half of the patients were classified as nr-axSpA (n = 52, 54%; 95% CI 44-63). As the ASAS criteria entry element, a positive MRI was found in 50% of patients, positive HLA-B27 in 35%, and 15% of patients met both entry criteria.

3.3 | Differential features in nr-axSpA and r-axSpA

Sociodemographic, clinical, and laboratory characteristics at the time of diagnosis, and treatment in a year of follow up for both populations are shown in Table 2. We found no difference in terms of disease activity, functional impact, laboratory results, or treatments between nr-axSpA and AS. A higher frequency of being male was found in patients with AS.

In the logistic regression using radiographic compromise (according to NY criteria) as dependent variable, an independent association was found for male sex (odds ratio [OR] 4.8, 95% CI 1.4-17), and diagnostic delay of more than 2 years (OR 10, 95% CI 1.7-57).

3.4 | Sacroiliac MRI findings in r-axSpA vs nr-axSpA (readers agreement)

An MRI was obtained from all patients. Table 3 qualitatively details the lesions found in patients classified as nr-axSpA and r-axSpA. Those lesions showing statistically significant differences were included in the logistic regression analysis, using radiographic compromise (according to NY criteria) as dependent variable and adjusted for clinical and laboratory variables and diagnostic delay. An independent association was found for fat replacement (OR 4.6, 95% CI 1.1-19) and sclerosis (OR 7.6, 95% CI 1.4-41).

TABLE 1 Clinical, laboratory, and imaging features from all SpA patients, at the time of diagnosis

	Axial SpA (n = 97)
Age (years), mean (SD)	46 (12.4)
Male gender, %	44
Years of schooling, mean (SD)	13.4 (3.2)
LBP onset age (years), mean (SD)	40 (12.2)
LBP onset to diagnosis (months), median (IQR)	41 (15-121)
Smoking, %	41
Uveitis, %	5
Psoriasis, %	29
Inflammatory bowel disease, %	6
SpA family history, %	30
NSAIDs good response, %	67
Positive HLA-B27, %	40
Inflammatory LBP, %	83
Number of SpA features (DS)	3.7 (1.4)
SpA features >4, %	46
Positive sacroiliac X-ray, %	45
Positive sacroiliac MRI (any lesion), %	83
Positive enthesitis ultrasound, %	42
Positive sacroiliac maneuvers, %	57
Anterior chest pain, %	21
VAS pain, mean (SD)	6.9 (1.5)
VAS night pain, mean (SD)	5.6 (2.3)
Morning stiffness (minutes), median (IQR)	30 (15-40)
BASFI, mean (SD)	4.6 (1.3)
BASDAI, mean (SD)	4.4 (1.75)
Peripheral arthritis, %	25
Enthesitis, %	40
MASES, median (IQR)	0 (0-1)
HAQ-DI, median (IQR)	0.7 (0.5-1)
CRP (mg/L), median (IQR)	2 (1-6)
CRP >5 mg/L, %	43
ESR (mm/h), median (IQR)	17 (10-25)
Follow-up (months), median (IQR)	6 (3-24)
Biological treatment, % (1 year of follow-up)	46
TNF-b, %	31
IL17-b, %	11

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; HLA-B27, human leukocyte antigen B27; IL17-b, interleukin-17 blocker; IQR, interquartile range; LBP, low back pain; MASES, Maastrich Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SpA, spondyloarthritis; TNF-b, tumor necrosis factor blocker; VAS, visual analog scale.

TABLE 2 Differential features between r-axSpA and AS (no MRI)

	AS (n = 45)	nr-axSpA (n = 52)	*P* value
Age (years), mean (SD)	46.7 (13.2)	46.4 (11.8)	0.90
Male gender, %	64	29	0.001
Years of schooling, mean (SD)	13.1 (3.3)	13.6 (3.2)	0.47
LBP onset age (years), mean (SD)	40 (12.2)	40.3 (12.4)	0.91
LBP onset to diagnosis (months), median (IQR)	56 (24-123)	37.1 (12-121)	0.06
Diagnostic delay >2 years, %	82	61	**0.03**
Smoking, %	51	34	0.09
Uveitis, %	2.3	10	0.06
Psoriasis, %	30	27	0.78
Inflammatory bowel disease, %	9	4	0.22
SpA family history, %	36	25	0.22
NSAIDs good response, %	74	63	0.25
Positive HLA-B27, %	47	34	0.21
Inflammatory LBP, %	91	77	0.07
SpA features >4, %	64	44	0.05
Number of SpA features, mean (SD)	3.9 (1.2)	3.4 (1.5)	0.06
Positive enthesitis ultrasound, %	53	32	0.06
Positive sacroiliac maneuvers %	60	55	0.58
Anterior chest pain, %	31	14	0.05
VAS pain, mean (SD)	6.7 (1.7)	7.1 (1.3)	0.29
VAS night pain, mean (SD)	5.7 (2.4)	5.6 (2.3)	0.89
Morning stiffness (minutes), median (IQR)	30 (20-40)	30 (15-40)	0.34
BASFI, mean (SD)	4.6 (1.5)	4.6 (1.3)	0.97
BASDAI, mean (SD)	4.5 (1.8)	4.3 (1.7)	0.57
Peripheral arthritis, %	23	25	0.84
Enthesitis, %	49	33	0.11
MASES, mean (IQR)	0 (0-2)	0 (0-1)	0.13
HAQ-DI, median (IQR)	0.7 (0.5-1)	0.75 (0.5-1)	0.76
CRP (mg/L), median (IQR)	2 (1-5.2)	3 (1-8.2)	0.40
CRP >5 mg/L, %	41	46	0.60
ESR (mm/h), median (IQR)	17 (10-25)	17.5 (9.2-25)	0.84
Biological treatment, %	50	42	0.45
TNF-b, %	36	25	0.22
IL17-b, %	11	11	0.97

Note: The bold values indicate statisically significant.

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; HLA-B27, human leukocyte antigen B27; CRP, C-reactive protein; IL17-b, interleukin 17 blocker; IQR, interquartile range; LBP, low back pain; MASES, Maastrich Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis; SD, standard deviation; SpA, spondyloarthritis; TNF-b, tumor necrosis factor blocker; VAS, visual analog scale.

For the concordance exercise between rheumatologist and radiologist MRI readings, each lesion was assessed qualitatively (presence vs absence). The following results were obtained: edema: κ 0.84, $P \leq 0.001$ (95% CI 0.7-0.9); fatty change: κ 0.82, $P \leq 0.001$ (95% CI 0.7-0.9); erosions: κ 0.71, $P \leq 0.001$ (95% CI 0.6-0.8); and sclerosis: κ 0.8, $P \leq 0.001$ (95% CI 0.6-1.1). The concordance was considered good to very good by obtained κ values.

4 | DISCUSSION

In this study we have mainly been able to observe the differences between patients with AS and nr-axSpA, at the time of diagnosis. As has been seen in other international cohorts, there are no substantial differences between patients with one entity and the other. In the present work it can be observed how patients with AS have a significantly higher percentage of men, and a longer diagnostic delay. However, the rest of the clinical characteristics and burden of the disease are similar between one group and another.[5–7]

Although male sex, smoking and elevated C-reactive protein have been classically described as radiographic progression risk factors,[20,21] in this study only male sex was more frequent in AS patients compared with nr-axSpA patients, with no difference regarding inflammatory markers. In smoking status, a difference was observed with 51% vs 34% in patients with AS and nr-axSpA, but this was not statistically significant.

In other cohorts, significant differences are also usually observed in relation to biological treatment, which is usually lower in patients with nr-axSpA vs AS despite having the same disease burden.[22] In the present study, we have only noticed a trend towards a higher percentage of biological treatment in patients with AS vs nr-axSpA, this being non-significant.

TABLE 3 Sacroiliac MRI findings

	r-axSpA (n = 45)	nr-axSpA (n = 52)	*P* value	OR	95% CI
SI MRI: edema, %	64	63	0.95	1.1	0.4-2.5
SI MRI: Structural changes (any), %	70	67	0.74	1.1	0.5-2.7
SI MRI: fat replacement, %	53	24	0.008	3.6	1.3-9
SI MRI: erosions, %	66	35	0.007	3.6	1.3-9
SI MRI: sclerosis, %	31	13	0.05	3	1.2-9
SI MRI: bone bridges, %	16	0	0.005		

Note: The bold values indicate statisically significant.

Abbreviations: CI, confidence interval; MRI, magnetic resonaonce imaging; nr-axSpA, non-radiographic axial spondyloarthritis; OR, odds ratio; r-axSpA, radiographic axial spondyloarthritis; SI, sacroiliac.

The prevalence of HLA-B27 below 50% even in patients with r-axSpA is consistent with previous reports from Argentina and although its frequency was numerically higher in AS patients than in nr-axSpA patients, a statistically significant difference was not found.[23] The low prevalence of HLA-B27 in our region is characteristic.[24] As the result of the previously reported differences between axSpA patients from Latin America and those from Europe in terms of clinical characteristics and HLA-B27 prevalence, we consider that relying on local data is relevant to rheumatologists practicing in our country, as the lower HLA-B27 prevalence and the more frequent peripheral involvement may modify the pre-test probability of particular patients being evaluated for an SpA diagnosis.[25] This feature contributes to the greatest challenge when diagnosing our patients, imaging becoming a fundamental tool, especially MRI. Hence, most patients fulfilled the imaging arm of the ASAS classification criteria in our cohort.

The delay to diagnosis was longer in patients with AS, with a median of 56 months. It is noteworthy that although efforts are still being made to reduce this time, it is still prolonged.[26,27]

When the images were evaluated, we were able to observe a higher frequency of structural lesions in the MRI in patients with AS vs nr-axSpA.[28] These data are predictable by the same definition of AS, which is defined by greater structural damage, but at the same time they data help us to think about the importance of not confusing classification criteria with diagnostic criteria.[29] If we use the classification criteria as diagnostic criteria, patients with structural lesions, such as those observed mostly in patients with AS in our studies, could not be diagnosed as having axSpA. It is essential to know that there are no diagnostic criteria, there are only algorithms, such as the modified Berlin algorithm and the different recommendations that mark the diagnostic positivity of magnetic resonance recently published by the ASAS magnetic resonance group.[30,31]

Regarding the agreement between the rheumatologists and the imaging specialists, it was very good according to the κ values obtained. This demonstrates the importance of continuous training of rheumatologists and imaging specialists together, which helps in the correct detection of lesions, and in this way helps our patients.[32,33]

As for weaknesses, this study comes from a single-center experience with a relatively low number of patients and the sacroiliac joint MRI was analyzed using only qualitative definitions and not a formal quantitative score. However, the structured and complete evaluation in terms of clinical, laboratory, and imaging features for all the patients allows for a comprehensive characterization with complete data, in patients with and without radiological involvement alike and may be considered as a strength for this study. The multiplicity of data present at the time of diagnosis and the characteristics of the biological treatment per year add important information to the initiatives of Latin America to respond to challenges in the field of SpA, such as real-world evidence and the development of centers of excellence.[34,35]

In conclusion, in our cohort, half of the patients with axSpA were nr-axSpA at the time of diagnosis, with no differences found in terms of clinical characteristics, disease activity, functional capacity, or treatment at 1 year. The only differences found were the fact that patients with AS had a longer delay to diagnosis and the higher proportion of men. There were also differences in the MRI with more structural lesions in patients with AS. We also obtained very good concordance of MRI readings between rheumatologists and radiologists.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the conception and design of the work and acquisition and interpretation of the data. FS, RG, and RGS additionally analyzed the data and drafted the initial version of the manuscript. The final manuscript has been revised critically and approved by all the authors and they have given the necessary attention to ensure the integrity of the work.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

This observational study was approved by an institutional ethics committee and was conducted in accordance with the current Helsinki Declaration, the resolution 1480/11 of the local Health Ministry, and local regulations applicable to this type of study. Patient confidentiality was respected according to local law and informed consent was taken for publication.

CONSENT FOR PUBLICATION

The final manuscript has been seen and approved by all the authors and they have given the necessary attention to ensure the integrity of the work.

ORCID

Rodrigo Garcia Salinas https://orcid.org/0000-0002-5928-1092

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ORIGINAL ARTICLE

Sjögren syndrome is a hidden contributor of macrovascular and microvascular complications in patients with type 2 diabetes

Yu-Jih Su[1,2] | Pui-Ying Leong[3,4] | Yu-Hsun Wang[3,5] | James Cheng-Chung Wei[3,4,6]

[1]Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

[2]Center for Mitochondrial Research and Medicine, Chang Gung Memorial Hospital, Kaohsiung, Taiwan

[3]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan

[4]Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

[5]Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan

[6]Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

Correspondence
Yu-Hsun Wang and James Cheng-Chung Wei, Institute of Medicine, Chung Shan Medical University, No.110, Sec.1, Jianguo N. Rd., Taichung City 40201, Taiwan.
Emails: cshe731@csh.org.tw; jccwei@gmail.com

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Abstract

Objective: To investigate cardiovascular risk among diabetic patients with Sjögren syndrome.

Methods: This study was a nationwide population-based case-control study from 1997 to 2013, in which the association between autoimmune diseases and diabetes was investigated. The study population consisted of individuals with newly diagnosed type 2 diabetes with macrovascular or microvascular complications with at least two outpatient visits or one hospitalization as the outcome variables, and the exposure variables included traditional risk factors, medications, and autoimmune diseases. The odds ratio of cardiovascular events among each prevalent autoimmune disease and hydroxychloroquine's effect on cardiovascular risk were analyzed.

Results: The study included a total of 7026 individuals with diabetes with microvascular and macrovascular complications and the same number of patients in the control group. Sjögren syndrome was significantly higher in the diabetes complication group than in the non-complication group (0.8% vs 0.5%, $P = 0.036$). By using multivariate analysis, we found hypertension, hyperlipidemia, and Sjögren syndrome to be three independent risk factors for diabetes vascular complications (odds ratio [OR] 1.96, 95% confidence interval [CI] 1.82-2.10; OR 1.53, 95% CI 1.42-1.64; and OR 1.67, 95% CI 1.06-2.65; respectively, all $P < 0.05$). Treatment with traditional statins and aspirin might be able to overcome the increased risk of developing cardiovascular events while comparing between diabetes patients with and without Sjögren syndrome.

Conclusion: Sjögren syndrome is an unrecognized independent risk factor for cardiovascular events among diabetes patients, which indicates that patients with diabetes combined with Sjögren syndrome require closer follow up regarding cardiovascular complications in clinical settings. Treatment with hydroxychloroquine might not be enough to lower the cardiovascular risk significantly in diabetes patients with Sjögren syndrome.

KEYWORD
Sjögren syndrome,

Yu-Hsun Wang and James Cheng-Chung Wei contributed equally.

1 | INTRODUCTION

Type 2 diabetes mellitus is a chronic disease characterized by increased blood sugar, insulin resistance, and a relative lack of insulin. These metabolic abnormalities may cause vessel constriction, inflammation, and thrombosis.[1] Long-term and persistent injuries of type 2 diabetes mellitus are associated with both microvascular and macrovascular diseases that affect several organs, including the heart, brain, eyes, and kidneys.[2] Cardiovascular diseases may be the most common cause of death in individuals with diabetes,[3] and lifestyle modifications and effective treatment of diabetes with medications are required to reduce cardiovascular complications. Recognition of cardiovascular risk among individuals with type 2 diabetes mellitus remains largely suboptimal,[4] and several underlying conditions, such as hormonal risk factors, migraine, autoimmune diseases, and psycho-social stress, are not listed as traditional cardiovascular risks but have a detrimental cardiovascular effect in diabetes mellitus.[5]

The inter-relationship between autoimmune disease and diabetes in patients with type 2 diabetes mellitus is complicated. According to Ahlqvist et al,[6] adult-onset diabetes can be categorized into five different subgroups, with one subgroup being related to autoimmune pathogenesis, which is a latent autoimmune diabetes of adults. We believed that autoimmune-related diabetes should be treated with insulin-based therapy and some immune modulation medication, rather than oral antihyperglycemic agents, and better glycemic control was associated with fewer vascular complications during long-term follow up.[7] Again, Ahlqvist et al used their criteria to replicate similar results in several other populations,[8] the autoimmune characteristics of which could be identified in adult-onset autoimmune diabetes.[9] Patients with autoimmune diseases, such as rheumatoid arthritis, have underlying inflammation characteristics and a higher incidence rate of vascular events compared with the general population.[10] Furthermore, a recent article indicated that interleukin-1 may lead to activation of the immune system and could be a potential therapeutic target for DM.[11] Patients with diabetes and autoimmune diseases are encouraged to have closer follow up and screening for subclinical and clinical atherosclerosis.[12] In addition, body weight and body mass index are important factors in developing clinical diabetes in patients with autoimmune diseases and positive islet autoantibodies.[13]

Another interesting relationship between autoimmune disease and diabetes is found in those patients treated with immune checkpoint inhibitors who develop checkpoint inhibitor-associated diabetes;[14] the pathophysiology of this may be related to the effects of the checkpoint inhibitor agents to potentiate T-cell activity to damage the islet cell, just like the adult-onset autoimmune diabetes. Furthermore, the diabetes accounts for at least 10% of the risk of a first myocardial infarction.[15] Therefore, in the current study, we would like to determine the effect of immune modulatory medications on reducing cardiovascular risk among patients with diabetes and autoimmune diseases.

Our goal in this study is to determine whether autoimmune diseases produce a deterioration in diabetic outcome. If autoimmune disease was proved to be a factor associated with diabetic microvascular or macrovascular complications, we would like to know if treating the autoimmune diseases could reverse the risk. Hydroxychloroquine, a commonly used medication in autoimmune diseases such as rheumatoid arthritis[16] and systemic lupus erythematosus (SLE),[17,18] has been repeatedly found to have a potentially beneficial effect on glycemic control and lipid metabolism.[19–21] The efficacy is mild and subtle.[22] Among rheumatoid arthritis patients, the use of hydroxychloroquine was related to a risk reduction of incident diabetes.[23] In Taiwan's National Health Insurance Research Database studies, taking hydroxychloroquine has been associated with attenuating the risk of incident diabetes in a dose-dependent manner.[24] A similar result was also presented in patients with Sjögren syndrome (SjS)[25] and reductions in inflammatory chemokines were recorded in osteoarthritis.[26] However, whether hydroxychloroquine is potentially beneficial in preventing microvascular and macrovascular diseases in patients with type 2 DM remains unclear. Therefore, we conducted a nested case-control study to determine whether hydroxychloroquine could improve microvascular and macrovascular events in type 2 diabetes mellitus.

2 | MATERIALS AND METHODS

2.1 | Data source

This study was a nested case-control study using the National Health Insurance Research Database, which has enrolled almost 99% of the 23 million beneficiaries in Taiwan. The database includes all insurance claims data, including outpatient visits, emergency visits, and hospitalizations. One million individuals were sampled from the 23 million beneficiaries, and their data were collected from 1999 to 2013. The sampled database was de-identified, and the study was approved by the Institutional Review Board of Chung Shan Medical University Hospital.

2.2 | Study group

The study population consisted of patients with newly diagnosed type 2 diabetes (International Classification of Diseases ninth revision clinical modification [ICD-9-CM] codes 250, excluding 250.x1, 250.x3) who had used a hypoglycemic agent for 30 days from 2000 to 2012. In order to ensure only new-onset cases, we excluded diagnosis of macrovascular complications (including myocardial infarction, cerebral vascular accident, represented by ICD-9-CM codes 410-414, 430-438) and microvascular complications (including diabetic nephropathy, chronic kidney disease, represented by ICD-9-CM codes 250.4, 585, 586) before a diabetes diagnosis. The case group was diagnosed with macrovascular or microvascular complications with at least two outpatient visits or one hospitalization following the diagnosis of diabetes and 1 year apart. The control group had no history of diagnosis of macrovascular or microvascular

complications after diabetes diagnosis. The index date was set as the date of the patient's first diabetes complications. Moreover, 1:1 matching by age (±1 year old), sex, and diagnosis year of diabetes was used to provide an index date for the control group that corresponded to the case group (Figure 1). The exposures, including the age, blood pressure, lipidemia, and medications were recorded. The predictors of autoimmune disease that might exacerbate the microvascular or macrovascular complications of diabetes were recorded, which included rheumatoid arthritis, ankylosing spondylitis, SLE, and SjS. The potential confounders including the disease duration of diabetes, and some medications affecting outcome variables including aspirin and statins were also recorded. The effect modifier cumulative dose/days of hydroxychloroquine prescribed was analyzed.

2.3 | Hydroxychloroquine and covariates

Hydroxychloroquine use was calculated from the first date of diabetes to the index date. The baseline characteristics were age, gender, hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM codes 272.0-272.4), rheumatoid arthritis (ICD-9-CM code 714.0), ankylosing spondylitis (ICD-9-CM code 720.0), systemic lupus erythematosus (ICD-9-CM code 710.0), and SjS (ICD-9-CM code 710.2). These comorbidities were defined before the index date within 1 year with at least two outpatient visits or one hospitalization. In the final part, we determined that the cumulative days with prescription of hydroxychloroquine were representative data for the cumulative overall usage dose of hydroxychloroquine. In addition, we also recorded the use of aspirin and statins in this analysis. The following statins were included in our analysis: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin.

The outcome of diabetes was examined as either having macrovascular complications or microvascular complications. The macrovascular complications included ischemic heart disease (ICD-9 codes 410-414) and cerebrovascular disease (ICD-9 codes 430-437). The microvascular complications included diabetes with renal manifestations (ICD-9 code 250.4), chronic kidney disease (ICD-9 code 585), and renal failure (ICD-9 code 586). The comorbidities occurring 1 year before index date, include hypertension (ICD-9 codes 401-405), hyperlipidemia (ICD-9 codes 272.0-272.4), rheumatoid arthritis (ICD-9 code 714.0), ankylosing spondylitis (ICD-9 code 720.0), SLE (ICD-9 code 710.0), and SjS (ICD-9 code 710.2).

Diagnostic criteria of ischemic heart disease were mainly based on diagnostic stress tests[27] and those of cerebrovascular disease were based on the guideline recommendation.[28] Chronic kidney disease, renal failure, and renal manifestations were diagnosed according to the consensus.[29] The comorbidities were all diagnosed according to the guidelines as shown in references as follows, for hypertension,[30] dyslipidemia,[31] rheumatoid arthritis,[32] ankylosing spondylitis[33] (ICD-9 code 720.0), systemic lupus erythematosus,[34] and SjS.[35]

2.4 | Statistical analysis

To compare the characteristics of the case and control groups, we used χ^2 test for categorical variables and Student *t* test for continuous variables. Conditional logistic regression was used to estimate the odds ratio of hydroxychloroquine. Furthermore, the dose effect

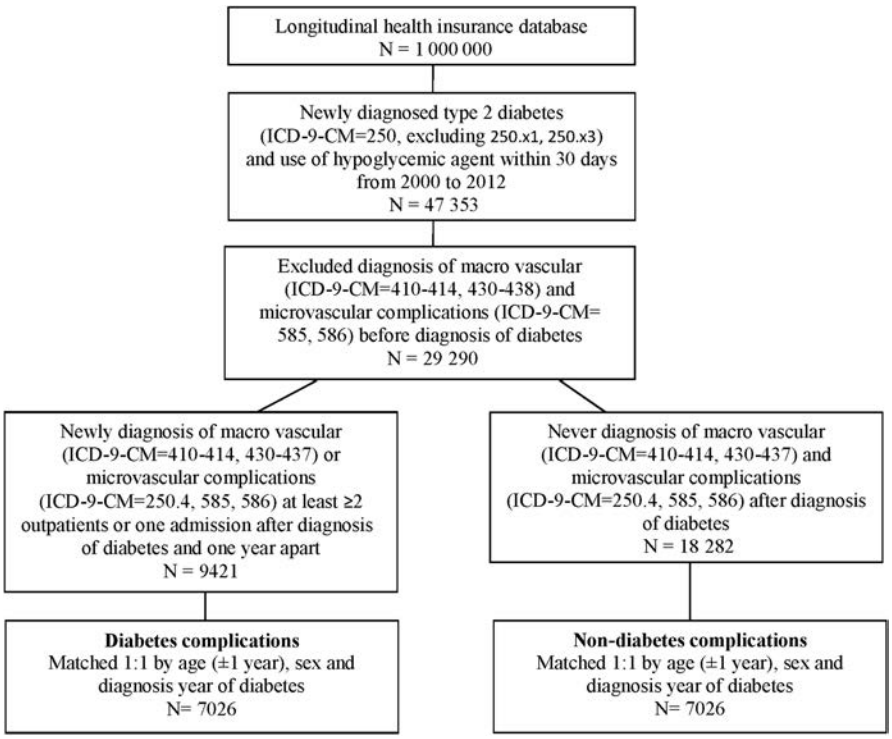

FIGURE 1 Flow diagram of the included patients. The encrypted longitudinal data of 1 million randomly selected participants was provided by the Taiwan National Health Insurance Database. Only 29 290 patients were qualified in the current study. We divided these 29 290 into two groups, one group was those patients with microvascular or macrovascular complications (n = 9421), and the other group was those patients without microvascular or macrovascular complications (n = 18 282). From these two groups, we matched participants for age, gender, and diagnosis year of diabetes with 1:1 ratio, leaving 7026 patients in each group.

of hydroxychloroquine was estimated by calculating the cumulative usage days. The statistical software used was SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics for study participants

Table 1 lists patient characteristics after a 1:1 matching of the following three factors: age differences within 1 year, gender, and the duration of diabetes between the diagnosis date and the index date. After matching, all the above parameters, as well as some rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and SLE (Table 1), were balanced between the diabetes complication group and the diabetes non-complication group.

This study included a total of 7026 patients in the study group and 7026 in the control group (Figure 1). Incidentally, we found that only one rheumatic disease, SjS, was significantly higher in the diabetes complication group than in the diabetes non-complication group (Tables 1, 0.8% vs 0.5%, $P = 0.036$). We found 56 SjS patients in the diabetes complication group, but only 36 SjS patients in the diabetes non-complication group (0.8% vs 0.5%, $P = 0.036$). We then investigated the prescription difference of medication used to treat SjS, which was hydroxychloroquine, in these two groups. The prescription rate of hydroxychloroquine was similar between the two groups (1.4% vs 1.3%, $P = 0.826$). We analyzed medications, statins and aspirin, and the results showed that the statins and aspirin were significantly higher in patients with diabetes complications (both $P < 0.001$) (Table S1).

3.2 | Conditional logistic regression of risk of diabetes complications analysis

As shown in Table 2, we used the conditional logistic regression method to check independent risk factors for diabetes vascular complications. Using univariate analysis, hypertension, hyperlipidemia, and SjS were shown as three factors associated with diabetes vascular complications (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.91-2.20; OR 1.64, 95% CI 1.53-1.76; and OR 1.59, 95% CI 1.03-2.44, respectively, all $P < 0.05$) (Table 2). With multivariate analysis, hypertension, hyperlipidemia, and SjS were shown as three independent risk factors for diabetes vascular complications (OR 1.96, 95% CI 1.82-2.10; OR 1.53, 95% CI 1.42-1.64; and OR 1.67, 95% CI 1.06-2.65, respectively, all $P < 0.05$) (Table 2). We analyzed medications, statins and aspirin, and SjS was no longer significant in multivariate analysis ($P = 0.084$; Table S2).

3.3 | The effect of hydroxychloroquine on lessening diabetes and comorbidities

In Table 3, we demonstrate the effect of hydroxychloroquine on diabetes and its vascular complications. We found that the percentage of patients with diabetes complications was similar between the hydroxychloroquine users and the non-hydroxychloroquine users. Taking SjS patients, for example, 17 of 26 patients with diabetes had vascular complications, and 39 of 66 patients with diabetes had no vascular complications, showing a similarity between these two subgroups without statistical difference (OR 1.31, 95% CI 0.51-3.37, $P = 0.578$). In general, our data demonstrated that the prescription of hydroxychloroquine did not affect diabetes vascular complications in each disease subgroup listed in Table 2. Hydroxychloroquine was not able to change the risk of diabetes complications in either combination treatment of aspirin or statins (both $P > 0.05$) (Table S3).

3.4 | Different dose effect of hydroxychloroquine in diabetes complications

As shown in Table 4, we examined the dose effect of hydroxychloroquine on diabetes complications. We recorded the prescription days and divided the cumulative prescription days into three subgroups: no use of hydroxychloroquine ever, use of hydroxychloroquine for 90 days or longer, and use of hydroxychloroquine for less than 90 days. We checked the number of patients with diabetes complications, which were almost the same between all three of these subgroups, and we observed no statistical differences between those patients who used either short-term or long-term hydroxychloroquine (90 days as the cut-off value) and those who never used (OR 1.02, 95% CI 0.66-1.58 and OR 0.90, 95% CI 0.56-1.43, respectively, all $P > 0.05$). Table S4 shows how the risk of diabetes complications in different dose effects of hydroxychloroquine remained the same as in Table 4; hydroxychloroquine did not affect the outcome.

3.5 | Diabetes macrovascular or microvascular complications analysis in patients who were prescribed hydroxychloroquine

We individually analyzed the hydroxychloroquine effects on either macrovascular or microvascular complications of diabetes (Table 5,). The results demonstrated neutral effects of hydroxychloroquine on both macrovascular and microvascular complications (OR 0.86, 95% CI 0.59-1.25 and OR 1.22, 95% CI 0.80-1.86, respectively, all $P > 0.05$). In Table S5, risk of diabetes complications in different dose effect of hydroxychloroquine is shown to remain the same as in Table 5; hydroxychloroquine did not affect the outcome.

4 | DISCUSSION

In this nationwide population-based nested case-control study from 1997 to 2013, we investigated the association between autoimmune diseases and diabetes in Taiwan. We identified a hidden cause of diabetes complications, namely, SjS. (Tables 1 and 2) SjS was significantly higher in the diabetes complication group than in the

TABLE 1 Demographic characteristics of all diabetes patients after 1:1 matching by age, sex, and diagnosis year of diabetes

	Diabetes complications (N = 7026)	Non-diabetes complications (N = 7026)	*P*-value
Age, y			
<40	325 (4.6)	302 (4.3)	.253
40-65	4596 (65.4)	4685 (66.7)	
≥65	2105 (30.0)	2039 (29.0)	
Mean ± SD	59.1 ± 11.8	59.0 ± 11.6	.461
Sex			
Female	2851 (40.6)	2851 (40.6)	1
Male	4175 (59.4)	4175 (59.4)	
Hypertension	4439 (63.2)	3255 (46.3)	<.001
Hyperlipidemia	3830 (54.5)	3009 (42.8)	<.001
Rheumatoid arthritis	89 (1.3)	77 (1.1)	.349
Ankylosing spondylitis	26 (0.4)	18 (0.3)	.227
Systemic lupus erythematosus	3 (0.0)	10 (0.1)	.052
Sjögren syndrome	56 (0.8)	36 (0.5)	.036
Hydroxychloroquine	96 (1.4)	93 (1.3)	.826
Diagnosis year of diabetes			
2000	1108 (15.8)	1108 (15.8)	1
2001	791 (11.3)	791 (11.3)	
2002	726 (10.3)	726 (10.3)	
2003	675 (9.6)	675 (9.6)	
2004	705 (10.0)	705 (10.0)	
2005	603 (8.6)	603 (8.6)	
2006	517 (7.4)	517 (7.4)	
2007	541 (7.7)	541 (7.7)	
2008	457 (6.5)	457 (6.5)	
2009	374 (5.3)	374 (5.3)	
2010	288 (4.1)	288 (4.1)	
2011	174 (2.5)	174 (2.5)	
2012	67 (1.0)	67 (1.0)	

non-complication group (0.8% vs 0.5%, $P = 0.036$, Table 1). Using multivariate analysis, we found hypertension, hyperlipidemia, and SjS to be three independent risk factors for diabetes vascular complications (Table 2). Use of hydroxychloroquine had a neutral effect on both macrovascular and microvascular complications in diabetic patients (Table 5). These results suggest that SjS exacerbates diabetes complications, the complications of which were independent of traditional known risk factors (hypertension and hyperlipidemia, see Table 2), and these complications might not be reversed by hydroxychloroquine treatment alone (Table 5).

A borderline effect of SLE on diabetes vascular complications among diabetes patients was noted, as shown in Table 1. SLE is considered a risk factor of vascular events under general conditions. In our current study, we provide real-world evidence to demonstrate that SjS may be a risk factor as risky as diabetes. Therefore, patients with a background of SLE are not at an increased cardiovascular system risk, even if the patient has concurrent diabetes (Table 1). On the other hand, although SLE shows higher non-diabetes-related complications, it does not reach statistical significance (Table 1, $P = 0.052$). We demonstrated that SLE is not an independent risk factor of cardiovascular events in diabetes patients (Table 1 and Table 2). However, surprisingly, we found that SjS is an independent risk factor of cardiovascular events in patients with diabetes (Table 2). Whether the situation of SjS-associated DM patients mimics latent autoimmune diabetes, ie, latent autoimmune diabetes of adults,[36] remains unclear, but our data point to an unrecognized link between the autoimmune disease, ie, SjS, and diabetes mellitus, suggesting that these SjS patients may have an underlying and subclinical autoantibody against islet cells.[37]

In previous data, diabetes patients had more than twice the relative risk of developing vascular complications compared with the general population.[38] Furthermore, SLE patients have a similar high

TABLE 2 Conditional logistic regression of risk of diabetes complications

	Univariate		Multivariate	
	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Hydroxychloroquine				
No	Reference		Reference	
Yes	1.03 (0.77-1.38)	0.825	0.96 (0.69-1.34)	0.811
Hypertension	2.05 (1.91-2.20)	<0.001	1.96 (1.82-2.10)	<0.001
Hyperlipidemia	1.64 (1.53-1.76)	<0.001	1.53 (1.42-1.64)	<0.001
Rheumatoid arthritis	1.16 (0.85-1.58)	0.346	1.12 (0.80-1.59)	0.503
Ankylosing spondylitis	1.44 (0.79-2.63)	0.230	1.49 (0.80-2.78)	0.214
Systemic lupus erythematosus	0.30 (0.08-1.09)	0.067	0.29 (0.07-1.13)	0.073
Sjögren syndrome	1.59 (1.03-2.44)	0.035	1.67 (1.06-2.65)	0.027

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

[a]Adjusted for hydroxychloroquine, hypertension, hyperlipidemia, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Sjögren syndrome.

TABLE 3 Subgroup analysis of hydroxychloroquine use and risk of diabetes complications

	Hydroxychloroquine		Non-hydroxychloroquine			
	N	No. of diabetes complications	N	No. of diabetes complications	OR (95% CI)	*P* value
Age, y						
<40	9	7	618	318	3.30 (0.68-16.02)	0.138
40-65	114	55	9167	4541	0.95 (0.66-1.37)	0.784
≥65	66	34	4078	2071	1.03 (0.63-1.68)	0.906
Sex						
Female	124	59	5578	2792	0.91 (0.63-1.29)	0.586
Male	65	37	8285	4138	1.32 (0.81-2.17)	0.264
Hypertension						
No	80	40	6278	2547	1.46 (0.94-2.28)	0.090
Yes	109	56	7585	4383	0.77 (0.53-1.13)	0.180
Hyperlipidemia						
No	89	42	7124	3154	1.12 (0.74-1.71)	0.582
Yes	100	54	6739	3776	0.92 (0.62-1.37)	0.685
Rheumatoid arthritis						
No	127	67	13759	6870	1.12 (0.79-1.59)	0.526
Yes	62	29	104	60	0.64 (0.34-1.21)	0.173
Ankylosing spondylitis						
No	187	95	13821	6905	1.03 (0.77-1.38)	0.819
Yes	2	1	42	25	0.68 (0.04-11.63)	0.790
Systemic lupus erythematosus						
No	178	93	13861	6930	1.09 (1.47-0.81)	0.551
Yes	11	3	2	0	NA	NA
Sjögren syndrome						
No	163	79	13797	6891	0.94 (0.69-1.28)	0.707
Yes	26	17	66	39	1.31 (0.51-3.37)	0.578

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

TABLE 4 Risk of diabetes complications in different dose effect of hydroxychloroquine

	N	No. of diabetes complications	Adjusted OR[a] (95% CI)	*P* value
Cumulative days of hydroxychloroquine				
No	13863	6930	Reference	
<90	95	48	1.02 (0.66-1.58)	0.936
≥90	94	48	0.90 (0.56-1.43)	0.650

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

[a]Adjusted for hydroxychloroquine, hypertension, hyperlipidemia, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Sjögren syndrome.

TABLE 5 Sub-outcome analysis of risk of diabetes complications in the hydroxychloroquine group

	N	No. of complications	Adjusted OR[a] (95% CI)	*P* value
Macrovascular complications				
Hydroxychloroquine				
No	11265	4332	Reference	0.420
Yes	149	56	0.86 (0.59-1.25)	
Microvascular complications				
Hydroxychloroquine				
No	9531	2598	Reference	0.361
Yes	133	40	1.22 (0.80-1.86)	

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

[a]Adjusted for hydroxychloroquine, hypertension, hyperlipidemia, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Sjögren syndrome.

risk of cardiovascular complications with diabetes in another study,[39] demonstrating that the relative risk of a cardiovascular event in SLE patients was just as high as diabetes. It is interesting that in our study, we demonstrated that SjS patients have a higher cardiovascular risk than SLE patients in diabetes patients (Table 2). SjS patients had already demonstrated higher cardiovascular risk when compared with the general population.[4,40] However, the combination of diabetes and SjS could present a different story, as demonstrated in Table 2. SjS is shown to be an independent risk factor, like hypertension or dyslipidemia, for cardiovascular complications. Both hypertension[41] and hyperlipidemia[42] are well known to add a higher probability of cardiovascular risk for diabetes patients. Our real-world evidence shows that SjS is another previously unrecognized independent risk factor for vascular complications in diabetes. Combined with the aforementioned condition of the possibility of a subclinical autoantibody against islet cells and latent autoimmune diabetes of adults, the elevated cardiovascular risks among SjS patients may simply reflect the possibility of subclinical insulin resistance among this particular group, but not the currently available clinical measurements, according to the Nord-Trøndelag Health Study.[43] Even the age of diabetes onset could be similar between latent autoimmune diabetes of adults and traditional type 2 diabetes mellitus,[44] as is the case in our current study (unpublished data, the age of diabetes onset is similar between each subgroup of diabetes patients).

Furthermore, the typical medication for treating SjS, which is hydroxychloroquine,[45] cannot reduce the risk of developing vascular events among patients with both diabetes and SjS. Neither the short-term treatment (less than 90 days) nor the long-term treatment (over 90 days) with hydroxychloroquine demonstrates efficacy in reducing cardiovascular events among diabetes patients. Furthermore, the traditional treatment of diabetes patients with statins[46,47] or anti-platelet agents[48,49] has been shown to be a useful method for reducing cardiovascular risk among diabetes patients. We took these medications, statins and aspirin, into consideration in this current study (Tables S1–S5). The use of statins and aspirin were significantly different between patients with and without diabetes (both $P<0.001$ in Table S1, compared with Table 1) The condition of confounding by indication was so significant that the statins and aspirin competed and the significance of the SjS no longer existed in multivariate analysis (SjS in multivariate analysis, $P = 0.084$ in Table S2, $P = 0.027$ in Table 2) Therefore, the association between vascular complication and diabetes may be partly attributed to the SjS disease itself, but the event rate cannot be lowered by treatment with hydroxychloroquine alone (Table 3), but might be reversed by combination treatment of statins and aspirin (Table S2).

Our team previously reported that hydroxychloroquine has a neutral effect on vascular events using a different method and calculation in another cohort study. Previous results demonstrated similar findings that the risk of vascular events in the hydroxychloroquine group was similar with the vascular events in the 1:3 ratio propensity score matched control group (hazard ratio 0.91; 95% CI 0.72-1.15).[50] In our previous study among SLE patients,[51] hydroxychloroquine users had higher comorbidities in several aspects, including hypertension, dyslipidemia, chronic kidney disease, and diabetes (all $P<0.05$). However, the differences did not reach statistical significance in coronary artery disease ($P = 0.81$) nor in gout ($P = 0.19$) between the hydroxychloroquine users and non-hydroxychloroquine users among the SLE patient cohort, which is similar to the result in this current study. In contrast to our other study of SjS cohort patients,[52] not only were significant differences in comorbidities found in the SjS cohort, but ischemic heart disease, congestive heart failure, and ischemic stroke also differed significantly between SjS patients and the 1:5 ratio age-, gender-, and index year-matched control patients (all $P<0.001$). Combining all this previous real-world evidence with our current study demonstrates that SjS may have even higher risks for

cardiovascular events than SLE. Although the SjS patients have concurrent diabetes, with higher risk of cardiovascular events, the risk cannot be fully reversed by hydroxychloroquine treatment only and required statins and aspirin co-treatment (Table S3). Risk of diabetes complications in different dose effect of hydroxychloroquine remained the same (comparing Tables S4 and S5 and Tables 4 and 5), which hydroxychloroquine did not affect the outcome.

Our study has several limitations. First, patients' compliance with the treatment in this cohort could not be accessed. For example, the prescription of hydroxychloroquine does not mean that the patient took their medication as prescribed. To counter that problem, we used the accumulative days of prescription to clarify whether hydroxychloroquine helps minimize vascular complications of diabetes. Second, no titers of laboratory examination were available in this retrospective study. Further clinical studies for determining whether tight control strategies of lipid profile or blood pressure would be necessary to prove our results. However, our study provides new insight into SjS comorbidities in diabetes patients with links to clinical vascular complications and offers clinicians better insight for controlling disease severity and improving prognosis in the future.

In conclusion, the current study clearly shows that aside from diabetes itself and the previously well-known risk factors of hypertension and hyperlipidemia, SjS is an unrecognized independent risk factor for cardiovascular events among diabetes patients, and the risk's odds ratio reaches 1.67, which is higher than that of hyperlipidemia (OR 1.53), but lower than that of hypertension (OR 1.96). Another interesting finding is that hydroxychloroquine was able to decrease all-cause mortality in SLE patients in another cohort, but hydroxychloroquine might not be enough to lower the cardiovascular risk significantly in diabetes patients with SjS in this study. Patients with both diabetes and SjS deserve a closer follow up regarding cardiovascular complications in clinical settings and require aggressive control.

AUTHOR CONTRIBUTIONS

Y-JS conceptualized the study; the project administration and supervision were by JC-CW. Data management and analysis was by Y-HW. Y-JS wrote the original draft and Y-JS and P-YL reviewed and edited it.

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CONFLICT OF INTEREST

James Cheng-Chung Wei is Editor-in-Chief of the journal and co-author of this article. He was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article.

DATA AVAILABILITY STATEMENT

Data will be available upon reasonable request.

ORCID

Yu-Jih Su https://orcid.org/0000-0002-7274-3458
James Cheng-Chung Wei https://orcid.org/0000-0002-1235-0679

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

Characteristics and risk factors of severe coronary artery disease in systemic lupus erythematosus: A multicenter, Chinese Rheumatism Date Center database study

Weiping Ci[1] | Jiuliang Zhao[2,3,4,5] | Wanting Qi[2,3,4,5] | Na Gao[1] | Junyan Qian[2,3,4,5] | Guohua Zhang[6] | Yuhua Wang[6] | Lili Pan[1] | Mengtao Li[2,3,4,5]

[1]Department of Rheumatology and Immunology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing, China

[2]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[3]National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology, Beijing, China

[4]State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH), Beijing, China

[5]Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China

[6]Department of Rheumatology and Immunology, Capital Medical University Affiliated Beijing Shijitan Hospital, Beijing, China

Correspondence
Mengtao Li, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No.1 Shuaifuyuan, Beijing, 100730, China.
Email: mengtao.li@cstar.org.cn

Lili Pan, Department of Rheumatology and Immunology, Capital Medical University Affiliated Beijing Anzhen Hospital, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China.
Email: lilypansxmu@sina.com

Abstract

Aim: Systemic lupus erythematosus (SLE) with severe coronary artery disease (CAD) is associated with increased mortality. This study aimed to assess the characteristics and risk factors of severe CAD in SLE.

Method: This multicenter, cross-sectional study enrolled consecutive patients with SLE included in the Chinese Rheumatism Date Center registry. Patients with severe CAD including angiography-confirmed stenosis ≥50% in the left main, ≥70% in other major coronary arteries, or myocardial infarction were classified into the CAD group. Patients without CAD were classified into the control group. Subgroups were stratified according to age (set as above and below 45 and 50 for men and women, respectively) and gender. Binary logistic regression analysis was performed to determine independent risk factors of severe CAD in SLE.

Results: Forty-three patients had severe CAD from a total of 3744 patients with SLE, 30 of whom were female; 35 belonged to the older age group and 8 belonged to the younger age group. In older patients, independent risk factors included age, 5 major CAD risk factors, SLE Disease Activity Index 2000 (SLEDAI-2K), hyperuricemia, and corticosteroid exposure. In younger patients, the risk factors were 5 major CAD risk factors and positive antiphospholipid antibody (APL). Male risk factors were age and 5 major CAD risk factors, whereas female risk factors were age, 5 major CAD risk factors, SLEDAI-2K, and positive APL. Three-vessel disease was most prevalent in patients with severe CAD.

Conclusion: We recommend screening for severe CAD in patients with SLE with age- and gender-stratified risk factors.

KEYWORDS
antiphospholipid antibody, coronary artery disease, hyperuricemia, risk factor, systemic lupus erythematosus

Weiping Ci and Jiuliang Zhao contributed equally to this study.

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a typical autoimmune disorder which predominately affects young and middle-aged women.[1] Patients with SLE have an enhanced risk of significant coronary stenosis and myocardial infarction.[2,3] Interestingly, a bimodal pattern has been observed in the mortality of SLE, in which lupus activity was the dominating factor for early deaths, whereas myocardial infarction with low disease activity was the primary cause of later deaths.[4] Over the last 5 decades, therapeutic measures for SLE have greatly improved and disease activity-related mortality has decreased, whereas cardiovascular-related mortality has remained unchanged.[5] Along with traditional cardiovascular risk factors, SLE disease-related factors, such as chronic inflammation, promote "accelerated atherosclerosis."[6] Severe coronary artery disease (CAD), for example, significant coronary stenosis and myocardial infarction, is associated with coronary revascularization and worse prognosis.[7,8] Early identification of severe CAD and active control of modifiable risk factors may be of great significance in improving the long-term outcomes for patients with SLE. However, risk factors of severe CAD for patients with SLE, let alone for age- and gender-stratified patients, have not been well explored. To address this issue, this study aimed to assess the characteristics and risk factors of severe CAD in patients with SLE.

2 | MATERIALS AND METHODS

2.1 | Patients

A total of 3744 consecutive patients with SLE included in the Chinese Rheumatism Date Center (CRDC) registry cohort between January 2009 and October 2020 were enrolled in this study. SLE was diagnosed according to the 1997 American College of Rheumatology criteria and/or the 2012 Systemic Lupus International Collaborating Clinics criteria.[9,10] The exclusion criteria included patients complicated by chronic or current infections, with other autoimmune diseases (with the exception of Sjögren's syndrome), and patients who did not undergo coronary angiogram despite clinical suspicion of severe CAD other than myocardial infarction. Patients with severe CAD were classified into the CAD group, and those without CAD were classified into the control group. A stenosis of ≥50% in the left main coronary artery or ≥70% in any other major coronary artery (diameter ≥2mm) confirmed by invasive coronary angiography or computed tomography angiography (CTA), or myocardial infarction was defined as severe CAD. Patient data were collected and compared between groups. Risk factors for severe CAD in SLE were analyzed. Additionally, to identify age- and gender-stratified risk factors for severe CAD, we divided patients into subgroups of older SLE (men aged ≥45 and women aged ≥50 years) and younger SLE (men aged <45 and women aged <50 years); and into subgroups of male SLE and female SLE.

This study was performed following the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Medical Ethics Committee of Capital Medical University affiliated Beijing Anzhen Hospital (No. 2021136X). Each patient enrolled provided informed consent.

2.2 | Data collection

Patient data were collected from the CRDC database and medical records, including demographic data, cardiovascular risk factors, disease activity, SLE-related organ damage, laboratory test findings, coronary angiographic findings, and therapeutic strategies. Disease activity was assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K).[11] A body mass index of ≥24 kg/m^2 was considered indicative of obesity or being overweight.[12] Five major CAD risk factors, that is, dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of CAD, were examined.[13] Dyslipidemia was defined as increased fasting triglyceride level of ≥1.7 mmol/L, total cholesterol level of ≥5.2 mmol/L, low-density lipoprotein cholesterol level of ≥3.4 mmol/L, and/or decreased fasting high-density lipoprotein cholesterol level of <1.0 mmol/L.[14] Diabetes mellitus was defined as a fasting plasma glucose level of ≥7.0 mmol/L, 2-h postprandial blood glucose level of ≥11.1 mmol/L, glycosylated hemoglobin A1C level of ≥6.5%, and/or a random plasma glucose level of ≥11.1 mmol/L with relevant symptoms.[15] A systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg were defined as diagnostic threshold for hypertension.[16] A fasting blood uric acid level of >420 μmol/L, tested twice at different times under normal diet conditions, was considered hyperuricemia.[17] Elevated serum inflammatory marker levels were defined as an erythrocyte sedimentation rate of >15 mm/1 h in men or >20 mm/1 h in women and/or high-sensitivity C-reactive protein level of >5 mg/dL in both genders. All the blood tests and SLEDAI-2K values were measured when the participants registered with the CRDC registry cohort. Lesions in the left main coronary artery were recorded as 2-vessel lesions.

2.3 | Statistical analysis

In this study, data were statistically analyzed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) or IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Normality assumption was verified with the Shapiro–Wilk test. Quantitative data are expressed as median with interquartile range (IQR) and were analyzed with the Mann–Whitney *U* test. Qualitative data are described as counts with percentage and were analyzed with an appropriate Chi-square test. Variables with clinical significance and *P* values of <.1 in the univariate analysis were included in the following multivariate analysis. Binary logistic regression analysis with a stepwise forward procedure based on maximum likelihood estimation was conducted to determine

independent risk factors of severe CAD for SLE. A 2-tailed *P* value of <.05 was considered to be significant. Line art was generated using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA).

3 | RESULTS

3.1 | Demographic data and clinical features

Of the 3744 patients with SLE, the median age was 35 years (IQR 29–45), and the male-to-female ratio was approximately 1:11. Among them, 43 patients were deemed to have severe CAD. In the CAD group, age was older ($P < .001$), male gender was prevalent ($P < .001$), and disease duration was longer compared with the control group ($P = .023$). Overweight or obese status, 5 major CAD risk factors, estimated glomerular filtration rate (eGFR) <60 mL/min, hyperuricemia, elevated serum inflammatory markers (all $P < .001$), and corticosteroid exposure ($P = .004$) were more common in the CAD group than in the control group (Table 1).

3.2 | Demographic data and clinical features in age- and gender-stratified subgroups

In addition, we stratified patients into subgroups of younger SLE (211 men aged <45 and 2889 women aged <50 years, n = 3100) and older SLE (92 men aged ≥45 and 552 women aged ≥50 years, n = 644). In both subgroups, the frequency of 5 major CAD risk factors and elevated serum inflammatory markers were greater in the CAD group than in the control group (younger SLE: $P < .001$, $P = .006$; older SLE: $P < .001$, $P = .005$, respectively). In the older SLE subgroup, CAD patients were found to be older, male gender was more prevalent, and being overweight or obese was more common compared to the control group ($P = .003$, $P = .003$, $P = .028$), but this was not the case in the younger SLE subgroup ($P > .05$). In the older SLE subgroup, CAD patients were found to have an elevated SLEDAI-2K score, a higher proportion of eGFR <60 mL/min, hyperuricemia, and corticosteroid exposure compared to control patients ($P = .025$, $P = .019$, $P < .001$, $P = .003$, respectively), but this was not found in the younger SLE subgroup ($P > .05$) (Table 2).

Furthermore, we stratified patients into male SLE (n = 303) and female SLE (n = 3441) subgroups. In both subgroups, CAD patients were found to be older, were more likely to be overweight or obese, and had a higher frequency of the 5 major CAD risk factors and hyperuricemia compared with control patients (male SLE: $P < .001$, $P = .026$, $P < .001$, $P = .007$; female SLE: $P < .001$, $P = .012$, $P < .001$, $P < .001$, respectively). In the female SLE subgroup, CAD patients had longer SLE disease duration, elevated SLEDAI-2K scores, a higher proportion of eGFR <60 mL/min, elevated serum inflammatory markers, and corticosteroid exposure compared to control patients ($P = .018$, $P = .017$, $P < .001$, $P < .001$, $P = .044$, respectively), but this was not found in the male SLE subgroup ($P > .05$) (Table 3).

3.3 | Risk factors for severe CAD

According to clinical significance and results of the univariate analysis, age, male gender, SLE disease duration, overweight or obese status, presence of the 5 major CAD risk factors, SLEDAI-2K values, hyperuricemia, elevated serum inflammatory marker levels, and corticosteroid exposure were used, and the binary logistic regression analysis showed age (odds ratio [OR] = 1.107, $P < .001$), male gender (OR = 2.499, $P = .020$), presence of 5 major CAD risk factors (OR = 18.339, $P < .001$), SLEDAI-2K values (OR = 1.041, $P = .019$), hyperuricemia (OR = 2.601, $P = .029$), and corticosteroid exposure (OR = 5.942, $P = .005$) as independent risk factors for severe CAD in patients with SLE (Figure 1A). For men aged ≥45 and women aged ≥50 years, risk factors were age (OR = 1.081, $P = .001$), presence of 5 major CAD risk factors (OR = 16.567, $P < .001$), SLEDAI-2K values (OR = 1.050, $P = .015$), hyperuricemia (OR = 3.536, $P = .011$), and corticosteroid exposure (OR = 4.859, $P = .015$) (Figure 1B). Therefore, these variables and antiphospholipid antibody (APL), excluding corticosteroid exposure, were used in the multivariate analysis, and the presence of 5 major CAD risk factors (OR = 52.767, $P < .001$) and positive APL (OR = 8.841, $P = .003$) were identified as independent risk factors for severe CAD in men aged <45 and women aged <50 years (Figure 1C). For male patients with SLE, these variables, excluding gender, were used in the multivariate analysis, and age (OR = 1.078, $P = .002$) and the presence of 5 major CAD risk factors (OR = 11.442, $P = .025$) were identified as independent risk factors for severe CAD (Figure 1D). Finally, these variables and APL, excluding gender, were used in the multivariate analysis, and age (OR = 1.118, $P < .001$), the presence of 5 major CAD risk factors (OR = 34.769, $P < .001$), SLEDAI-2K (OR = 1.063, $P = .003$), and positive APL (OR = 6.660, $P < .001$) were identified as independent risk factors for severe CAD in female patients with SLE (Figure 1E).

3.4 | Coronary angiographic findings in patients with SLE complicated with severe CAD

Twenty-eight (65.12%, 9 men aged ≥45 years and 11 women aged ≥50 years, and 2 men aged <45 years and 6 women aged <50 years) of the 43 patients with severe CAD had myocardial infarction. Thirty-nine patients (90.7%, 9 men aged ≥45 and 24 women aged ≥50 years, and 2 men aged <45 and 4 women aged <50 years) underwent coronary angiography (including 31 invasive coronary angiography and 8 CTA), and 3-vessel disease was most frequently detected (18/39, 46.15%). Figure 2 shows images of 3-vessel disease in a patient with SLE complicated with severe CAD. The most common site of coronary lesions was the left anterior descending coronary artery (31/39, 79.49%), followed by the left circumflex coronary artery (24/39, 61.54%), right coronary artery (23/39, 58.97%), and left main coronary artery (2/39, 5.13%). Two patients with positive APL had myocardial infarction and normal coronary arteries, which was more prevalent in the younger SLE subgroup than in the older

TABLE 1 Demographic data and clinical features in patients with SLE

Parameters	Total (N = 3744)	Control group (n = 3701)	CAD group (n = 43)	*P* value
Age, y, median (P25, P75)	35.00 (29.00, 45.00)	35.00 (29.00, 45.00)	59.00 (50.00, 66.50)	<.001***
Female, n (%)	3441 (91.91)	3411 (92.16)	30 (69.77)	<.001***
SLE disease duration, y, median (P25, P75)	8.00 (4.00, 12.00)	8.00 (4.00, 12.00)	11.00 (4.00, 19.00)	.023*
Overweight or obese, n (%)	723 (19.31)	705 (19.05)	18 (41.86)	<.001***
5 major CAD risk factors[a], n (%)	771 (20.59)	732 (19.78)	39 (90.70)	<.001***
Dyslipidemia	465 (12.42)	437 (11.81)	28 (65.12)	<.001***
Diabetes mellitus	56 (1.50)	49 (1.32)	7 (16.28)	<.001***
Hypertension	188 (5.02)	162 (4.38)	26 (60.47)	<.001***
Smoking	126 (3.37)	113 (3.05)	13 (30.23)	<.001***
Family history of CAD	106 (2.83)	99 (2.67)	7 (16.28)	<.001***
Rash, n (%)	1972 (52.67)	1958 (52.90)	14 (32.56)	.008**
Photosensitivity, n (%)	344 (9.19)	342 (9.24)	2 (4.65)	.441
Oral ulcers, n (%)	989 (26.42)	986 (26.64)	3 (6.98)	.004**
Arthritis, n (%)	1904 (50.85)	1888 (51.01)	16 (37.21)	.072
Serositis, n (%)	719 (19.20)	716 (19.35)	3 (6.98)	.041*
Renal disorder, n (%)	1729 (46.18)	1719 (46.45)	10 (23.26)	.002**
Neurologic disorder, n (%)	594 (15.87)	592 (16.00)	2 (4.65)	.043*
Hemolytic anemia, n (%)	465 (12.42)	464 (12.54)	1 (2.33)	.044*
Leukopenia or lymphopenia, n (%)	1121 (29.94)	1115 (30.13)	6 (13.95)	.021*
Thrombocytopenia, n (%)	866 (23.13)	856 (23.13)	10 (23.26)	.984
SLEDAI-2K, median (P25, P75)	3.00 (0.00, 8.00)	3.00 (0.00, 8.00)	5.50 (0.00, 14.00)	.054
eGFR <60 mL/min, n (%)	198 (5.29)	189 (5.11)	9 (20.93)	<.001***
Hyperuricemia, n (%)	131 (3.50)	121 (3.27)	10 (23.26)	<.001***
Elevated serum inflammatory marker[b], n (%)	1028 (27.46)	1003 (27.10)	25 (58.14)	<.001***
ANA, n (%)	3670 (98.02)	3627 (98.00)	43 (100.00)	1.000
Anti-dsDNA, n (%)	2334 (62.34)	2309 (62.39)	25 (58.14)	.568
APL, n (%)	744 (19.87)	732 (19.78)	12 (27.91)	.184
Low complement, n (%)	1599 (42.71)	1583 (42.77)	16 (37.21)	.463
Corticosteroids, n (%)	2767 (73.90)	2727 (73.68)	40 (93.02)	.004**
Immunosuppressants, n (%)	2961 (79.09)	2926 (79.06)	35 (81.40)	.708
Anti-malarial drugs, n (%)	2407 (64.29)	2383 (64.39)	24 (55.81)	.243

Abbreviations: ANA, antinuclear antibody; APL, antiphospholipid antibody; CAD, coronary artery disease; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.*$P<.05$, **$P<.01$, ***$P<.001$.

[a]5 major CAD risk factors: any of dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of CAD.

[b]Serum inflammatory marker: erythrocyte sedimentation rate and/or high-sensitivity C-reactive protein.

SLE subgroup (2/6 [33.33%] vs 0/33 [0.00%], $P = .020$). Moreover, left circumflex coronary artery was less frequently involved in the younger SLE subgroup than in the older SLE subgroup (1/6 [16.67%] vs 23/33 [69.70%], $P = .024$) (Figure 3A). However, no differences were detected in the number or site of the involved coronary arteries between the genders ($P > .05$) (Figure 3B).

4 | DISCUSSION

Our results suggest that the characteristics of and risk factors for severe CAD differed in age- and gender-stratified patients with SLE. In older patients, independent risk factors included age, 5 major CAD risk factors, SLEDAI-2K, hyperuricemia, and corticosteroid exposure. In younger patients, the risk factors were 5 major CAD risk factors and positive APL. Male risk factors were age and 5 major CAD risk factors, whereas female risk factors were age, 5 major CAD risk factors, SLEDAI-2K, and positive APL. Additionally, 3-vessel disease was most prevalent in patients with severe CAD.

Cardiovascular disease is a primary cause of death in SLE worldwide, whereas its pathogenesis is complex.[18] Coronary involvement varies among coronary atherosclerosis, coronary arteritis, coronary microartery vasculitis, and normal coronary artery with thrombosis in patients with SLE.[19] Among them, coronary arteritis

TABLE 2 Demographic data and clinical features in age-stratified patients with SLE

Parameters	Men aged <45 and women aged <50 years			Men aged ≥45 and women aged ≥50 years		
	Control group (n = 3092)	CAD group (n = 8)	*P* value	Control group (n = 609)	CAD group (n = 35)	*P* value
Age, y, median (P25, P75)	33.00 (28.00, 39.00)	38.50 (36.75, 41.25)	.073	55.00 (52.00, 60.00)	60.00 (53.00, 68.00)	.003**
Female, n (%)	2883 (93.24)	6 (75.00)	.098	528 (86.70)	24 (68.57)	.003**
SLE disease duration, y, median (P25, P75)	7.00 (4.00, 11.00)	9.00 (1.75, 15.50)	.880	10.00 (5.00, 15.00)	12.00 (4.00, 19.50)	.275
Overweight or obese, n (%)	547 (17.69)	3 (37.50)	.317	158 (25.94)	15 (42.86)	.028*
5 major CAD risk factors[a], n (%)	549 (17.76)	7 (87.50)	<.001***	183 (30.05)	32 (91.43)	<.001***
SLEDAI-2K, median (P25, P75)	3.00 (0.00, 8.00)	5.00 (2.00, 15.00)	.310	2.00 (0.00, 7.00)	6.00 (0.00, 12.50)	.025*
eGFR <60 mL/min, n (%)	133 (4.30)	1 (12.50)	.298	56 (9.20)	8 (22.86)	.019*
Hyperuricemia, n (%)	97 (3.14)	1 (12.50)	.227	24 (3.94)	9 (25.71)	<.001***
Elevated serum inflammatory marker[b], n (%)	812 (26.26)	6 (75.00)	.006 **	191 (31.36)	19 (54.29)	.005**
APL, n (%)	628 (20.31)	4 (50.00)	.101	104 (17.08)	8 (22.86)	.380
Corticosteroids, n (%)	2317 (74.94)	8 (100.00)	.220	410 (67.32)	32 (91.43)	.003**
Immunosuppressants, n (%)	2486 (80.40)	8 (100.00)	.342	440 (72.25)	27 (77.14)	.528
Anti-malarial drugs, n (%)	2055 (66.46)	4 (50.00)	.542	328 (53.86)	20 (57.14)	.705

Abbreviations: APL, antiphospholipid antibody; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.*$P < .05$, **$P < .01$, ***$P < .001$.

[a]5 major CAD risk factors: any of dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of CAD.

[b]Serum inflammatory marker: erythrocyte sedimentation rate and/or high-sensitivity C-reactive protein.

TABLE 3 Demographic data and clinical features in gender-stratified patients with SLE

Parameters	Male			Female		
	Control group (n = 290)	CAD group (n = 13)	*P* value	Control group (n = 3411)	CAD group (n = 30)	*P* value
Age, y, median (P25, P75)	35.00 (26.00, 46.00)	55.00 (49.00, 59.00)	<.001***	35.00 (30.00, 44.00)	59.50 (50.25, 67.75)	<.001***
SLE disease duration, y, median (P25, P75)	6.00 (3.00, 11.00)	7.00 (4.00, 15.00)	.288	8.00 (4.00, 12.00)	12.50 (4.25, 19.75)	.018*
Overweight or obese, n (%)	66 (22.76)	7 (53.85)	.026*	639 (18.73)	11 (36.67)	.012*
5 major CAD risk factors[a], n (%)	103 (35.52)	12 (92.31)	<.001***	629 (18.44)	27 (90.00)	<.001***
SLEDAI-2K, median (P25, P75)	4.00 (0.00, 12.00)	4.50 (0.00, 5.25)	.395	3.00 (0.00, 8.00)	8.00 (0.50, 14.75)	.017*
eGFR <60 mL/min, n (%)	24 (8.28)	2 (15.38)	.697	165 (4.84)	7 (23.33)	<.001***
Hyperuricemia, n (%)	16 (5.52)	4 (30.77)	.007**	105 (3.08)	6 (20.00)	<.001***
Elevated serum inflammatory marker[b], n (%)	78 (26.90)	7 (53.85)	.072	925 (27.12)	18 (60.00)	<.001***
APL, n (%)	69 (23.79)	2 (15.38)	.715	663 (19.44)	10 (33.33)	.056
Corticosteroids, n (%)	210 (72.41)	13 (100.00)	.059	2517 (73.79)	27 (90.00)	.044*
Immunosuppressants, n (%)	227 (78.28)	11 (84.62)	.842	2699 (79.13)	24 (80.00)	.907
Anti-malarial drugs, n (%)	174 (60.00)	7 (53.85)	.658	2209 (64.76)	17 (56.67)	.356

Abbreviations: APL, antiphospholipid antibody; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.*$P < .05$, **$P < .01$, ***$P < .001$.

[a]5 major CAD risk factors: any of dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of CAD.

[b]Serum inflammatory marker: erythrocyte sedimentation rate and/or high-sensitivity C-reactive protein.

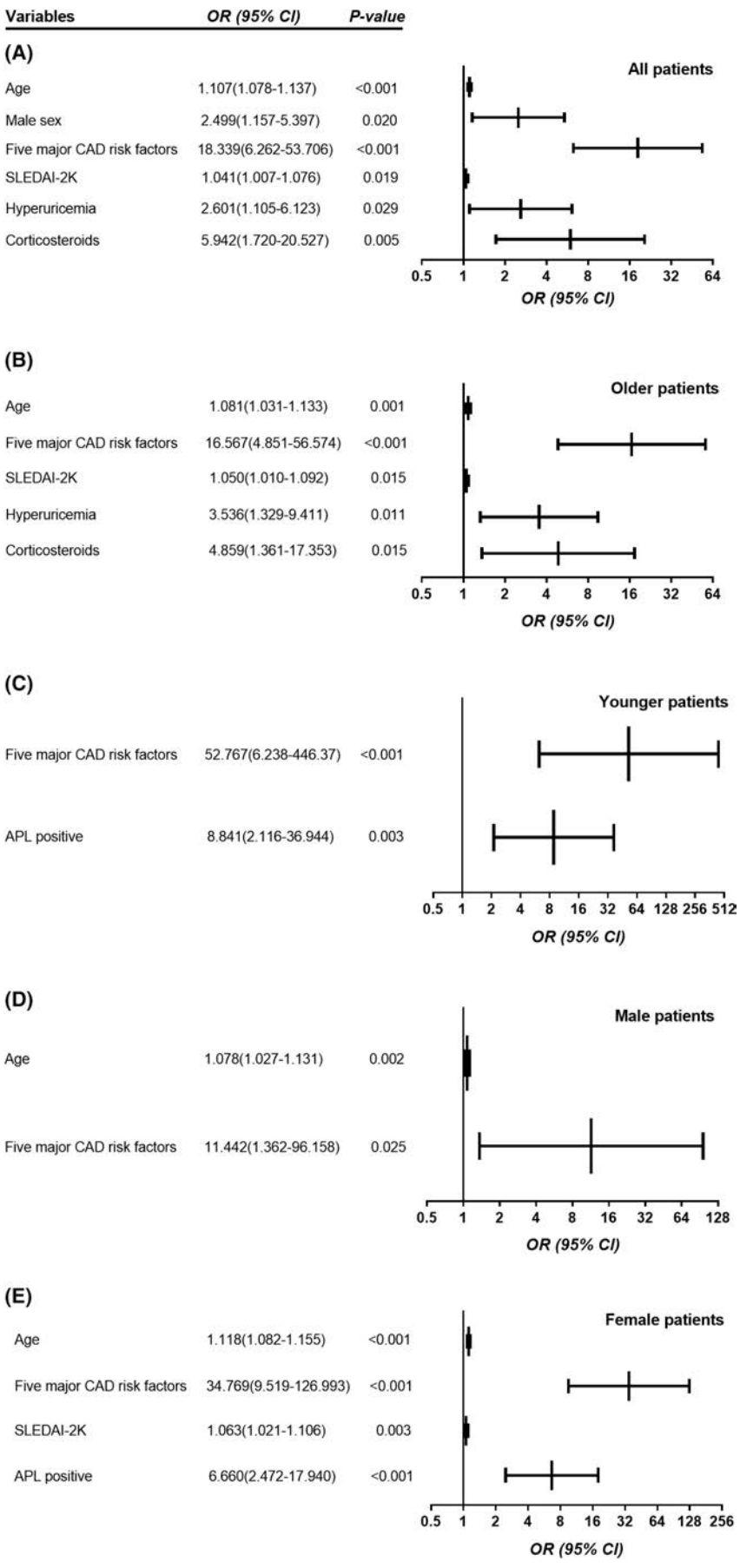

FIGURE 1 Forest plots of risk factors for severe CAD in patients with SLE. Risk factors for severe CAD in all patients (A), in older patients (men aged ≥45 and women aged ≥50 years) (B), in younger patients (men aged <45 and women aged <50 years) (C), in male patients (D), and in female patients (E) with SLE. APL, antiphospholipid antibody; CAD, coronary artery disease; CI, confidence interval; OR, odds ratio; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000. Five major CAD risk factors: any of dyslipidemia, diabetes mellitus, hypertension, smoking and family history of CAD

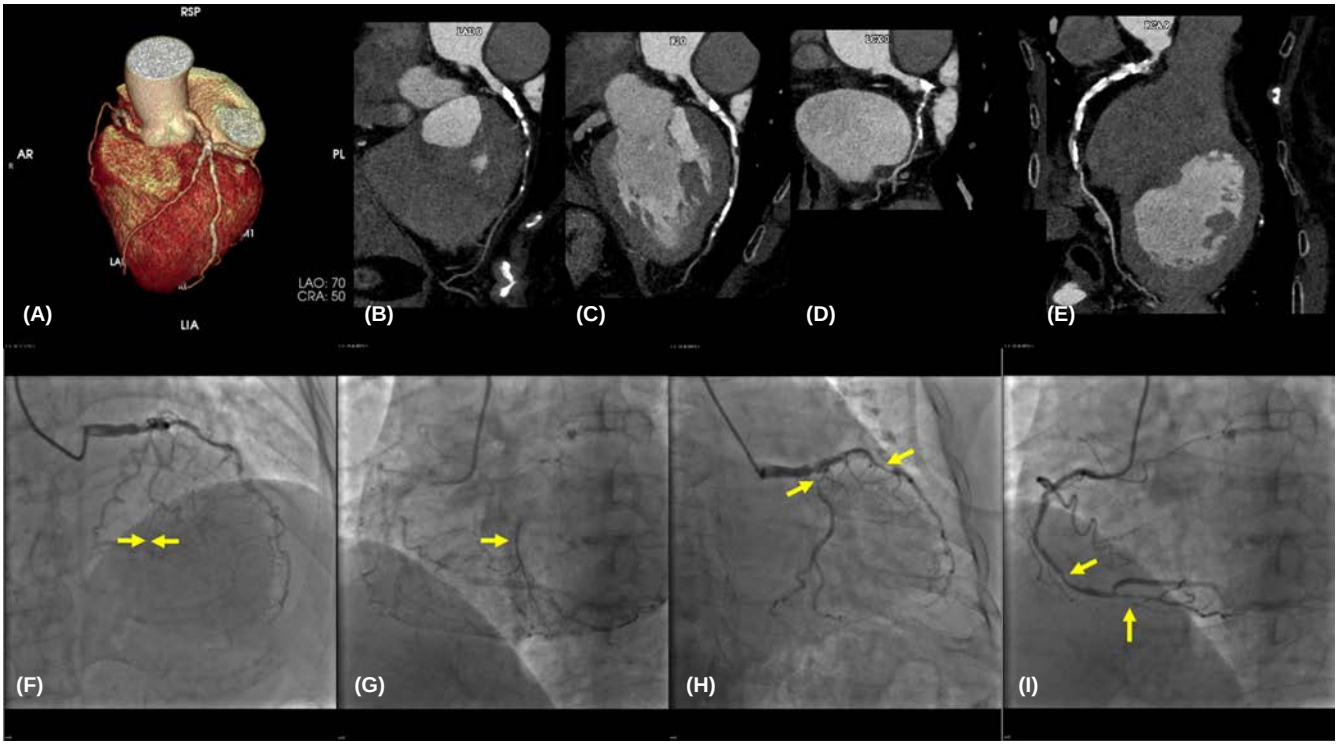

FIGURE 2 Images for 3-vessel disease in a 59-year-old woman with systemic lupus erythematosus for 19 years who presented with chest pain and hypertension for 10 years. Reconstructed imaging of coronary computed tomographic angiography (CTA) (A); CTA demonstrates severe calcification in the left anterior descending coronary artery (LAD) (B), intermediate (C), right coronary artery (RCA) (E), and moderate calcification in the left circumflex coronary artery (LCX) (D). Invasive coronary angiography shows occlusion of LAD (F), totally occluded LAD reinjected by RCA (G), significant stenosis of LCX and moderate stenosis of intermediate (H), and multiple stenosis of RCA (I) (yellow arrows)

rarely occurs and is far less common than coronary injury caused by atherosclerosis.[20] Similarly, we found that most vasculitis-related manifestations of SLE (eg, rash, oral ulcers, serositis, renal disorder, neurologic disorder, hemolytic anemia, and leucopenia or lymphopenia) were less common in patients with severe CAD than in other patients. Both traditional and disease-specified risk factors contribute to the pathogenesis of CAD in SLE.[21] Accordingly, our results showed that age, male gender, presence of 5 major CAD risk factors, disease activity, and corticosteroid exposure were all predictors for severe CAD in SLE. Moreover, we found a higher prevalence of hyperuricemia, along with elevated serum inflammatory markers and decreased eGFR in patients with severe CAD. A study reported that uric acid is associated with the exacerbation of lupus nephritis; however, whether hyperuricemia is the cause or consequence of the development of renal manifestation in lupus or merely contributes to the progression of the disease remains unclear.[22] Essentially, serum uric acid is not only related to renal damage, but also associated with global damage in SLE.[23] In this study, we found hyperuricemia to be an independent risk factor for severe CAD which could lead to an approximately 2.6-fold increased risk of developing severe CAD in SLE. Promoting platelet adhesiveness, stimulating oxygen free radical formation, causing endothelial dysfunction and inflammation, and inducing oxidative stress may be the predominant mechanisms of hyperuricemia on atherosclerosis.[24]

Premature CAD is relatively rare, and has been defined as CAD in men aged <45 and women aged <50 years in patients with various forms of immune-mediated inflammatory disease.[25] Although the prevalence of CAD varies with age in patients with SLE, it significantly increases compared with the general population.[26] In the present study, male patients aged <45 and female patients aged <50 years accounted for 83% of the total participants, and approximately 92% of them were women. Although the presence of 5 major CAD risk factors was found to be a risk factor for all subgroups, dissimilarity was found according to the stratification by age and gender. In subgroups stratified by age, one difference found was hyperuricemia; although it was prevalent in both older and younger SLE patients with severe CAD compared with their counterparts without CAD, it was only found to be an independent risk factor for severe CAD in older patients with SLE, which could increase the risk for severe CAD by 3.5 times. Another significant dissimilarity was corticosteroid therapy, which could lead to a 4.9-fold risk of severe CAD in older patients with SLE. Essentially, all younger patients with SLE and severe CAD took corticosteroids, and the frequency was over 25% higher than in their counterparts without CAD. We inferred that there might be a potential association between corticosteroid therapy and severe CAD in younger patients with SLE, were it not for their relatively rare incidence of severe CAD. As long-term corticosteroid therapy could result in a significantly high risk for organ damage such as CAD, minimizing

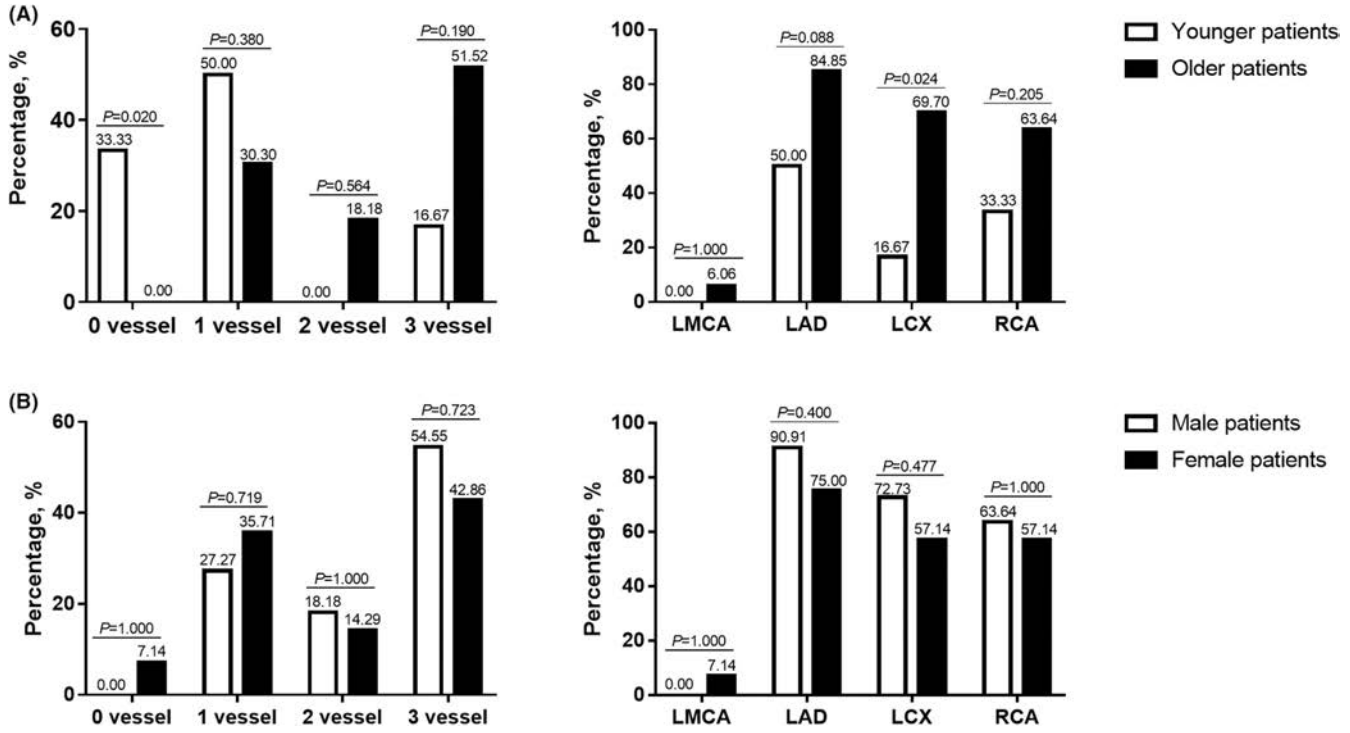

FIGURE 3 Age- and gender-stratified coronary angiographic findings in patients with SLE complicated with severe CAD. Number and site of involved coronary arteries stratified by age (A), and by gender (B). CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; RCA, right coronary artery; SLE, systemic lupus erythematosus. Older patients: men aged ≥45 and women aged ≥50 years; younger patients: men aged <45 and women aged <50 years

corticosteroid exposure during SLE treatment as appropriate may be of great importance on reducing the prevalence of severe CAD.[27] Disease activity was found to be another risk factor for severe CAD in older and in female patients with SLE, potentially resulting in a 5% and 6% incremental risk, respectively. However, similar results regarding disease activity were not found in younger or male patients with SLE. Additionally, our study showed that the prevalence of positive APL was over 27% higher in younger patients with SLE with severe CAD relative to their older counterparts, and was nearly 18% higher in female patients with SLE with severe CAD relative to their male counterparts. In fact, APL was identified as an independent risk factor for severe CAD in both younger and female patients with SLE, which can increase the morbidity of severe CAD by 8.8 times and 6.7 times, respectively. APL is a series of autoantibodies mainly composed of antiβ_2-glycoprotein I antibodies, anticardiolipin antibodies, and lupus anticoagulant, which not only contributes to premature atherosclerosis in SLE, but also plays a key role in the formation of venous and arterial thrombosis.[2,28] This may be an explanation for the higher prevalence of myocardial infarction with normal coronary arteries in younger SLE patients with severe CAD compared with their older counterparts. Finally, we found that 3-vessel disease was most commonly detected in SLE with severe CAD, indicating an extensive coronary involvement in those patients.

This study has some limitations. As this was an observational, cross-sectional study, there was a likelihood of selection bias, given that most of the patients with SLE were young and middle-aged women. Moreover, 28 patients with no coronary angiogram despite clinical suspicion of severe CAD were excluded, which might have contributed to the low prevalence of severe CAD in this study. In addition, as cardiovascular medication exposure such as statin and aspirin began after CAD diagnosis for most of our participants with SLE and severe CAD, we did not take cardiovascular medication exposure into account when assessing the characteristics and risk factors of severe CAD in patients with SLE. Our results should be confirmed by a prospective, randomized controlled trial in the future.

In conclusion, we strongly recommend screening for severe CAD in older patients with 5 major CAD risk factors, active disease, hyperuricemia, and corticosteroid exposure. In younger patients, we strongly recommend screening those with the presence of 5 major CAD risk factors and positive APL. Among men, we strongly recommend screening patients with older age and the presence of 5 major CAD risk factors. Finally, among women, we strongly recommend screening patients with older age, the presence of 5 major CAD risk factors, active disease, and positive APL. Early identification of severe CAD and active control for modifiable risk factors may be of great significance in improving the long-term outcomes for patients with SLE.

AUTHOR CONTRIBUTIONS

ML and LP took responsibility for the study, directed the concept and design, and helped throughout the whole process. ML, LP, WC, and JZ designed the study. WC, JZ, WQ, NG, JQ, GZ, and YW

participated in the data collection. WC, JZ, WQ, and JQ performed statistical analysis and data interpretation. WC drafted the manuscript. ML, LP, JZ, WQ, NG, JQ, GZ, and YW helped revise the manuscript. WC and JZ contributed equally to this study.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

No additional data are available.

ORCID

Weiping Ci https://orcid.org/0000-0001-9647-0653

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ORIGINAL ARTICLE

Outcomes of coronavirus disease 19 patients with a history of rheumatoid arthritis: A retrospective registry-based study in Iran

Mahsa Zargaran[1] | Shafieh Movassaghi[2] | Monireh Sadat Seyyedsalehi[3] | Kazem Zendehdel[3] | Abdolrahman Rostamian[2]

[1]Department of Internal Medicine, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Rheumatology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3]Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Abdolrahman Rostamian, Department of Rheumatology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Email: arostamian@tums.ac.ir

Abstract

Background: We aimed to study the outcomes of coronavirus disease 2019 (COVID-19) in patients with a history of rheumatoid arthritis (RA) in Iran, where most patients receive corticosteroids and are at high risk for COVID-19 infection.

Method: We collected the demographic, diagnostic, and treatment data of all COVID-19 patients by the clinical COVID-19 registry system. We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry. The primary outcome was mortality due to COVID-19. We also studied the risk of intensive care unit admission and intubation in RA patients compared to non-RA patients. We used multiple logistic regression analysis to study the association between RA and the risk of COVID-19 outcomes.

Result: We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry. The RA patients had a higher mean age (59.9 years) than the non-RA patients (57.7 years). The group of RA patients had a larger proportion of women (76.3%) than the non-RA patients (40.8%). The death rate due to COVID-19 was significantly higher in RA patients than non-RA patients (odds ratio [OR] = 2.69, 95% confidence interval [CI] = 1.24-5.81). The OR was higher among those who received prednisolone than among those who did not (OR = 3.59, 95% CI = 1.54-7.81). The odds of intubation were statistically significant among patients who received corticosteroid therapy (OR = 2.58, 95% CI = 1.07-6.18).

Conclusion: The risk of COVID-19 outcomes was higher in RA patients than non-RA patients, especially for RA patients who received a low dose of prednisolone. The results of this study can be used to triage RA patients who get infected by COVID-19. Further studies with larger sample sizes are required to more precisely define the high-risk groups.

KEYWORDS
COVID-19, outcome, pandemic, rheumatoid arthritis

1 | INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) has caused a global pandemic, experienced by more than 200 countries, and resulted in more than 4 million deaths.[1] About 5 million people contracted COVID-19 disease in the Islamic Republic of Iran from February 1, 2020, to June 10, 2021, and more than 100 000 patients died due to this disease.[2]

Clinical features and outcomes of COVID-19 patients are associated with different risk factors, including gender, age, comorbidity, the severity of disease, and oxygen saturation at admission.[3] The most important comorbidities associated with poor outcomes in these COVID-19 patients include diabetes, hypertension, cardiovascular disease, obesity, chronic liver disease, chronic kidney disease, and asthma.[4]

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disorder, and RA patients usually take immunosuppressive agents. Because of the impairment of the immune system and the iatrogenic effect of corticosteroids and immunosuppressive medicine, these patients may be at high risk for severe infections. Available evidence indicates a small elevation in the risk of infection in RA patients compared to the general population.[5] However, some studies showed no association between a history of rheumatologic diseases and risk of COVID-19 infection.[6] A meta-analysis of 23 studies showed that the relative risk of COVID-19 infection among patients with a history of rheumatologic diseases was 1.52 (95% 1.16-2.00) compared to the general population. Some studies showed that the risk of COVID-19 infection was higher than the risk of developing other rheumatologic diseases in China, Spain, Italy, the UK, and the USA.[5,7]

Therefore, COVID-19 patients with a history of RA would require more attention and probably intensive care when admitted to the hospitals than the general population.[5,7] Several studies reported that COVID-19 patients with rheumatologic diseases had a higher risk of COVID-19 outcomes than other COVID-19 patients.[5] However, the data on COVID-19 outcomes among RA patients are limited, especially in low and middle-income countries, where the treatment regimens of rheumatic diseases and the management of COVID-19 are different from those in high-income countries. In Iran, most RA patients receive low-dose daily corticosteroids, which may increase the risk of severity of COVID-19 infection and outcomes in these patients.

In this work, we compared the COVID-19 outcomes of RA patients with those of non-RA patients in Iran. To the best of our knowledge, this is the first study to evaluate the outcome of RA patients in a low- or middle-income country.[8]

2 | MATERIALS AND METHODS

2.1 | Patients

We used data from the Clinical COVID-19 Registry of Imam Khomeini Hospital between February 1, 2020, and June 10, 2021. We registered 2254 COVID-19 patients in the program, of whom 38 had a history of RA. We confirmed COVID-19 infection by clinical evaluation, computed tomography scan, or reverse transcription polymerase chain reaction (RT-PCR) test. We included only those patients who had positive RT-PCR test results and excluded patients whose RT-PCR test results were negative (n = 786, 25%) or unknown (n = 106, 3.4%). We reviewed the patient files and contacted the RA patients or their next of kin to confirm their diagnosis and collect additional data related to their condition, including their treatment history.

2.2 | Statistical analysis

We used descriptive statistics to study the distribution of the patients' characteristics. Because the follow-up time was very short, the hazard was not proportional during the follow-up period. Therefore, we performed multivariate logistic regression models and estimated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI). ORs were adjusted for age, gender, comorbidities, and oxygen saturation level. We considered patients' histories of cancer, liver diseases, chronic kidney disease, diabetes, heart disease, hypertension, neurologic disease, stroke, lung disease, human immunodeficiency virus infection, autoimmune diseases, and organ transplantation; we also created a summary variable to adjust for comorbidities. We performed logistic regression analyses for different outcomes, including death, intensive care unit (ICU) admission, and intubation. All analyses were performed in Stata14 (Stata Statistical Software: Release 14, College Station, TX, USA).

3 | RESULTS

We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry (Table 1). The RA patients had a higher mean age (59.9) than non-RA patients (57.7), as well as a higher proportion of women (76.3% vs 40.8%). Multivariate analyses showed that the odds of death due to COVID-19 were 2.69 times higher in RA patients than non-RA patients (OR = 2.69, 95% CI = 1.24-5.81) (Table 2). The OR was especially high among RA patients who received prednisolone (OR = 3.59, 95% CI = 1.54-7.81). Although the excess risk of ICU admission was not statistically significant, we found that the odds of intubation were statistically significant among patients who received corticosteroid therapy (OR = 2.58, 95% CI = 1.07-6.18).

4 | DISCUSSION

RA patients have a slightly increased risk of COVID-19 infection compared with non-RA patients because their immune systems are impaired.[5] Moreover, the risk of infection is a side effect of corticosteroids commonly used to treat RA.[9-11] We found a higher risk of death and intubation in RA patients compared to non-RA patients,

especially among patients who received low-dose corticosteroid therapy.

A few previous studies on RA patients presented similar results. The risk of death due to COVID-19 was 35% higher in RA patients than in non-RA patients in a study conducted in the US.[12] A UK-based study revealed that RA patients had severe COVID-19 outcomes.[13] A retrospective study showed that old age and the use of glucocorticoids were risk factors for severe COVID-19 outcomes but that the use of other classes of disease-modifying antirheumatic drugs was not. Similarly, among 600 cases in England, 46% required hospitalization. Old age and underlying conditions were associated with hospitalization.

Another study showed that hydroxychloroquine use has no association with hospitalization, but the use of high-dose glucocorticoids (more than 10 mg per day of prednisolone) influenced the mortality rate. Patients who received disease-modifying antirheumatic drugs were less likely than others to be hospitalized.[14] Another British retrospective study of 3729 RA patients found that COVID-19-related deaths were associated with factors such as old age, male gender, some comorbidities, and disease activity.[15] Although initial publications warned about increasing mortality rates in immune-suppressed cases, a recent analysis indicated that immune-suppressed patients had similar or even lower mortality rates than the general population.[16] Moreover, data about the pathophysiology of COVID-19 infection shows that some anti-rheumatoid medicines can manage COVID-19.[7]

A major strength of this study is that it considered a large, high-quality COVID-19 registry that allowed us to adjust for several important confounding factors, such as age, gender, oxygen saturation, and several comorbidities. We also actively reviewed the patient files and contacted the RA patients to confirm their history of RA and their use of different treatment regimens.

However, this study also suffered from some limitations. Unfortunately, detailed data for RA, such as disease duration and severity, medications taken before hospitalization, rheumatoid factor level, and cyclic citrullinated peptide levels, were not available. In addition, we did not have sufficient power to carry out sub-group

TABLE 1 Characteristics of COVID-19 patients with rheumatoid arthritis (RA COVID-19) and without rheumatoid arthritis (non-RA COVID-19) at Imam Khomeini Hospital, Tehran, Iran

Variable	RA COVID-19 n (%)[a]	Non-RA COVID-19 n (%)
Number of patients	38	2216
Mean age (SD), in y	59.9 (±11.9)	57.7 (±16.9)
Gender, female	29 (76.3)	904 (40.8)
Comorbidity	20 (53.6)	1417 (63.9)
Mortality	12 (31.6)	424 (19.1)
Intensive care unit admission	10 (26.3)	463 (20.9)
Intubation	8 (15.7)	265 (12.0)
Abnormal computed tomography scan	34 (89.47)	1820 (82.5)
Mean duration of stay, (SD), in d	5.68 (±4.59)	6.53 (±7.84)
Mean O_2 saturation percentage (SD)	88.6 (±6.8)	88.9 (±8.0)
RA drug history		
Hydroxychloroquine	18 (47.4)	–
Methotrexate	20 (52.6)	–
Prednisolone	31 (81.6)	–

[a]We reported percentages in parenthesis, unless otherwise noted.

TABLE 2 COVID-19 outcomes in rheumatoid arthritis patients and non-rheumatoid arthritis patients with positive reverse transcription polymerase chain reaction COVID-19 tests

Outcome	Patient group	No. outcome (%)	Crude OR	Adjusted OR (95% CI)[a]	*P* value
Death	Non-RA COVID-19	424 (19.7)	Reference	Reference	–
	RA COVID-19	12 (31.6)	1.95 (0.98-3.90)	**2.69 (1.24-5.81)**	**0.012**
	Hydroxychloroquine	5 (27.8)	1.61 (0.57-4.54)	2.61 (0.81-8.41)	0.11
	Methotrexate	6 (30)	1.80 (0.68-4.70)	2.13 (0.76-6.00)	0.15
	Prednisolone	11 (35.5)	**2.32 (1.11-4.89)**	**3.59 (1.54-7.81)**	**0.003**
Intensive care unit admission	Non-RA COVID-19	463 (24.5)	Reference	Reference	
	RA COVID-19	10 (29.4)	1.28 (0.61-2.71)	1.4 (0.67-3.23)	0.34
	Hydroxychloroquine	6 (37.5)	1.85 (0.67-5.12)	2.5 (0.82-4.70)	0.11
	Methotrexate	6 (33.3)	1.54 (0.58-4.12)	1.69 (0.60-4.70)	0.32
	Prednisolone	9 (32.1)	1.46 (0.66-3.25)	1.80 (0.76-4.20)	0.18
Intubation	Non-RA COVID-19	327 (14.8)	Reference	Reference	
	RA COVID-19	8 (21.1)	1.54 (0.70-3.39)	1.81 (0.79-4.17)	0.16
	Hydroxychloroquine	3 (16.7)	1.15 (0.33-3.98)	1.50 (0.39-5.70)	0.56
	Methotrexate	4 (20.0)	1.44 (0.48-4.32)	1.51 (0.48-4.76)	0.48
	Prednisolone	8 (25.8)	2.02 (0.89-4.54)	**2.58 (1.07-6.18)**	**0.03**

Note: Bolded estimates indicate that the results were statistically significant.

[a]All ORs (odds ratios) are adjusted for age, gender, comorbidities, and O_2 saturation.

analyses. Studies large enough to allow sub-group analyses should be conducted in the future.

5 | CONCLUSION

The risk of death due to COVID-19 infection is higher in RA patients than in non-RA patients, especially among those who receive corticosteroid therapy. The results of this study can be considered when triaging RA patients who contract COVID-19. Further studies with larger sample sizes are required to more precisely define high-risk groups.

AUTHOR CONTRIBUTIONS

MZ, AR, and KZ designed the study. MZ and MSS collected the data. KZ and MSS analyzed the data. MZ and MSS prepared the first draft of the manuscript. All authors were involved in the interpretation of the results and approval of the final version. MZ wrote the first draft of the paper and implemented the comments and suggestions from other authors and prepared the final draft of the paper. AR, SM, and KZ took full responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors have met authorship criteria.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID

Abdolrahman Rostamian https://orcid.org/0000-0002-9234-6919

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CASE REPORT

A case of palmoplantar pustular psoriasis induced by hydroxychloroquine in a patient with systemic lupus erythematosus

Bilgin Karaalioğlu | Fatih Yıldırım | Melek Yalçın Mutlu | Gamze Akkuzu | Duygu Sevinç Özgür | Cemal Bes

Department of Rheumatology, University of Health Sciences Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey

Correspondence
Bilgin Karaalioğlu, Department of Rheumatology, University of Health Sciences Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey.
Email: bilginkaraaloglu@gmail.com

Abstract

Palmoplantar pustular psoriasis (PPP) is a rare clinical form of psoriasis. It is usually seen on the palms and soles, and affects patients' quality of life. In most cases, topical or systemic treatments are not sufficiently effective, so management of PPP is generally difficult. Hydroxychloroquine (HQ) is an antimalarial drug that is widely used in many autoimmune rheumatic diseases, mainly in systemic lupus erythematosus (SLE). Several reports describe the induction and exacerbation of psoriasis by HQ. Within this report, we aimed to put emphasis on considering possible drug effects by presenting a case of PPP, induced by HQ.

KEYWORDS
Hydroxychloroquine, systemic lupus erythematosus, palmoplantar pustular psoriasis

1 | INTRODUCTION

Palmoplantar pustular psoriasis (PPP) is a rare clinical form of psoriasis. It is usually seen on the palms and soles, and affects patients' quality of life. In most cases, topical or systemic treatments are not sufficiently effective, so management of PPP is generally difficult.[1] Hydroxychloroquine (HQ) is an antimalarial drug that is widely used in many autoimmune rheumatic diseases, mainly in systemic lupus erythematosus (SLE). Several reports describe the induction and exacerbation of psoriasis by HQ.[2] Within this report, we aimed to put emphasis on considering possible drug effects by presenting a case of PPP, induced by HQ.

2 | CASE PRESENTATION

A 49-year-old female patient was diagnosed with SLE 20 years ago with arthritis, positive anti-nuclear antibody, positive anti-dsDNA test, and hypocomplementemia. Within the past 10 years, there had been no drug use for the medication of SLE. She applied to the hospital with various complaints, including joint pain, photosensitivity, weakness, and malar erythema. Controls that we carried out showed us anti-nuclear antibody positivity, anti-dsDNA positivity, and hypocomplementemia. Based on her clinical observation and test results, she was diagnosed with SLE. For this purpose, prednisolone (5 mg/day) and HQ (400 mg/day) treatment was started; however, the patient reapplied after a month with complaints of papulopustular lesions on both soles and palms (Figure 1). Following this, a skin biopsy was taken from the lesions and diagnosed as pustular psoriasis by dermatology. Because the patient and her family had no history of psoriasis, it was thought that the situation could be drug-related. Following the related diagnosis, the use of HQ was stopped while prednisolone (5 mg/day) and topical (containing calcipotriol, betamethasone dipropionate, and salicylic acid) and psoralen and ultraviolet A radiation (PUVA) treatments were applied. The lesions had regressed after 1½ months. Because we know that HQ can have a beneficial effect in each stage of SLE disease, we first consider that the situation may be caused by co-substances of the drug so did not give up on using it directly. For this purpose, HQ produced by another company was given to our patient. However, PPP lesions

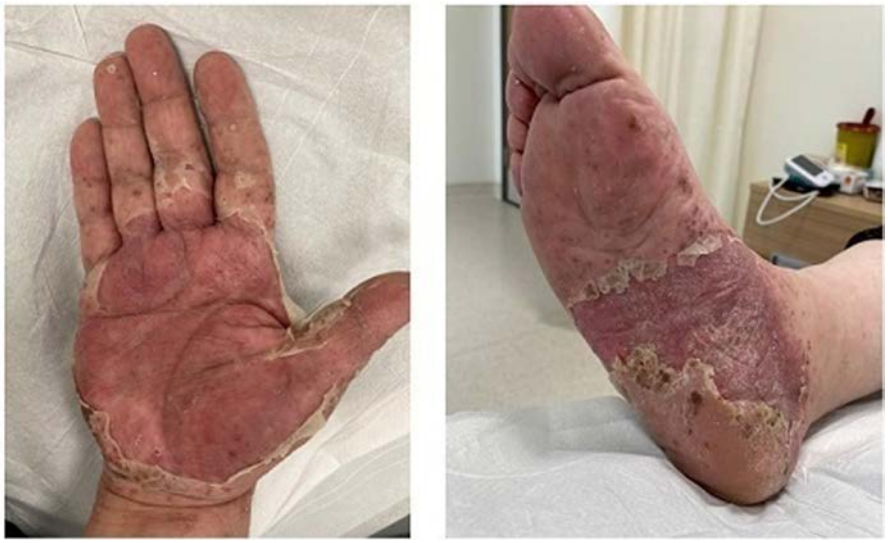

FIGURE 1 Lesions that progressed after hydroxychloroquine treatment. However, the patient was also treated by a dermatologist

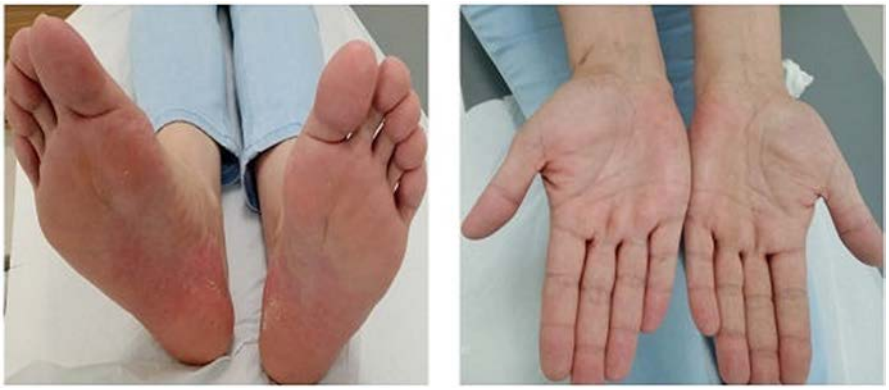

FIGURE 2 Hydroxychloroquine treatment was discontinued. After 4 months of follow up, the lesions were completely recovered

recurred a few days after administering the new HQ drug. The recurrence made us think that the reason for the PPP could be the main substance of the drug—HQ. Because the lesions were so characteristic for PPP, dermatology did not request another biopsy. When the patient developed PPP lesions when using HQ drugs from two different brands, it was determined that the lesions were drug-related. As a result, HQ treatment was stopped, and during the 4 months of follow up the lesions healed completely (Figure 2).

3 | DISCUSSION

Psoriasis is a systemic inflammatory disease that primarily affects the skin.[3] Its estimated prevalence in adults ranges from 0.5% to 11.4%.[4,5] Recently, the effect of drugs on the formation or aggravation of psoriasis has been studied. The effect of some drugs, such as β blockers, lithium, antimalarial drugs, terbinafine, and immune checkpoint inhibitors, on psoriasis has already been proven. Paradoxically, anti-tumor necrosis factor-α (TNF-α) inhibitors used in the treatment of psoriasis may also cause drug-related psoriasis.[6]

PPP is the most common variant of pustular psoriasis, presenting as small sterile pustular lesions on the palms and soles. The prevalence of the disease is estimated to be 0.01%. Women are affected more often than men.[7] It affects the quality of life negatively because of itching, pain, and the unhealthy appearance of the skin. The pathogenesis of PPP is not fully understood. It mainly occurs as the result of cigarette smoking; however, tonsillitis, dental infections, and stress can also be the reason for it. CARD14 and AP1S3 mutations, overactivation of the interleukin-36 (IL-36) pathway, and as a result, TNF-α IL-8, IL-17, IL-23 overproduction, are thought to be involved in the genetic pathogenesis of PPP.[8]

Paradoxically, PPP has been reported to develop during treatment with anti-TNF-α inhibitors. Within the study conducted by Shmidt et al, the majority of the patients were diagnosed with Crohn disease and rheumatoid arthritis. The use of infliximab, adalimumab, or etanercept caused the development of psoriasis in patients and 45% developed PPP.[9] Seol et al also reported a case of PPP induced by adalimumab and golimumab in a patient with ankylosing spondylitis.[10]

The mechanism by which HQ exacerbates or causes the formation psoriasis is not fully understood. HQ may increase IL-17 and IL-23, which are involved in the formation of psoriasis, or it may affect cholesterol metabolism, which is essential for the skin. In addition, HQ is an inhibitor of the epidermal transglutaminase activity, which causes the accumulation of the epidermal cell.[11]

Below, we summarize some of the recent case studies that are related to the formation or exacerbation of psoriasis when using HQ.

Muskaan et al described the development of psoriasis caused by HQ in different types and locations.[12] In the review, there were 18 patients reported with psoriasis-related complications due to the use of HQ. Four of these patients were using HQ because of SLE; however, half of the patients (9/18) did not have a history of psoriasis before use of HQ. Another point that should be emphasized is that growth of psoriasis was different from 4 days to 3.5 years after the use of HQ. None of the patients had isolated PPP, and in most it spread to different parts of the body.[12]

Wang et al described a 41-year-old women with erythrodermic psoriasis after the use of HQ. Psoriasis and SLE share two single nucleotide polymorphisms and both result in increased levels of IL-17, IL-23, and IL-12.[13] Therefore, the use of HQ in SLE may induce the growth of psoriasis through increasing levels of IL-17 and IL-23.

Shindo et al have reported the growth of serious generalized pustular psoriasis in a 34-year-old patient with SLE after 21 days of HQ use.[14] In our patient, PPP recurred after using a new HQ drug. Because the lesions were so characteristic, dermatology did not re-apply for biopsy again. During this period, discontinuation of the HQ and adding psoriasis treatment were enough for the lesions to fully recover. We did not apply any additional treatment for SLE. These findings support the idea that recurrence of psoriasis can be drug-related. In addition, we objectively evaluated drug-associated psoriasis by using the Naranjo adverse drug reaction probability scale. According to this scale, our case received 10 points and was categorized as "patient with definite drug relation".[15]

Although HQ is used so frequently in rheumatologic diseases, it rarely causes psoriasis. So far, isolated PPP was not reported to be caused by HQ, as we did not encounter it when we reviewed the literature.

4 | CONCLUSION

Recognition of drug-induced psoriasis is vital to ensure optimal management of the disease. Even discontinuation of the causative drug can provide complete recovery from the disease. HQ treatment, which is frequently used in rheumatology, may cause new psoriasis formation or exacerbation of existing lesions, and should be taken into consideration in such cases.

AUTHORS' CONTRIBUTIONS

BK and CB designed the case report, analyzed data, and prepared the manuscript. FY, MM, GA, and DO collected data by examining the patient during the treatment period.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Bilgin Karaalioğlu https://orcid.org/0000-0001-7584-8549

Cemal Bes https://orcid.org/0000-0002-1730-2991

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CASE REPORT

A Giant Silence – An atypical association of sensorineural hearing loss with Giant Cell Arteritis

Yu Feng Shi | Sameer Malik

Concord Hospital, Sydney, New South Wales, Australia

Correspondence
Yu Feng Shi, Concord Hospital, Concord, New South Wales 2139, Australia.
Email: yufeng.shi@health.nsw.gov.au

Abstract

Giant cell arteritis (GCA) is a chronic vasculitic disorder predominantly affecting medium to large sized arteries, prevalent in the 50 plus age group. This case illustrates an atypical presentation of this disease in the form of bilateral sensorineural hearing loss (SNHL). Apart from the presence of constitutional and vertiginous symptoms, there were essentially no classical features of GCA. Differentials were broad including infection, malignancy and medication toxicity as well as brain, eye and ear syndromes such as Cogan's syndrome, all of which were eventually excluded. Her diagnosis was ultimately confirmed on positron emission tomography, which highlights the diagnostic importance of this modality. She was managed with corticosteroids then tocilizumab and is making a gradual recovery. Literature review demonstrates that SNHL is more prevalent than previously suggested in GCA, although this does not have widespread recognition. Mechanisms of SNHL in GCA include vascular occlusion, immunological mechanisms including cross reactivity with viral antigens and direct viral infection. SNHL does appear to improve with corticosteroids. This case emphasizes the importance of considering GCA as an important differential in SNHL.

KEYWORDS
clinical aspects, disease etiology and pathogenesis, giant cell arteritis, sensorineural hearing loss, vasculitides

1 | BACKGROUND

Giant cell arteritis (GCA) is a chronic vasculitic disorder predominantly affecting medium to large sized arteries. It is the most common systemic arteritis in European and American populations, with a prevalence of 0.2% in those aged over 50 years.[1]

Aging is the biggest risk factor with individuals >50 years old predominantly affected, with peak incidence at age 70-80 years.[2] Other risk factors include Scandinavian ethnicity, female gender, family history and polymyalgia rheumatica.[3]

The classic symptoms of presentation include acute to subacute onset of headache, jaw claudication, scalp tenderness and constitutional symptoms.[4] Serious complications of visual loss and extra-cranial arterial manifestations such as aortic aneurysms can also occur.[4,5]

Sensorineural hearing loss (SNHL) represents an atypical presentation of GCA, with only a few documented case reports. This case illustrates a debilitating presentation of GCA and highlights GCA as an important differential in the consideration of SNHL.

2 | CASE PRESENTATION

A 67-year-old independent Chinese woman presented to the emergency department with a 4 days history of profound, progressive

bilateral hearing loss commencing in the left ear. This was accompanied by tinnitus and vertigo. Her symptoms began 4 days after receiving the ChAdOx1-S recombinant vaccine (Astra Zeneca).

Her tinnitus started in her left ear, progressed to her right the next day and resulted in bilateral complete hearing loss within 4 days. Constitutional symptoms included subjective fevers for 4 days at home and 5 kg of weight loss in the preceding months. She also described hip and shoulder girdle pain 12 months prior to presentation without formal diagnosis.

Other features included a dry cough which resolved weeks prior to this presentation and mild bilateral pain in her pinna. She had no history of head trauma. She did not experience headache, scalp tenderness, jaw claudication or visual disturbance.

Her medical comorbidities included ischemic heart disease, degenerative disc disease in the cervical spine, dyslipidemia, gastroesophageal reflux disease and smoking with a >20 pack year history.

On examination, she was febrile to 38.9°C, but all other vital signs were within normal limits. She had left-sided gaze-evoked nystagmus and an entirely absent response to auditory stimuli with a Weber test. The remainder of her cranial nerves and neurological exam were normal, although she had a slightly unsteady gait and equivocal Romberg's test. There were no signs of connective tissue disease and her cardiovascular, respiratory and gastrointestinal examinations were unremarkable. Ophthalmological examination revealed mild exophoria, bilateral myopia, early cataracts and possible left eye glaucoma. There were no features of optic nerve ischemia. Ear, nose and throat examination was essentially normal except for a small mucous retention cyst at right vallecula and mild bilateral erythema of the pinna suggestive of perichondritis.

3 | INVESTIGATIONS

Initial audiometry demonstrated complete bilateral sensorineural hearing loss and tympanometry showed normal middle ear pressure and compliance in both ears.

Laboratory studies demonstrated elevated inflammatory markers with white cell count of 11.1×10^9/L (reference range [RR] 3.9-9.5×10^9/L), with a neutrophil predominance of 9.6×10^9/L (RR 2.0-8.0×10^9/L), elevated C-reactive protein (CRP) to 168 mg/L (RR ≤ 4 mg/L) and erythrocyte sedimentation rate (ESR) of 127 mm/h (RR <12 mm/h). Autoimmune, myeloma, hemolysis and infection screening were all negative except for positive antinuclear antibodies at 1:80 with a speckled pattern. These include anti-neutrophil cytoplasmic autoantibodies, extractable nuclear antigen antibodies, immunoglobulin G subclasses, anti-cyclic citrullinated peptides, rheumatoid factor and antiphospholipid antibodies all testing negative or within normal limits. She had a normocytic anemia with a hemoglobin of 78 g/L (RR 115-165 g/L) and mean corpuscular volume of 85.2 fL (RR 80-100 fL). Iron studies were also suggestive of iron deficiency anemia in the context of anemia of chronic disease with reduced transferrin saturation of 9% (RR 20%-50%), iron levels of 3 μmol/L (RR 5-30.4 μmol/L) and a ferritin of 386 μg/L (RR 30-300 μg/L); however, a soluble transferrin receptor result would be more conclusive. COVID-19 polymerase chain reaction test was negative.

Of coagulation tests, international normalized ratio was normal and proteins C and S were elevated at 287% (RR 70%-180%) and 175% (RR 60%-150%) respectively. Further vaccine-induced thrombotic thrombocytopenia testing was not engaged in, due to platelet count persistently ranging in the normal to thrombocytosis range.

Computed tomography (CT) and magnetic resonance imaging of the brain were unremarkable and review by a neurologist, otolaryngologist and ophthalmologist yielded no further findings than as discussed earlier. CT scans of the chest, abdomen, pelvis were also normal.

A positron emission tomography (PET) scan (see Figure 1A–C) revealed significant uptake in the ascending thoracic aorta as well as in both internal carotid arteries and subclavian artery, suggestive of a large vessel vasculitis, most in keeping with GCA. Arterial temporal duplex study was normal with no evidence of halo sign or stenosis and the patient declined a temporal artery biopsy.

4 | TREATMENT

The patient was commenced on intravenous methylprednisolone (1 g daily) for 5 days and with addition of 6 total doses of intratympanic steroids (0.8 mL of 8 mg/2 mL) when there was minimal improvement. She was subsequently commenced on oral prednisone 50 mg daily with a progressive 26 week wean.

5 | PROGRESS

There was some improvement in audiometry (see Table 1).

In her left ear at 250 Hz, tones were only audible at 80 dBHL. In the right ear at 250 Hz, tones were audible at 90 dBHL, and at 500 Hz, they were audible at 100 dBHL. She was unable to distinguish voices.

Her inflammatory markers began to improve rapidly with CRP falling to <10 mg/L and ESR falling to 25 mm/h within 2 weeks.

Approximately 1 month after discharge from her hospital admission, she was commenced on methotrexate for 2 weeks. This was then switched to tocilizumab 162 mg fortnightly when stock became available as a steroid-sparing agent. She now remains on a 162 mg weekly dose. She has also been fitted with hearing aids and can understand loud voices. Her dizziness continues to improve.

6 | DISCUSSION

GCA is a large vessel vasculitis characterized by the formation of "giant cells" from the fusion of macrophages into multinucleated aggregates, an event driven by inflammatory cytokines released by T cells.[6,7] The exact pathogenesis is not yet completely understood.[8]

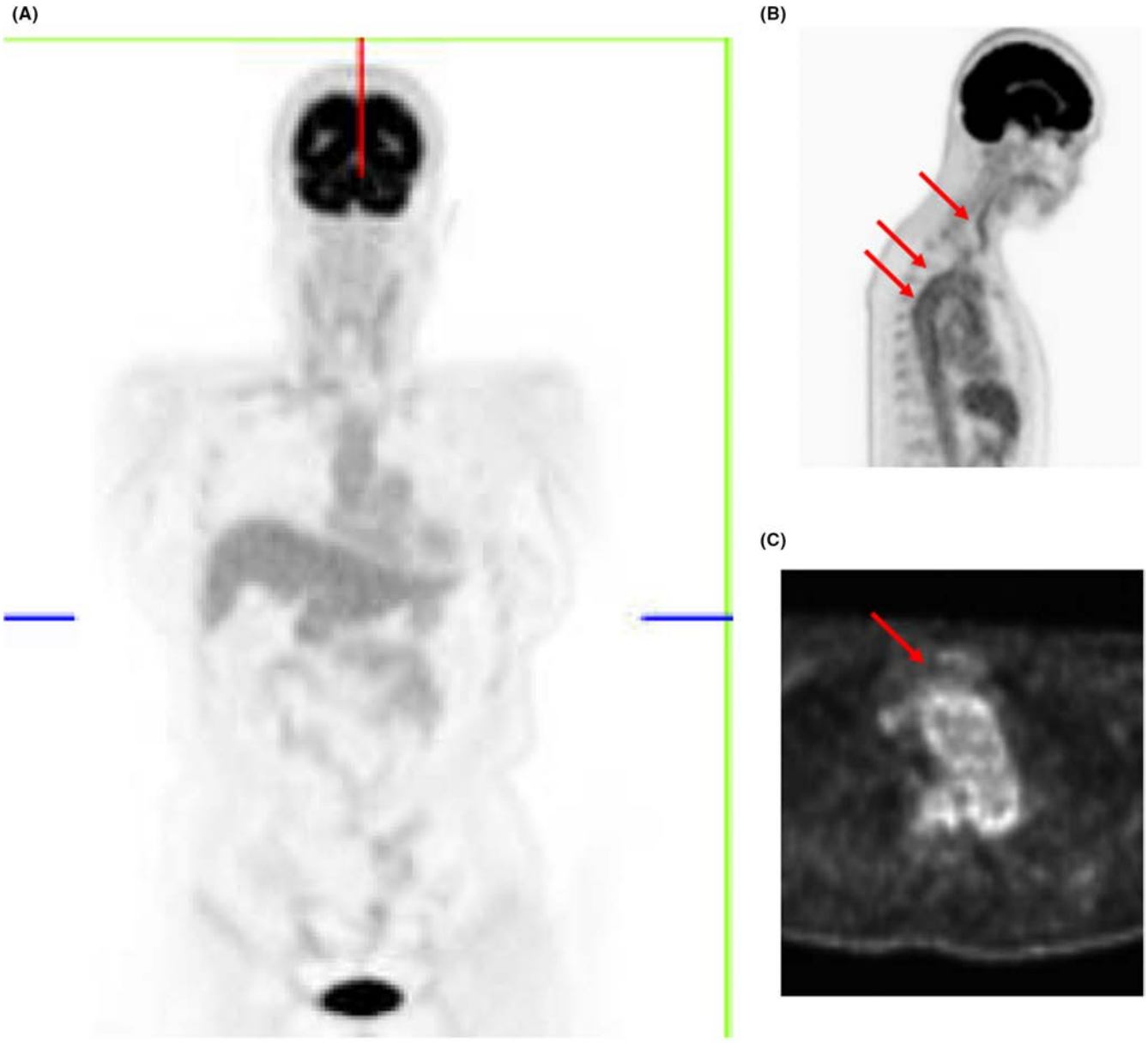

FIGURE 1 A. Whole-body positron emission tomography (PET) findings. B. PET image demonstrating increased metabolism in thoracic ascending aorta and both internal carotid arteries suggestive of large vessel vasculitis. C. PET image demonstrating increased metabolism in aortic arch, also suggestive of large vessel vasculitis

SNHL is an atypical complication of GCA, thought to be uncommon. Such cases have been reported since 1946[9] but there have only been a few. Subsequent isolated cases were illustrated by Malmvall and Bengtsson[10] which showed no hearing improvement after steroid administration.

Recent studies demonstrate that SNHL may not be as uncommon as previously thought. Saravanan[11] shows that 35% of GCA patients had concurrent hearing loss. Similarly, a retrospective study by Chu[12] of Chinese patients demonstrated hearing loss in 25% of patients, although again, neither study commented specifically on hearing loss in the absence of other classical features of GCA.

Improvement of hearing post-steroids occurs in 56% of patients,[11] with early administration of steroids important in the recovery of SNHL.[13] Recovery from vertiginous symptoms was not as pronounced as recovery of hearing loss.[11]

The mechanism of deafness is not entirely understood but may involve arterial wall inflammation of the posterior circulation or terminal cochleovestibular vasculature.[14] Multiple theories have been suggested regarding the exact mechanism, including vascular occlusion, immunological mechanisms and viral infection.[12] Vascular occlusion occurs when vasculitic vessels prone to thrombosis occlude and cause downstream ischemia and necrosis.[15] The immunological mechanism suggests circulating antibodies may cross-react with inner ear antigens and cause immune-mediated damage potentially through direct antibody-mediated damage of inner ear structures.[16] Direct viral infection has been postulated to damage the inner

TABLE 1 Timeline of clinical course

Time post-symptom onset	Event
D 0	Development of profound bilateral hearing loss
D 4	Hospital admission
D 4-20	Various inconclusive investigations and initial trial of intravenous methylprednisolone (D 5-11)
D 20	Positron emission tomography imaging demonstrating likely diagnosis of giant cell arteritis
D 30	Discharge from hospital and ongoing corticosteroid weaning
D 60	Commencement of methotrexate
D 77 - present	Commencement of tocilizumab and cessation of methotrexate

TABLE 2 Analysis of differentials

Differential	Supporting evidence	Conflicting evidence
Giant cell arteritis (GCA)	Diagnostic positron emission tomography (PET) findings Response to immunosuppressive therapy including tocilizumab Some constitutional clinical features suggestive of GCA	Absence of clinical features of cranial GCA
COVID vaccine-related audio-vestibular disorder	Proximity of sensorineural hearing loss (SNHL) with COVID vaccine Case reports of audio-vestibular disorder associated with COVID-19 vaccines documented	Unlikely vaccine-induced thrombotic thrombocytopenia due to normal platelet counts or thrombocytosis Recent cross-sectional study and case series finds no association between COVID-19 vaccination and SNHL Significantly more research required
Ototoxic medication	Association exists between mirtazapine and irreversible SNHL in 1 case report[21]	Mirtazapine is a regular medication, not recently started Does not explain other findings including PET results Hearing loss with mirtazapine initiation was rapid in reported case
Infectious agent	Presence of raised inflammatory markers and fever	Entire infection screen was negative with no infectious organisms either isolated or identified on polymerase chain reaction testing
Neoplastic process	Clinical features of SNHL and constitutional features such as weight loss and fever	Extensive imaging findings demonstrating no signs of mass lesion or metastases

ear structures. although no direct histopathological evidence has supported this. Alternately, viral antigens could trigger antibodies against inner ear antigens such as type 2 collagen or phospholipids, which could cause an acquired thrombophilia affecting the inner ear and triggering the immunological mechanism.[12]

This case was notable for the absence of features of cranial GCA. Although the patient did demonstrate some suggestive features including constitutional symptoms and biochemistry suggestive of an inflammatory process, the differentials remained broad. This included infection, ototoxic drugs, neoplasms, autoimmune causes, thrombosis after COVID-19 Astra Zeneca vaccine and vascular disorders. Specifically, brain, eye and ear syndromes were considered, such as Cogan's syndrome. However, these were eventually ruled out as she did not meet the criteria.

The other manifestations of cranial nerve VIII involvement including dizziness and nystagmus localized the lesion and its bilateral nature suggested a systemic inflammatory process; however, this was not definitive for GCA. The presence of a syndrome suggestive of polymyalgia rheumatica increased the clinical suspicion for GCA.

Vaccine-induced thrombotic thrombocytopenia was considered less likely due to persistently normal platelet count or thrombocytosis.

Specifically, COVID-19 vaccine-related audio-vestibular disorder was a possibility. Recent case reports illustrate its association with SNHL, including by Tsetsos et al and Medina et al,[17–19] which specifically cite involvement of the Astra Zeneca vaccine. In contrast, Ekobena et al reports associations of SNHL with only messenger RNA vaccines. However, a combined cross-sectional and case series

study by Formeister et al[20] involving 555 cases of SNHL demonstrated no association of COVID-19 vaccination with SNHL. With the highly suggestive PET findings, an association with GCA is favored over this key differential.

A tabular consideration of differential is included (see Table 2).

The literature thus demonstrates that SNHL is not as uncommon a manifestation of GCA as previously believed and highlights GCA as a key differential to be considered in SNHL, especially in the setting of a systemic inflammatory process. This case also illustrates the importance of PET imaging as an important diagnostic tool in GCA. Although temporal artery biopsy is the gold standard in the diagnosis of cranial GCA,[22] PET is demonstrated as an important method in diagnosis of extra-cranial GCA.[23]

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

ORCID

Yu Feng Shi https://orcid.org/0000-0001-5156-9721

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APLAR GRAND ROUND CASE

Systemic lupus erythematosus following human papillomavirus vaccination: A case-based review

Nan He[1] | Xiaomei Leng[2] | Xiaofeng Zeng[2]

[1]The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

[2]Peking Union Medical College Hospital, Beijing, China

Correspondence
Xiaomei Leng, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing 100730, China.
Email: lpumch@126.com

Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune diseases (AIDs) with many pathogenic factors, ranging from genetic to epigenetic to environmental. The human papillomavirus (HPV), a viral infectious agent, is a common contributor to the onset and exacerbation of SLE. HPV infections are more prevalent among SLE patients than healthy individuals, bringing about a substantial need for treatment. While HPV recombinant gene vaccines are accepted as a universal method for infection prevention, they pose a risk for adverse events such as fever, joint pain, and rashes. In rare cases, they might even trigger AIDs such as SLE, especially in patients with a personal or family history of such diseases. In this article, we provide a report of a case of SLE onset following HPV vaccination and a review of 11 similar cases. An analysis of 12 patients revealed that 7 cases of SLE developed between 3 weeks and 2 months post-vaccination. Symptoms of SLE generally manifest as fatigue, fever, joint pain, and myalgia. Two patients had lupus nephritis, 2 showed central nervous system involvement, including abnormal behavior and epileptic seizures, and 1 had intestinal pseudo-obstruction. All patients showed rapid remission with glucocorticoid and immunosuppressive therapy and remained stable during several months of follow-up.

KEYWORDS
human papillomavirus, mechanism, systemic lupus erythematosus, vaccination

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by inflammation, with a higher morbidity rate in women aged 15-45 years than in men. The pathogenesis of SLE is complex and genetic susceptibility is induced by environmental factors, with viral infections being 1 such example.[1] In etiological studies of SLE, it was found that the human papillomavirus (HPV) infection rate among patients is higher than that of the general population.[2] HPV-infected patients are also at a significantly higher risk for cervical cancer. Therefore, in 2006, the Food and Drug Administration recommended that women 9 to 26 years of age receive the HPV vaccine. The suggested age for HPV vaccination coincides with the age of high SLE incidence, making the relationship between the HPV vaccine and SLE incidence a notable concern.

This report describes a patient who developed SLE after receiving a quadrivalent HPV vaccine. Based on the Vaccine Adverse Event Reporting System (VAERS) database and SLE case series reported by several companies after HPV vaccination, a literature review was conducted to examine the relationship between HPV vaccination and SLE.

2 | CASE DESCRIPTION

A 31-year-old female patient developed a red maculopapular rash without pruritus or pain over the dorsal aspect of her hand bilaterally

and her forehead. The lesions were slightly higher than the skin level 1 week after the first recombinant human papillomavirus quadrivalent (Types 6, 11, 16, 18) vaccine (GARDASIL®) and regressed spontaneously a few days later. Two months later, the rash reappeared 1 week after receiving the second dose of the HPV quadrivalent vaccine (GARDASIL®), presenting as a red rash on the face and extremities, aggravated by ultraviolet exposure. She developed a fever lasting for 1 week with a T_{max} of 38.5°C, with arthralgia, hair loss, and poor appetite. Her medical and family history were unremarkable before the onset of the autoimmune disorder. Laboratory test results were as follows: white blood cells (WBC), 2.67×10^9/L; 24-hour proteinuria, 0.28 g; anti-nuclear antibody titer of 1:1000 homogeneous pattern, anti-u1RNP antibodies, anti-Ro (Sjögren's syndrome A [SSA]), anti-La (SSB) antibodies, anti-histone antibody, anti-nucleosome antibody positivity, and high positive anti-double-stranded DNA (dsDNA) antibodies; complement C3, 0.6 g/L; immunoglobulin G (IgG), 18.2 g/L; erythrocyte sedimentation rate (ESR), 34 mm/h; normal anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibody, anti-β2GP1 antibody, and lupus anticoagulant; and negative Coombs' test. She was diagnosed with SLE and given methylprednisolone tablets (20 mg twice daily) and hydroxychloroquine (0.2 g twice daily). The symptoms improved significantly with treatment, with the rash, fever, and proteinuria all resolving. In addition, the WBC rose to 7.51×10^9/L, complement C3 0.95 g/L, IgG 17.7 g/L, and her ANA titer decreased to 1:320. Positive anti-Ro (SSA), anti-La (SSB), and anti-dsDNA antibodies were also detected. Treatment-wise, the methylprednisolone dosage was gradually reduced to 8 mg/d, and hydroxychloroquine continued to 0.2 g twice daily. After 10 months, the patient remained in remission. Re-examination of the autoantibodies revealed an ANA titer of 1:320 (homogeneous pattern), negative anti-dsDNA antibodies, and positive anti-Ro (SSA) and anti-La (SSB) antibodies.

After searching the literature on SLE after HPV vaccination since 2006, 11 similar cases were identified (Table 1).

3 | SEARCH STRATEGY

We reviewed all available English literature published between January 2006 and March 2021 (PubMed/MEDLINE and Web of Science) on SLE cases following HPV vaccination. We used the keywords "systemic lupus erythematosus" OR "SLE" OR "lupus" AND "Human papillomavirus vaccination" OR "HPV" OR "HP vaccine" OR "HP vaccination" OR "HP vaccinate". Previously existing cases of SLE that had flared after injection of the HPV vaccine were excluded from the reviewed lists.

4 | LITERATURE REVIEW (TABLE 1)

In addition to the aforementioned case reports with a more detailed medical history, Geier et al also reported 28 cases of SLE after HPV vaccination in the VAERS database in 2016.[4] However, no specific clinical or laboratory data were available for these patients. Symptoms are reported to develop between 4 and 5 months after the second dose. Common clinical manifestations were fatigue, fever, arthralgia, and myalgia, with minimal involvement of the vital organs. However, we also noted 2 cases of pathologically confirmed lupus nephritis and 2 cases of central nervous system involvement, specifically behavioral abnormalities and epileptic seizures. A case of intestinal pseudo-obstruction has also been reported. The findings suggest that in some cases, typical SLE lesions of vital organs can occur in addition to common manifestations in the skin mucosa, joints, and muscles. Patients typically show autoantibodies for various factors in laboratory tests, including ANA, anti-dsDNA, anti-SSA, anti-phospholipid antibodies, and hypocomplementemia. It is worth noting that 53.8% (7/13) of the patients had a prior history or family history of autoimmune disease. In terms of treatment and prognosis, these patients responded well to hormones and immunosuppressive agents, responded quickly to treatment, and remained stable during the follow-up period.

5 | DISCUSSION

Despite extensive data demonstrating the safety and efficacy of HPV vaccines, adverse events have occurred in the VAERS surveillance systems, and in some cases, most of which are mild to moderate and self-alleviating in the short term. In the general population, only mild local reactions and general symptoms such as fatigue, headache, and myalgia have been reported after immunization.[5] However, there have been a few reports of severe adverse reactions after HPV vaccination in some individuals or those with a susceptible genetic background, including venous thrombosis, hypersensitivity, motor neuron disease, and AIDs. Examples include SLE or SLE-like,[6,7] spondyloarthritis,[8] rheumatoid arthritis, Behçet's disease,[9] and adult-onset Still's disease.[10] Our case and those reviewed in the literature suggest a temporal association between immunization with HPV vaccines and the appearance of SLE.

The molecular simulation mechanism that causes the body to produce an immune cross-reaction may be a reason for adverse reactions caused by the HPV vaccine. The HPV vaccine is composed of virus-like particles expressing HPV6, 11, 16, and 18 type L1 proteins; the purification and addition of an adjuvant (aluminum hydroxyl-phosphate sulfate) introduce HPV-like proteins (mainly L1 virus protein) to the vaccine. Molecular homology between human proteins and viral peptides can cause cross-immune reactions with the L1 viral peptides.[2] Furthermore, HPV and SLE patients share a common peptide chain, which increases the likelihood of adverse events. Segal et al found a vast peptide overlap with human proteins comprising lupus Ku autoantigen proteins p86 and p70, lupus brain antigen one homolog, lupus antigen expressed in neurons and muscles, natural killer cell IgG-like receptors, complement proteins C4-A and C4-B, and complement receptor CD19. Through molecular simulations, cross-reactions of the body's immune system are induced, which leads to the occurrence of SLE.[2]

TABLE 1 Summary of published cases of SLE after HPV vaccination

Case no.	Age	Gender	No. of vaccines	Onset of symptoms	Clinical manifestation	Autoantibody	AID history or family history	Treatment	Prognosis
Case1[7]	15	Female	2nd	2 mo	Intermittent fever , myalgia , arthritis, and malar rash	Anti-dsDNA , anti-Sm , anti-nRNP , anti-SSA	No	Prednisolone	Remission
Case2[8]	20	Female	2nd	1 mo	Myalgia, arthralgia , Raynaud's phenomenon , livedo reticularis	ANA 1:160 , lupus anticoagulant , anti-CCP	No	Prednisolone and hydroxychloroquine	Remission
Case3[8]	19	Female	1st	1 mo	Myalgia , arthralgia , arthritis , weakness, oral ulcers, fever , Raynaud's phenomenon , alopecia	Anti-dsDNA and anti-Sm, anti-nRNP hypocomplementemia	Autoimmune type 1 diabetes of her father	Cyclophosphamide and corticosteroid, hydroxychloroquine and azathioprine	Remission
Case4[3]	17	Female	2nd	2 mo	Arthralgias, rashes , livedo reticularis, bipedal edema, Class III lupus nephritis	ANA 1:640 and anti-dsDNA hypocomplementemia	No	Steroids, cyclophosphamide	Remission
Case5[3]	45	Female	2nd	4 mo	Fever, arthritis, malar rash, oral ulcers, ascites, intestinal pseudo-obstruction, behavioral changes	ANA 1:320 , anti-dsDNA , anti-SSA、anti-SSB , anti-histone hypocomplementemia	Rheumatoid arthritis	Prednisone, hydroxychloroquine	Remission
Case6[6]	32	Female	3rd	5 d	Weakness, severe myalgia, polyarthralgia, anorexia, skin rash, malar rash, aphthous stomatitis, pharyngodynia, cervical, hair loss	ANA, anti-dsDNA, anti-SSA, anti-SSB , hypocomplementemia	Autoimmune thyroid disease in family	Prednisone , hydroxychloroquine	Remission
Case7[6]	29	Female	2nd	3 wk	Weakness, diarrhea, malar rash, photosensitivity, arthritis, alopecia	ANA, anti-dsDNA, hypocomplementemia	Immune thrombocytopenia	Corticosteroids, azathioprine, and hydroxychloroquine	Remission
Case8[6]	16	Female	1st	8 d	Fever, asthenia, polyarthralgia, erythematous annular cutaneous lesions	ANA , lupus anticoagulant	Raynaud's phenomenon, her maternal aunt was diagnosed with systemic sclerosis	Prednisolone	Remission
Case9[6]	16	Female	2nd	3 wk	Fever, pharyngodynia, erythematous skin lesions , asthenia, anorexia, polyarthralgia, headache	Anti-cardiolipin IgM , lupus anticoagulant	Raynaud's phenomenon	Naproxen , omega-3 polyunsaturated fatty acids	Remission
Case10[6]	19	Female	2nd	10 d	Malar rash, skin rash, arthritis, alopecia	ANA, anti-dsDNA , hypocomplementemia	No	Corticosteroids, hydroxychloroquine, belimumab	Remission
Case11[6]	13	Female	2nd	3 wk	Erythematous rash, fever, periorbital edema, weight loss, malaise, fatigue, anemia, class II lupus nephritis, epilepsy	ANA, anti-Sm, anti-nRNP, anti-SSA, hypocomplementemia	Autoimmune diseases including SLE of her family members	Steroids, cyclophosphamide, hydroxychloroquine, antiepileptic medication	Remission
Case12	31	Female	2nd	1 wk	Erythematous rash, fever, fatigue	ANA 1:1000, anti-dsDNA, anti-SSA, anti-SSB , anti-histone, anti-nucleosome, hypocomplementemia	No	Prednisolone and hydroxychloroquine	Remission

Abbreviations: ANA, anti-nuclear antibodies; anti-Sm, anti-Smith antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-nRNP, anti-nuclear ribonucleoprotein antibody; anti-SSA, anti-Ro antibodies; anti-SSB, anti-La antibodies; anti-CCP, anti-cyclic citrullinated peptide antibody; AIDs, autoimmune diseases; HPV, human papillomavirus; SLE, systemic lupus erythematosus.

In a recent study on the association between SLE and vaccination, Kotliarov et al concluded that the 10-gene signature captures responsiveness to vaccination or predicts SLE flares in multiple cell subsets in the peripheral blood.[11] Moreover, the SLE-derived module was enriched for type I interferon-related transcripts. The activation status of an individual predicts vaccine responses to both adjuvanted and non-adjuvanted influenza vaccines in patients with AIDs.[12] Thus, vaccines based on pathogen-specific sequences may avoid potential cross-reaction risks associated with vaccination regimens.[13]

Other studies have suggested that vaccine-induced AIDs may be related to the aluminum adjuvants in vaccines.[14] It is believed that aluminum in adjuvants stimulates the innate and adaptive immune systems through different mechanisms, leading to the release of pro-inflammatory cytokines such as IL-1B and IL-18, which are involved in various autoimmune responses.[15] Moreover, the aluminum-containing adjuvant is one of the main adjuvants that leads to adjuvant-induced autoimmune syndrome induced by adjuvants (ASIA syndrome). However, other studies suggest that there is no increase in the incidence of autoimmune disease among those vaccinated with aluminum adjuvants compared to those who are not.[16] Ameratunga et al suggested that the link between vaccination and autoimmunity is likely to be false and most likely the result of random events or confusion rather than causality. Aluminum-containing adjuvants have been used for more than 90 years to enhance the immune response to vaccines. Aluminum is commonly used as an adjuvant and additive to prime and boost the immune system in vaccines.[17] Although the bioavailability of aluminum in vaccines differs from that of aluminum derived from water, food, or inhalation, and the exposure of young children to aluminum from vaccines is not precisely defined, the total aluminum exposure from immunization is likely significantly lower than the level that causes neurotoxicity.[18]

The most widely accepted view is that AIDs after HPV vaccination occur due to patients' common genetic or epigenetic susceptibilities. While a personal or family history of autoimmunity should be considered a risk factor for such adverse events, vaccination accelerates the transition of patients from subclinical to dominant autoimmunity.[19] Grimaldi-Bensouda et al suggested that a personal or family history of autoimmune disease is a risk factor for post-vaccination development of autoimmune disease or clinical symptoms.[19] However, when the data were adjusted for individual and family history of autoimmunity, the association was no longer confirmed. Epidemiological studies have shown that vaccine responses have familial aggregation. Human leukocyte antigen (HLA) and non-HLA gene markers affect the heterogeneous response to vaccines, suggesting that genetics, molecular similarities, and aluminum adjuvant stimulation are potentially dangerous factors for patients with a family history of autoimmune or prior autoimmune disease.

However, Shoenfeld et al proposed the hypothesis that HPV infection is a trigger for SLE development in prone individuals.[2] In addition, the prevalence of HPV in patients with SLE is higher than that in those unaffected by HPV because of the combined influence of autoimmune dysfunction and long-term use of glucocorticoids and immunosuppressants.[20] Furthermore, HPV vaccination showed a safe profile and immunogenicity in childhood SLE patients.[21] Thus, the European League Against Rheumatism recommends the vaccination of patients with autoimmune inflammatory rheumatic diseases in adulthood and SLE patients during adolescence.[22]

6 | CONCLUSION

Considering the high risk of HPV infection and the dilemma that HPV vaccination may induce SLE, we suggest taking a detailed history and family history of AIDs before HPV vaccination in young women. For those with a prior or family history of autoimmune diseases, an individualized analysis should be conducted by assessing individual and family autoimmunity and performing genetic tests to determine the risk of developing AIDs after HPV vaccination.[8] A pre-immunization assessment of autoantibody and HLA status will be a marker for at-risk individuals. More research is needed to determine who is likely to develop AIDs after immunization, which may be able to allow us to develop molecular immune signatures of adaptive and maladaptive immune responses to vaccines, develop early biomarkers of vaccine response in vaccine trials, identify who should receive the vaccine and at what dose, and increase safety and public confidence in vaccines by reducing the likelihood of serious adverse events related to vaccines.[23]

AUTHOR CONTRIBUTIONS

Nan He contributed to the conception, design, data acquisition and write-up of the manuscript. Xiaomei Leng and Xiaofeng Zeng contributed to data acquisition, critical review of the manuscript for important intellectual content and final approval of the manuscript.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ORCID

Nan He https://orcid.org/0000-0003-1944-9564

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