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EDITORIAL

Tofacitinib for sarcoidosis, a new potential treatment

Sarcoidosis is a multisystem granulomatous syndrome with a wide range of clinical manifestations,[1] with pulmonary involvement being the most common.[2] Sarcoidosis is characterized by the accumulation of lymphocytes and mononuclear phagocytes that induce the formation of non-caseating epithelioid granulomas with secondary derangement of normal tissue or organ anatomy and function.[3] The disease occurs worldwide, with an incidence between 1.4 and 64 per 100 000, and peaks at 30–60 years of age.[3,4] Studies have shown that genetic, host immune, and environmental factors interact to cause sarcoidosis, but the etiological determinants of the disease remain uncertain.[5] Thus far, apart from the tuberculin known to trigger the formation of the sarcoid granuloma, many have been the candidate antigens associated with the onset and the progression of the disease. These include bacterial DNA,[6] the major histocompatibility complex (MHC) class II molecules, vimentin (a peptide derived from the cytoskeleton)[7] and peripheral blood mononuclear cells (PBMCs) with vimentin triggers.[8] There is no standard treatment for sarcoidosis; nevertheless, corticosteroids are commonly prescribed. However, because of the potential toxicities of corticosteroids, alternative medications need to be considered.[9]

Tofacitinib is a potent selective inhibitor of the Janus kinase (JAK) family of tyrosine kinases, which comprises 4 non-receptor tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]), each with specificity for a different set of cytokine receptors.[10] In cellular assays, tofacitinib preferentially inhibits signaling via heterodimeric cytokine receptors that associate with JAK3 and/or JAK1.[10] Tofacitinib has been clinically approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, and other rheumatic diseases and is a promising new drug.

A recent study by Damsky et al[11] has opened new avenues for the treatment of sarcoidosis. In this open-label trial, 10 patients with cutaneous sarcoidosis were treated with tofacitinib. The primary outcome was the change in cutaneous sarcoidosis activity and morphology instrument activity score after 6 months of treatment. All patients experienced improvement in their skin, with 6 patients showing a complete response. This study suggests that tofacitinib treatment alleviates sarcoidosis symptoms and works mainly by inhibiting the interferon (IFN)-γ activation pathway of CD4+ T cells, a type 1 immune response. Although studies on JAK inhibitors are increasing, only a few cases of sarcoidosis treatment have been reported, and larger studies are needed to further evaluate this treatment approach.

Sarcoidosis is characterized by the presence of well-formed non-caseous granulomas composed of epithelioid macrophages in affected tissues. Microscopically, lymphocyte infiltration is mainly observed in CD4+ T cells.[12] During granulomatous inflammation, macrophages produce interleukin (IL)-6, IL-12, IL-18, IL-23, tumor necrosis factor (TNF)-α and T cell chemokines,[12,13] lymphocytes secrete high levels of IFN-γ and other cytokines, such as IL-2 and IL-17, and monocytes recruit chemokines.[12] These mutually reinforcing cytokine programs might create a self-sustaining loop that exacerbates and perpetuates inflammation. Activation of the JAK–STAT (signal transducer and activator of transcription) pathway is induced by cytokine binding to surface receptors, culminating in the regulation of transcription by STATs. JAK inhibitors block this pathway at the level of JAKs, thereby preventing STAT activation (Figure 1). Studies have shown that granuloma formation involves the coordinated activity of several cytokines, chemokines, and other signals.[13] The predominant type 1 immune response (eg, cytokines including IL-2, IL-12, IL-18, and IFN-γ), the type 3 cytokines (eg, IL-17 family) or the coproduction of type 1 (IFN-γ) and type 3 (IL-17) cytokines (Th17.1 phenotype) identified in sarcoidosis. Moreover, type 2 cytokines are also involved.[11] These cytokines have been implicated in sarcoidosis via the JAK–STAT pathway. It has been reported in the tissues and blood of sarcoidosis patients. However, this disease and those correlating most closely with disease activity and response to therapy remain imprecisely defined, which has hindered therapeutic progress in sarcoidosis.

In response, Damsky et al went further and, using molecular analyses, determined that type 1 cytokines but not type 2 or type 3 cytokines were activated at baseline and were closely correlated with disease activity and response to therapy. The authors suggested that IFN-γ is a key driver of sarcoidosis and a critical cytokine targeted by tofacitinib for effective treatment. This suggests that the elevation of IFN-γ correlates with disease activity, and makes teleological sense given the fundamental role of IFN-γ in classical macrophage activation, granuloma formation, and protection against *Mycobacterium tuberculosis*. Tofacitinib inhibits IFN-γ via JAK1/2 signaling. Moreover, the activity of other cytokines, including granulocyte-macrophage colony-stimulating factor (JAK2), IL-15 (JAK1/3), IL-6 (JAK1/2), IL-12 (JAK2/TYK2), and TNF (JAK-independent), is also evident in sarcoidosis.

Although some cases of sarcoidosis spontaneously resolve, many are chronic and require ongoing treatment. Currently, corticosteroids are the only Food and Drug Administration-approved drugs for

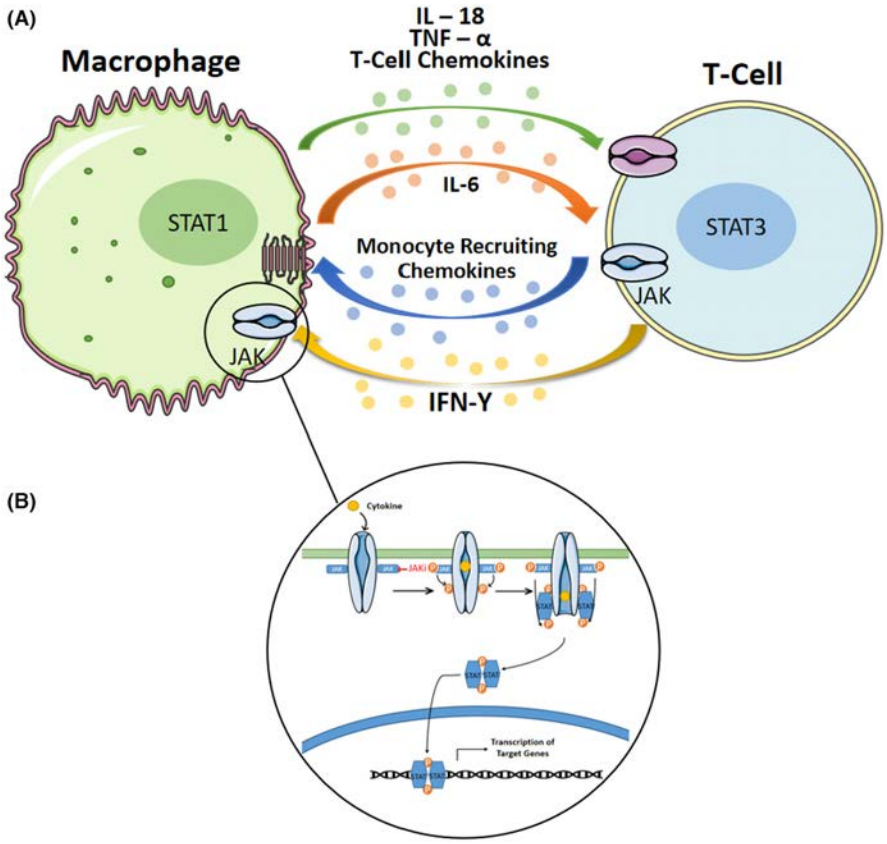

FIGURE 1 Molecular mechanism of T cell-induced macrophage activation and the Janus kinase – signal transducer and activator of transcription (JAK–STAT) pathway. A, $CD4^+$ T cells secrete interferon (IFN)-γ and monocyte-recruiting chemokines, resulting in monocyte recruitment and activation. IFN-γ signaling activates STAT1 in macrophages via JAK1 and JAK2. Following activation, macrophages produce interleukin (IL)-6, IL-18, tumor necrosis factor (TNF)-α, and T cell chemokines. IL-6 is a JAK–STAT-dependent cytokine that activates STAT3 by signaling JAK1, JAK2, and tyrosine kinase (TYK)2 in T cells. Conversely, IL-18, TNF-α, CD40, and chemokines do not signal via the JAK–STAT pathway. B, Cytokine binding at the cell surface leads to recruitment and activation by phosphorylation of JAK proteins. This, in turn, leads to the recruitment and activation of STAT proteins by phosphorylation, leading to dimerization and nuclear translocation of STAT proteins, which affects gene transcription.

treating sarcoidosis. However, they are not ideal for treating chronic diseases because of their many side effects. Other corticosteroid-preserving therapies for sarcoidosis, including methotrexate and TNF-α inhibitors, have low success rates, and some studies have shown that the efficacy of these therapies is not significant.[14] The extensive clinical manifestations of sarcoidosis cause great discomfort to patients and lead to anxiety, depression, and other emotional problems.[15] This highlights the need for in-depth research on the treatment of sarcoidosis, and here, in this prospective trial, we seek to provide new insights into the treatment of sarcoidosis.

The first JAK inhibitor was approved in 2011, and currently, there are 9 JAK inhibitor drugs on the market and many more in clinical studies. JAK inhibitors have a wide range of applications and are mainly used in the treatment of autoimmune diseases and tumors. In autoimmune diseases, tofacitinib is often used to treat rheumatoid arthritis and ankylosing spondylitis. However, some studies have shown that it also has great potential in the treatment of other immune diseases, such as polyarticular refractory juvenile idiopathic arthritis,[15] anti-melanoma differentiation-associated protein 5 juvenile dermatomyositis-associated interstitial lung disease,[16] synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome,[17,18] and cutaneous leukocytoclastic vasculitis (CLV).[19] This is mainly attributed to small molecule inhibitors of JAK in an oral preparation that inhibit JAK1 and JAK3, interfere with JAK signaling pathways downstream from inflammatory cytokine receptors, inhibit most inflammatory cytokines, block the inflammatory cascade reaction, and activate biological agents with strong anti-inflammatory effects. In addition, it is important to note that when using JAK inhibitors, precautions should be taken based on their biological function. The biggest problem is that the use of JAK inhibitors increases the risk of infection, anemia, and leukopenia.[20] Other side effects are still under investigation, including cardiovascular disease, gastrointestinal perforation, and the risk of cancer,[18] all of which limit the clinical use and development of these drugs to a certain extent.

In conclusion, although research on the pathogenesis and treatment of sarcoidosis has progressed in recent years, the pathogenesis of sarcoidosis has not been elucidated, and its treatment is also ineffective. Tofacitinib may become a new treatment for sarcoidosis.

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. Peer-review was handled independently by Associate Editor Chih-Wei Chen to minimize bias.

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REVIEW

Management of non-renal manifestations of systemic lupus erythematosus: A systematic literature review for the APLAR consensus statements

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Abstract

The prevalence of systemic lupus erythematosus (SLE) is higher in Asians than Caucasians, with higher frequency of renal and other major organ manifestations that carry a poorer prognosis. The outcome of SLE is still unsatisfactory in many parts of the Asia Pacific region due to limited access to healthcare systems, poor treatment adherence and adverse reactions to therapies. The Asia Pacific League of Associations for Rheumatology (APLAR) SLE special interest group has recently published a set of consensus recommendation statements for the management of SLE in the Asia Pacific region. The current article is a supplement of systematic literature search (SLR) to the prevalence and treatment of non-renal manifestations of SLE in Asian patients.

KEYWORDS
lupus, neuropsychiatric, non-renal, prognosis, severe

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder which predominantly affects women of the reproductive age. The disease is characterized by an unpredictable course with variable prognosis. As a result of improved therapeutics and supportive care for complications, the prognosis of SLE has markedly improved in the second half of the 20th century, but survival with SLE has since plateaued.[1] A recent meta-analysis showed that renal disease, infective and thrombotic complications are the major causes

of death in SLE patients.[2] Management of major organ disease in SLE is still a great challenge because these manifestations are potentially life-threatening. Aggressive immunosuppressive therapies may led to increased mortality and morbidity because of treatment-related side effects. Survival in SLE varies greatly among Asian countries, contributed to by disparities in healthcare systems, availability of costly medications, treatment adherence/tolerance and frequency of infective and cardiovascular complications in different populations.[3,4] The Asia Pacific League of Associations for Rheumatology (APLAR) SLE special interest group has recently developed the first set of consensus recommendations for the management of SLE in the Asia Pacific region by means of a Delphi exercise involving 29 key rheumatologists/nephrologists in the region and 3 SLE patients.[5] The statements were developed from the existing literature, with the important aim of incorporating Asian experience. The current work is a supplement to the systematic literature review (SLR) for the APLAR SLE management consensus statements on the prevalence, diagnosis and management of non-renal manifestations of SLE (statements 7, 22–32),[5] with focus on studies conducted in the Asia Pacific region. The SLR of lupus nephritis will be presented in a separate article.

The clinical questions consisted of: (1) prevalence of neuropsychiatric (NP) manifestations in Asian patients with SLE; (2) treatment and outcome of NP manifestations in Asian SLE patients; (3) management of thrombotic antiphospholipid syndrome (APS) in Asian SLE patients; and (4) prevalence and treatment of articular, dermatological and other non-renal severe organ manifestations of SLE (eg diffuse alveolar hemorrhage, hemophagocytic syndrome) in Asian SLE patients.

2 | METHODS

2.1 | Search strategy and eligibility criteria

A SLR was conducted to address the fore-mentioned clinical questions. The search terms and filters in the PubMed database from the year 1990 to April 2020 are shown in Table S1. Additional studies not retrieved from the search strategy but are relevant to the APLAR statements were added as "articles from other sources". Only clinical trials (randomized controlled trials [RCTs]), longitudinal cohort and cross-sectional observational studies, including registries, case series and case reports published in English were included.

2.2 | Results of literature search

Table S2 shows the results of the literature search. A total of 1115 articles were included, 1056 of which were excluded. The reasons for exclusion were one of the following: pediatric studies, single case reports, review or conference reports, laboratory works and studies (Asian or non-Asian) that were not relevant for the APLAR statements (data not shown). Together with 23 articles from other sources, 82 articles were included in this review.

2.3 | Serious non-renal manifestations of SLE

2.3.1 | Neuropsychiatric SLE (NPSLE)

NPSLE manifestations are heterogeneous. The prevalence, clinical course and outcome of NPSLE differ substantially among studies world-wide, depending on patient selection, definitions of NP involvement and whether screening tests are performed in asymptomatic patients. Although the American College of Rheumatology[6] has defined NPSLE manifestations according to specified inclusion and exclusion criteria, symptoms such as headache, mild anxiety and mood disorders, mild cognitive impairment and polyneuropathy without electrophysiological confirmation (as defined by Ainiala et al[7]) may be under-recognized. In the absence of pathognomonic tests or biomarkers, NP manifestations attributed to SLE (primary NPSLE) rely heavily on clinical judgment of physicians. Studies in Asian countries reported NPSLE manifestations attributed to SLE occurred in 4%–19% of patients at diagnosis[8–23] and 6%–40% during the course of the disease.[9,10,13–30]

Despite the availability of a number of laboratory tests, imaging techniques (eg quantitative magnetic resonance imaging [MRI], functional MRI, positron emission tomography [PET], single-photon emission computed tomography [SPECT]) and biomarkers (antibodies and cytokines), no single investigation was found to be specific for NPSLE. Thus, thorough investigation to exclude differential diagnoses such as infective and metabolic causes, medication side effects, and malignancy is essential for establishing a diagnosis of primary NPSLE.

NPSLE manifestations are mediated by either an inflammatory or thrombotic mechanism. NPSLE manifestations that are often considered as inflammatory in origin include psychosis, acute confusional state, aseptic meningitis, transverse myelitis, optic neuritis, peripheral and cranial neuropathy, mononeuritis multiplex and myasthenia gravis. These manifestations may occur in association with SLE activity in other organs or in the setting of a SLE flare,[31] and often require aggressive immunosuppressive treatment.

2.3.2 | Immunosuppressive treatment of NPSLE

Major NPSLE manifestations are often excluded in RCTs (RCTs) of novel therapeutic agents for SLE. Although the prevalence of NPSLE does not appear to be low in Asian patients, there are no controlled trials on the role of immunosuppressive therapies. Studies in the Caucasian population[32–35] are often small in sample size and the reported outcomes include all kinds of NP manifestations. Moreover, the definitions for clinical improvement and remission are inconsistent.

Case series[32] and retrospective studies[35,36] in Caucasian patients showed efficacy of high-dose glucocorticoid and intravenous pulse cyclophosphamide in severe NPSLE. Only one RCT was available to compare pulse methylprednisolone combined with intravenous cyclophosphamide with methylprednisolone alone in 32 Mexican patients with severe NPSLE.[33] Improvement was reported in 95% of patients treated with the combination regimen as compared to only 46.2% in those treated with methylprednisolone alone after 24 months (relative risk [RR] 2.05 [1.13–3.73] for a response). There was no difference in the incidence of adverse events, organ damage accrual and mortality between the 2 treatment arms. A prospective comparative study from Yugoslavia showed that patients with NPSLE treated with low-dose of intravenous cyclophosphamide (200–400 mg/mo) and prednisone (mean 20.5 mg/d; n = 37) had significantly better improvement in clinical symptoms, relapse rate and electrophysiological studies of cerebral function (eg electroencephalography [EEG] and evoked potentials [EP]) than other patients (n = 23) who were treated with prednisone (mean 20.5 mg/d) with and without antimalarials.[34]

For specific NPSLE manifestations, combined glucocorticoid and intravenous cyclophosphamide has been used with success in open series of transverse myelitis,[37,38] peripheral neuropathy[39] and psychosis[40] in Caucasian patients. One open-label study in Hong Kong described good clinical response in 13 Chinese patients with lupus psychosis treated with oral cyclophosphamide and glucocorticoid for 6 months.[41]

The differentiation between lupus psychosis and glucocorticoid-induced psychosis can be difficult. The temporal relationship between the onset of psychiatric symptoms and glucocorticoid initiation or dosage augmentation, and improvement after dosage reduction or controlled withdrawal suggest a drug-induced adverse effect. Concomitant disease activity in other systems, the anti-ribosomal P antibodies and imaging abnormalities raises the possibility of active psychiatric lupus but these are neither sensitive nor specific for the diagnosis. In Asian patients with SLE, glucocorticoid-induced psychosis occurs in 5% of patients, which is unpredictable by the route and dosage of glucocorticoids used or a history of similar problems.[42] Risk factors for glucocorticoid-induced psychosis include low serum albumin, a personal or family history of psychiatric disorders. Patients should be informed of psychiatric side effects of glucocorticoids and close observation after treatment initiation is needed.

In the APLAR consensus, a combination of moderate or high-dose glucocorticoids (including pulse methylprednisolone) and cyclophosphamide is recommended for serious NPSLE manifestations that are inflammatory in origin (statement 22). For NPSLE manifestations that did not respond to glucocorticoids and cyclophosphamide, observational studies have demonstrated promising results of rituximab (RTX).[43]

A pooled analysis of 35 patients with refractory NPSLE, including 46% Asians, reported that 85% of patients achieved a complete or partial response after 1 course (375 mg/m^2 weekly for 2–4 weeks or 500–1000 mg 2 weeks apart) of RTX treatment.[44] The most frequent adverse event reported was infection (in 29% of patients). No cases of severe infusion reaction or cytopenia were reported.

Two case series of rituximab in NPSLE were reported from Japan.[45,46] Iwata et al[45] retrospectively analyzed 63 SLE patients with refractory manifestations treated with RTX (weekly 375 mg/m^2 or 2-weekly 1 g regimen), including 28 patients with NPSLE (neurologic disorders and myelitis). Improvement was observed in 79% of patients. The commonest side effect was infection, which resolved with antibiotic treatment in all cases. There was no treatment-related death. Infusion reaction, mostly mild, was reported in 16/63 patients.

Another case series from Japan demonstrated improvement of NPSLE via RTX treatment in 10 patients who had inadequate response to previous immunosuppressive drugs (intravenous cyclophosphamide or cyclosporin A) or plasma exchange.[46] Acute confusional state, seizure, psychosis and SLE Disease Activity Index (SLEDAI) improved at day 28 after treatment with RTX in all patients most received 375 mg/m^2 weekly for 2 doses in combination with low to moderate dose of glucocorticoid (15–40 mg prednisolone or 1–3 mg betamethasone).[46] A case series from China demonstrated that 4 of 6 patients with severe transverse myelitis responded completely at 12 months to a regimen of combination pulse methylprednisolone and RTX (500 mg weekly or biweekly 2 two infusions) as first-line treatment.[47]

Thus, RTX might be considered in NPSLE that is inflammatory in origin and refractory to conventional immunosuppressive agents such as cyclophosphamide (statement 23). However, the optimal dosing schedule of rituximab for NPSLE remains uncertain. Whether the weekly 375 mg/m^2 regimen (for 4 doses) or the 2-weekly regimen (1 g or 500 mg for 2 doses)[44,46] is more effective is unknown due to the lack of controlled trials.

2.3.3 | Symptomatic treatment of NPSLE

Symptomatic treatment such as anticonvulsants, antidepressants, anxiolytics and antipsychotics is required for certain NPSLE manifestations (statement 24). Nevertheless, RCTs are lacking.

Psychosis attributed to SLE usually has a favorable response to immunosuppressive agents.[33,41,46,48] However, symptomatic control of delusion or hallucination are required before a clinical response is achieved. SLE patients are generally more prone to adverse events from anti-psychotic drugs because of drug–drug interaction with other SLE medications. The first-generation anti-psychotic drugs, such as haloperidol, might induce extrapyramidal side effects in NPSLE patients.[49] Second-generation anti-psychotic drugs such as olanzapine have fewer movement side effects but marrow suppression has been reported.[50]

Acute cognitive dysfunction (delirium) due to NPSLE usually improves after treatment with immunosuppressive treatment, although prolonged supportive care may be needed.[33,46,51] In SLE patients with chronic cognitive dysfunction, a RCT of memantine, a serotoninergic receptor and nicotine acetylcholine receptor

antagonist, did not demonstrate benefit of the drug over placebo.[52] A non-randomized, uncontrolled pilot study of 17 American SLE patients with chronic cognitive dysfunction reported improvement after participation in a psycho-educational support program.[53]

Mood disorders, particularly depression and anxiety, are common in Asian SLE patients.[54] Results from the Korean Lupus Network registry showed that smoking status, organ damage and antiphospholipid antibodies were associated with depression, while higher education level and income were protective.[55] A RCT did not show efficacy of psychotherapy in alleviating stress as an adjunct to standard of care in 133 Canadian SLE patients.[56] In contrast, another RCT involving 80 Brazilian female SLE patients showed that weekly psychotherapy sessions for 20 weeks reduced the level of anxiety and depression better than usual care alone.[57]

2.4 | Other non-renal major organ manifestations of SLE

In addition to renal and neuropsychiatric manifestations, SLE may cause serious disease in other organs such as diffuse alveolar hemorrhage (DAH), myocarditis, pancreatitis, mesenteric vasculitis, as well as hematological involvement that includes severe immune thrombocytopenia, thrombotic thrombocytopenic purpura (TTP) and hemophagocytic syndrome.

DAH was reported in 1.4%–2.0% of SLE patients.[58,59] Presentation includes hemoptysis, hypoxemia, pulmonary infiltrates, fall in hemoglobin and bronchoalveolar lavage showing hemosiderin-laden macrophages.[60] Despite aggressive treatment,[60] mortality was more than 50% according to a literature review.[58] Acute myocarditis may develop in 1.6%–5.7% of SLE patients.[61,62] Most patients experienced symptoms of heart failure and echocardiography often showed reduced left ventricular ejection fraction (<50%) and wall motion abnormalities.[63] The mortality rate of lupus myocarditis is approximately 20%.[64] Mesenteric vasculitis and pancreatitis due to active SLE may lead to signs and symptoms of acute abdomen.[65] Lupus pancreatitis is uncommon (2%–2.6% of patients)[66–68] but mortality is high (up to 37%).[66,68]

Thrombotic thrombocytopenic purpura (TTP) is an uncommon hematological manifestation of SLE. A prevalence of 2.2% was reported in a cohort of Korean SLE patients and the in-hospital mortality was high (46%).[69] Hemophagocytic syndrome was reported in 5.1% of patients with SLE and most patients responded to aggressive immunosuppressive therapies.[70] In a Chinese study, moderate to severe thrombocytopenia was described in 15.2% of patients with SLE admitted to hospital and was associated with more hemorrhagic complications.[71]

Despite the lack of controlled trials, early aggressive immunosuppressive therapy is important to improve the outcome of these serious lupus manifestations.[63,72,73] Several studies reported success of treatment with either high-dose glucocorticoids (including methylprednisolone pulses) alone or in combination with cyclophosphamide, intravenous immunoglobulin (IVIG) or plasma exchange in DAH,[58–60] TTP[69,74] and myocarditis.[63,72,73,75] Case reports also showed efficacy of RTX in DAH[58] and myocarditis.[62]

In the case of serious SLE manifestation associated with concomitant infection, plasma exchange with minimal immunosuppression could be an alternative.[76] Plasma exchange combined with glucocorticoids was shown in a retrospective study to be more effective than glucocorticoid alone in inducing remission of lupus pancreatitis.[66] Although plasma exchange has been reported to be effective in DAH and TTP, it is uncertain if survival can be improved.[77,78]

The APLAR consensus panel recommends moderate- to high-dose glucocorticoids (including pulse methylprednisolone) in combination with cyclophosphamide in treating severe and life-threatening SLE manifestations (statement 28). Plasma exchange may be considered for DAH, TTP and some severe hematological manifestations such as hemophagocytosis (statement 29).

2.5 | Less serious non-renal manifestations of SLE

2.5.1 | Articular and cutaneous manifestations

The optimal treatment for non-life-threatening organ disease of SLE remains poorly defined because of the paucity of controlled trials. Hydroxychloroquine (HCQ) is predominantly used to treat articular and dermatological SLE disease but because of its multiple benefits, it is currently recommended for all SLE patients (statement 7).[5]

Yokogawa et al[79] conducted a multicenter, double-blind RCT in Japanese SLE patients with active cutaneous lesions, defined as a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score of ≥4. Patients were randomized in a 3:1 ratio to receive HCQ (200, 200/400 or 400 mg referred to the 6 mg/ideal body weight kg) or placebo for 16 weeks, followed by a single-blind period of 36 weeks in which all patients received the same doses of HCQ. The mean CLASI score at week 16 reduced significantly from baseline in both the HCQ and placebo groups (mean difference of CLASI for the HCQ and placebo groups: −4.6 vs −3.2, respectively). There was no significant difference in the improvement between the 2 groups. However, investigator's global assessment demonstrated a significantly greater proportion of patients with "improvement" and "marked improvement" in HCQ-treated patients (51.4% vs. 8.7%, $P = .0002$).

Methotrexate (MTX) is not uncommonly used in patients with articular and dermatological manifestations, especially in HCQ-refractory disease. In a RCT conducted in Bangladesh,[80] SLE patients with articular or cutaneous manifestations were randomly assigned to MTX 10 mg/wk or chloroquine 150 mg/d for 24 weeks. MTX appeared to be as effective as chloroquine as measured by visual analog scale pain, resolution of skin rash and improvement in SLEDAI score. The toxicity profile was acceptable with mild and reversible alanine aminotransferase elevation in 13% of the MTX-treated patients.

A meta-analysis was performed on 3 RCTs and 9 observational studies involving Asian and non-Asian patients regarding the

efficacy of MTX in SLE.[81] All these studies recruited SLE patients with arthritis or mucocutaneous disease. MTX was effective in reducing disease activity in terms of SLEDAI score (odds ratio [OR] 0.44 [0.28–0.71]) and glucocorticoid (GC) dosage (OR 0.34 [0.20–0.56]). MTX is recommended by the APLAR consensus for persistent skin and articular manifestations that do not respond to HCQ (statement 31).

2.6 | The role of IVIG

Most published studies of (IVI) in non-renal SLE are uncontrolled and retrospective in nature. Very few studies have ever been conducted in Asia.[80,82–84] An open-label retrospective study of 20 SLE patients in Israel reported efficacy of IVIG in 17 (85%) patients after 1–8 courses.[85] Manifestations that responded to IVIG included arthritis, fever, thrombocytopenia and neuropsychiatric symptoms. Other series reported beneficial effect of IVIG in refractory cutaneous SLE lesions in non-Asian patients.[86,87] IVIG helps reduce disease activity of SLE and may be considered in patients with concurrent infections or in whom intensive immunosuppression is contraindicated.[83,88] IVIG is usually administered at a total dose of 2 g/kg over 2–5 days. A retrospective study of 62 SLE Israeli patients reported that low-dose IVIG (0.5 g/kg), which was associated with lower cost, was effective in reducing overall lupus activity, but thrombocytopenia, alopecia and vasculitis might not respond.[82] The APLAR consensus recommends IVIG for refractory SLE, particularly hematological or when other immunosuppressive regimens are ineffective or contraindicated (statement 30).

2.7 | The role of belimumab

Belimumab, a human monoclonal antibody which inhibits the soluble B-lymphocyte stimulator (BLyS) protein, is the first biologic agent approved for SLE treatment. A pooled analysis of the BLISS 52 and 76 trials revealed that patients with more active SLE (SLEDAI ≥10), low complement, anti-double-stranded DNA positivity and higher daily dose of prednisolone (≥7.5 mg/d) at baseline were associated with higher ORs of achieving the primary SLE Responder Index (SRI)-4 response as compared to placebo.[89]

Four pivotal RCTs of belimumab were conducted in patients with renal SLE and had included patients in the Asia Pacific region.[90–93] In 3 RCTs, patients with active non-renal SLE despite standard of care (SOC) treatment were recruited. Improvement in disease activity without a significant increase in frequency of adverse events was demonstrated with belimumab over placebo. One of these RCTs was conducted in north-eastern Asian countries (BLISS-NEA), namely China, Japan and Korea.[93] Similar to the other studies,[93–95] belimumab was shown to significantly improve disease activity and reduce GC dose without new safety signals in Asian patients. A recent meta-analysis of 6 RCTs of belimumab in SLE confirmed efficacy of the drug in achieving the SRI-4 response, a GC-sparing effect and improvement of quality of life.[96]

Extension studies showed that in patients who respond to belimumab, continuous treatment for 8 years was associated with no increase in organ damage.[94] More recently, the BLISS-LN RCT has confirmed the efficacy of belimumab in lupus nephritis.[92] Addition of belimumab on SOC (mycophenolate mofetil or Euro-Lupus intravenous cyclophosphamide regimen) was shown to increase the primary efficacy renal response rate compared to placebo at 2 years. The results of this study were released after our Delphi exercise and more detailed discussion has to be left for a future update of the APLAR consensus. Delphi members did not recommend belimumab as first-line therapy of SLE, partly because of the issue of cost-effectiveness, which is particularly important in the Asia Pacific region. Thus, belimumab may be considered as an add-on therapy for patients with SLE, including renal disease, who do not respond optimally to first-line therapies (statement 32). Pooled data of the phase II belimumab trials in SLE showed a non-significant increase in psychiatric adverse events that included suicide ideation, depression, anxiety and insomnia in the belimumab compared to the placebo arms.[97] Belimumab is not indicated in patients with severe NPSLE and caution should be exhibited in those with a history of psychiatric symptoms and suicidal attempts.

2.8 | Thrombotic antiphospholipid syndrome (APS) in SLE

APS is generally less common in Asian patients. Several cross-sectional studies of SLE patients from Hong Kong showed that 6.5%–10.3% of patients had concomitant APS.[98,99] Arterial thrombosis appeared to be more common than venous thrombosis in SLE-related APS. Nine retrospective Asian studies reported the clinical manifestations of APS[100–107] and the sample size ranged from 40 to 252 patients. SLE accounts for the majority of secondary APS patients in these Asian studies (50.4%–95%).[103–107] A Korean study utilizing data from the national insurance registry reported 3088 patients newly diagnosed as having APS between 2009 and 2016.[105] In women, the onset of APS occurred most frequently in the age ranges of 30–39 and 70–79 years, whereas in men, APS was most commonly diagnosed in the age range of 70–79 years.

Several studies of APS reported a higher or equal frequency of venous thrombosis (calf vein and/or pulmonary embolism) as compared to arterial thrombosis.[104,107,108] Among APS patients with arterial thrombosis, cerebrovascular accident (stroke) was the commonest cause.[102–104,107,108] Despite anticoagulation therapy, recurrence of thrombosis occurred in 8.6%–24% of patients,[106–108] with higher recurrence rate observed for arterial thrombosis. Bleeding complications developed in 28%–36% of patients, which was often related to over-anticoagulation by vitamin K antagonist.[107,108] One longitudinal study reported mortality in 20% of SLE-related APS patients, which was significantly higher

than SLE patients without concomitant APS (9%; $P = .02$).[99] APS was also associated with mortality related to arterial thrombosis in SLE patients.

There are no treatment trials of APS specifically conducted in Asian patients. In Caucasians, 2 retrospective studies have shown that warfarin was superior to aspirin in preventing recurrence of thrombosis in patients with the APS.[105,109,110] On the other hand, in patients with ischemic stroke and single time positive lupus anticoagulant or anticardiolipin antibodies, one RCT showed no difference between warfarin and aspirin in the reduction of subsequent arterial events over 2 years.[111] In APS patients with arterial or venous thrombosis, RCTs and cohort studies revealed no difference in recurrence rate between high intensity (international normalization ratio [INR] 3.0–4.0) and standard intensity warfarin (INR 2.0–3.0).[112]

The direct oral anticoagulants (DOACs) have been tested in patients with the APS. A RCT (RAPS) involving 116 patients with APS and a history of venous thrombosis compared the effect of rivaroxaban and standard intensity warfarin and showed a higher *ex vivo* endogenous thrombin potential in the rivaroxaban arm (RAPS), although this did not meet the non-inferiority threshold to warfarin.[113] Despite the absence of new thrombotic events or major bleeding episodes in both treatment arms after 6 months, this study was not designed to compare the clinical efficacy of the regimens and the follow-up was too short for safety analysis. A phase III RCT (TRAPS) comparing the efficacy of warfarin to rivaroxaban in patients with APS and triple positive antiphospholipid antibodies was prematurely terminated because of an excess of thrombotic and bleeding events in rivaroxaban-treated patients after a mean of 569 days.[114] A total of 115 patients were available for follow-up after study closure. At 3 years, 2/6 (33.3%) patients who remained on rivaroxaban developed recurrent thrombotic events, which was significantly more common than patients treated with or switched to warfarin (6/109 [5.7%]).[115] Another open-label non-inferiority RCT from Spain randomized 195 adult patients with thrombotic APS (61% patients had triple positive antiphospholipid antibodies) to either rivaroxaban or standard intensity warfarin.[116] After 3 years, rivaroxaban did not show non-inferiority to dose-adjusted warfarin and, in fact, showed a non-significantly higher risk of recurrence of thrombosis.

Taking all the evidence together, in the APLAR SLE consensus, members agreed that thromboembolic APS in SLE should be treated with anticoagulation, with warfarin recommended to maintain INR between 2.0 and 3.0 in Asian patients (statement 25).[5] In the absence of new data showing better efficacy of higher dosages of the DOACs than warfarin, DOACs are not recommended in patients with thromboembolic SLE with a high-risk antiphospholipid antibody profile (statement 26).

Cohort studies have suggested benefit of low-dose aspirin as primary prevention of thrombotic events in patients with SLE and persistently positive antiphospholipid antibodies.[117] A meta-analysis reported a protective effect of low-dose aspirin against thrombosis in a subgroup of SLE patients who were asymptomatic carriers of the antiphospholipid antibodies.[118] In the APLAR consensus, it was agreed that low-dose aspirin prophylaxis may be considered in patients with SLE who have a high-risk antiphospholipid antibody profile, especially when concomitant atherosclerotic risk factors are present (statement 27).

3 | DISCUSSION

This article summarizes the SLR of the prevalence and treatment of neuropsychiatric and other non-renal manifestations of SLE, with a special focus on Asian studies. Overall, there is a lack of high-quality controlled trials in these areas.

NP involvement in SLE significantly reduces quality of life and increases risk of mortality.[119] The prevalence of NPSLE is 6%–40%[9,10,13–29] in Asian patients, which is similar to that of Caucasians (4%–38%).[120–122] The most common NPSLE manifestations in Caucasian patients are seizure disorders, cerebrovascular disease and acute confusional state.[123] In contrast, psychosis, headache, and cognitive dysfunction are more commonly reported in Asian patients.[124,125]

A combination of moderate- to high-dose glucocorticoids (including methylprednisolone pulses) with cyclophosphamide is the first-line therapy for severe NPSLE that is inflammatory in origin. Most previous studies used intravenous pulse cyclophosphamide for NPSLE but one study in Asian SLE patients with psychosis showed that oral route of cyclophosphamide was effective in lupus psychosis.[41] Rituximab has been used with success in Asian patients with refractory NPSLE.[46,47] However, whether the weekly regimen based on body surface area or the 2-weekly fixed dose regimen is more effective requires further evaluation.

Although certain life-threatening non-renal SLE manifestations are rare, their mortality is very high. Owing to the lack of RCTs in these conditions, the use of high-dose glucocorticoids and cyclophosphamide was referred from studies in lupus nephritis and NPSLE. Additional IVIG or plasma exchange may be required in refractory disease or when intense immunosuppression is contraindicated.

Belimumab has proven efficacy and safety in Asian patients with SLE and lupus nephritis. Owing to its cost, the APLAR consensus recommends adding on belimumab for SLE manifestations that do not respond optimally to SOC. The cost-effectiveness of belimumab as first-line treatment of lupus nephritis will be the focus in the next update of the APLAR SLE management consensus. Hydroxychloroquine remains the mainstay of treatment for articular and dermatologic manifestations of SLE. There is growing evidence of methotrexate in refractory disease. Leflunomide has been shown by small series to reduce SLE disease activity that included arthritis and skin lesions.[126,127] However, severe skin reaction to the drug has been reported.[128,129]

Due to the lack of therapeutic trials of APS in Asian patients, treatment recommendations of thrombotic APS were extrapolated from the non-Asian literature. Further studies of direct oral anticoagulants in venous thrombosis are needed in Asian patients without the high-risk antiphospholipid antibody profile.

4 | CONCLUSION

There is a general paucity of controlled trials world-wide in the treatment of non-renal major organ manifestations of SLE. This is probably related to the low prevalence of some of these manifestations and the lack of validated organ-specific standardized tools to assess for clinical improvement. Extrapolation of the evidence from the western literature is often needed to guide treatment in Asian patients. More collaboration in the Asia Pacific region is needed to create registries of SLE regarding efficacy and adverse events to different therapeutic regimens, and design RCTs of novel biologic and targeted agents in Asian SLE patients. This is an endeavor of the APLAR SLE special interest group in addition to updating treatment consensus.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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REVIEW

Emerging role of EZH2 in rheumatic diseases: A comprehensive review

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Abstract

Enhancer of zeste homolog 2 (EZH2) is a histone methylated enzyme. It trimethylates histone 3 lysine 27 (H3K27) to regulate epigenetic processes. Recently, studies showed excessive expression of EZH2 in rheumatic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, and systemic sclerosis. Moreover, epigenetic modification of EZH2 regulates differentiation and proliferation of different immune cells. Therefore, in this review, we comprehensively discuss the role of EZH2 in rheumatic diseases. Collection of the evidence may provide a basis for further understanding the role of EZH2 and give potential for targeting these diseases.

KEYWORDS
epigenetics, EZH2, rheumatic diseases

1 | INTRODUCTION

Enhancer of zeste homolog 2 (EZH2) was first discovered in 1996.[1,2] Human EZH2 gene is located at 7q36.1. EZH2 is expressed in bone marrow, lymph nodes, and testes.[3] EZH2 is an enzymatic subunit of polycomb repressive complex 2 (PRC2). It binds embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12), Jarid2, adipocyte enhancer binding protein 2 (AEBP2), and retinoblastoma-associated protein 46/48 (RbAp46/48) to regulate histone methylation and transcriptional repression.[4,5] Histone 3 lysine 27 (H3K27) is a downstream molecule for EZH2. H3K27 can be tri-methylated (H3K27me3) to repress target gene expression and regulate epigenetic events.[6,7]

Rheumatic diseases are chronic inflammatory diseases. The diseases often involve intermittent pain, swelling, limited movement, or disability. There are more than 200 defined rheumatic diseases, such as systemic lupus erythematosus (SLE), osteoarthritis (OA), rheumatoid arthritis (RA), gout, ankylosing spondylitis, psoriatic arthritis and systemic sclerosis (SSc). Although many studies have discussed risk factors related to these diseases, the clear pathogenesis is yet to be clarified. Recently, increasing evidence suggested epigenetic mechanisms in the pathogenesis of rheumatic diseases, especially the role of EZH2. Therefore, we discussed EZH2 and these disorders based on available evidence. Hopefully, targeting EZH2 in rheumatic diseases will give potential in the future.

2 | EZH2 AND EPIGENETIC MODIFICATION

Epigenetics means a heritable modulation of chromatin architecture instead of recoding or mutating in DNA sequence.[8,9] Epigenetic modification mainly includes DNA methylation and histone modification.[10] EZH2 is considered to be a modifier in epigenetic changes.

DNA methylation is the most discussed epigenetic modification. It refers to a methyl group that transfers to the C5 position in cytosine to form 5-methylcytosine. This process is mediated by DNA methyltransferases (DNMTs).[11] EZH2 expression is positively related

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to DNMT expression. After interacting with DNMTs, EZH2 represses the expression of tumor suppressor genes such as endothelial pas domain protein 1 gene (EPAS1), Vax2, oculocutaneous albinism 2 (OCA2), and promotes the expression of anti-tumor genes such as integrin beta 2 (ITGB2), NDGR1, ankyrin repeat and BTB/POZ domain containing protein 1 (ABTB1), and ras association domain family member 5 (RASSF5).[12] EZH2 binds to DNMTs at promoters of myelin transcription factor 1 (MYT1), Wnt family member 1 (WNT1), potassium voltage-gated channel subfamily A member 1 (KCNA1), cannabinoid receptor 1 (CNR1), to promote its methylation.[13,14] EZH2 mutation can modify the structure and transcriptional activity of chromatins by increasing H3K27me3.[15,16] Moreover, EZH2 promotes DNA stability via silencing long non-coding RNAs (lncRNAs) such as PHACTR2-AS1 (PAS1), lnc-β-Catm.[17,18] Histone methylation is the main histone modification. Histone methylation was discovered in 2000 and its role in silencing gene transcription was recognized in 2003.[19,20] Upon stimulation with specific enzymes, the histone tails can be acetylated, methylated, and phosphorylated, which then affect DNA accessibility.[21] Non-coding RNA, cytosolic methylation, and phosphorylation are some other epigenetic modifications. For instance, lncRNA small nucleolar RNA host gene 1 (SNHG1) interacts with EZH2, contributing to colorectal cancer cell growth.[22] Similarly, EZH2 cooperates with nuclear enriched abundant transcript 1 (NEAT1), EPB41L4A-AS2, and zinc finger protein 217 (ZNF217), regulating migration of neutrophils, and dendritic cells.[23–25] Therefore, epigenetic modification of EZH2 may regulate downstream inflammatory signaling.

3 | IMMUNE CELL

3.1 | Innate immunity

3.1.1 | Monocyte

Monocyte is a kind of immune cell in innate immunity.[26,27] There is high expression of EZH2 in tumor tissues, which may regulate recruitment, proliferation, and activation of monocytes.[28–32] EZH2 was highly expressed in peripheral blood monocytes of pediatric pneumonia patients, and there was up-regulated apoptosis of monocytes.[33] Activated Sirt6/EZH2/FOXC1 pathway in monocytes reduced secretion of tumor necrosis factor (TNF)-α.[27] EZH2 impaired the process of monocytes differentiation into osteoclasts by repressing the expression of transcription factors V-maf musculoaponeurotic fibrosarcoma oncogene homolog B (MafB), interferon regulatory factor 8 (IRF8), and arginase 1.[34] Silencing EZH2 in monocytes activates innate immune responses via promoting LRRC33 expression.[35] Overexpression of LINC00341 recruits EZH2 to the promoter region of vascular cell adhesion molecular 1 (VCAM1) gene to suppress VCAM1, reducing adhesion capacity of monocytes.[36] Furthermore, EZH2 gene deficiency inhibited the ability of monocytes to adhere to endothelial cells.[37] Inhibiting role of EZH2 by an EZH2 inhibitor GSK126 could reduce monocytes adhesion[38] (Figure 1). Together, EZH2 may regulate monocytes adhesion.

3.1.2 | Macrophages

Macrophages regulate phagocytosis. Monocytes-derived macrophages can differentiate into 2 subsets: M1 and M2 subtypes. M1 macrophages act as pro-inflammatory cells by secreting pro-inflammatory cytokines. M2 macrophages induce immune tolerance, promote neovascularization, and tumor cell proliferation and metastasis.[39] EZH2 inhibitors suppress M1 macrophage differentiation, polarization and inhibit TNF-α production.[40–42] Inhibiting EZH2 by GSK126 reduced formation of foam cells, which can attenuate progression of atherosclerosis.[38] EZH2 silencing inhibited CC chemokine ligand 2 (CCL2) expression, repressing macrophage infiltration.[43] Furthermore, EZH2-targeted macrophages increase lipid accumulation and inhibit osteoclastogenesis.[44,45] Therefore, EZH2 promotes the role of M1 macrophages, and inhibits M2 macrophages.

3.1.3 | Dendritic cells

Dendritic cells (DC) initiate innate immune responses.[46] EZH2 deficiency reduces the number of mature DCs by inhibiting transcription factor: runt-related transcription factor 1 (RUNX1).[47] EZH2 was highly expressed in histiocytic and DC neoplasms.[48] EZH2 interacted with the Vav family and methylation of talin protein, and reduced proliferation of DCs.[25,49,50] Together, EZH2 is involved in DCs maturation and proliferation.

3.1.4 | Neutrophils

Neutrophils are the front-line trooper in innate immune system.[51] In EZH2 gene deficient mice, neutrophils were difficult to adhere to some other immune cells, and the ability of neutrophil migration was inhibited.[25] EZH2 promotes transcription of integrin co-activator talin1 in neutrophils under inflammatory conditions.[52] Phosphorylated EZH2 promoted infiltration of immuno-suppressive neutrophils in the mice with tumors complicating with brain metastasis.[53] Therefore, neutrophils were regulated by EZH2.

3.2 | Adaptive immunity

3.2.1 | T cells

T cells derive from bone marrow. EZH2 regulates differentiation, self-renewal, and survival of hematopoietic stem cells (HSC).[54–58] In the thymus, EZH2 deficiency suppressed differentiation of early T cell precursors (ETPs).[59] Knocking out EZH2 gene in wild-type mice promoted the expansion of natural killer T cells.[60–62] The differentiation and interleukin (IL)-4 generation of invariant natural killer T cells can be up-regulated by EZH2.[63] In peripheral blood, EZH2 is required for function of CD8+ and CD4+ T cells. Effector and memory

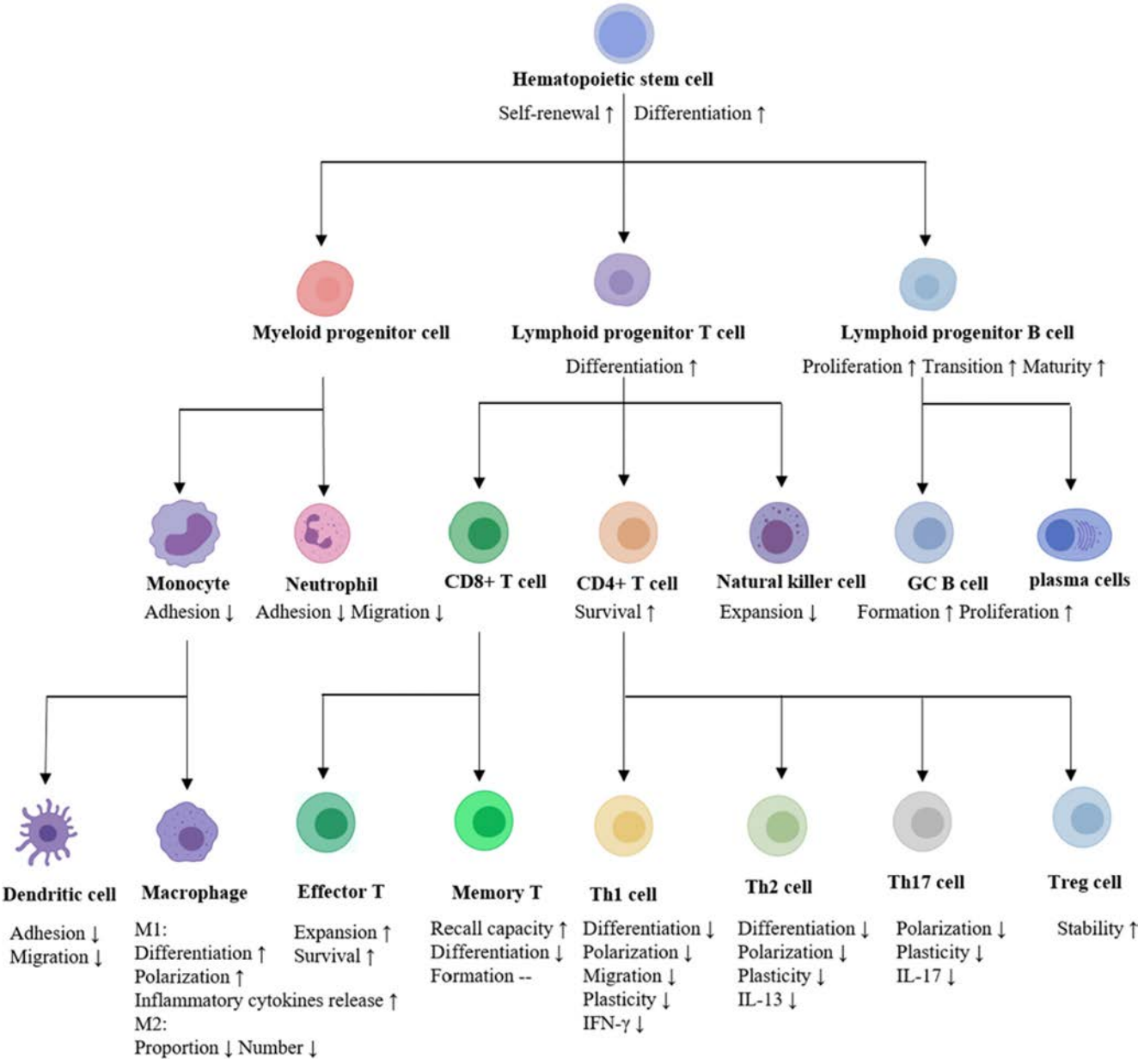

FIGURE 1 Role of enhancer of zeste homolog 2 (EZH2) in different immune cells. EZH2 promotes hematopoietic stem cell self-renewal and differentiation. Overexpressed EZH2 in neutrophils and dendritic cells reduced adhesion and migration of the cells. EZH2 up-regulates inflammatory cytokines production in M1 macrophages, and decreases proportion and total number of M2 macrophages. EZH2 inhibits differentiation, polarization, plasticity, and inflammatory cytokines production in different T cells. Overexpression of EZH2 in lymphoid progenitor B cells increases ability for proliferation, transition and maturation of the cells.

CD8+ T cells are 2 major subsets of CD8+ T cells. EZH2 facilitates survival and expansion of effector CD8+ T cell.[64–66] EZH2 affects survival of naive CD4+ T cells.[61] Differentiation of Th1 and Th2 cells was suppressed by EZH2, where EZH2 targets IFN-α, Tbx21, IL-4, GATA-3 via H3K27me3 modification.[67,68] High expression of EZH2 targets T-bet, GATA-3 to repress plasticity of Th1 and Th2 cell.[69,70] EZH2 regulates migration of Th1 cell via suppressing chemokine ligand 10 and the C-X-C motif chemokine receptor 3 (CXCL10/CXCR3) axis.[71,72] There was increased polarization and plasticity of Th1, Th2, and Th17 cells from EZH2 gene deficient CD4+ T cells.[66,69,73] EZH2 reduced secretion of IFN-γ, IL-13, and IL-17.[73] For Treg cells, EZH2 binds forkhead protein box P3 (FOXP3) to promote Treg cells stability.[74–76] In contrast, expression of genes related to Treg cells instability, such as Neuropilin-1 and basic leucine zipper transcription factor 2 (BACH2) were inhibited by EZH2 stimulation.[76–78] All these indicate that EZH2 regulates roles of different T cells.

3.2.2 | B cells

B cells are developed in bone marrow, matured in secondary lymphatic organs. B cells produce high-affinity antibodies, and secret

cytokines in adaptive immunity. In bone marrow, EZH2 is highly expressed in the pre-B cell, regulates B cell proliferation via Igλ transcription suppression and VDJ recombination (VDJ recombination refers to a process in which T cells and B cells randomly assemble different gene segments, including variable [V], diversity [D], and joining [J] genes).[79] In immature B cells, expression of EZH2 was relatively low.[80] The transition of pro-B from the pre-B cell can be blocked by absence of EZH2. EZH2 affects development of early B cell antigen receptors. EZH2 binds H3K27me3 to up-regulate expression of genes in the Igh, Igk locus, promoting proliferation of B cells.[81–83] In secondary lymphatic organs, EZH2 expression was the highest in germinal center (GC) B cells and was the lowest in memory B cells, and plasma cells.[84,85] Cyclin-dependent kinase inhibitor 1a (CDKN1A) is a cell cycle inhibitor. EZH2 inhibits expression of CDKN1A. EZH2 binds CDKN1A to promote formation and proliferation of GC B cells.[85,86] EZH2 interacts with a cell cycle regulator E2F1, which then inhibits CDKN1A, and induces GC B cell formation.[87] In plasma cells, EZH2 deficiency damaged the differentiation of plasma cells.[86] A study discussed the role of Tazemetostat (an EZH2 inhibitor) in patients with B cell non-Hodgkin lymphoma, showing that inhibiting EZH2 significantly improved the disease.[88] Therefore, EZH2 performs a stage-specific role in B cells.

4 | EZH2 AND RHEUMATIC DISEASES

Rheumatic diseases are mediated by inflammation or autoimmunity, along with chronic pain of joints or connective tissue damage. Studies showed that EZH2 was abnormally expressed in different rheumatic diseases.

4.1 | SLE

SLE is a common rheumatic disease. Compared to healthy controls, monocytes, and neutrophils in lupus patients showed high expression of EZH2. EZH2 expression was higher in CD4+ T cells and B cells in lupus patients as compared to those in controls.[16,89] Up-regulation of EZH2 both in human peripheral blood mononuclear cells (PBMCs) and kidney tissues was observed in SLE patients with lupus nephritis as compared to those in SLE patients without lupus nephritis.[90] High expression of EZH2 was positively related to disease activity.[91] However, a study evaluating EZH2 expression in SLE reported there was down-regulation of EZH2 in CD4+ T cells.[92] There was high expression of EZH2 in lupus mice.[93,94] The difference in EZH2 expression may correlate with ethnic heterogeneity, different tissue sources, and methods to detect EZH2.

EZH2 is involved in lupus progression by regulating different signaling. Activated mechanistic target of rapamycin 1 (mTOR) and increased glycolysis in CD4+ T cells are able to increase EZH2 expression, which further accelerates lupus disease activity. Increased EZH2 expression was negatively associated with expression of miR-26a and miR-101.[16,95,96] In B cells from SLE patients, expression of miR-26 was lower as compared to that in controls.[97] EZH2 interacted with activated Syk and mTORC1, and restrained BACH2 expression, inhibiting B cells differentiation and autoantibodies production.[97] EZH2 interacted with B cell lymphoma 6 (BCL-6), histone deacetylase 5 (HDAC5), and suppressed miR-142-3p/5p expression by modulating histone methylation and acetylation of the miR-142 promoter.[98] EZH2 also inhibited junctional adhesion molecule-A (JAM-A) pathway mediated CD4+ T cell adhesion and migration, hematopoietic progenitor kinase 1 (HPK1) signal mediated T cell activation in lupus.[16,99] In lupus mice, EZH2 activates E4 promoter-binding protein 4 (E4BP4) to down-regulate BCL-6 transcription.[100] EZH2 binds to the PI3K/AKT pathway, promoting differentiation of naive CD4+ T cells into Treg cells.[94] Moreover, Igκ germline transcription during B lymphopoiesis was suppressed by the STAT5/EZH2/Eκi/IL-17R pathway.[101] Thus, EZH2 binds to different downstream signaling, regulating lupus development.

4.2 | RA

RA is an inflammatory autoimmune disease.[102,103] Regarding the pathogenesis, genetic, ethological, and environmental factors have been widely discussed, and the role of epigenetics is emergingly discussed recently.

Fibroblast-like synoviocytes (FLSs) promote joint inflammation and destruction in RA pathology.[104,105] EZH2 was highly expressed in the synovial tissue of RA patients, and was positively related to proliferation, invasion, and migration of RA FLSs. High expression of EZH2 was related to elevated expression of TNF-α, IL-1β, IL-6, IL-17, matrix metalloproteinase-2 (MMP-2), and MMP-9 in RA FLSs.[106] Furthermore, EHZ2 interacted with lnc-IL7R to promote RA-FLS proliferation, and inhibit apoptosis by methylation of p16 and p21 promoters.[107] RA synovial fibroblasts (RASFs) secrete IL-6, IL-8 in response to IL-1β or TNF-α stimulation.[108] High expression of EZH2 promotes RASF proliferation by down-regulation of secreted frizzled-related protein 1 (SFRP1).[109,110] Bone homeostasis is balanced by osteoblasts/osteoclasts ratio. EZH2 stimulation promoted osteoclasts differentiation, leading to cartilage damage.[111] The axis receptor activator of nuclear factor-kappa B ligand (RANKL)/EZH2/H3K27me3/IRF8/nuclear factor of activated T cell cytoplasmic 1 (NFATc1) promoted osteoclastogenesis.[45] However, inhibition of EZH2 by GSK126 accelerated osteoblasts differentiation.[112] Furthermore, EZH2 was recruited to macrophage c-mer tyrosine kinase (MERTK), peroxisome proliferator-activated receptor gamma (PPARG), and RANK promoters and departed from suppressor of cytokine signaling 1 (SOCS1), erythroblastosis virus transcription factor-7 (ETV7) promoters after stimulation with IFN-γ.[113] Inhibition of EZH2 in CD4+ T cells from RA patients suppressed FOXP3 transcription and Treg cells differentiation via down-regulating RUNX1, up-regulating SMAD7 expression.[114] Therefore, expression of EZH2 was elevated in RA patients, and promoted RA progress.

4.3 | OA

OA is characterized by cartilage degradation, joint dysfunction, pain, and stiffness. This disease affects more than 527 million people (7.09% of the global population).[115,116] It is suggested that age, gender, weight, behavior, genes, and environment may correlate with the pathogenesis of this disorder. Moreover, epigenetics is a key in regulating the development of the disease.

In normal cartilage, chondrocytes maintain a stable resting phenotype and do not proliferate, whereas the cells were proliferated and differentiated in cartilage from OA patients.[117] lncRNAs or miRNAs bind EZH2 to regulate cartilage formation and remodeling. For instance, lncRNA CIR binds EZH2 to recruit H3K27me3 at the atonal homolog 8 (ATOH8) promoter region, which then down-regulates expression of ATOH8 and inhibits chondrogenic differentiation.[118] lncRNA maternally expressed gene 3 (MEG3) interacted with EZH2, restrained differentiation of mesenchymal stem cells into chondrocytes by inhibiting tribbles homolog (TRIB2).[119] Overexpression of Syndecan 1 induced cartilage degeneration. This process was related to low expression of miR-138, where EZH2 hypermethylated the miR-138 promoter.[120] Similarly, EZH2 negatively regulated miR-17-5p and miR-19b-3p expression, and promoted chondrocyte apoptosis and extracellular matrix (ECM) degradation.[121] Interestingly, inhibition of EZH2 suppressed Atg12 signaling, resulting in reduced chondrocytes survival and formation, and inducing spontaneous injury of articular cartilage.[122] Intra-articular injection of EZH2 inhibitor in OA mice models slowed cartilage degradation and improved motor functions.[123] Cartilage hypertrophy and inflammation were inhibited by EPZ-6438 and DZNep (both of them are inhibitors of EZH2).[124,125] Moreover, expression of collagen X (COLX), Hedgehog, matrix metalloproteinase-13 (MMP-13), and a disintegrin and metalloprotease with thrombospondin motifs-4 (ADAMT-4), ADAMT-5 was up-regulated by EZH2 activation. Therefore, EZH2 inhibition may act as a benefit for OA treatment.[111,126] However, in an OA mouse model with EZH2 gene deficiency, there was elevated expression of MMP-13 and type X collagen, implying that EZH2 deletion increased cartilage hypertrophy.[127] EZH2 deficiency down-regulated expression of wound healing-related genes, such as TNF superfamily member 13b (TNFSF13B).[127] EZH2 deficiency promotes chondrocyte maturation and endochondral ossification.[128] Together, EZH2 regulates different downstream signaling to be involved in OA pathogenesis. The exact mechanisms need to be clarified in the future.

4.4 | SSc

Higher expression of EZH2 in SSc patients was observed compared to that in controls.[129] Overexpression of EZH2 promoted activation of the Notch pathway via inhibiting miR-34a, and then increased expression of α-SMA.[130] EZH2 interacted with the axis HOX transcript antisense RNA (HOTAIR)/H3K27me3/miR-34a, and up-regulated GLI2 expression, resulting in fibrosis.[131] By contrast, EZH2 inhibition reduced migration of dermal fibroblasts, down-regulated expression of collagen 1A1 (COL1A1), transforming growth factor beta (TGFB), fos-related antigen 2 (FRA2), and FLI1. EZH2 inhibited angiogenesis by repressing the Notch signaling pathway, suggesting that EZH2 may take a part in SSc pathogenesis.[129]

5 | CONCLUSION

Effects of EZH2 on different immune cells seem relatively clear. EZH2 catalyzes H3K27 into H3K27me3, then, binds to PRC2, or interacts with PRC1, and finally silences target genes. Moreover, studies about DNA methylation, non-coding RNA, and cytosolic methylation with EZH2 were widely reported. However, several aspects are yet to be discussed. First, selection of EZH2 inhibitor should receive much attention. There are at least 5 inhibitors. However, different EZH2 inhibitors may have distinct mechanisms to inhibit function of EZH2. For example, GSK126 competitively binds the SAM region to inhibit the function of EZH2.[132] DZNep represses histone methylation for EZH1 or 20 other methyltransferases.[133] Second, the adverse effects of EZH2 blockage should be realized. To date, most studies have shown that EZH2 promoted pathogenesis of rheumatic diseases; however, some studies have shown that EZH2 is required for chondrocytes formation and inhibiting EZH2 may damage bone quality, and aggravate OA development. Third, targeting EZH2 in different rheumatic diseases needs to be discussed in the future with larger sample sizes and different ethnicities.

AUTHOR CONTRIBUTIONS

WX, QH, and AH designed, wrote this paper. All of the co-authors agreed on submission of the paper.

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CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

Datasets are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Colchicine resistance: Associated factors and its effect on health-related quality of life in patients with familial Mediterranean fever

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Abstract

Aim: To determine the factors associated with colchicine resistance and the effect of colchicine resistance on health-related quality of life (QoL) in patients with familial Mediterranean fever (FMF).

Methods: Demographic and clinical features, *MEFV* gene mutations, and Pras disease severity scores were recorded. QoL was assessed using the Short Form-36 (SF-36) and FMF-QoL scales. Colchicine resistance was defined as at least 1 attack per month for 6 months at the maximum tolerated dose of colchicine in fully compliant patients.

Results: The mean age of 118 patients (90 female, 28 male) with FMF was 38.4 ± 12.5 years. The percentage of colchicine-resistant patients was 19.5%. In univariable analysis, smoking (odds ratio [OR] = 2.885; 95% confidence interval [CI] = 1.104–7.539; $P = 0.031$), attack duration (OR = 1.955; 95% CI = 1.137–3.360; $P = 0.015$), presence of arthritis (OR = 5.235; 95% CI = 1.508–18.179; $P = 0.009$), and disease severity score (OR = 1.790; 95% CI = 1.334–2.402; $P < 0.001$) were associated with colchicine resistance. The FMF-QoL and subscales of SF-36 except for role emotional and vitality, were different between colchicine-resistant and non-resistant patients ($P < 0.05$).

Conclusion: Smoking, attack duration, presence of arthritis, and disease severity were associated with colchicine resistance in fully compliant FMF patients. Colchicine-resistant patients had poorer health-related QoL.

KEYWORDS
colchicine, drug therapy, familial Mediterranean fever, quality of life

1 | INTRODUCTION

Familial Mediterranean fever (FMF) is a disease characterized by recurrent, self-limiting episodes of fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema with autosomal recessive inheritance. Patients are usually asymptomatic between the attacks. It predominantly affects people from the Mediterranean region and is the most frequent autoinflammatory disease. FMF can result in the development of secondary amyloidosis.[1–5]

The main goals of FMF management include preventing attacks, chronic inflammation, and complications.[6] Colchicine is an effective treatment in patients with FMF for preventing attacks and

amyloidosis.[7,8] The recommended dose of colchicine for adults is a starting dose of 1.0–1.5 mg/d, with a maximum of 3 mg/d.[6]

Although it has been shown that approximately 60% of FMF patients respond to colchicine therapy, 20%–30% of patients partially respond, and 5%–10% do not respond.[3,8] The unresponsiveness to treatment may occur due to factors affecting disease severity and colchicine bioavailability, including colchicine metabolism and potential drug–drug interactions.[9,10] Patients with M694V homozygous mutation have been demonstrated to be more frequently colchicine-resistant.[11,12] Clinical findings such as leg pain, erysipelas-like erythema, and protracted complaints were also found to be associated with lower colchicine response.[13] Genetic variations affecting colchicine bioavailability and concomitant drugs interfering with colchicine transport and metabolism can also affect colchicine response.[9] It has been shown that the response to colchicine therapy can be affected by P-glycoprotein multi-drug transporter (ABCB1) polymorphisms.[14]

The definition of colchicine resistance in patients with FMF is not standard and several definitions have been recommended. According to the European League Against Rheumatism recommendations,[6] at least 1 attack per month with the maximum tolerated dose of colchicine over a 6-months period has been suggested to be resistant to colchicine. More than 6 attacks in a year or more than three attacks in 4–6 months in fully compliant FMF patients were also recommended as the definition of colchicine resistance.[15] However, definitions that include both clinical and laboratory criteria have been shown to meet patients with colchicine resistance at a higher rate.[16] Therefore, persistent disease activity, including recurrent FMF attacks or elevated acute-phase reactants (APR) between attacks, was recently suggested to be accepted as colchicine resistance.[17]

Evaluation of colchicine resistance in FMF patients is essential to prevent the long-term complications of FMF. However, there are conflicting reports regarding the factors associated with colchicine resistance, and no standardized definition of colchicine resistance is available. This study aimed to identify the frequency of colchicine resistance, determine the factors associated with colchicine resistance, and compare health-related quality of life (QoL) between colchicine-resistant and non-resistant FMF patients.

2 | MATERIALS AND METHODS

2.1 | Study design and cohort

This cross-sectional study included 118 patients with FMF diagnosed by the Livneh criteria.[18] Patients who applied to the outpatient clinic of the Rheumatology Division of Marmara University Faculty of Medicine were consecutively included in the study between July 2019 to December 2020. The exclusion criteria for the study were non-compliance with colchicine treatment and being younger than 18 years old.

This study was approved by the Ethics Committee of the Marmara University Faculty of Medicine (insert number: 09.2019.667; date of approval: July 26, 2019). Informed consent was obtained from all participants.

2.2 | Demographic and clinical variables

Data on age, gender, smoking status, body mass index (BMI), obesity (BMI > 30 kg/m^2), family history of FMF and amyloidosis, disease duration (months), age at symptom onset, age at diagnosis, delay in diagnosis, and medications were recorded. The frequency, duration, and characteristics of the attacks, the presence of amyloidosis, and *MEFV* mutation analysis were noted. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum amyloid A (SAA) levels were recorded. An increase in CRP or SAA between attacks was accepted as the elevated attack-free APR. According to the Pras severity score, ≤5 points were classified as a mild disease, 6–10 points as moderate, and ≥10 points as severe FMF disease.[19]

Fully compliant patients with at least 1 attack per month for 6 months at the maximum tolerated dose of colchicine were considered resistant or unresponsive to colchicine.[6] Taking a regular daily dose of colchicine was defined as compliance with the colchicine treatment with the patient's self-report.

2.3 | QoL assessment

The FMF-QoL Scale and Short Form-36 (SF-36) were used to assess health-related QoL in patients with FMF.[20,21]

2.4 | Statistical analysis

Chi-square and Fisher's exact tests were used to assess the differences between categorical variables. Comparisons of continuous variables were done using the Mann–Whitney *U* test. The factors associated with colchicine resistance (dependent variable) were determined using univariable logistic regression. Age, gender, obesity, smoking status, family history, disease duration, age at symptom onset, age at diagnosis, delay in diagnosis, disease severity, duration of attacks, FMF-related manifestations, and *MEFV* mutational status were independent variables. Multivariable analysis was performed using variables with $P < 0.10$ in the univariable analyses. Descriptive data were analyzed using frequency, median, min-max, mean, and standard deviation. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

3 | RESULTS

The mean age of 118 patients (90 female, 28 male) with FMF was 38.4 ± 12.5 years. The mean disease duration was 197.40 ± 149.03 months. *MEFV* mutation analysis was available for

92 of the 118 patients. The percentage of homozygous and heterozygous mutations was 22.9% and 44.1%, respectively. The features of all participants are listed in Table 1.

The percentage of patients with colchicine resistance was 19.5%. The colchicine-resistant and non-resistant patients did not differ regarding age, gender, obesity, disease duration, delay in diagnosis, age at symptom onset and diagnosis, or positive family history ($P > 0.05$). The percentage of smokers, attack duration, arthritis, final colchicine dosage, and Pras severity scores were significantly higher in the colchicine-resistant group ($P < 0.05$). The distributions of *MEFV* gene mutations were not different between the groups ($P > 0.05$). Comparisons of the clinical, demographic, and genetic features between colchicine-resistant and non-resistant patients with FMF are shown in Table 2.

In univariable analysis, smoking (odds ratio [OR] = 2.885; 95% confidence interval [CI] = 1.104–7.539; $P = 0.031$), attack duration (OR = 1.955; 95% CI = 1.137–3.360; $P = 0.015$), presence of arthritis (OR = 5.235; 95% CI = 1.508–18.179; $P = 0.009$), and disease severity score (OR = 1.790; 95% CI = 1.334–2.402; $P < 0.001$) were factors associated with colchicine resistance. Other independent factors were not significantly associated ($P > 0.10$). When smoking, attack duration, presence of arthritis, and disease severity were included in the multivariable model as the independent variable, multivariable analysis showed that the factors associated with colchicine resistance were attack duration (OR = 1.954; 95% CI = 1.024–3.729; $P = 0.042$) and presence of arthritis (OR = 8.354; 95% CI = 1.216–57.373; $P = 0.031$).

The FMF-QoL scale and the subscales of SF-36 were significantly different between colchicine-resistant and non-resistant patients ($P < 0.05$). However, role emotional and vitality subscales of the SF-36 were similar between groups ($P = 0.078$ and $P = 0.070$, respectively). The comparison of health-related QoL between colchicine-resistant and non-resistant patients is given in Table 3.

4 | DISCUSSION

The present study determined the frequency of colchicine resistance, its associations with demographic, clinical, and genetic features, and its impact on health-related QoL in patients with FMF.

The percentage of colchicine-resistant patients in this study was 19.5%. Previous studies have reported that approximately 5%–10% of FMF patients were not responsive to colchicine.[10,15,22] Long-term administration of colchicine in pediatric FMF patients has been shown to provide complete remission in 64% of patients. The rate of partial remission was 31%, with the remission of a single symptom or a reduction in the frequency and severity of all symptoms.[23] A retrospective study reported that <10% of FMF patients were colchicine-resistant according to the frequency of attacks, presence of persistent subclinical inflammation or secondary amyloidosis.[24] Another study reported that 12.4% of FMF patients in their cohort were unresponsive to colchicine with at least three attacks per year or persistently elevated AFR.[25] In a previous study, the percentage of resistance to colchicine according to the statements of the patients was 16%, but the rate of true unresponsiveness after correction regarding regular colchicine use was determined as 5%.[26] Compared to previous studies, a relatively high rate of colchicine resistance was found in our study. This may be

TABLE 1 Demographic, clinical and genetic characteristics of the patients

Gender, n (%)	
Female	90 (76.3)
Male	28 (23.7)
Age, mean ± SD	38.4 ± 12.5
Body mass index, kg/m^2, mean ± SD	26.36 ± 5.26
Family history of familial Mediterranean fever, n (%)	77 (65.3)
Family history of amyloidosis, n (%)	9 (7.6)
Duration of disease, mo, mean ± SD	197.40 ± 149.03
Age at symptom onset, y, mean ± SD	18.35 ± 12.33
Age at diagnosis, y, mean ± SD	29.35 ± 13.56
Delay in diagnosis, y, median (min-max)	6 (0–44)
Pras disease severity score, n (%)	
Mild	62 (52.5)
Moderate	48 (40.7)
Severe	8 (6.8)
MEFV gene mutation, n (%)	
Homozygous mutation	27 (22.9)
Heterozygous mutation	52 (44.1)
Mutation negative	13 (11.0)
Mutation unknown	26 (22.0)

TABLE 2 Comparison of colchicine-resistant and non-resistant patients with FMF

	Colchicine-resistant n = 23 median (range)/n (%)	Colchicine non-resistant n = 95 median (range)/n (%)	*P*
Age	36 (25–42)	39 (28–47)	0.207
Gender			
Female	18 (78.3)	72 (75.8)	0.803
Male	5 (21.7)	23 (24.2)	
Family history of FMF	12 (52.2)	65 (68.4)	0.142
Family history of amyloidosis	0	9 (9.5)	0.307
Obesity	6 (26.1)	17 (17.9)	0.387
Smoker	10 (43.5)	20 (21.1)	0.027
Disease duration, mo	132 (60–264)	180 (72–300)	0.532
Age at symptoms onset	20 (7–24)	15 (10–25)	0.854
Age at diagnosis	28 (17–37)	29 (18–41)	0.447
Delay in diagnosis, y	5 (1–17)	7 (1–18)	0.682
Attack duration, d	3 (2–3)	2 (1–3)	0.006
Clinical findings			
Fever	15 (65.2)	79 (83.2)	0.081
Abdominal pain	20 (87.0)	88 (92.6)	0.407
Chest pain	10 (43.5)	30 (31.6)	0.279
Arthralgia	10 (43.5)	28 (29.5)	0.197
Myalgia	7 (30.4)	27 (28.4)	0.848
Arthritis	6 (26.1)	6 (6.3)	0.012
ELE	1 (4.3)	0	0.195
Leg pain	6 (26.1)	15 (15.8)	0.241
PFM	1 (5.9)	3 (4.5)	0.808
PA	0	0	
Sacroiliitis	3 (13.0)	6 (6.3)	0.375
Spondyloarthritis	4 (17.4)	10 (10.5)	0.470
Pras severity score			
Mild	6 (26.1)	56 (58.9)	0.001
Moderate	12 (52.2)	36 (37.9)	
Severe	5 (21.7)	3 (3.2)	
Elevated attack-free APRs	9 (39.1)	23 (24.2)	0.149
Final colchicine dosage, mg/d	1.5 (1–2)	1.5 (1–1.5)	0.024
MEFV gene mutation			
Homozygous mutation	6 (33.3)	21 (28.4)	0.420
Heterozygous mutation	8 (44.4)	44 (59.5)	
Mutation negative	4 (22.2)	9 (12.2)	
M694V homozygous	5 (27.8)	18 (24.3)	0.767
M694V heterozygous	5 (27.8)	27 (36.5)	0.487

Note: Continuous variables were given as median (25%–75%) values. Categorical variables were presented as frequency (n) and percentage.

Abbreviations: APR, acute-phase reactant; ELE, erysipelas-like erythema; FMF, familial Mediterranean fever; PA, protracted arthritis; PFM protracted febrile myalgia.

TABLE 3 Comparison of quality of life in colchicine-resistant and non-resistant patients with FMF

	Colchicine-resistant n = 23 median (range)/n (%)	Colchicine non-resistant n = 95 median (range)/n (%)	*P*
FMF-QoL	39 (30–50)	27 (17.5–38.5)	0.004
SF-36			
Physical function	55 (45–70)	70 (55–90)	0.006
Physical role	0 (0–50)	75 (25–100)	0.001
Role emotional	33.3 (0–66.7)	66.7 (0–100)	0.078
Vitality	40 (20–50)	45 (30–60)	0.070
Mental health	48 (36–56)	56 (44–72)	0.020
Social function	50 (25–50)	62.5 (50–75)	0.001
Bodily pain	22.5 (12.5–45)	57.5 (45–77.5)	<0.001
General health	25 (10–50)	45 (30–55)	0.004

Note: Continuous variables were given as median (25–75%) values. Categorical variables were presented as frequency (n) and percentage.

Abbreviations: FMF, familial Mediterranean fever; FMF-QoL, quality of life scale in familial Mediterranean fever; SF-36, Short Form-36.

due to the different definitions used in the studies on colchicine unresponsiveness. Additionally, the patient populations included in these studies differ in ethnicity and age groups. Furthermore, as reported in previous studies, compliance with colchicine therapy is an important component of colchicine response.[24,26] Although patients incompatible with colchicine treatment were not included in our study, both treatment compliance and attack frequency were based on the patient's statements.

We found a predominance of females in both subgroups, but no significant difference in gender distribution between the colchicine-resistant and non-resistant groups. However, another study found that female gender was associated with colchicine efficacy.[27] The duration of disease, delay in diagnosis, age at symptom onset, age at diagnosis, familial history of FMF, and amyloidosis did not differ between the colchicine-resistant and non-resistant groups in our study. Previous studies have also reported similar results.[13,27,28] Although we found no difference in obesity between the groups, the percentage of smokers was significantly higher in colchicine-resistant FMF patients. Another study found no difference in smoking habits between colchicine-responsive and colchicine-unresponsive patients.[28] However, there are no data on the effects of smoking on the pharmacokinetics of colchicine. This effect should be investigated further in future studies.

In the current study, the duration of attacks was longer in the colchicine-resistant patients. FMF-related manifestations, except arthritis, were similar between the groups; however, arthritis was more common in the colchicine-resistant group. Similarly, another study reported that colchicine had less effect on joint manifestations of FMF[29] and clinic findings such as leg pain, erysipelas-like erythema, and protracted complaints were associated with lower colchicine response.[13] In addition to colchicine, specific treatments are required in concomitant conditions such as sacroiliitis. These patients can require additional treatment for symptoms attributable to the associated condition.[17] In our study, the percentage of sacroiliitis was similar in patients with and without colchicine resistance.

We found that the distribution of *MEFV* gene mutations was not different between colchicine-resistant and non-resistant FMF patients. Although patients with M694V homozygous mutations have been demonstrated to be more colchicine-resistant in previous studies,[11–13,30] another study found no association between genetic mutations and colchicine efficacy, similar to our results.[27] The present study found no relationship between colchicine resistance and *MEFV* gene mutations in patients with FMF, which needs to be confirmed in larger epidemiologic studies.

As expected, patients with colchicine resistance showed higher disease severity scores and colchicine doses. There was no difference in elevated attack-free APR levels between colchicine-resistant and non-resistant FMF patients in our study. A previous study reported that disease severity scores, colchicine dosages, and elevated attack-free APR levels were higher in patients who were unresponsive to colchicine.[13] The fact that the presence of elevated attack-free APR was not different between the groups in our study may be due to the small sample size. Additionally, it is necessary to determine whether there is another plausible explanation for the elevated APR levels.

In the present study, univariable logistic regression analysis revealed that the factors associated with colchicine resistance were smoking, attack duration, presence of arthritis, and disease severity. According to the multivariable analysis, only attack duration and the presence of arthritis were found to be associated with colchicine resistance. The results of our study differed in some respects from previous data on colchicine resistance in patients with FMF.[11–13,28] However, the patients included in these studies were of different ethnicities. Moreover, the definition of colchicine resistance varies widely between studies. In addition, the small sample size of our study may have affected the results.

On the other hand, the FMF-QoL scale and the subscales of SF-36, except for role emotional and vitality subscales, were significantly different between colchicine-resistant and non-resistant groups, and FMF patients with colchicine resistance had poorer QoL in the current

study. Bodur et al[31] found a significant association between the frequency of more than 1 attack per month and FMF-QoL. Another study reported the association of FMF-QoL scale with the annual number of attacks and disease severity.[20] In a previous study that examined the relationship between colchicine response and SF-36, patients with colchicine response had higher scores of SF-36 subscales, including physical function, physical role function, and emotional role function scores.[32] Our study results are in line with data on the association of colchicine response with health-related QoL in patients with FMF.

The strengths of the present study are that it is not retrospective and it provides data on the effect of colchicine resistance on health-related QoL. The main limitations of this study are the small sample size from a single center and the higher-than-expected female–male ratio. On the other hand, we evaluated treatment compliance and attack frequency based on the patient's statement. The problem is that there is no method other than clinical evaluation to determine response to colchicine. Patient diaries could be used to evaluate patient adherence to treatment and the frequency of attacks more objectively instead of patient self-report.

In conclusion, while most patients with FMF respond well to colchicine, some may be resistant. Colchicine resistance is critical in the treatment of patients with FMF as it causes the development of amyloidosis with continued inflammation. The causes of colchicine resistance are multifactorial and adherence to treatment should also be considered. The present study demonstrated that smoking, attack duration, presence of arthritis, and disease severity are factors associated with colchicine resistance in fully compliant FMF patients. Patients with colchicine-resistant FMF had a poorer health-related QoL.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. Material preparation, data collection and analysis, and writing of the first draft of the manuscript were performed by all authors, and all authors commented on the previous versions of the manuscript. All the authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The Ethics Committee of Marmara University Faculty of Medicine approved the study.

INFORMED CONSENT

Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Prevalence of peripheral neuropathy and myopathy in patients post-COVID-19 infection

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Abstract

Background: Severe acute respiratory syndrome (SARS-CoV-2), caused by the Coronavirus 2019 (COVID-19), has become a life-threatening epidemic, affecting multiple organs, including the nervous system. Recent studies have documented that COVID-19-associated peripheral neuropathy is a common and frequent problem, with central and peripheral nervous system complications.

Objective: This work aims to evaluate the peripheral nerves and muscle involvement after COVID-19 infection, in addition to studying the prevalence rate and risk factors of their affection.

Methods: The study involved 400 patients, divided into 2 groups, with a history of COVID-19 infection with or without symptoms of neuromuscular affection, and 30 gender- and age-matched healthy volunteers were involved as controls. They were referred to the Department of Rheumatology and Rehabilitation for electro-diagnosis. All participants performed complete clinical examination and laboratory measures with an electrophysiological study.

Results: The prevalence of peripheral neuropathy and myopathy in post-COVID-19 patients was 56.3% among all patients. A significant difference was detected among patients of both groups regarding serum creatine phosphokinase level, clinical signs, and electrophysiologic findings of neuropathy and myopathy compared to the control group, with more prominent features among the symptomatic group. Histories of hospitalization, severe and long-lasting respiratory symptoms were risk factors for developing neuromuscular complications.

Conclusions: The present study could indicate that muscle involvement and peripheral nerve affection are common problems even among asymptomatic patients after COVID-19 infection, especially in the presence of any risk factors.

KEYWORDS
COVID-19, electrophysiology, myopathy, peripheral neuropathy, prevalence, risk factors

1 | INTRODUCTION

Severe acute respiratory syndrome (SARS-CoV-2), caused by COVID-19, is a life-threatening epidemic because it affects several organs, including the nervous, cardiovascular, and renal systems.[1–6]

Myopathy, neuropathy, polyradiculopathy (Guillain-Barré syndrome), stroke, cerebral perfusion abnormalities, and other neuromuscular manifestations of an ever-expanding spectrum have been reported.[7–10]

Retrograde neurotransmission through infected neurons is one of the recently discovered routes of COVID-19 entry into the central

nervous system, including its entry through the olfactory nerve and vascular endothelium infection.[4,11]

It has been suggested that the severity of COVID-19 infection is highly associated with neurological manifestations, such as cytokine storm, with rapid cytokine release that results from the host's immune response reaction to the viral infection, causing neuropathy and neurological manifestations. Thus, till now, it is unknown whether the neurological manifestations caused by COVID-19 are caused by the direct viral infection or indirect systemic inflammation in response to the virus infection.[12]

Recent studies documented that COVID-19-associated peripheral neuropathy is a common and frequent problem, with neuromuscular complications. This phenomenon is particularly common in those with comorbidities, such as diabetes mellitus, which may result from immune processes or as side effects of some medications used to manage COVID-19 symptoms, such as hydroxychloroquine, clindamycin, and steroids. To a lesser extent, prolonged hospitalization may cause entrapment neuropathy (peripheral nerve compression).[12–16]

Numerous studies reported myalgia or muscle fatigue during acute infection with COVID-19, which is likely to develop among critically ill patients and adversely affect patient outcomes.[17]

Accordingly, this study aims to evaluate the peripheral nerves and muscle involvement in (symptomatic and asymptomatic) patients post-COVID-19 infection, in addition to examining the prevalence rate and risk factors related to their affection.

2 | METHODS

This cross-sectional study was conducted on 400 patients with a history of COVID-19 infection who went to the electrophysiological unit at the Physical Medicine, Rheumatology and Rehabilitation Department. The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Menoufia University, with an IRB number PMRR620212, and the patients' informed consents were signed by all participants. Patients' data were collected from March 2020 to December 2021 from Menoufia University Hospital.

The current study included 400 patients with a history of COVID-19 infection, above18 years old. Both genders were divided into 2 groups; the first group included 210 patients who had symptoms of neuropathy and myopathy involving pain (burning, stabbing, or shooting pain in the affected areas), tingling, numbness, paresthesia of the limbs, weakness, myalgia, and easy fatigability. The second group included asymptomatic post-COVID-19 patients, in addition to 30 non-COVID-19 infected age- and gender-matched healthy volunteers who served as the control group.

Patients in the study groups were diagnosed having COVID-19 according to the New COVID-19 Pneumonia Prevention and Control Program (5th edition) by meeting 1 or both criteria of chest computed tomography symptoms and reverse transcription-polymerase chain reaction (RT-PCR), published by the WHO interim guidance.[18]

The present study excluded patients with previous trauma, surgery, fractures, systemic inflammatory or metabolic disorders, pregnancy, and a history of smoking or alcohol consumption that can cause neuropathy or myopathy.

All subjects had general and local clinical neurological examination of the 4 limbs, including assessment of muscle tone, power, endurance, sensations, reflexes, and pain assessment. In addition, they underwent laboratory measurements, including erythrocyte sedimentation rate, complete blood count (CBC), C-reactive protein, liver and kidney functions, hepatitis C virus antibody, and serum creatine phosphokinase (CPK). Furthermore, the electrophysiological parameters, including the study of sensory and motor conductivity of the median, ulnar, radial, tibial, peroneal, and sural nerves, were included with respect to the distal motor and peak sensory latency, amplitude, motor and sensory conduction velocity. The electromyography of 1st dorsal interosseous, biceps, triceps, gastrocnemius-soleus, tibialis posterior, and vastus lateralis was performed on both sides at rest (regarding insertional activity), at minimal activity (regarding motor unit action potential [MUAP] amplitude, and duration), and at maximal activity (regarding interference pattern) using a Nihon Kohden apparatus to assess the grade of nerve and muscle affection post-COVID-19 infection in symptomatic and asymptomatic patients vs (non-infected) healthy controls, for early detection of any muscular affection to improve management and prevent a worsening of the patients' outcomes. The assessment was performed by the same investigator.

3 | STATISTICAL STUDY

On an IBM-compatible computer, data were tabulated and analyzed using SPSS (Statistical Package for Social Science) Software version 20 (SPSS Inc., Chicago, IL, USA). The quantitative data were described as numbers and percentages, and also described as mean ± *SD*, median and interquartile range (IQR). Student's *t* test and Mann–Whitney *U* test were used to compare 2 sets of qualitative data with normal and abnormal distribution, respectively. Analysis of variance and Kruskal-Wallis tests were used to assess the difference of more than 2 groups in the normal and abnormal distribution of data, respectively. Qualitative data were analyzed using the Chi-square test. The independent risk factors for neuromuscular affection among COVID-19 patients were assessed using univariate and multivariable binary logistic regression analysis, which was presented as odds ratios (OR) with 95% confidence intervals (CI). The significance was considered when a *P* value was less than .05.[19]

4 | RESULTS

As shown in Table 1, there were insignificant differences between the 3 studied groups regarding age and gender. Moreover, both patient groups had a non-significant difference in the time-lapsed post-infection period.

TABLE 1 Demographic and clinical data of patients in the study groups

	G1 (symptomatic) N = 210	G2 (asymptomatic) N = 190	G3 (control) N = 30	*P* value
Age	37.93 ± 7.4	39.78 ± 6.9	35.7 ± 8.6	.708
Gender No. (%)				
Male	130 (62%)	120 (63%)	19 (63.3%)	.96
Female	80 (38%)	70 (37%)	11 (36.7%)	
Time of study post-infection, d				
Median IQR	92 (30–220)	87 (26–208)	-	.6
Clinical data, all patients				
Neuropathy	120 (57.2%)	40 (21%)	0 (0%)	<.001
Myopathy	50 (24%)	15 (7.8%)	0 (0%)	<.001

Note: P1 = G1 vs G2,P2 = G1 vs G3, P3 = G2 vs G3.
Abbreviation: IQR, interquartile range.

TABLE 2 Clinical and laboratory measures among subjects of the studied groups

Lab measures, and clinical symptoms and signs	G1 (symptomatic) N = 210	G2 (asymptomatic) N = 190	G3 (control) N = 30	*P* value
Serum CPK, μg/mL	754 ± 120	221 ± 65	93 ± 7.9	P1 = .001 P2 = .001 P3 = .001
Decreased/absent ankle reflexes	46 (22%)	10 (5%)	0 (0%)	P1 = .0001 P2 = .004 P3 = .19
Impaired pinprick sensation of feet/toes	55 (26%)	9 (4.7%)	0 (0%)	P1 = .0001 P2 = .001 P3=0.22
Impaired vibration of toes	67 (32%)	11 (5.8%)	0 (0%)	P1 = .001 P2 = .001 P3 = .18
Weakness of shoulder girdle muscles	19 (9%)	10 (5.3%)	0 (0%)	P1 = .14 P2 = .09 P3 = .19
Weakness of pelvic girdle muscles	31 (14.8%)	10 (5.3%)	0 (0%)	P1 = .002 P2 = .001 P3 = .19

Note: P1 = G1 vs G2, P2 = G1 vs G3, P3 = G2 vs G3.
Abbreviation: CPK, creatin phosphokinase.

Prevalence of post-COVID-19 neuromuscular affection among all patients was 56.3%, and it was 81% among symptomatic patients and 28.8% among the asymptomatic group.

In the symptomatic group, about 57.2% had neuropathy, and 24% had myopathy vs 21%, and 7.8%, respectively, in the asymptomatic group.

The elevated serum CPK level and clinical signs of neuropathy and myopathy were characteristic of the symptomatic patients group when compared to both the control and asymptomatic groups, as in Table 2.

Table 3 showed a significantly higher rate of sensorimotor demyelinating and axonal polyneuropathy of the studied nerves among the patient groups compared to the controls. Additionally, it showed a significantly higher rate of these findings among the symptomatic group than the asymptomatic one.

Table 4 showed a statistically significant presence of insertional activity, with decreased amplitude and prolonged duration of MUAP, and incomplete interference pattern of the studied muscles among patients of both groups compared to the control, with significantly higher affection among the symptomatic group than the asymptomatic.

Table 5 shows the risk factors for developing myopathy and neuropathy among patients of the studied groups that were significantly higher in the symptomatic group, such as hospitalization (42.8% of

TABLE 3 Motor nerve conductive study (MNCS) and sensory nerve conductive study (SNCS) among subjects of the studied groups

MNCS, mean ± *SD*	G1 (symptomatic) (210)	G2 (asymptomatic) (190)	G3 (control) (30)	*P* value	SNCS, mean ± *SD*	G1	G2	G3 (control)	*P* value
Median nerve, DML	7.4 ± 1.5	4.9 ± 1.2	4.2 ± 2.2	P1 = .01 P2 = .05 P3 = .01	PSL	4.8 ± 2.5	3.9 ± 1.2	2.3 ± 0.2	P1 = .4 P2 = .01 P3 = .02
Amplitude	2.1 ± 0.7	3.5 ± 1.5	4.5 ± 1.3	P1 = .05 P2 = .05 P3 = .01	Amplitude	10 ± 3.8	15 ± 3.9	20 ± 5.9	P1 = .05 P2 = .03 P3 = .01
MCV	45 ± 3.1	47 ± 1.3	49 ± 2.5	P1 = .4 P2 = .01 P3 = .1	SCV	47 ± 2.9	48 ± 2.4	49 ± 1.4	P1 = .4 P2 = .2 P3 = .1
Ulnar nerve, DML	5.2 ± 2.6	3.3 ± 1.5	2.1 ± 1.2	P1 = .03 P2 = .01 P3 = .1	PSL	5.2 ± 2.8	3.1 ± 1.4	2.1 ± 1.1	P1 = .04 P2 = .02 P3 = .1
Amplitude	3.9 ± 3.7	4 ± 1.8	6 ± 2.5	P1 = .9 P2 = .01 P3 = .05	Amplitude	11 ± 3.6	15 ± 3.9	17 ± 4.8	P1 = .04 P2 = .01 P3 = .03
MCV	42 ± 2.8	48 ± 1.1	49 ± 2.1	P1 = .03 P2 = .01 P3 = .5	SCV	46 ± 3.4	47 ± 2.5	49 ± 3.2	P1 = .9 P2 = .5 P3 = .2
Radial nerve, DML	3.4 ± 1.5	2.7 ± 1.5	1.9 ± 1.8	P1 = .8 P2 = .01 P3 = .4	PSL	5.2 ± 2.4	3.2 ± 1.6	2.2 ± 2.1	P1 = .03 P2 = .01 P3 = .2
Amplitude	2.3 ± 2.5	3.9 ± 2.4	5.9 ± 3.8	P1 = .6 P2 = .01 P3 = .02	Amplitude	11 ± 2.9	14 ± 3.3	16 ± 5.6	P1 = .6 P2 = .05 P3 = .3
Motor, MCV	47 ± 2.8	49.3 ± 2	50.2 ± 1.9	P1 = .6 P2 = .5 P3 = .8	SCV	45 ± 2.8	49.3 ± 2	50.2 ± 1.9	P1 = .05 P2 = .3 P3 = .7
Tibial nerve, DML	6.4 ± 2.4	3.9 ± 1.5	3.5 ± 1.3	P1 = .03 P2 = .01 P3 = .2	Sural nerve, PSL	6.5 ± 2.6	3.7 ± 1.6	3.3 ± 0.6	P1 = .04 P2 = .02 P3 = .6
Amplitude	3.5 ± 0.6	5 ± 3.4	7 ± 4.3	P1 = .4 P2 = .03 P3 = .01	Amplitude	4 ± 2.3	7.1 ± 2.4	7.5 ± 3.8	P1 = .05 P2 = .02 P3 = .1
MCV	40 ± 2.1	40 ± 2.9	41 ± 3.5	P1 = .4 P2=.8 P3 = .9					

(Continues)

TABLE 3 (Continued)

MNCS, mean ± *SD*	G1 (symptomatic) (210)	G2 (asymptomatic) (190)	G3 (control) (30)	*P* value	SNCS, mean ± *SD*	G1	G2	G3 (control)	*P* value
Peroneal nerve, DML	7.2 ± 1.7	4 ± 1.9	3 ± 1.8	P1 = .01 P2 = .05 P3 = .3					
Amplitude	1.9 ± 0.08	2.9 ± 2.5	4 ± 2.8	P1 = .7 P2 = .01 P3 = .02					
MCV	40 ± 2.4	41 ± 1.4	44 ± 2.3	P1 = .4 P2 = .02 P3 = .01					

Abbreviations: DML, distal motor latency; MCV, motor conductive velocity; PSL, peak sensory latency; SCV, sensory conductive velocity.

symptomatic patients were hospitalized vs 6.3% in the asymptomatic group), long-lasting respiratory symptoms (15.2% of symptomatic patients vs 2.6% of asymptomatic patients), severe respiratory symptoms (22.3% of symptomatic patients vs 3.7% of asymptomatic patients).

Univariate analysis of the suggested risk factors for post-COVID-19 neuromuscular affection included hospitalization (OR 9.7, 95% CI 1.5–23.8), long-lasting respiratory symptoms of more than 2 weeks (OR 8.9, 95% CI 2.7–10.6), the presence of severe respiratory symptoms during infection (OR 10.4, 95% CI 3.2–21.4), and multivariate regression analysis demonstrated that the presence of long-lasting, and severe respiratory symptoms were independent risk factors for the occurrence of post-COVID-19 neuromuscular complications (OR 6.2, 95% CI 1.7–9.5 and OR 7.5, 95% CI 1.1–12.4) as presented in Table 6.

5 | DISCUSSION

This article aims to evaluate the peripheral nerves and muscle involvement among patients (symptomatic and asymptomatic) post-COVID-19 infection, in addition to studying the prevalence rate and risk factors of their affection.

Several previous studies reported neuromuscular involvement among post-COVID-19 patients. Therefore, to the best of our knowledge, this is the first study conducted on a large sample of patients with variable durations after infection with COVID-19, and the first to document sensorimotor axonal and demyelinating neuropathy and myopathy even among asymptomatic post-COVID-19 patients, with clarification of the risk factors of developing neuromuscular affection among them.

The present study revealed that 56.3% of post-COVID-19 patients had neuromuscular affection among both symptomatic and asymptomatic patients. There was a significant difference among patients of both groups regarding serum CPK level, clinical signs, and electrophysiologic study findings of neuropathy and myopathy compared to the control (non-infected) group, with significantly higher differences among the symptomatic group.

We also reported multiple risk factors associated with neuromuscular affection among post-COVID-19 patients as regards hospitalization, severe, and long-lasting respiratory symptoms of more than 2 weeks.

The risk factors for developing myopathy and neuropathy among asymptomatic post-COVID-19 patients were significantly lower than that in the symptomatic group; accordingly, they had a lower prevalence of neuropathy and myopathy.

Our results are consistent with Bagnato,[20] who documented that 81% of post-COVID-19 patients had neuropathies, and myopathies with substantial weakness and functional impairment.

Moreover, Ftiha et al[12] also documented that 36.4% of patients in their study group had peripheral neuropathy after COVID-19 infection.

Similarly, Vanhorebeek[17] concluded that muscle involvement during COVID-19 infection was characterized by myalgia in 40% and muscle tiredness in 70% of patients.

TABLE 4 Electromyography (EMG) among subjects of the study group

	At rest., presence of insertional activity, mean ± *SD*				At maximal activity, incomplete interference, pattern, mean ± *SD*			
	G1 (symp)	G2 (asymp)	G3 (control)		G1 (symp)	G2 (asymp)	G3 (control)	
	n = 210	*N* = 190	*N* = 30	*P* value	N = 210	N = 190	N = 30	*P* value
1st dorsal interosseous	69 ± 7.5	16 ± 3.2	0 ± 0	P1 = .001 P2 = .001 P3 = .001	57 ± 2.8	17.3 ± 2.8	0 ± 0	P1 = .001 P2 = .008 P3 = .007
Biceps brachii	57 ± 5.9	10 ± 3.3	0 ± 0	P1 = .002 P2 = .001 P3 = .02	49 ± 3.2	16 ± 1.5	0 ± 0	P1 = .001 P2 = .001 P3 = .007
Triceps brachii	49 ± 7.9	18 ± 1.4	0 ± 0	P1 = .003 P2 = .001 P3 = .01	52 ± 3.6	19 ± 1.8	0 ± 0	P1 = .001 P2 = .001 P3 = .005
Tibialis posterior	21 ± 6.8	17 ± 4.7	0 ± 0	P1 = .04 P2 = .008 P3 = .007	39 ± 3.4	18 ± 2.7	0 ± 0	P1 = .001 P2 = .001 P3 = .004
Gastrocnemius-soleus	37 ± 8.6	13 ± 9.6	0 ± 0	P1 = .001 P2 = .001 P3 = .00	33 ± 2.7	16 ± 3.7	0 ± 0	P1 = .002 P2 = .001 P3 = .007
Vastus lateralis	8 ± 5.8	16 ± 4.5	0 ± 0	P1 = .004 P2 = .001 P3 = .009	27 ± 5.2	17.7 ± 2.9	0 ± 0	P1 = .009 P2 = .004 P3 = .002
	Amplitude of MUAP (μV) among groups, mean ± *SD*				Duration of MUAP (μS) among groups, mean ± *SD*			
At minimal activity	G1	G2	G3	*P* value	G1	G2	G3	*P* value
1st dorsal interosseous	250 ± 75	520 ± 72	640 ± 67	P1 = .03 P2 = .01 P3 = .02	3.7 ± 2.8	7.3 ± 6.8	9.3 ± 5.7	P1 = .02 P2 = .01 P3 = .31
Biceps brachii	317 ± 57.9	610 ± 33	760 ± 99	P1 = .02 P2 = .01 P3 = .3	5.7 ± 3.2	6.2 ± 5.8	11.2 ± 5	P1 = .8 P2 = .03 P3 = .02
Triceps brachii	490 ± 77.9	720 ± 94	890 ± 120	P1 = .02 P2 = .01 P3 = .05	3.2 ± 3.6	7.9 ± 7.8	8.5 ± 4.9	P1 = .05 P2 = .03 P3 = .2
Tibialis posterior	219 ± 56.8	567 ± 170	794 ± 160	P1 = .04 P2 = .02 P3 = .03	2.9 ± 3.4	8.8 ± 4.7	10 ± 5.3	P1 = .02 P2 = .05 P3 = .1
Gastrocnemius-soleus	370 ± 87.6	537 ± 96	667 ± 88	P1 = .05 P2 = .01 P3 = .05	4.3 ± 2.7	6.7 ± 6.7	8.2 ± 4.9	P1 = .7 P2 = .05 P3 = .2
Vastus lateralis	658 ± 55.8	667 ± 125	789 ± 140	P1 = .7 P2 = .5 P3 = .3	7.5 ± 5.2	7.7 ± 4.9	9.1 ± 3.2	P1 = .6 P2 = .4 P3 = .7

Note: P1 = G1 vs G2, P2 = G1 vs G3, P3 = G2 vs G3, μV = microvolt, μS = microsec.
G1 symp = symptomatic group; G2 asymp = asymptomatic group; MUAP = motor unit action potential.

In the same way, Pinzon et al,[21] Guidon and Amato,[22] Li et al,[23] and Sanchez et al.[24] documented that about 19.2%, 33%, and 56% of COVID-19 infected patients had myalgia or muscle injury with elevated creatine kinase levels.

In accordance with our results, Faqihi et al,[25] Sejvar et al,[26] Jacobs et al,[27] Mehta et al,[28] Faqihi et al,[29] Paterson et al,[30] and Wu et al[31] also reported peripheral neuropathy in post-COVID-19 patients.

As all the mentioned studies agree with our results, we could suggested that neuromuscular involvement is a common complication post-COVID-19 infection, even in asymptomatic patients, and the different degrees of affection and functional impairment in different

TABLE 5 Risk factors to develop myopathy and neuropathy among patients of the studied groups

	G1 (symptomatic) N = 210	G2 (asymptomatic) N = 190	*P* value
Hospitalization	90 (42.8%)	12 (6.3%)	.001
Severe respiratory symptoms	47 (22.3%)	7 (3.7%)	.002
Long-lasting respiratory symptoms, more than 15 d	32 (15.2%)	5 (2.6%)	.004

TABLE 6 Univariate and multivariate regression analysis for the association between variables and the presence of neuropathy and myopathy among COVID-19 patients groups

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*p* value
Hospitalization	9.7	1.5–23.8	.008	1.15	0.91–7.41	.12
Old age, long-lasting respiratory symptoms, 15–40 d	8.9	2.7–10.6	.01	6.2	1.7–9.5	.02
Severe respiratory symptoms	10.4	3.2–21.4	.02	7.5	1.1–12.4	.005

studies can be explained according to the severity of COVID-19 infection and the presence of other risk factors in those patients.

In another way, Bureau et al[32] observed the low incidence of peripheral neuropathy post-COVID-19 infection in their study group. That could be explained by the fact their study group patients had a mild COVID-19 infection as they fully recovered after a short period and they were not hospitalized.

In agreement with our results, Frithiof et al[33] documented that prolonged hospitalization and severe respiratory distress symptoms are independent predictors closely related to neuromuscular complications after infection with COVID-19. They reported that 79% of COVID-19 infected patients had neuromuscular affection.

Our results revealed the presence of neuromuscular symptoms among patients for a relatively long period post-COVID-19 infection, as the median assessment time for patients in the 2 study groups was 92, and 87 days post-infection.

In accordance with our results, a study performed by Elkind et al reported a long time delay between COVID-19 viral infection onset and the appearance of neuromuscular complications.[34]

In another way, Zhao et al[35] showed that neurological disorders, such as in the cases of Guillain-Barré syndrome, are related to the early symptoms of COVID-19 infection, which arises as a para-infectious rather than a post-infectious complication in some patients.

Accordingly, the early association between COVID-19 infection and Guillain-Barré syndrome could be explained since this rare disorder is usually associated with infection or soon after infection.

Therefore, our study could not be certain about the time of appearance of neuromuscular complications, either post-infection or para-infection, as these complications were presented during the time of the study among symptomatic and asymptomatic patients of the study groups.

6 | CONCLUSION

The present study implies that muscle involvement and peripheral nerve affection are common problems even among asymptomatic post-COVID-19 patients, especially in the presence of any risk factors, such as a history of long hospitalization, severe, and long-lasting respiratory symptoms. Thus, in order to improve management and prevent a worsening of the patients' outcomes, we must be aware of the presence of any neurologic symptoms in patients after COVID-19 infection.

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CONFLICT OF INTERESTS

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Comparative safety of Janus kinase inhibitors and tumor necrosis factor inhibitors in patients undergoing treatment for rheumatoid arthritis

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Abstract

Objectives: Since 2010, biological disease-modifying antirheumatic drugs (bDMARDs) have been the dominant mode of treatment for rheumatoid arthritis (RA). However, the safety of DMARDs, such as tumor necrosis factor inhibitors (TNFis) and Janus kinase inhibitors (JAKis), in treating patients with RA is a concern. We compared the safety outcomes of JAKis and TNFis in RA patients in clinical settings.

Methods: Patients diagnosed with RA between 2015 and 2017 were identified from the Taiwan National Health Insurance Research Database and followed till 2018. Propensity score stabilized weighting was used to balance the baseline characteristics of the JAKis and TNFis groups. The incidences of safety outcomes, namely cardiovascular (CV) events, tuberculosis (TB), total hip replacement (THR), total knee replacement (TKR), and all-cause mortality, were compared between the 2 study groups.

Results: A total of 3179 patients with RA who were administered JAKis (n = 822) and TNFis (n = 2357) were included in this study. The mean follow-up duration was 2.02 years in the JAKis group and 2.10 in the TNFis group. All-cause mortality had the highest incidence rate, followed by TKR, THR, CV events, and TB. A lower incidence rate of the study outcomes was observed in the JAKis group than in the TNFis group but without statistical significance.

Conclusion: Comparable safety issues and mortality rates were observed for JAKis and TNFis in RA patients treated in real-world settings.

KEYWORDS
drug treatment, epidemiology, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease requiring persistent medication to control disease activity and prevent further disability.[1] In the past decade, the treatment of RA has changed with the introduction of disease-modifying antirheumatic drugs (DMARDs) that are based on the concepts of "treat-to-target" and "treatment of early RA." The timely initiation of DMARDs is included in the recommendations of the European League Against Rheumatism.[2]

The introduction of biological DMARDs (bDMARDs) has considerably changed the prognosis of RA. In 2009, Janus kinase inhibitors (JAKis), such as tofacitinib, were approved for treating moderate-to-severe RA by the United States Food and Drug Administration (US FDA); JAKis were then introduced in 2014 in Taiwan. However, reliable predictors are not available for selecting a specific therapy

for individual RA patients. In Taiwan, rheumatologists and patients share the decision-making process, taking into account the preferences and comorbidities of the patients.

A "Drug Safety Communication" of the US FDA warned about an increased risk of heart-related severe events, cancer, blood clots, and death for JAKis used to treat certain chronic inflammatory diseases.[3] The warning was based on Pfizer's ORAL surveillance study that revealed an increased risk of cardiovascular events and malignancy in patients treated with JAKis compared to those treated with TNFis.

In 1995, Taiwan launched the National Health Insurance (NHI) program for its citizens and residents,[4] and treatment of RA with TNFis and JAKis became reimbursable in 2003 and 2014, respectively.[5] This study compared the safety profiles of TNFis and JAKis in patients with RA by using the NHI Research Database (NHIRD).

2 | PATIENTS AND METHODS

2.1 | Data sources

In this study, the Taiwan NHIRD and Taiwan Death Registry (TDR) were the primary data sources. The NHIRD contains detailed information on patient registration and original claims data, including demographic (year of birth, gender, place of residence, and insurance premiums) and outpatient and inpatient details (dates of inpatient and outpatient visits, medical diagnostic codes and prescription details, medical expenditures, examination code, operation or procedure code, and discharge status). The TDR contains the dates of death and the underlying causes of death for deceased residents of Taiwan. The completeness of the TDR and the accuracy of cause-of-death coding in Taiwan are well-recognized.[6] A unique personal identifier assigned to each resident of Taiwan allows for linking the NHIRD and TDR. To ensure confidentiality, unique personal identifiers are encrypted before data are released to researchers. The NHIRD and TDR are available at the Health and Welfare Data Science Center or its subcenters to further protect privacy, and only summarized results, not individual data, are provided to data seekers. The diagnostic coding system in the NHI database follows the *International Classification of Diseases* (*ICD*), *Ninth Revision* [*Tenth Revision*], *Clinical Modification* (*ICD-9-CM* from 2000 to 2015 and *ICD-10-CM* from 2016 to present). The validity, representativeness, and clinical consistency of the NHI database have been described elsewhere.[4,7]

This study had no identification number of each patient in the NHIRD. In addition, the TDR data were encrypted. Based on these factors, the Institutional Review Board (IRB) of Chang Gung Medical Foundation (IRB-CGMF) (201901028B1) exempted this study from the requirement to obtain an informed consent form from the participants.

2.2 | Study design and study population

Newly diagnosed RA (*ICD-9-CM*: 714.0 and *ICD-10-CM*: M05-06) patients were identified from 1995 to 2017. To reduce misclassification of RA, only RA patients with a catastrophic illness certificate, issued after a formal review by an expert panel commissioned by the NHI Administration, were enrolled. The review panel uses the 1987 and 2010 classification criteria to determine the accuracy of an RA diagnosis. In this study, after the identification of RA patients, the index date was defined as the date of the new RA diagnosis. Patients younger than 18 and older than 80 (n = 520) at the index date were excluded because of data scarcity. In addition, patients who never received DMARD treatment after RA diagnosis (n = 4472), never received bDMARDs treatment (n = 46 410), or received TNFi treatment before 2015 or after 2017 (n = 9818) were excluded (Figure 1).

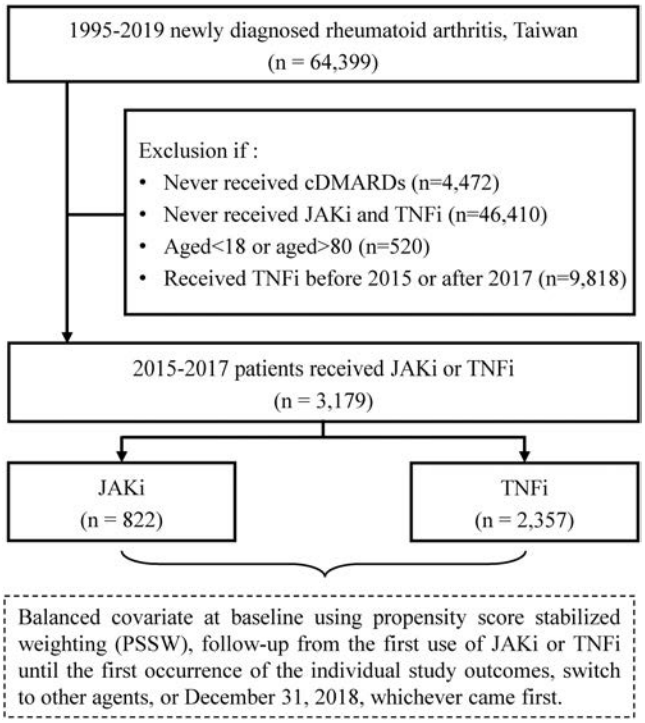

FIGURE 1 Flowchart for identifying patients with rheumatoid arthritis in the Taiwan National Health Insurance Research Database. cDMARDs, conventional disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitor; TNFi, tumor necrosis factor inhibitor

The covariates at baseline were balanced using propensity score stabilized weighting (PSSW). Moreover, follow-up was performed from the first use of JAKis or TNFis until the first occurrence of the individual study outcomes, switch to other agents, or December 31, 2018, whichever came first.

2.3 | Intervention

In this study, RA patients treated only with conventional DMARDs (cDMARDs) were defined as biologic-naïve patients. In Taiwan, the use of TNFis for the treatment of RA dramatically increased in 2003,[5] with etanercept first being available in 2003. Other TNFis like adalimumab and golimumab were introduced in Taiwan in 2005 and 2012, respectively. JAKis, such as tofacitinib, were used in

Taiwan in 2014. In our study, tofacitinib was the only JAKi used, as baricitinib was introduced in Taiwan after March 2019.

2.4 | Safety outcomes

The safety outcomes included coronary heart disease (CHD), stroke, overall thromboembolism (OVT), deep vein thrombosis (DVT), total hip replacement (THR), total knee replacement (TKR), tuberculosis (TB), malignancy, and all-cause mortality. To reduce misclassification of the study outcomes, CHD, stroke, OVT, DVT, THR, TKR, TB, and malignancy had to be the primary discharge diagnosis. The mortality data were extracted from the TDR. The procedure codes were 64162B and 64170B for THR, and 64164B and 64169B for TKR, respectively. Please refer to Table S1 about the ICD codes for the study outcomes.

2.5 | Covariates

Numerous comorbidities were related to the safety outcomes, including diabetes, hypertension, chronic kidney disease, and malignancy. These comorbidities had to appear in outpatient visits twice or inpatients once within a year before the index date. Please refer to Table S1 about the ICD codes for these comorbidities. Various concomitant medications were related to the safety outcomes, including steroids, methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, cyclosporine, azathioprine, penicillamine. These concomitant medications should be used at least 3 months within the 1 year before the index date. Please refer to Table S2 about anatomical therapeutic chemical codes for these concomitant medications.

2.6 | Statistical analysis

The baseline characteristics (Table 1) between the 2 medication groups were balanced using PSSW;[8] generalized boosted models were applied for this purpose.[9] The balance of baseline characteristics between the 2 medication groups was assessed using the absolute standardized mean difference (ASMD), with the value of ASMD ≤0.1 indicating an insignificant difference.[10] The incidence rate of safety profiles was the total number of study outcomes divided by patient-years at risk during the follow-up period. The risk of study outcomes for JAKis vs TNFis (reference) was estimated using survival analysis (Kaplan–Meier method and Cox's proportional hazards model). The study group was the only covariate in Cox's model because the 2 study groups were well-balanced after PSSW.[11] Sensitivity analysis was performed on those aged ≧50 to determine whether the risks of safety outcomes were maintained as the entire sample. PSSW was conducted again to ensure a good balance in all covariates between the 2 medication groups. The significance level of this study is .05.

3 | RESULTS

3.1 | Baseline characteristics

We identified 64 339 patients with incident RA diagnosed between 1995 and 2017. Following the exclusion of patients aged younger than 18 and older than 80, those who did not receive DMARD treatment after RA diagnosis, those who never received JAKis or TNFis, and those who received TNFis before 2015 or after 2017, 3179 patients with RA were eligible for the analyses (Figure 1). Because of the introduction of tofacitinib after December 2014, it was the only medication in the JAKi group. Baricitinib was the second JAKi introduced and was available after March 2019. The medications of the TNFi group included etanercept, adalimumab, and golimumab. Finally, 822 patients in the JAKi group and 2359 patients in the TNFi group were included in this study. We identified RA patients receiving cDMARDs and bDMARDs in each half-year period (Figure 1).

Before PSSW, the 2 study groups were similar regarding age, gender, comorbidities, and prescribed concomitant medications, except more patients in the JAKi group used hydroxychloroquine and leflunomide than in the TNFi group. After PSSW, the 2 study groups were well-balanced in all covariates (Table 1). In addition, the prescription rate (Figure 2A) and prescription duration (Figure 2B) for concomitant medications dropped slowly over time. More importantly, the prescription rate and prescription duration over time were similar between the 2 medication groups.

3.2 | CHD

Figure 3A displays the cumulative incidence of CHD in the JAKi and TNFi groups. The incidence rates of CHD (per 100 patient-years) were 0.48 and 0.45 for the JAKi and TNFi groups, respectively. The Cox regression model was applied, and a comparison of the JAKi group with the TNFi group revealed a hazard ratio of 1.03 (0.45-2.36; $P = .9463$; Table 2).

3.3 | Stroke

Figure 3B presents the cumulative incidence rates of stroke. The incidence rates of stroke in the JAKi and TNFi groups were 0.33 per 100 patient-years and 0.46 per 100 patient-years, respectively (Table 2). The Cox regression model was applied, and a comparison of the JAKi group with the TNFi group revealed a hazard ratio of 0.75 (0.29-1.94; $P = .5519$). However, statistically significant differences were not observed between the 2 groups.

3.4 | OVT

Figure 3C depicts the cumulative incidence rate of OVT. The incidence rates of OVT in the JAKi and TNFi groups were 0.32 per 100

TABLE 1 Baseline characteristics of patients in the JAKi and TNFi groups.

	Before PSSW					After PSSW				
	JAKi (n = 822)		TNFi (n = 2357)			JAKi (n = 822)		TNFi (n = 2357)		
	n	%	n	%	ASMD	n	%	n	%	ASMD
Age, y										
Min (max)	19	(80)	18	(80)	0.0614	19	(80)	18	(80)	0.0165
Mean (SD)	56.42	(12.86)	55.12	(12.71)		56.02	(12.11)	55.81	(12.68)	
Median (IQR)	57.5	(18)	56	(17)		57	(17)	57	(17)	
Male	160	19.46	537	22.78	0.0813	159.0	20.45	513.4	21.91	0.0362
Follow-up duration, y	2.02		2.10			2.02		2.10		
Comorbidity										
Diabetes	141	17.15	400	16.97	0.0049	130.8	16.82	396.8	16.94	0.0033
Hypertension	267	32.48	809	34.32	0.0390	255.5	32.85	793.2	33.85	0.0216
Chronic kidney disease	91	11.07	253	10.73	0.0108	81.9	10.53	251.7	10.74	0.0071
Malignancy	23	2.80	54	2.29	0.0322	18.1	2.33	54.7	2.33	0.0002
Concomitant medication										
Steroid	608	73.97	1766	74.93	0.0220	584.2	75.12	1751.0	74.73	0.0090
Methotrexate	696	84.67	1930	81.88	0.0747	648.4	83.39	1936.5	82.65	0.0198
Hydroxychloroquine	613	74.57	1638	69.50	0.1133	558.6	71.84	1657.4	70.74	0.0247
Leflunomide	171	20.80	602	25.54	0.1124	186.1	23.94	571.6	24.39	0.0108
Sulfasalazine	178	21.65	598	25.37	0.0877	183.3	23.57	571.5	24.39	0.0194
Cyclosporine	50	6.08	157	6.66	0.0237	48.1	6.18	152.6	6.51	0.0139
Azathioprine	13	1.58	44	1.87	0.0219	14.7	1.89	42.6	1.82	0.0059
Penicillamine	0	0.00	6	0.25	0.0714	0	0.00	5.7	0.24	0.0699

Abbreviations: ASMD, absolute standardized mean difference; IQR, interquartile range; JAKi, Janus kinase inhibitor; PSSW, propensity score stabilized weighting; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

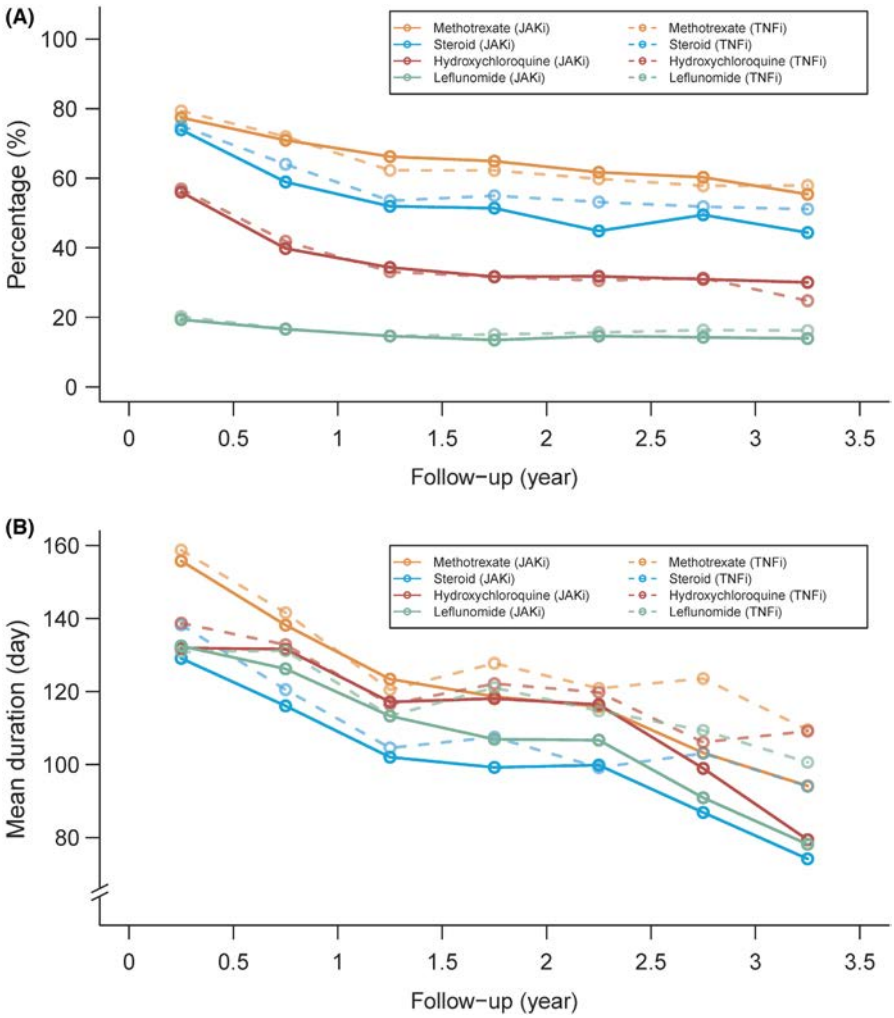

FIGURE 2 The half-year use of concomitant medications in the JAKi and TNFi groups. A, The percentage of concomitant medication prescriptions. B, The mean duration in days among those prescribed the concomitant medications. JAKi, Janus kinase inhibitor; TNFi, tumor necrosis factor inhibitor

patient-years and 0.48 per 100 patient-years, respectively (Table 2). The Cox regression model was applied, and the comparison of the JAKi group with the TNFi group revealed a hazard ratio of 0.65 (0.25-1.70; $P = .3810$). However, statistically significant differences were not observed between the 2 groups.

3.5 | DVT

Figure 3D provides the cumulative incidence rate of DVT. The incidence rates of DVT in the JAKi and TNFi groups were 0.26 per 100 patient-years and 0.44 per 100 patient-years, respectively (Table 2). The Cox regression model was applied, and a comparison of the JAKi group with the TNFi group revealed a hazard ratio of 0.57 (0.20-1.64; $P = .3010$). However, statistically significant differences were not observed between the 2 groups.

3.6 | TB

Figure 3E provides the cumulative incidence rate of TB. The incidence rates of TB in the JAKi group and the TNFi group were 0.29 per 100 patient-years and 0.49 per 100 patient-years, respectively (Table 2). The Cox regression model was applied, and the comparison of the JAKi group with the TNFi group revealed a hazard ratio of 0.60 (0.22-1.62; $P = .3122$). However, statistically significant differences were not observed between the 2 groups.

3.7 | Joint replacement rate

Figure 3F,G provides the incidence rates of THR and TKR. The incidence rates of THR in the JAKi and TNFi groups were 0.47 per 100 patient-years and 0.53 per 100 patient-years, respectively (Table 2). The Cox regression model was applied, and the comparison of the JAKi group with the TNFi group revealed a hazard ratio of 0.86 (0.38-1.95; $P = .7211$). The incidence rates of TKR in the JAKi and TNFi groups were 1.11 per 100 patient-years and 1.02 per 100 patient-years, respectively (Table 2). The Cox regression model, a comparison of the JAKi group with the TNFi group, revealed a hazard ratio of 1.09 (0.63-1.89; $P = .7580$). Statistically significant differences in THR and TKR were not observed between the 2 groups.

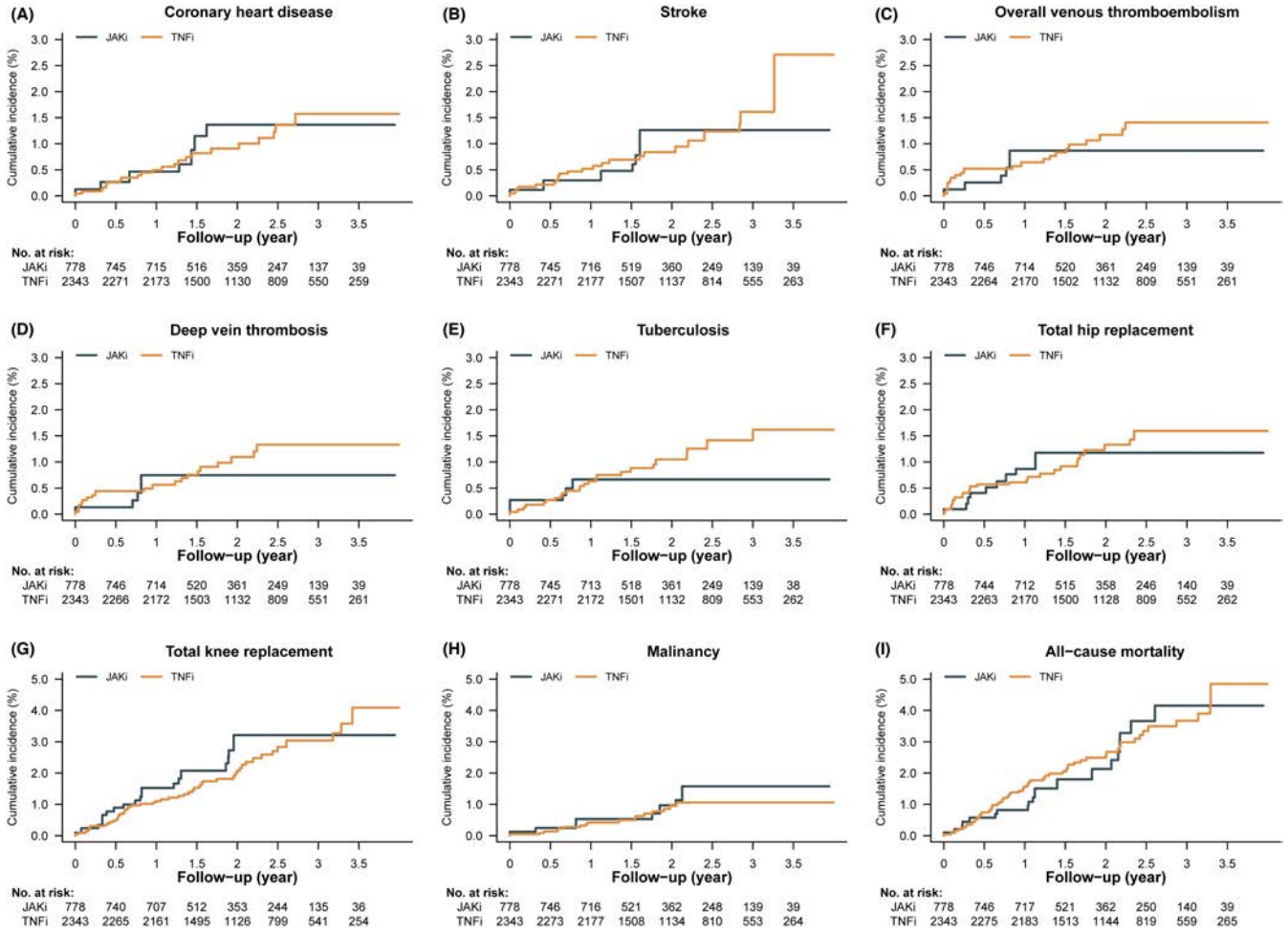

FIGURE 3 Cumulative incidence of safety outcomes in the JAKi and TNFi groups. JAKi, Janus kinase inhibitor; TNFi, tumor necrosis factor inhibitor

3.8 | Malignancy

Figure 3H displays the cumulative incidence rate of malignancy in the JAKi and TNFi groups. The incidence rates of malignancy in the JAKi and TNFi groups were 0.39 per 100 patient-years and 0.35 per 100 patient-years, respectively (Table 2). The Cox regression model indicated that, when comparing the JAKi group with the TNFi group, the hazard ratio was 1.10 (0.44-2.78; $P = .8353$). An increased incidence of malignancy was thus not observed in the JAKi group.

3.9 | All-cause mortality

Figure 3I presents the cumulative incidence rate of all-cause mortality. The incidence rates of all-cause mortality in the JAKi and TNFi groups were 1.17 per 100 patient-years and 1.29 per 100 patient-years, respectively (Table 2). Again, using the Cox regression model, we compared the JAKi group with the TNFi group and revealed a hazard ratio of 091 (0.54-1.52; $P = .7099$). Statistically significant differences were not observed between the 2 groups.

3.10 | Sensitivity analysis

After restricting to those aged ≧50, the rates of diabetes and hypertension were higher than that of the entire sample. Before and after PSSW, the 2 medication groups were similar regarding comorbidities. For concomitant medications, the prescription rate was similar between those aged ≧50 and the entire sample. After PSSW, the prescription rate of concomitant medications was well-balanced between the 2 medication groups (Table S3).

The incidence rates of safety outcomes (CHD, stroke, OVT, DVT, TB, THR, TKR, malignancy, and all-cause mortality) were higher in those aged ≧50 than in the entire sample. After PSSW, an insignificant difference in these incidence rates between the 2 medication groups was seen in those aged ≧50 (Table S4).

4 | DISCUSSION

This nationwide study observed similar safety profiles (CHD, stroke, OVT, DVT, TB, THR, TKR, malignancy, and all-cause mortality) in the JAKi and TNFi groups.

TABLE 2 Incidence rate of safety outcomes in RA patients treated with JAKi and TNFi after PSSW

	Incidence (per 100 person-years)		Cox's results	
	JAKi (n = 822)	TNFi (n = 2357)	HR (95% CI)	*P* value
Coronary heart disease	0.48 (0.20-0.92)	0.45 (0.26-0.64)	1.03 (0.45-2.36)	.9463
Stroke	0.33 (0.11-0.72)	0.46 (0.27-0.65)	0.75 (0.29-1.94)	.5519
Overall venous thromboembolism	0.32 (0.11-0.70)	0.48 (0.29-0.68)	0.65 (0.25-1.70)	.3810
Deep vein thrombosis	0.26 (0.07-0.62)	0.44 (0.26-0.63)	0.57 (0.20-1.64)	.3010
Tuberculosis	0.29 (0.09-0.66)	0.49 (0.29-0.68)	0.60 (0.22-1.62)	.3122
Total hip replacement	0.47 (0.19-0.91)	0.53 (0.33-0.74)	0.86 (0.38-1.95)	.7211
Total knee replacement	1.11 (0.59-1.63)	1.02 (0.74-1.30)	1.09 (0.63-1.89)	.7580
Malignancy	0.39 (0.14-0.80)	0.35 (0.18-0.51)	1.10 (0.44-2.78)	.8353
All-cause mortality	1.17 (0.64-1.70)	1.29 (0.97-1.61)	0.91 (0.54-1.52)	.7099

Abbreviations: JAKi, Janus kinase inhibitor; PSSW, propensity score stabilized weighting; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

The pivotal strength of our analysis is the employment of PSSW to provide a nationwide perspective on the safety outcomes of JAKis and TNFis in the treatment of RA. In Taiwan, patients with moderate-to-severe RA are prescribed bDMARDs, with TNFis being the leading bDMARD-naïve treatment choice. In Taiwan, tofacitinib was the first oral bDMARD introduced in 2014; it was thus the only JAKi in our study because the second JAKi was only introduced after March 2019. The oral form of tofacitinib became a popular treatment choice after its introduction in 2014. Advantages and disadvantages of cDMARDs and bDMARDs have been reported previously by clinical trials or meta-analyses, but these were limited by a small sample size or poor planning. The results of this study provide real-world evidence of the safety outcomes of JAKis and TNFis in nationwide use. Increased risks were not observed with the usage of JAKis and TNFis.

Previous studies have reported varying results, including an increased risk of cardiovascular events in patients with RA. In a previous study, the risk of diabetes in RA patients was twice the hazard ratio, which was much higher than that of the nondiabetic controls.[12] Moreover, an increased risk of cardiovascular events was reported after some treatment interventions. For example, recent studies have mentioned high risks of cardiovascular disease and malignancy in RA patients treated with tofacitinib. The ORAL surveillance study demonstrated that tofacitinib was no worse than TNFis for cardiovascular diseases and malignancy.[13] Based on these studies, a "Drug Safety Communication" was published by the US FDA to add warnings regarding an increased risk of heart-related severe events and cancer.[3] The European Medicines Agency concluded that tofacitinib could increase the risk of blood clots in the lungs and deep veins in patients already at high risk. However, a newly published study from the United States revealed that tofacitinib did not increase the risk of cardiovascular outcomes in patients with RA treated in real-world settings.[14]

Moreover, a meta-analysis mentioned that using JAKis as an adjunct to methotrexate (MTX) was not associated with an increased risk of malignancy compared with using MTX alone.[15] Therefore, adding JAKis to MTX therapy does not increase the malignancy risk for RA patients. Our study revealed similar safety outcomes, specifically concerning cardiovascular events and malignancy, in patients treated with JAKis or TNFis.

Previous studies have also revealed increased risks of OVT and DVT.[16,17] In clinical trials, RA patients on JAKis experienced an increased risk of OVT.[18] The decision of the US FDA to delay the approval of baricitinib for treating RA due to concerns regarding thromboembolic events was, therefore, justified.[19] However, the decision also attracted attention to tofacitinib. A meta-analysis recently reported that the pooled incident ratio did not support the current warnings of thrombotic risk for JAKis.[20] Our study did not reveal increased thrombotic risks, which may be explained by the generally low thromboembolic risk of Asian patients.

A previous study reported an increased risk of TB after the introduction of TNFis.[21] Some studies have also mentioned increased TB risk after biological treatments.[22] Tofacitinib was reported to have a stable TB incidence rate in a long-term extension clinical trial study.[23] We also speculate that TB risk may be lower in patients treated with JAKis. Our study did not reveal any difference in the TB incidence rate between the JAKi and TNFi groups, which may be because a risk management plan is employed before TNFi treatment according to our local guidelines.

Joint replacement rates for patients with RA are a cause of concern.[24] Our study observed comparable safety incidence rates of joint replacement between the JAKi and TNFi groups. The all-cause mortality rate of patients with RA has decreased over the past decades; however, it remains higher than that of the general population.[25,26] A few studies have revealed increased mortality in patients treated with cDMARDs but not those treated with bDMARDs. However, these studies did not identify the type of bDMARDs used to analyze mortality.[27] Long-term extension clinical trials have also reported a stable mortality rate in patients treated with JAKis or TNFis.[23,28,29] Similarly, our study observed comparable all-cause mortality in the JAKi and TNFi groups.

Our study has some limitations. First, misclassification of patients with RA by using *ICD* codes is a concern. However, we expect such a problem to be minimal because of the rigorous review of RA

diagnoses before issuing a catastrophic illness certificate. Second, data on patient habits, such as cigarette smoking, alcohol consumption, and exercise, are unavailable in NHIRD, although these variables are associated with the study outcomes. Third, the NHIRD does not include detailed laboratory results, such as erythrocyte sedimentation rate, C-reactive protein and disease activity, of the patients.

In conclusion, the safety outcomes of CHD, stroke, OVT, DVT, TB, joint replacement rates, malignancy, and all-cause mortality were similar in both groups. In addition, the risk of adverse events and mortality did not increase in the JAKi group compared with the TNFi group.

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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

Comparison of SARIMA model and Holt-Winters model in predicting the incidence of Sjögren's syndrome

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Abstract

Objective: To analyze the prevalence trend of Sjögren's syndrome in the Department of Immunology and Rheumatology of Nanjing Zhongda Hospital from January 2015 to December 2019, and compare the application of SARIMA model and Holt-Winters model in predicting the number of cases of Sjögren's syndrome.

Methods: All of the data from the Department of Immunology and Rheumatology of Nanjing Zhongda Hospital were collected. The number of monthly cases from January 2015 to December 2019 was regarded as the training set, and it was used to establish the SARIMA model and Holt-Winters model. The number of monthly incidences from January 2020 to December 2020 was regarded as the test set, and it was used to check the model performance.

Results: The optimal model of SARIMA is ARIMA (0,1,1) $(2,1,1)_{12}$ model, and the optimal model of Holt-Winters model is Holt-Winters addition model. It was found that the Holt-Winters addition model produced the smallest error.

Conclusion: Holt-Winters addition model produces better prediction accuracy of the model.

KEYWORDS
ARIMA model, Holt-Winters model, Sjögren's syndrome

1 | INTRODUCTION

Sjögren's syndrome (SS) is a lymphoproliferative disease with autoimmune features characterized by mononuclear cell infiltration of exocrine glands. These lymphoid infiltrations lead to dryness of the eyes and dryness of the mouth.[1] Most patients with extra-glandular involvement, present with a variety of manifestations, depending on the tissue/organ affected. The most frequently affected are the pulmonary, neurologic, musculoskeletal, hematologic, renal, cardiac, reticuloendothelial, endocrine, cutaneous, and gastrointestinal systems.[2,3] In addition, SS can cause substantial serologic autoimmune reactivity and in some instances is associated with other connective-tissue autoimmune disorders, such as rheumatoid arthritis, scleroderma, or systemic lupus erythematosus. These lead to SS patients having considerable burden of disease in the long term.[4]

The disease is divided into primary (pSS) and secondary (sSS), and pSS is clinically more common. pSS is a global disease, and the prevalence in the Chinese population ranges from 0.3% to 0.7%.[5] It affects more women than men with an average of 9:1, with a peak prevalence in the fourth to fifth decades of life.[6] According to Frost and Sullivan data, the incidence of SS in China has increased steadily from 2016 to 2020. It is expected that the number of SS patients in China will reach 641 800 in 2025, an increase of 1.7% compared with 2020.[7] These show that the number of people suffering from the disease is growing rapidly and therefore accurate and effective prediction of the number of cases of SS is of great significance to disease prevention and treatment.

The SARIMA model and Holt-Winters model are the 2 most widely used approaches to time series forecasting, which are applicable to different types of time series models, and can reflect the time change

and periodic change of the original data.[8] While the Holt-Winter model is based on a description of the trend and seasonality in the data, ARIMA models aim to describe the autocorrelations in the data.[8,9]

This study proposes to establish a SARIMA model and Holt-Winters model by the number of monthly incidences from January 2015 to December 2019. The number of monthly incidences from January 2020 to December 2020 was used to check the model performance. By comparing the 2 models, the optimal model can be selected. It is of great significance for disease prevention and resource allocation.

2 | DATA AND METHODS

2.1 | Data source

The cases of SS which were admitted to the Department of Immunology and Rheumatology of Nanjing Zhongda Hospital from January 2015 to December 2019 were collected. All the diagnoses were in accordance with the international classification diagnostic standard of pSS in 2002[10] and the classification diagnostic standard of pSS recommended by the American Rheumatology Society and European Anti-rheumatism Alliance in 2016.[11] Finally, 499 male cases and 4760 female cases were included.

2.2 | The analysis method

Based on the number of monthly cases at the Rheumatology Department of Nanjing Zhongda Hospital from January 2015 to December 2019, 2 models were established by using R language, and were applied to forecast the number of monthly cases from January 2020 to December 2020.

2.3 | SARIMA model

This feature is that it can process the data of seasonal time series, which is usually recorded as ARIMA (p, d, q)×(P, D, Q)$_s$ (p is the autoregressive order, d is the difference in times when the sequence is stable, q is the moving average order, P is the seasonal autoregressive order, D is the seasonal difference times, Q is the seasonal moving average order, s is the cycle length of the seasonal cycle).[12]

2.3.1 | Modeling method

The conventional modeling steps include 4 steps: stationarity test, model order determination, parameter estimation and model test, and sequence prediction.[13]

① Observe the period of the time series and determine the period length s.

② The stability of time series is ensured by difference, and the value of D is determined.

③ Determination of non-seasonal models by autocorrelation and partial autocorrelation p,q value.

④ The D, P and Q values of the seasonal model are determined by the sequence diagram, autocorrelation and partial autocorrelation diagram of seasonal decomposition.

⑤ Substitute the selected p, q, d and the possible values of P, Q, D into the SARIMA model.

⑥ The optimal model is selected according to the minimum value of Akaike information criterion (AIC) and the model without statistical significance of box Ljung test.

2.4 | Holt-Winters model

2.4.1 | Introduction to Holt-Winters model

This model is characterized by removing some random fluctuations, correcting the tendency of seasonality at the same time. It gives different weights to the data of each period, and reasonably forecasting the future development trend. The component form of Holt-Winters model consisted of 4 equations, namely the forecast equation and 3 smoothing equations.[14]

2.4.2 | Model equation

① The component form for the additive method is:

$$\hat{y}_{t+h|t} = \ell_t + hb_t + s_{t+h-m(k+1)} \quad (1)$$

$$\ell_t = \alpha(y_t - s_{t-m}) + (1-\alpha)(\ell_{t-1} + b_{t-1}) \quad (2)$$

$$b_t = \beta^*(\ell t - \ell_{t-1}) + (1-\beta^*)b_{t-1} \quad (3)$$

$$s_t = \gamma(y_t - \ell_{t-1} - b_{t-1}) + (1-\gamma)s_{t-m} \quad (4)$$

② The component form for the multiplicative method is:

$$\hat{y}_{t+h|t} = (\ell_t + hb_t)s_{t+h-m(k+1)} \quad (5)$$

$$\ell_t = \alpha\frac{y_t}{s_{t-m}} + (1-\alpha)(\ell_{t-1} + b_{t-1}) \quad (6)$$

$$b_t = \beta^*(\ell t - \ell_{t-1}) + (1-\beta^*)b_{t-1} \quad (7)$$

$$s_t = \gamma\frac{y_t}{(\ell_{t-1} + b_{t-1})} + (1-\gamma)s_{t-m} \quad (8)$$

where ℓ_t, b_t and s_t stand for level, trend and seasonal components, respectively, along with the corresponding smoothing factors α, β^* and γ. The seasonality is denoted by m, while k is the integer part of the fraction (h − 1)/m.[15]

2.5 | Statistical treatment

R4.1.1 was used to establish the SARIMA model, Holt-Winters model and drawing graphics. Mean absolute percentage error (MAPE), root mean square error (RMSE) and Theil's U-statistics were used in this study in order to compare the forecasting accuracy of the 2 models.

$$\text{Theil's U} = \frac{\sqrt{\sum_{i=1}^{N}(Y_i - F_i)^2}}{\sqrt{\sum_{i=1}^{N} Y_i^2} + \sqrt{\sum_{i=1}^{N} F_i^2}} \quad (9)$$

$$\text{MAPE} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{Y_i - F_i}{Y_i}\right| \times 100 \quad (10)$$

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{N}(Y_i - F_i)^2}{N}} \quad (11)$$

where Y_i is the real data, F_i are the forecasted values and N is the total number of observations.[16]

3 | RESULTS

The summary results are shown in Figure 1. According to Figure 1, the number of monthly cases at the Rheumatology Department of Nanjing Zhongda Hospital from January 2015 to December 2019 is relatively stable, with obvious periodicity and high incidence in winter.

3.1 | The analysis of SARIMA model results

Figure 1 shows the obvious seasonality, so the SARIMA model of seasonal difference is adopted in this study. A seasonal difference and a first difference were taken to obtain stationary data in this study, and then autocorrelation and partial autocorrelation diagrams of the stationary series were made. It is preliminarily determined that the SARIMA model is ARIMA(0,1,1) $(1,1,2)_{12}$. The optimal SARIMA model was determined by trying the parameters of different models. The results showed that the optimal model was ARIMA(0,1,1) $(2,1,1)_{12}$ and passed the box Ljung test ($\chi^2 = 17.949$, $P = .209$) which indicates that the fitting residual is a random variation sequence. Validation of model results are shown in Figure 2. The fitting results of ARIMA(0,1,1) $(2,1,1)_{12}$ were obtained by using R language analysis, as shown in Table 1.

3.2 | The analysis of Holt-Winters model results

The ets () function of R software was used for automatic prediction. This software automatically selects the model with the highest fitting degree to the original data. The results show that the Holt-Winter addition model produces better prediction accuracy of the model (Table 2).

3.3 | Comparison of model forecasting results

The 2 models were used to forecast the number of the monthly cases of SS from January to December 2020. Of the results predicted by both models, only the actual number of cases from February to April 2020 was not in the 95% confidence interval predicted by either model.

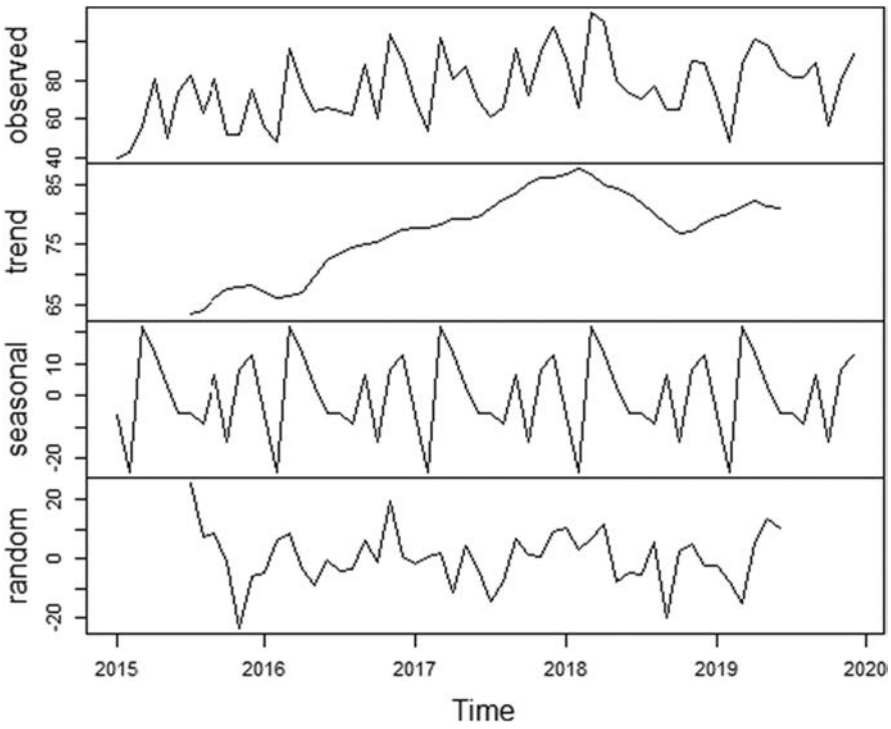

FIGURE 1 Decomposition of additive time series

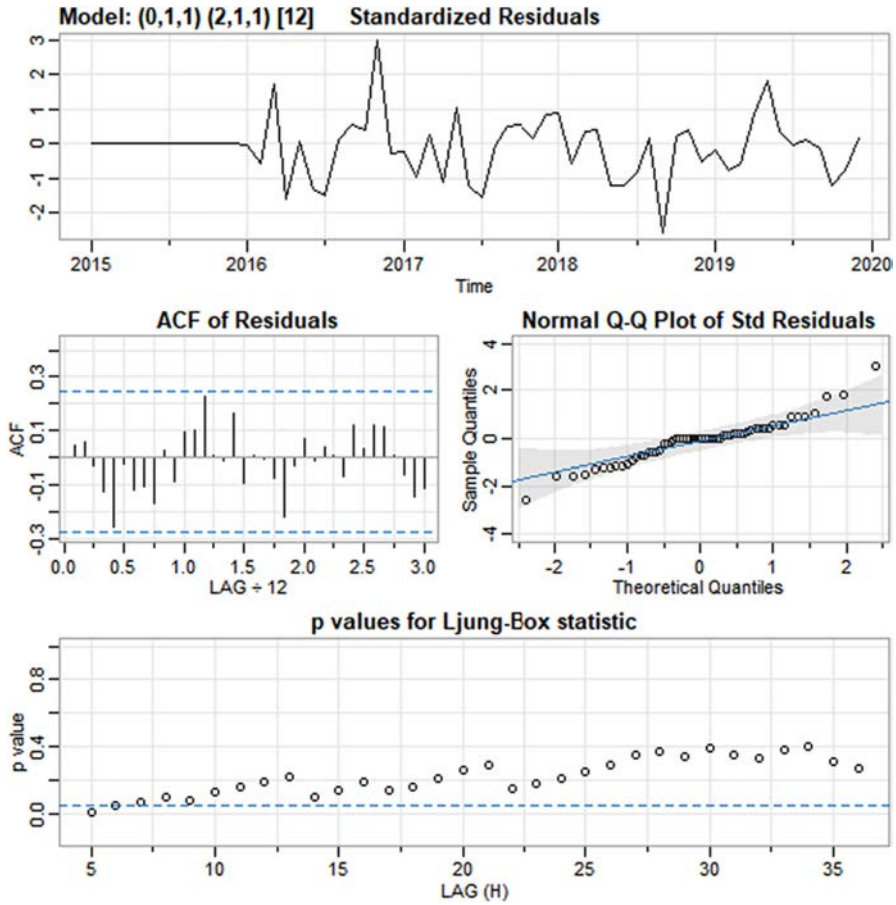

FIGURE 2 Model checking

		Effectiveness		Box-Ljung test	
	AIC	RMSE	MAPE (%)	χ^2	*P*
ARIMA(0,1,1)(1,1,2)$_{12}$	397.36	16.165	15.050	21.738	.084
ARIMA(1,1,1)(1,1,2)$_{12}$	397.92	16.054	14.766	20.447	.083
ARIMA(0,1,3)(1,1,2)$_{12}$	398.90	15.845	14.083	15.362	.222
ARIMA(2,1,1)(1,1,2)$_{12}$	398.54	16.247	14.643	18.735	.095
ARIMA(2,1,1)(2,1,1)$_{12}$	398.50	15.929	14.477	15.062	.238
ARIMA(0,1,1)(2,1,1)$_{12}$	397.36	15.102	14.014	17.949	.209

TABLE 1 Model effectiveness, test and model fitting results

Abbreviations: AIC, Akaike information criterion; MAPE, mean absolute percentage error; RMSE, root mean square error.

	Parameter			Fitting evaluation	
	Alpha	Gamma	Delta	RMSE	MAPE (%)
Holt-Winters addition model	0.302	2.099E-7	<0.001	11.062	11.561
Holt-Winters multiplicative model	0.009	0.001	0.197	12.838	13.276

TABLE 2 Evaluation and comparison of Holt-Winters fitting results

Abbreviations: MAPE, mean absolute percentage error; RMSE, root mean square error.

Overall, it was found that the 2 models predicted the number of monthly cases well within the acceptable levels. For the Holt-Winters addition model, RMSE, MAPE and U-statistics are 15.102, 14.014 and 0.140, respectively. For the SARIMA model, RMSE, MAPE and U-statistics are 11.062, 11.561 and 0.132, respectively. The coefficients were derived after removing the outliers. It is clear

that the Holt-Winters addition model produced the smallest error, as shown in Table 3 and Figure 3.

4 | DISCUSSION

As can be seen from Figure 1, the number of cases from February to April 2020 is significantly lower than that in previous years. In early 2020, COVID-19 broke out. In this period, Nanjing government implemented closed management. The complexity of medical procedures and the higher risk of medical treatment were the possible reasons for the decline in hospital case numbers.[17,18] According to Figure 1, it can see that the peak number of all cases of SS is in March and April. The valley values are all from January to February, and the possible reasons for the lowest values are as follows. (1) January to February of each year is the lunar new year. Influenced by traditional ideas, people think it is unlucky to go to the hospital for examination during the Spring Festival, resulting in the reduction of the number of hospital cases from January to February.[19] (2) March to April is the peak period of population mobility, people return to Nanjing to work one after another. It increases the accumulated patients who did not go to the hospital for examination from January to February.[20] In addition, it can be seen from Figure 1 that November December is also a relatively high incidence month of pSS. Some research shows that cold weather is an aggravating factor of SS, and windy weather is the most common weather condition affecting the symptoms of SS. These are obvious weather characteristics in spring and winter.[21]

Whether according to research or in terms of the actual situation at Nanjing Zhongda Hospital, during the season of high prevalence of SS, there are obviously not enough beds in the Rheumatology Department.[22] Some patients who need to be hospitalized often need to make appointments and wait until the last patient is discharged before they can be admitted, which often delays the best treatment time. In addition, during these seasons, such as autumn, patients are hospitalized for longer days, which not only increases the burden of disease on patients, but also increases the burden on hospital beds and workload for medical staff. Relevant departments often need to change their scheduling and increase their staff to take care of patients during these seasons.[23,24] In addition, for the diagnosis of the disease during these seasons, it is important to increase the number of medical examinations to reduce the rate of missed diagnoses.[25]

These suggest that the government needs to strengthen people's awareness of the prevention of high-risk diseases. This will reduce the incidence at the level of primary prevention. In seasons of high disease incidence, patients with SS need to focus on protection to reduce the burden of disease brought about by seasonal changes and to maximize their recovery.[26,27]

Many scholars have studied the disease prediction model. Some research shows that the ARIMA model is flexible in application, not bound by data types and has strong applicability. The SARIMA model is a model for relatively stable time series data, which integrates time trend, seasonal, periodic changes, random errors and other factors, quantifying the parameters of the model,[28,29] while the principle of the Holt-Winters model is relatively simple, and the prediction accuracy for diseases with periodic onset regularity is high.[30] It gives different weights to the distance of the data on the time line, which is suitable for predicting single time series data.[31] In this study, it is found that the MAPE, RMSE and Theil's U-statistics of the Holt-Winters addition model are less than those of the ARIMA(0,1,1)

TABLE 3 Comparison of prediction results of 2 models

		$ARIMA(0,1,1)(2,1,1)_{12}$		Holt-Winters addition model	
Month of 2020	Actual value	Estimate	95% CI	Estimate	95% CI
1	65	72	44–101	73	50–95
2	8	57	24–87	59	36–82
3	27	96	65–128	99	75–123
4	61	99	66–131	97	72–122
5	54	86	52–121	83	57–109
6	66	83	48–119	81	54–108
7	59	81	44–118	79	52–107
8	54	79	40–117	77	49–105
9	82	92	53–131	91	62–120
10	59	67	26–107	68	38–98
11	89	89	47–131	91	61–122
12	76	98	55–141	98	67–130
RMSE	15.102			11.062	
MAPE (%)	14.014			11.561	
U-statistics	0.140			0.132	

Abbreviations: MAPE, mean absolute percentage error; RMSE, root mean square error.

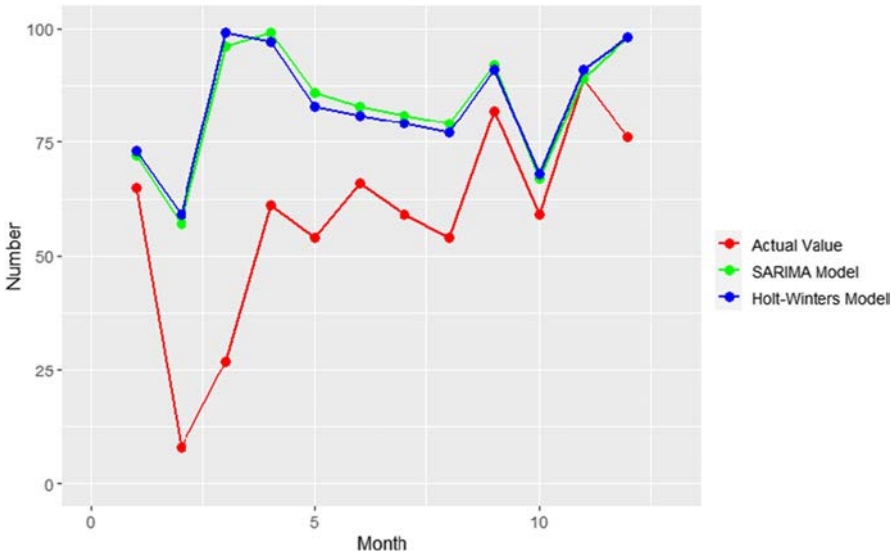

FIGURE 3 Model prediction comparison

$(2,1,1)_{12}$ model, and the prediction accuracy of the number of diseases in 2020 is also better than the SARIMA model. This may be caused by the characteristics of the model. In terms of model alone, the SARIMA model is more suitable for predicting data with stable change trend than the Holt-Winters model, while the Holt-Winters model is suitable for data with a single change trend. As shown in Figure 1, although the onset of pSS is obviously seasonal, the change is not stable, so some information will be lost in the process of establishment of the SARIMA model. Further, it can be seen from the Figure 1 that the original data will increase significantly in a specific season, and different weights are given to this model. Therefore, the Holt-Winter addition model is more suitable for forecasting the incidence of SS in this study.

In this study, the prediction effect of the Holt-Winters addition model is better than that of SARIMA for SS. However, it can be seen from Table 3 that the number of monthly cases from February 2020 to April 2020 is significantly different from that in previous years. In this paper, the calculation of Theil's U-statistics also excludes the data of these months. What is more, this study only uses the data of 5 years as the test set, and the sample size may be slightly insufficient. More samples are needed to create the training set. In addition, it is a hospital-based study, so there may be admission rate bias and detection signal bias.[32,33] These lead to the deviation between the real data and the recorded data, and also affect the prediction accuracy of the model. Therefore, more methods are needed to prove that the Holt-Winters addition model is better than SARIMA, such as expanding the sample size.[34]

The Holt-Winters model is established by using historical data without considering the interference of other factors. Therefore, the model has certain reference value for the prediction of pSS. However, in practical work, the model should be revised to improve the prediction accuracy of the model taking into account the interference of various external changes. At present, there is no method to treat SS; genetic factors, virus infection and sex hormones are the risk factors of the disease. The purpose of this study is to provide assistance in the rational allocation of medical resources and staff, clues for the prevention and treatment of this disease from data analysis.

CONFLICT OF INTEREST

None.

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ORIGINAL ARTICLE

Validation of the Korean Leeds satisfaction questionnaire in rheumatoid arthritis with Rasch models

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Abstract

Objectives: We conducted the cross-cultural adaptation and validation of the Leeds Satisfaction Questionnaire (LSQ) for patients with rheumatoid arthritis (RA) in Korea.

Methods: The adaptation of the LSQ from English into Korean was based on guidelines for cross-cultural adaptation for self-report measures. Patients with RA were recruited from an outpatient clinic of a university hospital in South Korea. Validation of the Korean-LSQ with Rasch models was carried out using WINSTEPS. Model fit was determined by Infit and Outfit statistics (≥0.50 and ≤1.50), including the separation index (≥2.00) and reliability index (≥0.80).

Results: The data set comprised 125 patients (82.4% female), with median (interquartile range) age 49.0 (37-57) years, and disease duration of 2.5 (1.2-3.8) years. The total and subscale scores of the Korean-LSQ demonstrated excellent or good test-retest reliability (0.88 for total, 0.71-0.82 for subscales), and items in the scale also revealed a high internal consistency ($\alpha = 0.93$). The six subscales of the Korean-LSQ were found to have a good fit to the Rasch model and good reliability (Person separation index = 2.63 and reliability index = 0.87; item separation index = 37.03 and reliability index >0.99). In addition, the unidimensionality of the scale was confirmed by the principal component analysis based on the Rasch residuals.

Conclusion: Fit to the Rasch model confirmed that the construct validity, reliability, and unidimensionality of the LSQ were preserved following the adaptation into Korean. The Korean-LSQ is a valid and reliable tool for measuring satisfaction with care in Korean patients with RA.

KEYWORDS
cross-cultural validation, Leeds Satisfaction Questionnaire, Rasch model, rheumatoid arthritis

1 | INTRODUCTION

The target of treatment for patients with rheumatoid arthritis (RA) is to achieve the remission or low disease activity state.[1,2] However, according to two studies,[3,4] approximately 12% and 38% of patients with RA do not achieve remission according to disease activity indices, solely because of a patient global assessment score greater than 1, despite having no signs of significant inflammation. A recent proposal has suggested that the management of RA should be guided by a dual treat-to-target strategy: the control of inflammation (biological remission), and the control of disease impact (symptom remission).[5] In addition, patient satisfaction is an

important indicator of quality of care.[6] Satisfaction with care is a predictor of (or associated with) functional status, overall well-being, and future health-related behaviors in various chronic diseases.[7–9] Patient satisfaction has also been a predictor of increased adherence to treatment, which is associated with active and engaged self-management of long-term conditions.[10,11] Increased patient satisfaction improves patients' management of RA, because patients are more likely to be able and willing to actively self-manage their health conditions.[12] Therefore, increased satisfaction can support patients to feel more able to take responsibility for their health and can benefit from associated improved health outcomes.[13] Patient satisfaction can also fluctuate based on health conditions, including differences in patient satisfaction based on the number of health conditions that patients live with.[14] Patient satisfaction is therefore a key outcome of interest to improve quality of life in people with RA.

Care-related factors associated with higher patient satisfaction in patients with RA include being treated with respect and having their feelings respected, having medical issues explained clearly, and being able to access the clinic easily in person or via telephone.[15] Patient satisfaction is also associated with patients being able to access their preferred mode of contact with clinics, telehealth options that are easy to use and options for support that reduce travel time.[16] However, patient satisfaction with these factors also differed between health conditions, suggesting the need for condition-specific ways of capturing patient satisfaction.

There are challenges in measuring patients' satisfaction with their care. Qualitative research methods can offer the opportunity to generate rich data about how satisfied patients are with their care. However, exploring patient satisfaction this way is resource heavy and does not allow for reliable comparison between patients or over time. Therefore, understanding patient satisfaction using a questionnaire can provide a means to inform person-centered care and service improvements. Moreover, a questionnaire for assessing patient satisfaction with care for patients with RA in Korea is needed.

The Leeds Satisfaction Questionnaire (LSQ)[17] is a patient-completed questionnaire designed to measure satisfaction among patients attending a rheumatology outpatient clinic. It was developed in the UK and comprises 45 items grouped into six subscales: general satisfaction, information, empathy, technical competence, attitude, access, and continuity. This study aimed to undertake a cross-cultural adaptation of the LSQ into Korean, and validate the Korean-LSQ in patients with RA. The LSQ was selected as the most appropriate measure for this study because it was originally developed with patients with RA.[17,18] It has demonstrable validity and reliability including responsiveness in randomized controlled trials in people with RA[18–21] and other rheumatic conditions.[22,23] The LSQ has also been successfully translated into other languages, demonstrating cross-cultural validity,[19,24] therefore setting this tool apart from other measures of patient satisfaction.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This was a cross-sectional study involving cross-cultural adaptation of the LSQ into Korean, followed by a survey to validate the adapted tool with Rasch models.

2.1.1 | Leeds satisfaction questionnaire

The LSQ is a patient-reported outcome questionnaire developed to measure satisfaction among patients attending an outpatient rheumatology clinic.[17] The patients' response for their level of agreement was based on 45 questions, with responses on a scale between 1 (strongly agree) and 5 (strongly disagree). As mentioned above, the LSQ consists of six subscales The scores were entered in the appropriate boxes on the analysis sheet, under columns A, B, C, and so on (Table S1). This automatically sorted the statement into the correct groups. If the box contains an 'r', it indicates that the score must be re-coded. This provided a score out of 5 for each subscale. Scores above 3 indicated satisfaction, and below 3 signified dissatisfaction. The mean results for each subscale were then combined to provide a total measure of overall satisfaction. It takes about 15 minutes for the patient to complete.

2.1.2 | Cross-cultural adaptation

The cross-cultural adaptation of LSQ into Korean was performed with standardized guidelines of patient-reported outcome measures suggested by Beaton et al.[25] The forward translation from English into Korean was performed by two independent translators. A third unbiased person held a meeting to discuss translation differences, and one combined version was produced together with a report documenting the process and how issues were resolved. Back-translation was performed by two bilingual back-translators whose mother tongue was English and who were blinded to the original version. This was a process of validity checking to ensure that the translated version accurately reflected the item content of the original version. The expert committee reviewed all the versions and components of the questionnaire and all translated versions, discussing discrepancies raised in previous stages, and a consensus was reached on all items. The pre-final version of the Korean-LSQ was produced for field testing. The field test of the adapted Korean-LSQ included 30 patients recruited from the rheumatology outpatient clinic at a university hospital in Korea. These 30 patients completed the Korean-LSQ and were asked what they thought was meant by each questionnaire item and provided their response.

2.1.3 | Study population

Patients were recruited from the rheumatology outpatient clinic at a university hospital in Korea in person. All consented patients were

included consecutively in the study. The inclusion criteria were as follows:

- Korean patients with RA diagnosed according to the 1987 ACR and the 2010 ACR/EULAR classification criteria for participants;[26,27]
- 18 years of age or older;
- willingness to complete the questionnaire.

The exclusion criterion was a diagnosis of an additional rheumatic disease.

2.1.4 | Cross-cultural validation

Participants then completed the final translated version of the Korean-LSQ. Patient demographic data such as age, gender, educational background, and self-reported disease duration were also collected. Upon agreement, we asked patients to reply by mail after completing the same questionnaire 2 weeks after the first survey to estimate test-retest reliability.

2.2 | Ethical consideration

This study was approved by the Institutional Review Board of Hanyang University Hospital (HYUN 2015-07-026-001). All patients provided informed consent.

2.3 | Statistical analyses

Descriptive statistics were summarized using measures of central tendency (median) and interquartile range (IQR) for continuous data and frequencies (%) were for categorical data. The internal consistency reliability (ICR) is assessed by estimating the Cronbach's α to measure inter-relatedness of the items. A value of α greater than 0.7 is considered an acceptable ICR among items.[28] Test-retest reliability was assessed using intra-class correlation coefficients based on patient completion of the questionnaire 3-5 days apart.[29]

Testing validity with Rasch models

The Rasch model provides formal representation of fundamental measurement;[30] so when data from the questionnaire are shown to fit to the model, it implies they have a criterion-related construct validity,[31] objectivity,[32] reliability,[33] and statistical sufficiency.[34] Rasch analysis comprised three phases: (a) initial testing of all individual 45 items for fit to the Rasch model, (b) testing each subscale for fit to the Rasch model, and (c) final testing of the overall scale, using subscale scores as "testlets" for fit to the Rasch model.

To assess unidimensionality, principal component analysis (PCA) of Rasch item residuals was used to examine if the Rasch model explains at least 40% of the variance while the eigenvalue of the first residual factor does not exceed 3.[35] The fit of the observed data to the Rasch model was assessed by the mean-square (MnSq) of infit and outfit.[36,37] Infit focused on the difference between the observed and expected response for items with difficulty level near a persons' ability level. Outfit includes the differences for all items, irrespective of how far the item difficulty is from the ability of the person.[30] An item MnSq fit statistic of the range from 0.5 to 1.5 is an acceptable fit to the Rasch model.[38,39] Positive and high values (>0.3) of point-measure correlation indicated that the items were working in the same direction to measure a single basic construct.[40] In the Rasch model analysis, reliability indices above 0.8 and 0.9, and equivalently, separation indices larger than 2 and 3, were considered good and excellent, respectively.[40]

After performing PCA to examine the unidimensionality of the subscales, the local independence was assessed in each subscale.[40,41] Generally, standardized Rasch residual correlation values greater than 0.7 indicate local dependency between items because they indicate that more than 50% of the variance is shared between items.[42] Following the fit to the model and reliability tests, differential item functioning (DIF) analysis was carried out to examine the invariance of measurement in each subscale. DIF logit scores were compared for each item between men and women using the Welch t test.[43] In further analysis of each subscale, the Rasch rating scale functioning was analyzed to examine the appropriateness of the five-point rating scale of the Korean-LSQ.

General data analyses were conducted using the R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria), and the Rasch model analysis, which was carried out using the Rasch computer program WINSTEPS version 3.91.1 (http://www.winsteps.com/winsteps.htm). All tests were two-sided, and values of P less than 0.05 indicated statistical significance.

3 | RESULTS

3.1 | Cross-cultural adaptation

Issues regarding translation included ambiguity, inexactness of certain concepts, or idiomatic expressions. For example, patients who participated in field tests had difficulty figuring out whom they were referring to as "they" or "the person I see in the clinic". Those two terms were then replaced with "my physician" because, in Korean medical services, the person the patient sees in the outpatient clinic is usually the physician. All issues and resolutions are described in Table S2.

3.2 | Baseline characteristics of patients

Patients with RA (n = 125) from an outpatient clinic in a tertiary referral hospital who completed the Korean-LSQ were included. Their clinical and demographic characteristics are presented in Table 1.

The median age was 49 years, and 103 (82.4%) were women. The median disease duration of RA was 2½ years, and the median education duration was 12 years. Among 125 patients, 15 (12%) were treated with biologic disease-modifying anti-rheumatic drugs. Of the patients who completed the first survey, 107 (85.6%) completed the second survey 2 weeks later.

3.3 | Descriptive statistics of Korean-LSQ and its ICR

Descriptive statistics of each scale and total scores were given using a five-number summary (min, Q_1, median, Q_3, max) (Table 2). The median (IQR) of the Korean-LSQ total scores was 3.81 (3.51-4.09). The median satisfaction score was lowest (3.50) in "access and continuity", and highest (4.25) in "technical competence". The ceiling and floor effects were observed in a range of 0%-10%, so they were considered negligible.

In terms of ICR, the overall Cronbach's α of the Korean-LSQ was 0.94, which supported an acceptable ICR among items. Cronbach's α in each subscale ranged from 0.67 to 0.84, except for general satisfaction (α = 0.58) involving three items only. After removing the three items, the overall Cronbach's α decreased to 0.92, supporting an acceptable ICR also. Intra-class correlation coefficient of the total scores was 0.89 and of the corresponding subscales ranged from 0.71 to 0.82, demonstrating an excellent or good test-retest reliability between the two measures (Table 2).

TABLE 1 Baseline characteristics of study population (n = 125)

Variables	
Demographics	
Age (years)	49.0 (37.0-57.0)
Female	103 (82.4)
Disease duration (years)	2.5 (1.2-3.8)
Education duration (years)	12.0 (12.0-16.0)
Employed	76 (60.8)
Regular exercise	46 (36.8)
Smoking (n = 124)	
Non-smoker	94 (75.8)
Previous smoker	15 (12.1)
Current smoker	15 (12.1)
Disease status	
DAS28-ESR	3.2 (2.5-4.6)
DAS28-CRP	3.0 (2.2-3.9)
Patient GH VAS (mm)	40.0 (20.0-50.0)
Physician GH VAS (mm)	15.0 (5.0-30.0)
Pain VAS (mm)	30.0 (20.0-50.0)
Sleep disturbance VAS (mm)	10.0 (0.0-50.0)
Fatigue VAS (mm)	30.0 (0.0-50.0)
HAQ-DI (n = 124)	0.4 (0.0-0.9)
EQ-5D	0.8 (0.8-0.9)
Medication	
Methotrexate	100 (80.0)
Corticosteroid	100 (80.0)
Biologic DMARDs	15 (12.0)

Note: Categorical data are presented as frequency (%), and continuous data are presented as median (interquartile range).

Abbreviations: DAS28-ESR, disease activity score in 28 joints with erythrocyte sedimentation rate; DAS28-CRP, disease activity score in 28 joints with C-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; EQ-5D, EuroQol-5 dimension; GH, General health; HAQ-DI, health assessment questionnaires-disability index; VAS, visual analog scale.

3.4 | Cross-cultural validation in patients with RA using the Rasch model

Initial testing of the individual 45 items for fit with Rasch model

Table S3 presents the results of the individual item fit and domain fit statistics. Most individual items (40 of the 45) displayed an acceptable fit to the model. Five items deviating from the model with infit and outfit greater than 1.50 were:

Item 1: *They do not seem to listen to anything I tell them during my consultation.*

Item 2: *I feel that I'm in good hands when I come to the clinic.*

Item 10: *Visiting the clinic is not a stressful occasion.*

Item 28: *I am encouraged to ask questions about my arthritis.*

Item 44: *I see the same person nearly every time I come to clinic.*

In addition, the person separation index of 4.14 indicated that the Korean-LSQ items separated the 125 participants into five to six statistically distinct satisfaction levels, suggesting the patient's well-differentiated satisfaction levels. Person reliability (0.94) confirmed the high reliability of the Korean-LSQ items. Item separation and reliability indices were estimated as 6.52 and 0.98, respectively, supporting that the item's discrimination power was excellent (Table S3).

Testing of each subscale for fit with the Rasch model

Following initial analysis for all 45 items, Rasch PCA on item residuals was conducted in each subscale of the Korean-LSQ. Most subscales satisfied the criterion of unidimensionality (explained variance: 41.4%-58.3%, eigenvalue of first residual factor: 1.39-2.17) except "Technical competence" (explained variance: 38.6%, eigenvalue of first residual factor: 1.88). (Table 3). Any evidence of local dependence was not observed in other subdomains except for "General satisfaction" with a magnitude of standardized Rasch residual correlations around 0.7: Item 5 with Items 37 and 13 (−0.72 and −0.68, respectively) (Table S4).

Five items deviating from the model with both infit and outfit MnSq greater than 1.50 in the initial analysis were still out of range for infit or outfit MnSq in the analysis of each subscale (Table 4): Item 28 in "Information", Item 10 in "Empathy",

TABLE 2 Descriptive statistics, internal consistency, and test-retest reliability

	Score					Floor effect (%)	Ceiling effect (%)	ICR (α)	ICC (95% CI)
	Min	Q_1	Median	Q_3	Max				
General satisfaction	2.00	3.33	3.67	4.00	5.00	0.00	5.60	0.58	0.74 (0.64 to 0.81)
Information	1.67	3.50	3.83	4.00	5.00	0.00	2.40	0.84	0.79 (0.70 to 0.85)
Empathy	2.13	3.25	3.75	4.00	5.00	0.00	1.60	0.72	0.77 (0.68 to 0.84)
Technical competence	2.75	3.88	4.25	4.63	5.00	0.00	8.80	0.81	0.71 (0.60 to 0.79)
Attitude	1.83	3.50	3.83	4.17	5.00	0.00	5.60	0.67	0.79 (0.71 to 0.85)
Access & continuity	2.00	3.13	3.50	4.00	5.00	0.00	3.20	0.75	0.82 (0.75 to 0.87)
Overall domains[a]	2.22	3.51	3.81	4.09	4.90	0.00	0.00	0.90[b]	0.89 (0.83 to 0.92)

Abbreviations: α, Cronbach's α; CI, confidence interval; ICC, intra-class correlation coefficients (excellent, >0.75; good, 0.6-0.75; fair, 0.4-0.6; poor, <0.4); ICR, internal consistency reliability; Max, maximum; Min, minimum; Q_1, first quantile; Q_3, third quantile.

[a]The satisfaction score in overall domains is calculated as the mean of subscale scores.

[b]Cronbach's α for six subscale scores is 0.90, but 0.94 for all single 45 items in the whole domain.

TABLE 3 Rasch principal component analysis of each subscale of the Korean-LSQ

Subscale	Variance explained	Unexplained variance	First contrast explained variance	First contrast eigenvalue
General satisfaction	57.8%	42.2%	28.0%	1.99
Information	41.4%	58.6%	10.6%	2.17
Empathy	45.7%	54.3%	11.9%	1.76
Technical competence	38.6%	61.4%	14.5%	1.88
Attitude	47.1%	52.9%	12.2%	1.39
Access & continuity	58.3%	41.7%	10.4%	1.99
Overall Korean-LSQ (using subscale scores)	71.5%	28.5%	9.1%	1.92

Item 2 in "Technical competence", Item 1 in "Attitude", Item 44 in "Access & continuity". All of these items produced acceptable point-measure correlations greater than 0.3 in the analysis of each subscale.

Next, in each subscale, DIF logit scores were compared for each item between groups of men and women. In most subscales, there were no DIF in the patient's satisfaction level except for two of the 45 items; Item 34: Prescriptions for new tablets are given without any explanation ($P = 0.003$) in "Information" and Item 41: Sometimes the person I see in clinic is too busy to spend enough time with me ($P = 0.010$) in "Attitude" (Table S5).

Finally, Rasch rating scale functioning analysis in each subscale revealed that most distributions of the observed frequencies were negatively skewed; only 2%-5% of the patients in the first category, while 28%-48% of the patients in the fourth category and 21%-43% of patients in the fifth category. In all subscales, outfit MnSq of each rating category was less than 2.0 except the first category. Disordering of thresholds (structural calibration) was detected in three subscales ("Information", "Technical competence", and "Attitude") where the threshold of "not sure" is reversed with an adjacent category "agree" or "disagree." However, collapsing adjacent categories is viewed as unnecessary because the average measure of each rating category increases as the rating value increases (Table S6).

Testing the overall scale using domain scores (testlets)

Following Rasch analysis in each subscale, the overall scale utilizing subscale scores (testlets) was shown to fit the Rasch model. PCA based on the residuals revealed that the Rasch testlet model explained 71.5% of the variance, and the first contrast explained 8.4%-9.1% of the variance (eigenvalue = 1.92-1.95), thereby supporting unidimensionality of the Korean-LSQ (Table 3). Infit and outfit MnSq values were 0.66-1.49 and 0.66-1.45, respectively, suggesting an acceptable model fit. Point-measure correlations were between 0.79 and 0.84, supporting an acceptable fit to the Rasch testlet model. In addition, the person separation index of 9.91 indicated that the Korean-LSQ items separated the 125 participants into 13 or 14 strata, indicating the patient's well-differentiated satisfaction levels. Person reliability (0.99) confirmed the high reliability of the Korean-LSQ subscales. Item separation and reliability indices were estimated as 2.91 and 0.98, respectively, supporting high confidence in the item's discrimination power (Table 4).

4 | DISCUSSION

This study generated a valid version of the LSQ to assess the satisfaction with care in patients with RA in South Korea. In the first analysis, five items (out of 45) exhibited lack of fit to the model

TABLE 4 Rasch model analyses of Korean-LSQ

Item	Measure	Mean square		Point measure correlation	Rasch separation		Rasch reliability	
		Infit	Outfit		Person	Item	Person	Item
General satisfaction (three items)								
5	1.30	1.10	1.16	0.74	1.28	6.58	0.62	0.98
13	−1.16	0.98	0.84	0.68				
37	−0.14	0.90	0.86	0.71				
Information (12 items)								
4	−0.42	1.41	1.40	0.47	2.34	5.21	0.85	0.96
6	0.81	0.99	1.01	0.59				
7	−0.40	1.32	1.17	0.48				
8	0.25	1.34	1.32	0.55				
11	0.45	0.73	0.69	0.66				
15	−0.36	1.05	0.92	0.53				
16	−0.83	0.72	0.70	0.54				
23	0.05	0.70	0.71	0.65				
28	1.10	1.61	2.07	0.37				
34	−1.09	0.88	0.76	0.55				
35	−0.09	1.02	0.98	0.54				
42	0.52	0.72	0.75	0.64				
Empathy (eight items)								
3	1.28	1.14	1.18	0.56	1.59	6.91	0.72	0.98
10	0.59	1.87	2.26	0.32				
17	−0.72	0.80	0.77	0.53				
18	0.46	0.84	0.93	0.61				
24	−1.33	0.84	0.78	0.54				
25	−0.32	0.79	0.87	0.59				
30	0.60	0.93	0.95	0.64				
32	−0.56	0.59	0.58	0.56				
Technical competence (eight items)								
2	0.32	1.57	1.37	0.61	1.82	4.06	0.77	0.94
9	0.08	0.85	0.72	0.66				
21	−0.35	1.15	0.94	0.59				
22	−0.69	1.19	1.02	0.57				
27	−0.80	0.70	0.63	0.62				
33	0.60	0.94	1.05	0.59				
39	−0.25	1.03	0.93	0.62				
40	1.08	1.26	1.65	0.58				
Attitude (six items)								
1	−1.61	2.36	2.26	0.34	1.38	6.76	0.66	0.98
12	0.36	0.86	0.82	0.61				
20	−0.03	0.74	0.80	0.58				
26	0.37	1.12	1.14	0.55				
41	−0.24	0.94	0.92	0.61				
45	1.15	0.87	0.86	0.68				
Access & continuity (eight items)								
14	0.81	0.78	0.76	0.72	1.87	9.38	0.78	0.99

(Continues)

TABLE 4 (Continued)

Item	Measure	Mean square		Point measure correlation	Rasch separation		Rasch reliability	
		Infit	Outfit		Person	Item	Person	Item
19	−0.28	1.05	1.14	0.52				
29	0.77	0.70	0.69	0.73				
31	0.96	0.83	0.84	0.70				
36	0.91	0.99	0.98	0.66				
38	−2.25	1.21	1.91	0.26				
43	0.56	1.07	1.13	0.61				
44	−1.49	1.64	1.52	0.32				
Rasch testlet analysis (using six subscale scores)								
General satisfaction	−0.05	0.66	0.66	0.81	9.91	2.91	0.99	0.98
Information	−0.16	1.44	1.42	0.84				
Empathy	0.22	1.06	1.06	0.82				
Technical competence	−0.13	1.10	1.14	0.80				
Attitude	−0.08	0.98	1.00	0.81				
Access & continuity	0.25	1.49	1.45	0.79				

with infit and outfit greater than 1.50. However, when the LSQ was analyzed as a six-subscale questionnaire, it displayed good fit to the model.

Current treatment recommendations for RA include shared decisions between patients and rheumatologists as an overarching principle.[1,2] In terms of shared decision-making process, satisfaction with care is important because it is likely to be associated with adherence to treatments and self-management activities.[44] Recent studies have shown that satisfaction with care and adherence to treatment were highly associated with likelihood of achieving low disease activity or remission.[37] Also, patient satisfaction has been shown to be associated with tapering glucocorticoids in patient with RA.[45] The Korean-LSQ would help to assess different aspects of satisfaction with care in patients with RA. Tools for assessing different aspects of patient satisfaction are scarce and different studies assess patients' satisfaction differently, some asking only one or two questions.

The Korean-LSQ is a valid and reliable tool for measuring satisfaction with care among Korean patients with RA; however, this study has several limitations. First, the study population is not a random sample, so selection bias cannot be ruled out. However, to reduce the bias, all consented patients were included consecutively in the study according to the inclusion and exclusion criteria. Second, not all individual items did fit well, but subscales (as "testlets") of the Korean-LSQ supported an acceptable fit to the Rasch model. Rasch PCA based on subscale also revealed a robust unidimensional nature of the Korean-LSQ. Third, only internal validity and test-retest reliability were assessed in this study. External validity, for example, comparisons with other outcomes, would have added another confidence level. Finally, satisfaction may depend on the patient's cultural background. The Korean-LSQ was adapted to the Korean language and culture in the process of cross-cultural adaptation. However, some issues in the cross-cultural adaptation process were due to differences in the style of formulating questionnaire items in English and Korean. In Korean, the passive voice is infrequently used and discouraged because of the uncertainty of the doer. The expert committee discussed and solved the problems by finding Korean equivalents that would be comprehensible and accurate from a medical perspective (Table S2).

Our study was based on the standardized guidelines for cross-cultural adaptation of patient-reported outcome measures.[46] Furthermore, several tests of validity and reliability were conducted to ensure robust conclusions. Finally, a valid Korean-LSQ that could assess the patient satisfaction of Korean patients with RA was successfully generated. This will be a useful tool to understand RA patients' satisfaction around aspects of their care, and to evaluate outcomes in clinical studies.

In conclusion, a thorough validation process has established the Korean-LSQ as a valid and reliable tool. Therefore, the test provides an accurate measure of patient satisfaction on care for Korean patients with RA. This tool can help to assess patients' satisfaction in clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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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

The effect of rheumatoid arthritis on upper extremity functions: A kinematic perspective

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Abstract

Aim: To examine the global upper extremity kinematics in 3D while performing "jar opening motion" in Rheumatoid Arthritis (RA) and to compare these with healthy individuals.

Method: Twenty-four women (12 healthy, 12 RA) were included. Evaluations were made with a JAMAR dynamometer, Health Assessment Questionnaire, and 3D kinematic analysis of global upper extremity during "jar opening motion." The time taken during "jar opening motion" was analyzed in 2 parts (Part 1, Part 2), with total time: part 1 + part 2. In addition, shoulder-to-table distance; elbow flexion angle; wrist extension angle; the area scanned and angular rotation by arm, forearm and hand were used in the analysis.

Results: Between groups, there was a statistical difference in: bilateral hand grip strength; part 1, part 2, total time; shoulder-to-table distance; elbow flexion angle; the area scanned by hand; angular rotation of arm and hand in favor of the healthy group ($P < .05$). In stepwise multiple regression analysis, the most predictive variable for disability was elbow flexion, explaining 53.9% of disability.

Conclusion: Compared to healthy individuals, individuals with RA have slower motion, more elbow flexion, less hand grip strength, circular pattern in hand, rotation in arm and hand. Increased disability may result in greater load on elbow flexion.

KEYWORDS
kinematics, motion, rheumatoid arthritis, upper extremity

1 | INTRODUCTION

Rheumatoid Arthritis (RA), a chronic progressive inflammatory disease, can affect any joint symmetrically, but mostly wrist and little finger joint involvement is seen.[1] Upper extremity involvement is around 80%–90% and the involvement is usually seen in the early stages of the disease.[2,3] RA affects approximately 1% of the world population and is 3 times more common in women than men.[4]

The hands play a very important role in performing various daily and professional activities, including functions such as grasping and pinching.[5,6] Good positioning of the hand during performance and good upper extremity stabilization are essential for effective upper extremity function. This can be achieved with good proximal muscle control.[7] Adequate joint excursion, muscle strength and endurance, contributes to the successful completion and coordination of various holding functions.[5,6] Weakness in upper extremity and hand grip strengths and decreased range of motion of wrist and shoulder joints have been associated with upper extremity disability, which causes various limitations in participation in many physical activities.[7] Patients with RA also complain of these

symptoms, which cause them to have more difficulty in performing activities of daily living.[8]

In a previous study, it was found that upper extremity sensorimotor deficits of RA patients compared with healthy individuals were global, and it was stated that these deficits decreased upper extremity functionality and increased disability in these patients.[9] The majority of studies evaluating the upper extremities of individuals with RA examines the joints in isolation rather than "global" (ie, multijoint) upper extremity assessments, in which many muscle groups and joints are included for functional integrity.[10–12] Current measurements for range of motion in RA are still based on traditional goniometric assessments,[13] whereas, global upper extremity assessment may reveal more realistic data in estimating upper extremity performance.[9] Many joint deformities in RA have moved away from their original plane of motion, and therefore it is more difficult to accurately assess motion in individuals with RA using hand-held goniometers.[14–17] Due to the complexity of 3D movement patterns of the anatomical structures and the joints, 3D measurements may be the ideal method for determining the functional range of motion of the upper extremity joints.[12] Repeatable tests and clinical examinations confirm that these methods are feasible and practical in determining the true functional range of motion of normal and deformed structures. [14–17]

The aim of this study is to examine the global upper extremity kinematics in 3D while performing the jar opening motion, which is an activity that is frequently used in daily life and reported that they have difficulties/inability to do so, in order to evaluate the presence or effect of global motor deficits in the upper extremities in individuals with RA and to compare these with healthy individuals. Our hypothesis is that individuals with RA have global (multijoint) upper extremity motor disability, and this deficit contributes to upper extremity and hand dysfunction and disability.

2 | METHODS

In our study, which was planned as a cross sectional study, individuals with RA were evaluated by comparing with healthy controls. Participants consisted of 2 groups as RA group (n: 12) and healthy group (n: 12).

2.1 | Participants

A total of 24 women, 12 healthy and 12 with RA diagnosed according to the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria, were included in the study. Inclusion criteria: (a) be in the age range of 18–65 years; (b) volunteer to participate in the study; (c) the dominant side is right; (d) established RA of at least 1 year duration;[18] (e) stable drug therapy for at least 3 months; (f) have a female gender. Exclusion criteria: (a) having another disease that may affect physical condition; (b) having a history of upper extremity injury or surgery in the last 1 year; (c) cognitive disability causing inability to cooperate; (d) being pregnant; (e) concurrent autoimmune or inflammatory disease; (f) diseases affecting the central nervous system (eg, multiple sclerosis, Parkinson's disease); and (g) serious psychiatric conditions (eg, psychotic disorders). Participants who could not understand and follow the experimental instructions were also excluded from the study.

Ethics approval of the study was obtained from the local Clinical Research Ethics Committee at the board meeting dated 02.11.2021 and numbered 20. Verbal information was given to all individuals and an informed consent form was signed.

2.2 | Evaluations

All assessments were performed by the same investigator according to standardized test protocols and in the same conditions. After the demographic data were recorded, hand grip strength was evaluated with a JAMAR dynamometer (Sammons Preston); disability was assessed with the Health Assessment Questionnaire (HAQ). Finally, after all the necessary preparations were made, the global upper extremity kinematics of all participants were evaluated in 3D during the "jar opening motion." The 3D processing and examination of the recorded images were carried out in the Simi Motion Analysis Program. All assessments were performed in the afternoon part of the day to minimize potential performance biases related to fluctuating characteristic of RA. Evaluations took approximately 40–45 minutes.

2.2.1 | Hand grip strength

Hand grip strength measurements were performed with a JAMAR hand dynamometer in accordance with the standardized instructions of the American Society for Surgery of the Hand and the American Society of Hand Therapists. Participants sat in an upright position in a standard chair with their backs not touching the chair. The shoulder was in adduction, the elbow was in 90° flexion, and the forearm was in a neutral position. The wrist was in the position between 0° and 30° dorsiflexion and 0° and 15° ulnar deviations. The dynamometer was placed on the palms of the participants with the proximal and distal interphalangeal joints flexed and the thumb abducted to 90°. Evaluation was started with the dominant hand. Participants were asked to hold the dynamometer for 5 seconds. The measurement was repeated 3 times with 1-minute rest intervals and recorded in kilograms. The mean value was used in the analyses.[19]

2.2.2 | HAQ

HAQ consists of 20 questions and 8 sections related to activities of daily living. These sections are dressing, arising, eating, walking, hygiene, reach, grip, and activities. Total scoring is between 0–3. Higher scores indicate worse function and greater disability.[20]

2.2.3 | 3D kinematic analysis

The schematic display of the experimental setup for the 3D kinematic analysis during the jar opening motion is in Figure 1. Participants performed the "jar opening motion" in a standing position from the beginning to the end, in order to be suitable for the movement form they perform during their daily lives. Before any image was recorded, a total of 3 reflective markers were placed on the participant's dominant upper extremity anatomical points (acromion, humerus lateral epicondyle and ulna styloid process).

In addition, in order to determine the position of a segment with 6 degrees of freedom (3 axis translation + 3 axis rotation) in 3D space, rigid materials that attach tightly to the segment and have at least 3 fixed pointers on it were used.[21] For this purpose, in addition to the markers placed on the anatomical points, 3 more reflective markers were placed on the upper arm, forearm and hand to be fixed on the same plane (Figure 2). During the jar opening motion, we calculated angles at the upper arm, forearm and hand segments using Cardan angles of an x, y'-z'' rotation sequence.[22] All computing was performed by Matlab software.

Participants were asked to open the lid of a fixed standard jar on a fixed standard table. The image of the movement was recorded with two high-speed (Basler A602f-HDR, 100 Hz, GER) cameras. The 3D analysis of the recorded images was carried out in the Simi Motion Analysis Program (SIMI 7.5 Reality Motion Systems GmbH, Germany). Participants started the "jar opening motion" with the start command and completed the motion with the jar lid fully opened. During the motion, the time was recorded in milliseconds. The time obtained during the "jar opening motion" was analyzed in 2 parts. The moment when the jar lid started to open was determined as the cut point. Part 1 time: from starting command to the first opening moment of the jar lid. Part 2 time: the first opening moment of the jar lid to the completed moment of opening the jar lid. Total time: part 1 time + part 2 time (Table 1).

In addition, the following data were used in the analysis:

- shoulder-to-table distance (cm)
- elbow flexion angle (°)
- wrist extension angle (°)
- the area scanned by arm, forearm and hand on the horizontal, frontal and sagittal planes
- angular rotation of arm, forearm and hand in transverse, sagittal and vertical axes.

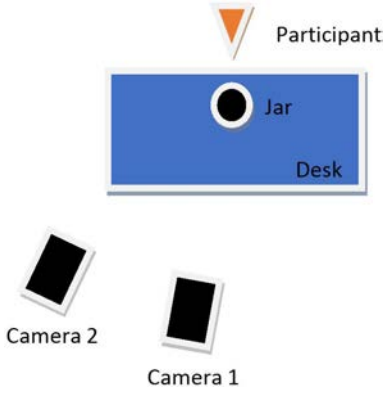

FIGURE 1 Schematic display of the experimental setup for the 3D kinematic analysis during the jar opening motion.

2.3 | Statistical analysis

As a result of the power analysis based on the results of hand grip strength results in the reference study,[23] it was calculated that 95% power could be obtained at a 95% confidence level when a minimum of 22 subjects were included (minimum 11 per group; *d*: 1.45). The data were analyzed using IBM SPSS Statistics vn.22 software. Continuous variables were stated as median (min-max) values and categorical variables as number and percentage. The Mann-Whitney U test was used to compare the independent group differences. Relationships between HAQ and other continuous variables in the RA group were evaluated with Pearson correlation analysis and Spearman's rank correlation according to whether they had a normal distribution or not. Correlation was categorized as low (*r*: 0.10-0.29), moderate (*r*: 0.30-0.49), or high (*r*: 0.50-1.00).[24] In order to determine the predictive power of the part 2 time, total time and forearm angular rotation (transverse, sagittal and vertical axes) independent variables, the "stepwise multiple regression" analysis method was used. A value of $P < .05$ was accepted as statistically significant.

3 | RESULTS

The demographic and descriptive data of the participants are shown in Table 2. There was a difference between the groups in terms of age, body weight and body mass index (Table 3).

When the data were analyzed between groups, there was a statistical difference in: hand grip strength right (*P*: .001) and left (*P*: .001); part 1 time (*P*: .032), part 2 time (*P*: .038) and total time (*P*: .007); shoulder-to-table distance in the starting command (*P*: .015), in the first opening moment of the jar lid (*P*: 0.007) and in the completed moment of opening the jar lid (*P*: .008); elbow flexion angle in the first opening moment of the jar lid (*P*: .024); the area scanned by hand on frontal (*P*: .038) and sagittal planes (*P*: .024); angular rotation of arm (*P*: .001) and hand (*P*: .014) in vertical axis in favor of the healthy group (Table 3).

In the correlation analysis among HAQ and other continuous variables in the RA group, HAQ was highly correlated with part 2 time (*r*: 0.755); total time (*r*: 0.579); angular rotation of forearm in transverse axis (*r*: 0.734), sagittal axis (*r*: 0.615) and vertical axis (*r*: 0.629; $P < .05$; Table 3).

In order to determine the predictive power of the disability of individuals with RA, the "stepwise multiple regression" analysis was performed. In the regression analysis, only 4 variables (total time, forearm angular rotation in transverse, sagittal and vertical axes) were examined. Variables that had a statistically significant

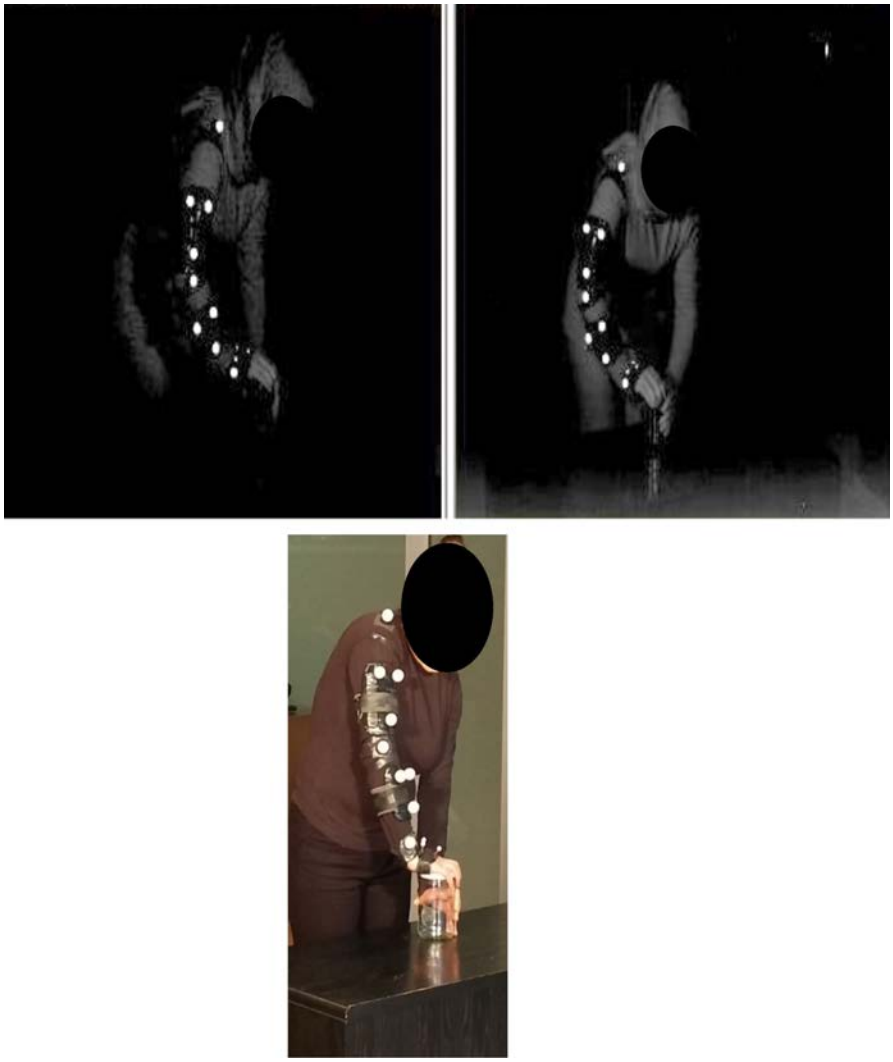

FIGURE 2 Placement of reflective markers at points determined along the dominant upper extremity.

TABLE 1 Times obtained during the "jar opening motion" and used for analysis

Part 1 time		Part 2 time		
From	To	From	To	Total time
Starting command	The first opening moment of the jar lid	The first opening moment of the jar lid	The completed moment of opening the jar lid	Part 1 time + Part 2 time

relationship with HAQ (shown in Table 3) were examined by multivariate regression model. Since there was a statistically strong correlation between total time and part 2 time, variance inflation factor values were examined and excluded from the model. As seen in Table 4, stepwise multiple regression analysis to predict disability in individuals with RA was completed in a single step. Angular rotation of forearm in transverse axis was found to be a significant predictor of disability in individuals with RA, and 53.9% of the total variance was explained. The bivariate correlation between disability and angular rotation of forearm in transverse axis was found to be positive and significant (Table 4).

4 | DISCUSSION

As a result of this study, it was observed that the bilateral hand grip strength of individuals with RA was lower compared to healthy individuals. In the 3D kinematic analysis of "jar opening motion," which is one of the motions that are frequently used in daily life and that individuals with RA report the most difficulty, it was determined that individuals with RA completed the motion longer in 2 parts and in the total time compared to healthy individuals. In addition, it was found that shoulder-to-table distances were shorter in the starting command, in the first opening moment of the jar lid and in the completed

TABLE 2 The demographic and descriptive data of the participants

	RA group (n: 12)		Healthy group (n: 12)	
Variables	**Median (min/max)**	**Mean ± SD**	**Median (min/max)**	**Mean ± SD**
Age, y	45 (30/61)	45.16 ± 10.16	22 (20/27)	22.83 ± 2.03
Height, m	1.59 (1.50/1.72)	1.60 ± 0.05	1.63 (1.56/1.70)	1.63 ± 0.04
Body weight, kg	75.50 (50/96)	73.66 ± 13.25	56.50 (46/75)	56.75 ± 8.98
Body mass index, kg/m^2	28.69 (18.82/37.97)	28.76 ± 4.82	20.04 (17.31/26.35)	21.16 ± 2.89
Duration of disease, y	7 (4/30)	11.58 ± 9.57	-	-
Health Assessment Questionnaire	0.75 (0/1.87)	0.76 ± 0.62	-	-
Hand grip strength-right, kg	18.49 (10/24.33)	18.41 ± 4.09	24.66 (21.33/32.66)	25.19 ± 3.51
Hand grip strength-left, kg	18.49 (9.33/21.66)	16.99 ± 3.80	22.33 (18.33/31.66)	22.52 ± 3.57
Part 1 time, ms	46.50 (16/89)	50.50 ± 25.59	23 (5/96)	29.58 ± 24.44
Part 2 time, ms	111.50 (58/385)	161 ± 97.41	93 (40/163)	96.50 ± 37.55
Total time, ms	194 (108/406)	211.50 ± 95.83	116 (50/259)	126.08 ± 53.98
Shoulder-to-table distance, cm[a]	55.23 (45.99/65.07)	55.44 ± 6.97	62.90 (52.08/70.99)	62.84 ± 5.27
Shoulder-to-table distance, cm[b]	53.44 (43.53/65.15)	53.86 ± 6.66	62.11 (51.83/70.76)	61.76 ± 4.99
Shoulder-to-table distance, cm[c]	52.79 (41.29/65.62)	52.76 ± 6.99	60.04 (48.35/68.85)	59.66 ± 5.17
Elbow flexion angle, °[,a]	61.90 (28.08/111.24)	66.04 ± 23.75	46.71 (30.30/87.42)	49.98 ± 17.16
Elbow flexion angle, °[,b]	66.85 (27.49/111.69)	71.42 ± 22.37	51.65 (41.64/87.76)	55.42 ± 13.23
Elbow flexion angle, °[,c]	71.05 (30.69/110.33)	74.03 ± 21.26	62.04 (41.87/91.67)	63.30 ± 12.22
Wrist extension angle, °[,a]	65.13 (39.21/111.74)	66.24 ± 18.65	73.08 (46.77/91.58)	72.06 ± 15.47
Wrist extension angle, °[,b]	68.06 (43.85/111.46)	70.70 ± 18.31	76.56 (55.50/100.88)	76.28 ± 14.34
Wrist extension angle, °[,c]	68.52 (46.91/114.42)	73.05 ± 17.68	85.39 (51.38/95.39)	79.54 ± 14.69
Arm (area scanned)				
Horizontal plane	19.10 (6.35/26.36)	16.81 ± 7.85	22.38 (11.65/34.31)	22.31 ± 5.81
Frontal plane	16.60 (4.08/33.98)	16.72 ± 9.26	22.75 (15.01/36.22)	24.21 ± 7.52
Sagittal plane	7.35 (2.09/22.74)	9.63 ± 6.90	12.88 (5.90/21.96)	13.36 ± 5.34
Forearm (area scanned)				
Horizontal plane	4.85 (2.75/18.58)	7.38 ± 5.22	9.56 (6.83/18.39)	10.26 ± 3.30
Frontal plane	13.72 (2.82/24.23)	12.98 ± 6.96	18.75 (5.83/37.95)	19.32 ± 8.61
Sagittal plane	7.78 (2.56/14.83)	7.94 ± 4.08	8.16 (3.19/17.90)	8.59 ± 4.67
Hand (area scanned)				
Horizontal plane	12.49 (7.64/24.43)	14.06 ± 5.59	13.50 (10.04/23.22)	14.59 ± 4.06
Frontal plane	39.25 (22.24/80.26)	45.36 ± 19.80	66.69 (13.53/85.43)	63.18 ± 20.42
Sagittal plane	21.9 (6.03/47.59)	22.49 ± 11.61	36.91 (19.16/53.60)	36.19 ± 12.51
Arm angular rotation				
Transverse axis	19.54 (6.67/24.58)	16.77 ± 6.76	22.46 (10.72/36.82)	22.07 ± 7.28
Sagittal axis	14.93 (4.25/32.37)	16.52 ± 10.64	18.35 (1.78/34.57)	18.66 ± 11.36
Vertical axis	11.72 (6.10/23.40)	13.31 ± 5.67	27.72 (17.13/50.08)	29.08 ± 9.02
Forearm angular rotation				
Transverse axis	10.77 (3.15/17.15)	10.26 ± 5.05	8.96 (3.66/31.24)	10.51 ± 7.67
Sagittal axis	14.91 (9.50/32.60)	17.52 ± 8.11	14.68 (4.21/27.08)	15.90 ± 6.60
Vertical axis	27.78 (5.03/47.55)	27.69 ± 12.57	39.59 (20.27/62.18)	40.28 ± 14.78

(Continues)

TABLE 2 (Continued)

Variables	RA group (n: 12)		Healthy group (n: 12)	
	Median (min/max)	Mean ± SD	Median (min/max)	Mean ± SD
Hand angular rotation				
Transverse axis	11.82 (5.21/39.61)	15.22 ± 10.17	12.16 (6.72/38.34)	14.41 ± 8.46
Sagittal axis	10.89 (3.18/35.24)	12.42 ± 8.11	13.32 (6.84/26.51)	14.29 ± 5.93
Vertical axis	60.43 (30.41/151.76)	64.85 ± 34.08	85.86 (61.34/150.95)	89.94 ± 23.12

Note: Part 1: starting command - the first opening moment of the jar lid; Part 2: the first opening moment of the jar lid - the completed moment of opening the jar lid.

[a]Starting command

[b]The first opening moment of the jar lid

[c]The completed moment of opening the jar lid.

moment of opening the jar lid; and elbow flexion angle was more in the first opening moment of the jar lid in RA. We think that these differences occur due to the compensatory mechanisms of individuals with RA to produce more strength. It was determined that the hand scanned less area on the frontal plane and sagittal plane, that is, the hand made less of a circular pattern, and the arm and hand performed less angular rotation in the vertical axis. Results showed that the most predictive variable for disability in individuals with RA was elbow flexion (angular rotation of forearm in transverse axis), and it explained 53.9% of disability.

Many activities of daily living, such as opening doors, opening jars, lifting and carrying heavy items, require hand strength.[25] It has been reported that the decrease in grip and pinch strength, which can be easily measured with portable dynamometers, is a strong indicator of functional disability in RA patients.[26] Loss of flexion and extension of the hand joints in individuals with RA affect fine-motor skills and dexterity in the hand and grip, and this causes physical disability and causes difficulties in performing activities of daily living.[27] The hand strength of individuals with RA is 75% lower than healthy individuals.[28] In parallel with the literature, we found that individuals with RA, who we compared to healthy people, had lower strengths of both hands.

However, there is limited data on the relationship between involvement of certain joints and objective measures of hand function. Such information can be useful for targeted rehabilitation and other interventions. The potential importance of such findings is underlined by the proven success of structured rehabilitation programs in RA.[29,30] To date, small joints such as metacarpophalangeal, proximal interphalangeal and wrists were examined among the most affected joints in RA.[31] In contrast, large joints have not been extensively studied.[32] Joints of the upper extremities, including the shoulder, are also affected in RA and this makes it difficult to place the hand in suitable positions for efficient function.[33] Although deficits in upper extremity range of movement are commonly described as a consequence of RA, little quantitative information is available in the literature.[34]

Although it has been stated that the most ideal method for determining the functional range of motion of the upper extremity joints due to the complexity in the 3D movement patterns of the anatomical structures and joints, may be 3D measurements,[12] to our knowledge there is only one study in the literature that evaluates the actual movement performance of the functional deficits of the upper extremity joints in RA from a 3D perspective in detail.[23] In this study, the effects of kinematic disorder in the deformed rheumatoid thumb on hand function were investigated. It was emphasized that better understanding of the effects of upper extremity structural pathologies on upper extremity kinematics during activities that are frequently performed in daily life may support clinical decisions regarding the treatment of this complex disease.[35,36]

It would not be wrong to say that "jar opening motion" is one of the activities that is considered important in the evaluation of upper extremity-related disabilities of individuals with RA, because there are questions about jar opening activity in frequently used outcome measures in the evaluation of disability in RA, such as Disabilities of the Arm, Shoulder and Hand,[37] Michigan Hand Outcomes Questionnaire,[38] Duruöz Hand Index[39] and Arthritis Impact Measurement Scale 2,[40] and HAQ.[20,41] Therefore, in this study, we examined the global upper extremity kinematics in 3D terms with the "jar opening motion", which is one of the activities that individuals with RA frequently use in daily life and have the most difficulty with, and compared this with healthy individuals.

According to the results we obtained, individuals with RA performed the "jar opening motion" in a longer time than healthy individuals. During the "jar opening motion" activity, the shoulder-to-table distance of individuals with RA is less than healthy individuals. This made us think that individuals with RA have more trunk flexion to release the strength required to perform the "jar opening motion" activity, and thus they need strength support from larger muscle groups other than the upper extremities. In addition, the fact that individuals with RA had higher elbow flexion angle in the first opening moment of the jar lid compared to healthy individuals, led to the opinion that they increased the elbow flexion angle in addition to trunk flexion in order to provide more strength support to the hand. Because it has been suggested in the literature that muscle strength in the upper extremity is related to grip strength,[42] multiple components have been reported to contribute to grip strength. It was emphasized that different muscle groups in the distal part of the upper extremities, especially forearm flexor activation and extensor synergists, generate strength. It is important that the wrist is stabilized by the extensor muscles when the hand is strongly gripped.[43]

TABLE 3 Comparison of the data between groups and the relationship between Health Assessment Questionnaire (HAQ) and other data in the Rheumatoid Arthritis (RA) group

	Between RA group and healthy group	HAQ RA group (n: 12)		
Variables	***P***[a]	***r***	***P***[b]	
Age, y	**.001**		.362	
Height, m	.128		.299	
Body weight, kg	**.001**		.562	
Body mass index, kg/m^2	**.001**		.829	
Hand grip strength-right, kg	**.001**		.486	
Hand grip strength-left, kg	**.001**		.895	
Part 1 time, ms	**.032**		.251	
Part 2 time, ms	**.038**	0.755	**.005**[c]	High
Total time, ms	**.007**	0.579	**.048**	High
Shoulder-to-table distance, cm[d]	**.015**		.606	
Shoulder-to-table distance, cm[e]	**.007**		.548	
Shoulder-to-table distance, cm[f]	**.008**		.450	
Elbow flexion angle, °[d]	.073		.258	
Elbow flexion angle, °[e]	**.024**		.246	
Elbow flexion angle, °[f]	.083		.185	
Wrist extension angle, °[d]	.204		.118	
Wrist extension angle, °[e]	.356		.187	
Wrist extension angle, °[f]	.184		.105	
Arm (area scanned)				
Horizontal plane	.094		.334	
Frontal plane	.065		.189	
Sagittal plane	.133		.735[c]	
Forearm (area scanned)				
Horizontal plane	.073		.052[c]	
Frontal plane	.073		.379	
Sagittal plane	.773		.793	
Hand (area scanned)				
Horizontal plane	.603		.322	
Frontal plane	**.038**		.663	
Sagittal plane	**.024**		.996	
Arm angular rotation				
Transverse axis	.094		.338	
Sagittal axis	.603		.201	
Vertical axis	**.001**		.632	
Forearm angular rotation				
Transverse axis	.644	0.734	**.007**	High
Sagittal axis	.908	0.615	**.033**	High
Vertical axis	.057	0.629	**.028**	High
Hand angular rotation				
Transverse axis	.862		.605	
Sagittal axis	.326		.309[c]	
Vertical axis	**.014**		.868	

Note: Part 1: starting command - the first opening moment of the jar lid; Part 2: the first opening moment of the jar lid - the completed moment of opening the jar lid. Statistical significance for the bold values was $P < .05$

[a]Mann-Whitney U test.

[b]Pearson correlation analysis.

[c]Spearman's rank correlation.

[d]Starting command.

[e]The first opening moment of the jar lid.

[f]The completed moment of opening the jar lid.

TABLE 4 Results of stepwise multiple regression analysis of predicting variables for disability in Rheumatoid Arthritis (RA)

Variables	*B*	SE	Beta	*t*	*F*	*R*	R^2	DW
Forearm angular rotation – transverse axis**	0.09	0.026	0.734	3.418	11.683	0.734	0.539	2.382

Note: Variables in the initial model: Total time, ms; forearm angular rotation - transverse axis; forearm angular rotation - sagittal axis; forearm angular rotation - vertical axis. ** $P < .001$.

Abbreviation: DW, Durbin-Watson.

In addition, according to the results, we determined that the hand scanned less area on the frontal plane and sagittal plane, that is, the hand made less a circular pattern, and the arm and hand performed less angular rotation in the vertical axis in the individuals with RA compared to the healthy controls. Considering the activity we evaluated, our inferences from these results are that individuals with RA make less a circular pattern of the hand and less rotation of the hand and arm during the "jar opening motion" compared to healthy controls.

In the evaluation of clinical trials, it has been reported that HAQ, which evaluates grip strength, number of swollen joints, patient-reported pain and functional status measured in RA, is an outcome measure in intermediate responsiveness.[44] Therefore, HAQ was used in the evaluation of disability in our study. It has been stated that the 3 joints that contribute the most to HAQ scores in the upper extremity in patients with RA are the shoulder, elbow and wrist.[45] As a result of the stepwise multiple regression analysis, we have obtained the result that the variable that most predicts disability in individuals with RA is elbow flexion (angular rotation of forearm in transverse axis), that is, the increase in disability affects the increase in flexion movement in the elbow and explains 53.9% of the disability scores.

The strengths of our study are that the evaluations were made by the same people, standard test protocols were applied, and the proximal joints, which are of great importance for the functionality of the hand, were evaluated in 3D with the "jar opening motion," which is often done in daily life.

Our limitation is that the shoulder joint could not be evaluated. If the data of the shoulder joint could be obtained, results could have been demonstrated with a more holistic approach.

We think there is a need to evaluate the shoulder, the cervical region, perhaps bilateral upper extremity, even trunk movements with 3D kinematic analyses in order to obtain more detailed information about upper extremity effects of individuals with RA in future studies. Detailed kinematic information that can be given according to the level of influence of the hand can also be valuable information.

According to the data we obtained from the results of this study, we recommend the use of strengthening exercises to increase the circular and rotational movements of the hand in order to reduce the load on the elbow in daily activities and to eliminate the inadequacy in hand functions due to the decrease in upper extremity strength and range of movement, and hand dexterity exercises due to performing the motion for a longer time in the treatment of individuals with RA and evaluating their effectiveness.

5 | CONCLUSIONS

It was observed that bilateral hand grip strengths were lower, "jar opening motion" took longer, shoulder-to-table distances were shorter, elbow flexion was greater, circular pattern in the hand was less and angular rotation in the hand and arm was less during "jar opening motion" in individuals with RA compared to healthy individuals. The variable that most predicts disability in individuals with RA is elbow flexion (angular rotation of forearm in transverse axis) and explains 53.9% of disability score.

AUTHOR CONTRIBUTIONS

All authors participated in the design of the study. Diagnosis of RA patients and eligibility for inclusion criteria: MT and VC. 3D kinematic analysis: AA and HK. Other evaluations, statistical analyses and article writing: EGK. Statistical interpretation: FU, AA, HK, BBC and EGK. All authors contributed to the critical revision of the manuscript for important intellectual content, approved the final version and are accountable for the integrity of its content.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ETHICS STATEMENT

Local Ethics Committee (decision dated 02.11.2021 and numbered 20).

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ORIGINAL ARTICLE

High-resolution Doppler ultrasound in systemic sclerosis: Analysis of digital arteries and nailfold microvasculature using 18-5 MHz and 33-9 MHz probes

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Abstract

Introduction: Newly developed Doppler techniques enable the sampling of slow vascular flows and the extrapolation of spectral parameters in distal arterioles. The aim of this study was to investigate the role of spectral analysis performed by means of ultra-high frequency ultrasound (US) in the evaluation of the peripheral vascular bed of systemic sclerosis (SSc) patients.

Methods: Both hands of 33 patients affected by diffuse cutaneous SSc and 34 volunteers were evaluated with a US machine equipped with 33-9 MHz and 18-5 MHz transducers. Proximal resistive index and the peak systolic velocity (pRI and pPSV, respectively), were calculated at the level of the second interdigital artery. The distal resistive index (dRI) was calculated at the level of a nailfold arteriole of the third finger. All SSc patients had been previously divided into 4 subgroups according to their nailfold videocapillaroscopic (NVC) patterns following accepted criteria.

Results: SSc patients showed a significantly slower systolic velocity at the level of the second interdigital artery (pPSV [SD] = 8.38 [3] cm/s vs pPSV [SD] = 11.14 [4.5] cm/s; $P = .005$) and a higher dRI (dRI [SD] = 0.65 (0.14) vs dRI [SD] = 0.57 [0.11]; $P = .0115$). No differences were found between the pRI values measured in the SSc patients and those of the controls (pRI [SD] = 0.76 [0.11] vs pRI [SD] = 0.73 [0.12]; $P = .359$]. The subgroup analysis did not show any significant difference when pPSV, pRI and dRI were compared among NVC morphological patterns.

Conclusion: High-resolution Doppler analysis of digital distal arterioles may disclose subtle abnormalities in the downstream microvasculature of SSc patients that could

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be missed when the examination is performed at a more proximal level and/or using lower Doppler frequencies.

KEYWORDS
connective tissue diseases, nailfold videocapillaroscopy, scleroderma patterns, systemic sclerosis, ultrasound

1 | INTRODUCTION

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by vascular hyper-reactivity and fibrotic changes affecting the skin and visceral organs. Most evidence suggests that microvascular injury plays a key role in SSc pathogenesis, and processes like vasospasm, impaired angiogenesis, increased platelet aggregation, and intimal fibrosis all represent hallmarks of the disease, even in its early phases.[1,2] Nailfold videocapillaroscopy (NVC) is an increasingly more used method for the evaluation of the peripheral vascular bed of rheumatological patients, and the identification of abnormal nailfold capillaries plays an acknowledged role in SSc diagnosis.[3] In addition, specific NVC findings allow for the distinction between 3 different stages of the disease (ie early, active and late) and, in certain contexts, these findings may assist clinicians in targeting therapeutic decisions.[4] However, NVC only enables a morphological evaluation of nailfold capillaries and the same pattern of alterations may be demonstrated in people with different rheumatological diseases or in healthy subjects.[5] Doppler ultrasound (US) and spectral analysis of vessels are established methods for the clinical evaluation of several conditions determining fibrosis and parenchymal subversion of visceral organs, allowing for the extrapolation of several parameters that can provide essential information about disease progression and the response to therapy, such as arterial peak systolic velocity (PSV) and resistive index (RI).[6,7] PSV corresponds to each tall "peak" in the spectral Doppler waveform, and its value can vary depending on vessel properties (high- or low-resistance) and pathological processes (eg vessel stenosis or occlusion); RI is the difference between the peak systolic and end-diastolic flow velocities divided by the PSV and expresses the resistance and the vascular compliance in a pulsatile vascular system. Recent technological advancements in US equipment, with the introduction of ultra-high frequency probes (frequency bands >30 MHz) and the progressive refinement of image-processing algorithms, have opened up new perspectives for the evaluation of sub-millimetric structures in very distal districts. In addition, newly developed Doppler techniques, by means of specific motion-suppression algorithms that isolate and eliminate clutters, now enable the sampling of slow vascular flows and the extrapolation of spectral parameters in distal arterioles.[8,9] On this basis, the aim of our study was to investigate the potential role of spectral analysis performed by means of ultra-high frequency US in the evaluation of the peripheral vascular bed of SSc patients.

2 | MATERIALS AND METHODS

2.1 | Investigated populations

Both hands of 33 patients with SSc (6 male, 27 female; mean age [SD] = 63.9 [14] years) and 34 healthy controls (8 male, 26 female, mean age [SD] = 48 [1.14] years) were evaluated using US by an experienced sonologist with specific skill in musculoskeletal and vascular imaging. The examiner was blinded to the clinical status of the subjects. All patients fulfilled the 2013 American College of Rheumatology / European Alliance of Associations for Rheumatology diagnostic criteria for SSc and had been previously divided into 4 subgroups (ie scleroderma-like, early, active and late patterns) according to NVC findings as described in the literature.[10,11] NVC was performed by an experienced rheumatologist not more than 1 month before the US examination. Patients with active digital ulcers or ulnar artery occlusion were excluded from the study due to the impossibility to perform US on damaged skin. All the concomitant therapies were recorded and symptomatic compounds, influencing the peripheral blood flow (ie endovenous iloprost), were withdrawn 10 days before the US examination. This study was approved by the local ethics committee (CER Liguria: 5/2022—DB id 12 123) and informed consent was obtained from all patients.

2.2 | US evaluation

US was performed on both hands of the patients and controls, at the same hour of the day (between 14:00 and 18:00 hours) after a period of acclimatization in a room with a controlled temperature. Patients were invited to sit in front of the examination bed, with both hands laying on the bed. A US machine, equipped with 33-9 MHz (frequency band for Doppler imaging, 10–18 MHz) and 18-5 MHz (frequency band for Doppler imaging, 5–11 MHz) transducers (Aplio i800, Canon Medical System, Otawara, Japan), was used by the same sonologist for the evaluation of patients and controls. For both hands, the RI and the PSV were calculated at the level of the second interdigital artery (proximal resistive index and peak velocity, pRI and pPSV, respectively), orienting the 18-5 MHz transducer along the long-axis of the vessel on the palmar aspect of the third interdigital space. The interdigital artery was at first observed running approximately parallel to the skin and then changing its course, traveling obliquely from the surface to deeper down when approaching the base of the finger. Spectral analysis was performed at the level where the vessel

presented the most oblique course and after having directed the US beam to obtain an incidence angle of 60° with the artery inferior (Figure 1); given its depth relative to the skin, the interdigital artery was not suitable for examination with the 33–9 Mhz transducer, so both the pRI and pPSV were calculated using the 18–5 Mhz transducer. Next, the distal RI (dRI) was calculated performing Doppler spectral analysis at the level of a nailfold arteriole of the third finger. In contrast to the interdigital artery, to study the nailfold and to calculate the dRI, we employed the 33–9 MhZ probe given its higher spatial resolution compared to the 18–5 transducer and its ability to show very small vessels with the use of a newly developed Doppler technique. The nailfold was initially investigated in a longitudinal plane, placing the 33-9 MHz probe on the dorsal aspect of the middle and distal phalanxes of the third fingers. After the activation of microvascular flow settings, the color box was shifted to the soft tissue beneath the hyperechogenic profile of the nail and dRI was calculated in one of the small regional arterioles (Figure 2). At this level, the PSV was not measured due to the impossibility of obtaining the images of nailfold vessels in their long-axis and adjusting the incidence angle between the US beam and the blood flow. On the other hand, the calculation of the dRI was possible as this is a purely adimensional parameter and its measurement does not require any rectification of the incidence angle. During the US examination, a large amount of gel was applied between the probe and the skin of the patients in order to avoid any alteration of the results due to soft tissue compression. In regard to the US parameters, the mean of the 2 measurements, respectively collected from the right and left hand, was considered for analysis. When it was not possible to measure a parameter in one of the patient's 2 hands, we took into account the measurement that had already been collected from the other hand as the mean value.

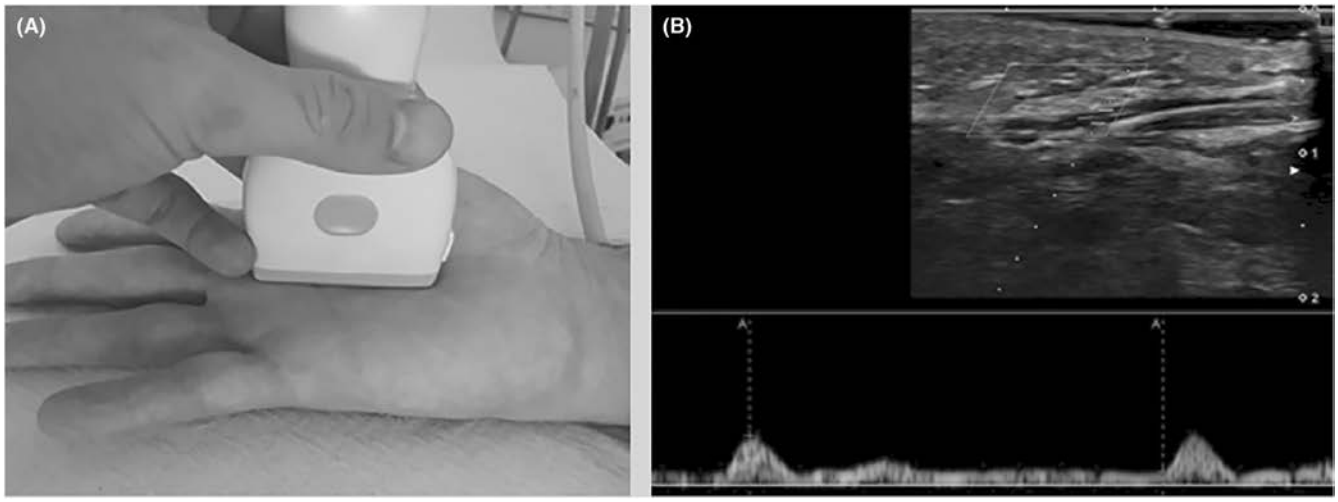

FIGURE 1 Peak velocity and proximal resistive index. (A) Photograph demonstrates the position of the probe at the third interdigital space. (B) Spectral analysis performed with an 18-5 MHz ultrasound transducer

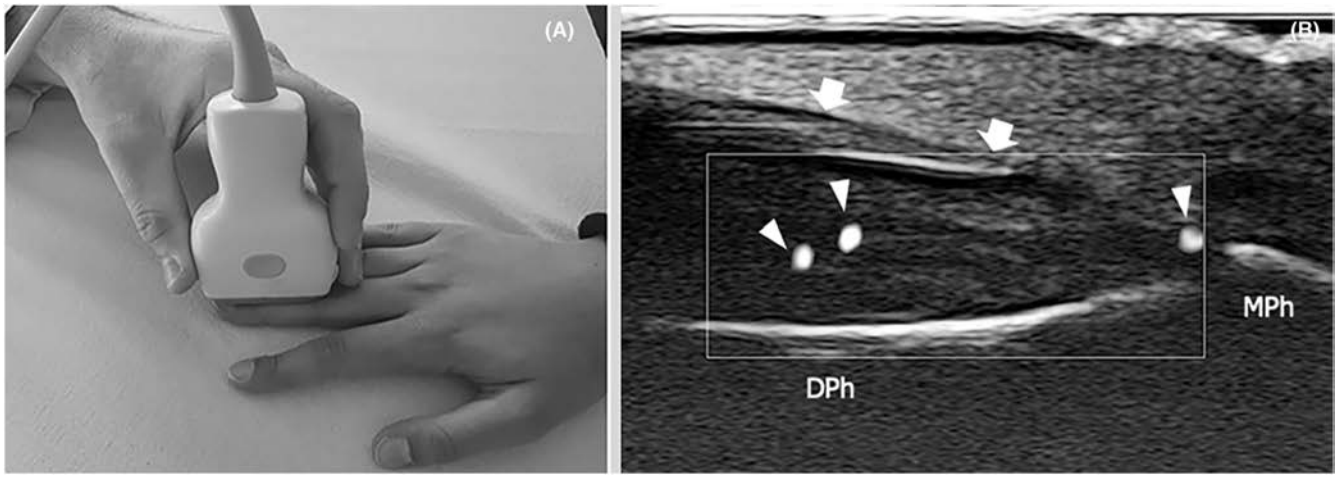

FIGURE 2 Distal resistive index. (A) Photograph demonstrates the position of the probe at the level of the dorsal aspect of the distal phalanx. (B) Long axis 33-9 MHz ultrasound image demonstrates several small vascular spots (arrowheads) in the soft tissues underneath the nail (arrows). MPh, middle phalanx; DPh, distal phalanx

2.3 | NVC examinations

NVC was performed using a 200× optical probe and images were detected and stored by means of ad-hoc software (DS-Medica, Milano, Italy). The examinations were performed in a room with a controlled temperature and a drop of immersion oil was applied to the nailfold to maximize the translucency of the keratin layer. All the patients' fingers, with the exception of the thumbs, were examined to detect the overall NVC pattern. Of note, the "scleroderma-like" pattern is a transition pattern between the next SSc NCV patterns (mainly observed in mixed connective tissue diseases), the "early" NVC pattern is characterized by a relatively well-preserved capillary arrangement and by numerous capillaries, whereas a moderate loss of capillaries and abnormal distribution in the nailfold typify the "active" NVC pattern. Finally, in the "late" NVC pattern, a severe loss of capillaries with extensive avascular areas and total disorganization of the normal capillary array are commonly observed.

2.4 | Statistical analysis

Metric data are presented as mean ± standard deviation (SD) and range (minimum–maximum). To investigate differences among the NVC subgroups and between the patients and the controls, we applied analysis of variance or Kruskal-Wallis test as appropriate, using the Kolmogorov–Smirnov test to verify normality. *P* values lower than .05 were considered statistically significant. Pearson's correlation coefficient was calculated between the US flow parameters of all the patients.

TABLE 1 Demographic characteristics of the investigated population

	Overall N = 67	Cases n = 33	Controls n = 34
Gender, n (%)			
Male	14 (21%)	6 (18%)	8 (24%)
Female	53 (79%)	27 (82%)	26 (76%)
Age, mean (SD)	55.90 (16.11)	63.97 (14.05)	48.06 (14.12)
BMI, mean (SD)	23.53 (3.75)	24.01 (4.62)	23.04 (2.60)
VCS pattern, n (%)			
Scleroderma-like	---	7 (21%)	---
Early	---	4 (12%)	---
Active	---	14 (42%)	---
Late	---	8 (24%)	---
Raynaud phenomenon, n (%)	---	33 (100%)	---
Raynaud's duration, mean, y	---	16	---
Diabetes	---	1 (3%)	1 (3%)
Arterial hypertension	---	15 (45%)	8
CAD	---	1 (3%)	---
Smoking	---	5 (15%)	6 (17%)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; SD, standard deviation; VCS, videocapillaroscopy.

3 | RESULTS

3.1 | Demographic data and NVC examination

Demographic characteristics are summarized in Tables 1 and 2. All the patients had previous episodes of Raynaud's phenomenon and 82% of them had been treated with iloprost. The collection of the US parameters was successfully performed in most patients and in all the individuals of the control group. More specifically, it was possible to calculate dRI in 26 (78.8%) and the pRI and pPSV in 32 cases (97%) from the patients' group. The detection and sampling of the nailfold vessel flow was generally easier in the controls than in the patients, probably as a consequence of the disease-related depletion of the distal vascular bed which occurs in people with SSc. The nailfold NVC categorized the patients as follows: $n = 7$, scleroderma-like pattern; $n = 4$, early pattern; $n = 14$, active pattern; and $n = 8$, late pattern.

3.2 | US evaluation

Tables 3 and 4 summarize the results of the study. The US examination with the spectral analysis took, on average, 20 minutes per patient. SSc patients demonstrated a significantly slower systolic velocity at the level of the second interdigital artery (pPSV [SD] = 8.38 [3] cm/s vs pPSV [SD] = 11.14 (4.5) cm/s; $P = .005$) and a higher dRI (dRI [SD] = 0.65 [0.14] vs dRI [SD] = 0.57 [0.11]; $P = .0115$) compared to controls. No differences were found between the pRI values measured in the patients and those of the controls (pRI [SD] = 0.76 [0.11] vs pRI [SD] = 0.73 [0.12]; $P = .359$). The subgroup analysis did not show any significant difference when pPSV, pRI and dRI were compared among NVC categories. Pearson's test demonstrated no significant correlation between the patients' flow indices.

4 | DISCUSSION

Although SSc is considered an idiopathic, small-vessel vasculopathy, the production of auto-antibodies and fibroblast dysfunction are all thought to represent the main pathogenic processes leading to clinical manifestations. In particular, it has been speculated that the primum movens of SSc consists of an auto-immune reaction directed against the small vessels and characterized by the production of anti-endothelial auto-antibodies (which may be demonstrated in the sera of up to 84% of patients with SSc) and the activation of T-cells releasing proteolytic granzymes.[12,13] This leads to a widespread

TABLE 2 Antibody profiles and therapy of the investigated population

	Overall N = 67	Cases n = 33	Controls n = 34
ACA	---	13 (39%)	---
Anti-Scl-70 Ab	---	12 (36%)	---
APA	---	4 (12%)	---
Anti-PM/Scl100 Ab	---	1 (3%)	---
AMA	---	2 (6%)	---
Anti-Ro52 Ab	---	1 (3%)	---
Anti-CCP Ab	---	1 (3%)	---
RF	---	2 (6%)	---
Anti-NOR90 Ab	---	1 (3%)	---
ACPA	---	1 (3%)	---
Antiphospholipid Ab	---	1 (3%)	---
Anti-Ku Ab	---	2 (6%)	---
Anti-PM/Scl-75	---	1 (3%)	---
ASA = 1, n (%)	---	28 (85%)	---
Aminaphtone, n (%)	---	27 (82%)	---
Methotrexate, n (%)	---	7 (21%)	---
Prednisolone, n (%)	---	3 (9%)	---
Hydroxy hydroquinone, n (%)	---	2 (6%)	---
Cyclosporine, n (%)	---	6 (18%)	---
Mycophenolate mofetil, n (%)	---	8 (24%)	---
VitD, n (%)	---	32 (97%)	---
ACE inhibitor, n (%)	---	18 (55%)	---
Ca antagonist, n (%)	---	2 (6%)	---
PPI, n (%)	---	25 (76%)	---
Endothelin receptors antagonist, n (%)	---	9 (27%)	---
Iloprost, n (%)	---	27 (82%)	---
Nintedanib, n (%)	---	2 (6%)	---

Abbtreviations: ACA, anticentromere antibodies; Ab, antibodies; APA, antipolymer antibodies; PM: polymyositis; AMA, antimitochondrial antibodies; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; NOR, nucleolus organizer region; ACPA, anti-citrullinated protein/peptide antibodies; ASA, acetylsalicylic acid; VitD, vitamin D; ACE, angiotensin-converting enzyme; Ca, calcium; PPI, proton pump inhibitors.

obliterative vasculopathy with the predominant involvement of distal arterioles and capillaries, eventually resulting in diffuse ischemic damage, involving both the skin and visceral organs.

The relevance of peripheral vasculopathy in SSc pathogenesis has led to a growing interest in developing a tool enabling an in-depth evaluation of the distal vascular district of patients affected by this condition. Recently, the advent of high-resolution US and the refinement of Doppler technology have opened promising perspectives about the possible extrapolation of quantitative parameters reflecting the status of distal arteries in SSc patients.[14] Our

TABLE 3 Mean (SD) of US parameters among cases/controls and by NVC groups; *P* values for US parameters differences among NVC groups and between cases and controls. Cases showed higher resistive index (*P* = .0115) and slower systolic velocity at the level of the second interdigital artery (*P* = .005)

	Cases N = 33	VCS = 0 n = 7 (21%)	VCS = 1 n = 4 (12%)	VCS = 2 n = 14 (42%)	VCS = 3 n = 8 (24%)	Controls n = 34	VCS classes	Cases vs controls
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*P* value	*P* value
dRI	0.65 (0.14) n = 26	0.67 (0.11) n = 6	0.83 (0.22) n = 2	0.64 (0.14) n = 13	0.59 (0.14) n = 5	0.57 (0.11) n = 33	.2540	.0115
pRI	0.76 (0.11) n = 32	0.73 (0.11) n = 7	0.72 (0.07) n = 4	0.76 (0.09) n = 14	0.81 (0.14) n = 7	0.73 (0.12) n = 34	.5354	.3596
PV, cm/s	8.38 (3.00) n = 32	7.30 (2.57) n = 7	8.51 (4.03) n = 4	9.00 (3.36) n = 14	8.16 (2.20) n = 7	11.14 (4.50) n = 34	.6868	.0050

Abbreviations: VCS, videocapillaroscopy; SD, standard deviation; dRI, distal resistive index; pRI, proximal resistive index; PV, peak velocity.

TABLE 4 Pearson's test demonstrated no significant correlation between the patients' flow indices.

Pearson's correlation coefficient (R) Significance (*P*) Number of observations (n)	Proximal resistive index	Peak sistolic velocity	Distal resistive index
Proximal resistive index	1.00000 (R) 32 (n)	0.19500 (R) .2848 (*P*) 32 (n)	0.15274 (R) .4563 (*P*) 26 (n)
Peak sistolic velocity	−0.19500 (R) .2848 (*P*) 32 (n)	1.00000 (R) 32 (n)	−0.07717 (R) .7079 (*P*) 26 (n)
Distal resistive index	0.15274 (R) .4563 (*P*) 26 (n)	−0.07717 (R) .7079 (*P*) 26 (n)	1.00000 (R) 26 (n)

work is based on the assumption that the increased sensitivity of Doppler imaging could provide information about the status of the microvasculature at the most peripheral level of extremities, and that disease-related changes affecting the distal bed could be better characterized when the Doppler signal is sampled closer to the area of expected abnormalities. On the other hand, the detection of slow blood flows in nailfold capillaries requires ultra-high frequencies and specific motion-suppression algorithms to discriminate very slow, almost stationary, flows from interstitial fluid movements.

To the best of our knowledge, this is the first study showing the disease-related variations of nailfold blood flow detected by means of US spectral analysis in SSc patients. In our patient group, US showed an increased dRI at the level of nailfold arterioles. Interestingly, the slowing-down of PSV was the only alteration in the blood flow dynamics detected at the level of the interdigital artery, whereas pRI was unaffected. These results may be partially explained by consideration of the fact that vasculopathy in SSc has been demonstrated to involve predominantly the most peripheral downstream circulation, more specifically arterioles and capillaries,[15–17] and that the RI reflects the resistances to blood flow determined by the compliance of vessels located distal to the site of measurement. In other terms, the more proximal the sampling site, the more unselective and undiscriminating the analysis of blood flow since measurements derive from non-specific analysis of affected (minor) and nonaffected (prevalent) microvascular areas. In this perspective, the calculation of pRI at the level of the interdigital artery may not allow for the detection of a pathological process affecting the small arterioles of the nailfold, as the augmented resistances in the distal district could be partially mitigated by the normal compliances found in more proximal and unaffected vessels. These findings are in accordance with a recently published paper in which the authors were unable to demonstrate any correlation between the RI of digital arteries at the level of the proximal phalanx and nailfold perfusion.[18] On the other hand, it is more difficult to explain the significant slowing-down in the interdigital artery systolic velocity that was observed in patients. It could be hypothesized that the progressive depletion of the distal vascular bed may induce complex changes in the proximal district in an attempt to maintain perfusion, among which vasodilatation may be responsible for the regional decrease in blood flow velocity, but further investigations are necessary to confirm our findings.

However, our study has several limitations. First, we were able to recruit a small number of patients and it was not possible to extrapolate flow parameters from all of them. Second, no correlation between pRI, dRI and PSV and NVC categories was found, possibly due to the small number of samples considered in our analysis. In addition, we investigated only a small part of the parameters provided by spectral analysis, excluding other data, such as the diastolic velocity, which could have been able to provide additional clues to understanding the complex changes occurring in vessels of patients with SSc. Finally, we cannot exclude the possibility of the influence of some patients' therapies on flow parameters, as it was not possible to evaluate patients when they were not in their specific treatment cycle.

In conclusion, the ability to perform spectral Doppler analysis of small distal arterioles by means of ultra-high frequency US transducers is opening new perspectives to disclose subtle abnormalities in the downstream microvasculature of SSc patients that could be missed when Doppler examination is performed at a more proximal level and/or using lower Doppler frequencies. Further studies are needed in order to investigate the ultimate role of the microvascular Doppler US in the assessment of peripheral vasculopathy in SSc patients and its potential in providing useful data in clinical diagnosis and follow up.

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CONFLICT OF INTEREST

The authors have no conflict of interest related to this work.

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ORIGINAL ARTICLE

The long-term persistence of tumor necrosis factor inhibitors in patients with moderate to severe immune-mediated rheumatic diseases: A nation-wide, population-based real-world study

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Abstract

Objectives: We aimed to compare the long-term persistence between different tumor necrosis factor-alpha inhibitors (TNFis) with immune-mediated rheumatic diseases (IMRD). This study can potentially provide insights into the real-world evidence regarding safety and effectiveness of TNFi treatment in a Chinese population.

Methods: We enrolled newly diagnosed IMRD patients in this active comparator, retrospective cohort study by using National Taiwan insurance claim datasets. The drug survivals of first-line TNFi agents, including etanercept, golimumab, and adalimumab were compared. Propensity score matching was conducted to control the confounding effect from the observed covariates. The cumulative proportion of discontinuation was calculated over 5 years. The multiple-variable regression and propensity score analysis was used for confounding adjustment.

Results: After propensity score matching, there were 2267 patients identified in each etanercept, golimumab, and adalimumab group. We observed the 5-year cumulative proportion of discontinuation was 52.80%, 45.85%, and 56.86% in etanercept, golimumab, and adalimumab, respectively. Compared with golimumab, increase of 31% (95% CI: 20-43) and 38% (95% CI: 26-50) risk of discontinuation were observed in etanercept and adalimumab. The factors including female gender, increasing age, long hospital stays, without co-medication with nonsteroidal

anti-inflammatory drugs or methotrexate were associated were discontinuation of first-line TNFi treatment.

Conclusion: Golimumab had better drug survival than etanercept or adalimumab over 5 years of observation in Asian IMRD patients. Gender, age, longer hospital stays, concomitant use of disease-modifying antirheumatic drugs were associated with survival with TNFis.

KEYWORDS
drug persistence, immune-mediated rheumatic diseases, TNF-α inhibitor

1 | INTRODUCTION

Immune-mediated rheumatic diseases (IMRD), such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), can either cause joint damage or chronic systemic inflammation. The EpiReumaPt study[1] demonstrated that patients with rheumatic and musculoskeletal diseases had poorer health-related quality of life and higher disability score. Papadimitropoulos et al[2] estimated that RA contributed 0.13% of world disability-adjusted life-years. The treatment of rheumatic diseases could reduce the pain and inflammation in these patients, and disease-modifying antirheumatic drugs (DMARDs) modify the subsequent risk of all-cause mortality,[3] cardiovascular disease,[4] and infections[3,5] in rheumatic patients. Generally, DMARDs had benefits for patients with IMRD; however, the relationships between patient and medical provider, self-efficacy, beliefs about the drugs, and side effects were associated the discontinuation of treatment.[6,7]

Efficacious agents for rheumatic diseases treatment are recommended by the European Alliance of Associations for Rheumatology (EULAR) based on prognostic factors, remission, disease activity, and safety.[8] The biological DMARDs (b-DMARDs), such as inhibitors of tumor necrosis factor (TNF)-α, interleukin (IL)23 and IL17 and so forth, are the most effective type of agents for reduction of disease activity nowadays when prognostically unfavorable factors are presented. A cross-sectional study demonstrates that RA patients have higher remission probability in the TNF-α inhibitor-treated group than the control group.[9] A meta-analysis indicates that biologic continuation is associated with low disease activity, remission, and radiographic progression.[10] Discontinuation of b-DMARDs can result in poor remission and increased relapse rate, which is still an unmet need in rheumatic disease treatment.[11]

The persistence of TNF-alpha inhibitors (TNFis) has been evaluated in Western countries as well as Asian populations in Japan and Korea.[12–15] The Spanish registry study BIOBADASER[16] observed that drug survival was significantly higher in patients with spondyloarthritis than RA patients. A systemic review concludes that golimumab had higher persistence than other TNFis (including etanercept, adalimumab, and certolizumab pegol) in patients with RA, PsA, or axial SpA.[17] However, studies that compare the persistence between different TNFis have not been conducted for Chinese patients with IMRD.

This study is a retrospective population-based cohort study. The national health insurance research datasets were used to compare the 5 years drug persistence between first-line TNFis (including etanercept, golimumab, and adalimumab) in patients with IMRD. This study can potentially provide insights into the real-world evidence about safety and effectiveness of TNFi treatment.

2 | MATERIALS AND METHODS

2.1 | Data source

We applied for access to Taiwan National Health Insurance (NHI) Research Database (NHIRD), and Death Registry dataset between years 2008 and 2017. The NHI program provides almost all healthcare services in Taiwan.[18] The NHIRD was accessed in the Health and Welfare Data Science Center (HWDSC), Ministry of Health and Welfare, Taiwan. This study has been approved by the Institutional Review Board of the Chung Shan Medical University Hospital (CSMUH No: CS19012) and founded by Chung Shan Medical University Hospital (Grand No: CSH-2020-C-004). The personal and hospital identity information was encrypted, all analysis work was performed through a virtual private network, that provides encrypted connection and ensures safety of sensitive data in HWDSC.

We selected TNFi agents by using Anatomical Therapeutic Chemical Classification System (ATC) code, including etanercept (ATC codes: L04AA11, L04AB01), golimumab (ATC code: L04AB06), and adalimumab (ATC code: L04AA17). Adalimumab, etanercept, and golimumab were covered since September 2004, March 2003, and January 2012, respectively, in the Taiwan NHI program. RA patients could apply for TNFis since 2003; however, the AS and PsA patients were coved since August 2009. Table S1 shows the approved dose of TNFi in Taiwan during 2009 to 2017. Etanercept is 25 mg twice per week. Golimumab is 50 mg every 4 weeks. Adalimumab is 40 every other week. The coverage and regulation for prior authorization of TNFis were modified to meet the treatment guideline in different time frames. Therefore, we selected the sub-samples who had similar initial years between study groups by propensity score matching.

2.2 | Study population

Newly diagnosed IMRD patients, new users, active comparator, retrospective cohort study design was conducted. We selected the patients who were newly diagnosed with RA (International Classification of Diseases [ICD]-9: 714.0, ICD-10: M05, M06), AS (ICD-9: 720.0, ICD-10: M45), or PsA (ICD-9: 696.0, ICD-10: M07, M09.0, L40.5) from 2010 to 2017. Furthermore, we included the patients who were initially subcutaneously administered TNFi agents (naïve to TNFi agents) for analysis.

The index date was defined as the first prescription of the first-line TNFi agent, and the baseline was the period within 1 year before the index date. The exclusion criteria included missing demographic data, the index date before 2009 or after September 2017, and those who had cancer, chronic kidney disease, or pneumonia at baseline.

2.3 | Definition of drug persistence

Drug persistence of the first-line treatment with different TNFis for each disease indication will be separately determined. The discontinued users were classed as if patients switched to another TNFi drug or refilled a prescription of TNFi more than 3 months since the last prescription. The 3-month interval was chosen based on the distribution of prescription refills; the gap of 3 months was used in most related studies.[19] The definitions of study event and censored point are showed in Figure S1.

When calculating drug persistence in RA patients, the local tapering policy of using TNFi in RA patient needs to be considered. RA patients who achieve remission defined as 28 joints Disease Activity Score (DAS28) < 2.6 for 6 months after 2 years of treatment, will face dose reduction in their third year of treatment. Therefore, the cumulative probability of drug persistence was calculated every year over the 5-year observation, to explore any potential influence of dose reduction on drug survival. We also observed the proportion of patients who switched to another TNFi stratified by the first-line TNFi.

2.4 | Study covariates

We transferred the continuous variables into ordinal or nominal variable. For example, age was calculated in years, then we classified the age group as <20 years, intervals of 10 years for each group from 20-30 to 70-80 years, and ≥80 years. The level of urbanization was defined by the Liu et al study:[20] the urbanization levels included high urbanization, moderate urbanization, developing town, general town, aged town, agriculture town, and village. Categories of geographic area in Taipei include north, central, south, Kaohsiung-Pingtung, and east. Co-morbidities, including hypertension (ICD-9: 401-405), ischemic stroke (ICD-9: 433-438), diabetes mellitus (ICD-9: 250), liver disease (ICD-9: 070.2-070.9, 570-573, 790.4), chronic obstructive pulmonary disease (COPD, ICD-9: 490-492, 493-496), and depression (ICD-9: 296, 300, 309, 311) were identified when ICD-9 codes were recorded at baseline. The medications, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, leflunomide, methotrexate, azathioprine, ciclosporin, and sulfasalazine were classified as non-user and user at baseline. These covariates were included in regression adjustment or propensity score analysis.

2.5 | Statistical analysis

The mean with standard deviation was used for continuous variables, and frequency with proportion was conducted for categorical variable. Analysis using large sample size is likely to find a statistically significant difference even when the effect size is negligible or small.[21] We used absolute standardized difference (ASD)[22] to compare the statistical values of baseline covariates between groups in the large sample observational study.

We obtained the cumulative proportion of discontinuation over 5 years after the index date. All study individuals were followed from the index date until the occurrence of drug discontinuation or the right censored date (death or 31DEC2017). The time to event analysis was applied to compare the rate of drug persistence between 3 TNFi treatments by indication. We estimated the cumulative drug survival probability by using the Kaplan–Meier method, and compared the difference by log-rank test. The multiple Cox proportional hazard regression was used for estimation of the adjusted hazard ratios that were pairwise comparisons of discontinuation between treatment groups.

In this observational study, the patients were not randomly allocated into study groups, and the baseline characteristics are often unbalance between groups. Propensity score matching (PSM) is a common method for balancing the characteristics between study groups. The propensity score is the conditional probability of receiving golimumab which was estimated by using logistic regression that comprised the covariates including the disease indication, initial year of anti-TNF treatment, gender, age, type of insurance, level of urbanization, co-morbidities (hypertension, ischemic stroke, diabetes mellitus, liver disease, COPD and depression) and co-medication (aspirin, NSAIDs, hydroxychloroquine, leflunomide, methotrexate, azathioprine, ciclosporin, sulfasalazine). PSM was conducted on a 1:1 basis, and the greedy nearest neighbor algorithm was used for selecting the paired population. The adaptive PSM is determined by examining the maximum ASD of baseline covariates among 3 groups.[22]

We also determined the persistence of TNF-alpha inhibitors by stratified analysis. In the stratified analysis, we examined the potential interaction effect between specific characteristics (demographics, concomitant medication and comorbidity) with type of TNFi on persistence. The 2-tailed significance level of .05 was used in this study. SAS V. 9.4 software (SAS Institute Inc.) was used for statistical work.

3 | RESULTS

3.1 | Baseline characteristics in different types of TNFi users

Initially we found 19 637 patients who ever used TNFi between 2008-2017. After exclusion (study flow chart in Figure 1), there were 6185, 2267, and 6884 patients in etanercept, golimumab, and adalimumab groups. Table S2 shows the baseline characteristics in study groups before PSM. The TNFi users had a higher proportion of RA patients. Compared with etanercept, golimumab and adalimumab users were more likely to have AS and PsA. The unbalanced (defined as maximum absolute standardized difference, Max ASD > 0.1) characteristics, including index year, gender, urbanization, length of hospital stay, and antirheumatic drugs at baseline were observed between study groups. After the PSM (Table 1), there was 2267 individuals in each group, and the baseline characteristics showed small differences (Max ASD ≤ 0.1) among groups.

3.2 | Rate of discontinuation

Table 2 shows that the incidence density rates (per 100 person-months) of discontinuation were 1.46 (95% CI: 1.37-1.57), 1.18 (1.09-1.27), and 1.71 (1.60-1.82) in propensity score matched etanercept, golimumab, and adalimumab users, respectively. The median persistence was estimated at 4.4, 5.9, and 3.5 years in etanercept, golimumab, and adalimumab naïve users. We observed the cumulative proportion of discontinuation; results showed 1-year proportions were 18.54% (95% CI = 16.72-20.56), 15.14% (95% CI = 13.58-16.70), and 20.46% (95% CI = 18.45-22.69) in etanercept, golimumab, and adalimumab respectively; 3-year proportions were 40.70% (95% CI = 37.94-43.66), 33.55% (95% CI = 31.20-35.90), and 44.57% (95% CI = 41.55-47.81); and 5-year proportions were 52.80% (95% CI = 49.12-56.76), 45.85% (95% CI = 42.54-49.16), and 56.86% (95% CI = 52.89-61.12). After stratifying by disease indication, golimumab had consistent low incidence of discontinuation. Figure 2A-D shows the cumulative proportion of drug persistence of etanercept, golimumab, and adalimumab over 5 years after the index

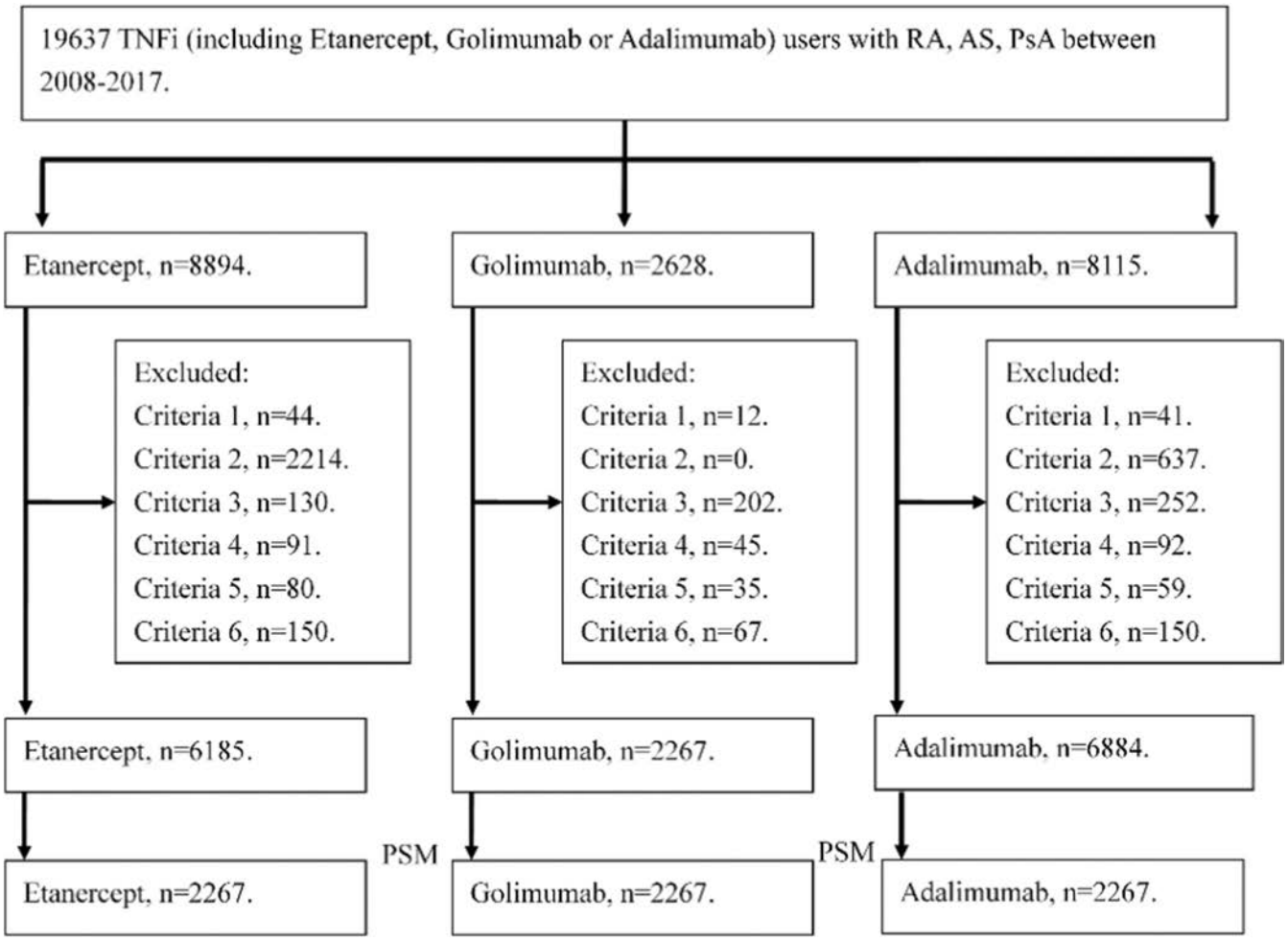

FIGURE 1 Excluded criteria included (1) missing demographic data, (2) prevalent (before January 2009) TNFi users, (3) new users after September 2017, (4) cancer patients at baseline, (5) chronic kidney disease patients at baseline, (6) pneumonia patient at baseline. AS, ankylosing spondylitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, TNF-alpha inhibitor

TABLE 1 Baseline characteristics in different TNFi users after propensity score matching

	Etanercept	Golimumab	Adalimumab	Max ASD
N	2267	2267	2267	
Indication				
RA	1400 (61.76%)	1369 (60.39%)	1378 (60.79%)	0.028
AS	570 (25.14%)	599 (26.42%)	600 (26.47%)	0.030
PsA	297 (13.10%)	299 (13.19%)	289 (12.75%)	0.013
Index y (initial y)				
2009-2012	125 (5.51%)	126 (5.56%)	126 (5.56%)	0.002
2013-2017	2142 (94.49%)	2141 (94.44%)	2141 (94.44%)	
Gender				
Male	931 (41.07%)	935 (41.24%)	937 (41.33%)	0.005
Female	1336 (58.93%)	1332 (58.76%)	1330 (58.67%)	
Age, mean ± SD	46.14 ± 14.79	46.23 ± 14.52	46.09 ± 14.64	0.060
Unit type of insured				
Government	126 (5.56%)	126 (5.56%)	127 (5.60%)	0.031
Privately held company	1452 (64.05%)	1433 (63.21%)	1436 (63.34%)	
Agricultural organizations	280 (12.35%)	286 (12.62%)	286 (12.62%)	
Low-income	22 (0.97%)	21 (0.93%)	23 (1.01%)	
Non-labor force	354 (15.62%)	370 (16.32%)	369 (16.28%)	
Others	33 (1.46%)	31 (1.37%)	26 (1.15%)	
Level of urbanization				
High urbanization	671 (29.60%)	679 (29.95%)	691 (30.48%)	0.090
Moderate urbanization	726 (32.02%)	720 (31.76%)	708 (31.23%)	
Developing town	355 (15.66%)	356 (15.70%)	353 (15.57%)	
General town	301 (13.28%)	288 (12.70%)	292 (12.88%)	
Aged town	53 (2.34%)	58 (2.56%)	57 (2.51%)	
Agriculture town	95 (4.19%)	92 (4.06%)	102 (4.50%)	
Village	66 (2.91%)	74 (3.26%)	64 (2.82%)	
Length of hospital stay				
0	2053 (90.56%)	2046 (90.25%)	2049 (90.38%)	0.082
1-6	127 (5.60%)	142 (6.26%)	140 (6.18%)	
7-13	51 (2.25%)	45 (1.99%)	50 (2.21%)	
≥14	36 (1.59%)	34 (1.50%)	28 (1.24%)	
Comorbidity				
Hypertension	424 (18.70%)	422 (18.61%)	418 (18.44%)	0.007
Ischemic stroke	42 (1.85%)	46 (2.03%)	42 (1.85%)	0.013
Diabetes mellitus	181 (7.98%)	188 (8.29%)	200 (8.82%)	0.030
Liver disease	186 (8.20%)	189 (8.34%)	203 (8.95%)	0.027
Chronic obstructive pulmonary disease	44 (1.94%)	44 (1.94%)	47 (2.07%)	0.009
Depression	263 (11.60%)	260 (11.47%)	266 (11.73%)	0.008
Co-medication				
Aspirin				
Non-user	2081 (91.80%)	2079 (91.71%)	2079 (91.71%)	0.000
User	186 (8.21%)	188 (8.29%)	188 (8.29%)	

(Continues)

TABLE 1 (Continued)

	Etanercept	Golimumab	Adalimumab	Max ASD
Nonsteroidal anti-inflammatory drugs				
Non-user	25 (1.10%)	28 (1.24%)	25 (1.10%)	0.020
User	2242 (98.9%)	2239 (98.77%)	2242 (98.9%)	
Hydroxychloroquine				
Non-user	1137 (50.15%)	1193 (52.62%)	1173 (51.74%)	0.063
User	1130 (49.85%)	1074 (47.38%)	1094 (48.25%)	
Leflunomide				
Non-user	1554 (68.55%)	1502 (66.25%)	1514 (66.78%)	0.080
User	713 (31.46%)	765 (33.75%)	753 (33.21%)	
Methotrexate				
Non-user	652 (28.76%)	675 (29.78%)	662 (29.20%)	0.026
User	1615 (71.24%)	1592 (70.22%)	1605 (70.8%)	
Azathioprine				
Non-user	2199 (97.00%)	2197 (96.91%)	2206 (97.31%)	0.000
User	68 (3%)	70 (3.09%)	61 (2.69%)	
Ciclosporin				
Non-user	1985 (87.56%)	1984 (87.52%)	2007 (88.53%)	0.044
User	282 (12.44%)	283 (12.49%)	260 (11.46%)	
Sulfasalazine				
Non-user	681 (30.04%)	706 (31.14%)	683 (30.13%)	0.042
User	1586 (69.96%)	1561 (68.86%)	1584 (69.87%)	

Abbreviations: AS, ankylosing spondylitis; Max ASD, maximum absolute standardized difference; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, TNF-alpha inhibitor.

date in IMRD, RA, AS, and PsA individuals. The highest drug persistence was estimated in the golimumab group, and the similar persistence rates were found among etanercept and adalimumab users. In PsA patients, the etanercept users had the worst persistence rate.

3.3 | The factors associated with discontinuation of TNFi treatment

We used the multiple Cox regression model to estimate the adjusted hazard ratio (aHR) for the discontinuation of TNFi treatment. Compared with golimumab, significantly higher risk of discontinuation was found in etanercept (aHR = 1.31, 95% CI: 1.20-1.43), and adalimumab (aHR = 1.38, 1.26-1.50) (Table S3). The AS patients had lower aHR of discontinuation compared with RA or PsA patients. In addition, we found significantly higher risk in females, those aged more than 60 years, with long hospital stays, and comorbid with liver disease. The co-medication with NSAIDs, methotrexate, had significantly decreased probability of discontinuation.

For stratified analysis, Table S4 provides the aHR of discontinuation compared between etanercept (aHR1) or adalimumab (aHR2) with golimumab. We observed the golimumab group had consistent lower risk in every subgroup, and the etanercept group had similar risk with the adalimumab group. We found the potential interaction effect between golimumab with gender, age, length of hospital stay, and cumulative dose of conventional DMARDs on discontinuation.

4 | DISCUSSION

For naïve TNFi treatment among Taiwan patients with moderate to severe inflammatory joint diseases, we found higher persistence rate in golimumab users than etanercept or adalimumab, and similar persistence rates between etanercept and adalimumab users. When differences of discontinuation were evaluated in the PSM cohorts, the finding did not change. Compared with golimumab, increase of 31% and 38% risk on discontinuation were observed in propensity score matched etanercept and adalimumab users.

Swedish research concluded that IMRD patients who initiated treatment with golimumab had significantly higher 42-month drug persistence than patients with etanercept or adalimumab, and similar drug survival was found between etanercept and adalimumab.[23] The recent systemic review study by Maniadakis et al,[19] indicated golimumab has the best drug compliance compared with other TNFis. Luttropp et al[24] suggest that golimumab provides a good performance of efficacy, safety and treatment satisfaction than other TNFis. Anti-drug antibodies also affect treatment efficacy; a review study[25] demonstrated the antibodies against TNFi were higher in adalimumab users, and lower in patients with

TABLE 2 The incidence density and cumulative proportion of discontinuation for TNFi treatment among propensity score matching

	Etanercept	Golimumab	Adalimumab
All IMRD population			
N	2267	2267	2267
Median followed time, mo	24	19	19
Followed person-mo	59 938	54 883	52 336
Observed event	878	647	893
Incidence density rate[a] (95% CI)	1.46 (1.37-1.57)	1.18 (1.09-1.27)	1.71 (1.60-1.82)
Cumulative probability, % (95% CI)			
1-y	18.54 (16.72-20.56)	15.14 (13.58-16.70)	20.46 (18.45-22.69)
2-y	31.33 (28.98-33.87)	26.45 (24.39-28.51)	36.26 (33.54-39.20)
3-y	40.70 (37.94-43.66)	33.55 (31.20-35.90)	44.57 (41.55-47.81)
4-y	47.05 (43.97-50.34)	40.86 (38.10-43.62)	52.71 (49.26-56.40)
5-y	52.80 (49.12-56.76)	45.85 (42.54-49.16)	56.86 (52.89-61.12)
RA patients			
N	1400	1369	1378
Median followed time, mo	24	19	18
Followed person-mo	38 018	32 783	31 811
Observed event before end of study	595	462	588
Incidence density rate[a] (95% CI)	1.56 (1.44-1.70)	1.41 (1.29-1.54)	1.85 (1.70-2.00)
Cumulative probability, % (95% CI)			
1-y	19.83 (17.67-21.99)	17.72 (15.58-19.86)	22.00 (19.73-24.27)
2-y	33.17 (30.54-35.80)	30.86 (28.12-33.60)	39.23 (36.37-42.09)
3-y	43.35 (40.45-46.25)	38.50 (35.42-41.58)	47.13 (44.03-50.23)
4-y	50.42 (47.28-53.56)	46.86 (43.33-50.39)	55.63 (52.20-59.06)
5-y	56.11 (52.46-59.76)	51.81 (47.71-55.91)	61.13 (57.21-65.05)
AS patients			
N	570	599	600
Median followed time, mo	25	23	21
Followed person-mo	14 857	15 672	14 444
Observed event before end of study	156	123	182
Incidence density rate[a] (95% CI)	1.05 (0.90-1.22)	0.78 (0.66-0.94)	1.26 (1.10-1.45)
Cumulative probability, % (95% CI)			
1-y	13.73 (10.79-16.67)	10.10 (7.55-12.65)	16.04 (12.98-19.10)
2-y	23.48 (19.66-27.30)	18.57 (15.04-22.10)	30.29 (26.23-34.35)
3-y	31.93 (27.46-36.40)	24.40 (20.23-28.57)	36.40 (31.95-40.85)
4-y	37.62 (32.64-42.60)	29.77 (24.83-34.71)	43.80 (38.66-48.94)
5-y	43.33 (37.27-49.39)	34.78 (28.53-41.03)	46.42 (40.74-52.10)
PsA patients			
N	297	299	289
Median followed time, mo	20	18	18
Followed person-mo	7063	6428	6081
Observed event before end of study	127	62	123
Incidence density rate[a] (95% CI)	1.80 (1.51-2.14)	0.96 (0.75-1.24)	2.02 (1.70-2.41)

(Continues)

TABLE 2 (Continued)

	Etanercept	Golimumab	Adalimumab
Cumulative probability, % (95% CI)			
1-y	22.70 (17.78-27.62)	13.28 (9.18-17.38)	22.80 (17.76-27.84)
2-y	38.55 (32.55-44.55)	21.26 (15.91-26.61)	35.94 (29.84-42.04)
3-y	47.41 (40.88-53.94)	28.04 (21.40-34.68)	51.79 (44.64-58.94)
4-y	51.61 (44.65-58.57)	32.68 (24.66-40.70)	60.87 (52.76-68.98)
5-y	61.29 (52.39-70.19)	37.02 (25.89-48.15)	66.08 (56.34-75.82)

Abbreviations: AS, ankylosing spondylitis; IMRD, immune-mediated rheumatic diseases; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, TNF-alpha inhibitor.

[a]Incidence density rate was presented as per 100 person-mo.

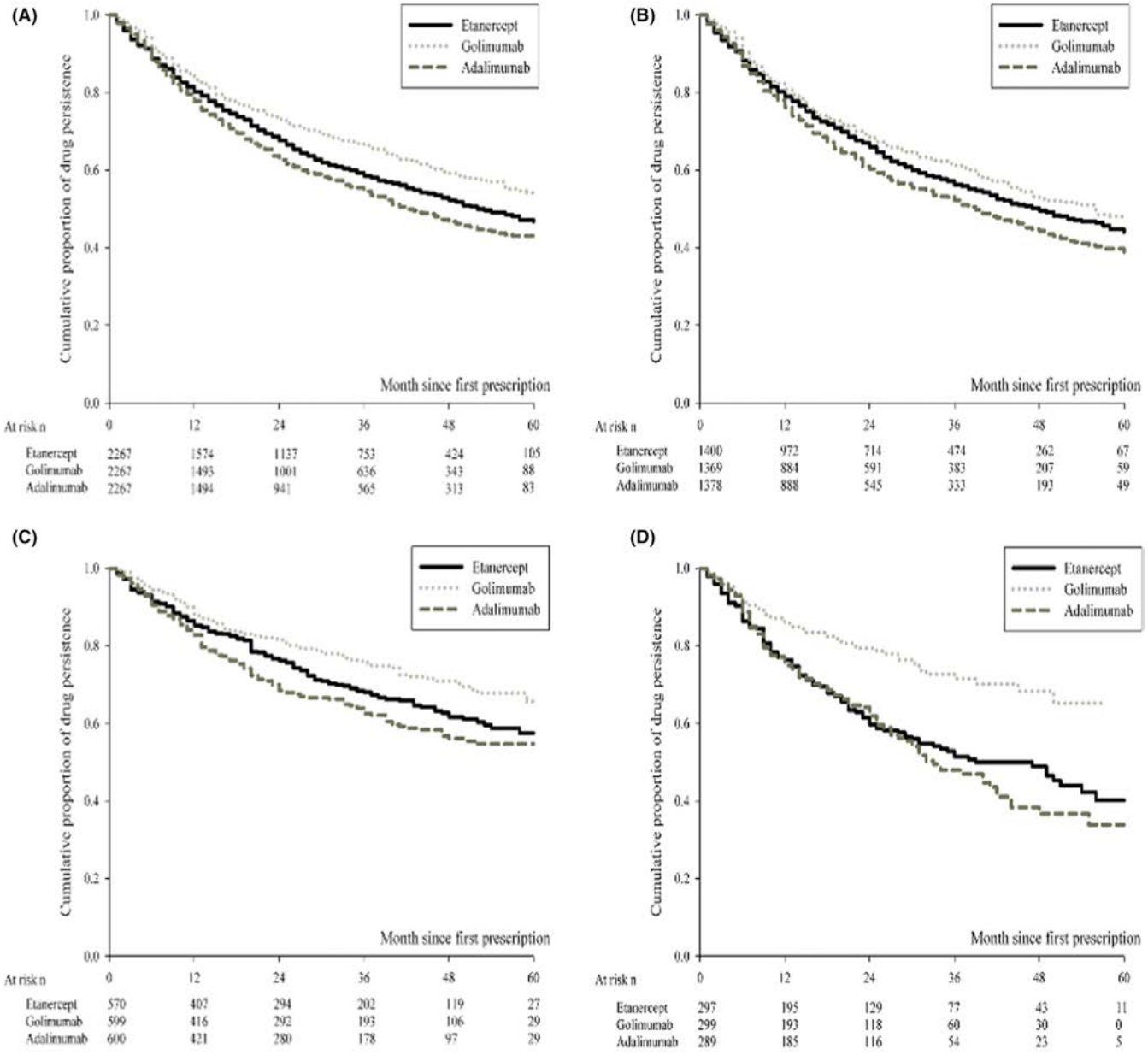

FIGURE 2 Kaplan–Meier survival curves of drug persistence for tumor necrosis factor inhibitor (TNFi) treatment in propensity score matched (A) all immune-mediated rheumatic diseases (IMRD), (B) rheumatoid arthritis (RA), (C) ankylosing spondylitis (AS), and (D) psoriatic arthritis (PsA) patients

etanercept and golimumab. However, the detection of anti-drug antibodies varied by the sensitivity of assays,[26] and further study is needed to compare the reaction of antibodies between these TNFi agents.[27] However, the Australian study that included 2612 patients indicated there was no statistical difference of 60-month drug persistence among first-line treatment of etanercept, adalimumab or golimumab;[28] the inconsistent finding might due to the difference in race or the policy of drug approval between Australia and Taiwan.

Drug persistence varied depending on the study design, including geographic area, data source (claim databases vs registries), definition of discontinuation (gap between refills).[19] There are several reasons which may lead to self-discontinuation of b-DMARDs, including out-of-pocket expenditures,[29] low level of pain, mode and interval of administration, negative beliefs about the treatment, treated with more than 1 line biologics, and poor medical and social support.[30] In our study, we found higher persistence rate of TNFi treatment in Taiwan; the potential reason is TNFi treatment is covered by the Taiwan NHI program, and TNFi agents are administered in clinics or hospitals.

This study found significantly lower risk of discontinuation in AS patients compared with RA or PsA patients. This finding is also reported in a systematic review[17] that involved 4 open-label trials analyzed for the persistence of golimumab. We suggested the difference between indications is contributed to by patient characteristics. Generally, AS patients had higher proportion of male gender and young age. Esposito et al[31] showed that female gender and increased age are associated with worse persistence. Flouri et al[32] demonstrated that male gender had better response to TNFi treatment. The adverse events of TNFi treatment increase in the elder patients.[32,33] In our study, the higher risk of discontinuation was also observed in females and elder IMRD patients.

We observed that patients who had longer hospital stays (≥7 days) had greater the chances of discontinuation. Hospitalized patients with long-term care usual had severe and chronic diseases, they usually need surgery and specific medications, that lead TNFi agents to be suspended to prevent adverse events from surgery or therapy. The hospitalized patients also had higher Charlson comorbidity index scores that are positively associated with discontinuation of TNFi in previous Asia studies.[12,35] The concomitant use of DMARDs is the major factor affecting the persistence of TNFi, especially co-therapy with methotrexate.[36,37] Our study also indicated high dose (more than the median) of methotrexate can decrease the risk of discontinuation.

The strength of this real-world research include that we identified a nation-wide and large sample size of first-line TNFi users from 2009 to 2017. Yang et al[34] only investigated drug persistence in RA patients from a single center, and comparison was restricted among etanercept and adalimumab. Although Korean[12,13] and Japanese[14] studies provided the persistence of TNFis and the associated factors in Asia populations, there was limited evidence for golimumab users and Chinese patients. Second, we used the propensity score analysis to balance the baseline characteristics, including indication, index year, gender, age, level of urbanization, geographic area, length of hospital stay, comorbidity and co-DMARDs.

There were several limitations in our study. First, the laboratory test, antibodies against TNFi, image report, and index of disease activity (such as DAS28, Simple Disease Activity Index, and Clinical Disease Activity Index) were not contained in NHIRD datasets, our finding might be confounded by these unmeasured factors. Second, we cannot identify drug efficacy, side effects, achieved remission in the insurance claim datasets; however, past studies had indicated the persistence associated with the balance of efficacy and adverse events. Third, we did not consider the second or third line TNFi therapy, because golimumab was covered in Taiwan NHIRD after January 2012, that limited us to discover the drug persistence in 2- or 3-line treatment. Finally, adherence or compliance was not evaluated in this study; however, TNFi was administered by injection in the clinic or hospital in Taiwan. We suggest the persistence rate was similar with the adherence rate.

5 | CONCLUSIONS

We found IMRD patients initiated with golimumab had the lowest risk of discontinuation compared with etanercept or adalimumab. Golimumab provides good drug persistence rate, further study can analyze the possible predictors, such as the efficacy, side effect, pain management, and anti-drug reaction that could affect the drug persistence of these TNFis in a Chinese population.

AUTHOR CONTRIBUTIONS

Conceptualization, J.-Y.H., P.-Y.L., H.-H.C. and J.C.-C.W.; methodology, J.-Y.H. and J.C.-C.W.; formal analysis, J.-Y.H.; data curation, J.-Y.H.; writing—original draft preparation, J.-Y.H. and J.C.-C.W.; writing—review and editing, P.-Y.L., H.-H.C. and A.K.; funding acquisition, J.-Y.H. All authors have read and agreed to the published version of the manuscript.

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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. Peer review was handled independently by Associate Editor, Chih-Wei Chen to minimize bias.

DATA AVAILABILITY STATEMENT

Due to the ethical and legal issues, the raw or sub-sets of data are not publicly available. The NHIRD can be applied for research at HWDSC, Taiwan. Please see the detailed instruction at website: https://dep.mohw.gov.tw/DOS/np-2497-113.html (in Chinese).

INFORMED CONSENT STATEMENT

The Institutional Review Board of the Chung Shan Medical University Hospital (CSMUH No: CS19012) approved this study, and patient consent was waived due to anonymized data.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study has been approved by Institutional Review Board of the Chung Shan Medical University Hospital (CSMUH No: CS19012).

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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

Adult-onset Still's disease in Western Australia: Epidemiology, comorbidity and long-term outcome

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Abstract

Aim: Adult-onset Still's disease (ASD) is a rare, potentially life-threatening autoinflammatory condition. As reported prevalence shows regional variation and long-term outcome data are scarce, we investigated epidemiology and long-term health outcomes of ASD in Western Australia (WA).

Methods: Population-based cohort study using longitudinally linked administrative health data from all WA hospitals between 1999 and 2013 for ASD patients (ICD-10-AM M06.1) and controls matched for age, gender, and index year. Rate ratios and odds ratios (RR/OR) with 95% confidence intervals (CI) compared ASD patients with controls.

Results: The average ASD incidence (n = 52) was 0.22/100 000 with 2.4/100 000 point-prevalence as of December 31, 2013. ASD patients (median age 41.5 years, 59.6% female) had higher odds of previous liver disease (OR 2.67, 95% CI 1.31-5.45), fever (OR 54.10, 95% CI 6.60-433.0), rash (OR 15.70, 95% CI 4.08-60.80), and serious infections (OR 4.36, 95% CI 2.11-22.80) than controls. Despite biological disease-modifying antirheumatic drugs in 27% of patients, ASD patients had higher odds for joint replacement (n = 7, 13.5%) (OR 45.5, 95% CI 4.57-93.70), osteoporosis (OR 31.3, 95% CI 3.43-97), and serious infections (RR 5.68; 95% CI 6.61-8.74) during follow up. However, crude mortality (11.5% vs 7.5%; $P = 0.34$), survival at 1 and 5 years ($P = 0.78$), and last modified Charlson Comorbidity score (median 2 vs 2) were similar between groups.

Conclusion: The epidemiology and demographics of ASD in Western Australia fall within the internationally reported range. ASD patients present increased rates of liver disease, rash, and serious infections before disease onset. Mortality following ASD was not increased for 5 years despite high rates of chronic arthritis requiring joint replacement, serious infections, and osteoporosis.

KEYWORDS
adults, comorbidity, epidemiology, lookback, Still's disease, survival

1 | INTRODUCTION

Still's disease (SD) is a rare systemic inflammatory disease of unknown origin, first described in children by Sir George Still more than a century ago.[1] Bywaters et al described in 1971 a series of adult women with clinical features reminiscent of SD and proposed the term adult-onset Still's disease (ASD).[2] ASD has reported prevalence ranges from 1 to 34 cases per million[3–5] and typically presents with a mixture of symptoms where daily fever spikes, sore throat, evanescent rash, and polyarthritis in the presence of neutrophilia and elevated acute-phase reactants are the most frequent findings.[3] However, myalgia, lymphadenopathy, fulminant hepatitis, serositis, consumption coagulopathy, and myocarditis can also occur.[6–8] ASD is a diagnosis of exclusion and, as a result, is usually only considered when treatment of suspected infections has been unsuccessful.[3,6] ASD is classified as an autoinflammatory disease where a complex interplay of genetic, infectious, and other environmental factors trigger overproduction of proinflammatory cytokines, which drive the clinical manifestations and ultimately can lead to the life-threatening macrophage activation syndrome ("cytokine storm").[7,8] The clinical course of ASD is unpredictable because it appears self-limiting in some patients but leads to recurrent exacerbations of systemic inflammation and/or the development of chronic deforming arthritis in many others.[9–11] With scarce data available from Australasia, we investigated the epidemiological characteristics, previous conditions, and long-term clinical outcomes in patients hospitalized for ASD in Western Australia (WA) over a 14-year period.

2 | MATERIALS AND METHODS

2.1 | Data sources

Data were derived from the WA Rheumatic Disease Epidemiological Registry (WARDER) that contains routinely collected longitudinal linked health data for patients with rheumatic diseases from hospitals for the entire state of WA as described elsewhere.[12,13] Sourced from the Hospital Morbidity Data Collection, WA Cancer Registry, WA Mortality Registry or the Emergency Department Data Collection in the state of WA (population 2.5 million) these datasets are linked through a validated process of probabilistic matching and clerical review to provide deidentified individual longitudinal health data over the period 1980-2015. The final data set contained sociodemographic data, all principal and secondary diagnoses for all earlier and subsequent hospital contacts for each participant, information on principal and secondary procedures performed, length and type of admission (eg, intensive care) in addition to diagnostic codes for any ED visit, ever-recorded cancer type, and time and cause of death during the observation period. WARDER also contains a large age- and sex-matched "comparator" group of patients selected from the WA Electoral Roll on the basis of requiring hospital care in the study period but not having a registered diagnostic code for rheumatic disease in any data collection linked through the WA Data Linkage System (WADLS).

2.2 | Study cohort

For this population-level observational study we included persons over 16 years of age with a recorded first diagnosis of ASD (International Statistical Classification of Diseases 10th revision Australian modification [ICD-10-AM] M06.10-M06.19) while residing in WA between January 1999 and December 2013. We excluded patients with possible ASD before 1999 because no specific coding for ASD was available in the ICD-9-Clinical modification with code 714.2 "Other rheumatoid arthritis with visceral or systemic involvement" considered too ambiguous. In an earlier study, ICD-10 coding for ASD was found to have 83% positive predictive value for a clinical diagnosis of ASD and 78% sensitivity for fulfillment of the Yamaguchi criteria.[14] For this study, each ASD patient was matched with up to five controls matched for age and gender but also for the same year of requiring hospital admission as the incident ASD case. WARDER controls are not healthy controls because they required hospitalization for a wide range of indications other than inflammatory rheumatic disease (see Figure S1), but survival in WARDER controls has been shown to be similar to that in the general population.[15] Date and primary causes of death were extracted from the WA Death Registry.

2.3 | Outcome ascertainment

As the first hospital contact was not necessarily for ASD, we defined a time-zero (T_0), which for ASD patients was the date of ASD diagnosis and for each control the date that most closely mirrored T_0 for the matched ASD patient. We defined the lookback period as all observation time before T_0 and follow up as all observation time more than 30 days after T_0. We defined the occurrence of serious infections as episodes leading to presentation at the Emergency Department and/or hospital admission resulting in an infectious disease code.[13] Study measures were the presence of specific ASD manifestations (Table S1) and the documented accrual of organ-system-specific, as well as overall weighted, comorbidity before and after T_0 according to the validated and prognostically important Charlson comorbidity index (CCI), in-hospital mortality, re-admission rate within 30 days, and survival at 1 and 5 years of T_0.

2.4 | Statistical analyses

Descriptive statistics are presented as median plus interquartile range (IQR) for numeric variables and proportions for categorical variables, unless otherwise indicated. Historical population data for WA were obtained from the Australian Bureau of Statistics (https://www.abs.gov.au/statistics/people/population/national-state-and-territory-popul

ation/latest-release#data-downloads-data-cubes). Average annual incidence and point prevalence rates are given per 100000 population with the total number of cases as numerator and a denominator based on the adult population in that year. A generalized log-linear regression model (Poisson) was used to analyze the trend in the number of cases per year. Differences for numeric results were compared by non-parametric methods (Kruskal-Wallis) and for proportions by χ^2 test with Yates correction where needed. All-cause hospitalization and Emergency Department visit rates (expressed as number per 100 person-years at risk) and odds for comorbidity/complications in ASD patients and controls were compared by conditional maximum likelihood estimates of odds ratios (OR) and rate ratios (RR) with 95% confidence intervals (CI). Kaplan-Meier estimates were used to compare survival between ASD and control with *P* values presented from the log-rank test. Analyses were performed using SPSS v27.0 software (IBM, Armonk, NY, USA) with two-sided *P*-values less than 0.05 considered to be statistically significant.

2.5 | Ethics

This project was approved by the Human Research Ethics Committee at the WA Department of Health (HREC 2016.24) with the condition to prevent potential identification by confidentializing small numbers (n < 5).

3 | RESULTS

There were 52 incident cases of ASD in the study period, comprising 31 females (59.6%, median age 42 years) and 21 males (40.4%, median age 39 years). The average annual incidence for ASD was 0.22/100000 (95% CI 0.14-0.32) and did not change significantly (R^2 = 0.21, *P* = 0.34) over the 14-year period (Figure 1). With 46 surviving patients the point-prevalence of ASD on December 31, 2013 was 2.4 per 100000 (95% CI 1.79-3.2).

Demographic and previous medical details of the ASD patients (Table 1) showed few gender differences regarding age at onset, regional presentation, or insurance status. Median length of hospital stay for first ASD presentation was 9 days (IQR 4.5-21.5) with some patients (n < 5, 5.7%) requiring intensive care unit admission. ASD-related complications included acute kidney injury (7.7%), consumption coagulopathy (7.7%), serositis (5.8%), macrophage activation syndrome (MAS) (1.9%), and in-hospital mortality (1.9%), with no significant differences between male and female patients (Table S2).

During a median lookback period of 203 months (IQR 40-280), ASD patients had higher rates/100 person-years for hospital admission and ED presentations before diagnosis than controls as well as higher odds of being diagnosed with liver disease, fever of unknown origin, rash, and serious infections (Table 2). Forty-eight ASD patients (92.3%) had at least one hospital contact in the year before diagnosis. Most ASD patients (89.5%) and controls (96.9%) had recorded comorbidity before T_0 and although median CCI scores were similar between the groups, slightly more ASD patients had multimorbidity (m-CCI ≥2) (Table 2).

Readmission within 1 month after discharge was more frequent in ASD patients than controls (19.2% vs 9.6%, *P* = 0.003) with five out of ten ASD patients readmitted with disease flare as the primary diagnosis. During a median follow up of 49 months (IQR 24-84) a total of 36 ASD flares occurred in 13 (25%) patients for a flare rate of 14.7/100 person-years (Table 3). Forty-eight ASD patients and 177 controls required hospital care beyond 30 days of follow up (94% vs 78%, respectively; OR 3.45, 95% CI 1.27-11.7) with higher rates for both admission and Emergency Department visits in ASD patients (Table 3). Among these ASD patients a total of 13/48 (27%) received intravenous biological disease-modifying antirheumatic drug therapy, of which seven patients (13.5%) underwent joint replacement surgery after a median period of 77 months (IQR 64-103) with total hip (40%) and knee (40%) replacement the most frequent procedures. Osteonecrosis (ICD-10 code M87) was diagnosed in a 51 year old female patient 6 months

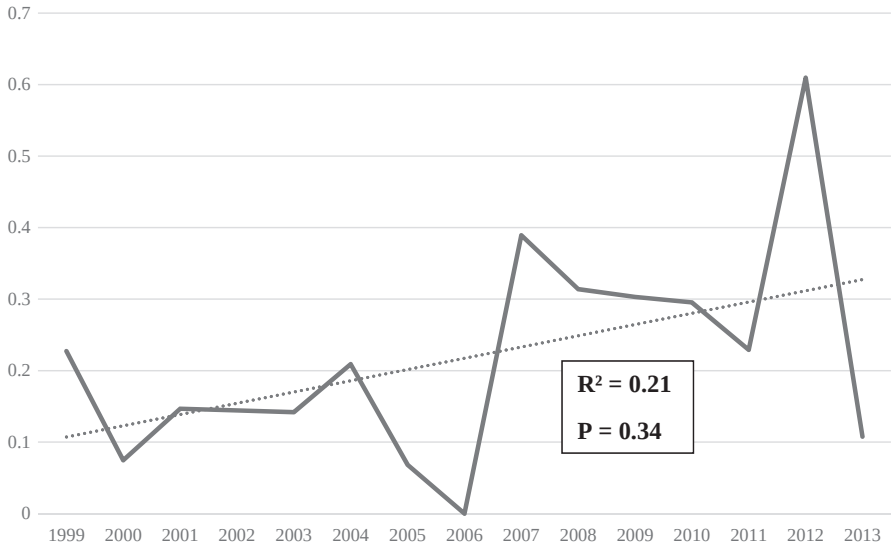

FIGURE 1 Annual incidence rate with trendline of adult-onset Still's disease in Western Australia per 100000 population over the study period

TABLE 1 Patient characteristics at first ASD presentation

	All (n = 52)	Female (n = 31)	Male (n = 21)	*P* value
Age onset (years)	41.5 (31-56)	42 (32-51)	39 (25-64)	0.64
Indigenous background	<5 (1.9)	<5 (3.2)	0	NA
Country of birth				
Australia	39 (75%)	24 (77.4%)	15 (71.4%)	
Europe	6 (11.5%)	<5 (12.9%)	<5 (9.5%)	
Asia	6 (11.5%)	<5 (6.4%)	<5 (19%)	
Africa	<5 (2.5%)	<5 (3.2%)	-	
Hospital location				
Metropolitan	44 (85%)	26 (84%)	18 (86%)	0.73
Regional	8 (15%)	5 (16%)	<5 (14%)	
Admitted from Emergency Department	28 (54%)	16 (52%)	12 (57%)	0.25
Insurance status				
Public	35 (67%)	21 (68%)	14 (67%)	0.96
Private	17 (33%)	10 (33%)	7 (33%)	
Complications observed				
Acute renal failure	<5 (7.7%)	<5 (3.2%)	<5 (14.3%)	0.17
Consumption coagulopathy	<5 (7.7%)	<5 (6.4%)	<5 (9.5%)	0.39
Serositis	<5 (7.7%)	<5 (3.2%)	<5 (14.3%)	0.17
MAS/ARDS	<5 (1.9%)	0	<5 (4.7%)	-
Procedures performed				
Skin biopsy	6 (11.5%)	<5 (12.9%)	<5 (9.5%)	0.45
BM biopsy	8 (15.4%)	5 (16.1%)	<5 (14.3%)	0.78
Liver biopsy	<5 (5.8%)	0	<5 (9.5%)	-
Lymph gland biopsy	<5 (1.9%)	<5 (3.2%)	<5 (4.7%)	0.66
Arthrocentesis	10 (19.2%)	6 (19.4%)	<5 (19%)	0.91
LOS (days)	9 (4.5-21.5)	8 (5-11)	11 (3-26.5)	0.17
Required ICU admission	<5 (5.8%)	<5 (3.2%)	<5 (9.5%)	0.28

Note: Small numbers are given as <5 because of Human Research Ethics Committee requirements to prevent identification. Data represent median values (interquartile range) or frequency (%)

Abbreviations: ARDS, acute respiratory distress syndrome; ASD, adult-onset Still's disease; BM, bone marrow; ICU, intensive care unit; LOS, length of stay; MAS, macrophage activation syndrome.

after ASD diagnosis and in a 62 year old male patient >10 years after ASD diagnosis but no formal diagnosis of steroid-induced osteonecrosis (Y42.0) was recorded. The overall frequency (27% vs 8%, $P < 0.01$) and the rate of serious infections per 100 person-years (20 vs 3.6; RR 5.68, 95% CI 6.61-8.74) remained increased for ASD patients over the observation period (Table 3). There was however no significant difference between ASD patients and controls in crude mortality (6/52, 11.5% vs 18/228, 7.5%; $P = 0.34$) or survival rates over 5 years ($P = 0.78$) (Figure 2). Adjusting for the baseline presence of DM or CVD did not significantly influence survival rates between patients and controls (log-rank $P = 0.74$ and $P = 0.82$, respectively). The most frequent cause of death was malignancy in ASD patients (n = 6) (melanoma in two, metastasis of unknown primary in one with no registered cases of lymphoproliferative malignancies) and cardiovascular events in controls (n = 18) (Figure S2).

4 | DISCUSSION

In this population-based study stretching over 14 years, the average annual incidence of ASD in WA was 0.22/100 000, while point-prevalence at December 31, 2013 was 2.4/100 000 and ASD was associated with 1.9% in-hospital mortality. Compared with matched controls, ASD patients had significantly higher odds of serious infections and liver disease pre-diagnosis, but survival during follow up was similar for both groups, despite an ASD flare rate of 14.7/100 person-years and increased odds for chronic arthritis, joint replacement surgery, osteoporosis, and serious infections in ASD patients.

The ASD incidence based on case series varies from 0.16/100 000 in France to 0.4/100 000 in Norway, and a questionnaire-based survey in Japan in 1993 found 144 ASD patients (87% fulfilled classification criteria) and estimated the national incidence at 0.28/100 000 and prevalence at 1.1/100 000.[4,5,16] Using population-wide hospital

TABLE 2 Patient characteristics and previous medical conditions in ASD patients and controls during lookback period

	ASD	Controls	RR/OR (95% CI)	*P* value
Age at first hospital contact (years)	25 (16-40.5)	25 (17-41)	-	0.85
Lookback (months)	203 (40-280)	190 (73-260)	-	0.81
Total person-years	752	3211	-	-
ED visit rate/100 person-years	29.4 (25.7-33.5)	11.5 (10.3-12.6)	2.42 (1.25-4.91)	0.007
Admission rate/100 person-years	79.5 (62.9-97.9)	47.4 (36.2-61.3)	1.71 (1.2-2.5)	0.003
Previous diagnoses				
Chronic pulmonary disease	46 (88.5)	219 (96.1)	0.32 (0.11-0.93)	0.04
Liver disease	15 (28.8)	30 (13.2)	2.67 (1.31-5.45)	0.01
Cardiovascular event	<5 (3.8)	15 (6.6)	0.57 (0.13-2.64)	0.75
Diabetes mellitus	8 (3.5)	84 (7.7)	0.31 (0.13-0.68)	0.02
Cancer	<5 (5.8)	19 (8.3)	0.67 (0.19-2.37)	0.77
Peptic ulcer disease	<5 (7.7)	<5 (1.8)	4.67 (1.13-19.32)	0.04
Renal disease	<5 (5.8)	6 (2.6)	2.27 (0.55-9.38)	0.38
FUO	10 (19.2)	<5 (0.4)	54.1 (6.6-433.4)	<0.001
Rash	9 (17.3)	<5 (1.3)	15.7 (4.08-60.8)	<0.001
Sore throat	<5 (3.8)	0 (0)	NA	NA
Serious infection	8 (15.4)	10 (4.4)	4.36 (2.11-22.8)	0.001
m-CCI score at time zero	1 (1-2)	1 (1-2)	-	0.68
m-CCI = 0	6 (11.5%)	7 (3.1)	-	0.02
m-CCI = 1	27 (51.9%)	153 (67.1)		
m-CCI ≥2	19 (36.5%)	68 (29.8)		

Note: Small numbers are given as <5 because of Human Research Ethics Committee requirements to prevent identification. Data represent median values (interquartile range) or frequency (%) with rate ratio and odds ratios (95% confidence intervals).

Abbreviations: ASD, adult-onset Still's disease; CI, confidence interval; ED, Emergency Department; FUO, fever of unknown origin; m-CCI, modified Charlson comorbidity Index (without the rheumatic disease); OR, odds ratio; RR, rate ratio.

admission data, we found an annual incidence (0.22) and prevalence (2.4) of ASD that was comparable with a recent population-based study from Poland using hospital discharge records between 2009 and 2018 that estimated annual incidence rate at 0.32/100 000 and point-prevalence of 2.7/100 000 by 2019.[17] With both age at diagnosis (42.5 years) and the female predominance (59.6%) also in the middle of the range reported in the literature, our findings indicate that ASD remains a relatively uncommon condition in WA for which there does not appear to be a substantial difference based on region or over time.[4,5,16–18]

ASD remains a diagnosis of exclusion as exemplified by the high number of procedural investigations performed during ASD admission to exclude other causes of disease manifestations and the relatively prolonged length of hospital stay of 9 days, which is higher than the 6 days reported from the USA.[19] ASD-related complications including kidney failure, consumption coagulopathy, and hemophagocytic lymphohistiocytosis/MAS were observed infrequently in line with findings from other studies,[17,18] although higher complications rates are reported in studies from dedicated/specialized centres.[20–22] As a result, in-hospital mortality was relatively low at 1.9% comparable with data from the USA and Poland,[17,18] but much lower than the 16% reported from Italy, mainly due to a high number of patients with fatal MAS.[21]

Baseline comorbidity scores (without the rheumatic disease component, because this was excluded in controls) at ASD diagnosis were not higher than in non-ASD controls in our study, although the average CCI scores in the US survey, which included the score for rheumatic disease, were reportedly higher in ASD patients than controls (1.33 vs 0.81).[18] The specific comorbid conditions that could potentially predispose to ASD in this study were a higher rate of previous serious infections and existing liver disease. Although infections have long been considered a trigger for ASD in (genetically) predisposed individuals,[23,24] we did not find evidence of an increased rate of specific serious infections, including pneumonia, sepsis, or bacteremia, urinary tract infection, and skin and soft-tissue infections. As almost 95% of all serious infections had

TABLE 3 Frequency of new complications registered in ASD patients and controls during follow up period.

	ASD (n = 48)	Controls (n = 177)	OR (95% CI)	*P* value
Follow up period (months)	42 (22-80)	49 (24-89)	-	0.51
Total person years	245	927	-	-
30-day readmission	10 (19.2)	15 (6.6)	3.52 (1.41-8.40)	0.003
ASD flare rate (n = 36)	14.7 (10.5-20.1)	-	-	-
Serious infections rate	20 (14.8-26.4)	3.6 (2.5-5.0)	5.68 (3.61-8.74)	<0.01
Subsequent diagnoses				
Joint replacement surgery	7 (13.5)	0	45.5 (4.57-93.1)	<0.001
Osteoporosis	5 (9.6)	0	31.26 (3.43-97)	<0.001
Chronic pulmonary disease	45 (93.7)	154 (87.0)	2.24 (0.6-7.81)	0.31
Liver disease	16 (20.8)	27 (15.3)	2.78 (1.33-5.74)	0.007
Cardiovascular event	7 (14.6)	15 (8.5)	1.86 (0.71-7.84)	0.27
Diabetes mellitus	<5 (2.1)	<5 (1.1)	1.86 (0.51-2.16)	0.52
Cancer	<5 (8.3)	10 (5.9)	1.51 (0.79-5.87)	0.51
Peptic ulcer disease	<5 (2.1)	<5 (0.6)	3.75 (0.23-60.9)	0.38
Renal disease	<5 (6.2)	9 (5.1)	1.24 (0.33-4.78)	0.72
ED visit rate	105 (93-120)	49 (44-54)	2.15 (1.85-2.50)	<0.01
Admission rate[a]	168 (151-184)	58 (54-63)	2.87 (2.52-3.26)	<0.01
Median m-CCI at last obs. Comorbidity score	2 (1-2)	2 (1-2)	-	0.11
m-CCI at last obs. =0	9	52	-	0.24
m-CCI at last obs. =1	32	109		
m-CCI at last obs. ≥2	7	16		

Note: Data represent median values (interquartile range), frequency (%) or rate/100 person-years with odds ratios presented with 95% confidence intervals.

Abbreviations: ASD, adult-onset Still's disease; CI, confidence interval; ED, Emergency Department; m-CCI, modified Charlson comorbidity Index (without the rheumatic disease); OR, odds ratio.

[a]Excluding admissions for drug infusions. Small numbers are given as <5 because of Human Research Ethics Committee requirements to prevent identification.

microbiological confirmation, it is less likely that ASD disease flares were misdiagnosed as serious infections, but it has been suggested that a particular combination of pathogenic microorganisms with genetic susceptibility (variations in, for example, human leukocyte antigen or cytokine genes) are likely essential determinants of ASD development and severity.[23,25] The prevalence of chronic lung disease over a nearly 20-year period before diagnosis was high although not different for ASD patients and controls. The relevant CCI codes include conditions such as bronchitis, smoking, asthma, and emphysema, which are not specific for ASD and are frequent diagnoses in hospitalized patients. Although abnormal liver enzymes are a recognized feature of ASD, it is unclear whether the higher rate of pre-existing liver disease in ASD patients versus controls (28.8% vs 13.2%) reflected impending ASD or classifies as a specific risk factor that will require further study.

There are limited data on long-term survival in ASD.[26] Crude mortality was 11.5% over a median follow up of 4.2 years in this study, which falls within the 25% mortality rate (n = 2 of 8) from

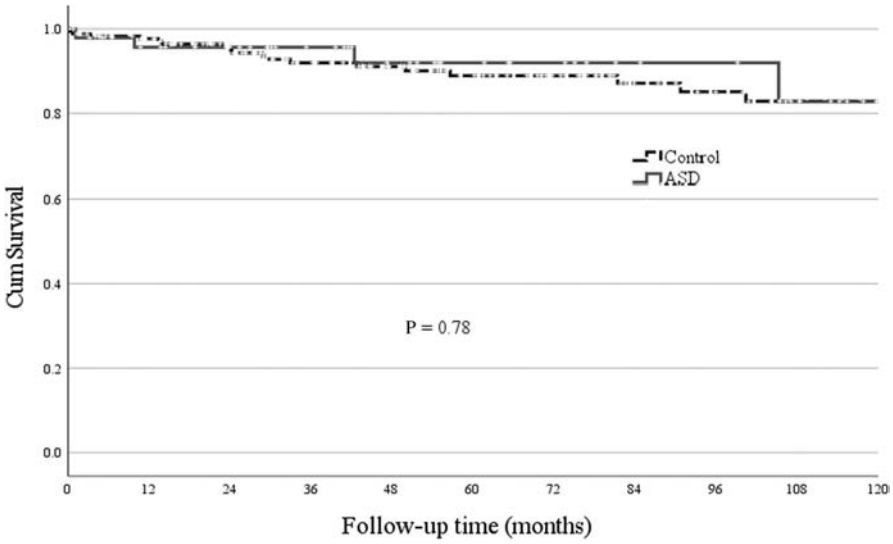

FIGURE 2 Kaplan-Meyer curves and log-rank test result for survival beyond 30 days in adult-onset Still's disease patients and age-/gender-matched hospitalized controls

France after more than 10 years of follow up, the 9.8% mortality rate over 3.9 years of follow up reported from a single center study in China, and the 5.4% mortality rate over 2.8 years from Japan.[5,10,16,26,27] Crude mortality rates may be influenced by other population-specific and comorbid factors, but the inclusion of a matched cohort of hospitalized controls provided comparative data demonstrating that overall survival up to 5 years was not worse for ASD patients compared with other hospitalized patients. Cardiovascular death was less and cancer-related death was more frequent in ASD patients compared with controls. All cancers in ASD patients were solid organ malignancies and although not significant because of low numbers/statistical power, this supports the need for monitoring for the possibility of malignancy-associated ASD.[28,29]

Joint and bone complications were the main long-term problems in up to 30% of ASD patients. The risk of chronic erosive arthropathy in a subgroup of ASD patients has long been recognized and despite the empirical use of biological drug therapy in 27% of patients a relatively large number of patients in this study (n = 7, 13.5%) required joint replacement surgery for symptomatic relief in the long run.[30,31] ASD treatment is deduced from observational studies and although randomized controlled trials to support the therapy of choice in ASD patients are lacking there is increasing evidence that cytokine targeting treatment is beneficial.[32–35] As detailed medication data are not available in ICD-10-AM, we were unable to analyze this in depth (with infliximab available in Australia since 2003 and tocilizumab since 2010). Glucocorticoids are usually required to induce rapid remission of ASD symptoms,[19,30] which makes the occurrence of osteoporosis in nearly 10% of ASD patients and early osteonecrosis in one patient noteworthy as it confirms the need for effective alternative ways to achieve early disease control. The frequency of serious infections since ASD diagnosis (27%) is slightly higher than the 21% observed by Lenert et al.[18] and while this may partly be due to immunomodulating treatment, the fact that a considerable proportion of ASD patients also had serious infections before diagnosis lends some support to the idea of an inherent susceptibility to infection in ASD patients.[36]

The strength of this study is the reliance on a validated database with good diagnostic accuracy, reliable data linkage, long term follow up and inclusion of an age- and gender-matched control group to determine differences in the main outcomes, especially serious infection and mortality. The limitations of this study relate to the fact that our data are based on a physician-based discharge diagnosis of ASD and lack the detailed clinical and laboratory data to determine if patients fulfilled ASD classification criteria. However, a recent chart review found a 78% sensitivity for fulfilling Yamaguchi criteria in administrative hospital data, which reduces the likelihood of diagnostic error.[14] The population-wide capture of ASD through mandatory reporting of hospital discharge diagnoses also makes it unlikely that we have missed the rare ASD patients seen solely as outpatients. Nonetheless, the relatively small number of cases with wide confidence intervals makes it challenging to compare outcome measures and a larger (national) cohort with even longer follow up may provide additional information.

5 | CONCLUSIONS

ASD is as uncommon in WA as in other regions. Serious infection appears to be a major risk factor. Despite high rates of chronic arthritis and joint replacement, osteoporosis and serious infections, 5-year survival is not significantly negatively impacted. This may be because the most serious complication, hemophagocytic lymphohistiocytosis/MAS, is less common in population cohorts compared with specialist center studies.

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CONFLICT OF INTEREST

The authors report no competing interests with regards to this study.

DATA AVAILABILITY STATEMENT

Approval for use of de-identified data was obtained from the Human Research Ethics Committee (HREC) at the WA Department of Health (WADOH HREC# 2016.24). As this study was considered low risk by the WA Health HREC and due to the de-identified nature of the linked health data set, the requirement for patient consent was waived. WA Health is proprietor of this administrative health data data set. Restrictions apply to the availability of these data, which were used under license of WA Health Data Linkage Branch for the current study. Data are however available from the authors upon reasonable request and after permission of WA Health and WA Data Linkage Branch.

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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

Ankle and foot pathologies in early rheumatoid arthritis, what can ultrasound tell us?

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Abstract

Background: Rheumatoid arthritis (RA) is a systemic autoimmune polyarticular disease. Despite being commonly affected in RA, the ankle and foot do not receive much attention, particularly in early disease. The precise diagnosis of their involvement and its impact on health is a clinical challenge that requires accurate assessment.

Aim: To determine the role of ultrasound in evaluation of ankle and foot pathologies and assess its impact on functional activity in newly diagnosed RA patients.

Methods: The study was conducted on 152 RA patients and 52 healthy controls. Patients were subjected to history taking, clinical examination, and ultrasound scan. Impact on health was measured by health assessment questionnaire, as well as foot function index.

Results: In a cohort of patients with early RA with median duration of 1 month, tibialis posterior (TP) tenosynovitis (45.4%) was the most common pathology, followed by tibiotalar (TTJ) synovitis (39.8%), and peroneal tenosynovitis (39.1%). In terms of disease duration, TTJ ($P = .001$) foot pathologies were less common in early RA and tended to worsen over time, whereas TP ($P = .048$) and peroneal tenosynovitis ($P = .011$) were more common in early RA. In multivariate analysis TTJ, subtalar synovitis, forefoot pathologies, TP tenosynovitis, and Achilles enthesitis were found to be significant predictors of functional disability. The most important predictors of ankle pain were TTJ synovitis, TP tenosynovitis, peroneal tenosynovitis, and plantar fasciitis.

Conclusion: Ankle and foot involvement is a common issue of early RA, and it has a significant impact on quality of life. Ultrasound is a reliable tool for evaluating various abnormalities in this complex area, allowing for better management.

KEYWORDS
ankle, early, foot, rheumatoid arthritis, ultrasound

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by changes in the synovial tissue of joints, cartilage, and bone, and, less commonly, extra-articular locations.[1] Foot and ankle pain are common complaints among RA patients throughout the disease's progression, affecting their overall health. As a result, it is critical to improve their early detection.[2]

Identifying ankle pathologies is critical for initiating treatment as soon as possible to avoid deterioration.[3] Assessing the characteristics of inflammation in the joint and its impact on the functional status of RA patients will allow clinicians to target treatment interventions and improve symptoms.[4]

Ultrasound is a sensitive imaging tool that allows identification of the affected anatomic structures, explaining the cause of ankle pain when present and revealing subclinical disease in asymptomatic ankles.[5] Previous research has shown that ankle joint evaluation is undervalued in many clinical and sonographic scores used for RA patient evaluation and follow up. More effort is required to detect the value of ankle joint examination in RA and the assessment of ultrasonographic signs according to frequency, disease duration, and activity.[6]

Considering the scarcity of studies on the ankle and foot involvement in RA, especially in the early stages of the disease, we decided to investigate the extent of ankle involvement in rheumatoid patients with early disease duration and to emphasize the impact of ankle pathologies on patients' functional activity.

2 | MATERIALS AND METHODS

A cross-sectional study was conducted on 152 patients diagnosed with RA using the American College of Rheumatology/European League Against Rheumatism criteria with or without ankle pain, as well as 52 healthy controls (age- and gender-matched) with no history of or current joint disease. Patients were chosen from the rheumatology and immunology unit, within 1 year of the study's start. Patients who were younger than 18 years, who had diabetes or hepatitis C virus infection, who were pregnant, who had overlap with other connective-tissue diseases or previous ankle surgery or trauma, and who received ankle injections were all excluded.

All patients had a history taken that included the following information: age, gender, place of residence, disease duration, presence or absence of ankle pain, and duration of ankle pain if present. For the patient's ankle pain, a visual analogue scale (VAS) (0-10) was used. The study was approved by the medical ethics research committee at the Faculty of Medicine, Mansoura University. After ensuring confidentiality, each participant in this study provided informed written consent.

2.1 | Clinical examination

Tenderness, swelling of joints, and periarticular structures were detected during a standard clinical examination of the ankle and foot. Patients were considered symptomatic if there was pain at any joint or soft-tissue structure.

Patients were asked to fill out the following questionnaires to calculate the degree of functional disability of the overall function and the foot function: the Health assessment questionnaire, which consists of 20 questions that assess functional status, with scores ranging from 0 to 3 for each question; and the questionnaire on Foot Function Index (FFI),[7] which has 23 items divided into three subscales: pain (nine items), physical functioning (nine items), and limitation (five items). A percentage of the total score was computed. Reduced foot function was indicated by higher FFI scores.

2.2 | Disease activity

Disease activity score (DAS28) was used to assess RA activity by counting the number of swollen, tender joints. Erythrocyte sedimentation rate tests and the VAS score were also recorded. The results were then entered into a mathematical formula to produce a score.[8]

2.3 | Ultrasound examination

On the same day as the clinical examination, an experienced rheumatologist (MGA) with approximately 9 years of experience in musculoskeletal ultrasound scanned both ankles and feet of each patient. The examiner was not given access to the patients' clinical or laboratory data. The same person scanned all the patients with a Toshiba Xario 200 machine with 13 MHz superficial probe.

According to European League Against Rheumatism guidelines,[9] the following structures were investigated: joints including tibiotalar (TTJ), subtalar (STJ), talonavicular (TNJ), calcaneo-cuboid (CCJ), naviculo-cuneiform (NCJ), cuneiform-metatarsal, cuboid-metatarsal, metatarsophalangeals (MTP), tendons of tibialis anterior, extensor hallucis longus, extensor digitorum longus, tibialis posterior (TP), flexor digitorum longus, flexor hallucis longus, peroneals, Achilles, as well as retrocalcaneal bursa, and plantar fascia. The ultrasound examination involved initial gray-scale examination, followed by a power Doppler (PD) evaluation. The PD settings were constant (gain just below noise level, 750 Hz pulse repetition frequency, 8-10 MHz Doppler frequency, low wall filter).

Synovitis, tenosynovitis, bursitis, enthesitis, and erosions were all noted as abnormalities. Their interpretation was based on preliminary OMERACT definitions for ultrasound pathology.[10] Enthesitis was diagnosed if there was one of: tendon insertion pathology, bone erosion, enthesophyte, bursitis. Bursitis was defined as a well-defined, localized anechoic or hypoechoic area at the site of an anatomical bursa that could be compressed by the transducer.

2.4 | Statistical analysis

The IBM SPSS software package version 25.0 for Windows was used to analyze the data (IBM, Armonk, NY, USA). Numbers and

percentages were used to describe qualitative data. After testing normality with the Kolmogorov-Smirnov and Shapiro tests, quantitative data were described using the median (minimum and maximum) and interquartile range for non-parametric data and mean, standard deviation for parametric data. The χ^2 or Fisher exact test was used to compare qualitative variables, as appropriate. The significance of the obtained results was determined at the 5% level.

Linear regression was used with FFI and VAS as dependent variables. The independent variables used in the regression models were chosen from those that had a significant correlation with the FFI and VAS. To test the reliability of categorical variables with κ, reliability analysis was performed using κ agreement.[11]

3 | RESULTS

The current study included 152 RA patients with a mean age of 43.23 ± 12.5 years, with a higher prevalence of female (84.9%) than male (15.1%), as well as 52 age- and gender-matched healthy controls. The median of disease duration was 1 month. Two hundred ankles were symptomatic, and 104 were asymptomatic. The median duration of ankle pain was 3 months, with a VAS ranging from 0 to 9 and a median of 4. Patients were on methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and steroids. None of our patients were on biological therapy, and those taking more than 10 mg of steroids per day or taking non-steroidal anti-inflammatory drugs in the last 14 days were excluded. Table 1 displays detailed clinical and laboratory findings.

Clinical examinations were performed to detect tenderness and swelling at different joints of ankle and foot in addition to adjacent soft tissue. Detailed findings of the clinical examinations are shown in Table S1. The patients were classified according to presence or absence of ankle pain. There was a statistically significant difference between both groups regarding ankle and hindfoot pathologies ($P \leq .001$) in addition to NCJ ($P = .03$) and first ($P \leq .001$), second ($P = .027$), fifth ($P = .028$) MTP joints. Details are shown in Table S2.

3.1 | US scan

To the best of our knowledge this study contains the largest number published until now of structures scanned by US in ankle and foot, including 17 joints, 11 soft tissue structure per foot, for a total of 11 424 structures (6936 joint and 4488 soft tissue). Each foot was

TABLE 1 Demographics and clinical data of patients in the study

Demographic data	RA patients (n = 152)	Healthy controls (n = 52)
Age (years)	43.23 ± 12.53	43.07 ± 0.70
Gender	Female (84.9%) – male (15.1%)	Female (84.6%) – male (15.4%)
Disease duration (months)	1 (1-360)	
Ankle pain (n = 304)	200 painful ankles (65.8%) – 104 non-painful ankles (34.2%)	
Ankle pain duration (months)	3 (0-60)	
VAS (0-10)	4 (0-9)	
ESR (mm/h)	46.5 (5-125)	
CRP (mg/L)	12 (0-132)	
DAS28 score	3.8 (1.2-5.8)	
RF	106 (69.7%)	
ACPA	66 (43.4%)	
HAQ	1.8 (0.4-2.65)	
FFI	60 (15-92)	
MTX	63 (41.4%)	
Leflunomide	53 (34.9%)	
Hydroxychloroquine	66 (43.4%)	
Sulfasalazine	12 (7.9%)	
Steroid	40 (26.3%)	
Biologics	0 (0%)	

Note: All parameters are described in median (min-max) except age in mean ± SD.

Abbreviations: ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; DAS28, disease activity score of 28 joints; ESR, erythrocyte sedimentation rate; FFI, foot function index; HAQ, health assessment questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS, visual analogue scale.

TABLE 2 Ultrasound findings of ankle pathologies

Structure of ankle examined	Patients Ankles = (304)			Healthy controls Ankles = (104)		
	GS	PD	Erosion	GS	PD	Erosion
TTJ	121 (39.8%)	19 (6.3%)	1 (0.3%)	6 (5.8%)	0 (0%)	0 (0%)
Hindfoot	133 (43.8%)	23 (7.6%)	41 (13.5%)	4 (3.8%)	0 (0%)	0 (0%)
STJ	82 (27%)	9 (3%)	8 (2.6%)	0 (0%)	0 (0%)	0 (0%)
TNJ	113 (37.2%)	20 (6.6%)	35 (11.5%)	4 (3.8%)	0 (0%)	0 (0%)
CCJ	28 (9.2%)	4 (1.3%)	11 (3.6%)	0 (0%)	0 (0%)	0 (0%)
Midfoot	52 (17.1%)	3 (1%)	24 (7.9%)	0 (0%)	0 (0%)	0 (0%)
Naviculo-cuneiform joint	41 (13.5%)	2 (0.7%)	20 (6.6%)	0 (0%)	0 (0%)	0 (0%)
Cuneiform-metatarsal joint	26 (8.6%)	1 (0.3%)	10 (3.3%)	0 (0%)	0 (0%)	0 (0%)
Cuboid-metatarsal joint	12 (3.9%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	0 (0%)
Forefoot	139 (45.7%)	21 (6.9%)	43 (14.1%)	12 (11.5%)	4 (3.8%)	4 (3.8%)
MTP-1	97 (31.9%)	17 (5.6%)	34 (11.2%)	12 (11.5%)	4 (3.8%)	4 (3.8%)
MTP-2	79 (26%)	2 (0.7%)	9 (3%)	7 (6.7%)	0 (0%)	1 (1%)
MTP-3	64 (21.1%)	3 (1%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
MTP-4	39 (12.8%)	2 (0.7%)	3 (1%)	0 (0%)	0 (0%)	0 (0%)
MTP-5	38 (12.5%)	0 (0%)	7 (2.3%)	0 (0%)	0 (0%)	0 (0%)
TA	12 (3.9%)	0 (0%)		0 (0%)	0 (0%)	
EHL	3 (1%)	1 (0.3%)		0 (0%)	0 (0%)	
EDL	6 (2%)	0 (%)		0 (0%)	0 (0%)	
TP	138 (45.4%)	43 (14.1%)		4 (3.8%)	2 (1.9%)	
FDL	31 (10.2%)	6 (2%)		0 (0%)	0 (0%)	
FHL	12 (3.9%)	0 (0%)		0 (0%)	0 (0%)	
Peroneal tendons	119 (39.1%)	33 (10.9%)		0 (0%)	0 (0%)	
AT tendinopathy	96 (31.6%)	9 (3%)		5 (4.8%)	0 (0%)	
Calcaneal erosion	30 (9.9%)	0 (100%)	30 (9.9%)	2 (1.9%)	0 (0%)	0 (0%)
RCB	51 (16.8%)	6 (2%)		2 (1.9%)	0 (0%)	
Achilles enthesitis	115 (37.8%)			5 (4.8%)		
Plantar fascia	55 (18.1%)	0 (0%)	0 (0%)	4 (3.8%)	0 (0%)	0 (0%)

Abbreviations: AT, Achilles tendon; CCJ, calcaneocuboid joint; EDL, extensor digitorum longus; EHL, extensor hallucis longus; FDL, flexor digitorum longus; FHL, flexor hallucis longus; GS, gray scale; MTP, metatarsophalangeal; PD, power Doppler; RCB, retrocalcaneal bursa; STJ, subtalar joint; TA, tibialis anterior; TNJ, talonavicular joint; TP, tibialis posterior; TTJ, tibiotalar joint.

divided into the following sections: ankle (TTJ), hindfoot (STJ, TNJ, CCJ), midfoot (NCJ, cuneiform-metatarsal joint, cuboid-metatarsal joint), and forefoot including the five MTP joints.

Ankle and foot pathologies were significantly more frequent in RA patients than in healthy controls. In RA patients, synovitis was detected in TTJ (39.8%), followed by TNJ (37.2%), STJ (27%), and CCJ (9.2%). The most common soft-tissue pathology was tenosynovitis of TP (45.4%), peroneal tendons (39.1%), Achilles tendon enthesitis (37.8%). Positive PD signal was present in TP (14.1%), peroneal tendons (10.9%), hindfoot (7.6%), forefoot (6.9%), ankle (6.3%), and midfoot (1%). Table 2 shows the specifics of the ultrasound examination, Figure 1 shows some pathologies of patients in the study.

In terms of ankle pain, there was a statistically significant difference between symptomatic and asymptomatic ankles in hindfoot pathologies ($P = .001$), as well as the NCJ ($P = .03$) and the first, second, and fifth MTP joints ($P = .03$). Regarding relation of both gray-scale and PD findings to VAS scale of ankle pain, we found a significant relationship with stronger link of PD findings to higher VAS scores ($P = .001$).

When compared with disease activity, the findings revealed a significant relationship between TTJ synovitis ($P < .001$), as well as tenosynovitis of TP ($P = .007$), peroneal tendons ($P = .008$), and high disease activity. Hindfoot involvement was associated with moderate disease activity. Retrocalcaneal bursitis was more common in patients in remission. Positive PD signal was significantly related to high disease activity in all ankle and hindfoot structures ($P < .001$).

Patients were divided into two groups based on disease duration; the cut-off for the early RA group was 1 year. The established

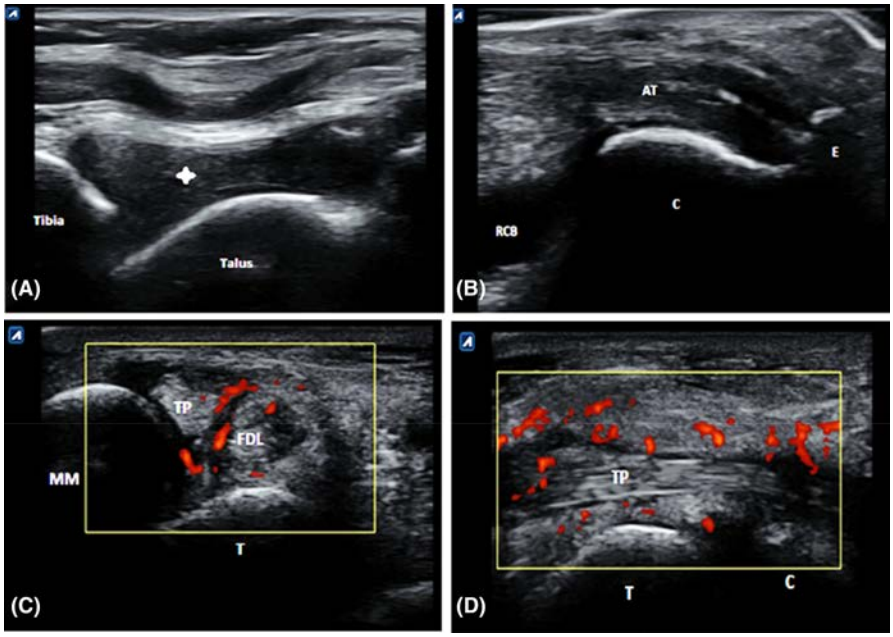

FIGURE 1 (A) Anterior longitudinal scan of ankle joint showing hypoechoic lesion (asterisk) within the tibiotalar recess denoting synovitis. (B) Posterior longitudinal scan of Achilles tendon insertion over calcaneus showing loss of tendon normal fibrillar echo pattern, enthesophyte formation, distention of retrocalcaneal bursa denoting Achilles enthesitis. (C,D) Scan of tibialis posterior tendon at the medial malleolus, showing anechoic lesion within the tendon sheath of tibialis posterior tendon with positive Doppler signal in both transverse (C) and longitudinal (D) scans denoting active tenosynovitis. AT, Achilles tendon; C, calcaneus; E, enthesophyte; FDL, flexor digitorum longus; MM, medial malleolus; RCB, retrocalcaneal bursa; T, talus; TP, tibialis posterior.

RA group (70 patients) had more TTJ synovitis, hindfoot, midfoot, and forefoot pathologies (52.1% vs 29.3%), (50% vs 38.4%), (22.9% vs 12.2%), and (54.3% vs 38.4%). Soft-tissue pathology, on the other hand, was more prevalent in the early disease group (82 patients) in TP (50.6% vs 39.3%) and peroneal tendons (45.7% vs 31.4%), as shown in Table 3.

3.2 | Impact on health

The study attempted to quantify the impact of ankle and foot pathologies on functional disability and foot function by comparing ultrasound pathologies with questionnaire scores. The findings revealed a significant link between foot and ankle pathologies and higher questionnaire scores. Linear regression analysis revealed that ankle, STJ, forefoot synovitis, TP tenosynovitis, and Achilles enthesitis were found to be predictors of foot functional disability. Also, severity of ankle pain was dependent on TTJ, TP, peroneal, and plantar fascia involvement, as shown in Table 4.

3.3 | Clinical examination vs ultrasound

In comparing clinical examination with ultrasound, we found poor agreement between both modalities in the CCJ ($P = .016$) and tibialis anterior tendon, and fair agreement in TTJ, TP, and peroneal tendons ($P < .001$). However, in plantar fascia pathologies, there was moderate agreement ($P < .001$). These results are shown in Table 5.

4 | DISCUSSION

The ankle and foot are prone to numerous pathological conditions that may contribute to their eventual functional impairment. So the identification of the inflamed joint and/or tendon by ultrasound might provide useful information.[5] Only a few studies have focused on this area in RA.

We worked on this knowledge gap in the literature and conducted our study to obtain more information about ankle and foot involvement in RA. In terms of pathology prevalence, the TTJ was the most affected (39.8%), followed by the TNJ (37.2%), the STJ (27%), and the CCJ (9.2%). Our findings were similar to those of Alsuwaidi et al[12] and Enache et al,[13] but differed from Suzuki et al,[14] who found higher frequencies of TTJ synovitis (76%), STJ synovitis (71%), and TNJ synovitis (59%). The difference could be explained by their small sample size of only 17 RA patients.

Regarding soft-tissue pathology, the most common was TP tenosynovitis (45.4%), followed by peroneal tenosynovitis (39.1%), Achilles enthesitis (37.8%), plantar fasciitis (18.1%), and retrocalcaneal bursitis (16.8%). Our findings were similar to those of Hernández-Díaz et al[5] and Harman and Tekeoğlu,[15] but less frequent than Alsuwaidi et al,[12] which could be explained by the different age and disease duration, as our study included younger patients with shorter disease duration.

Another significant finding in our study was the high prevalence of Achilles enthesitis (37.8%). Although it is commonly associated with spondyloarthropathy, some studies like those of Suzuki et al[14] or Genc et al,[16] have described it in about 40% of RA. Our results

TABLE 3 Comparison of ultrasound findings according to disease duration

Gray-scale ultrasound	Early RA Ankles = 164	Established RA Ankles = 140	Test of significance	*P*
TTJ	48 (29.3%)	73 (52.1%)	$\chi^2 = 16.49$	$P < .001$*
Hindfoot pathology	63 (38.4%)	70 (50%)	$\chi^2 = 4.12$	$P = .042$*
STJ	39 (23.8%)	43 (30.7%)	$\chi^2 = 1.84$	$P = .175$
TNJ	55 (33.5%)	58 (41.4%)	$\chi^2 = 2.01$	$P = .156$
CCJ	10 (6.1%)	18 (12.9%)	$\chi^2 = 4.13$	$P = .042$*
Midfoot pathology	20 (12.2%)	32 (22.9%)	$\chi^2 = 6.01$	$P = .014$*
Naviculo-cuneiform joint	20 (12.2%)	21 (15%)	$\chi^2 = 0.51$	$P = .475$
Cuneiform-metatarsal joint	11 (6.7%)	15 (10.7%)	$\chi^2 = 1.55$	$P = .213$
Cuboid-metatarsal joint	2 (1.2%)	10 (7.1%)	$\chi^2 = 6.99$	$P = .008$*
Forefoot pathology	63 (38.4%)	76 (54.3%)	$\chi^2 = 7.67$	$P = .006$*
MTP-1	46 (28%)	51 (36.4%)	$\chi^2 = 2.44$	$P = .118$
MTP-2	38 (23.2%)	41 (29.3%)	$\chi^2 = 1.47$	$P = .226$
MTP-3	29 (17.7%)	35 (25%)	$\chi^2 = 2.43$	$P = .119$
MTP-4	13 (7.9%)	26 (18.6%)	$\chi^2 = 7.65$	$P = .006$*
MTP-5	11 (6.7%)	27 (19.3%)	$\chi^2 = 10.93$	$P = .001$*
TA	2 (1.2%)	10 (7.1%)	$\chi^2 = 6.99$	$P = .008$*
EHL	0 (0%)	3 (2.1%)	FET	$P = .097$
EDL	4 (2.4%)	2 (1.4%)	$\chi^2 = 0.399$	$P = .528$
TP	83 (50.6%)	55 (39.3%)	$\chi^2 = 3.91$	$P = .048$*
FDL	16 (9.8%)	15 (10.7%)	$\chi^2 = 0.08$	$P = .783$
FHL	5 (3%)	7 (5%)	$\chi^2 = 0.758$	$P = .384$
Peroneal tendons	75 (45.7%)	44 (31.4%)	$\chi^2 = 6.49$	$P = .011$*
AT	37 (22.6%)	59 (42.1%)	$\chi^2 = 13.4$	$P < .001$*
RCB	24 (14.6%)	27 (19.3%)	$\chi^2 = 1.17$	$P = .279$
Achilles enthesitis	46 (28%)	69 (49.3%)	$\chi^2 = 14.48$	$P < .001$*
Calcaneal erosion	8 (4.9%)	22 (15.7%)	$\chi^2 = 9.97$	$P = .002$*
PF	27 (16.5%)	28 (20%)	$\chi^2 = 0.64$	$P = .425$

Abbreviations: AT, Achilles tendon; CCJ, calcaneocuboid joint; EDL, extensor digitorum longus; EHL, extensor hallucis longus; FDL, flexor digitorum longus; FET, fisher exact test; FHL, flexor hallucis longus; MTP, metatarsophalangeal; PF, plantar fascia; RA, rheumatoid arthritis; RCB, retrocalcaneal bursa; STJ, subtalar joint; TA, tibialis anterior; TNJ, talonavicular joint; TP, tibialis posterior; TTJ, tibiotalar joint; χ^2, chi square test.

* indicates significance *P* values (where *P* value $< .05$).

agree with them, and this should attract the attention to focus on Achilles tendon during follow up of RA.

Heel pain in RA is also considered a neglected area, with more attention paid in cases of spondyloarthropathy. At the heel, important sites must be evaluated: the Achilles tendon, retrocalcaneal bursa, as well as the adjacent cortical surface of the calcaneum.[17] Our findings showed the presence of retrocalcaneal bursitis with positive PD, and this matches with Serban et al,[18] who stated that retrocalcaneal bursa had a significant impact on patients' symptomatology and quality of life.

Previous research found a low PD frequency in TTJ.[12,19–21] Our data agree with them, and this could be explained by the low sensitivity of PD in large joints and deep anatomic areas. This highlights the importance of performing a thorough examination of the TTJ, including scanning the medial and lateral aspects to improve PD sensitivity in this complex area.

Regarding ankle pain, our study showed statistically significantly more pathological findings in painful ankles. Our results agree with Suzuki et al,[22] and differ from those of Alsuwaidi et al;[12] and this could be explained by the different age and disease duration. Soft-tissue pathology was also significantly higher in painful ankles than non-painful ankles. Those findings were similar to those of Enache et al,[13] who discovered a link between ankle pain and pathological findings in both the gray-scale and PD.

TABLE 4 Impact of ankle and foot pathologies on functional status in RA

	FFI				VAS			
Variable	Standardized coefficient	*P*	95% CI		Standardized coefficient	*P*	95% CI	
TTJ	0.265	<.001*	7.872	17.313	0.249	<.001*	0.801	2.151
STJ	0.124	.018*	1.144	11.884	0.084	.162	−0.220	1.315
TNJ	0.062	.283	−2.454	8.380	0.049	.455	−0.480	1.069
CCJ	−0.009	.856	−8.612	7.154	−0.017	.765	−1.299	0.956
Midfoot	0.036	.479	−3.916	8.328	0.109	.059	−0.033	1.717
Forefoot	0.124	.017*	1.024	10.583	0.085	.154	−0.188	1.179
TP	0.188	<.001*	3.997	13.526	0.153	.010*	0.211	1.574
Peroneal	0.050	.317	−2.301	7.078	0.114	.047*	0.008	1.349
AT enthesitis	0.148	.007*	1.961	12.266	−0.073	.243	−1.175	0.298
PF	0.066	.181	−1.875	9.883	0.114	**.045***	0.021	1.702

Abbreviations: AT, Achilles tendon; CCJ, calcaneocuboid joint; CI, confidence interval; FFI, foot function index; *P*, probability value; PF, plantar fascia; STJ, subtalar joint; TNJ, talonavicular joint; TP, tibialis posterior; TTJ, tibiotalar joint; VAS, visual analogue scale.
Significant results were bolded and marked with * (where *P* value $< .05$).

The association between positive PD findings and ankle pain is still being debated in the literature, with studies supporting the hypothesis that hypervascularization is associated with pain[23] and others finding no correlation.[24] In our study, positive PD appears to be significantly associated with pain in TTJ ($P = .011$), hindfoot ($P < .001$), STJ, TNJ ($P = .028$), forefoot ($P = .039$), TP ($P < .001$), peroneal ($P = .007$), and Achilles enthesitis ($P = .028$).

In RA patients, the prevalence of ankle joint involvement seems to have a tendency to increase with disease duration.[15] We focused on this point by categorizing patients into early and late disease duration groups. The established RA group had more joint affection, while the early RA group had more tendon affection. Our findings are consistent with those of Harman and Tekeoğlu,[15] Elsaman et al,[6] Alsuwaidi et al,[12] and Suzuki et al.[22] Our findings contradicted those of Hernández-Díaz et al,[5] who found higher prevalence joint pathologies in the first year. This could be explained by a difference in ethnicity or age group.

We also tested rheumatoid factor and anti-citrullinated protein antibody (ACPA) for the patients to denote their relations to pathologies. Previous studies denoted ACPA sensitivity ranged from 40% to 89%.[25] There is some variation according to ethnicity, age, and disease duration. Our patients showed incidence of ACPA of about 43.4% and this matches previous studies on the same ethnic population.

We tried to explore the impact of foot involvement on health. Our findings revealed a statistically significant link between ankle pathologies and higher Health assessment questionnaire and FFI scores. Our findings were consistent with those of Serban et al,[18] Harman and Tekeoğlu,[15] and Jeong et al,[26] who highlighted the association between hindfoot pathologies and functional disability. Our findings differ from those of Petterle et al.[27] This may be explained by their examination of only asymptomatic feet, whereas our sample size included both symptomatic and asymptomatic feet.

Previous studies attempted to identify predictors of disability. In one study, age, disease duration, and disease activity were found to be predictors of hindfoot valgus.[18] STJ, TP, and peroneal tenosynovitis were discovered to be predictors of FFI in another study.[15] We investigated more data, supported by our large sample size, and discovered TTJ, STJ, forefoot synovitis, TP tenosynovitis, and Achilles enthesitis to be predictors of impaired ankle and foot function. TTJ synovitis, TP, peroneal tenosynovitis, and plantar fasciitis were also found to be predictors of ankle pain severity.

Previous research has investigated the agreement between clinical examination and ultrasound. In an earlier study we investigated this point in the shoulder joint and discovered poor concordance between both modalities.[28] Numerous studies, particularly in the hands, have demonstrated the superiority of ultrasound and magnetic resonance imaging (MRI) to clinical examination in the early detection of inflammatory synovial lesions.[29]

Comparing clinical examination to ultrasound at the level of ankle joint, we found poor to fair agreement between both modalities. Our findings were consistent with those of Wakefield et al,[30] and Lehtinen et al,[31] who discovered a high concordance of ultrasound with MRI but a low concordance with clinical examination, and Toyota et al,[32] who highlighted the superiority of ultrasound over clinical examination in detecting ankle involvement.

We acknowledge that our study has several limitations, including the lack of a reference standard radiological modality, such as MRI, to confirm the ultrasound findings and the lack of a longitudinal follow up to determine the long-term clinical implications of these ultrasound findings.

In conclusion, the ankle and foot are frequently involved in early RA. The duration of the disease is an important consideration, with more soft-tissue pathologies in the first year and more joint involvement later.

Ankle and foot pathologies have a significant impact on the functional activity and quality of life of RA patients, and this needs to be assessed early and accurately using various modalities. Accurate ankle assessment has a big impact on patient's quality of life,

TABLE 5 Agreement between clinical examination and ultrasound in detection of ankle pathologies in RA

Structure	κ value	*P*	SE	Strength of agreement
TTJ synovitis	0.366	<.001*	0.051	Fair
STJ synovitis	0.255	<.001*	0.058	Fair
TNJ synovitis	0.299	<.001*	0.048	Fair
CCJ synovitis	0.096	.016*	0.075	Poor
TA tenosynovitis	0.039	.372	0.053	Poor
TP tenosynovitis	0.313	<.001*	0.053	Fair
Peroneal tenosynovitis	0.377	<.001*	0.055	Fair
AT enthesitis	0.350	<.001*	0.058	Fair
Plantar fasciitis	0.474	<.001*	0.070	Moderate

Abbreviations: AT, Achilles tendon; CCJ, calcaneocuboid joint; *P*, probability value; SE, standard error; STJ, subtalar joint; TA, tibialis anterior; TNJ, talonavicular joint; TP, tibialis posterior; TTJ, tibiotalar joint.

* indicates significance *P* values (where *P* value $< .05$).

physicians need to be aware of ankle pathologies to be able to treat them in an adequate and timely fashion so as to prevent permanent malalignment/irreversible damage to the foot. Ultrasound is a reliable tool that aids in diagnosis, prediction of functional disability, and proper management of ankle pathologies in RA. PD should be included during ultrasound scans to provide more information about disease activity and ankle pain severity. These data should be corroborated further in longitudinal studies.

AUTHOR CONTRIBUTIONS

MGA contributed to study design, ultrasound scan, data analysis, interpretation of results, and preparation of manuscript; SF contributed to data analysis, revision of the manuscript, and proofreading; AA and AFE contributed to study design, data analysis, and interpretation of results; and NA contributed to study design, data analysis, interpretation of results, and supervised the work.

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CONFLICT OF INTEREST

None declared.

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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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CASE REPORT

Reactive synovitis of the knee joint after COVID-19 vaccination: The first ultrastructural analysis of synovial fluid

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus 2019 disease (COVID-19) have spread all around the world since 2019 and have affected millions of people. The development of COVID-19 vaccines helped to decelerate the spread of the virus. However, as in the case of vaccines against other infectious diseases, adverse events can also present with COVID-19 vaccines.

Case Presentation: We report here a rare case of a 53-year-old man with knee-joint synovitis, after the first dose of messenger RNA vaccine, with no fever and a negative COVID-19 reverse transcription polymerase chain reaction test. During a clinical examination the suspicion of pyogenic arthritis was excluded by blood tests and by a complex joint effusion examination, including a microbiological and cytological-energy analysis of the synovial fluid. The treatment received by our patient consisted of 3 doses of dexamethasone administered intravenously over a period of 3 days. All the symptoms improved after this therapy, and in the 3-week follow-up period we recorded full recovery with no consequences.

Conclusion: Case reports on patients undergoing COVID-19 vaccination should be examined in order to detect rare and long-term side-effects. This is the first report to present the outcomes of an ultrastructural analysis of post-vaccination synovitis.

KEYWORDS
Covid-19 vaccination, cytological-energy analysis, reactive arthritis, synovial fluid

1 | BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus 2019 disease (COVID-19) have spread all around the world since 2019 and have affected millions of people. Although vaccines have helped to decelerate the spread of the disease, there have been adverse events associated with almost all types of COVID-19 vaccines. These adverse events are mostly mild, and they range from injection-side pain, muscle pain, fatigue and fever to autoimmune diseases such as reactive arthritis, systematic lupus erythematosus, vasculitis, and so on.[1] Severe symptoms are comparatively rare, and include severe pneumonia, acute respiratory distress syndrome, and even multiple organ failure.[2] Reactive arthritis is a sterile arthritis usually caused by an overstimulated autoimmune response by bacterial antigens deposited in the joints, typically followed by a gastrointestinal or urinary infection.[3] Although reactive arthritis is mostly associated with bacterial infection, viruses including SARS-CoV-2 have also been reported to trigger the condition.[4]

Our case reports the development of acute reactive arthritis after a COVID-19 vaccination. The primary suspicion of pyogenic arthritis was excluded by blood tests and by a complex

joint effusion examination of the synovial fluid (SF), including a cytological-energy analysis. Only 4 other cases of reactive arthritis after COVID-19 vaccination have been published until now in the literature.

2 | CASE PRESENTATION

Our patient is a 53-year-old Caucasian man with a medical history of arterial hypertension and diabetes mellitus type 2. He was admitted to the Internal Medicine Department in our small regional hospital with 4-day persisting swelling, pain and monoarticular synovitis. According to the patient, all these symptoms started 3 days after the first dose of a messenger RNA (mRNA) vaccine (BNT162b2 Pfizer/BioNTech®). The whole time, the patient had no fever. He had no history of trauma, rheumatic disease, or arthrosis in the affected knee joint. There were no pathological findings in the X-ray of the left knee (Figure 1). There were no abnormalities in the blood count, and C-reactive protein (CRP) was elevated to 91.8 mg/L.

The Orthopedic Department of our hospital was consulted to exclude the suspicion of pyogenic arthritis. During a physical examination, slightly limited flection due to the pain showed up. An ultrasound examination detected an effusion in the left knee joint. A puncture from the suprapatellar recess of the left knee guided by ultrasound was performed, and approximately 50 mL of serous SF sample were aspired; 20 mL of the SF sample were sent for a microbiological analysis, and the remaining 30 mL were sent for a cytological-energy analysis. The results from the cytological-energy analysis were known within hours and excluded a pyogenic inflammation process in the affected knee joint, since the metabolic activity was normal. In addition, elevated levels of CRP (22.0 mg/L) were revealed in the SF, which correlated with the levels in the blood sample. The normal level of aspartate aminotransferase (AST) in the SF (17.4 IU/L) excluded local tissue damage in the knee joint. The normal uric acid concentration (237.0 mmol/L) showed no gouty impairment in this location. The treatment that we established was 3 doses of dexamethasone administered intravenously over a period of 3 days. In the 3-day follow-up, it was observed that all the symptoms had improved, and that the CRP levels had decreased to 8.75 mg/L. According to the ultrasound a small amount of joint effusion persisted in the left knee. The effusion was punctured and was sent once more for a microbiological and cytological-energy analysis. The results from the microbiological analysis finally returned with no detection of microbes in either of the SF samples of the left knee. The results of the cytological-energy analysis confirmed again that there was no presence of an ongoing inflammatory process in the affected knee joint. The levels of CRP decreased to normal levels. The patient was sent home from the inpatient unit, and in the 3-week follow-up we recorded a full recovery of our patient with no consequences.

In the analysis of the first SF sample, pleocytosis of neutrophils was found (number of nucleated cells = 4680/1 μL; percentage of neutrophils = 89.0%; percentage of lymphocytes = 8.0%; percentage of monocytes = 3.0%) (Figure 2). The aerobic metabolism in the SF is determined by the coefficient of energy balance (KEB). In the first SF sample area the aerobic metabolism with KEB = 34.1 reliably excluded the purulent type of inflammation induced by extracellular bacteria.[5,6] The analysis of the second SF sample manifested a decrease in the cell count (360/1 μL) and a significant decrease in neutrophils (percentage of neutrophils = 6.0%; percentage of lymphocytes = 71.0%; percentage of monocytes = 23.0%) (Figure 3). The persisting aerobic metabolism in the SF sample area (KEB = 33.5) again excluded a significant inflammatory reaction in this site.[5,6]

An evaluation of these findings led us to the conclusion that there had been significant reactive changes in the knee joint, followed by regression.

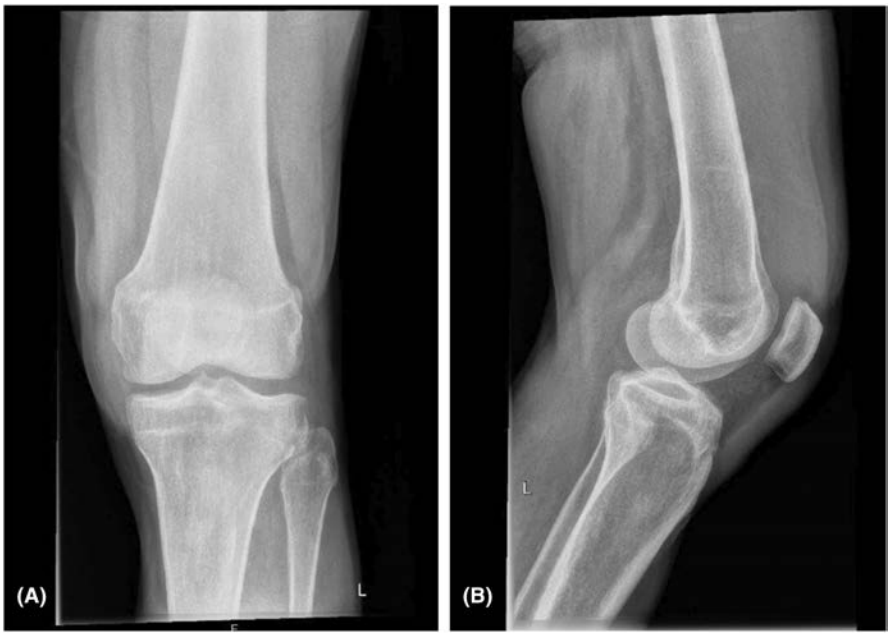

FIGURE 1 X-ray of the left knee: anterior-posterior (A), lateral (B) views

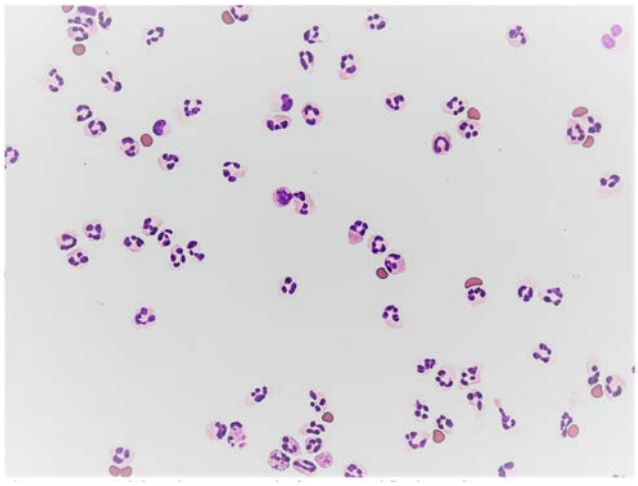

FIGURE 2 Neutrophil predominance in the first synovial fluid sample

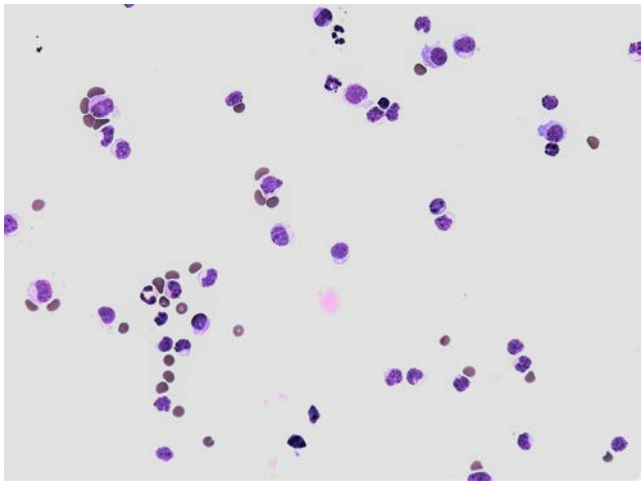

FIGURE 3 Lymphocyte predominance in the second synovial fluid sample

3 | DISCUSSION

Like COVID-19 vaccines, vaccines against other infectious diseases have helped to decelerate the spread of diseases. Although vaccination is a very beneficial option, adverse events and effects may also be present. Most of the reported adverse events after the Pfizer-BioNTech vaccine, which was the first mRNA vaccine, are mild and self-limited. They include injection-site pain, fatigue, muscle pain and fever. Severe reactions, for example autoimmune diseases such as reactive arthritis, systematic lupus erythematosus, vasculitis or anaphylactic shock are rare.[7] The mechanism of the development of an autoimmune disease after vaccination is not fully known. It may be caused by the inactivated virus or by the adjuvant found in the vaccines.[8]

Only 4 other cases of reactive arthritis after COVID-19 vaccination have been published in the literature, but none of them developed after the Pfizer-BioNTech vaccine. In 2 of these cases, reactive arthritis presented in small joints of the hand[9] and in 1 case in the elbow joint.[10] The last case report describes reactive arthritis in the knee joint, as in our case.[1] In all these cases, the onset of the symptoms of reactive arthritis appeared several days after inoculation. The treatment in all of the cases reported until now has included the application of a corticosteroid. However, the method of application has varied from oral administration to an intra-articular injection into the affected joint. In the treatment of arthritis of small hand joints, oral corticoid tablets were prescribed for 1 week.[9] The arthritis in the elbow joint and in the knee joint were treated with a single intra-articular injection of corticoids.[1,10] In our case, we used 3 doses applied intravenously for a period of 3 days. In all of the reported cases, the patients recovered fully without any recurrences or consequences.

In our case report, we applied a cytological-energy analysis of the knee joint effusion as a part of our diagnostic process. This is an accessible, rapid and affordable method which facilitates the clarification if there is an ongoing local inflammatory process in the joint effusion. The results of a cytological-energy analysis are available within a few hours after sampling. This is far earlier than the results of a microbiological analysis, which are available only after several days. If it is necessary to determine whether or not the inflammation is purulent, a cytological-energy analysis can promptly exclude pyogenic complication. This exclusion of an ongoing inflammatory process in the SF also clarifies that there is no ongoing inflammatory process in the extravascular body fluids.[11]

This is the first use of a cytological-energy analysis for analyzing joint effusion after a COVID-19 vaccination. This method reveals immunocompetent cells, and also their metabolic activity. In the first SF sample, before our treatment, there were predominantly neutrophils with a segmented nucleus. In the SF sample after the corticosteroid therapy the neutrophils were less numerous. We obtained information about the concentration of CRP. The levels of CRP were elevated in the first SF sample, which correlates with levels of CRP in the blood sample. In the second SF sample, the levels of CRP were substantially decreased as in the blood sample.

In both SF samples, before and after the treatment, there was normal metabolic activity. This excluded the presence of an ongoing inflammatory process with an oxidative burst. This analysis also reveals the levels of AST and uric acid in the SF sample. In our case report, there was a normal level of AST in the joint effusion, indicating there was no destruction of the tissue in the located area. In addition, the normal level of uric acid indicated that there were no gout alterations. A cytological-energy analysis of the SF can also be used in the diagnostic process, for typing the tumor and for accelerating the start of treatment.[6] There are also case reports in the literature of reactive arthritis developing during or after COVID-19 infection.[12–14]

4 | CONCLUSION

Although reactive synovitis after COVID-19 vaccination is rare, it should be taken into consideration in patients presenting with joint pain and swelling after inoculation, in order to exclude pyogenic complications. As we have presented in this case report, the cytological-energy

analysis can promptly exclude pyogenic inflammation. In the basis of this finding, effective treatment can be started without delay.

AUTHOR CONTRIBUTIONS

Writing - original draft preparation and conceptualization, E.V., P.K. and T.N. Supervision, T.N.; funding acquisition, T.N. All authors have read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

This was a purely observational case study which did not alter the patient's management and clinical outcomes. Thus, ethics approval was not required for this case report.

INFORMED CONSENT STATEMENT

Informed consent was obtained from the patient involved in the study. Written informed consent has been obtained from the patient to publish this paper.

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CASE REPORT

Coincidence of pachydermoperiostosis and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, a causal or casual association?

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Abstract

Pachydermoperiostosis (PDP) is a rare disorder characterized by skin thickening, acropachia, and periostosis. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is also an orphan disease featured by different dermatological and osteoarthritic manifestations. Herein, we report the first case of an adolescent male diagnosed with both PDP and SAPHO syndrome, presenting with digital clubbing, polyarthralgia, ostealgia, pachydermia and acne on his face, chest and back. Furthermore, we distinguish the characteristics of both diseases and explore the potential pathological mechanism for this coexistence in one patient. Further investigations are needed to establish the detailed pathophysiological association of these 2 diseases.

KEYWORDS
pachydermoperiostosis, PGE2, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome

1 | INTRODUCTION

Pachydermoperiostosis (PDP) is a rare genetic/hereditary disorder characterized by pachydermia, acropachia, and proliferation of periosteum. Periosteal new bone formation is a hallmark of this disease, which mostly affects the appendicular skeleton, usually bilaterally and symmetrically along the metadiaphyseal regions of long bones.[1] Meanwhile, osteitis and bone marrow edema are rarely seen in PDP.[2] Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is also an orphan disease featured by dermatological and osteoarthritic manifestations.[3] Different from PDP, osteitis is considered as the core pathological change of SAPHO syndrome, with a predilection on the anterior chest wall and axial skeleton.[4] Previously, some studies sporadically reported PDP combined with autoimmune diseases, such as ankylosing spondylitis, rheumatoid arthritis, and Crohn's disease.[5,6] However, no study has ever elaborated the coexistence of PDP and SAPHO syndrome.

Herein, we report a case diagnosed with both PDP and SAPHO syndrome, and describe the clinical presentations, laboratory and radiographic findings, and treatments.

Yuyin Feng, Afang Wang and Xia Dong equally contributed to this study.

2 | CASE REPORT

A male 18-year-old was referred to our hospital for intermittent low fever, thickened face skin and swelling of limbs from the age of 16 years. He was born to nonconsanguineous parents and his father had psoriasis vulgaris. None of his family members had similar features. He was not a smoker and denied any alcohol or substance abuse. His perinatal history and clinical health were normal until puberty when he was 16 years old. Since then, intermittent low fever appeared. After 2 months, a progressive thickening of forehead and nasal skin with seborrhea became evident, and tiny superficial acnes developed on his face and trunk, along with coarse hand features and swelling of both hands and feet. Chinese herbal decoction was taken intermittently for the treatment of rashes. Two years later, aforementioned symptoms worsened. Skeletal radiography demonstrated subperiostial bone formation, with bone diaphysial and cortical thickening. The diagnosis of this patient was not made at that time and oral total glucosides of paeony (0.6 g twice daily) was prescribed by the local hospital. After 6 months of therapy, his symptoms and signs were not effectively alleviated and got worse. Consequently, the patient discontinued this treatment and came to our hospital.

On admission, the patient was presented with thickening of the facial skin with prominent forehead skin folds and seborrhea, moderate acne conglobate, and nasal hypertrophy. Coarse hands, clubbing of all his fingers and toes were also noted (Figure 1). The patient had symmetrical enlargement of bilateral interphalangeal and waist joints free from tenderness, together with soft tissue swelling on his bilateral knees and ankles with obvious tenderness. The result of floating patella test was positive. He also complained that flexion of knees and ankles was restricted. No mammary, thyroid, cardiopulmonary or abdominal disease features were detected.

On evaluation of laboratory tests, bone γ-carboxyglutamic acid-containing protein (BGP), bone resorption markers including β-isomerized C-terminal telopeptide (β-CTX), hypersensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR) and platelet blood cell (PLT) count all increased as listed in Table 1. Other laboratory examinations, including assays for human leukocyte antigen-B27, rheumatoid factors, and blood antinuclear antibody, bone marrow bacterial culture, virus and antibody detection, tests for syphilis, hepatitis B and acquired immune deficiency syndrome, thyroid profile, sex hormones and cortisol assay, and glucose tolerance test, were unremarkable (Table 1).

Result of X-ray showed periostosis in fibula and tibia (Figure 2A) and magnetic resonance imaging (MRI) of lower limbs highlighted thickening of the bilateral tibiofibular cortex, abnormal signals in the medullary cavity of the bilateral middle tibia and right platform, and a small amount of effusion in bilateral knee joints. Otherwise, osseous density of the metaphysis of bilateral tibia and fibula was reduced without uneven thickening of the shaft (Figure 2B,C). Bone scintigraphy showed that all long bones of the extremities became thick and uptake of bilateral clavicle and feet heel increased. Whole-body positron emission tomography -computed tomography reported no obvious abnormality.

Because the patient manifested all 3 major features (pachydermia, periosteal proliferation and digital clubbing) with the absence of any cardiovascular, pulmonary, liver, intestinal and mediastinal diseases, a clinical diagnosis of complete form of PDP was made.[1] Based on the affected peripheral bones and the anterior chest wall as well as acne lesions, ruling out osteoarthritis malignancy and infection by bone biopsy, SAPHO syndrome should also be diagnosed.[4] The patient was prescribed etoricoxib and minocycline.

After 1 month of treatment, the patient's low fever, skin lesions and osteoarthritis symptoms were significantly relieved and there was a decrease of laboratory test results apart from BGP (Table 1). Review of MRI showed that bone marrow edema in the lower extremities was a lot better than before.

3 | DISCUSSION

With respect to the bone lesions in this case, osteoarthropathy can occur in both SAPHO syndrome and PDP disease, which have different manifestations. For patients with PDP, periostosis along the diaphysis of tubular bones in the extremities is considered as the

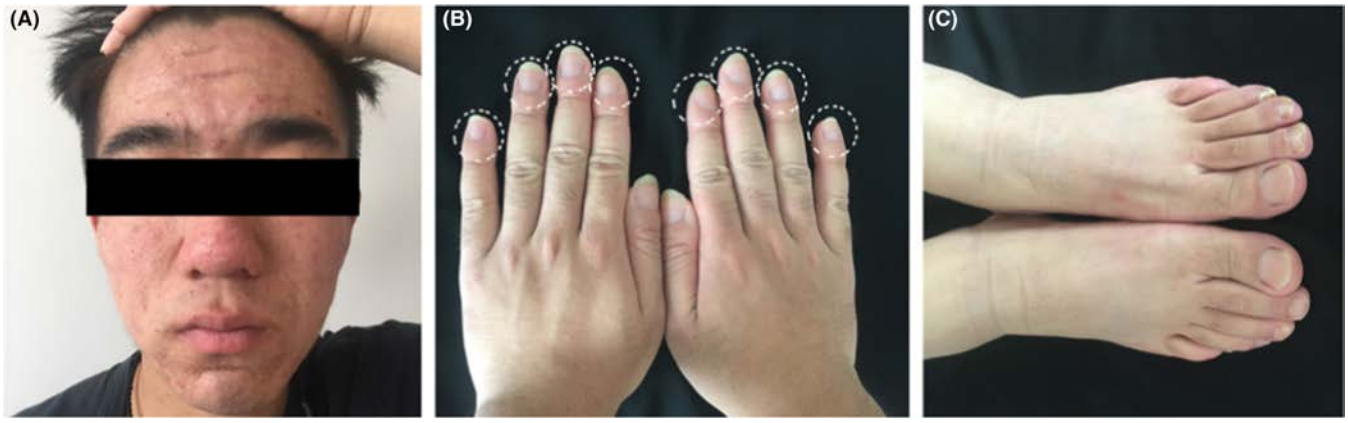

FIGURE 1 Photograph of the patient with digital clubbing. A, The thickening of the facial skin, prominent forehead skin folds and seborrhea, moderate acne conglobate and nasal hypertrophy. B, C, Clubbing of all the fingers and toes

TABLE 1 Laboratory tests and disease severity before and after treatment

Date	Platelet ($\times 10^9$/L)	hs-CRP (mg/L)	ESR (mm/h)	β-CTX (ng/mL)	BGP (ug/L)	Severity of acne (facial)[a]	Severity of acne (chest and back)[a]	VAS
August 7, 2017	314	21.66	16	7.27	13.9	Moderate	Moderate	6
September 11, 2017	270	0.85	6	2.12	38.8	Mild	Mild	4
November 6, 2017	N/A	N/A	N/A	N/A	N/A	Mild	Mild	3

Abbreviations: BGP, bone γ-carboxyglutamic acid-containing protein; ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; N/A, not available or not tested; VAS, visual analog scale/score; β-CTX, β-isomerized C-terminal telopeptide.

[a]Severity of acne was evaluated according to Guideline for diagnosis and treatment of acne (the 2014 revised edition).[16]

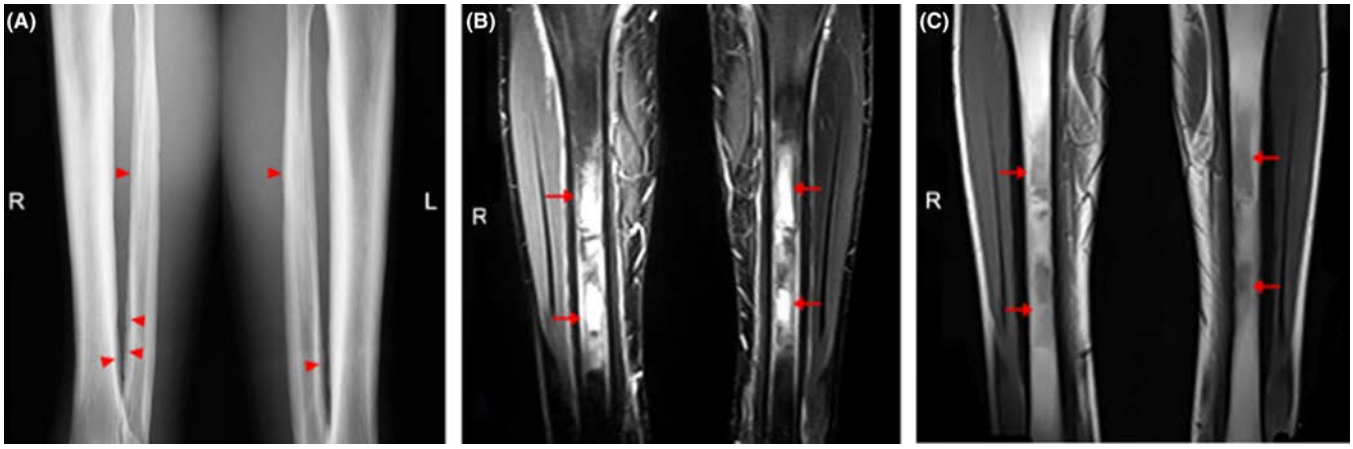

FIGURE 2 X-ray and magnetic resonance imaging (MRI) results of the fibula and tibia. A, Periosteal new bone formation (periostosis) in fibula and tibia (arrows) with associated cortical thickening. B, C, MRI of the bilateral tibia (T1-weighted image [WI] sequence) and MRI of the bilateral tibia (T2WI sequence) demonstrated hypo- and hyperintensity respectively. Bone marrow edema was revealed. SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis

imaging hallmark of PDP, generally sparing epiphyses in the early stage. At first, the periosteal reaction is limited to the diaphysis with a linear monolayer configuration, merely increasing the bone circumference with no alteration of its shape. As the disease progresses, periostosis can extend into the epiphyses and appear laminated or multilayered.[2] Although rare literature has demonstrated that periosteal osteogenesis could invade the medullary cavity, the density signal of the bone cortex and medullary was basically normal in these cases.[7] To our knowledge, no bone marrow edema or anterior chest wall involvement has been reported in PDP cases. So it is quite reasonable to consider that marrow edema and anterior chest wall lesions were caused by another disease in this case.

As regards SAPHO syndrome, the anterior chest wall is the most common site to be affected in adults, with a 60%-95% frequency.[8] Appendicular skeleton involvement is seen in 30% of patients, which is more common in younger patients.[8,9] Rather than an overgrowth pattern as in PDP, SAPHO syndrome always manifests as an osteolytic process, forming a sclerotic rim demarcating it from normal bone in the early stages. Extensive marrow edema can be recorded by MRI scanning during the active phase of SAPHO syndrome. With the development of SAPHO, a lytic and sclerotic scene turns up, making the progression of osteitis and hyperostosis more and more evident.[9] Taking their different pathogeneses, and detailed manifestations of this patient into consideration, we can suspect that both diseases played a role in the progression of skeletal lesions, and the onset of PDP was earlier than that of SAPHO syndrome.

There are some points of interest regarding other manifestations in this case. (a) Acne has been reported respectively in 44%-67% and 15%-18% of patients with PDP and SAPHO syndrome,[3,8–10] with no difference in the pathological manifestations between the 2 diseases. (b) For PDP patients, pachydermia morphologically features markable proliferation of fibroblasts in dermis and subcutaneous tissue, whereas epidermis tissue is always unremarkable. The number of mature sweat and sebaceous glands substantially increases and sometimes hyperplasia and/or hypertrophy of glandular cells can be seen.[10] However, in SAPHO patients, skin lesions including palmoplantar pustulosis, hidradenitis suppurativa and psoriasis are all histopathologically characterized by epidermal tissue abnormalities, and hyperkeratosis which may also result in a fake pachydermia in such patients.[3,8] (c) As for clubbing, it may be the only manifestation in PDP cases. Soft tissue swelling and acro-osteolysis, which often appear at the distal parts of fingers and toes, are 2 key features of clubbing.[2] SAPHO syndrome mainly affects the metadiaphyses of distal femur, proximal and distal tibia. Small tubular bones of the feet can also be involved but at a relatively low incidence.[3,8] Nevertheless, no clubbing symptom has been reported in SAPHO cases.

Both autosomal recessive and dominant inheritance models have been suggested for PDP with a variable expressivity. At present, 2 kinds of gene including the solute carrier organic anion transporter family, member 2A1 (SLCO2A1) gene which encodes a prostaglandin transporter and the hydroxyprostaglandin dehydrogenase (HPGD) gene which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH) have been identified, both impairing the degradation of PGE2 and resulting in PDP.[11] PGE2 shows a strong peripheral vasodilator effect by inducing the expression of vascular endothelial growth factor (VEGF), which may explain finger clubbing and skin thickening due to prolonged local vasodilation and also stimulates the activity of osteoclasts and osteoblasts, leading to bone reformation.[7] Apart from this, a positive correlation between serum VEGF levels and disease activity indices, such as CRP, has been demonstrated in psoriatic arthritis. However, similar evidence was limited in patients with SAPHO syndrome due to a small group size.[12] According to our patient's medical history, the onset of PDP was earlier than that of SAPHO syndrome, so we speculate that PGE2 may increase the activity of the osteoclast pathway in SAPHO syndrome.

On the other hand, an infectious hypothesis that a low virulence pathogen, particularly *Propionibacterium acnes*, triggers and maintains the progression of SAPHO disease has always been proposed. In this theory, a number of microbial substances produced by *P. acnes* activates the innate immune response of patients through Toll-like receptor 2. Furthermore, several studies reported that 42% of 90 SAPHO bone cultures were *P. acnes* positive, and 66% of 21 bone biopsies from a cohort of patients grew *P. acnes*, suggesting a potential role of *P. acnes* in SAPHO syndrome.[13] In this case, minocycline was effective in controlling the symptoms, which may also support this infectious etiology hypothesis to a certain degree. So we might also suppose that the hyperplasia of sebaceous glands and hypertrophy of glandular cells,[10] deriving from PDP disease, offered an ideal culture condition for *P. acnes*. After that, *P. acnes* activated the innate immune response in this patient and triggered the progression of SAPHO syndrome. Unfortunately, we did not test his serum PGE2, conduct bone culture or sequence genome of this patient at the time of initial presentation or follow-up.

At present, there is no specific treatment method for PDP. Drugs commonly used to relieve painful osteoarthropathy include salicylic acid, bisphosphonates, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and colchicine. In addition, tamoxifen has been reported to be effective for refractory arthralgia which cannot be alleviated by NSAIDs.[14] Given the knowledge that PGE2 plays a major role in pathogenesis of PDP, we prescribed etoricoxib, a cyclo-oxygenase-2 inhibitor, which can suppress the biosynthesis of PGE2 in inflammatory and neoplastic disorders.[14] As for acne conglobate, tetracyclines, such as minocycline, are considered first-line therapy in patients with moderate-to-severe inflammatory or noninflammatory acne. It can not only regulate the immunity, but also have notable anti-inflammatory effects.[15] Taking the severity of acnes into consideration, minocycline was finally recommended to this patient.

To our knowledge, this is the first reported case of PDP complicated with SAPHO syndrome in the literature. PDP and SAPHO syndrome have many similar clinical and imaging features and we should make detailed checks to distinguish them and take appropriate treatments. X-ray has a significant advantage in diagnosing periosteal thickening and MRI appears to be an important imaging option when distinguishing the acute period of SAPHO syndrome. Bone scintigraphy can clearly show the sites of involved bones of the whole body and help us further differentiate these 2 diseases. Nevertheless, with limited evidence, it is unclear whether there is an explicit connection between PDP and SAPHO syndrome, and we are just speculating that it is related to PGE2 or bacterial infection at present. And further investigations are needed to establish the detailed pathogenesis of SAPHO syndrome and PDP disease.

4 | KEY SUMMARY POINTS

This is the first reported case of PDP complicated with SAPHO syndrome in the literature. There are many similar clinical and imaging features in PDP and SAPHO syndrome. We should distinguish them carefully, take appropriate treatments and further explore the potential pathophysiological association between these 2 diseases.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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CASE REPORT

Canakinumab treatment in a young girl with refractory chronic recurrent multifocal osteomyelitis associated with pyoderma gangrenosum

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Abstract

Background: Chronic recurrent multifocal osteomyelitis (CRMO) is a bone inflammatory disorder characterized by osteolytic, usually multiple, symmetric lesions. Diagnosis is one of exclusion, and no standardized therapies are available. Presumed deregulation of the interleukin (IL)-1β axis, as observed in 2 monogenic autoinflammatory conditions such as Majeed syndrome (LPIN2 mutations) and deficiency of IL-1 receptor antagonist (IL1RN mutations) with CRMO-like bone involvement, suggests the blockade of IL-1 as potentially useful also in this condition, even if scarce data are available.

Case presentation: We report the case of a 13-year-old girl affected by a multidrug-resistant and pyoderma gangrenosum-complicated CRMO treated with canakinumab, a human monoclonal antibody targeting IL-1β.

Conclusion: In this young patient pyoderma gangrenosum and CRMO showed a rapid and satisfactory response to canakinumab, although over time a decreased efficacy in controlling bone disease was observed.

KEYWORDS
anakinra, canakinumab, chronic recurrent multifocal osteomyelitis, IL-1, pyoderma gangrenosum

1 | INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare bone disorder characterized by a sterile bone inflammation leading to osteolytic, hyperostotic, and osteosclerotic, multiple lesions.[1] Long bone metaphysis, pelvis, clavicle, ribs, vertebral bodies, and mandible are the typically affected sites.[2]

The disease onset is insidious, and the course prolonged and fluctuating. Patients may present fever, asthenia, and fatigue.[2] Bone pain shows a relapsing–remitting course. Articular, skin, gastrointestinal, or ocular involvement are frequently associated. Palmoplantar pustulosis, psoriasis, and acne are observed especially in adolescents,[3] while pyoderma gangrenosum (PG) has been rarely described.[4–11]

Inflammatory bone lesions appear as radiolucent, osteolytic, or sclerotic areas on plain radiographs; however, during the early stages, they may be undetectable.[2]

Furthermore, since many lesions may be asymptomatic, a whole-body magnetic resonance imaging (WB-MRI) is useful to recognize radiographically occult and clinically silent lesions, and the typical symmetric pattern of distribution.[3]

Sabrina Acierno and Francesca Angrisani contributed equally to the work.

Diagnosis is one of exclusion as no diagnostic biomarkers are available; bone biopsy can be required to exclude malignancies and infections.[3]

No standardized therapeutic protocols exist, even though many different treatments are currently employed, ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to disease-modifying antirheumatic drugs (DMARDs) up to biologic drugs.[12] A presumed deregulation of the interleukin (IL)-1β axis suggests the blockade of IL-1 as a potentially successful treatment.[12]

We report the case of a 13-year-old girl affected by a multidrug-resistant CRMO complicated by PG, treated with canakinumab, a human monoclonal antibody targeting IL-1β.

2 | CASE REPORT

A 13-year-old girl started to complain of rib cage pain, poorly responsive to common NSAIDs. Due to the association with fever, increased inflammatory markers, and osteolytic areas at I and II left ribs at plain radiograph, an infectious osteomyelitis was suspected, and a parenteral antibiotic therapy was unsuccessfully administered for 2 weeks. The patient was then transferred to our attention. A WB-MRI showed diffuse bone lesions distributed at I, II and III right ribs, II left rib, vertebral bodies of C7-D3, both humeral heads, and both greater trochanters. Bone biopsy (rib) revealed a mixed inflammatory cell infiltrate, without evidence of infection or malignancy, supporting the diagnosis of CRMO.

Due to the symptomatic presentation, the number of bone lesions and the vertebral involvement, bisphosphonates (neridronate, 2 mg/kg intravenously every 3 months) were prescribed together with methotrexate (15 mg/m^2 weekly subcutaneosly) and a 2-month course of naproxen (15 mg/kg/d in 2 doses). Despite a good clinical recovery, an unsatisfactory improvement in skeletal lesions was detected at the 7-month radiological control, and neridronate was replaced by an anti-tumor necrosis factor (TNF)α agent (adalimumab 40 mg every 2 weeks, subcutaneously).

Two months after the start of this new treatment, and about 11 months after the disease onset, a small papule presented at her anterior tibial surface and quickly enlarged, developing into a large and painful ulcer with a peripheral erythema (Figure 1).

Skin biopsy revealed necrotic epidermis with carcinomatous hyperplasia on the sides, and epidermal reactive neoangiogenesis, with fibrosis and a dense neutrophilic infiltrate compatible with PG.

At the same time back pain gradually developed and a new WB-MRI, 5 months after the previous one, showed the resolution of 3 of the old lesions, and the appearance of 2 new ones. Methotrexate was therefore stopped, adalimumab was switched to an anti-IL-1 blocker (canakinumab, 4 mg/kg/4 wk subcutaneously), and a 2-month cycle of prednisone (15 mg/d) was started. Topical treatment included steroids together with sterile saline solution.

One year later, due the adequate disease control with complete clinical remission and radiological resolution of the previous bone lesions, without new ones detected, canakinumab injection interval was extended (4 mg/kg/8 wk).

However, after 1 year of remission bone pain recurred, multiple ulcerative and painful skin lesions appeared at lower limbs, along with an increase in acute phase reactants and new active radiological bone lesions. Intervals of canakinumab injections were then reduced to 4 weeks, in association with a 3-months prednisone treatment. Bone pain, cutaneous ulcers, and inflammatory markers gradually improved.

At last follow-up, 8 months after the last therapeutic changes, and around 3 years and 8 months after the disease onset, the girl was off corticosteroids, only taking canakinumab every 4 weeks; she was in good general condition, skin lesions were completely healed with cribriform scarring (Figure 2), and laboratory exams were in the normal range. However, WB-MRI revealed new edematous bone lesions at C7, D1, D2, left sacroiliac joint, and ribs, despite being clinically asymptomatic, while resolution of 3 old ones was confirmed. Figure 3 presents a synopsis of the major events related to the clinical history of this patient.

3 | DISCUSSION

Canakinumab in pediatric age is approved for systemic juvenile idiopathic arthritis and some autoinflammatory periodic fever syndromes, while its use in CRMO is off label and still anecdotal.

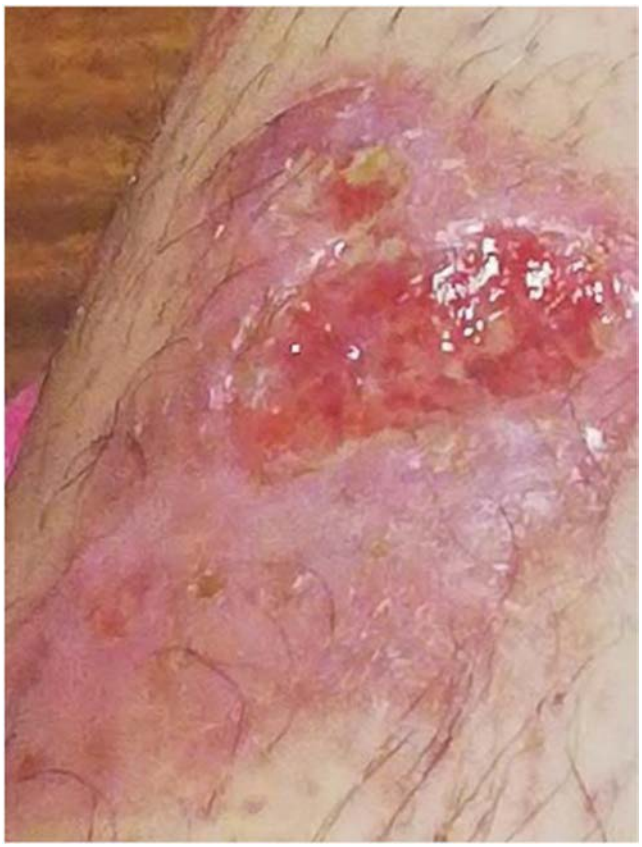

FIGURE 1 Active pyoderma gangrenosum at the anterior tibial surface presenting as a large and painful ulcer with a peripheral erythema

Therapy in CRMO aims to control pain, interrupt inflammation, and prevent complications.[13] However, it is currently based on expert opinion with relatively small case collections.

A survey of pediatric rheumatologists through Childhood Arthritis and Rheumatology Research Alliance (CARRA) identified NSAIDs as common first-line treatment, while DMARDs, TNF blockers, and bisphosphonates are mostly used as second-line drugs.[14,15] Zhao et al within the CARRA chronic nonbacterial osteomyelitis (CNO) working group proposed 3 consensus treatment plans for NSAID-refractory cases including classical DMARDs, TNF-alpha blockers with or without methotrexate, or bisphosphonates.[16]

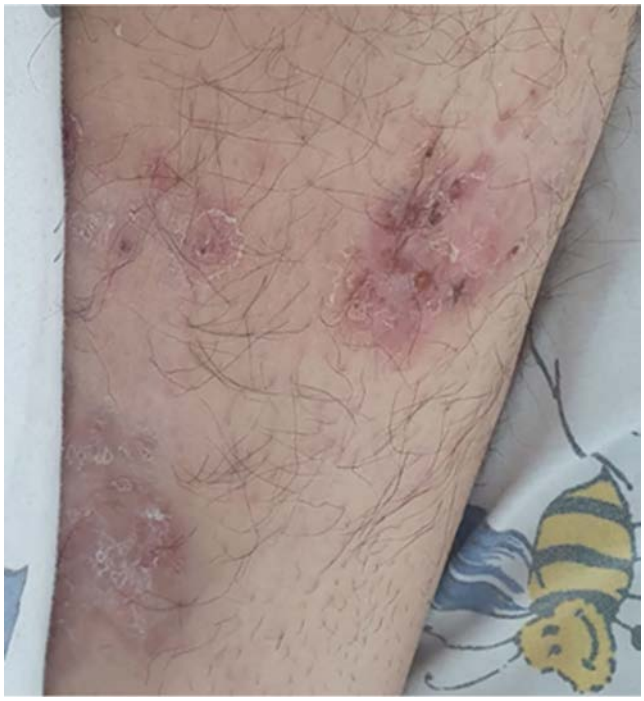

FIGURE 2 Pyoderma gangrenosum lesions completely healed with characteristic cribriform scarring within 8 mo of canakinumab treatment

In a murine model Cassel et al observed how bone inflammation in CRMO is mediated by IL-1β, although in an inflammasome-independent way.[17] An increased IL-1β secretion by peripheral blood mononuclear cells during the active phases and an over-expression of inflammasome components has been demonstrated by Scianaro et al.[12]

Two inherited monogenic autoinflammatory conditions such as Majeed syndrome (*LPIN2* mutations) and deficiency of IL-1 receptor antagonist (DIRA) (*IL1RN* mutations) with a CRMO-like bone involvement, and an IL-1 over-expression have been successfully treated with IL-1 blockers.[18–21] The IL-1 receptor antagonist anakinra, the soluble decoy receptor rilonacept, and the neutralizing monoclonal anti-IL-1β antibodies canakinumab, and gevokizumab represent the available IL-1 blockers.[12,22] Their use in CRMO is still circumscribed, mostly based on few clinical cases, and substantially restricted to anakinra.[23–27] Some isolated cases successfully treated with canakinumab have been described in patients affected by Majeed syndrome, and DIRA[21,28,29] Table 1 summarizes the main data about the use of canakinumab in autoinflammatory bone diseases obtained with a comprehensive search of the literature published on the PubMed database up to May 2022 in English (searching terms: "canakinumab" OR "interleukin 1β antibody" OR "ACZ885" AND "chronic non-bacterial osteomyelitis" OR "Chronic recurrent multifocal osteomyelitis" OR "CNO" OR "CRMO" OR "bone autoinflammatory syndromes" OR "osteomyelitis" OR "DIRA" OR "SAPHO" OR "PAPA" OR "PASH" OR "PAPASH" OR "Majeed Syndrome" OR "Interleukin-1 receptor antagonist" OR "interleukin-36 receptor antagonist"). Regarding CRMO, Moussa et al reported 2 patients treated with this drug.[30] They both had been initially unsuccessfully treated with naproxen and pamidronate, and then switched to canakinumab every 8 weeks, one of them after a further 5-year-period under infliximab. After an initial recovery, these children needed to reduce the interval between injections to 1 month due to CRMO relapse.

Our patient, a few weeks after the introduction of adalimumab for bone lesion persistence, developed PG skin lesions. PG is an ulcerative, often recurrent cutaneous condition that may present as a primary condition, or in association with other systemic

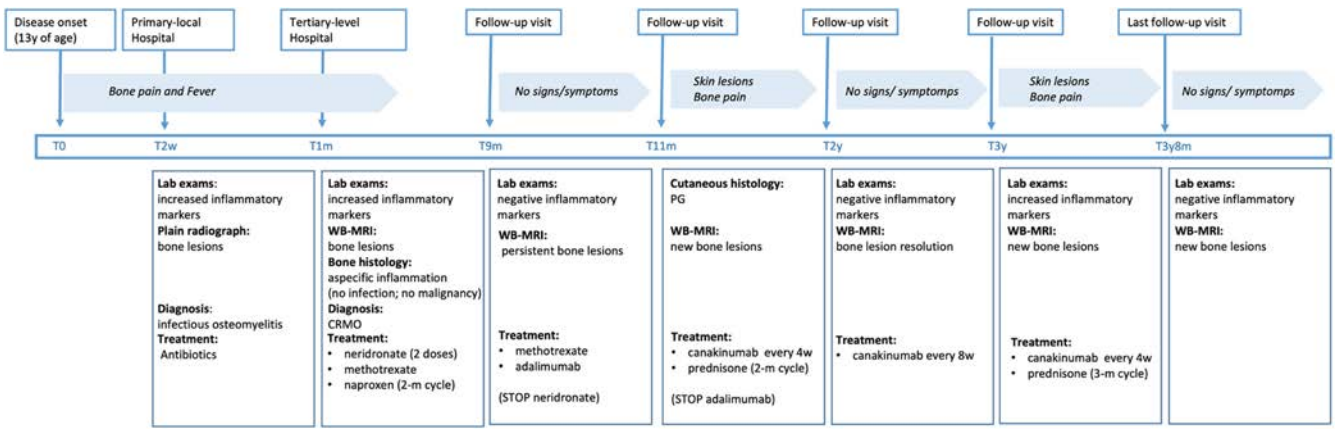

FIGURE 3 Timeline of key events in the described patient. CRMO, chronic recurrent multifocal osteomyelitis; m, month; PG, pyoderma gangrenosum; w, week; WB-MRI, whole-body magnetic resonance imaging; y, year

TABLE 1 Literature summary about to the use of canakinumab in bone autoinflammatory conditions

Patient	Disease	Country	Age onset	Symptoms/manifestations	Previous treatment	Canakinumab dose and duration therapy	Initial efficacy[a]	Short-term efficacy[b]	Long-term efficacy[c]	Final treatment	Adverse events to canakinumab	References
1	DIRA	Turkey	12 y	Pustular cutaneous lesions/ arthralgia of knees, ankles, elbows/arthritis left knee	None	150 mg s.c. every 6 wk	Yes	Yes	Yes	Canakinumab	None	34
2	DIRA	Turkey	13 mo	Recurrent episodes of fever/ serositis/pancreatitis/ pelvic CRMO	Colchicine, Corticosteroids, Anakinra	4 mg/kg s.c. every 4 wk	No	Yes	NA	Anakinra	None	35
3	DITRA	Morocco	2 mo	Erythematous rash/ migratory glossitis/ calcaneal osteomyelitis	corticosteroids, topical tacrolimus and systemic, Anakinra	2 and then 3 mg/kg every 8 wk	No	No	No	Canakinumab	None	36
4	Majeed	Turkey	6 mo	Severe pain and "pseudoparalysis" of extremities/objective joint swelling/CRMO of both tibiae/anemia	Corticosteroids, etanercept, anarkinra	4 mg/kg/4 wk	Yes	Yes	NA	Canakinumab	None	21
5	Majeed	Turkey	3 mo	Severe pain and "pseudoparalysis" extremities/recurrent fever/objective joint swelling /CRMO fibula radius and ulna/anemia	Corticosteroids etanercept anakinra	4 mg/kg/4 wk	Yes	Yes	NA	Canakinumab	None	21
6	CRMO	Arabia	7 y	Arthritis/tender right clavicle, arthralgia/ psoriasis/fractures in dorsal spine	Prednisone Pamidronate Infliximab Methotrexate	5 mg/kg s.c. every 8 wk shorten to 6 wk after the 6 dose and every 4 wk after 18 mo	Yes	Yes	Yes	Canakinumab	None	30
7	CRMO	Arabia	12 y	Bone ache, arthralgia	Naproxen Pamidronate Canakinumab	5 mg/kg s.c. every 8 wk after 4 injections passed at every 4 wk	Yes	Yes	No	Methotrexate Infliximab	None	1
8	CRMO	Italy	13 y	CRMO rib cage, vertebral, both femurs and homers; cutaneous manifestations	Naproxen Methotrexate Neridronate Adalimumab	4 mg/kg s.c. every 4 wk; 52 wk after passed every 8 wk and then after 52 wk reduced every 4 wk	Yes	Yes	Yes	Canakinumab	None	Present article

Abbreviations: CRMO, chronic recurrent multifocal osteomyelitis; DIRA, deficiency of interleukin (IL)-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor; NA, not applicable; s.c., subcutaneous.

[a]Initial efficacy 12 wk.

[b]Short-term efficacy 24 wk.

[c]Long-term efficacy >24 wk.

inflammatory diseases. Only few case reports highlight its association with CRMO. At first the possibility of a paradoxical reaction to anti-TNFα treatment was considered, since adalimumab is one of the most promising therapeutic choices for PG, rarely it also may induce inflammatory immune-mediated skin manifestations.[31,32] PG has been recently described as part of some genetic autoinflammatory conditions such as PAPA (pyogenic arthritis, PG and acne), PASH (PG, acne and suppurative hidradenitis), and PAPASH (pyogenic arthritis, acne, PG and suppurative hidradenitis), these are all characterized by cutaneous involvement with a neutrophilic infiltrate, an inflammasome impairment, and an overproduction of IL-1.[33]

In our patient canakinumab induced a rapid and satisfactory response, with bone pain and PG resolution, inflammatory markers normalization, and an almost complete radiological bone lesions recovery. This drug also proved to be safe and well tolerated.

However, 1 year after drug tapering a loss of efficacy was observed. Restoring the previous injection interval, a partial response was obtained, with pain relief, skin lesions healing, and inflammatory markers normalization, but with appearance of new radiologically detected bone lesions.

In our experience canakinumab proved to be effective and safe in the treatment of this multi-resistant CRMO case and beneficial in PG management. Over time a decline in bone lesion efficacy control was observed with new lesions appearance.

Even though data are still limited, IL-1 inhibition could represent a potential therapeutic choice in patients with severe or complicated features unresponsive to more conventional treatments.

AUTHOR CONTRIBUTIONS

Dr S. Acierno and Dr F. Angrisani wrote the article. Dr Achille Marino contributed to organize and write the article. Prof Rolando Cimaz and Prof Roberto Caporali provided grammar and stylistic revision, Dr Teresa Giani revised the literature.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest and deny any financial support for this article.

INFORMED CONSENT

Informed consent was obtained from legally authorized representatives.

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CASE REPORT

Systemic sclerosis with cerebral infarction and severe stenosis of internal carotid artery and coronary artery: A case report

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Abstract

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by microangiopathy, extensive fibrosis and autoantibody production. It is generally believed that microvascular disease is the hallmark of SSc. Macrovascular involvement is not initially considered as a feature of SSc, but its mortality is high, which should not be ignored. Up to the present, SSc patients with cerebral involvement and multiple macrovascular stenosis have been rarely described. We herein report a case of cerebral infarction and severe stenosis of the internal carotid artery and coronary artery associated with SSc.

KEYWORDS
arterial stenosis, case report, cerebral infarction, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystem autoimmune connective disease of unknown etiology affecting approximately 20 per million people.[1] Defined by the extent of skin involvement, SSc is subcategorized into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc).[2] SSc is characterized by microvascular damage and progressive fibrosis resulting in skin manifestation such as Raynaud's phenomenon (RP), skin thickening and digital ulceration as well as multiple organ manifestations.[3-5] Approximately 90% of the patients with SSc have gastrointestinal involvement, usually presenting as esophageal dysmotility.[6] Pulmonary involvement, the second most common internal organ involvement only to esophageal involvement, is currently the major cause of death in patients with SSc.[7] The cumulative survival from diagnosis has been estimated at 62.5% at 10 years.[8] As the highest individual mortality of all rheumatic diseases, SSc is still challenging for doctors.[7] Overall, the literature on cerebral infarction with multiple macrovascular stenosis in patients with SSc is lacking. We herein report a case of cerebral infarction and severe stenosis of the internal carotid artery and coronary artery associated with SSc.

2 | CASE PRESENTATION

A 62-year-old female patient was admitted to a neurology department with a 2-day history of slurred speech and immobility of the right limb. Five years ago, she was admitted to hospital due to RP, stiff skin, and ulceration of the fingers and feet. At that time, the physical examination revealed that she had obvious punctate depigmentation in the chest area, stiff skin of face, neck, chest and limbs, several ulcers with diameters of 1-2 cm of fingers, and an ulcer with a diameter of 1 cm of the left heel. Chest computed tomography (CT) showed interstitial fibrosis in the lower lobes of both lungs and calcification in the coronary artery (Figure 1). Immunological examination showed that antinuclear antibodies (ANA) and the anti-scl-70 antibodies were positive. Therefore, she was diagnosed with dcSSc. Then she was treated with prednisone (20 mg once per day), hydroxychloroquine (0.2 g twice per day), nifedipine (30 mg once per day), alprostadil (10 μg once per day), tramadol hydrochloride (10 mg once per night) and symptomatic treatment. Ten days later, the patient was discharged from the hospital. The prednisone dose was gradually reduced to 10 mg/d which was maintained. Two years ago, she was diagnosed with hypertension. She controlled her blood

Lanjing Wang and Min Chu have contributed equally to this work.

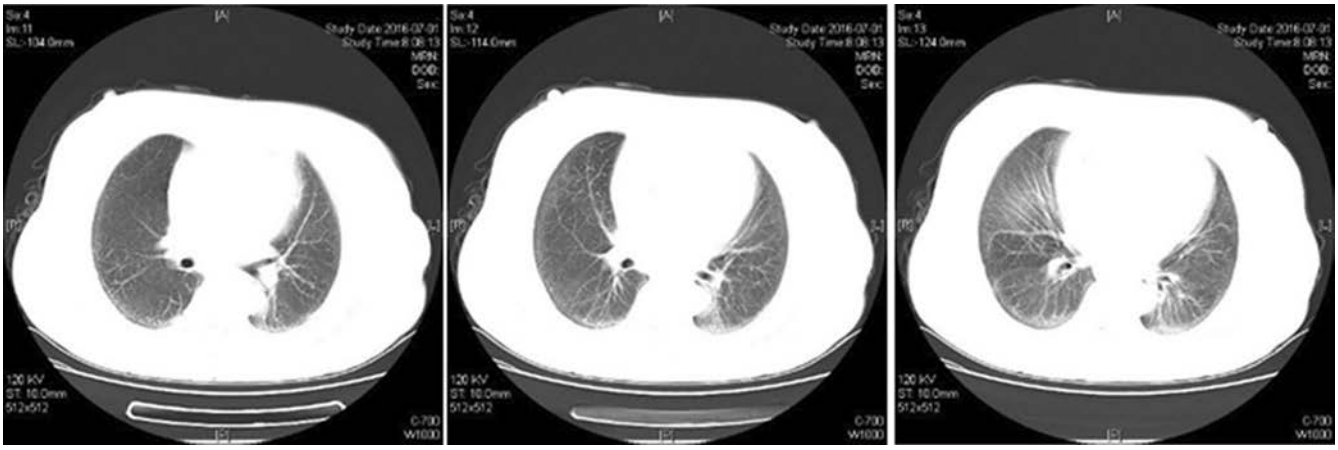

FIGURE 1 Chest computed tomography (CT) showing interstitial fibrosis in the lower lobes of both lungs

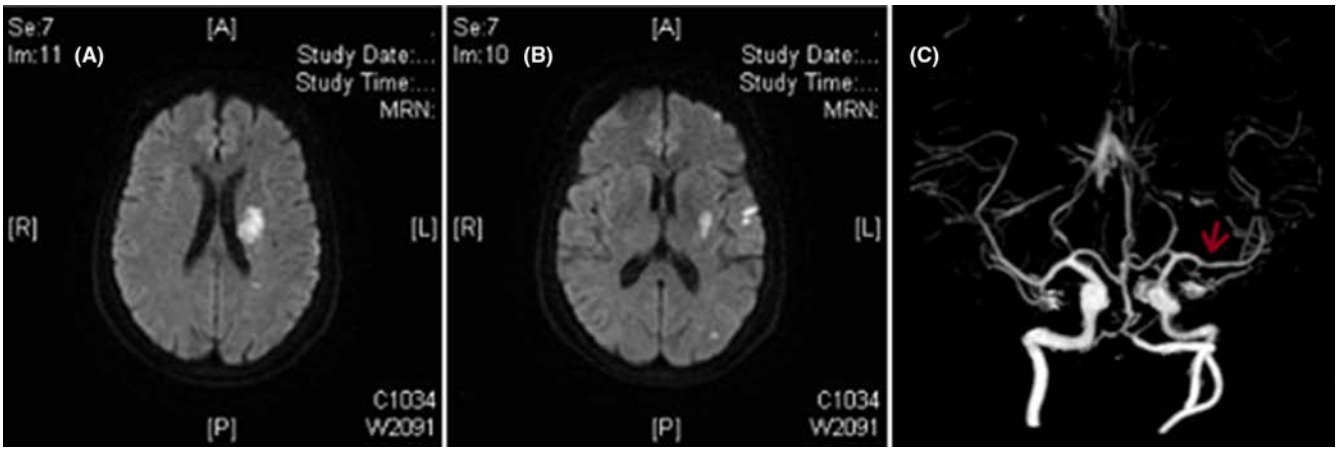

FIGURE 2 Diffusion-weighted magnetic resonance imaging (DWI) of the brain showing a high signal in the (A) left corona radiata-basal ganglia region, (B) left frontotemporal parietal occipital lobe. Computed tomography angiography showing mild stenosis of middle cerebral artery (C)

pressure within the normal range by taking benazepril (10 mg once per day).

Two days before admission, the patient developed slurred speech with immobility of the right limbs, accompanied by coughing while drinking water and difficulty swallowing. Physical examination at admission revealed blood pressure of 120/70 mm Hg and body mass index (BMI) of 22.43. She was sane and had slurred speech. Her bilateral pupils were equal size and circular. Pupillary light reflexes were sensitive. She exhibited no diplopia or nystagmus, and her eye movements were normal. Bilateral frontal lines are symmetrical, the right nasolabial fold was shallow, the tongue extended to the right. The muscle strength of the right upper limb was grade 2, right lower limb grade 4, left limbs grade 5. There was symmetrical presence of bilateral shallow sensations. Her tendon reflexes were active in all limbs with right Babinski sign. She had several ulcers of fingers and feet.

Main laboratory examination results were as follows: red blood cell count, 2.79×10^{12}/L; white blood cell count, 9.16×10^{9}/L; hemoglobin, 94 g/L; eosinophil count, 0.05×10^{9}/L; C-reactive protein, 7.69 mg/L, erythrocyte sedimentation rate, 9.1 mm/1 h; creatine kinase, 21.2 U/L; fasting blood glucose, 6.23 mmol/L; D-Dimer, 1240 ng/mL. Immunological examination showed positive anti-PM-Scl antibodies (++). Her cranial magnetic resonance imaging showed multiple cerebral infarctions (left corona radiata-basal ganglia region, left frontotemporal parietal occipital lobe) (Figure 2A,B). Head and neck computed tomography angiography showed carotid atherosclerosis, and severe stenosis in the initial segment of the left internal carotid artery, mild stenosis of left middle cerebral artery (Figure 2C). Lower extremity arterial ultrasound showed arteriosclerosis in both lower extremities.

She was treated with aspirin (0.1 g once per night), atorvastatin calcium (20 mg once per night), prednisone (10 mg once per day), hydroxychloroquine (0.2 g twice per day) and therapies of improving microcirculation. During hospitalization, she frequently experienced precordial discomfort, but no obvious abnormality in troponin I, myoglobin or creatine kinase isoenzymes MB. Echocardiogram revealed left atrial enlargement and electrocardiogram showed multilead ST-T segment depression. Coronary angiography revealed 90%

stenosis of the left main coronary artery (Figure 3A). Cerebral angiography showed severe stenosis at the origin of the left internal carotid artery (Figure 3C). Two stents were placed in the left coronary artery during the operation (Figure 3B is the postoperative image). Precordial discomfort was effectively relieved after the operation. Left carotid artery stent implantation was performed 6 days after the coronary stent implantation (Figure 3D is the postoperative image). After the operation, she was treated with dual antiplatelet therapy (aspirin and clopidogrel), anticoagulation therapy, and the rest of the treatment was the same as before. One week later, the muscle strength of her right upper limb recovered to grade 3, her speech became clear, and she did not complain of discomfort in the precordial area anymore.

After discharge, she continued to take dual antiplatelets and prednisone. After 1 year she changed to a single antiplatelet (aspirin). During the 2-year follow-up, she did not complain of any discomfort.

3 | DISCUSSION

Cerebral infarction, coronary artery stenosis and internal carotid artery stenosis were definitely diagnosed by clinical manifestations and imaging findings. This patient met the diagnostic criteria of SSc from the American College of Rheumatology and European League Against Rheumatism,[9] and based on the extent of skin involvement, she was diagnosed with dcSSc. According to the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guideline for the treatment of SSc, the patient was treated with glucocorticoids, immunosuppressants, vasodilators and symptomatic treatment.[10] Skin thickening was effectively relieved through therapy. During the follow-up, the patient's skin ulcers were persistent and recurrent, which was consistent with the disease characteristics of SSc.

Scholars generally agree that SSc can promote premature atherosclerosis and accelerate the progression of arterial stenosis.[11] A meta-analysis showed the prevalence of atherosclerosis was increased in all vessels in patients with SSc,[12] and SSc is associated with an increased risk of developing coronary heart disease and stroke.[11,13] In addition, Caimmi et al discovered that the prevalence of carotid plaques in patients with SSc was common, but only a small proportion of patients had significant stenosis.[4] Overall, the mechanisms of macrovascular disease in SSc remain unclear, may be secondary to cardiovascular risk factors, increased endothelial damage and disease-specific factors such as medications.[12] SSc affects the microcirculation and microvascular endothelial cells, accelerates the endurance of the vessel wall of the macrocirculation, then leads to blood vessel obstruction and tissue anoxia.[14,15]

This patient had a 2-year history of hypertension but it was well-controlled. The patient had no family history of cardio-cerebrovascular diseases and her BMI was normal. No other atherosclerosis-related risk factors had been found. The possibility of severe stenosis of multiple arteries in a short time was small, and the patient had positive

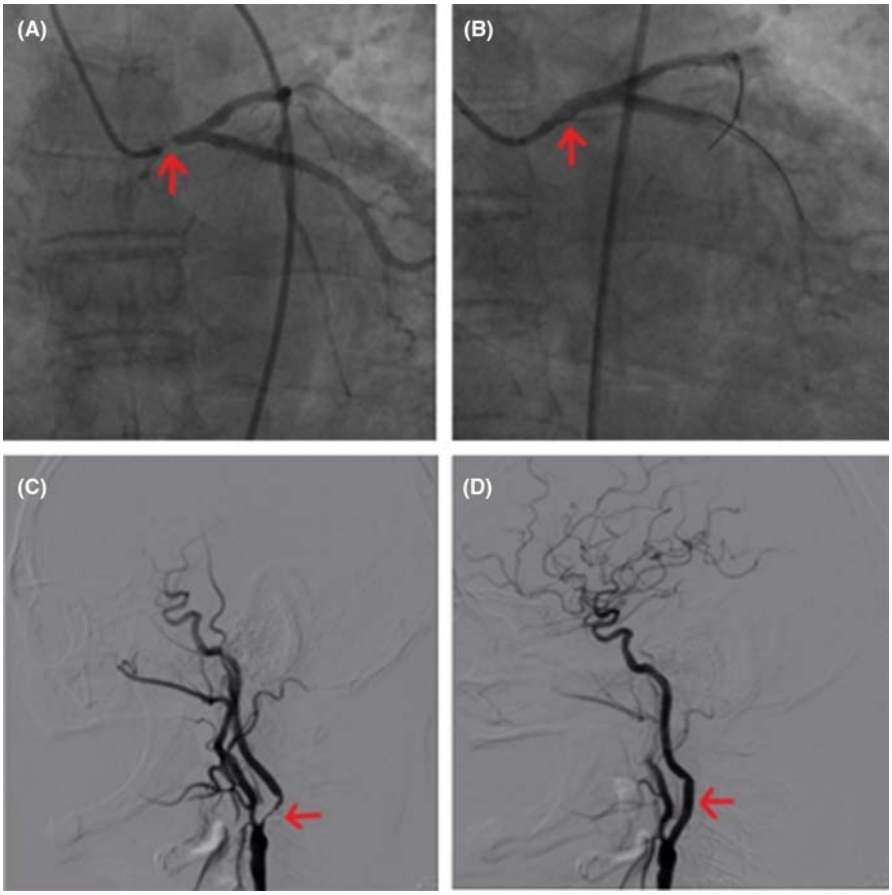

FIGURE 3 (A) Coronary angiography showing 90% stenosis of the left main coronary artery; (B) is the postoperative image. (C) Cerebral angiography showing severe stenosis at the origin of the left internal carotid artery; (D) is the postoperative image

anti-PM-Scl antibody. Therefore, we inferred that the mechanisms of the severe stenosis of multiple large arteries in this patient might be accelerated atherosclerosis caused by SSc on the one hand, and might be autoimmune vascular disease on the other hand. The causes and mechanisms of SSc complicated with cerebral infarction and multiple large arteries stenosis needs further exploration.

Due to the rarity and heterogeneity of SSc, its treatment may be challenging. At present, the treatment mainly focuses on protecting the function of organs and improving the quality of life of patients without specific preventive and treatment measures. Moreover, the treatment for SSc patients with atherosclerosis is knotty due to the role of glucocorticoid therapy in atherosclerosis being highly controversial.[16] A previous study suggested that low-dose prednisone did not increase the risk of atherosclerosis.[17] Recent studies demonstrated glucocorticoid was associated with a dose-dependent increase in risk of cardiovascular events, even low-dose glucocorticoid increases the risk of cardiovascular disease.[18,19] In contrast, Jeries et al discovered that glucocorticoids presented antiatherogenic effect by protecting macrophages from lipid accumulation and foam cell formation.[20] After comprehensive consideration, the patient in this case receiving long-term low-dose prednisone and immunosuppressant and had no recurrence of vascular events during the 2-year follow-up. Therefore, we tend to think the macrovascular stenosis may be more related to SSc instead of prednisone. To sum up, the effect of glucocorticoid therapy on SSc with atherosclerosis is uncertain. New therapeutic strategies for SSc with atherosclerosis need to be explored.

Although the incidence rate of cardio-cerebrovascular diseases caused by SSc combined with macrovascular stenosis is low, the consequences are disastrous, which needs to be paid full attention by clinicians. Further well-designed studies are warranted to explore the pathogenesis of SSc with macrovascular stenosis. SSc patients should not only undergo immunological examination, but also pay attention to the vascular imaging of heart and brain. Early detection, early diagnosis, and early treatment are crucial for long-term prognosis and improvement of life quality for SSc patients with macrovascular diseases.

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CORRESPONDENCE

Anti-SARS-CoV-2 vaccination, safety and disease exacerbation in Behçet's syndrome: Correspondence

Dear Editor,

we would like to share ideas on "Effects of anti-SARS-CoV-2 vaccination on safety and disease exacerbation in patients with Behçet syndrome in a monocentric cohort".[1] According to Apaydin et al, COVID-19 vaccines are well tolerated by Behçet's syndrome patients, whereas more side effects appear following messenger RNA vaccines. Regardless of the vaccine type, exacerbations following the COVID-19 vaccine are frequent, primarily involving the mucosa and joints, while exacerbations involving other organs are uncommon.[1] We both agree there may be a connection between the COVID-19 infection and the vaccine. Even while the COVID-19 vaccination is beneficial, we are all concerned that it might also be dangerous. It is impossible to tell what led to the hematologic issue in this case because there was insufficient pre-vaccination information on the health and immunological status of vaccine recipients. Due to conflicting facts, people may grow discouraged and oppose immunizations. Patient comorbidity may be the cause of the issue.[2] It was evident that the patient had a clinical illness, but this did not mean there were no other co-morbid diseases. A group of people with known pre-vaccination immunological and health statuses who were afterward followed to assess how the vaccine affected the disease would provide more conclusive evidence on this topic.

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CONFLICT OF INTEREST

None.

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CORRESPONDENCE

A novel combined thermography and clinical joint assessment approach discriminates ultrasound-detected joint inflammation severity in rheumatoid arthritis at more joint sites compared to thermography alone

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis with a world-wide prevalence of about 1%.[1] Despite therapeutic advances, many RA patients still do not respond adequately to treatment, remaining "difficult to treat".[2] New models of care incorporating modern musculoskeletal imaging may offer better assessment of joint inflammation,[3] and help guide treatment decisions as rheumatologists strive toward improved RA patient care through early disease diagnosis, better disease prognostication and monitoring of treatment response.[4] A recent systematic review[5] highlighted the growing interest in the use of thermography for the evaluation of inflammatory and degenerative joint diseases based on the publication trend in the last decade. With technology advancement, thermal cameras are now more sophisticated and compact, with portable machines offering improved spatial resolution and sensitivity of thermal sensors.[6] The rapid image acquisition allows for a fairly quick assessment and an objective evaluation of skin surface temperature overlying the target joint site(s) which can be conveniently performed in the setting of the doctor's office. Recently, a novel combined thermal and ultrasound imaging approach in RA was shown to fare better than either imaging modality alone in terms of correlation with the 28-joint Disease Activity Score (DAS28).[6] However, such an approach would require the use of both thermal and ultrasound imaging for joint assessment in RA. In this present study, we aim to test the use of thermography in combination with clinical assessment of joint swelling and tenderness vs thermography alone in discriminating the severity of ultrasound-detected joint inflammation at the RA hand and wrist joints. Joint inflammation is a cardinal feature of RA, and it has long been recognized that heat ("calor"), swelling ("tumor"), pain ("dolor") and redness ("rubor") are the 4 classic signs of inflammation.[7] Thermal imaging detects the heat component while clinical assessment of joint swelling and tenderness helps evaluate the swelling and pain components, respectively; hence providing the rationale to evaluate a combined thermography and clinical joint assessment (CTCA) approach in our present study. Clinical assessment of joint swelling and tenderness are routinely performed in outpatient rheumatology settings and form the clinical components of the widely utilized RA composite DAS28,[8] therefore making these simple clinical measures readily available for use.

Thermography was performed using a high-performance portable FLIR T640 thermal camera with predefined emissivity value of 0.98 for skin,[9] thermal sensitivity of <30 milli-Kelvin (mK) at 30°C and 640×480 pixel resolution. Using previously established methods,[6,9–11] thermography was performed by a designated trained research staff in the same draft-free (windowless) room with a controlled temperature of around 22°C,[11] with patients at rest for 15 minutes prior to the study to allow for acclimatization.[11] All physical objects (eg watches) obscuring the thermal camera's view had to be taken off. Each hand was placed in a neutral position on a flat table top and separately imaged with the thermal camera situated 50 cm directly above the hand. The target joint sites included the bilateral wrists, metacarpophalangeal joint (MCPJs) 1-5, thumb interphalangeal joints (IPJs) and the proximal IPJs (PIPJs) 2-5. Through the use of a regions-of-interests manual segmentation method,[10] a rectangular box was placed over each target joint site. Thereafter, at each target joint site, the maximum (Tmax), minimum (Tmin) and average (Tavg) temperature readings in °C (utilized in the published literature[6,9,10]) were recorded. Finally, the adjusted Tmax, Tmin and Tavg temperatures were derived by subtracting a control temperature[6] (defined as the lowest Tmin at the joints per subject) from the Tmax, Tmin and Tavg at each joint. Standardized ultrasound scanning based on the European Alliance of Associations for Rheumatology (EULAR) guidelines[12] was performed using the Mindray M9 ultrasound machine with a L14-6Ns linear probe. Ultrasound imaging was performed on the same day as the thermal imaging during each subject's study visit. The ultrasound images were acquired and scored by a single rheumatologist experienced in musculoskeletal ultrasonography, while separate research staff carried out the thermography. The following joint sites were scanned: bilateral wrists at the: (a) radiocarpal, intercarpal and (b) distal radioulnar joint recesses; bilateral MCPJs 1-5 at the dorsal joint recesses; bilateral thumb IPJs at the dorsal recesses; bilateral PIPJs 2-5 at the dorsal joint recesses. Ultrasound power Doppler (PD) and grayscale (GS) joint inflammation were graded semi-quantitatively (0 = none, 1 = mild, 2 = moderate and 3 = severe) using validated scoring methods[13,14] with acceptable inter/intra-rater reliability. Ultrasound GS joint inflammation scoring was based on an ultrasonographic atlas,[13] while PD joint inflammation scoring followed the PD severity scoring

definitions of Backhaus et al.[14] At each wrist, the average score at the 2 joint recesses was computed for both GS and PD scoring, since each wrist was scanned at 2 joint recesses while each finger joint was scanned at a single joint recess. CTCA-MAX, CTCA-MIN and CTCA-AVG are CTCA results computed by multiplying the adjusted Tmax, Tmin and Tavg at each joint by a factor of 2 when the joint was swollen and/or tender (clinical assessment performed as part of routine clinical care), and otherwise left unchanged. Without any precedence, we have arbitrarily utilized a "factor of 2" as our intent was to increase the clinical assessment weightage of joint swelling and tenderness on the CTCA scores since joint swelling and tenderness are known manifestations of clinical synovitis, and it is well recognized that swelling ("tumor") and pain ("dolor") are components of the 4 classic signs of inflammation.[7] Increasing the relative weightage of outcomes was recently used in a combined thermal and ultrasound imaging approach[6] at the patient level, although in our present study, this is applied to the CTCA approach at the joint level. Receiver operating characteristic (ROC) analysis assessed the performance of thermography and CTCA in identifying joints with ultrasound PD score >1 and GS score >1; the threshold values of >1 were chosen as it is not uncommon for degenerative joint disease such as hand osteoarthritis to exhibit low levels (grade 1) of ultrasound PD and GS joint inflammation.[15] A parameter was selected as a univariate predictor if statistically significant ($P < .05$) with area under the ROC curve (AUC) ≥0.70.

This cross-sectional study included 37 adult RA patients with the following baseline characteristics: mean (SD) age, 56.5 (13.8) years; majority were female (n = 28, 75.7%); majority were Chinese (n = 28, 75.7%); mean (SD) DAS28 4.43 (1.12); mean (SD) disease duration 30.9 (45.3) months; 31 (83.8%) patients were on one or more disease-modifying anti-rheumatic drugs (methotrexate, hydroxychloroquine, sulfasalazine, and/or tofacitinib); 26 (70.3%) patients were on prednisolone. Of the 22 joint sites examined, 3 joint sites for PD score >1 (bilateral wrists and right MCPJ 1) and 14 joint sites for GS score >1 (bilateral wrists, right MCPJs 1-5, left MCPJs 1-3, left thumb IPJ and right PIPJs 2-4) had sufficient ultrasound outcomes for analysis. The CTCA approach helps discriminate ultrasound-detected joint inflammation severity at more joint sites (bilateral wrists, MCPJs 2 and 3) when compared to thermography alone (left wrist, right MCPJ 1 and 3). For thermography alone, 3 joint sites (left wrist, right MCPJ 1 and 3) had at least one predictive parameter(s) which could help identify joints with ultrasound PD score >1 and/or GS score >1 (Table 1). For CTCA, 6 joint sites (bilateral wrists, MCPJs 2 and 3) had at least one predictive parameter(s) which could help identify joints with ultrasound PD score >1 and/or GS score >1 (Table 2). One possible explanation may be that the CTCA approach, by combining data from thermography and clinical joint assessment, has allowed a multi-faceted assessment of joint inflammation in RA. Our study did not find CTCA and thermography useful at the analyzed PIPJs and thumb IPJs (right PIPJs 2-4 and left thumb IPJ) in predicting the severity of ultrasound GS joint inflammation, while it is not possible to comment on their performance in predicting the severity of ultrasound PD joint inflammation at the PIPJs and thumb IPJs due to insufficient ultrasound PD outcomes for the analysis. At the bilateral wrists, it is noteworthy that all the CTCA parameters were predictive of the severity of both ultrasound PD and GS joint inflammation. At the bilateral MCPJs 2 and 3, although there were CTCA parameter(s) predictive of the severity of ultrasound GS

TABLE 1 Joint sites with at least one predictive parameter(s) with the use of thermography

Ultrasound criterion	Predictive parameter[a]	AUC (95% CI)	*P* value	Cut-off[b]	Sp (%)	Sn (%)
Left wrist						
PD score > 1	Adjusted Tmax	0.841 (0.691, 0.992)	.0052**	4.7	67.9	88.9
PD score > 1	Adjusted Tmin	0.813 (0.669, 0.958)	.0073**	2.85	71.4	88.9
PD score > 1	Adjusted Tavg	0.849 (0.714, 0.985)	.0062**	3.9	71.4	88.9
GS score > 1	Adjusted Tmax	0.827 (0.687, 0.966)	.0038**	4.7	68.0	75.0
GS score > 1	Adjusted Tmin	0.808 (0.67, 0.947)	.0047**	2.85	72.0	75.0
GS score > 1	Adjusted Tavg	0.837 (0.707, 0.967)	.0038**	3.9	72.0	75.0
Right MCPJ 1						
PD score > 1	Adjusted Tmax	0.897 (0.726, 1)	.0496*	5.7	70.6	100.0
GS score > 1	Adjusted Tmax	0.936 (0.813, 1)	.0325*	7.2	97.0	75.0
GS score > 1	Adjusted Tmin	0.932 (0.793, 1)	.0272*	3.95	100.0	75.0
GS score > 1	Adjusted Tavg	0.947 (0.868, 1)	.0357*	4.9	84.8	100.0
Right MCPJ 3						
GS score > 1	Adjusted Tmax	0.922 (0.76, 1)	.0391*	4.6	76.5	100.0

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; GS, grayscale; MCPJ, metacarpophalangeal joint; PD, power Doppler; Sn, sensitivity; Sp, specificity; Tavg, average temperature; Tmax, maximum temperature; Tmin, minimum temperature.

[a]Meeting the specified criteria of AUC ≥ 0.7 and $P < .05$.

[b]Cut-off determined using the Closest to Top Left method.

Statistical significance: *$P < .05$; **$P < .01$.

TABLE 2 Joint sites with at least one predictive parameter(s) using the combined thermography and clinical joint assessment (CTCA) approach

Ultrasound criterion	Left						Right					
	Predictive parameter[a]	AUC (95% CI)	*P* value	Cut-off[b]	Sp (%)	Sn (%)	Predictive parameter[a]	AUC (95% CI)	*P* value	Cut-off[b]	Sp (%)	Sn (%)
Bilateral wrists												
PD score > 1	CTCA-MAX	0.899 (0.797, 1)	.0031**	9.4	85.7	88.9	CTCA-MAX	0.776 (0.578, 0.973)	.0095**	7.3	77.8	80.0
PD score > 1	CTCA-MIN	0.861 (0.735, 0.987)	.0039**	5.7	85.7	88.9	CTCA-MIN	0.726 (0.526, 0.926)	.0287*	4.45	77.8	60.0
PD score > 1	CTCA-AVG	0.889 (0.781, 0.997)	.0031**	7.3	85.7	88.9	CTCA-AVG	0.761 (0.563, 0.959)	.0130*	5.95	81.5	70.0
GS score > 1	CTCA-MAX	0.918 (0.833, 1)	.0017**	8	84.0	91.7	CTCA-MAX	0.813 (0.632, 0.994)	.0038**	7.3	80.7	81.8
GS score > 1	CTCA-MIN	0.873 (0.761, 0.986)	.0017**	4.4	80.0	83.3	CTCA-MIN	0.766 (0.581, 0.951)	.0091**	4.45	80.8	63.6
GS score > 1	CTCA-AVG	0.913 (0.824, 1)	.0013**	5.5	84.0	91.7	CTCA-AVG	0.802 (0.62, 0.985)	.0045**	5.95	84.6	72.7
Bilateral MCPJ 2												
GS score > 1	-	-	-	-	-	-	CTCA-MAX	0.758 (0.494, 1)	.0117*	9.8	93.5	66.7
GS score > 1	CTCA-MIN	0.902 (0.775, 1)	.0298*	2.75	82.4	100.0	CTCA-MIN	0.739 (0.443, 1)	.0127*	3.9	96.8	66.7
GS score > 1	CTCA-AVG	0.931 (0.835, 1)	.0292*	4.7	88.2	100.0	CTCA-AVG	0.763 (0.474, 1)	.0093**	5.5	96.8	66.7
Bilateral MCPJ 3												
GS score > 1	CTCA-MAX	0.914 (0.735, 1)	.0474*	6.35	82.8	100.0	CTCA-MAX	0.873 (0.617, 1)	.0127*	12.2	100.0	66.7
GS score > 1	-	-	-	-	-	-	CTCA-MIN	0.902 (0.75, 1)	.0142*	3.15	76.5	100.0
GS score > 1	-	-	-	-	-	-	CTCA-AVG	0.902 (0.728, 1)	.0124*	4.1	73.5	100.0

Note: CTCA-MAX, CTCA-MIN and CTCA-AVG are combined thermography and clinical joint assessment results derived by multiplying the adjusted maximum (Tmax), minimum (Tmin) and average (Tavg) temperatures at each joint by a factor of 2 if the joint was swollen and/or tender, which otherwise remained unchanged.

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; GS, grayscale; MCPJ, metacarpophalangeal joint; PD, power Doppler; Sn, sensitivity; Sp, specificity.

[a]Meeting the specified criteria of AUC ≥ 0.7 and $P < .05$.

[b]Cut-off determined using the Closest to Top Left method.

Statistical significance: *$P < .05$, **$P < .01$.

joint inflammation, it is not possible to comment on the performance of CTCA in predicting the severity of ultrasound PD joint inflammation due to insufficient ultrasound PD outcomes at these joint sites for the analysis. Given that many joint sites were excluded from our present analysis due to small number of ultrasound outcomes, future larger scale RA studies with sufficient ultrasound outcomes will be required to thoroughly investigate the use of CTCA in comparison with thermography at the various joint sites.

AUTHOR CONTRIBUTIONS

YKT led this study (including the thermography) and was responsible for the overall study design. CH performed the ultrasound imaging. HHL and JCA provided the statistical analysis. All authors have been involved in results interpretation, manuscript drafting and have approved the manuscript for publication.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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APLAR GRAND ROUND CASE

A case of clinically amyopathic dermatomyositis in a Filipino woman

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Abstract

This is a case of a 59-year-old woman who presented with a 2-year history of heliotrope rash, Gottron's papules, shawl sign, V-neck sign, and muscle weakness. She was previously managed as a case of systemic lupus erythematosus and initially responded to unrecalled corticosteroids. She was admitted due to a 1-month progressively enlarging sacral mass, which eventually turned out to be an abscess. While the abscess was being treated, her autoimmune condition was worked up, and she was then managed as a case of clinically amyopathic dermatomyositis (CADM) with interstitial lung disease (ILD). She received corticosteroids and underwent the first cycle of cyclophosphamide infusion prior to discharge.

KEYWORDS
clinically amyopathic dermatomyositis, glucocorticoids, interstitial lung disease, sacral abscess

1 | INTRODUCTION

Dermatomyositis (DM), along with polymyositis (PM) and inclusion body myositis, belongs to a group of heterogeneous disorders called idiopathic inflammatory myopathies (IIMs) which is characterized by muscle weakness and muscle inflammation.[1] DM most commonly occurs between ages 40 to 60 years with an estimated incidence of 9.63 cases per million people. Females are affected twice as often as males.[2] Characteristic manifestations of DM include Gottron's papules, heliotrope rash, nail telangiectasia, non-erosive arthritis, and symmetric proximal muscle weakness. Muscle biopsy may reveal the presence of mononuclear cell infiltrates.[3] Anti-Jo-1 antibody, an immunological marker for DM, has a high diagnostic specificity, but is only present in 30% of patients.[3]

Being a systemic disease, DM can affect other organs of the body. It may present with interstitial lung disease (ILD), cardiac arrhythmias, and motility disorders.[3] ILD is a common manifestation of DM, and it can even precede the onset of characteristic muscle or skin manifestations.[4] DM also increases the likelihood of developing malignancy by approximately 6-fold. DM classification can be further subdivided into classic DM or clinically amyopathic DM (CADM). Between the two, CADM has a lower proportion of patients developing malignancy at around 14% to 20%, as opposed to 20% to 25% in classic DM.[5]

2 | CASE PRESENTATION

A 59-year-old woman was admitted due to a 1-month history of an enlarging nonmoveable, nonpruritic, and nontender sacral mass. She was initially worked up for possible malignancy; however, pelvic computed tomography (CT) scan revealed sacral abscess (Figure 1). Incision and drainage was done and culture studies revealed a pansensitive growth of *Proteus mirabilis*. The patient was treated with piperacillin-tazobactam for 14 days with noted resolution of the abscess.

During her course of admission, the patient was noted to have cutaneous rashes and with complaints of occasional joint pains. Upon re-history, she claimed to have had pink to reddish violaceous papules over metacarpophalangeal and interphalangeal joints of both hands, erythematous rashes on both eyelids, and maculopapular rashes on the upper chest which began almost 2 years prior to admission. No consultation or intervention was done. Nine months prior to admission, the above condition persisted, now associated

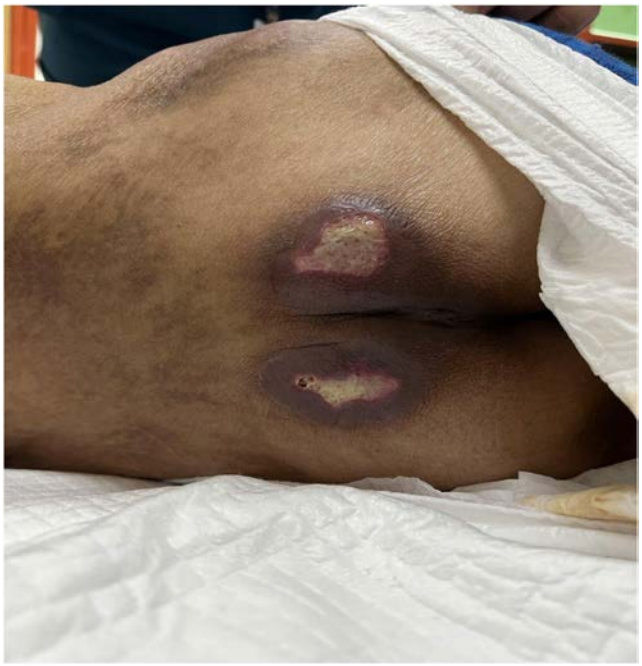

FIGURE 1 Sacral abscess prior to incision and drainage

with generalized non-specific muscle weakness. It was accompanied with arthralgia, arthritis, and digital ulcerations. The patient consulted at a local clinic and was diagnosed with systemic lupus erythematosus and was given unrecalled steroids for 2 weeks with noted improvement on joint pains. The patient was then lost to follow up.

The patient was a known hypertensive for 8 years, maintained and controlled with losartan. She was treated for pulmonary tuberculosis in 1977. She has no diabetes mellitus, asthma, allergies, history of atopy, or known malignancies. She is a nonsmoker, nonalcoholic beverage drinker, and previously worked as a security guard.

The patient was alert, coherent, with stable vital signs, and not in respiratory distress. She had anicteric sclerae, pink palpebral conjunctivae, no palpated cervical lymphadenopathies, had clear breath sounds, no breast or axillary masses, normal cardiac rhythm with no murmurs, had flabby nontender abdomen without organomegaly, no inguinal lymph nodes, had full and equal pulses with no bipedal edema. Neurologic exam revealed intact higher cortical functions as well as cranial nerves, normal motor strength on all extremities, normal sensory examination, +2 reflexes on brachial, patellar, and knees, no meningeal irritation signs, and no pathologic reflexes.

Examination of the skin revealed heliotrope rash (Figure 2A), hyperpigmented maculopapular rash on the upper chest (Figure 2B), hyperpigmented linear rashes over extensor surface of both arms (Figure 2C), Gottron's papules (Figure 2D), and with digital ulcerations (Figure 2E). She was managed as DM and received prednisone at 1 mg/kg/d.

Serum tests were done revealing positive antinuclear antibodies (ANA) at 1:100 dilution with fine speckled pattern. Creatine phosphokinase (CPK), CPK-MB, CPK-MM were all normal with values of 31 U/L (30–135 U/L), 23 U/L (<25 U/L), and 7.77 U/L (30–110 U/L), respectively. Liver function tests are unremarkable as well: aspartate aminotransferase 56 (5–34 U/L), alanine aminotransferase 31 (10–55 U/L), and lactate dehydrogenase 203 (125–220 U/L).

Neck to chest CT scan, whole abdominal to pelvic CT scan, and breast ultrasound did not show any nodularities or masses that may point to malignancy. Esophagogastroduodenoscopy and colonoscopy were also performed. Biopsy of gastric polyp and duodenal tissue showed chronic inflammation without any evidence of malignancy. However, chest CT scan revealed multiple patchy ground glass opacities with peripheral distribution in both lungs, suggestive of ILD. (Figure 3).

With an impression of ILD, the patient underwent pulmonary function test which revealed a low forced vital capacity (FVC) and low forced expiratory volume, probable moderate restrictive ventilatory defect with no significant bronchodilator response.

DLCO revealed the following results: DLCO 18.61 mL/min/mm Hg (14.57–26.05 mL/min/mm Hg) and total lung capacity (TLC) 3.31 L (3.26–5.23 L). Findings revealed a normal DLCO but with mild restrictive ventilatory defect with underlying obstructive ventilatory defect.

Dermatology service examined the patient. Systemic corticosteroids were continued and they started the patient on clobetasol propionate 0.05% ointment twice a day on affected erythematous areas for 2 weeks. Mild soap was advised for bathing.

Electromyography (EMG) and nerve conduction velocity of both upper and lower extremities revealed the following results. (1) Sensory amplitudes of the median nerves were reduced with slowing of sensory conduction velocities more on the right. (2) Motor amplitudes were moderately to severely reduced. Distal latencies were prolonged only on both median nerves and right peroneal nerve. (3) The right median F-waves were prolonged while the rest of the F-waves were normal. Tibial H-reflex responses showed normal latencies. (4) Needle electromyography (EMG) showed highly polyphasic motor units, some with early recruitment mostly in the proximal muscles of lower extremity more than the upper extremity. No spontaneous activity was seen. There was subtle evidence for a non-inflammatory myopathic process mostly involving the proximal lower extremity muscles. Considerations included metabolic vs steroid-induced myopathies.

Anti-Jo1 was done prior to the patient's discharge which revealed a result of 0.4 U/L (<7: negative, 7–10 equivocal, >10 positive). With complete resolution of the sacral abscess, improvement in muscle weakness and arthritis, and infusion of first cycle of cyclophosphamide, the patient was sent home well and improved with the following take-home medications: prednisone at 1 mg/kg/d and calcium + vitamin D tablet once a day.

3 | DISCUSSION

The patient was diagnosed with DM using the American College of Rheumatology-European League Against Rheumatism Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies.

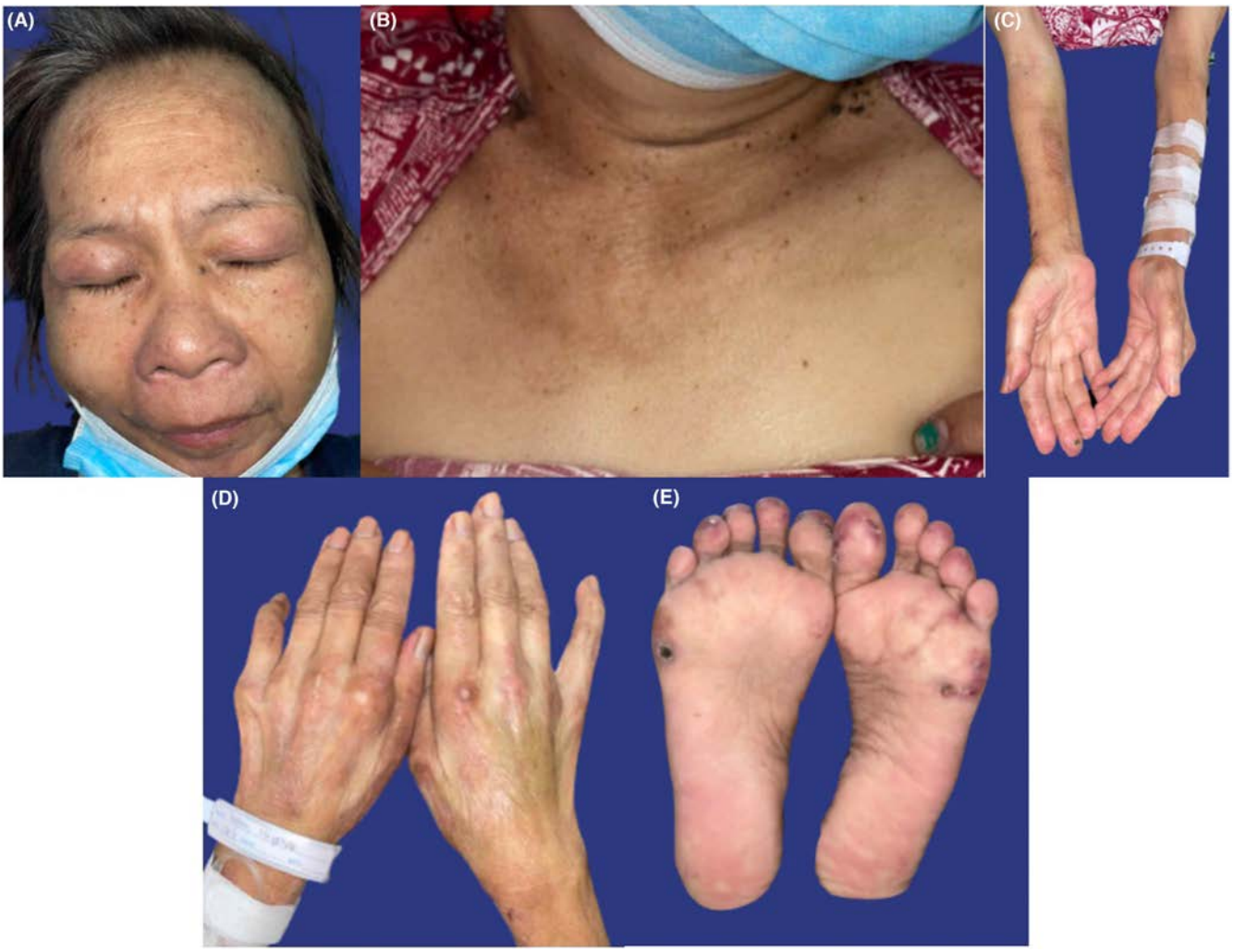

FIGURE 2 (A) Note the subtle periorbital erythema. (B) V sign: hyperpigmented (previously erythematous) irregularly shaped patches on the anterior chest. (C) Hyperpigmented linear rashes over the extensor surface of both arms. (D) Gottron papules: multiple linear irregularly shaped plaques on the proximal interphalangeal, metacarpophalangeal and distal interphalangeal joints. (E) Minute ulcerations on the digits of both toes

She satisfied the following criteria with corresponding probability scores: (1) age of onset of first related symptoms at 40+ years (2.1); (2) heliotrope rash (3.1); (3) Gottron's papules (2.1); (4) Gottron's sign (3.3). We were not able to obtain a muscle biopsy mentioned in the criteria because of the patient's financial difficulties. Anti-Jo-1 turned out negative. However, despite not having a muscle biopsy and a negative autoantibody result, the patient had a total score of 10.6 which has 99% probability for IIM. We further classified the patient as having DM based on the following: (1) onset of first symptoms at age >18 years, and (2) the presence of heliotrope rash, Gottron's papules and Gottron's sign. These criteria have a specificity of 82% and sensitivity of 87% when used without a muscle biopsy.[6] We also subclassified the condition as clinically amyopathic dermatomyositis (CADM) on the basis that the cutaneous manifestations occurred for more than 6 months without clinical, laboratory, or muscle testing evidence of myopathy.

Endoscopy, colonoscopy, and multiple imaging studies were performed in order to determine possible malignancy of the patient. DM patients have 3 to 8 times increased risk for developing malignancy, and therefore should be worked up at the time of diagnosis.[7] The most common cancer associated with DM in Southeast Asia is nasopharyngeal cancer, while breast, lung, and colon cancers are the 3 most common from patients in the West.[8] A local case report from Philippine General Hospital presented a 40-year old man with typical cutaneous manifestation of DM with no muscle weakness and normal CPK. He was diagnosed with CADM and workup for malignancy was done including chest X-ray, whole abdominal ultrasound, urinalysis, fecal occult blood test, and prostate specific antigen. The patient then developed cervical lymphadenopathies and underwent biopsy revealing a metastatic undifferentiated carcinoma.[5]

Neurophysiological studies have high sensitivity and specificity in diagnosing myopathies and are able to exclude other causes of weakness such as myasthenic syndromes, neuropathies with motor involvement, or motor neuron diseases.[9] These tests, according to Bohan and Peter, have a sensitivity of 89%.[10] In acute myopathies, it is recommended to conduct the study 3 weeks after

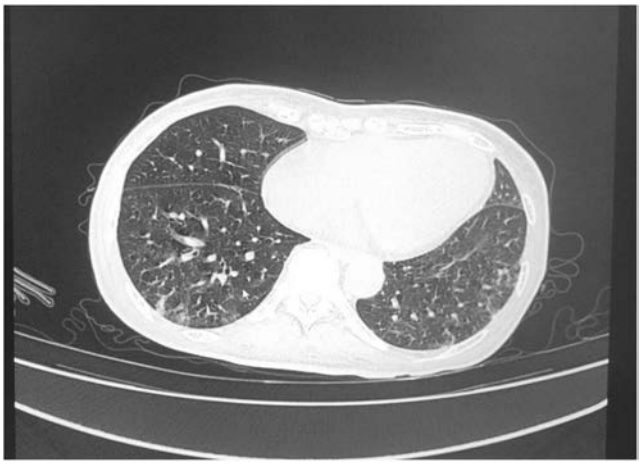

FIGURE 3 Plain chest computed tomography scan showing multiple patchy peripheral ground glass opacities in both lungs

symptom onset in order to ensure a higher sensitivity.[9] Another thing to consider when doing EMG is that it may cause elevation of CPK, which is also a blood test used in the classification criteria for DM. It is therefore recommended to do CPK determination before or 3 days after the EMG.[11] Findings in EMG for DM include fibrillation and positive waves, high frequency, or myotonic discharges.[9] The patient's EMG revealed a non-inflammatory myopathy involving proximal lower extremities muscles, with considerations of metabolic vs steroid-induced myopathies. Myopathic diseases are usually progressive, may present with atrophy in advanced diseases, and with elevated creatine kinase.[12] It is important to note that the patient had been taking prednisone for 3 weeks when the EMG was done.

The usual dermatologic manifestations of DM were present in our patient: the heliotrope rash, Gottron's papules, and the V-neck sign. Other characteristic rashes that were not observed include the shawl sign which refers to erythema on the upper back, posterior neck, and shoulders, and the holster sign which is a violaceous rash over the lateral hip. They can also present with scalp disease presenting with erythematous scaling plaques on the scalp.[7] On nailfold capillaroscopy, DM patients can have prominent dilated and tortuous blood vessels with accompanying avascular areas. The degree of vessel drop out as well as telangiectasias is a reflection of ongoing disease activity.[13] Exposure to sunlight worsens skin disease of DM, hence, protective clothing and application of sun block with at least 15 sun protection factor is recommended.[14]

ILD can affect 35%–40% of patients with IIMs such as DM and is usually associated with the presence of antisynthetase antibody.[15] The presentation of ILD in DM patients can present with 1 of these 3: (1) an acute, severe involvement; (2) chronic gradually progressive signs and symptoms; or (3) asymptomatic disease in which lung disease is incidentally diagnosed by imaging studies, just like how our patient presented.[16] Pulmonary function test (PFT) in ILD reveals a restrictive pattern described as low FVC or total lung capacity (TLC) <80% predicted for age.[7] Characteristic features on high-resolution chest CT scan include ground glass opacities (GGO), linear opacities, fibrosis with or without honeycombing, and bronchiectasis.[7] In a study published in the *European Respiratory Journal*, they noted that the most frequent CT findings are reticular and GGO.[17] The patient's chest CT scan revealed GGOs with peripheral distribution and PFT showed a low FVC suggestive of ILD. In the same study, they found that respiratory symptoms occurred 100 days after muscular symptoms and 340 days after the skin symptoms.[17] Early diagnosis and intervention are necessary to improve the prognosis. No standard treatment has been established yet, although combination therapy with high-dose glucocorticoid (1 mg/kg), a calcineurin inhibitor (tacrolimus or cyclosporine A), and cyclophosphamide should be considered as first-line therapy.[18]

Progressive ILD is more frequently observed in patients with CADM.[19] CADM comprises 10% to 20% of all DM patients with increased risk for rapid progressive ILD (RP-ILD) resulting in a higher rate of mortality.[20] CADM patients who have anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies are more likely to develop RP-ILD.[21] In a study done by Pedram et al (2011), it was found that CADM patients can eventually develop muscle weakness from 15 months to 6 years after the onset of their skin disease.[22]

The prognosis of DM patients is determined by ILD, hence it is important to control ILD to avoid poor outcomes and help maintain the patient's quality of life.[23] Since our patient had CADM with CTD-ILD, tight monitoring of clinical conditions is required. Monitoring of ILD is 3-tiered: (1) disease activity monitoring which includes determination of anti-MDA5 antibody titer, serum ferritin, and clinical signs such as skin rashes; (2) respiratory condition monitoring which includes observation for development of symptoms such as dyspnea, cough, as well as progression of GGOs on high-resolution CT; and (3) monitoring for adverse events including opportunistic infections since the patient is on immunosuppressive therapy. In Japan, routine monitoring for cytomegalovirus, pneumocystis pneumonia, and other fungal infections is done.[23]

The patient was discharged well and improved after infusion of cyclophosphamide with the following take-home medications: prednisone 50 mg/d (1 mg/kg/d) and calcium + vitamin D tablet once a day. She was regularly following up at rheumatology outpatient clinic for her cyclophosphamide infusion to complete 6 cycles.

4 | RECOMMENDATIONS

We recommend to determine other autoantibodies such as anti-MDA-5 which is usually positive in DM patients with rapidly progressive ILD. Anti-Mi-2 is not available in the Philippines but its positivity may point to classic DM, good response to treatment, and lower incidence of malignancy. One study found that serum ferritin is a useful marker and its elevation indicates a poor prognostic factor. Lastly, 2-dimensional echocardiography must be facilitated to rule out cardiac involvement.

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