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EDITORIAL

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Does methotrexate cause interstitial lung disease in rheumatoid arthritis: What is the evidence?

1 | INTRODUCTION

Low-dose methotrexate (LD-MTX) is presently the mainstay of treatment of rheumatoid arthritis (RA).[1-4] It is one of the safest drugs to treat RA.[5] Therefore, it is called "The Anchor Drug" in RA[6] and recommended by the American College of Rheumatology and European League Against Rheumatism as its first-line treatment.[7,8] Over time, its efficacy in treating several additional systemic immunoinflammatory rheumatic diseases (SIRDs)[9-19] has broadened its use worldwide. Even biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) work better when combined with MTX.[20] It has a long-retention rate further confirming its safety and efficacy.[21] With several decades of regular use in patients in routine rheumatology clinics world-over, rheumatologists have become comfortable and confident in routinely using MTX. With such overwhelming proof of its efficacy and safety, if for some reason(s) it cannot be prescribed to a patient with RA or SIRDs, managing such a patient becomes difficult. One such situation that has caused much discussion and controversy is the "triad" of methotrexate-RA-interstitial lung disease (ILD).[22]

2 | COMMON SIDE-EFFECTS OF LD-MTX

No drug is completely free of side-effects. LD-MTX is no exception. A detailed discussion of the same is beyond the scope of this review that focuses on issues related to lungs only. The readers may like to refer to a recent update on the topic for more detailed information.[23] Suffice it to say that in routine clinical practice adverse effects of LD-MTX are generally minor and easily manageable.[4]

3 | LD-MTX AND THE LUNG

In the context of treatment of RA with LD-MTX, if the patient shows features of ILD it is common to "blame" the drug promptly and "ban" it forever.

Consequently, it becomes challenging to treat such patients without LD-MTX. Therefore, it is essential to examine the evidence in favor or against the involvement of LD-MTX in the causation of rheumatoid lung disease, namely ILD. Emerging recent evidence has challenged the long-held view of the involvement of LD-MTX in RA-associated ILD.

4 | THE EVIDENCE FOR MTX LUNG TOXICITY

The first report of lung toxicity was presented by Albert M. Clarysse from Maxwell M. Wintrobe's hematology group (in Denver, Colorado, USA) at the XII Congress of International Society of Hematology, New York, in 1968[24] which was published in 1969.[25] The report included 7 consecutive patients with acute lymphoblastic leukemia who were treated intermittently with 13.3-20 mg MTX per square meter body surface after induction of remission with prednisone therapy. In authors' words "A respiratory illness characterized by fever, non-productive cough, severe dyspnea, cyanosis, and bilateral pulmonary infiltrates developed in all 7 patients while they were in hematology remission. The illness was severe and life-threatening in 6 of the 7 patients. All 7 recovered". The authors had noted there was marked eosinophilia in these patients during the acute phase of illness which made the treating physicians suspect acute/subacute hypersensitivity pneumonitis (HP) due to environmental exposures. Therefore, these patients were painstakingly investigated for different respiratory exposures including blastomycosis, coccidioidomycosis, histoplasmosis, tuberculosis and any exposure to birds. Finally, it is interesting to note that all 7 patients recovered after the drug was discontinued. It can be clearly seen this was an acute/subacute illness that had no resemblance to the chronic ILD seen in day-to-day clinical practice. Certainly, no pulmonologist will confuse typical HP described in these patients with routine ILD, a chronic idiopathic progressive fibrotic lung disease which reduces patient survival. In hindsight, the detailed histopathological finding of the lung biopsy from these patients was rather typical of HP with no resemblance to that of chronic idiopathic ILD, routinely seen in clinical practice. None of the above patients progressed into chronic ILD with any resemblance to idiopathic ILD.

The next major publication on MTX and lung disease was by Kremer et al in 1997 which also reviewed the literature on the topic. As against cancer, Kremer et al studied patients with

RA treated with MTX.[26] Six academic institutions and private practices participated in the study and collected information on patients with RA from July 1981 and June 1993. The authors selected patients using the Searles-McKendry criteria for MTX pneumonitis.[27] It is to be noted that the first point in the "Major criteria" states "Hypersensitivity pneumonitis by histopathologic examination (and without evidence of pathogenic organisms)". Therefore, by definition, what the authors were describing was not chronic idiopathic ILD but an entirely different lung condition namely, HP. For their study, Kremer et al identified 27 cases that met the criteria.[26] Clinical features included acute or subacute onset of progressive dyspnea, mostly dry cough and fever with mild eosinophilia in the majority during the acute phase. Lung biopsy was available in 20 patients. The histopathology was evaluated by experts with long experience in hypersensitivity lung disease and MTX toxicity who could make the distinction between RA lung disease and MTX-related HP. The paper describes the minute details of the histopathological distinction between HP and RA-ILD. Twenty cases were classified as having definite MTX lung injury on histopathologic evaluation. Four cases were categorized as probable, and 3 as possible. Four of the specimens were judged to have no MTX lung injury. Rheumatoid lung was not noted in any patient. Based upon these characteristics the authors conclude that MTX-related HP is a toxic reaction that usually occurs after a relatively short duration of treatment and it is not related to the cumulative dose. Thus, based upon this seminal paper, it can be summarized that MTX lung injury is a form of HP, a disease distinct from RA-ILD and the garden variety of chronic ILD.

Considering these 2 seminal earlier papers, it is obvious that LD-MTX may cause HP. These papers also clearly mention the distinction between HP and RA-ILD; the latter was not seen in these patients. In a paper on the long-term safety of LD-MTX in RA published in 2009, MTX HP was seen only in 0.43%.[28] The issue of MTX-related HP has been recently revisited.[22,23] In his 2018 review, Balk[23] quotes the figures of 1%-8% for MTX-related HP with 1 exceptionally high figure of 33%. Fragoulis et al in their detailed review on the same subject in 2019,22 came to their first conclusion that most of the high figures for MTX-related HP were reported in publications before the 1990s after which these figures fell to 0.43% as had been reported by Salliot and van der Heijde in 2009.28 Fragoulis et al also suggested that in recent years this figure may have fallen even further to 0.28% (13 cases reported in the 4544 MTX-treated patients).[22]

The second point discussed by Fragoulis et al is related to the occurrence of MTX-induced ILD in RA for which they found no evidence in the literature.[22] These authors quote several papers clearly establishing that MTX treatment has no role in causing rheumatoid lung disease. It seems that for reasons not clear, HP has been confused with ILD seen in RA. The latter point requires critical appraisal mainly because there is widespread misbelief among physicians that MTX causes ILD in patients with RA.

5 | DIFFICULTY IN DIFFERENTIATING CHRONIC HYPERSENSITIVITY PNEUMONIA, IDIOPATHIC PULMONARY FIBROSIS (IPF) AND NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

Chronic hypersensitivity pneumonitis (CHP) is an ILD that results from recurrent or long-standing exposure to environmental antigens and carries a poor prognosis with 5-year survival as low as 25%-30%.[29] Diagnosing CHP is difficult because the manifestations are nonspecific and may mimic IPF and NSIP.[30] Yet, the distinction of CHP from IPF and NSIP is important because each disease is managed differently.[30] Because CHP is caused by repeated pulmonary exposure to a variety of ubiquitous environmental small organic particles (antigens) including fungi, animal proteins, insects and occasionally chemical compounds,[31] avoidance of the inciting antigen is key to its management.[32] Thus, the literature review on CHP gives a possible clue to why MTX is getting the blame for RA-ILD. Could CHP be the disease that is being confused with RA-ILD for which MTX is getting the blame? It is a thought that needs to be discussed with pulmonologists. In discussion with pulmonologists and after a literature search,[33] it was evident that several features of CHP especially differential diagnosis between CHP and acute to subacute ILDs including diffuse alveolar damage, organizing pneumonia, eosinophilic pneumonia (EP), lymphocytic interstitial pneumonia, or cellular nonspecific interstitial pneumonia (NSIP) is often difficult even for specialists. Moreover, the epidemiology of CHP is not well known. and there are no reports of MTX-induced CHP. Therefore, the possibility of MTX causing CHP would remain a research agenda.

6 | LD-MTX DOES NOT CAUSE ILD—THE EVIDENCE

There are only a few high-quality studies suitable for use to analyze respiratory adverse events caused by LD-MTX. Fortunately, there have been 3 recent publications of 2 well-performed meta-analyses and one multivariate analysis on this issue.[34-36] Additionally, Fragoulis et al[22] have summarized the results of 2 of these studies[34,35] succinctly and argued strongly against the involvement of MTX in the causation of RA-ILD.

The first meta-analysis included 22 randomized controlled trials with 8584 patients, equally divided into 2 groups who received either MTX or a comparator conventional synthetic DMARD (csDMARD).[34] The results indicated an association of MTX with increased risk of infectious (relative risk [RR] 1.11, 95% CI 1.02-1.21), rather than non-infectious (RR 1.02, 95% CI 0.65) etiology of adverse effect in the lung. ILD being a non-infectious condition, the study seems to negate any association of MTX with non-infectious lung adverse effects. Higher rates of lung infection in patients with RA are well known.[37,38] Similarly, a higher than normal rate of ILD has also been reported in patients with RA.[39]

The second meta-analysis by the same group was carried out with the objective of evaluating the RR of lung involvement in patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with MTX.[35] It included 7 studies comprising 1640 patients with psoriasis, psoriatic arthritis and inflammatory bowel disease Of these, 818 patients were taking MTX and 812 other conventional synthetic DMARDs (csDMARDs). The study found no increase in overall respiratory adverse events in patients taking MTX (RR 1.03, 95% CI 0.90-1.17). On the separate assessment of infectious and non-infectious adverse events, no increase in infectious or non-infectious adverse events was observed (RR 1.02, 95% CI 0.88-1.19; and RR 1.07, 95% CI 0.58-1.96, respectively). However, there was 1 possible case with MTX-related HP. Thus, it could be concluded that it is not the MTX but the disease RA itself that makes a patient more prone to developing ILD rather than the treatment with MTX.

The third important publication, a multivariate analysis, published in the middle of 2019 is even more compelling because it shows that LD-MTX for treating RA could be protective against the development of ILD.[36] The study assessed predictive factors for RA-ILD in 2 early RA inception cohorts, namely, the early RA study (ERAS) and the early RA network (ERAN), from a standpoint of MTX exposure. ERAS recruited patients from 9 centers while ERAN recruited patients from 23 centers in England, Wales and Ireland from 1986 to 2012 with follow-up going on up to 25 years. Participants included 2701 patients with newly diagnosed RA. Data were collected on standardized forms that included demographics, drug therapies, clinical outcomes and the presence of RA-ILD, at the baseline, at 3-6 months follow-up and then annually. The primary outcome of the study was to evaluate the association of MTX exposure with the diagnosis of RA-ILD. There were 3 secondary outcomes of the study for any possible association of RA-ILD with: (a) demographic factors, (b) comorbidities and (c) RA-specific factors (serology, the association of MTX exposure with time to RA-ILD diagnosis). The study could find 92 patients who developed ILD during the stated period. MTX exposure was recorded in 39 (2.5%) of 1578 patients while in the non-MTX exposed cases ILD was recorded in 53 (4.8%) of 1114 patients. The primary analysis of RA-ILD cases who developed the disease only after the initiation of any of the csDMARD treatment (n = 67) showed that MTX exposure was not associated with the occurrence of RA-ILD (odds ratio [OR] 0.85, 95% CI 0.49-1.49, P = .578). In a more comprehensive analysis of patients who were found to have RA-ILD at RA diagnosis (n = 92), MTX exposure was associated with a significantly reduced risk of incident RA-ILD (OR 0.48, 95% CI 0.3-0.79, P = .004). Also, in those exposed to MTX, the time to ILD diagnosis was significantly longer (OR 0.41, 95% CI 0.23-0.75, P = .004). This study confirmed some of the other known risk factors for developing RA-ILD including higher age at the onset of RA, smoking (current or past), male gender, rheumatoid nodules and delay in appropriate treatment. The study concluded that MTX treatment was not associated with an increased risk of RA-ILD diagnosis. Based upon these results, the authors argued that, contrary to the belief, the presented evidence suggested that MTX may prevent or delay the onset of ILD in patients with RA.

7 | CONCLUSION

An extensive literature review revealed that all the papers on the topic of MTX-induced lung injury have described an acute or subacute lung disease that has clinical, radiographic and histopathological features typical of HP with no resemblance to RA-ILD and it responds to standard treatment recommended for HP. Mysteriously, the incidence of MH-pneumo seems to have gone down from the reported figures varying from 1%-8% published before 2009. Publications since then have shown that the MH-pneumo figures have come down to 0.43% in 2009[28] and now, 0.286% in the publications from 2019.[22] Also, since 2014 the publications of 2 meta-analyses,[34,35] 1 multivariate analysis[36] and 1 narrative review of literature on the topic of MTX and RA-ILD[22] have firmly refuted any association of LD-MTX with RA-ILD. Moreover, the available data tend to indicate that LD-MTX may actually be preventing or delaying the occurrence of RA-ILD.[36] The widespread misbelief regarding "MTX causing ILD" could have its root in misinterpreting MH-pneumo as being RA-ILD while the fact is that these are 2 entirely distinct pulmonary diseases with no relationship to each other. Therefore, discontinuing MTX treatment in RA-ILD would appear to be illogical and unreasonable.

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CONFLICT OF INTEREST

None.

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EXPERT COMMENTS

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Care for patients with rheumatic diseases during COVID-19 pandemic: A position statement from APLAR

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1 | INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China in December 2019. This disease now affects the whole world. Patients with rheumatic diseases are at higher risk of respiratory infections including influenza and pneumococcal pneumonia, which is attributed to the underlying disease, comorbidities and immunosuppressive therapy,[1] but to date we lack good information about the virus SARS-CoV-2. Nonetheless, immunosuppressive treatments are essential to control disease activity and prevent functional deterioration in these patients. Rheumatologists need to be vigilant in preventing rheumatic disease patients from contracting the disease during this pandemic, especially patients with chronic lung problems (eg scleroderma with lung fibrosis) and chronic kidney disease (eg lupus nephritis) and those on high-dose glucocorticoids and immunosuppressants (Appendix 1).

In the desperate search to find effective treatments for COVID-19, drugs largely used by rheumatologists have entered the spotlight, including the caution against use of non-steroidal anti-inflammatory drugs (NSAIDs), the potential of antimalarials and biologic disease-modifying anti-rheumatic drugs (bDMARDs), for example anti-interleukin-6 (IL-6) and targeted synthetic DMARDS (tsDMARDs) Janus-activated kinase (JAK) inhibitors to manage cytokine storm syndrome (CSS)/cytokine release syndrome associated with COVID-19. Here, we try to provide guidance regarding clinical decision-making both for patients with COVID-19 and those with rheumatic diseases, and strategies to mitigate further harm to these patients.

2 | METHODS

An Asia-Pacific League Against Rheumatism (APLAR) COVID-19 task force comprising rheumatologists from 9 Asia-Pacific countries

was convened on 31 March, 2020. A set of guidance statements was developed and refined based on best available evidence up to 26 April, 2020 and expert opinion. Given the overall limited nature of the data, a systematic review was not performed. The final guidance statements integrate both the task force members' assessment of the evidence quality and the ratio of risk and benefit from the treatment or action. We assert that the key guiding principle should be to "first do no harm," especially given the unknown efficacy of proposed DMARDs and biologics and their established potential harms. This guidance document has been reviewed and endorsed by the APLAR executive committee and the APLAR scientific committee chairpersons.

3 | HOW CAN WE MINIMIZE THE RISK OF RHEUMATIC DISEASE PATIENTS FROM EXPOSURE TO COVID-19?

In the absence of a vaccine or a therapeutic agent, a "mitigation approach", including "social distancing", frequent hand washing and quarantining strategies are the primary interventions to hamper the spread of infection.[2] Another approach, known as "suppression strategies" includes strict lockdown measures – social distancing in entire populations, the closure of schools and community spaces, aggressive case finding and contact tracing, have succeeded in maintaining low case counts of COVID-19. During this extraordinary time, the rheumatology community faces unprecedented challenges as care could be postponed/delayed or handled through virtual care to minimize contact exposure and to practice social distancing.

Comorbid conditions are common in patients with COVID-19.[3] Smoking can cause an increase in the release of IL-6 in bronchial epithelial cells,[4] and upregulate angiotensin-converting enzyme-2 (ACE2) receptors, the known receptor for SARS-CoV.[5] This is particularly relevant as some of the Asia-Pacific countries, for example China, has a high male smoking rate.[6] Globally the quality of evaluation, monitoring and treatment of comorbidities in rheumatic disease patients is variable with considerable scope for improvement.[7] Rheumatologists should be vigilant in assessing and managing comorbidities not only to improve morbidity and mortality, but hopefully to minimize risk of COVID-19 in rheumatic disease patients.

4 | NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

In patients with acute respiratory tract infections, short-term use of NSAIDs are associated with increased risk of cardiovascular events and nephrotoxicity,[8-10] higher rates of complications, and delays in the prescription of effective antibiotic treatment.[11] Despite the lack of evidence relating specifically to people with COVID-19, regular NSAID use should not be recommended as the first line option for managing the symptoms of COVID-19.[12] Nonetheless, arthritis patients taking NSAIDs for symptomatic relief should continue their treatment as needed.

5 | USE OF IMMUNOSUPPRESSANTS AND RISK OF COVID-19 INFECTION

Epidemiologic studies have identified advanced age, male gender and presence of comorbidities (hypertension, obesity, diabetes, coronary heart disease, chronic obstructive lung disease and chronic kidney disease) as poor prognostic factors for COVID-19.[13] Despite the lack of data on the true prevalence and risk of COVID-19 in rheumatic disease patients, immunosuppressed status (the use of chemotherapy or conditions requiring immunosuppressive treatment) was not reported to be a risk factor and risk for adverse outcome. One patient with systemic sclerosis-associated interstitial lung disease (SSC-ILD) on tocilizumab and 7 patients on bDMARDs or tsDMARDs who developed COVID-19 recovered uneventfully.[14-16] Nonetheless, at least 2 patients on rituximab[17] developed respiratory failure and 1 of them died despite treatment with tocilizumab.[18] In order to gather real-world data to inform treatment strategies and better characterize individuals at increased risk of infection, the COVID-19 Global Rheumatology Alliance has successfully developed online portals and case report forms to enable healthcare providers around the world to enter information on individuals with rheumatic disease who have been diagnosed with COVID-19, with clinical data of the first 110 patients published.[19] For now, patients with stable rheumatic diseases should continue their treatment. In case of infection (including COVID-19), treatment of infection gains precedence and immunosuppressive treatment may be de-escalated or temporarily withheld in consultation with the treating rheumatologist (Appendix 1).

5.1 | Glucocorticoid therapy

Acute lung injury and acute respiratory distress syndrome (ARDS) are partly caused by host immune responses. Severe COVID-19-associated pneumonia patients may exhibit features of systemic hyper-inflammation or CSS. COVID-19 infection with CSS typically occurs in subjects with ARDS and historically, non-survival in ARDS was linked to sustained IL-6 and IL-1 elevation.[20] Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance. The effectiveness of adjunctive glucocorticoid therapy in the management of COVID-19 infected patients remains controversial.[21,22] Until results from ongoing randomized-controlled trials are available, the World Health Organization (WHO) has advised against routine use of systemic corticosteroids for treatment of viral pneumonia outside of clinical trials unless they were indicated for other reasons (eg septic shock) (Appendix 2). In rheumatic disease patients on long-term steroids, it is very important to remind them not to stop their prednisone even if they develop symptoms suggestive of COVID-19 (Appendix 1). For patients with active

rheumatic disease, after excluding concurrent active infection, the prednisone dose could be increased carefully according to the severity of the organ manifestation, in spite of the risk of COVID-19.

5.2 | Conventional synthetic disease-modifying anti-rheumatic drugs

Preclinical and limited clinical data suggested that hydroxychloroquine (HCQ) and chloroquine (CLQ) have antiviral activities against SARS-CoV-2.[23-25] In contrast, a small but randomized study from China in patients with mild to moderate COVID-19 treated with HCQ or placebo found no difference in recovery rates,[26] and French investigators failed to confirm antiviral activity or clinical benefit of the HCQ and azithromycin combination in 11 hospitalized patients with severe COVID-19.[27] In a French series of 17 systemic lupus erythematosus (SLE) patients with COVID-19 on long-term HCQ, 11 (65%) and 5 (29%) developed respiratory failure and ARDS respectively despite having blood HCQ concentrations within the therapeutic range for the management of SLE.[28] Whether blood HCQ concentrations may be effective for the antiviral activity against SARS-CoV-2 remained uncertain. Nonetheless, data from this study suggest that HCQ may not be able to prevent severe COVID-19 in these patients. The US Food and Drug Administration (FDA) cautioned against use of HCQ or CLQ for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems (Appendix 2). The APLAR task force agreed there are insufficient clinical data to recommend either for or against HCQ or CLQ for COVID-19, and clinicians should monitor patients for adverse effects, especially prolonged QTc interval. Health authorities should ensure adequate supply of these drugs since the HCQ shortage not only will limit availability to patients with COVID-19 if efficacy is truly established but also represents a real risk to patients with rheumatic diseases.

On the other hand, rheumatologists should remind patients to continue HCQ and not to taper the dosage even if they develop symptoms suggestive of COVID-19 and reassurance should be given that this drug should not increase their risk of infection.

5.3 | Biologic disease-modifying anti-rheumatic drugs

Once hospitalized, for some patients with COVID-19, death can occur within a few days, many with ARDS, and some with multiorgan dysfunction syndrome.[14] In those critically ill patients, there are both clinical signs and symptoms, as well as laboratory abnormalities, that suggest a CSS is occurring in response to the viral infection. According to data from the Chinese cohorts, patients with severe disease and requiring intensive care often show leucopenia, lymphopenia, significantly higher levels of C-reactive protein (CRP), IL-6, IL-10, and tumor necrosis factor-α (TNF-α).[29] In this setting, biologic drugs selectively blocking inflammatory cytokines, such as TNF-α inhibitors, anti-IL-6, anti-IL-1 and JAK inhibitors are currently employed in the treatment of severe cases of COVID-19 in an experimental manner or undergoing clinical trials (Appendix 2).

Tocilizumab, has been shown effective in treating CSS, a common complication of chimeric antigen receptor-T cell therapy used for treating refractory acute lymphoblastic leukemia[30] and may be effective in Chinese COVID-19 patients with severe and critical disease.[31] Anti-IL-6R antibody is currently included in the treatment recommendation for Chinese COVID-19 patients (Appendix 2). These concepts have led to interests in JAK inhibitors, for example baricitinib, as potential treatments for CSS complicated with severe COVID-19.

ACE2 is a cell-surface protein widely existing on cells in the heart, kidney, blood vessels, especially alveolar epithelial cells. SARS-CoV-2 was believed to invade and enter lung cells through ACE2-mediated endocytosis. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and can be helpful in preventing virus infections. Baricitinib, apart from being a JAK inhibitor, is also an AAK1 inhibitor. Baricitinib was thought to be a possible candidate for treatment of COVID-19, considering its relative safety and high affinity.[32] On the other hand, JAK–STAT (signal transducer and activator of transcription) signal blocking by baricitinib produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection, and therefore may not be a suitable treatment.[33] While we are waiting for the results from the control trials to resolve this controversy, rheumatologists should be particularly cautious of serious infectious events on the use of this agent, in particular viral infection, for example herpes zoster.

6 | CONCLUSIONS

Rheumatologists worldwide are trying new strategies to optimize care for rheumatic disease patients during this unprecedented COVID-19 pandemic. Concerted efforts from healthcare providers in different healthcare systems are required to continue clinical assessments and ensure adequate supply of immunosuppressive therapy. Worsening of rheumatic disease may induce a systemic inflammatory state which may represent an adjunctive risk factor for major susceptibility to viral infection. On the other hand, rheumatologists are cautiously enthusiastic that a variety of immune-modulating drugs and targeted cytokine inhibitors available for rheumatic disease patients may also benefit patients as prophylaxis for COVID-19 or with COVID-19-induced CSS. Because of insufficient data, APLAR could not recommend any specific treatments for patients with COVID-19. Nevertheless, rheumatologists/immunologists are expert in the use of these agents and we should be to the forefront in advising around their application, noting risks and benefits are not yet clear and should not be taken for granted in

COVID-19. We emphasize the ongoing importance of critical review of emerging literature to inform current and future treatment decisions. International registries have been created to collect data on rheumatic patients with COVID-19. Ultimately, time and these registries will tell what the right decision is regarding maintaining current therapy for patients with rheumatic diseases. The APLAR task force will respond quickly and efficiently to place the evidence base behind our recommendations and update them should new findings emerge from clinical trials.

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APPENDIX 1

Key recommendations for managing patients with rheumatic diseases during the COVID-19 epidemic

Potential risk factors for SARS-COV-2 infection in patients with rheumatic diseases

- On immunosuppressive agents
- Chronic kidney disease, eg lupus nephritis
- With lung involvement, eg interstitial lung disease
- Elderly patients
- Frequently visiting medical clinic
- With underlying health conditions, such as smoking, obesity, hypertension and diabetes
- Pregnancy

Medication for patients with rheumatic diseases[a]

- Continue current treatment if disease is stable, and contact your doctor for suitable medicine if disease has flared
- Use of hydroxychloroquine (HCQ) and sulphasalazine (SLZ) should be continued and should not increase the risk of infection
- Use of other conventional synthetic disease-modifying drugs (csDMARDs, eg methotrexate, leflunomide) and immunosuppressants (eg cyclophosphamide, azathioprine, mycophenolate mofetil, tacrolimus) should be continued
- Corticosteroid use can be continued
- A new prescription of immunosuppressant or increase in dose of an ongoing immunosuppressant would need to be carefully discussed in epidemic areas
- Use of all biologic DMARDs should be continued if possible
- If infliximab infusion is not accessible, switching to other anti-tumor necrosis factor injection at home is encouraged
- Targeted synthetic DMARDs (Janus-activated kinase [JAK] inhibitors) including tofacitinib/baricitinib/upadacitinib can be continued

Surgery

- Postpone elective surgery, eg joint replacement surgery
- Screening for COVID-19 (symptoms suggestive of COVID-19, complete blood count, nasopharyngeal swab and chest X-ray or chest computed tomography according to local recommendation) before emergency surgery

Patients with rheumatic disease and fever

- Contact your rheumatologist about potential option to visit fever outpatient clinic with personal protection provisions if temperature continues over 38°C
- Patients must not suddenly stop prednisolone
- Suspend the use of immunosuppressants and biological agents after consultation with your rheumatologist, and follow appropriate local guidance for suspected COVID-19 if COVID-19 cannot be ruled out
- Patients can continue HCQ and SLZ if they are infected with COVID-19.

[a]Concerning glucocorticoids, immunosuppressants, csDAMRDs, bDMARDs and JAK inhibitors, the balance of safety and efficacy in viral infection as well as pulmonary inflammation remains unclear.

APPENDIX 2

Useful links for physicians regarding COVID-19

The following links would help rheumatologists understand the recent perspectives on COVID-19

Taylor & Francis: https://taylorandfrancis.com/coronavirus/

Elsevier: https://www.elsevier.com/connect/coronavirus-information-center

Wiley: https://novel-coronavirus.onlinelibrary.wiley.com/

Springer Nature: https://www.springernature.com/jp/researchers/campaigns/coronavirus/coronavirus-further-articles

Oxford University Press: https://academic.oup.com/journals/pages/coronavirus?cc=us&lang=en&

BMJ: https://www.bmj.com/coronavirus

New England Journal of Medicine: https://www.nejm.org/coronavirus

The Lancet: https://www.thelancet.com/coronavirus

The following links are from national or international organizations to help rheumatologists and patients to manage their diseases during COVID-19

European League Against Rheumatism (EULAR) guidance for patients on COVID 19: https://www.eular.org/eular_guidance_for_patients_covid19_outbreak.cfm

American College of Rheumatology (ACR): https://www.rheumatology.org/announcements

World Health Organization (WHO): Coronavirus disease (COVID-19) outbreak

German Society for Rheumatology - Patient section. (German only): Deutsche Gesellschaft für Rheumatologie - Patienten Bereich

British Society for Rheumatology guidance for rheumatologists:

https://www.rheumatology.org.uk/news-policy/details/covid19-coronavirus-update-members

Shielding policy in UK: https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

National Rheumatoid Arthritis Society: Coronavirus: What we know so far. https://www.nras.org.uk/coronavirus.

Medical Council of India: Telemedicine Practice Guidelines - Ministry of Health and Family

www.mohfw.gov.in›pdf›Telemedicine

Management of patients with COVID-19

WHO clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

National Institute of Health treatment guideline

https://covid19treatmentguidelines.nih.gov/introduction/

US Food and Drug Administration (FDA) cautions against the use of antimalarial agents outside hospital setting or clinical trial: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

Treatment recommendation for Chinese COVID-19 patients: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

The Australasian Society of Clinical Immunology and Allergy (ASCIA) positional statement: https://www.allergy.org.au/hp/papers

Research on DMARDs related to COVID-19

Clinicaltrial.gov: https://clinicaltrials.gov/ct2/results?cond=COVID-19

Hydroxychloroquine as post-exposure prophylaxis: https://clinicaltrials.gov/ct2/show/NCT04308668

Hydroxychloroquine for the Treatment of Patients with Mild to ModerateCOVID-19toPreventProgressiontoSevereInfectionorDeath: https://clinicaltrials.gov/ct2/show/NCT04323631?cond=COVID-19&draw=4&rank=21 Tocilizumab: https://clinicaltrials.gov/ct2/show/NCT04317092?cond=COVID-19&draw=2&rank=10

Sarilumab: https://clinicaltrials.gov/ct2/show/NCT04315298?cond=COVID-19&draw=3&rank=12

Baricitinib: https://www.clinicaltrials.gov/ct2/show/NCT04320277

https://clinicaltrials.gov/ct2/show/NCT04321993?cond=COVID-19&draw=2&rank=18

Rheumatology patient registry

The COVID-19 Global Rheumatology Alliance: https://rheum-covid.org/

EULAR: https://www.eular.org/eular_covid19_database.cfm

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REVIEW ARTICLE

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Update on disease pathogenesis, diagnosis, and management of primary Sjögren's syndrome

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Abstract

Primary Sjögren's syndrome (pSS) is a typical multisystem disease, characterized by lymphocytic infiltration of the exocrine glands leading to glandular dysfunction. Multiple systemic manifestations occur in those of serious conditions, with different courses and outcomes. Its pathogenesis is complex, and its diagnosis and management are being constantly updated and improved. We have failed to have much progress in targeted immunotherapy for pSS, and as yet this is still based on empirical treatment. Many studies have tried to define pSS more accurately, to study its pathogenesis, to find effective treatment strategies, opening up new avenues for early diagnosis and precise management of pSS.

KEYWORDS

diagnosis, management, pathogenesis, primary Sjögren's syndrome, prognosis

1 | INTRODUCTION

Primary Sjögren's syndrome (pSS) is a heterogeneous and complex disease primarily affecting females, and the ratio of affected men to women is 1-9. Based on changes in diagnostic criteria, the true prevalence of pSS is difficult to assess, about 0.5%-4.0%, which is the main multisystem autoimmune disease after rheumatoid arthritis (RA).[1] It is characterized by lymphocytic infiltration of exocrine glands leading to glandular dysfunction, and high titer of serum anti-SSA/B antibodies, which may lead to further systemic manifestations, including rash, arthritis, profound fatigue, nephritis, and lymphoma, that result in severe morbidity and a decreased quality of life, and can even be life-threatening.[2] It is also known as secondary SS (sSS) when it is associated with other autoimmune diseases such as RA. In recent years, research on pSS has been more of a combination of clinical experiments and basic research to further explore its pathogenesis and novel biomarkers. This review will summarize the latest research on the pathogenesis, diagnosis and management of pSS.

2 | PATHOGENESIS

The pathogenesis of pSS involves complex effects of multiple factors, which are generally believed to be related to genetic predisposition, environmental factors and immunological disorders.

The genetic factors closely related to pSS include human leukocyte antigen type-DR (HLA-DR) allele subtypes as well as some specific gene polymorphisms. Zhang et al analyzed the whole-genome expression profiles of salivary glands in non-sicca control groups and pSS patients; 379 differentially expressed genes (DEGs) were found to be involved in the pathogenesis of pSS. Three hundred genes were significantly up-regulated, and enriched in Gene Ontology terms of autoimmune responses. The remaining 79 DEGs related to salivary gland dysfunction were down-regulated.[3] Therefore, genomic studies are supposed to further explain the etiology and pathogenesis of pSS.

Based on the female preponderance in pSS, the X-chromosome has widely attracted attention. Given the interpretation of SS *GEO2R*

Jing Wang and Lingyan Zhou contributed to this work equally and should be regarded as co-first authors

gene datasets, Mougeot et al found that 58 X-chromosome genes were up-regulated. In addition, they also found *XIST* and its cis regulators were up-regulated such as *CHIC1*, *FTX*, and *RLIM*.[4,5] Numerous X-chromosome genes referred to SS pathogenesis can be adjusted by transcription factors which are differentially methylated and overexpressed in SS patients. However, the precise mechanism remains to be further studied.

Environmental factors, such as viral infections, are important triggers for pSS; data delineates that viral-induced autoimmunity can be triggered by various mechanisms such as epitope spreading, bystander activation, molecular mimicry, and infected B cells immortalization.[6] Sanosyan et al proved that Epstein-Barr virus (EBV) was highly expressed in exocrine gland biopsies of pSS patients, and it was highly associated with the markers of anti-SSA/B autoantibodies and B cells activation, suggesting a potential link between the EBV, B cells activation and pSS etiology.[7] However, the impact of viral infections on autoimmunity is a duality. Viral infections also lead to the activation of autoimmune responses, thus inhibiting the development of the immune response.[6] Therefore, molecular studies are necessary to understand virus-induced interactions between autoimmune and immune-related molecules, which would provide a comprehensive mechanism description with viral infections and autoimmune diseases.

Epithelial cells play an important role in the initiation and progress of immune and inflammatory response in pSS. Under the influence of genetic predisposition and environmental factors, critical epithelial cell pathways for example Janus-activated kinase/ signal transducers and activators of transcription (JAK-STAT) and epithelial growth factor signaling are activated, leading to excessive accumulation and activation of immune cells such as dendritic cells, B cells, and T cells. With the help of chemokine and adhesion factors, they migrate to the glands and develop a variety of pro-inflammatory factors to activate adjacent epithelial cells.[8] One kind of excessively accumulated dendritic cell can produce a high concentration of interferon (IFN)-α, which stimulates epithelial cells, T cells, and dendritic cells to produce B cell activating factor (BAFF). BAFF stimulates the maturation of abnormal B cells, causing them to produce autoantibodies in the lymphatic germinal center, which leads to the development of autoimmunity.

3 | DIAGNOSIS

How to effectively identify early stage patients and evaluate their therapeutic effects remains a huge challenge. Numerous classification criteria were established since the 1970s. The latest classification criteria have been acknowledged by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[9,10] As per the previous criteria,[11,12] the 2016 ACR/EULAR criteria also classifies a pSS patient through autoantibody testing, dryness measurement and histopathology. However, the difference is that the 2016 ACR/EULAR criteria adds a weighted score for each element, further refining the particular threshold for ocular staining score. Baer et al showed that the presence of anti-La/SSB antibodies alone had no significant correlation with the SS phenotype features and lacked specificity for the diagnosis of pSS, so the 2016 ACR/EULAR criteria eliminated anti-La/SSB antibodies and increased the weighted score of anti-Ro/SSA antibodies.[13] In addition, the presence of an extra-glandular manifestation was given credit in the 2016 ACR/EULAR criteria, allowing patients with this feature into clinical trials.

Antibodies of parotid secretory protein, carbonic anhydrase 6 (CA6), and salivary protein 1 (SP1) are considered potential biomarkers of pSS patients with early disease, and anti-RGI2, anti-alpha-enolase, and anti-cofilin-1 antibodies are biomarkers of mucosa-associated lymphoid tissue lymphoma. The detection of these antibodies provides an opportunity to establish clinical phenotypes, to identify specific disease stages, and to evaluate some complications.[14]

Due to its simplicity, non-invasiveness and high efficiency, salivary gland ultrasonography can accurately evaluate salivary gland function and improve the sensitivity of the 2016 ACR/EULAR criteria (from 87.4% to 91.1%), providing clinicians with more ideas for diagnosis and treatment.[15,16] Dynamic magnetic resonance (MR) sialography is effective in quantitatively evaluating salivary gland secretion function by the time-dependent volume change ratio curve. The volume of the parotid duct is constantly changing due to the secretion of saliva; 3D MR ductal imaging can quickly and accurately calculate the volume of the duct at each stage, improve the spatial resolution and more accurately evaluate the function of the parotid gland.[17]

Therefore, the diagnosis of pSS needs comprehensive evaluation and consideration. The diagnosis of "early SS" remains unclear, which requires a larger cohort study and a sufficiently long follow-up time.

4 | MANAGEMENT

Due to the complexity of pathogenesis and heterogeneity behind the clinical manifestations, many targeted immunomodulatory therapies for pSS have shown no benefits in clinical trials; so far no specific treatment for this disease has been approved. Management of pSS is still to refer to the therapeutic armamentarium of systemic lupus erythematosus and RA.

4.1 | Management of sicca symptoms

As many as a third of patients develop dry eye, and the severity of which is associated with disease activity.[18] Autologous serum eye drops contain a variety of nutrients such as growth factors, which effectively simulate tears and promote corneal repair and visual recovery.[19] As they are expensive and can only be purchased in special institutions, their use is restricted. Local application of

cyclosporin A (CsA) can effectively inhibit T cell activation in the lacrimal gland and conjunctiva, which improves the ocular inflammatory response. Chung et al indicated that a novel topical CsA 0.05% nano-emulsion effectively improved ocular surface sensitivity and inflammation.[20] Compared with the conventional emulsion, it shows faster improvement of ocular surface staining scores. Not only because it provides constant hormone levels for the cornea, but also reduces systemic adverse reactions caused by hormones, fluocinolone acetonide intravitreal therapy is a new choice for treating corneal diseases.[21]

Impaired salivary gland secretion function severely reduces food intake and nutrient absorption in patients.[22] Saliva substitutes are widely used in the treatment of dry mouth. Although they can ameliorate the symptoms, they cannot fundamentally improve the secretion function of salivary glands.[23] Salivary gland endoscopy can be used for the diagnosis and treatment of chronic obstructive salivary gland diseases caused by constriction, mucous plugs and sialoliths. Infusion of saline and corticosteroid solution into the salivary gland duct system can increase the salivary gland flow rate, alleviate the discomfort of patients, and improve quality of life.[24,25]

In summary, for most patients, dryness of the eyes and mouth has been present throughout the development of the disease, and clinical trials should evaluate the efficacy and adverse reactions of the drugs, as well as the impact on quality of life in pSS patients.

4.2 | Non-biological therapies

Total glucosides of paeony (TGP) is a common Chinese medicine, which has been recorded with analgesic, anti-inflammatory, immunomodulatory effects, and few side effects. Decreasing the substantial damage of glands and improving the secretion of lacrimal glands (Schirmer's test), are the significant functions of TGP.[26] At the same time, studies have shown that TGP can enhance the negative co-stimulation pathway programmed cell death protein 1 (PD-1)/PD-L1 expression by reducing the expression of soluble PD-1, further regulating Th17/Treg balance and reducing the production of autoantibodies. The incidence of side effects is only 10.9%.[27,28] A placebo-controlled JOQUER trial showed that hydroxychloroquine (HCQ) reduced the levels of type I IFNs and IFN-stimulated genes in peripheral blood of pSS patients, as well as reducing inflammatory markers, although it did not improve disease activity.[29] HCQ causes varying degrees of ocular toxicity and retinal damage, a number of clinical studies have developed a safe dose range and protocols to decrease adverse reactions.[30] In addition, Radstake et al showed that leflunomide (LEF) combined with HCQ can inhibit the proliferation of B and T cells, reduce the production of immunoglobulin and a variety of T follicular helper (Tfh)-related cytokines, and target multiple key pathways involved in pSS immunopathology. The combination of the 2 drugs was more efficient than single treatment.[31]

4.3 | Biological therapies

Biologicals for pSS have valuable application prospects, but their efficacy and safety are still controversial. Over-activation of B cells is the cornerstone of pSS. Targeted therapy of B cells has become a research focus in recent years.

Rituximab is a monoclonal antibody specific to the cluster of differentiation 20 (CD20) molecule expressed in B cells, clearing B lymphocytes by antibodies and complement-dependent cytotoxicity.[32] In large studies, rituximab had no significant effects on improving dryness, fatigue or composite primary endpoints.[28,33] Epratuzumab targets B cell-specific protein CD22, interferes with the formation of B cell receptor (BCR) signal complex, enhances the inhibitory effect of CD22 on BCR, reduces the count and activity of peripheral blood B cells, and improves the level of clinical markers related to disease activity. In all patients treated with epratuzumab, the B cell count, the levels of IgM and anti-Ro/SSA antibodies continued to decline.[34,35] Therefore, the 2 drugs can be utilized reasonably according to the patient's condition and play the best therapeutic effect.

BAFF is a critical factor in the pathogenesis of pSS which promotes the activation and proliferation of B lymphocytes.[36] A clinical study conducted by Dorner et al indicated that ianalumab (VAY736) treatment for pSS was safe and effective. Ianalumab can completely eliminate pathogenic B cells by direct lysis of B cells and blocking BAFF and its receptor signaling pathway, significantly improving the clinical parameters and laboratory indicators of patients. The main adverse reactions were minor infusion reactions due to injection administration.[37] To improve the effectiveness of the study, more representative patient groups should be included and reliable primary endpoints should be chosen to evaluate its clinical efficacy.

5 | PROGNOSIS

The quality of life and prognosis of patients varies with the severity of the disease. pSS patients with local symptoms have a good outcome. If the treatment is not timely, pSS can worsen and even be life-threatening. Infections, cardiovascular disease, and lymphoma are the leading causes of death.[38]

6 | CONCLUSION

pSS is a chronic autoimmune disease with a complex etiology. Management of pSS is still controversial. Therefore, it is imperative that basic and clinical research, and new understanding of the pathogenesis opens up new means for the treatment of the disease. It is believed that with more extensive and detailed research in the future, the treatment of pSS will surely make great progress.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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REVIEW

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WILEY

Effect of TNF-inhibitor therapy on spinal structural progression in ankylosing spondylitis patients: A systematic review and meta-analysis

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Abstract

To review the effect of tumor necrosis factor-alpha inhibitor (TNFi) therapies on radiographic progression in ankylosing spondylitis (AS) patients as evaluated by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Pubmed, MEDLINE, EMBASE, and the Cochrane Library databases were searched from inception to August 2019. All comparative and non-comparative studies that evaluated the clinical effectiveness of TNFi on radiographic progression as assessed by mSASSS change at a minimum follow-up of 1 year were included. The Newcastle–Ottawa Scale and Cochrane Collaboration Risk of Bias Tool were utilized to assess the methodological quality. Pooled analysis was performed for continuous and binomial variables where appropriate. Inter-rater reliability of mSASSS status and change scores were assessed with intra-class coefficients (ICC). Twenty-one studies were identified with a total of 4460 patients (mean age: 40.4 years [range 25.3-50 years]; 76% male; mean baseline mSASSS: 12.7 units [range 5.5-19.8 units]). All studies (3 randomized and 18 observational studies) were considered to have moderate-to-high methodological quality. The inter-rater reliability of mSASSS status and change scores from 14 of the 21 studies were excellent (ICC ranges, 0.91-0.99) and moderate-to-excellent (ICC ranges, 0.58-0.90), respectively. From the 21 studies, 11/21 (50%) demonstrated a delayed effect in mSASSS in AS patient administered TNFi. When stratifying these studies into those with ≤4 years of follow-up and >4 years follow-up, 3/11 (27%) and 8/10 (80%) studies respectively indicated a delayed effect of mSASSS with TNFi in AS patients. Pooling for meta-analysis from 3 studies (1159 patients) with study durations ranging 4-8 years, indicated that TNFi-treated patients had reduced odds of structural progression (odds ratio 0.81; 95% CI 0.68-0.96; $P = .01$; $I^2 = 0\%$). Mean rate of mSASSS change from 16 studies ranged from −0.15 to 7.3 mSASSS units for all AS patients. Meta-analysis indicated a numerical, but statistically non-significant, reduction in the rate of mSASSS change with TNFi treatment (7 studies [1438 patients]; mean difference, −0.24; 95% CI, −0.49-0.01; $P = .06$; $I^2 = 0\%$). This systematic review

Level of Evidence: Level IV systematic review of Level I through IV studies.

and meta-analysis indicated that >4 years of TNFi usage was associated with delayed structural progression by mSASSS. The narrative analysis of the data from 21 studies further confirmed that studies with >4 years of follow-up had delayed structural progression with TNFi use in AS patients. The systematic review also confirmed that mSASSS has good-to-excellent inter-rater reliability in AS.

KEYWORDS

ankylosing spondylitis, anti-tumor necrosis factor-alpha, modified Stoke Ankylosing Spondylitis Spine Score, mSASSS, radiological progression, TNF inhibitors

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine and sacroiliac joints affecting nearly 0.5% of the population.1 AS usually starts in early adulthood with the leading manifestation being the presence of inflammatory back pain. Extraspinal features including uveitis, arthritis, and psoriasis may also accompany AS presentation.2 New bone formation in the entheses is one of the distinct features of AS, which produces functional impairments and disability.3

Conventional radiography is the gold standard for assessing structural progression and the modified Stoke AS Spine Score (mSASSS) is the preferred method for quantifying structural progression in AS.4,5 A minimum 2-year follow-up interval is required to ensure sufficient sensitivity to reliably detect structural progression.6 Studies have shown a change of 2 mSASSS units in 2 years (rate ≥ 1 unit/y) or the development of new syndesmophyte(s) is evidence of structural progression.7-9 In this respect, approximately 20%-45% of the biologic-naive AS patients showed structural progression at 2 years follow-up.10-13

Aside from symptom resolution, disease modification has gained recognition as an important outcome in the assessment of treatment success.10,11 Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment options in symptomatic AS. If disease activity persists despite NSAIDs, then tumor necrosis factor-alpha inhibitors (TNFi) are considered.14,15 However, similar to NSAIDs, the clinical effectiveness of TNFi agents in halting structural progression in AS remains controversial.8,10,16-18 The inconsistencies between studies assessing TNFi disease-modifying potential for halting structural progression in AS, and the lack of consensus regarding this topic in the literature, has prompted this review. We aimed to synthesize the effect of TNFi therapies on structural progression in AS patients as evaluated by the mSASSS. We hypothesized that the long-term utilization (ie greater than 4 years) of TNFi agents will delay structural progression in AS patients.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.19 Two authors (PA and IS) collectively performed a search in the electronic databases Medline, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and www.clinicaltrials.gov from inception to August 2019 for studies with varied study designs. This search was performed using the following keyword combinations: (ankylosing spondylitis OR spondylitis) AND (radiographic progression OR X-ray OR mSASSS) AND (tumor necrosis factor-alpha inhibitors OR tumor necrosis factor blockers). The search strategy was restricted to human studies; however, no language or publication date restrictions were applied. The primary author (PA) manually cross-referenced all included studies and past review articles on the topic to ensure search completeness.

2.2 | Eligibility criteria

Studies fulfilling all of the following inclusion criteria were included: (a) published randomized controlled trials (RCTs), non-randomized comparative studies, or non-comparative cohort studies that reported radiographic outcomes; (b) studies administering TNFi treatment; (c) minimum clinical follow-up of 2 years; (d) adult patients (≥18 years) with a diagnosis of AS, as defined by the 1984 modified New York criteria20; and (e) studies utilizing the mSASSS criteria4 (total score 0-72) for assessing structural progression. Case studies, editorials/commentaries, review articles, and basic science articles were excluded.

2.3 | Study selection

The primary author (PA) removed the duplicate articles from the generated search. Afterwards, 2 authors (PA and IS) independently screened the title and abstracts of all identified articles and assessed their eligibility based on the inclusion criteria. Studies that were considered potentially relevant by at least 1 reviewer (PA and IS) received full-text screening. If any uncertainty of study eligibility was encountered, the study was included until the full-text review. Two independent reviewers (PA and IS) assessed the final inclusion of full-text articles and any disagreement was resolved through discussion with the senior author (NH) until a

final consensus was reached. At all phases of study screening, the journal titles, author names, or supporting institutions were not blinded for any reviewer.

2.4 | Methodological quality assessment of included studies

Quality appraisal of case-control and cohort studies was assessed by 2 independent reviewers (PA and IS) using the Newcastle–Ottawa Quality Scale (NOS).21 Any disagreements were discussed until a final consensus was established. The NOS uses a star-based grading system that ranks studies out of 9 to 10 stars based on study design. For the case-control studies the risk of bias was assessed across 3 domains: (1) selection (0-4 stars), (2) comparability of groups based on designer analysis (0-2 stars), and (3) outcome/exposure (0-3 stars). The risk of bias for cohort studies were also assessed using 3 domains: (1) selection (0-5 stars), (2) comparability (0-2 stars), and (3) outcome/exposure (0-3 stars). The higher the number of stars allocated to a study translates to the higher study quality.

The risk of bias for RCTs was assessed utilizing the Cochrane Collaboration Risk of Bias Tool (CROB).22 This instrument is divided into 5 domains, including bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; bias in selection of the reported result. Additionally, signaling questions in the CROB aims to collect information relevant to an assessment of risk of bias, with response options such as Yes; Probably yes; Probably no; No; and No information. Overall, the RCTs can be at either low, moderate, or high risk of bias.

2.5 | Data extraction and management

Two reviewers (PA and IS) divided the included studies and extracted data independently into a standardized collection form using Microsoft Excel 2013 (Microsoft). Any discrepancies were resolved by the senior author (NH). All data pertaining to general study information (author, year, study design), demographic data (sample size, mean age, gender, human leukocyte antigen B27 [HLA-B27] positive, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], smoking history, disease duration), follow-up data, TNFi information (type, dosage, duration), concomitant medications usage, radiographic outcomes (mSASSS and syndesmophytes data) were extracted.

2.6 | Outcomes

The primary outcome was the odds of structural progression as evaluated by the mSASSS scoring system. Secondary aims included

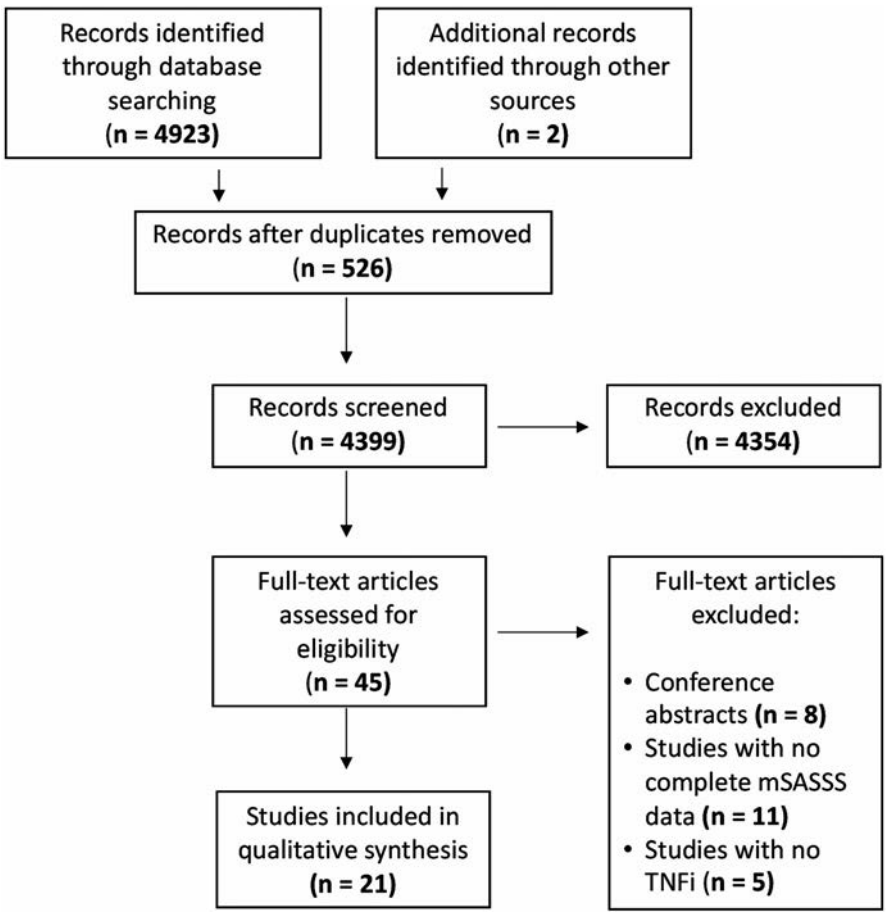

FIGURE 1 Search strategy results

the mean and annual rates of mSASSS change. We also assessed the reliability of mSASSS scoring.

2.7 | Statistical analysis

Descriptive statistics, including measures of central tendency, dispersion, and frequency were used to analyze study and patient characteristics, as well as clinical outcomes. Frequency-weighted averages were pooled for general study characteristics including sample size, age, gender, follow-up, CRP, ESR, disease duration, baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI) across eligible studies. A meta-analysis was conducted where applicable using the random-effects model. For continuous outcomes, the mean difference (MD) was obtained and calculated from the inverse variance method. When the standard deviation (SD) was not provided for specific continuous outcomes and the appropriate statistical range was provided, then the SD was calculated to impute these values from a well-established statistical formula described by Hozo et al23 For dichotomous outcomes, the odds ratio (OR) was calculated using the Mantel-Haenszel method. For all outcome variables, we tested heterogeneity between studies using a standard Chi-square test, and the calculation of an *I* statistic24 was used to quantify heterogeneity. Ninety-five percent confidence intervals (CI) were calculated from all point estimates and a *P* value of <.05 was considered statically significant. Where meta-analysis was not appropriate, a narrative analysis of relevant studies was conducted. Studies were stratified to ≤4 years or >4 years of study duration to ensure sufficient sensitivity of mSASSS change and to observe any possible delayed beneficial effect of TNFi therapy.

3 | RESULTS

3.1 | Systematic search

The search results are summarized in Figure 1. A total of 4399 articles remained after duplicates were removal (n = 526). After title and abstract screening, 45 articles remained eligible for full-text review. From which, 24 articles were excluded, and 21 articles met the inclusion criteria, consisting of 3 RCTs,25-27 5 prospective or retrospective cohort studies with formal controls,8,28-31 6 RCTs with open-labeled extension or retrospective analysis of an RCT with a historical cohort,18,32-36 and 7 prospective or retrospective non-comparative non-randomized studies.37-43

3.2 | General study characteristics

A total of 4460 patients (76% male) were included in this study with a mean age of 40.4 years (range 25.3-50). Specifically, 3372 patients (74% male; mean age 39.7 years) and 1088 patients (79% male; mean age 41.7 years) were TNFi-treated and TNFi-naïve patients, respectively (Table 1). Sixteen studies reported the number of patients positive for HLA-B27, in which 2330/2792 (83.5%) TNFi-treated and 740/812 (91%) TNFi-naïve patients were HLA-B27 positive.8,18,26,28-29,31,33-35,37-43 Disease duration from all included studies was 12.6 years (range 4.1-21 years). The mean CRP level presented from 16 studies for all patients was 2.8 mg/dL (range 1.1-15.8 mg/dL).8,18,26-31,34,37,39-43 Precisely, the CRP level for TNFi-treated and TNFi-naïve patients was 3.1 mg/dL (range 1.1-15.8 mg/dL) and 2.4 mg/dL (range 1.1-8.3 mg/dL), respectively. From 19 studies that reported the BASDAI, the mean BASDAI was 5.4 (range 3.2-6.7).8,18,25-30,32-39,41-43 The mean BASDAI was 6.0 (range 4.2-6.7) and 4.4 (range 3.2-6.6) for the TNFi-treated and TNFi-naïve patients, respectively. The mean BASMI from 5 studies was 3.5 (range 2.2-4.4) and the mean BASMI in TNFi-treated and TNFi-naïve patients was 3.4 (range 2.2-4.4) and 3.7 (range 3.4-4), respectively.26-27,33,41,42 The mean BASFI, reported in 11 studies, was 4.6 (range 3.1-5.7) and the mean BASFI was 5.0 (range 3.1-5.7) and 4.0 (range 3.1-5.5) for the TNFi-treated and TNFi-naïve groups, respectiv ely.18,26-27,30,32-35,39,42

The overall mean baseline mSASSS score from all included studies was 12.7 (range 5.5-19.8). Specifically, the mean baseline mSASSS was 12.4 units (range 5.5-19.8) for the TNFi group and 13.1 units (range 5.9-19) for the TNFi-naïve group. Baseline syndesmophytes was reported in 3 studies and was higher in the TNFi group when compared to the TNFi-naïve group (3.1 [range 1.6-4] vs 2.9 [range 1.4-3.7]).29,34,37 Eight studies indicated that 438/1100 (40%) and 86/192 (45%) of TNFi-treated patients and TNFi-naïve patients had the presence of baseline syndesmophytes, respectively.26-29,34,37-39

3.3 | Control groups

Twelve of the 21 included studies8,18,25-26,28,30,32-36 were comparative studies that provided control groups, which were TNFi-naïve. Specifically, 6 comparative studies utilized historical cohorts as their TNFi-naïve control group, of which 4 studies18,32-33,35 used the Outcome in AS International Study (OASIS) cohort, 1 study36 compared against the German AS cohort (GESPIC), while another study35 used the Herne cohort (HC), all of which were treated according to the standard of care. The remaining 6 studies8,25-26,28,30,31 compared TNFi-treated AS patients against formal controls, which received the standard care without TNFi.

3.4 | Study methodological quality assessment

Quality appraisal of all non-randomized studies ranged from moderate-to-high methodological quality as indicated by the NOS (Table A1). All 3 RCTs as assessed by the CROB indicated low risk of bias (Table A2).

TABLE 1 Baseline study characteristics of all included studies

Reference	Study duration (y)	Sample size (% male)		Mean age (y)		Disease duration (y)		CRP (mg/dL)
		TNFi	CON	TNFi	CON	TNFi	CON	TNFi
Randomized studies								
Dijkmans et al (2009)25	2	43	39	43 (both groups)	12.5	12.5	NR	NR
Braun et al (2013)26	4	138 (74%)	78 (71%)	41.0 (range 31.0-50.0)	38.0 (range 30-47)	11 (6.0-18.0)	16 (6-24)	1.10 (range 0.50 - 2.50)
Van der Heijde et al (2018)27	4	174 (73%)	N/A	41.5 ± 11.7	N/A	9.1 (range 0.3-50.9)	N/A	14.2 (range 0.1-174.8)
Formal controlled studies								
Haroon et al (2013)8	NR	201 (83%)	133 (67%)	39.43 ± 13.2	42.50 ± 14.6	16.47 ± 11.8	16.38 ± 14.4	1.33 ± 2.0
Kim et al (2016)31	5	269 (85%)	341 (92%)	40.44 ± 9.39	37.94 ± 8.87	11.33 ± 7.51	8.04 ± 6.57	2.52 ± 3.15
Pedersen et al (2011)30	2	23 ± 18	27 ± 25	40.4 ± 12.1	40.3 ± 13.4	18.2 ± 11.4	15 ± 10	15.8 ± 15.1
Park et al (2016)29	4	49 (86%)	116 (86%)	42.5 ± 13.2	38.4 ± 12.2	9.3 ± 7.9	9.2 ± 6.2	35/49 had > 0.5
Park et al (2019)28	4	135 (81%)	80 (76%)	32.8 ± 11.5	34.4 ± 11.9	4.3 ± 2.7	4.1 ± 2.9	2.2 ± 2.7
Historical cohort comparison studies								
Van Der Heijde et al (May 2008)18	2	257 (75%)	76 (71%)	41 ± 10.2	48 ± 12.3	10 ± 8.5	12 ± 9.8	2 ± 2.20
Baraliakos et al (2014)34	8	22 (64%)	34 (85%)	39.2 ± 7.6	50 ± 11.5	15.8 ± 8.5	20.7 ± 5.7	2.6 ± 2.0
Van Der Heijde et al (2009)32	2	307 (77%)	169 (69%))	41.8 ± 11.5	43.6 ± 12.7	11.2 ± 9.3	11.3 ± 8.7	1.9 ± 2.5
Baraliakos et al (2007)35	4	NR	NR	43.8 ± 7.6	44.6 ± 11.7	19.4 ± 9.3	21 ± 11.6	NR
Baraliakos et al (2005)36	2	41 (63%)	41 (71%)	38.9 (range 21-53)	34.8 (range 22-76)	15.5 (range 3-35)	5.5 (range 1-10)	NR
Van Der Heijde et al (Oct 2008)33	2	201 (78%)	70 (67%)	39.6 ± 10.6	44.2 ± 12.5	10.2 ± 8.7	9.9 ± 8.8	NR
Non-controlled non-randomized studies								
Maas et al (2015)37	6	176 (69%)	N/A	42.3 ± 11.1	N/A	14 (7-23)	N/A	12 (4-22)
Jeong et al (2018) 40	2	151 (89%)	N/A	25.3 ± 10.2	N/A	60.9 ± 68.6 mo	N/A	2.91 ± 3.08
Mass et al (2017)38	6	80 (70%)	N/A	41.3 ± 10.5	N/A	14 (8-24)	N/A	14 (7-23)
Mass et al (2017)39	8	210 (69%)	N/A	41.6 ± 11.5	N/A	14 (8-24)	N/A	13 (4-22)
Molnar et al (2017)41	10	432 (66%)	N/A	40.3 ± 11.0	N/A	13.8 ± 9.7	N/A	8.0 (3.0-11.0)
Poddubnyy et al (2016)42	10	60 (73%)	N/A	37.5 ± 7.4	N/A	13.8 ± 8.3	N/A	23.5 ± 18.3
VanderSlik et al (2018)43	2	254 (69%)	N/A	42.9 ± 12.0	N/A	16 (8-25)	N/A	13 (5-22)

Abbreviations: BASDI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CON, control group; CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; N/A, not applicable; NR, not reported; TNFi, tumor necrosis factor-alpha inhibitor.

	BASDI		BASFI		Baseline mSASSS value		Baseline syndesmophytes	
CON	TNFi	CON	TNFi	CON	TNFi	CON	TNFi	CON
60.9	58.6	NR	NR	18.27 ± 21.0	11.95 ± 16.8	NR	NR	
1.15 (range 0.30-2.40)	6.6 (5.6-7.6)	6.6 (5.7-7.7)	5.0 (3.2-6.7)	4.9 (3.5-6.8)	11.7 ± 16.4	16.1 ± 18.7	NR	NR
N/A	6.4 ± 1.6	N/A	5.7 ± 2.2	N/A	13.2 ± 18.2	N/A	13.2 ± 18.2	N/A
1.69 ± 1.9	4.64 ± 2.5	3.61 ± 2.4	NR	NR	10.60 ± 14.9	8.20 ± 13.8	NR	NR
1.64 ± 1.96	NR	NR	NR	NR	15.68 ± 15.49	18.87 ± 17.96	NR	NR
8.3 ± 13.4	5.1 ± 2.0	5.0 ± 2.3	4.7 ± 2.3	3.2 ± 2.8	14.5 ± 16.1	10.0 (12.1)	NR	NR
84/116 had > 0.5	2.4 ± 0.8	1.9 ± 0.7	NR	NR	17.3 ± 17.7	11.9 ± 16.0	27 ± 55.5	41 ± 35.3
1.1 ± 1.3	6.7 ± 1.6	3.2 ± 1.6	NR	NR	6.2 ± 9.9	7.3 ± 10.8	6.2 ± 9.9	7.3 ± 10.8
1.5 ± 1.81	63 ± 20.9	47 ± 19.8	54 ± 20.7	55 ± 16.6	16 ± 18.3	19 ± 20.8	16 ± 18.3	19 ± 20.8
2.0 ± 1.6	6.2 ± 1.4	4.3 ± 1.4	5.3 ± 1.5	3.4 ± 1.5	13.2 ± 17.6	14.2 ± 13.8	13.2 ± 17.6	14.2 ± 13.8
1.5 ± 1.9	6.2 ± 1.7	3.4 ± 2.1	5.3 ± 2.1	3.1 ± 2.4	19.8 ± 19.3	15.8 ± 17.6	19.8 ± 19.3	15.8 ± 17.6
NR	6.6 ± 1.4	3.4 ± 2.1	3.5 ± 1.9	3.3 ± 2.5	11.6 ± 15.3	12.7 ± 17.4	11.6 ± 15.3	12.7 ± 17.4
NR	6.3 (range 3.8-8.8)	3.2 (range 0.2-7)	NR	NR	12.1 ± 16.9	5.9 ± 13.4	12.1 ± 16.9	5.9 ± 13.4
NR	6.5 ± 1.5	4.9 ± 2.3	5.7 ± 1.9	4.9 ± 2.3	17.7 ± 17.9	17.5 ± 19.1	17.7 ± 17.9	17.5 ± 19.1
N/A	6.1 ± 1.6	N/A	NR	N/A	16.9 ± 16.7	N/A	16.9 ± 16.7	N/A
N/A	NR	N/A	NR	N/A	7.6 10.8	N/A	7.6 10.8	N/A
N/A	6.0 ± 1.7	N/A	5.6 (3.6-7.1)	N/A	8.7 ± 13.3	N/A	8.7 ± 13.3	N/A
N/A	6.0 ± 1.7	N/A	NR	N/A	10.0 ± 15.5	N/A	10.0 ± 15.5	N/A
N/A	4.2 ± 2.3	N/A	3.1 ± 2.6	N/A	6.6 ± 12.5	N/A	6.6 ± 12.5	N/A
N/A	6.4 ± 1.3	N/A	5.2 ± 1.9	N/A	11.1 ± 16.1	N/A	11.1 ± 16.1	N/A
N/A	6.1 ± 1.7	N/A	NR	N/A	5.5 (1.0-18.0)	N/A	5.5 (1.0-18.0)	N/A

TABLE 2 TNF-inhibitor treatment information from all included studies

Reference	TNFi (n)	Dosage	Duration
Haroon et al (2013)8	NR (n = 201)	NR	2.5 ± 2.8 y
Kim et al (2016)31	NR	NR	NR
Van Der Hejide et al (May 2008)18	Etanercept (n = 257)	25 mg/twice a week	72-96 wk
Baraliakos et al (2014)34	Infliximab (n = 22)	5 mg/kg every 6 wk	N.R
Van Der Hejide et al (2009)32	Adalimumab (n = 307)	40 mg/every other week	78 wk
Baraliakos et al (2007)35	Infliximab (n = 33)	5 mg/kg every 6 wk	144 wk
Baraliakos et al (2005)36	Infliximab (n = 41)	5 mg/kg every 6 wk	96 wk
Van Der Hejide et al (oct 2008)33	Infliximab (n = 201)	5 mg/kg every 6 wk	96 wk
Dijkmans et al (2009)25	Etanercept (n = 43)	25 mg/twice a week	96 wk
Braun et al (2013)26	Golimumab (n = 138)	50 mg/every 4 wk	4 y
Park et al (2019)28	NR	N.R	NR
Maas et al (2015)37	Infliximab (n = 27) Etanercept (n = 110) Adalimumab (n = 39)	Infliximab: 5 mg/kg at 0, 2, 6 wk and then every 8 wk Etanercept: 50 mg (once) or 25 mg (twice)/every week Adalimumab: 40 mg/every 2 wk	302 wk
Jeong et al (2018)40	Infliximab (n = 23) Etanercept (n = 52) Adalimumab (n = 75) Golimumab (n = 1)	NR	NR
Maas et al (2017)38	Infliximab (n = 15) Etanercept (n = 50) Adalimumab (n = 15)	NR	5.4 ± 1.2 y
Maas et al (2017)39	Infliximab (n = 28) Etanercept (n = 132) Adalimumab (n = 50)	NR	3.9-7.8 y
Molnar et al (2017)41	NR	NR	2.1 ± 1.7 y
Park et al (2016)29	Etanercept (n = 58) Adalimumab (n = 107)	NR	4.9 ± 2.2 y
Pedersen et al (2011)30	Infliximab (n = 11) Etanercept (n = 10) Adalimumab (n = 2)	Infliximab: 3-5 mg/kg Etanercept: 25 mg/twice every week Adalimumab: 40 mg/every 2 wk	2 y
Poddubnyy et al (2016)42	Infliximab (n = 17) Etanercept (n = 43)	NR	NR
vanderSlik et al (2018)43	Infliximab (n = 35) Etanercept (n = 155) Adalimumab (n = 64)	NR	NR
van der Heijde et al (2018)27	Certolizumab pegol (n = 174)	400 mg at week 0, 2, 4 followed by either 200 mg/every 2 wk or 400 mg/every 4 wk	204 wk

Abbreviations: NR, not reported; TNFi, tumor necrosis factor inhibitors.

3.5 | TNF-inhibitor characteristics

Details regarding the TNFi type, dosage, and duration of use are presented in Table 2. Seventeen studies explicitly reported TNFi details, from which the most frequently prescribed TNFi was etanercept. More specifically, from these studies the number of AS patients on infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol were 453/2335 (19.4%), 910/2335 (39%), 659/2335 (28.2%), 139/2335 (6%), and 174/2335 (7.4%), respectively. The duration of TNFi use from all eligible studies ranged from 72 to 302 weeks. However, delayed usage of TNFi was not eligible for data extraction by all included studies, therefore a cut-off period of TNFi delay usage on the effect of spinal structural progression was not suggested. Five of the 21 studies37-40,43 indicated switching of the type of TNFi during the study duration. From these 5 studies, 4 studies37,39-40,43 clearly indicated that 141/661 (21%) patients switched to another TNFi during the follow-up period. Two of the 21 studies29,40 also provided a TNFi tapering dose group and the corresponding TNFi index. From 1 study29 116/165 (70%) patients were included in the tapering group and the mean TNFi index was 0.68. In the other study, 109/151 (73%) patients were included in the tapering group with a mean TNFi index of 0.43.

3.6 | Concomitant medication usage

Concomitant medication usage was reported in 14 of the 21 included studies. With regard to NSAID usage, data pooling was permitted from 10 of the 14 studies,18,26,29-30,32-33,38-39,41,43 from which 1811/2245 (80%) TNFi-treated and 409/500 (82%) TNFi-naïve AS patients utilized concomitant NSAIDs. The remaining 3 studies 30,34,37 indicated that AS patients who were TNFi-treated were also permitted NSAIDs therapy but failed to explicitly state the precise number of AS patients on this therapy. In addition, 2 studies26,32 reported the concomitant use of corticosteroids, in which 30/307 (9.7%) and 3/169 (1.7%) were TNFi-treated and TNFi-naïve AS patients. Lastly, 5 studies indicated the concomitant use of DMARDs,18,26,32,38,39 in which 273/992 (27.5%) and 61/323 (19%) were TNFi-treated and TNFi-naïve patients, respectively.

3.7 | Reliability of assessing mSASSS

All 21 studies reported that mSASSS reviewers were blinded for patients' treatment allocation and radiographic sequence . Fourteen studies8,26-29,31-34,37,39-42 explicitly stated the intra-class correlation (ICC),44 which was used to quantify the reliability of radiographic scoring between reviewers. Overall, the ICC change scores ranged from moderate-to-excellent (range, 0.58-0.90) and the ICC status scores were considered excellent (range, 0.91-0.99) from the 14 eligible studies with study durations ranging 2-10 years.

3.8 | Overall effect of TNFi treatment on the mSASSS

All 21 studies reported the effect of TNFi treatment on structural progression based upon the mSASSS (Table 3). However, the mSASSS was heterogeneously reported, and therefore narratively synthesized. From all 21 studies, 11/21 (50%) demonstrated a significant delayed effect in structural progression in AS patients administered TNFi treatment. When stratifying studies that had ≤4 years or >4 years of study duration, 3/11 (27%) and 8/10 (80%) studies indicated a significant delayed effect in structural progression with TNFi treatment in AS patients, respectively.

Of these 21 studies, 12 were comparative studies (ie with formal or historical TNFi-naïve controls) with study durations ranging 2-8 years.8,18,25-26,28,30-36 From these investigations, 5/12 (42%) comparative studies significantly favored TNFi patients over TNFi-naïve patients with respect to structural progression. More precisely, 8 comparative studies18,25,28-30,32-33,36 had ≤4 years of study duration, in which only 2/8 (25%) indicated a significant delayed effect in structural progression with TNFi treatment when compared against TNFi-naïve AS patients, whereas, 4 comparative studies had >4 years of study duration, in which 3/4 (75%) indicated a significant delayed effect in structural progression with TNFi treatment when compared against TNFi-naïve AS patients.8,31,34

The remaining 9 non-comparative studies had study durations ranging 2-10 years.27,29,37-43 From these studies, 6/9 (67%) indicated a significant delayed effect in structural progression with TNFi treatment. Specifically, 3 studies27,40,43 had ≤4 years of study duration, in which only 1/3 (33%) indicated a significant delayed effect in structural progression with TNFi treatment. In comparison, 6 non-comparative studies29,37-39,41,42 had >4 years of study duration, in which 5/6 (83%) indicated a significant delayed effect in structural progression with TNFi treatment.

3.9 | Odds of structural radiological progression as evaluated by mSASSS

The effect of TNFi on the odds of structural progression as evaluated by mSASSS was reported in 3 of the 21 studies. These 3 studies8,28,31 with formal controls (study durations ranging 4-8 years) explicitly provided the odds of structural progression from the entire study population between TNFi and TNF-naïve patients that were eligible for statistical pooling. From this, statistical pooling indicated that TNFi-treated patients had a significantly reduced odds of structural progression based on mSASSS scoring system (3 studies [1159 patients]; OR 0.81; 95% CI, 0.68 to 0.96; $P = .01$; $I^2 = 0\%$) (Figure 2).

3.10 | Rate of mSASSS change

The rate of mSASSS change was reported as either the mean change from baseline to final follow-up or as the annual rate of change. Sixteen18,25-28,30-33,35-37,39,41-43 of the 21 studies (durations range: 2-10 years) reported the mean rate of mSASSS change from baseline to final follow-up, which ranged from −0.15 to 7.3 mSASSS units for all patients. Of these 16 studies, 10 were comparative studies18,25-26,28,30-33,35,36 (durations: 2-5 years), in which the mean rate of mSASSS change for TNFi and TNF-naïve patients ranged from 0.36-7.3 and −0.15-4.73 mSASSS units, respectively. Overall, from these 10 studies, 8/10 (80%) studies exhibited numerically lower mean rates of mSASSS change with TNFi treatment when compared to TNFi-naïve patients.18,25-26,28,30,33,35,36 However, only 3/8 (38%) studies indicated statistically significant difference favoring TNFi-treated patients over TNF-naïve patients.

The rate of mSASSS change was reported as an annual rate of change by 4 of the 21 studies, which ranged 0.4-1.5 mSASSS units.26,29,34,40 Of these 4 studies, 3 were comparative studies; however, only 2 studies provided the values for both TNFi and TNF-naïve patients. In this, annual rates for TNFi and TNF-naïve patients ranged 0.4-0.9 and 0.5-1.5 mSASSS units, respectively.26,34 Both comparative studies had numerically lower annual rates of mSASSS change with TNFi-treated patients. However, from these 2 studies, the annual rate of change was not statistically different between TNFi and TNF-naïve groups.

TABLE 3 Summary of mSASSS data from all included studies assessing structural radiological progression in AS patients using TNFi

References	Study duration (y)	mSASSS at final follow-up		Mean mSASSS change (baseline to final follow-up)		Annual mSASSS change
		TNFi	CON	TNFi	CON	TNFi
Randomized studies						
Dijkmans et al (2009)25	2	18.63 ± 20.9	11.79 ± 16.8	+0.36 (95% CI −0.1 to 0.8)	−0.15 (95% CI −0.7 to 0.4)	NR
Braun et al (2013)26	4	NR	NR	1.3 ± 4.1 (50 mg); 2 ± 5.6 (100 mg)	2.1 ± 5.2	0.4 ± 1.7 (50 mg); 0.5 ± 1.4 (100 mg)
Van der Heijde et al (2018)27	4	14.16	N/A	0-2 y: 0.67 (95% CI 0.21 to 1.13) 2-4 y: 0.31 (95% CI 0.02 to 0.60) 0-4 y: 0.98 (95% CI 0.34 to 1.63)	N/A	NR
Formal controlled studies						
Haroon et al (2013)8	NR	NR	NR	NR	NR	NR
Kim et al (2016)31	5	NR	NR	6.14 ± 2*	4.73 ± 1.01*	NR
Pedersen et al (2011)30	2	NR	NR	1.4 ± 1.9	1.5 ± 3.1	NR
Park et al (2019)28	4	NR	NR	Entire population 1.30 ± 2.97	NR	NR
Park et al (2016)29	4	NR	NR	NR	NR	0.90
Historical cohort comparison studies						
Van Der Heijde et al (May 2008)18	2	NR	NR	0.91 ± 2.45	1.27 ± 3.64	NR
Baraliakos et al (2014)34	8	20.2 ± 21.4	25.9 ± 17.8	NR	NR	0.9 ± 0.8
Van Der Heijde et al (2009)32	2	NR	NR	0.9 ± 3.3	0.8 ± 2.6	NR
Baraliakos et al (2007)35	4	13.3 ± 16.7	17.1 ± 19.6	1.6 ± 2.6	4.4	NR
Baraliakos et al (2005)36	2	12.5 ± 17	6.6 ± 14.8	0.4 ± 2.7	0.7 ± 2.8	NR
Van Der Heijde et al (Oct 2008)33	2	18.1 ± 17.5	18.4 ± 19	0.9 ± 2.6	1.2 ± 3.9	NR
Non-controlled non-randomized studies						
Maas et al (2015)37	6	2 y: 17.5 ± 17.2 4 y: 21.4 ± 18.5 6 y: 21.4 ± 18.7	N/A	1.3	N/A	NR
Jeong et al (2018)40	2	NR	N/A	NR	N/A	1.01 ± 1.23
Mass et al (2017)38	6	NR	N/A	NR	N/A	NR
Mass et al (2017)39	8	NR	N/A	New: 0-2 y: 1.6 ± 2.8 0-4 y: 3.5 ± 4.6 0-6 y: 4.2 ± 4.8 0-8 y: 7.0 ± 6.3	N/A	N.R
Molnar et al (2017)41	10	NR	N/A	0.9 ± 2.3	N/A	NR
Poddubnyy et al (2016)42	10	17.2 ± 17.7	N/A	1.2	N/A	NR
VanderSlik et al (2018)43	2	NR	N/A	7.3 (IQR: 1.4-22.9)	N/A	NR

Abbreviations: CI, confidence interval; CON, control group; IQR, interquartile range; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; N/A, not applicable; NR, not reported; SDC, smallest detectable change; TNFi, tumor necrosis factor-alpha inhibitor.

*Standard error of mean.

	Final or new syndesmophytes		Patient progressors	
CON	TNFi	CON	TNFi	CON
NR	NR	NR	NR	NR
0.5 ± 1.3	NR	NR	>2 units in 27.8% of all TNFi at 4 y. >2 units in 26.1% 50 mg group; 28.7% 100 mg group at 4 y	28.8% placebo-50 mg at 4 y
N/A	5/85 (5.9%) ≥1 syndesmophyte	N/A	>0 units in 37.7% at 4 y >2 units in 19.7% at 4 y	N/A
NR	NR	NR	NR	NR
NR	NR	NR	NR	NR
NR	Final: 0.52 ± 0.8; New: 1.0 ± 0.6; 8/23 ≥ 1 new syndesmophyte	Final: 0.70 ± 1.4; New: 2.7 ± 0.8; 9/27 ≥ 1 new syndesmophyte	NR	NR
N/A	NR	NR	NR	
NR	NR	N.R	31.1%	21.8%
NR	NR	NR	55% with ≤ 0 units	55% with ≤ 0 units
1.5 ± 1.4	Final: 6.4 ± 4.8; New: 1.0 ± 0.6	Final: 4.6 ± 6.4; New: 2.7 ± 0.8	NR	NR
NR	NR	NR	55% with ≤ 0 units	58% with ≤ 0 units
NR	NR	NR	NR	NR
NR	NR	NR	>1 unit in 17%	>1 unit in 12%
NR	NR	NR	>1 unit: 34% >2 units: 20% >3 units: 15% >4 units: 11%	>1 unit: 35% >2 units: 18% >3 units: 10% >4 units: 7%
N/A	NR	N/A	70% with < 2 units 18% with 2-5 units 2% with > 5 units	N/A
N/A	NR	N/A	NR	N/A
N/A	NR	N/A	NR	N/A
N/A	New: 0-2 y: 42/163 0-4 y: 63/132 0-6 y: 45/80 0-8 y: 27/41	N/A	>SDC 0-2 y (2.3 SDC): 25% 0-4 y (2.7 SDC): 38% 0-6 y (3.2 SDC): 44% 0-8 y (4.3 SDC): 59%	N/A
N/A	NR	N/A	NR	N/A
N/A	NR	N/A	NR	N/A
N/A	NR	N/A	NR	N/A

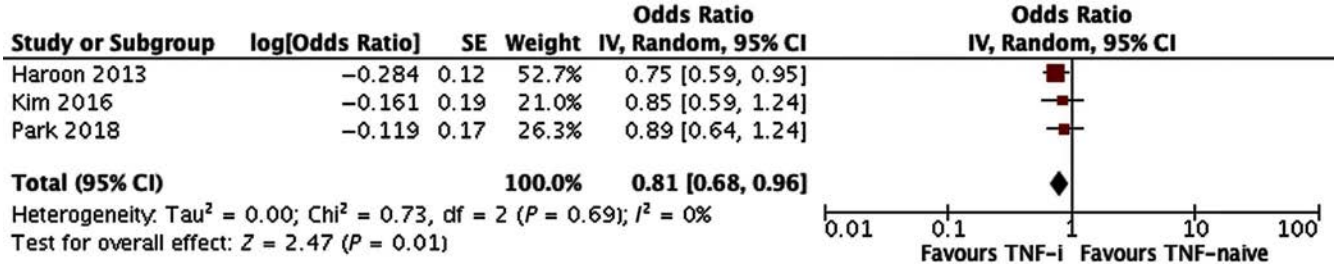

FIGURE 2 Forest plot illustrating result of the pooled analysis for the odds of radiological progression in tumor necrosis factor inhibitor patients. Abbreviations: CI, confidence interval; IV, inverse variance

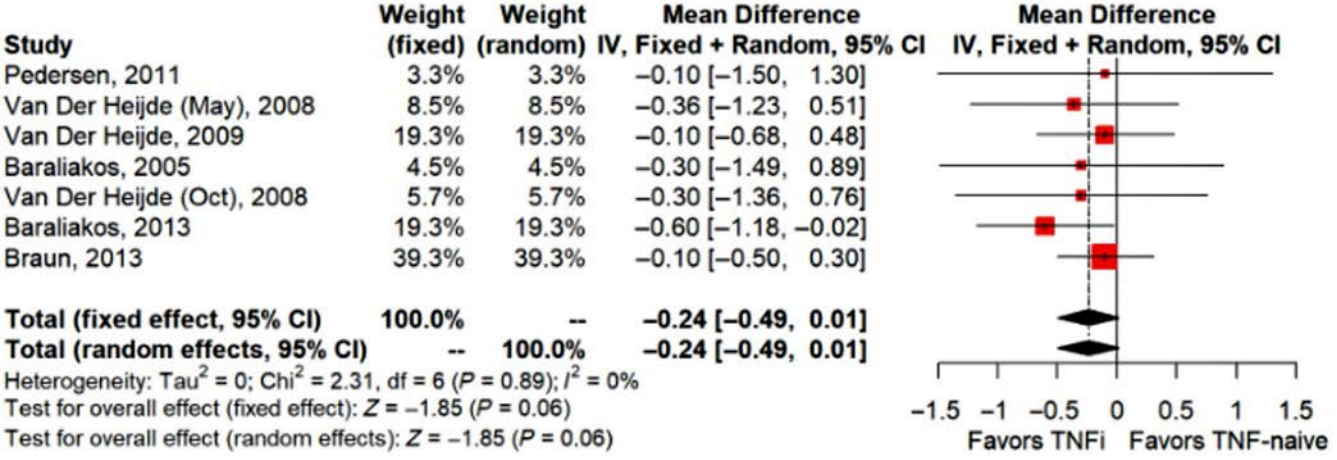

FIGURE 3 Forest plot illustrating result of the pooled analysis for the mean rate of modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) change between tumor necrosis factor inhibitor (TNFi) and TNF-naïve patients. Abbreviations: CI, confidence interval; MD, mean difference

Collectively, pooling of studies reporting either the mean change from baseline to final follow-up or the annual rate of change was permissible from 7 comparative studies (durations range: 2-8 years).18,26,30,32-34,36 The meta-analysis indicated a numerically, but statistically non-significant, improvement in the rate of mSASSS change with TNFi treatment (7 studies [1438 patients]; MD, −0.24; 95% CI, −0.49-0.01; $P = .06$; $I^2 = 0\%$) (Figure 3).

4 | DISCUSSION

The main finding from this study suggests that >4 years of TNFi therapy usage may reduce spinal structural progression in AS patients, as evaluated by mSASSS. Further, the findings confirm that mSASSS has good-to-excellent inter-rater reliability in assessing structural progression in AS.

New spinal bone formation is one of the hallmark features of AS, which may cause spinal deformity, functional impairment, and disability.2,3 The primary goals of AS treatment are to mitigate symptoms and inflammation, prevent structural progression, and preserve functionality.9 Recently, investigations have been conducted on the disease-modifying potential of TNFi therapies, which have indicated decreased structural progression in TNFi-treated patients.8,39,41

Specifically, 1 study investigated 334 AS patients of whom 201 were treated with TNFi and had a 50% reduction in the odds of structural progression.8 Subsequently, another study with 432 AS patients reported a similar 50% reduction rate in the odds of structural progression in TNFi-treated AS patients.41 One study with 210 AS patients receiving TNFi exhibited a linear course with stable progression rates at 4 years of follow-up. Beyond that period, there was a nonlinear course with reduced structural progression suggesting a beneficial effect with long-term TNFi usage.39 In a more recent study, there was less structural progression with long-term use (2-4 years) compared to the initial periods (0-2 years) suggesting a late-onset effect of TNFi therapy on structural progression.27 In contrast, other studies, including RCTs, did not replicate the abovementioned effects of TNFi on structural progression.25,26 This could be attributed to the relatively short follow-up periods, as the gradual nature of AS progression may require longer follow-up periods to illustrate significant structural change.

TNF has been shown to play a key role in promoting bone formation by mature osteoblasts and increased osteoclastic resorption.45-47 TNF is upregulated through the Wnt signaling pathway, which can regulate new bone formation by promoting spinal inflammation.45-47 Magnetic resonance imaging (MRI) studies indicate that inflamed vertebral edges were associated with new syndesmophyte formation.30,48-52 Additionally, spinal inflammation in

AS has been associated with new blood vessel formation at the inflamed vertebral sites.26,40 Therefore, suppressing spinal inflammation, and the resultant pain and stiffness, are major treatment goals of AS in the short term and to prevent ankylosis in the long-term.

TNFi therapy has been shown to significantly improve the clinical signs and symptoms associated with AS disease activity.41,53-55 Moreover, studies have detected that TNFi agents can reduce spinal inflammation, as evaluated by MRI, and serum levels of inflammatory biomarkers.40,56-59 Despite these findings, the relationship between spinal inflammation and structural progression remains unclear as the inhibition of structural progression was not detected following TNFi treatment in some patients. This may be attributed to the fact that the prevention of bone formation may be dependent on the timing of TNFi administration and that bone formation in AS is only partly associated with spinal inflammation.26,40 In fact, 1 study8 reported that AS patients who delayed using TNFi for >10 years had greater structural progression than those who initiated earlier TNFi treatment. These findings indicate that early initiation and long-term duration of TNFi utilization are important factors for inhibiting structural progression.60

The mSASSS is a reliable, valid, and most widely used scoring system for quantifying structural progression in AS.4-5,61,62 The mSASSS scoring relies on changes obtained from anterior corners of lumbar and cervical vertebrae. A recent review indicated that mSASSS sufficiently correlates with disease signs and symptoms, spinal mobility, and functionality.62 However, the inability to assess the posterior sites of the cervical and lumbar vertebrae, the zygoapophyseal joints, and the thoracic spine owing to technical reasons and the superimposed lung tissue are limitations associated with the mSASSS scoring method.62

When considering the potential disease-modifying effect of TNFi treatments, certain disease and patient factors should be addressed. The presence of damage, including syndesmophytes, and high disease activity are well-known factors related to structural progression.38,63-65 Certain behavioral and lifestyle factors, such as smoking or physically laboring jobs, may be correlated with structural progression10,11 and therefore should be accounted for in order to identify the independent effect of TNFi on structural progression.

It is also important to consider the cost-effectiveness of TNFi treatment in AS. The associated costs with TNFi have led to the development of guidelines to prescribe these therapies to suitable candidates who will yield the most benefit.66 Studies from the UK demonstrated that TNFi treatments are more cost-effective than conventional care, with secukinumab and golimumab being the most cost-effective therapies.67,68 Specifically, TNFi therapies resulted in increased quality-adjusted life-years (QALYs) when compared to conventional care.67 From a Canadian study, 150 mg of secukinumab achieved the highest QALYs (16.46) at the lowest cost.69 Studies reported that infliximab therapy for active AS patients should be directly and indirectly cost-effective both from the societal and healthcare system perspective as it may improve work ability, reduce sick days, and decrease the risk of permanent work disability.66,70

Several limitations exist with this study. First, the heterogeneity in TNFi between studies reduces the generalizability of results, as the optimal TNFi agent is unknown and is highly contingent upon various patient-related factors. However, all TNFi agents have been shown to be clinically effective and safe.53,71 Second, the delayed usage of TNFi data was not reported or eligible for data extraction by all included studies, therefore a cut-off period of TNFi delay usage on the effect of spinal structural progression was not suggested. Third, the concomitant treatment usage and various baseline factors (ie baseline damage, disease duration) may influence radiographic outcomes, possibly obscuring the net effect of TNFi on structural progression. Although this was not addressed in our study, other studies have confirmed these are important factors.62,72,73 Fourth, the inclusion of varying study designs potentially introduces confounding and selection bias. However, including these studies permitted a comprehensive review of the literature. Lastly, heterogeneity existed with reporting mSASSS data (ie mean or annual rate of change) and despite there being an accepted consensus on classifying structural progression as ≥2 mSASSS units, there was heterogeneity in cut-off criteria among included studies for structural progression.

5 | CONCLUSION

This systematic review and meta-analysis indicated that >4 years of TNFi usage was associated with delayed structural progression by mSASSS. The narrative analysis of the data from 21 studies further confirmed that studies with >4 years of follow-up had delayed structural progression with TNFi use in AS patients. The systematic review also confirmed that mSASSS has good-to-excellent inter-rater reliability in AS.

CONFLICT OF INTEREST

None.

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TABLE A1 Quality Appraisal of included studies as assessed by the Newcastle–Ottawa Scale (NOS)

NOS	Reference								
	Haroon et al (2013)8	Kim et al (2016)31	Baraliakos et al (2014)34	Baraliakos et al (2007)35	Baraliakos et al (2005)36	Park et al (2016)29	Van der Heijde et al (2009)32	Van der Heijde et al (May 2008)18	Van der Heijde et al (Oct 2008)33
Selection									
Representativeness of the exposed cohort	★	★	★	★	★	★	★	★	★
Selection of the non-exposed cohort	★	★	–	–	–	★	–	–	–
Ascertainment of exposure	★	★	★	★	★	★	★	★	★
Demonstration that outcome was not present at start of study	★	★	★	★	★	★	★	★	★
Comparability									
Comparability of cohorts	★★	★★	★★	★	★★	★★	★★	★★	★★
Outcome									
Assessment of outcome	★	★	★	★	★	★	★	★	★
Was follow-up long enough	★	★	★	★	★	★	★	★	★
Adequacy of follow-up of cohorts	★	★	★	★	★	★	★	★	★

NOS	Reference								
	Maas et al. (2015)36	Jeong et al. (2018)39	Maas et al. (2017)37	Maas et al. (2017)38	Molnar et al. (2018)40	Park et al. (2019)27	Pedersen et al. (2011)29	Poddubnyy et al. (2016)41	Van der Slik et al. (2019)42
Selection									
Representativeness of the exposed cohort	★	★	★	★	★	★	★	–	★
Selection of the non-exposed cohort	–	–	–	–	–	★	★	–	★
Ascertainment of exposure	★	★	★	★	★	★	★	★	★
Demonstration that outcome was not present at start of study	★	★	★	★	★	★	★	★	★
Comparability									
Comparability of cohorts	–	–	–	–	–	★	★	★★	★★

(Continues)

TABLE A1 (Continued)

NOS	Reference								
	Maas et al. (2015)36	Jeong et al. (2018)39	Maas et al. (2017)37	Maas et al. (2017)38	Molnar et al. (2018)40	Park et al. (2019)27	Pedersen et al. (2011)29	Poddubnyy et al. (2016)41	Van der Slik et al. (2019)42
Outcome									
Assessment of outcome	★	★	★	★	★	★	★	★	★
Was follow-up long enough	★	★	★	★	★	★	★	★	★
Adequacy of follow-up of cohorts	★	★	★	★	★	★	★	★	★

Note: [a]Please note that the NOS permits studies to be awarded a maximum of 1 star for each category in the selection and outcome sections, and maximum 2 stars for the comparability section.

TABLE A2 Quality assessment of RCTs using the Cochrane risk of bias tool

Reference	Randomization process	Deviation from intended interventions	Missing data outcome	Measurement of outcome	Selection of reported result	Overall risk of bias
Dijkmans et al (2009)25						
Braun et al (2014)26						
Van der Hejide et al (2018)27						

Note: Please note that this tool permits studies to be awarded either low (green), high (red), or moderate/some concerns, (yellow) risks of biases based on the 5 domains.

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ORIGINAL ARTICLE

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Ultrasonographic evaluation of subclinical enthesitis in patients with psoriasis

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Abstract

Aim: The primary objective of this study was to assess the ultrasonographic signs of subclinical enthesitis in patients with psoriasis. Secondary objective was to examine the associations between the clinical assessments of enthesitis, severity of psoriasis, and the ultrasonographic signs of enthesitis.

Method: This study included 30 patients with psoriasis who did not have clinically detectable arthritis or enthesitis and 30 healthy volunteers as a control group. In the patient group, PASI, NAPSI, MASES, and SPARCC scores were calculated, and in the control group, MASES and SPARCC scores were calculated. Acute, chronic, and total enthesitis scores were calculated by ultrasonographic examination of the enthesis points that are assessed during calculation of SPARCC score, performed by a researcher blinded to the clinical assessments.

Result: In the ultrasonographic assessment, total enthesitis score was significantly higher in the patient group compared with the control group (P = .04). There was no significant difference between the groups regarding acute or chronic enthesitis scores. NAPSI, PASI, MASES, or SPARCC scores did not show correlation with the ultrasonographically acute, chronic, or total enthesitis scores. There was a low-level correlation between MASES and SPARCC scores in the patient group, which was statistically significant (P = .03). No significant correlation was found between other clinical scores. There was no significant difference between patient and control groups in terms of MASES and SPARCC scores.

Conclusion: Entheseal changes may be frequently observed in patients with psoriasis who are asymptomatic. Musculoskeletal ultrasonography (MUS) may be utilized to detect such abnormalities at the early period.

KEYWORDS

psoriasis, subclinical enthesitis, ultrasonography

1 | INTRODUCTION

Psoriasis is a prevalent, chronic, immune-mediated skin disease.[1,2] Although it was considered as an inflammatory disease of the skin in the past, the current view is that an inflammatory status with systemic involvement plays a role in disease etiology.[2]

One of the major clinical features of psoriatic arthritis (PsA) is enthesitis.[3] Enthesitis and arthritis are presented as soft tissue swelling accompanied by palpation, tenderness, erythema, and increased temperature in the examination of the enthesis and joint areas.[4] Studies in the literature have shown that entheses are the areas where inflammation occurs the earliest in PsA.[5] Despite this importance, entheseal abnormalities may be unnoticed in clinical examination of asymptomatic patients.[2,3]

Ultrasound studies have shown high incidence of entheseal abnormalities in patients with psoriasis who do not have clinical symptoms of arthropathy or enthesitis.[2-3,6] It is thought that utilization of ultrasonography to detect early signs of PsA can offer a window of opportunity to administer effective treatments, and would improve prognosis and clinical course by helping to prevent permanent damage.[2]

In cohorts of spondyloarthropathy, several scoring tools have been used for ultrasonographic assessment of enthesitis.[7] Spondyloarthritis Research Consortium Canada Scoring System (SPARCC) is only used to evaluate peripheral entheses that are easier to visualize by radiography and ultrasonography. Therefore, SPARCC may be more appropriate for comparison between clinical and imaging findings.[8] To our knowledge, this is the first study in the literature evaluating the points that are examined clinically for calculation of SPARCC index with ultrasonography for assessment of the presence of subclinical enthesitis in patients with psoriasis.

The primary aim of this study is an ultrasonographical assessment of signs of subclinical enthesitis in patients with psoriasis. The secondary aim is to investigate the associations between Psoriasis Area and Severity Index (PASI) and Nail Psoriasis Severity Index (NAPSI) which are used to assess the severity of psoriasis, Maastricht Ankylosing Spondylitis Entheses Score (MASES) and SPARCC which are used to assess the presence of enthesitis, and ultrasonographical findings of enthesitis.

2 | MATERIALS AND METHODS

The study included 30 patients who were diagnosed with psoriasis in the Dermatology Department of Gazi University Faculty of Medicine between October 2014 and June 2015 and did not have clinically detectable arthritis and without complaints of enthesitis, along with 30 healthy volunteers.

The study inclusion criteria for the patient group were: age over 18 years, being under follow up by the Dermatology Department due to the diagnosis of psoriasis and receiving topical or systemic treatment for this purpose. The study exclusion criteria for the patient group were: presence of clinically detectable signs of arthritis, history of serious trauma, surgical intervention or injection to the enthesis regions to be examined, known inflammatory rheumatic disease and fibromyalgia. Age- and gender-matched healthy volunteers were included in the control group.

The study was approved by the Ethics Committee of Gazi University Faculty of Medicine and conformed to the principles of the Helsinki Declaration. All patients signed an informed consent form.

For all participants, demographic data including age, gender, body mass index (BMI), and comorbid diseases were recorded. All participants in the study were right-handed.

The disease severity of patients with psoriasis was assessed by a dermatologist from the Dermatology Department by calculating PASI and NAPSI.[9]

The presence of enthesitis in both patients with psoriasis and healthy volunteers was assessed by a physiatrist from Physical Medicine and Rehabilitation Department by calculation of MASES and SPARCC enthesitis index.[9]

For ultrasonographical examination, MyLab 70 XV ultrasonography device (EsaoteBiomedica) present in the Physical Medicine and Rehabilitation Department of Gazi University Faculty of Medicine was used with the multifrequency (6-18 mHz) linear probe and standard musculoskeletal ultrasound (MUS) gel. Musculoskeletal system ultrasonography was performed by an experienced physiatrist who was blinded to clinical findings, ultrasonographically examining enthesis points that were examined clinically while calculating SPARCC enthesis index (bilateral Achilles tendon, bilateral calcaneal insertion of plantar fascia, bilateral insertions of patellar tendon at the base of the patella, bilateral insertions of quadriceps tendon at the upper border of the patella, bilateral greater trochanter, bilateral insertions of supraspinatus tendon at the greater tuberosity of the humerus, bilateral medial and lateral epicondyles) to assess presence of findings of enthesitis including alteration of thickness of tendon or aponeurosis, change in echogenicity, presence of enthesopathy, intratendinous calcification, presence of tear in tendon or aponeurosis, and erosion or cortical irregularity in the entheseal area, presence of bursitis and positivity of power Doppler (PD) signal.[10] For each area, presence or absence of each sign was assessed. Criteria for acute enthesitis were alteration in echogenicity, increased thickness, bursitis, PD signal. Criteria for chronic enthesitis were calcification, enthesopathy, tear, erosion, cortical irregularity. Each criterion was scored 0 if absent and 1 if present. Acute, chronic and total (acute plus chronic) scores were obtained for each participant. Then we calculated mean value for the patient and control groups, which were then compared. This sonographic scoring system is similar to the study of Hamdi et al, with addition of calcification and cortical irregularity.[8] Each enthesis region was examined in longitudinal and transverse planes (Figure 1).

2.1 | Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 20.0 software. For evaluation of data, descriptive statistics were expressed as a mean ± standard deviation for

continuous variables and as count and percentage (%) for categorical variables. Normality assessment for the data was made using Kolmogorov-Smirnov and Shapiro-Wilks tests, and homogeneity of variances was tested with Levene's test. Comparison of means in two independent groups was made with independent two samples *t* test for parametric data, and with Mann-Whitney *U* test for non-parametric data. Comparison of more than two means for non-parametric data was made with Kruskal-Wallis one-way analysis of variance. Comparison of qualitative data between two independent groups was made with the Chi-square test, or with Fisher's exact Chi-square test when expected numbers were small. Assessment of correlations within groups was made with Pearson's correlation test for parametric data and Spearman's correlation test for non-parametric data. For all analyses, $P < .05$ was accepted as statistically significant.

2.2 | Ethics committee approval

Prior to conduction of the study, it was approved by Gazi University Faculty of Medicine Ethics Committee. (Issue No:464, Date: 13.10.2014). The study conforms to the principles of the Helsinki Declaration. All patients signed an informed consent form.

3 | RESULTS

The study included totally 60 participants; there were 30 patients with psoriasis in the patient group and 30 healthy volunteers in the control group. There was no significant difference between patient and control groups regarding the distribution of gender (n = 15 each in the patient group and control group), mean age (44.87 ± 9.27 in the patient group, 41 ± 6.01 in the control group, $P = .06$), mean BMI (29.37 ± 5.65 in the patient group, 27.07 ± 5.03 in the control group, $P = .1$), or comorbid diseases (3 patients had type 2 diabetes mellitus, 2 had primary essential hypertension, 2 had coronary artery disease, 1 had multiple sclerosis, and 1 had chronic kidney disease; in the patient group, 1 patient had type 2 diabetes mellitus, 1 patient had primary essential hypertension, 1 patient had coronary artery disease, 2 had hypothyroidism, 1 had asthma in the control group [n = 9 in the patient group, n = 6 in the control group, $P = .55$]).

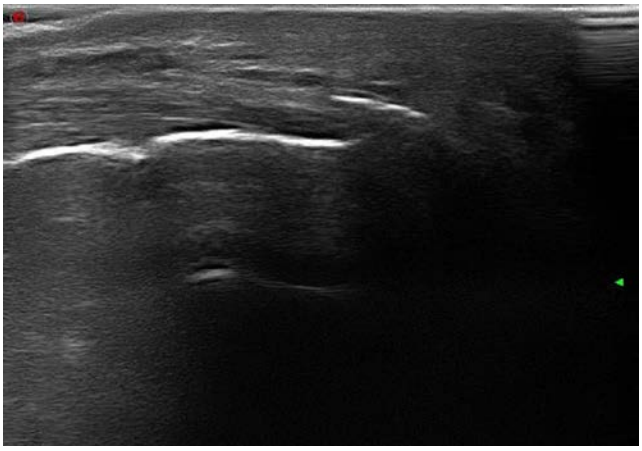

FIGURE 1 Enthesopathy in insertion of Achilles tendon in a participant from patient group

Correlations between MASES, SPARCC, PASI and NAPSI scores in the patient group are shown in Table 1.

Correlation analysis results have shown a low level of positive correlation between MASES score and SPARCC score, which was statistically significant ($P = .03$). No significant correlation was found between other variables.

In the patient group, mean (mean ± SD) MASES and SPARCC scores were 0.60 ± 1.42 and 0.86 ± 1.52, respectively; whereas in the control group, mean MASES and SPARCC scores were 0.53 ± 1.25 and 1.20 ± 1.51, respectively. There was no significant difference between patient and control groups regarding MASES and SPARCC scores ($P = .77/P = .19$).

In relation to the comparison of patient and control groups regarding the ultrasonographic evaluation of enthesis regions, there was a significant difference between the groups with regard to the presence of cortical irregularity in right patellar and left supraspinatus tendons ($P = .01$). Other evaluated enthesis regions did not show a significant difference between the groups regarding ultrasonographic evaluation criteria (Tables 2 and 3). All participants in the study were right-handed.

Table 4 shows comparison of acute, chronic and total enthesitis scores across patient and control groups.

Total enthesitis score was significantly higher in the patient group compared to the control group ($P = .04$). Acute and chronic enthesitis scores did not show a significant difference between the groups.

TABLE 1 Correlations between clinical scores in patients with psoriasis

	PASI	NAPSI	MASES	SPARCC
PASI				
r	1	.31	−.04	−.18
P		.09	.79	.33
NAPSI				
r	.31	1	.00	.04
P	.09		1	.80
MASES				
r	−.04	.00	1	**.38**
P	.79	1		**.03**
SPARCC				
r	−.18	.04	**.38**	1
P	.33	.80	**.03**	

Abbreviations: MASES, Maastricht Ankylosing Spondylitis Entheses Score; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; SPARCC, Spondyloarthritis Research Consortium of Canada.

Significant *P* values were written in bold.

TABLE 2 Comparison of ultrasonography findings across patient and control groups, right side[a]

	Patient n/control n								
	Alteration in echogenicity	Increased thickness	Calcified deposits	Enthesopathy	Tear	Erosion	Cortical irregularities	Bursitis	Power Doppler signal
Right medial epicondyle	0/0	0/0	0/0	0/0	0/0	0/0	2/1 *P* = 1	NA	1/0 *P* = 1
Right lateral epicondyle	0/0	0/0	0/0	0/0	0/0	0/0	1/3 *P* = .61	NA	0/0
Right supraspinatus tendon	2/0 *P* = .49	0/0	0/0	1/0 *P* = 1	6/3 *P* = .47	0/0	8/11 *P* = .58	2/3 *P* = 1	0/0
Right greater trochanter	0/0	0/0	0/0	0/0	0/0	0/0	3/2 *P* = 1	0/0	0/0
Right quadriceps tendon	0/0	0/0	0/0	0/0	0/0	0/0	3/1 *P* = .61	0/0	0/0
Right patellar tendon	1/0 *P* = 1	1/0 *P* = 1	0/0	1/0 *P* = 1	0/0	0/0	10/0 **P = .01**	0/0	0/0
Right Achilles tendon	0/0	0/0	0/0	11/9 *P* = .78	0/0	0/0	3/ 2 *P* = 1	5/1 *P* = .19	0/0
Right plantar fascia	0/0	0/0	0/0	1/1 *P* = 1	0/0	0/0	1/1 *P* = 1	NA	0/0

Abbreviation: NA, not applicable

[a]For data as 0/0 in patient and control groups, *P* value cannot be calculated as the data is constant.

Significant *P* values were written in bold.

TABLE 3 Comparison of ultrasonography findings across patient and control groups -left side[a]

	Patient n/control n								
	Alteration in echogenicity	Increased thickness	Calcified deposits	Enthesopathy	Tear	Erosion	Cortical irregularities	Bursitis	Power Doppler signal
Left medial epicondyle	0/0	0/0	0/0	1/1 *P* = 1	0/0	0/0	1/0 *P* = 1	NA	0/1 *P* = 1
Left lateral epicondyle	0/0	0/0	0/0	0/0	0/0	0/0	3/4 *P* = 1	NA	1/0 *P* = 1
Left supraspinatus tendon	4/0 *P* = .11	0/0	0/0	0/0	6/7 *P* = 1	1/0 *P* = 1	16/6 **P = .01**	0/4 *P* = .11	0/0
Left greater trochanter	0/0	0/0	0/0	0/0	0/0	0/0	9/8 *P* = .95	0/0	0/0
Left quadriceps tendon	0/0	0/0	0/0	2/0 *P* = .49	0/0	0/0	2/1 *P* = 1	0/0	0/0
Left patellar tendon	0/0	0/0	0/0	0/0	0/0	0/0	4/0 *P* = .11	0/0	0/0
Left Achilles tendon	0/0	0/0	0/0	13/11 *P* = .79	0/0	0/0	3/3 *P* = 1	8/2 *P* = .08	0/0
Left plantar fascia	0/0	0/0	0/0	2/1 *P* = .1	0/0	0/0	2/0 *P* = .49	NA	0/0

Abbreviation: NA, not applicable.

[a]For data as 0/0 in patient and control groups, *P*-value cannot be calculated as the data is constant.

Significant *P* values were written in bold.

TABLE 4 Comparison of acute (alteration in echogenicity, increased thickness, bursitis, power Doppler signal), chronic (calcification, enthesopathy, tear, erosion, cortical irregularity) and total enthesitis scores (mean ± SD) across patient and control groups

N = 30	Mean ± SD	*P*
Acute enthesitis score		
Patient	0.83 ± 1.08	.05
Control	0.37 ± 0.71	
Chronic enthesitis score		
Patient	3.87 ± 3.20	.14
Control	2.53 ± 2.09	
Total enthesitis score		
Patient	4.70 ± 3.54	**.04**
Control	2.90 ± 2.36	
Echogenicity		
Patient	0.23 ± 0.67	*
Control	0.00*	
Thickness		
Patient	0.03 ± 0.18	*
Control	0.00*	
Bursitis		
Patient	0.50 ± 0.86	.49
Control	0.33 ± 0.66	
Power Doppler signal		
Patient	0.07 ± 0.25	.55
Control	0.03 ± 0.18	
Calcification		
Patient	0.00*	*
Control	0.00*	
Enthesopathy		
Patient	1.07 ± 1.36	.52
Control	0.77 ± 0.97	
Tear		
Patient	0.40 ± 0.72	.68
Control	0.30 ± 0.59	
Erosion		
Patient	0.03 ± 0.18	*
Control	0.00*	
Cortical irregularities		
Patient	2.37 ± 2.15	.09
Control	1.47 ± 1.59	

*Since all the observed values of these variables were 0, no comparative analysis was made.

Significant *P* values were written in bold.

There was no significant difference between patient and control groups regarding mean values of bursitis, PD signal, enthesophyte, tear, or cortical irregularity.

TABLE 5 Correlation of acute, chronic and total enthesitis scores with PASI, NAPSI, MASES, and SPARCC scores in patient group

	PASI	NAPSI	MASES	SPARCC
Acute enthesitis score				
r	.03	.04	−.02	.24
P	.87	.82	.88	.19
Chronic enthesitis score				
r	.18	.05	.05	.03
P	.34	.78	.76	.85
Total enthesitis score				
r	.15	.02	.08	.09
P	.40	.90	.66	.61

Abbreviations: MASES, Maastricht Ankylosing Spondylitis Entheses Score; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; SPARCC, Spondyloarthritis Research Consortium of Canada.

In the patient group, mean echogenicity alteration value was 0.23 ± 0.67, mean increased thickness value was 0.03 ± 0.18, and mean erosion value was 0.03 ± 0.18; whereas these findings were not present in the control group. Calcification was not detected in either group.

Table 5 shows correlations between acute, chronic and total enthesitis scores with PASI, NAPSI, MASES and SPARCC scores in the patient group.

There was no significant correlation between acute, chronic, total enthesitis scores and PASI, NAPSI, MASES, SPARCC scores in the patient group.

4 | DISCUSSION

In the present study including patients with psoriasis along with healthy volunteers as controls, the key points used in the assessment of SPARCC index were examined ultrasonographically in order to compare the findings associated with subclinical enthesitis between the groups. To our knowledge, this is the first study in the literature evaluating the points that are examined clinically for calculation of SPARCC index with ultrasonography for assessment of the presence of subclinical enthesitis in patients with psoriasis.

Enthesitis is considered to be the primary pathological abnormality in PsA, and synovitis is thought to develop due to cytokines released from the enthesis regions.[5,7] Elnady et al reported that during a 2-year follow up of psoriasis patients without clinical signs of PsA, psoriasis patients who developed PsA showed a higher prevalence of baseline enthesitis than those who did not develop PsA.[11] Marchesoni et al compared 76 patients with PsA and 26 patients with rheumatoid arthritis and reported that inflammatory and structural changes in all enthesis areas were significantly more prominent in the PsA group.[12]

In cohorts of spondyloarthropathy, several scoring tools have been used for ultrasonographic assessment of enthesitis.[7] There is no internationally recognized and established scoring system for enthesitis.[3,7] In 2005, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group proposed to examine ultrasonographical abnormalities of enthesopathies under two categories as active inflammation and structural changes.[3,13] These include abnormal hypoechogenicity (loss of normal fibrillar structure), increased thickness of tendon or ligament at attachment sites, Doppler signal positivity, enthesophyte, and bone changes including erosion and cortical irregularities.[1,7,14] Apart from this, some authors recommended to refer to intratendinous calcification and tear as chronic changes, and bursitis as acute changes.[15] Outcome Measures in Rheumatoid Arthritis Clinical Trials recommendations require that total gray scale (GS) and PD scores are calculated individually for each enthesis region to obtain a final total score. In their study, Hamdi et al examined the relationship between clinical and sonographic enthesitis scores in ankylosing spondylitis. During the sonographic assessment of enthesitis, they evaluated abnormal echogenicity, increased thickness of tendon or ligament at the attachment site, Doppler signal and bursitis as acute signs, and presence of enthesophytes, erosion, and intratendinous tear as chronic signs. They assessed presence or absence of these signs for each enthesis region and compared acute, chronic and total sonographic enthesitis scores across patient and control groups.[8] Similarly, in our study, we assessed abnormal echogenicity, increased the thickness of tendon or ligament at the bone-attachment site, Doppler signal positivity and bursitis as acute signs, and enthesophytes, erosions, tendon tear and additionally intratendinous calcification and cortical irregularity as part of OMERACT recommendations as chronic sonographic signs of enthesitis. For each enthesis region examined, these signs were recorded as either present or absent, and we compared acute, chronic and overall enthesitis scores across patient and control groups.

During the ultrasonographic examination, an adequate number of enthesis regions should be assessed for accurate results. Previous studies have often used scoring systems that included lower extremity entheses that are more frequently affected.[16] Spondyloarthritis Research Consortium Canada Scoring System, on the other hand, is only used to evaluate peripheral entheses that are easier to visualize by radiography and ultrasonography. Therefore, SPARCC may be more appropriate for comparison between clinical and imaging findings.[8] Our study is the first in which points that are examined for tenderness during calculation of the clinical score SPARCC are assessed with ultrasonography for signs of enthesitis.

Ultrasound studies have shown that clinical examination has less sensitivity compared to ultrasonography in diagnosing enthesitis; therefore entheseal abnormalities may be overlooked in clinically asymptomatic patients.[2,7] Galuzzo et al reported that abnormalities were more frequent in entheses around the ankle in asymptomatic PsA patients.[17] Balint et al examined 35 patients with spondyloarthropathies of which 7 were PsA, and while they detected entheseal abnormality clinically in 22% of patients, this rate increased up to 56% with the ultrasonographic assessment.[18] In contrast, Freeston et al compared 42 patients with early PsA and 10 controls and observed that PsA and control groups were similar in terms of the frequency of ultrasonographic signs suggestive of enthesitis. They detected subclinical enthesitis signs in only 4% of entheses without tenderness, and in 24% of entheses showing tenderness. They observed that activation in the clinical examination was correlated with activation in ultrasonographic assessment.[7] Hamdi et al examined the correlation between clinical and ultrasonographic enthesitis scores in their study including 60 patients with ankylosing spondylitis; and they found correlations between MASES score and acute sonographic enthesitis score, between SPARCC and MASES and total sonographic enthesitis score, whereas they did not find a correlation between clinical scores and chronic sonographic scores.[8] On the other hand the ULISSE study showed that tenderness upon pressure on the entheseal site was more frequent in fibromyalgia than in patients with PsA and psoriasis, although assessment by MUS showed a higher prevalence of signs of entheseal involvement in patients with PsA and psoriasis than in patients with fibromyalgia.[19] In our study, we did not find any correlation between ultrasonographic findings and the clinical enthesitis scores MASES and SPARCC.

The incidence of subclinical enthesitis was found to be increased in patients with psoriasis who do not have musculoskeletal symptoms compared to the normal population.[3,5] Subclinical enthesitis and synovitis were detected in 39.5% of psoriasis and 10% of controls and was significantly higher in the psoriasis group in the study by Elnady et al[11] De Filippis et al found entheseal abnormalities with MUS in 25% of patients with psoriasis who did not show any findings during routine clinical examinations.[20] Özçakar et al examined 30 patients with psoriasis and 20 healthy controls and found the increased thickness of Achilles tendon in patients with psoriasis who did not have symptoms of enthesitis.[21] Similarly, De Simone et al detected ultrasonographic abnormalities in Achilles tendon in 59.2% of patients with psoriasis.[22] Gutierrez et al compared 45 patients with psoriasis and controls and showed an increased frequency of enthesopathy at lower extremities in patients with psoriasis. The frequencies of enthesopathy signs were 8.4% in the control group compared to 32.9% in the psoriasis group, and they found significantly higher Glasgow Ultrasound Enthesitis Scoring Scale (GUESS) scores in patients with psoriasis.[23] Naredo et al compared 160 patients with psoriasis who did not have musculoskeletal symptoms and 60 controls; they reported that the percentage of entheses showing at least 1 MUS abnormality suggesting enthesopathy was 11.6% in the psoriasis group, and 5.3% in the control group, and was significantly higher in the psoriasis group.[6] Arquacalda et al evaluated the prevalence of enthesitis with MUS in patients with psoriasis with and without musculoskeletal symptoms who were receiving systemic treatment for skin symptoms and showed a high prevalence of subclinical enthesitis in patients with psoriasis without musculoskeletal symptoms.[3] Gisondi et al used GUESS scoring system to assess entheseal abnormalities in 30 patients with psoriasis who did not have PsA symptoms and 30 controls. They observed that GUESS score was significantly

higher in patients with psoriasis although they did not have particular symptoms. They also observed that tendon thickness and number of enthesophytes were significantly higher in patients with psoriasis compared to the controls. Retrocalcaneal bursitis was observed in patients with psoriasis, but not in the control group. In addition, they observed there was no correlation between GUESS score and time after diagnosis of psoriasis, the severity of psoriasis, or severity of nail involvement.[5] In our study, we also found that total enthesitis score was significantly higher in the psoriasis group compared to the control group. We did not observe a correlation between NAPSI and PASI scores and ultrasonographic scores.

In our study, cortical irregularity at the proximal patellar tendon attachment site was found to be significantly higher compared to the control group. Naredo et al found the frequency of enthesopathy in the proximal patellar tendon was significantly higher in psoriasis patients compared to the control group.[6] Delle Sedie et al found that the prevalence of knee enthesitis involving quadricipital and patellar enthesis was 39.7% in 83 patients with PsA.[24] McGonagle et al stated that entheseal changes are more common in lower extremities due to a type of Kobner phenomenon caused by biomechanical stress.[25]

The findings of enthesopathy in the Achilles tendon were common in both the patient and control groups in our study. In the studies of Gutierrez et al, Naredo et al and Freeston et al, the most common enthesopathy was found in the Achilles enthesis in both psoriasis patients and the control groups.[6-7,23] This may be due to the difficulty in distinguishing true enthesopathies from mechanical or degenerative bone protrusions. The frequency of changes such as cortical irregularity and enthesopathy in the control group were similar to the patient group; this may reflect the importance of mechanical stress on the lower extremity.[7,23]

In our study, cortical irregularity at the supraspinatus tendon attachment site was significantly higher in patients with psoriasis compared to the control group. Riente et al investigated ultrasonographic abnormalities in the shoulder in 97 PsA patients; they observed that the changes related to the supraspinatus tendon were the most frequent changes.[26]

Nail psoriasis is a predecessor for PsA development, possibly indicating a relationship between nail psoriasis and systemic enthesopathy.[27] Ash et al compared 46 patients with psoriasis, 31 of whom had nail disease and 21 controls, and they showed total enthesitis MUS scores which show both inflammation and chronic changes were higher in those with nail disease, and that the severity of nail lesions was correlated with ultrasonographic inflammatory and chronic lesion development.[27] In contrast, Arquacalda et al did not find a significant difference between patients with and without nail disease in terms of the frequency of enthesitis detected in MUS.[3] In our study, we also did not find a correlation between NAPSI and MUS scores.

We did not observe any association between PASI score and ultrasonographic enthesitis signs in patients with psoriasis. Consistent with our findings, Ash et al did not observe an association between PASI score and ultrasonographic scores.[27] But in contrast, Pistone et al investigated the frequency of Achilles enthesitis in patients with psoriasis, and observed significantly higher GUESS scores compared to controls, and showed a correlation between PASI and GUESS scores.[28] Moshrif et al showed there was a significant positive correlation between the occurrence of enthesitis and PASI score.[29]

In our study, there was no significant difference between patient and control groups regarding MASES and SPARCC scores. In their study, Naredo et al also did not find significant difference between psoriasis and control groups regarding MASES scores.[6]

In relation to the associations between MASES, SPARCC, NAPSI and PASI scores in patients with psoriasis, we only found a correlation between MASES and SPARCC scores. In their study, Hamdi et al investigated the relationship between clinical and ultrasonographic enthesitis scores in 60 patients with ankylosing spondylitis and showed a significant correlation between SPARCC and MASES scores.[8]

There are some limitations to our study. First, the researcher who performed the ultrasonographic assessments was blinded to clinical findings and patient information; however, psoriatic plaques that are present in the examination areas may have given a clue to distinguish between patients and controls. To reduce the effect of this condition, the ultrasonographic assessment was performed in a dark room, and participants were asked not to inform the examiner about their clinical conditions. Second, the ultrasound is operator-dependent and to rule out this pitfall in research, it should be done by two observers with inter-reader coefficient assessment. Another limitation is the limited generalizability of the results due to a small number of patients. Finally, since the number of patients was small, we could not analyze ultrasonographic signs in different treatment groups. Nevertheless, future longitudinal MUS studies encompassing large populations, investigating the frequency of entheseal abnormalities and their response to treatment in patients with psoriasis receiving different treatments are necessary.

5 | CONCLUSIONS

Subclinical enthesitis is not uncommon in psoriasis patients free from clinical enthesitis; MUS is a valid modality to assess early enthesitis in such patients. In our population supraspinatus tendon and patella tendon are the most common affected sites. Among patients with psoriasis, ultrasonographic enthesitis scores did not show correlation with the clinical assessment scores MASES, SPARCC, PASI or NAPSI.

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Effects of Andersson lesion treatment in ankylosing spondylitis: A medical record review study focused on medium- to long-term outcomes

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Abstract

The present study aimed to evaluate the clinical efficacy of Andersson lesion (AL) treatments and prognostic factors using medium- to long-term follow-up data and discuss the clinical characteristics and treatment of AL. Forty-eight consecutive AL cases at our center from June 2011 to March 2018 were retrospectively analyzed, including 13 cases treated conservatively and 35 treated surgically. Epidemiological characteristics, treatment modalities, clinical features and outcomes, and prognostic factors of the Japanese Orthopaedic Association (JOA) recovery rate were reviewed. Neurological functional recovery was evaluated by American Spinal Injury Association (ASIA) classification. Clinical efficacy was evaluated by JOA score, visual analog scale (VAS) score, and Cobb's angle. The mean overall follow-up duration was 44.5±18.5 months (range, 27–85 months). There were 36 male and 12 female patients, with a mean age of 49.4±13.1 years (range, 26–72 years). The most common lesion location was the thoracolumbar region, i.e., T10-L2 (n=33; 68.8%), followed by the thoracic (n=10) and lumbar (n=5) regions. Patients treated surgically showed significantly better JOA scores, VAS scores and Cobb's angles at the final follow-up than did patients treated conservatively ($P<.05$). Univariate and binary logistic regression analyses identified two prognostic factors of the JOA score recovery rate: treatment modality (OR=0.157; 95%CI, 0.028–0.89; $P=.036$) and bone fusion (OR=9.965; 95%CI, 2.052–48.387; $P=.004$). Conservative treatment and bone nonunion predict worse JOA score recovery. Surgery remains the optimal treatment for AL in ankylosing spondylitis patients, with better clinical efficacy demonstrated by medium- to long-term follow-up data.

KEYWORDS

Andersson lesion, ankylosing spondylitis, medium- to long-term follow-up, retrospective study, treatment outcome

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1 | INTRODUCTION

Ankylosing spondylitis (AS) is a well-known chronic inflammatory rheumatic disease which results in progressive structural damage and motion restriction of the spine.[1-4] Over time, diverse inflammatory changes in the spine can lead to vertebral osteoporosis and biomechanical alterations. AS is associated with a high rate of spinal fractures due to early-onset osteoporosis, with an incidence reportedly 5 times greater in AS patients than in the age-matched general population. Subsequently, repeated stress and biomechanical instability progress to nonunion, resulting in hypertrophic pseudoarthrosis.[5,6] Andersson lesion (AL) is a rare complication in AS patients, presenting as a destructive vertebral or discovertebral lesion of the spine that is relatively uncommon. The reported prevalence rates range from 1.5% to 28%.[7,8] In 1937, this lesion was first described by Andersson, and was characterized by a state of chronic mobile nonunion with an essential posterior element fracture or unfused facet joints associated with the anterior lesion.[1,9] With the progression of AL, these destructive spinal changes may result in localized, progressive, and painful kyphotic deformity and neurological deficits that necessitate treatment.

For a long time, there has seemed to be a discrepancy in the treatment of AL between rheumatologists and orthopedic surgeons. Generally, the mainstay of the initial treatment for AL is surgical decompression, instrumentation, bone grafting, and fusion after the failure of conservative treatment, such as plaster immobilization or halo vest immobilization.[10-12] Currently, the ultimate goal of surgery in AL patients is to not only restore spinal stability but also decompress the spinal canal, facilitating healing and fusion of the spinal lesion and the relief of persistent back pain. However, the surgical treatment of AL is associated with considerable adverse effects, including neurological impairment, nonunion and progressive kyphotic deformity.[6,13,14] Based on several recent studies, patients with surgical treatment have better clinical outcomes than do those who receive conservative treatment.[11-12,15] Moreover, the prognostic factors of AL remain controversial. Reported prognostic factors include age, gender, symptom duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), human leukocyte antigen (HLA)-B27 positivity, lesion location, steroid treatment, osteoporosis, pseudarthrosis, neurological impairment, Cobb's angle of kyphosis, bone fusion and treatment modality.[1,3,5-8,13] Because most clinical studies on AL have been based on case reports and retrospective studies of small samples, large investigations of the medium- to long-term outcomes of this lesion are lacking.[5,7,16]

In this study, we retrospectively analyzed 48 patients with AL at our center to determine the medium- to long-term outcomes and prognostic factors related to this lesion. Furthermore, we compared the medium- to long-term therapeutic effects of the surgical and conservative treatment of AL and discussed the clinical management of AL.

2 | MATERIALS AND METHODS

2.1 | Patient selection and data collection

Forty-eight consecutive patients were diagnosed with AL at our center between June 2011 and March 2018. All of the patients underwent plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), areal bone mineral density (aBMD) (g/cm^2) measurements using dual-energy X-ray absorptiometry (DEXA) on the femur neck, and physical examination by a spine surgeon as soon as possible after admission. Surgical specimens were sent to the laboratory for histopathological examinations. The clinical data of these patients were retrospectively reviewed. The recorded information included patient age, gender, duration of symptoms before admission, clinical manifestations, ESR, CRP, HLA-B27 positivity, steroid treatment, osteoporosis, lesion location, American Spinal Injury Association (ASIA) classification, visual analog scale (VAS) score, pseudarthrosis, neurological impairment, Cobb's angle, treatment modality, and bone fusion.

2.2 | Evaluation of neurological status

Neurological status was evaluated according to the ASIA classification. The ASIA scale consists of 5 grades (A: a complete spinal cord injury; B: incomplete injuries with some degree of sensory function but no motor function; C: a motor grade less than 3 below the neurological level of injury; D: a motor grade of at least 3 below the neurological level of injury; E: normal motor and sensory examinations, but still may have abnormal reflexes or other neurological phenomena). The medium- to long-term outcomes also included the rate of improvement in the Japanese Orthopedic Association (JOA) score. Postoperative change in the JOA score was calculated by subtracting the preoperative JOA score from the postoperative JOA score, and changes were compared between the groups. The recovery rate was calculated according to the method of Hirabayashi et al[17] as follows: (recovery rate % = [(postoperative JOA − preoperative JOA)/(17 [full score] − preoperative JOA)] × 100%), and a recovery rate of ≥25% was defined as effective for the treatment of AL. A recovery rate of 100% was the best possible postoperative improvement.

2.3 | Statistical analysis

Age, ESR, CRP, and symptom duration were analyzed as continuous numerical variables. Gender, HLA-B27 positivity, steroid treatment, osteoporosis, lesion location, pseudarthrosis, neurological impairment, Cobb's angle, treatment modality, and bone fusion were analyzed as categorical variables. Univariate and multivariate (for relevant variables) regression analyses were performed to determine prognostic factors of the JOA score recovery rate. Pearson's Chi-squared test was employed for categorical variables, whereas the nonparametric Mann-Whitney *U* test was used for nonnormally distributed numerical variables. An independent-samples *t* test was used for comparisons of normally distributed continuous numerical variables between groups. Statistical significance was defined as $P < .05$. All statistical analyses were completed using SPSS Statistics package (version 22.0; IBM).

3 | RESULTS

3.1 | Patient characteristics

A summary of the clinical and demographic characteristics of the 48 patients is presented in Table 1. The average age of the patients was 49.4 ± 13.1 years (range 26-72 years). The ratio of males to females was 3:1. The most common initial symptom was back pain (n = 22; 45.8%), followed by spinal cord compression (n = 11; 23%), severe kyphotic deformity (n = 12; 25%), and others (n = 3; 6.2%). Thirty-three lesions were located in the thoracolumbar region, that is, T10-L2 (68.8%), and 10 were located in the thoracic region (20.8%). The mean duration of symptoms was 38.0 ± 24.1 months (range 11-150 months). In addition, the mean aBMD at the femur neck of the patients was 0.835 ± 0.168 g/cm^2 (range, 0.701-0.925 g/cm^2), which indicated that the mean T score was −1.8 ± 0.95 (range 0.6 to −3.2).

As shown in Figure 3, neurological deficits were found in 9 of the patients treated with surgery and 2 of the patients who underwent conservative treatment. According to the ASIA grading system, 37 cases were classified as E, 8 cases as D, and 3 cases as C. On examination, 3 patients with neurological deficits with an ASIA grade of C had significant decreases in muscle power (2-3/5) and tendon reflexes in the bilateral lower extremities. The other 8 patients had slight decreases in motor ability (4/5) and reflex of the legs. The average follow-up time was 44.5 ± 18.5 months (range 27-85 months). None of the patients died during follow-up.

3.2 | Laboratory blood test findings

On admission, the ESR and CRP levels were 23.6 ± 14.9 (range, 4-66) and 14.9 ± 9.9 (range 4-46), respectively (Table 1). Moreover, HLA-B27 positivity was found in 20 cases.

3.3 | Treatment and outcome

3.3.1 | Conservative treatment (n = 13)

Thirteen patients (2 ASIA grade D cases and 11 ASIA grade E cases) with slight spinal cord compression and confined changes on MRI were unwilling to undergo surgery. These patients had participated in conservative therapies, including bracing, resting, physiotherapy and analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), calcium tablets, calcitriol or a supplemental neurotrophic drug. Of these, 4 patients with inflammatory lesions had received anti-tumor necrosis factor (TNF)-α therapy because their symptoms failed to improve. Symptomatic treatment slightly improved the condition of these patients.

3.3.2 | Surgical treatment (n = 35)

When patients were diagnosed with AL, surgical treatment, which included an anterior, posterior or combined anterior and posterior approach with instrumentation, was recommended. Among these patients, 3 patients underwent treatment using a 1-stage anterior approach at the site of AL, 27 underwent treatment via a posterior approach, and 5 underwent treatment using a combined approach. During these procedures, osteotomy was performed in 19 patients, and 21 patients underwent bone grafting. All patients underwent surgery and were managed by the same group of doctors. There were no major complications related to the treatment. The average operation time was 320.6 ± 85.2 minutes (range 268-372 minutes), and the mean blood loss was 909.6 ± 538.2 mL (range 775-1522 mL). In addition, 25 patients required blood transfusions during hospitalization. The mean hospital stay duration was 17.4 ± 3.2 days (range 15-26 days). The surgical histopathology results showed non-bacterial inflammation infiltrated by lymphocytes and macrophages. The lesion included degenerative fibrocartilage tissue and fragments of necrotic bone and cartilage. No infectious inflammation or tumor cells were observed. During the follow-up period, only 6 (17.1%, 6/35) patients required reoperation due to implant failure or infection after the initial operation. At the time of the last follow-up, no instrumentation complications were observed. Representative patients who underwent surgical treatment are shown in Figures 1 and 2.

3.3.3 | Outcomes

JOA score

For patients treated with surgery, the average JOA score was 9.1 ± 1.5 (range 5.5-14) on admission and 13.2 ± 2.2 (range 7.5-17) at the final follow-up. In the conservative treatment group, the average JOA score was 11.5 ± 2.9 (range 6.5-14) on admission and 12.1 ± 0.8 (range 8.5-16) at the final follow-up. Although no significant difference in the JOA score on admission was found between the surgical and conservative treatment groups, a significant difference was noted at the final follow-up ($P < .05$, Table 2). The average postoperative change in JOA score at final follow-up after surgery was 4.2 ± 1.5 (range 4.5-9) points in the surgical treatment group and 2.2 ± 0.8 (range −0.5-4) points in the conservative treatment group, with significant differences noted at the final follow-up ($P < .001$). The average postoperative JOA score recovery rate at the final follow-up after surgery was 68.5% (21%-85%) in the surgical treatment group and 18.7% (−10.5%-53%) in the conservative treatment group; thus, the JOA score recovery rate was significantly higher in the surgical treatment group than in the conservative treatment group ($P < .001$) at the final follow-up after surgery. Moreover, the same results were observed for the VAS score and Cobb's angle (Table 2).

Neurological status

All patients were clinically assessed according to the ASIA classification system (Figure 3). Among patients treated with surgery, on admission, the ASIA grade was C in 3 cases, D in 6 cases, and E in 26 cases; at the final follow-up, the ASIA grade was D in 2 cases and E in 33 cases. In the conservative treatment group, the

TABLE 1 Patient characteristics

Characteristic			Value	
Age (y)	Mean (y ± SD)		49.4 ± 13.1	
	Range		26-72	
Gender	Male		36	75%
	Female		12	25%
Duration of symptoms before admission, mo	Mean (± SD)		38.0 ± 24.1	
	Range		11-150	
Initial symptom	Back pain		22	45.8%
	Spinal cord compression		11	23%
	Severe kyphotic deformity		12	25%
	Other		3	6.2%
ESR, mm/h, on admission	Mean (±SD)		23.6 ± 14.9	
	Range		4-66	
CRP, mg/L, on admission	Mean (±SD)		14.9 ± 9.9	
	Range		4-46	
Lesion location	Thoracolumbar region		33	68.8%
	Thoracic region		10	20.8%
	Lumbar region		5	10.4%
ASIA grade on admission	C		3	6.2%
	D		8	16.7%
	E		37	77.1%
VAS score on admission	<4		23	47.9%
	4-6		22	45.8%
	>6		3	6.3%
Cobb's angle on admission	<30°		30	62.5%
	30-60°		14	29.2%
	>60°		4	8.3%
Treatment modality	Conservative treatment		13	27.1%
	Surgical treatment		35	72.9%
BMD	Areal BMD (g/cm^2)	Mean (±SD)	0.835 ± 0.168	
		Range	0.701-0.925	
	T score	Mean (±SD)	−1.8 ± 0.95	
		Range	0.6 to −3.2	
Surgical treatment (n = 35)	Anterior approach		3	8.6%
	Posterior approach		27	77.1%
	Combined anterior and posterior approach		5	14.3%
	Osteotomy	Yes	19	54.3%
		No	16	45.7%
	Fixation of segment	>3	22	62.9%
		≤3	13	37.1%
	Bone grafting	Yes	21	60%
		No	14	40%
Follow-up, mo	Mean (±SD)		44.5 ± 18.5	
	Range		27-85	

Abbreviations: ASIA, American Spinal Injury Association; BMD, bone mineral density; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; thoracolumbar region, T10-L2; VAS, visual analog scale.

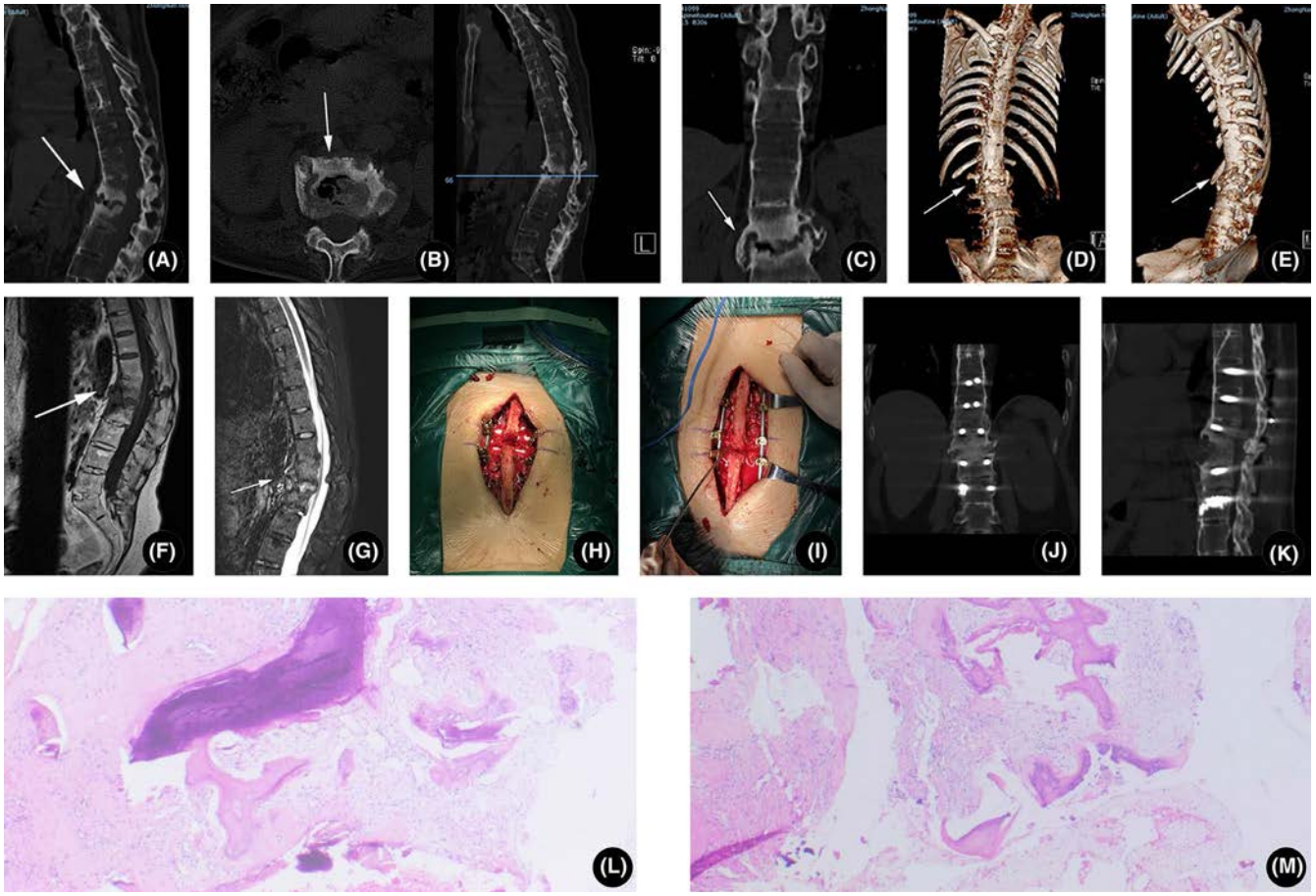

FIGURE 1 A 49-y-old female patient with ankylosing spondylitis (AS) complicated by Andersson legion (AL) with extensive bony destruction of the L1-L2 level is presented. Sagittal (A), axial-sagittal (B), and coronal (C) computed tomography (CT) scans demonstrate obvious anterior osteolysis surrounded by an irregular sclerotic zone. Extensive resorption and sclerosis extend into the adjacent vertebral body, causing the formation of pseudarthrosis (white arrow). Preoperative 3-dimensional CT reconstructions (D-E) show the nonunion of a posterior column fracture at L1-L2. The preoperative sagittal T1-weighted image (F) shows an AL with characteristically mixed-intensity changes in the vertebral body and a hypointense lesion (white arrow). Preoperative sagittal short inversion time inversion recovery (STIR) sequence images (G) reveal a central destructive zone surrounded by an area with hyperintensity, which suggests sclerosis, with mixed-intensity changes in adjacent vertebral bodies (white arrow). An intraoperative photograph (H-I) shows that surgical treatment was performed. Coronal (J) and sagittal (K) CT scans at the 9-mo follow-up visit show solid fusion at the level of pseudarthrosis and good implant positioning. The surgical histopathology results (L: hematoxylin and eosin, original magnification 40×, M: hematoxylin and eosin, original magnification 100×) show that the lesions were fragments of necrotic bone and cartilage infiltrated by lymphocytes and macrophages. No infectious inflammation or tumor cells are observed

ASIA grade on admission was D in 2 cases and E in 11 cases. The ASIA grade at the final follow-up was D in 1 case and E in 12 cases. Neurological deterioration was not observed during the follow-up period. Meanwhile, similar to the JOA scores, significant differences were observed between the 2 groups at the final follow-up ($P < .05$).

3.4 | Univariate and binary logistic regression analyses of prognostic factors of JOA score recovery rate

The univariate and multivariate results are presented in Tables 3 and 4, respectively. We examined all of the variables collected by the univariate analysis using Pearson's Chi-squared test, Mann-Whitney *U* test, and independent-samples *t* test. In this analysis, 3 factors showed significant predictive relationships with the rate of improvement in the JOA score ($P < .05$; Table 3). As a result, osteoporosis, treatment modality and bone fusion were entered into the binary logistic regression analysis, but only 2 of these predictive factors were significantly related to the JOA score recovery rate, that is, treatment modality and bone fusion (Table 4). Patients in the surgical treatment group were 6.369 (1/0.157) times more likely to achieve a better JOA score recovery rate (≥25%) than those in the conservative treatment group (OR = 0.157; 95% CI 0.028-0.89; $P < .05$). Patients with bone fusion were 9.965 times more likely to achieve a better JOA score recovery rate (≥25%) than those with bone nonunion (OR = 9.965; 95% CI 2.052-48.387; $P < .05$).

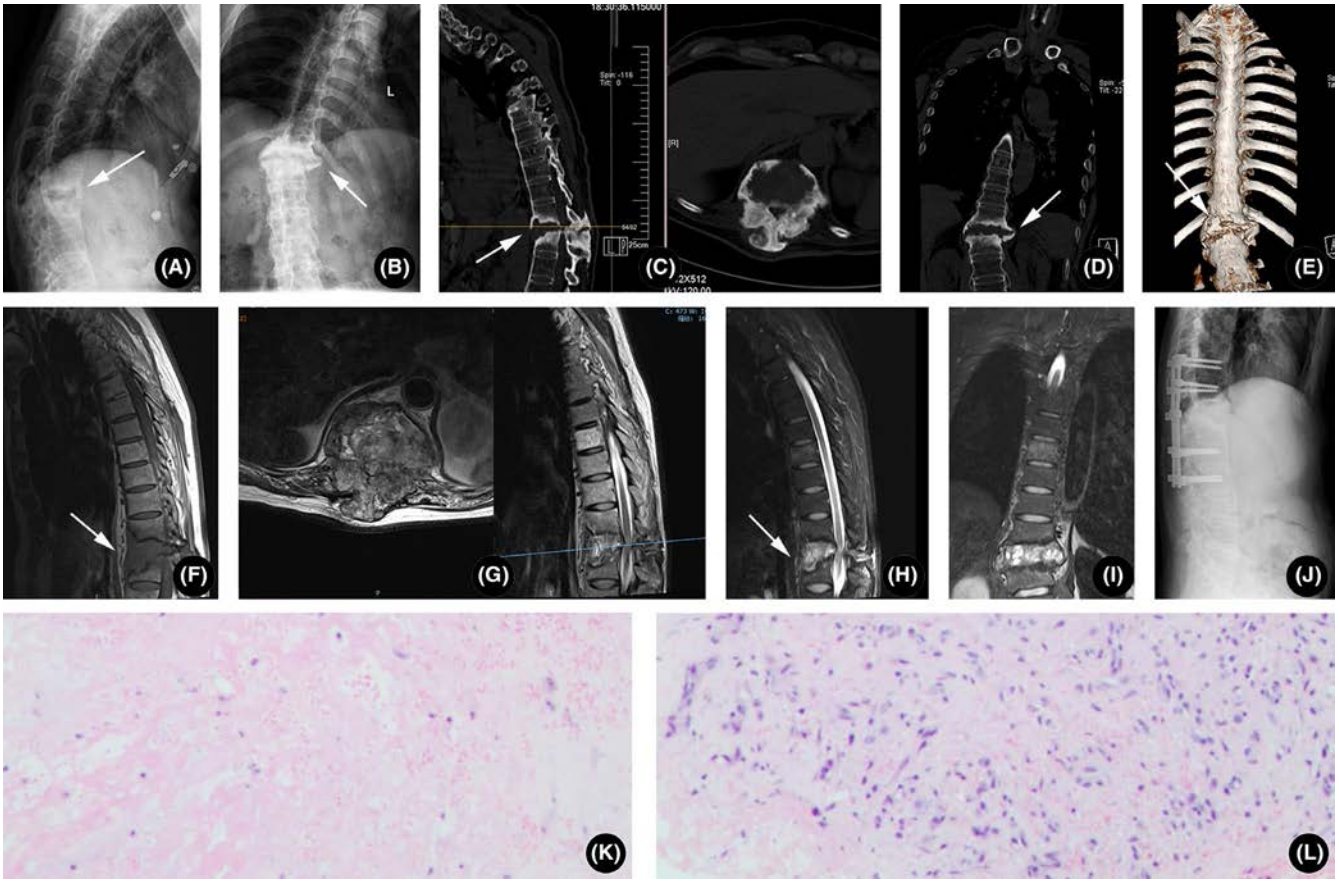

FIGURE 2 A 55-y-old male patient with ankylosing spondylitis (AS) complicated by Andersson legion (AL) at the level of T11-T12 is presented. Preoperative lateral (A) and anteroposterior (B) plain radiographs of the thoracic region demonstrate the presence of advanced features of ankyloses and spinal lesions with sclerosed irregular margins (white arrow). Preoperative sagittal-axial (C) and coronal (D) computed tomography (CT) scans demonstrate extensive destruction with lesions at the T11-T12 level. The lesions affect the posterior structure of the spine, resulting in narrowing of the spinal canal (white arrow). Preoperative 3-dimensional CT reconstructions (E) show bone nonunion with irregular discovertebral osteolysis at T11-T12 (white arrow). Preoperative sagittal T1-weighted (F) and axial-sagittal T2-weighted (G) images show fibrous tissue hyperplasia, a mixed signal intensity of sclerotic bone, necrotic tissue on T2-weighted images and an intermediate signal intensity on T1-weighted images, with vertebral canal intrusion (white arrow). Sagittal (H) and coronal (I) sagittal short inversion time inversion recovery (STIR) sequence images show a central lesion with cortical destruction at the posterior elements of the T11-T12 level exhibiting a hyperintense signal (white arrow). At 27 months after surgery, lateral (J) plain radiographs show correction of the deformity and the sagittal imbalance with solid fusion at the level of pseudarthrosis and good implant positioning. The histopathological examinations (K: hematoxylin and eosin, original magnification 40×, L: hematoxylin and eosin, original magnification 100×) show that the lesions corresponded to degenerative fibrocartilage tissue with calcification. No infectious inflammation or tumor cells are observed

4 | DISCUSSION

The main finding of our study is that surgery remains the optimal treatment for AL in AS patients, as better clinical efficacy was demonstrated by the medium- to long-term follow-up data. There were no major complications in this study. Clinically, AL can be easily misdiagnosed for various reasons, such as a lack of awareness about the lesion, osteoporosis, and radiographic resemblance to metastatic disease or infective spondylodiscitis.[1-2,18] In particular, patients with AL often have a history of minor or even no trauma. After a relatively short disease duration, activity-related back pain and kyphotic deformity, or even neurological deficits, gradually develop. Often, AL is misdiagnosed as infective spondylodiscitis or other tumorous conditions, such as spinal tuberculosis, especially in highly endemic areas for tuberculosis.[4,13,18,19] However, in patients with AS who have localized vertebral/discovertebral lesions without soft tissue swelling and a paravertebral mass on radiographic presentation, AL should be the first consideration.[3,17,20,21] Because of the unique features and complexity of the spinal column, orthopedic surgeons, rheumatologists and even radiologists may not be able to determine an early definite diagnosis. Furthermore, several different terms have been used to describe AL, such as "discovertebral lesion", "vertebral lesion", "destructive vertebral lesion", "spondylodiscitis", "pseudarthrosis" and "stress fracture".[7,13,15,22] In 1972, Cawley et al[1] reviewed the literature and concluded that AL is a delayed complication of AS that manifests as a localized lesion in the vertebral rim that can cause spinal pseudarthrosis and aggravate kyphotic deformity, sagittal imbalance, and pain. As reported in several previous studies,[6,19,22,23] AL most commonly occurs in middle-aged males (63%-86%) who experience long-term progression from a slight fracture or

TABLE 2 Comparison of the JOA scores, VAS scores and Cobb's angles between groups

		Surgical treatment (n = 35)	Conservative treatment (n = 13)	*t*	*P* value
JOA score (points)	On admission	9.1 ± 1.5 (5.5-14)	11.5 ± 2.9 (6.5-14)	0.136	.892
	At final follow-up	13.2 ± 2.2 (7.5-17)	12.1 ± 0.8 (8.5-16)	2.415	.02*
	Score change	4.2 ± 1.5 (4.5-9)	2.2 ± 0.8 (−0.5-4)	6.57	<.001*
	Recovery rate	68.5% (21%-85%)	18.7% (−10.5%-53%)	3.267	<.001*
VAS score (points)	On admission	3.9 ± 1.8	4.1 ± 1.3	−0.41	.686
	At final follow-up	1.6 ± 1.5	3.0 ± 1.2	−3.01	.004*
Cobb's angle (kyphosis)	On admission	37.1 ± 14.5	28.8 ± 11.7	1.838	.072
	At final follow-up	19.2 ± 3.9	38.6 ± 12.3	−8.38	<.001*

Note: Values represent the mean ± SD unless otherwise indicated.
Abbreviations: JOA, Japanese Orthopedic Association; VAS, visual analog scale.
*$P < .05$.

inflammatory reaction to severe erosion. The etiology of AL has yet to be clearly demonstrated. Several factors, including inflammation, trauma, and mechanical stress, have been successively regarded as potential etiologies.[2,6,12,13] Regardless of the precise etiology, for all patients with AL, a final common pathway may exist, in which continuous mechanical stress prevents fusion of the lesion, followed by the development of pseudarthrosis. In general, all of the regions of the spine in AS are susceptible, but this lesion most commonly involves the thoracolumbar region, that is, T10-L2, which can be attributed to the fact that this region is a transitional zone with high stress risers.[7,17,24]

In our series, AL often occurred in middle-aged adults (mean age, 49.4 ± 13.1 years), and the male-to-female ratio was 3:1, which is consistent with previous observations documented in the literature.[5,7-8,12] AL was commonly located in the thoracolumbar region (T10-L2) due to mechanical stress and mobility. The most common symptoms were back pain, followed by spinal cord compression and severe kyphotic deformity. However, patients may also be asymptomatic, with AL revealed by routine imaging evaluation of the spine. Here, we present a series of cases of AL from a single center to provide more insight into the clinical features, long-term outcomes, and prognostic factors of this lesion.

According to a review of the literature, our group found that the prognostic factors related to AL could generally be divided into the following 4 categories: patient-related factors, symptomatic factors, radiographic factors, and surgical factors.[1-2,5,7-8,10,12,14,19,25] Currently, with the routine use of MRI and CT, fractures or nonfusion of the facet joints can be detected at an early stage, which can facilitate the accurate diagnosis and the assessment of prognostic factors of AL. A CT scan is important for revealing osteolysis with surrounding reactive sclerosis and vertebral osteophytes, which can facilitate preoperative planning. Furthermore, MRI is considered a better diagnostic modality than CT.[3,8,13] In a study of 56 patients with AS, Vries et al[12] concluded that to detect AL in these patients, MRI should be combined with conventional spine radiography, which often also reveals osteoporosis. Often, patients with AL are vulnerable to early-onset osteoporosis, which is secondary to autoimmune inflammation and significantly related to the outcome of AL. In our series, the number of osteoporosis cases accounted for the majority of patients (27 cases, 56.3%). High rates of osteoporosis may be associated with poor clinical outcomes in patients with AL.[4,8] Finkelstein et al[24] suggested that spinal fractures significantly contribute to poor outcomes and significantly increase the risk of disability, morbidity, and mortality, eventually allowing progression to pseudarthrosis. In our study, osteoporosis was not identified as a prognostic factor of JOA score recovery rate, which could be due to a quantitative bias. Additionally, for most patients with osteoporosis, our surgeons emphasize treatment with anti-osteoporosis therapy at early stages. Studies have shown that the treatment modality, such as surgical intervention and general conservative treatment, is

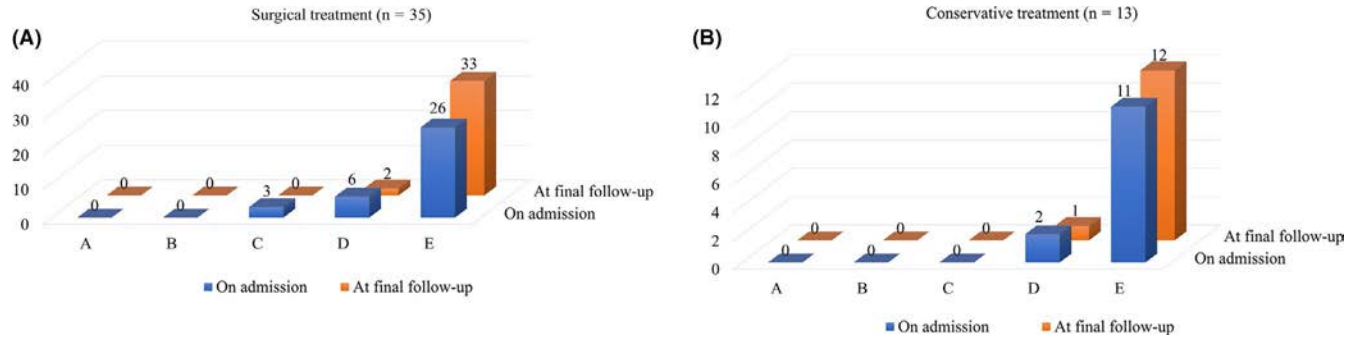

FIGURE 3 American Spinal Injury Association (ASIA) impairment scale for surgical (A) and conservative (B) treatment of Andersson lesion (AL)

TABLE 3 Univariate analysis of prognostic factors in the surgical treatment of Andersson lesion in ankylosing spondylitis

Variable		No. of patients	JOA score recovery rate		Recovery rate (%)	$t/\chi^2/Z$	*P* value
			<25% (n = 18)	≥25% (n = 30)			
Sex	Male	36	14	22	61.1	0.119	.731
	Female	12	4	8	66.7		
Age		48	52.67 ± 12.81	47.4 ± 13.07	62.5	1.362	.18
Duration of symptoms before admission, mo		48	36.5 (21.75-54.75)	34 (17.75-45.25)	62.5	−0.69	.489
ESR, mm/h		48	22.5 (12-36.5)	17.5 (11-33.5)	62.5	−1.18	.237
CRP, mg/L		48	11 (7.75-24.25)	11 (7-21.25)	62.5	−0.46	.646
HLA-B27 positivity	Yes	20	9	11	55	0.823	.364
	No	28	9	19	67.9		
Steroid treatment	Yes	11	6	5	45.5	1.769	.184
	No	37	12	25	67.6		
Osteoporosis	Yes	27	14	13	48.1	5.424	.02*
	No	21	4	17	81		
Lesion region	Thoracolumbar region	33	13	20	60.6	0.304	.859
	Thoracic region	10	3	7	70		
	Lumbar region	5	2	3	60		
Pseudarthrosis	Yes	29	10	19	65.5	0.285	.594
	No	19	8	11	57.9		
Neurological impairment	Yes	11	4	7	63.6	0.008	.929
	No	37	14	23	62.2		
Cobb's angle (kyphosis)	<30°	30	12	18	60	0.824	.663
	30-60°	14	4	10	71.4		
	>60°	4	2	2	50		
Treatment modality	Conservative treatment	13	9	4	30.8	7.659	.006*
	Surgical treatment	35	9	26	74.3		
Bone fusion	Yes	29	5	24	82.8	12.83	<.001*
	No	19	13	6	31.6		

Abbreviations: JOA, Japanese Orthopedic Association; thoracolumbar region, T10-L2.
*$P < .05$.

TABLE 4 Binary logistic regression analysis of prognostic factors in the surgical treatment of Andersson lesion in ankylosing spondylitis

Variable		β	SE	Wald χ^2	*df*	*P* value	OR value	95% CI	
								Lower	Upper
Osteoporosis	Yes	−0.428	0.82	0.273	1	.601	0.652	0.131	3.248
	No	0	–	–	–	–	1	–	–
Treatment modality	Conservative treatment	−1.853	0.886	4.375	1	.036*	0.157	0.028	0.89
	Surgical treatment	0	–	–	–	–	1	–	–
Bone fusion	Yes	2.299	0.806	8.132	1	.004*	9.965	2.052	48.387
	No	0	–	–	0	–	1	–	–

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; β, coefficient from binary logistic regression model.
*$P < .05$.

related to the outcomes of AL.[16-17,19,24] Chang et al[25] have shown that because of its superior fusion ability in AS, surgical treatment can successfully achieve bone fusion in AL patients without bone grafts. In our study, we found that treatment modality and bone fusion were significantly related to JOA score recovery rate. Thus, our study supports this opinion. However, there are still disputes regarding the prognostic factors, and only a few previous studies have reported the medium- to long-term outcomes of AL treatment

in AS in relation to JOA recovery rate.[11,23,26] The role of laboratory tests in patients with AL is also controversial. Both ESR and CRP levels may be elevated in patients with AL and may be involved in the clinical disease activity of AL. These patients may also be positive for HLA-B27.[1,3,8,11] In our study, there were no significant differences in ESR, CRP levels or HLA-B27 status with respect to the JOA score recovery rate.

To the best of our knowledge, there are no clear guidelines in the literature describing management strategies for such lesions. In our center, for most patients, conservative treatment is often initially recommended, and several researchers have reported that conservative treatment can be effective.[15,17] The use of NSAIDs during the active phases of the disease can relieve the pain and control non-bacterial inflammation.[5-6,8,12] Dihlmann et al[18] described that patients with AL can achieve the spontaneous relief of back pain through conservative management. In addition, new therapies have recently been introduced, including anti-TNF-α therapy.[8,10,15,16] In 2011, Bruzzese et al[15] reported 2 cases of AL that were successfully treated with anti-TNF therapy, and subsequently, Joshi et al[16] demonstrated that therapy with anti-TNF-α agents can significantly improve the signs, symptoms, and function of patients with AS. According to a retrospective review of 622 patients with AS, Park et al[4] subdivided AL in AS into inflammatory and traumatic types and suggested that conservative treatment, such as with anti-TNF agents, be used to treat the pain of inflammatory lesions. Additionally, surgical treatment was suggested to alleviate the pain, deformity and instability of traumatic lesions. However, Vries et al[12] proposed that the efficacy of treating AS conservatively in older patients and in more severe cases with complete ankylosis of the spine was still debatable. There is no more accurate evidence that patients with symptomatic AL can benefit from such drugs, although they are effective in the treatment of AS. However, at the more mobile thoracolumbar levels, that is, T10-L2, Bron et al[8] noted that conservative management is less effective and that surgery is mandatory to achieve neurological decompression, correct kyphotic deformity and restore spinal stability, thereby facilitating bone healing and fusion of the lesion. Although numerous surgical techniques have been advocated, including instrumented and noninstrumented stabilization through anterior, posterior or combined approaches, the main argument is focused on the necessity of bone grafting and fusion. Bone grafting and fusion are generally accepted as an optimal surgical procedure to treat AL in AS patients and can achieve satisfactory correction of local kyphosis and good safety.[21,23,25,26] In 2006, Chang et al[25] reported that bone grafting was not necessary because of the excellent higher fusion ability of AS patients. In 2011, Wang et al[13] showed that posterior instrumentation can achieve solid immobilization, which should be the focus of the treatment of AL, whereas lesion curettage and anterior bone grafting were not necessary. In 2017, Ling et al[23] concluded that posterior grade 4 osteotomy with bone grafting can achieve successful fusion and good clinical outcomes at the final follow-up. To date, there have been few studies on the prognostic factors of JOA score recovery rate in the treatment of AL in patients with AS. In this follow-up study on AL treatment, 35 patients (72.9%) were surgically treated, and their JOA scores, VAS scores and Cobb's angles at the final follow-up were significantly better than those of patients who were treated conservatively (13 cases). Furthermore, the JOA score recovery rate during the medium- to long-term follow-up was related to treatment modality and bone fusion. Therefore, the curative effect of surgical treatment is superior to that of conservative treatment. Moreover, radiological union should be rigorously monitored.[7,9,13] According to our study and recommendations, surgical treatment should be considered for patients with unbearable pain, symptom progression, progressive kyphotic deformity or neurological deficits. We also believe that achieving successful bone fusion by instrumentation is the most effective treatment for AL, which also demonstrates the significant role of instability in the development of AL.

5 | STUDY LIMITATIONS

Several limitations existed in this study. (a) The sample size was relatively small to validate the role of candidate treatment modality and bone fusion in AL prognostic factors. Additionally, this study was performed in a single center, and patients mainly came from middle China. Thus, a nationwide multicenter study with a larger sample size is needed in the future. (b) The possible mechanism could be further explored, such as the associations of clinical disease activity and related factors.

6 | CONCLUSIONS

In summary, AL is a relatively uncommon discovertebral lesion in patients with AS. We believe our findings provide valuable information for determining the treatment and prognostic factors of AL. Surgery is an effective and safe method for treating AL, especially for patients with kyphotic deformity and obvious symptoms of nerve compression. In addition, successful bone fusion should be the focus of the treatment of AL.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

MHW and FFY performed the studies, participated in collecting the data, and helped draft the manuscript. ASP performed the data

analysis and contributed to the study design. JL conceived the study and contributed to the study design and coordination. All authors have read and approved the final manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

All procedures in the studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The present study was retrospective; for this type of study, the local ethics committee waives the requirement for formal consent.

DATA AVAILABILITY STATEMENT

The datasets supporting the conclusions of the present study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

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Hospital admission and associated factors among individuals presenting to healthcare facilities for low back pain in Ethiopia

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Abstract

Aim: The aim of this paper is to analyze hospital admission and associated factors following presentation to healthcare facilities for low back pain (LBP) in Ethiopia.

Methods: A population-based cross-sectional study was conducted between June and November 2018 in South-west Shewa zone of Oromia regional state. Data were collected by face-to-face interviews of adults (≥18 years) with self-reported LBP using a newly developed and validated instrument. All the statistical analyses of (n = 543) individuals with a 1-year history of presentation to healthcare facilities for LBP were performed using R version 3.5.1. The log-binomial regression model was fitted and prevalence ratios with 95% confidence intervals (CIs) were calculated to identify factors associated with hospitalization and the significance level was considered at the *P* value of ≤ .05.

Results: The proportion of hospital admissions following presentation to healthcare facilities for LBP was 14.4%, 95% CI 11.4-17.3, with an average length of stay (LOS) 7.4 days, 95% CI 6.4-8.8. The admission rate was 18.5%, 95% CI 13.4-23.3 in females and 11.4%, 95% CI 8.0-15.1 in males. Multiple factors, such as gender, age, living conditions, residential environment, alcohol consumption status, intensity of pain, and presence of additional spinal pain, were found to be independently associated with hospitalization for LBP.

Conclusions: The burden on the individuals and the Ethiopian healthcare system as a result of LBP is evident by the rate of hospital admissions. Further evidence on LBP case referral procedures is needed to allow health policy makers to develop appropriate management strategies capable of dealing with the increasing epidemiology of LBP.

KEYWORDS

associated factors, hospital admission, low back pain, presentation to healthcare facilities

1 | INTRODUCTION

Globally, low back pain (LBP) is one of the most prevalent public health issues[1,2] and results in significant healthcare expenditure.[3] The mean point prevalence of LBP among the general population has been estimated to be 11.9%[4] and the lifetime prevalence to range between 49% and 90%.[5] However, the prevalence of LBP varies significantly between countries as a function of socio-economic and demographic structures.[6,7] For example, Fujii and Matsudaira[8] found that the 1-month and lifetime prevalence of

LBP in the Japanese adult population was 36% and 83%, respectively, while Macfarlane et al[9] estimated the 1-month prevalence of LBP to be 28.5% among the UK population aged 25 years or more. Alternatively, a study among 40-79-year-old Koreans estimated the point prevalence of LBP to be 36.5% (26.2% in males and 43.9% in females).[10] This variation in the prevalence rates of LBP can also be attributed to several factors, including the difference in the type of prevalence being studied, case definitions, and the methods applied to investigate the prevalence of LBP.[4,11] Moreover, social norms, local healthcare approaches, and legislation were argued to be the most significant factors influencing the prevalence and associated impacts of LBP, including disability.[12]

The prevalence and consequences of LBP are also seen to be high in low- and middle-income countries, causing a great concern among communities, researchers, and public health program planners in these regions.[13-15] Pagare et al[16] indicated that the lifetime prevalence of LBP in the Indian general population was 75%, while a nationwide longitudinal study in Thailand showed that 30% of the study cohorts had a history of LBP in the years 2009 and 2013.[17] A recent study in Brazil also showed that the 1-week prevalence of LBP was 28.8% (39% in males and 60.9% in females).[18] In Africa, a recent systematic review of the literature showed that the point, annual, and lifetime prevalence of LBP in the region was 39%, 57%, and 47%, respectively.[19] Despite there being no population-based study in Ethiopia, a large epidemiological study undertaken with 190 593 participants from 43 low- and middle-income countries estimated the prevalence of LBP in Ethiopia to range between 13.7% and 25.3%.[20] The same authors also demonstrated that LBP is associated with increased mental health conditions, such as depression, anxiety and stress in low- and middle-income countries, including Ethiopia.

In high-income countries, such as the USA and Australia, the epidemiology of LBP is well studied and the data show that a significant proportion of LBP patients being admitted to hospital following presentation to emergency departments.[3,21] For example, the USA study showed that between 1998 and 2007, LBP accounted for a total of 183 151 individuals to be admitted to hospital across the country, of which 118 962 (65%) were admitted after presentation to emergency departments.[3] The study in Australia also indicated that the rate of hospital admission through emergency departments was 17.6%.[21] Evidence also demonstrates that the rate of hospital admission for LBP following presentation to emergency departments is increasing over time.[22] Population-based epidemiological studies also estimated that the impact of LBP, including a frequent and a large deal of ambulatory medical care visits and hospitalization will increase with time. For example, a 15-year time-series study in England demonstrated that hospitalization for LBP increased from 127.1 in 1999 to 216.3 in 2013 per 100 000 population,[23] representing a 1.7-fold rise over the course of 15 years or an annual rise of 7.6 per 100 000 population. Laffont et al[24] argued that LBP is the most common cause of pain in the adult population and the most common health problem prompting patients to seek ambulatory medical visits.

In low-income countries, such as those in Africa, there is no literature documenting the information about hospital admission for LBP and associated factors, particularly among the individuals presenting to healthcare facilities for the optimal management of pain. However, it would be important to note that the data on hospitalization for LBP can be seen as an indicator of a severe low back disorder.[25] A better understanding of the factors that significantly associate with hospital admission for LBP may also help clinicians to plan and implement evidence-based management of individual patients, particularly to appropriately address the factors while providing healthcare services. Furthermore, hospital admission is a significant contributor to the medical care costs of LBP, reflecting the resource-intense nature of LBP hospitalization.[22] It would, therefore, be important to analyze the implications of LBP measured as hospital admissions and associated factors following presentation to healthcare facilities for pain in Ethiopia, as one of the low-income countries.

2 | METHODS

2.1 | Study design and setting

A population-based cross-sectional study was conducted between June and November 2018 in South-west Shewa zone of Oromia regional state, Ethiopia.

2.2 | Study sample, sampling procedure, and data collection

The study sample was calculated using a single population proportion formula. With this formula, a total of 1981 adults (≥18 years) with LBP were calculated to be included in the study. The sampling procedure involved multiple stages. Firstly, 3 districts (1 urban and 2 rural) were selected from the 11 districts in South-west Shewa zone considering a recommendation in the literature.[26] Secondly, 2 kebeles (the smallest administrative unit in Ethiopia) from each of the 3 districts, totaling 6 kebeles, were randomly selected. Finally, the households within the selected kebeles were selected using a systematic random sampling procedure and individuals (≥18 years) with LBP were interviewed. In a household, only 1 individual with LBP was interviewed. In case there were 2 or more individuals with LBP in the selected household, 1 individual was selected with a lottery method, while the next household was visited in case there was no individual with LBP in the household. The total number of individuals interviewed from each kebele was proportional to the total number of households in the respective kebeles. In this way, a total of 1981 individuals with LBP were contacted to be interviewed, of whom 169 did not participate in the study and 1269 did not have a 1-year history of presentation to healthcare facilities to utilize health services for the optimal management of their LBP. Thus, the remaining 543 individuals who reported at least 1 presentation to any of the health institutions for their LBP in the past 1-year were included in the analysis of this paper (Figure 1). The

detailed procedure that includes sample size calculation, sampling technique, the identification of individuals with LBP, and data collection, is described elsewhere.[27]

2.3 | Data collection instrument

A newly developed and validated measurement instrument was used to collect the data. The instrument was composed of multiple items designed to collect various information, including socio-demographic characteristics, beliefs about LBP, pain-interrelated factors, sleeping problems/insomnia, depressive symptoms, health behaviors/lifestyle habits, pain-associated sequelae, and healthcare utilization including hospitalization for LBP. The instrument is proved to have an overall good level of content and factorial validity, internal consistency reliability, and temporal stability to measure the proposed information when applied to the same study population. The details of the psychometric properties of the instrument are described elsewhere.[28]

2.4 | Statistical analyses

The statistical analyses were performed using R version 3.5.1. Hospital admission was calculated with a 95% confidence interval (CI) to describe the proportion of individuals admitted to hospital following presentation to healthcare facilities for LBP. A log-binomial regression model was fitted and prevalence ratios with 95% CIs were calculated to identify factors associated with hospital admission and the significance level was considered at the *P* value of ≤ .05.

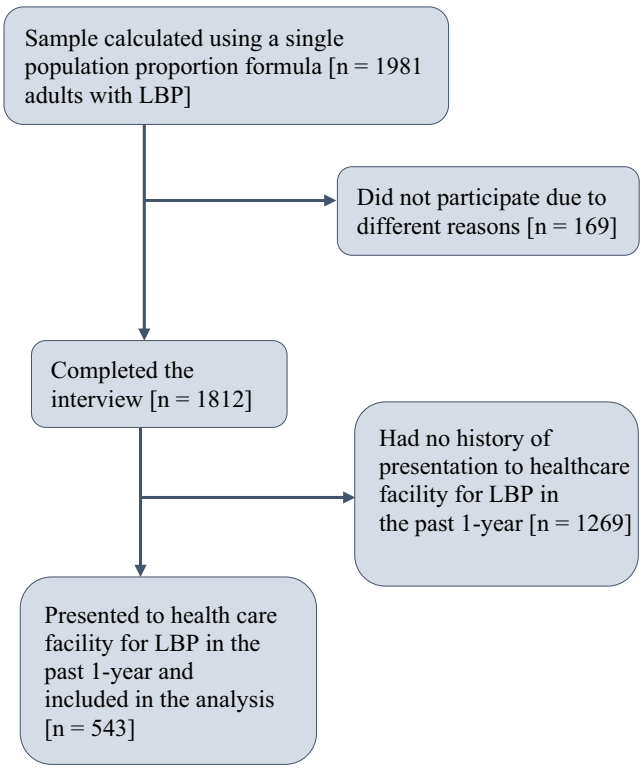

FIGURE 1 Flow diagram demonstrating sample included in the analysis

3 | RESULTS

3.1 | Socio-demographic profile of individuals presenting to healthcare facilities for LBP in the past year

Of the 543 individuals with a 1-year history of presentation to healthcare facilities for LBP, 316 (58.2%) were male and 205 (37.8%) had attended elementary school. The median age of these individuals was 43 years (interquartile range [IQR] 33-55 years). Nearly two-thirds (64.8%) were living in rural settings (Table 1).

3.2 | Health behaviors, beliefs about the pain, and pain-interrelated profile of individuals presenting to healthcare facilities for LBP in the past year

Health-compromising behaviors, such as smoking and khat (a plant with leaves and stem tips which are chewed for their stimulating effect) chewing were uncommon among the participants with a 1-year history of presentation to healthcare facilities for LBP; only 15 (2.7%) and 37 (6.8%), respectively, were smokers and khat chewers at the time of conducting the study. The majority, 350 (64.5%) of the individuals had negative beliefs about LBP (for example, believing that the pain is not curable and makes everything in life worse). Long-lasting LBP, that is, pain lasting 1-5 years and >5 years were observed in 210 (38.7%) and 88 (16.2%) people, respectively. A large impact of LBP, in terms of days off work, was reported by nearly two-thirds (64.3%) of the individuals (Table S1).

3.3 | Hospital admission following presentation to healthcare facilities for LBP

From a total of 543 individuals with a 1-year history of presentation to healthcare facilities for LBP, 78 (14.4%, 95% CI 11.4-17.3) were admitted to hospital. This accounts for 4.3%, 95% CI 3.4-5.3 of the total sample with LBP (n = 1812). The proportion of hospitalization was 42 (18.5%, 95% CI 13.4-23.3) in females and 36 (11.4%, 95% CI 8.0-15.1) in males. The average length of stay (LOS) in the hospital was 7.4 days, 95% CI 6.4-8.8 or median (IQR) 6.5 (3-10) days. Of those hospitalized patients, 21 (26.9%, 95% CI 17.8-37.8) were managed by a surgical procedure. This accounts for 3.9%, 95% CI 2.4-5.5 of the patients who presented to healthcare facilities and utilized health services for their LBP in the past year (n = 543). There was no statistically significant difference in the proportion of surgical interventions between genders (33.3% in females and 19.4% in males, Pearson Chi-square = 1.901, *P* = .168).

TABLE 1 Socio-demographic profile of individuals presenting to healthcare facilities for low back pain in the past year (n = 543)

	Total		Admitted to hospital		Not admitted to hospital	
Characteristics	n	%	n	%	n	%
Gender						
Male	316	58.2	36	11.4	280	88.6
Female	227	41.8	42	18.5	185	81.5
Age, y						
18-29	83	15.3	4	4.8	79	95.2
30-39	146	26.9	20	13.7	126	86.3
40-49	120	22.1	19	15.8	101	84.2
≥50	194	35.7	35	18.0	159	82.0
Educational level						
No formal education	86	15.8	14	16.3	72	83.7
Elementary (grades 1-8)	205	37.8	26	12.7	179	87.3
Secondary (grades 9-12)	100	18.4	8	8.0	92	92.0
Technical/vocational certificate	31	5.7	2	6.5	29	93.5
Diploma	48	8.8	4	8.3	44	91.7
First degree or higher	73	13.5	24	32.9	49	67.1
Residence area						
Urban	191	35.2	41	21.5	150	78.5
Rural	352	64.8	37	10.5	315	89.5
Marital status						
Single	60	11.0	11	18.3	49	81.7
Married	411	75.7	57	13.9	354	86.1
Cohabited[a]	7	1.3	-	-	7	100
Separated	11	2.0	3	27.3	8	72.7
Divorced	13	2.4	-	-	13	100
Widowed	41	7.6	7	17.1	34	82.9
Living conditions						
Living with nuclear family	491	90.4	67	13.6	424	86.4
Living with non-nuclear family	13	2.4	1	7.7	12	92.3
Living alone	39	7.2	10	25.6	29	74.4

[a]Couples not officially married but living together as a wife/husband; n: number (frequency).

3.4 | Factors associated with hospital admission for LBP

Using the log-binomial regression analysis, socio-demographic factors, including gender, age, residential area, and living conditions, were identified to be independently associated with hospitalization. When adjusted for age, the prevalence ratio of hospitalization was higher in females than males (adjusted prevalence ratio [APR] =1.81, 95% CI 1.20-2.75). Similarly, on adjustment for gender, there was a nonlinear dose-dependent association between age groups and hospitalization (test for trend P = .009). Thus, as age group increased from 18-29 to 30-39 to 40-49 to ≥50 years, the prevalence ratio for hospitalization increased correspondingly (30-39 years of age, APR = 3.00, 95% CI 1.19-10.02; 40-49 years of age, APR = 3.50, 95% CI 1.38-11.71; ≥50 years of age, APR = 4.32, 95% CI 1.80-14.12). When compared with the urban residents, the rural residents were 45% less likely to be hospitalized (APR = 0.55, 95% CI 0.34-0.90). Despite no statistically significant difference in the history of hospitalization between participants living with their nuclear family and non-nuclear family, participants living alone were 2.54 times more likely to be hospitalized than participants living with their nuclear family (APR = 2.54, 95% CI 1.34-4.15). Educational level and marital status of the individuals were not statistically associated with hospitalization. From a list of health-compromising behaviors, such as smoking, alcohol consumption, and khat chewing, only alcohol consumption status was associated with hospital admission. Compared with current alcohol consumers, the history of reporting hospital admission was 64% (APR = 0.36, 95% CI 0.18-0.67) and 42% (APR = 0.58, 95% CI 0.37-0.91) lower in former consumers and those who never consumed alcohol, respectively (Table 2).

Intensity of pain was strongly associated with hospitalization. Compared with individuals with mild pain, those individuals with moderate and severe pain, respectively, were 2.46 (APR = 2.46, 95% CI 1.15-5.52) and 8.84 (APR = 8.84, 95% CI 4.82-18.13) times more likely to be admitted to hospital. Presence of additional spinal pain was also statistically associated with hospitalization. Individuals who had additional spinal pain were 1.46 times more likely to report a history of hospital admission when compared with individuals who had no additional spinal pain (APR = 1.46, 95% CI 1.01-2.13). In the unadjusted log-binomial regression model, pain spreading down the leg(s) was also associated with a higher history of hospital admission (unadjusted PR = 2.46, 95% CI 1.57-3.70). However, on adjustment for intensity of pain, there was no statistically significant difference in the history of hospitalization across pain spreading and not spreading down the leg(s). Self-reported general health, depressive symptoms, and insomnia were also not associated statistically with hospitalization for LBP (Table 3).

4 | DISCUSSION

4.1 | Hospital admission for LBP

At the societal level, the worldwide high prevalence of LBP and associated socio-economic impact[29] suggest that LBP requires immediate attention from researchers, policy makers, and healthcare funders.[24,30] Hospitalization for LBP reflects the severe effects of

TABLE 2 Socio-demographic factors and health behaviors associated with hospital admission for low back pain

Factors	PR (95% CI)	*P* value	APR (95% CI)	*P* value
Gender				
Male[a]				
Female	1.62 (1.08-2.46)	.021	1.81 (1.20-2.75)	.004
Age, y				
18-29[a]				
30-39	2.84 (1.12-9.53)	.049	3.00 (1.19-10.02)	.038
40-49	3.29 (1.29-11.03)	.025	3.50 (1.38-11.71)	.018
≥50	3.74 (1.56-12.24)	.010	4.32 (1.80-14.12)	.004
Educational level				
No formal education[a]				
Elementary (grade 1-8)	0.78 (0.44-1.46)	.414	0.84 (0.47-1.57)	.556
Secondary (grade 9-12)	0.49 (0.21-1.09)	.089	0.46 (0.19-1.02)	.061
Technical/vocational certificate	0.40 (0.06-1.31)	.203	0.31 (0.05-1.04)	.120
Diploma	0.51 (0.15-1.33)	.213	0.44 (0.13-1.15)	.127
First degree or higher	2.02 (1.15-3.73)	.018	1.45 (0.79-2.81)	.249
Residence				
Urban[a]				
Rural	0.49 (0.32-0.74)	<.001	0.55 (0.34-0.90)	.017
Living with				
Nuclear family[a]				
Non-nuclear family	0.56 (0.03-2.23)	.554	0.87 (0.05-3.31)	.878
Alone	1.88 (0.98-3.16)	.033	2.54 (1.34-4.15)	<.001
Smoking status				
Current smoker[a]				
Former smoker	0.65 (0.24-2.16)	.425	0.51 (0.18-1.89)	.233
Never smoked	0.51 (0.25-1.52)	.133	0.43 (0.21-1.42)	.066
Alcohol consumption status				
Current consumer[a]				
Former consumer	0.37 (0.19-0.68)	.003	0.36 (0.18-0.67)	.002
Never consumed	0.58 (0.37-0.90)	.014	0.58 (0.37-0.91)	.017
Khat chewing status				
Current chewer[a]				
Former chewer	1.35 (0.44-4.29)	.594	2.14 (0.63-7.52)	.221
Never chewed	1.05 (0.51-2.85)	.913	1.95 (0.81-5.68)	.162

Abbreviations: APR, adjusted prevalence ratio; in the models to compute the APR for educational level and residence, the respective variables were adjusted for each other; in the models to compute the APR for smoking, alcohol consumption, and khat chewing, the respective variables were adjusted for one another; PR, unadjusted prevalence ratio; the model to compute the APR for age was adjusted for gender; the models to compute the APR for gender and living conditions were adjusted for age.

[a]Reference category.

pain and suffering for the patient.[25] Mattila et al[31] argued that hospitalization for LBP is a process beginning with the individual's perception of pain and severely reduced function of the back. However, the history of hospitalization and associated factors among individuals presenting to healthcare facilities for LBP have not been well examined, particularly in low- and middle-income countries where the epidemiology and associated burden of LBP is estimated to increase at a higher rate in the coming years. The present study, which investigated hospital admission and associated factors following presentation to healthcare facilities for LBP in Ethiopia, is believed to be the first of its kind in the country.

In this study, 14.4% of individuals presenting to healthcare facilities for LBP in the past year were admitted to hospital, with an average median (IQR) LOS 6.5 (3-10) days. This demonstrates that LBP is a substantial public health problem posing a significant impact in view of hospitalization and associated expenses. A comparable finding was observed in an

TABLE 3 Beliefs about the pain and pain-interrelated factors associated with hospital admission for low back pain

Factors	PR (95% CI)	*P* value	APR (95% CI)	*P* value
Beliefs about LBP				
Positive beliefs[a]				
Negative beliefs	1.10 (0.72-1.74)	.660	1.16 (0.79-1.75)	.468
Pain spreading down the leg(s)				
No[a]				
Yes	2.46 (1.57-3.70)	<.001	1.34 (0.89-1.95)	.145
Pain intensity				
Mild[a]				
Moderate	2.74 (1.28-6.16)	.011	2.46 (1.15-5.52)	.023
Severe	10.56 (5.84-21.45)	<.001	8.84 (4.82-18.13)	<.001
Presence of additional spinal pain				
No[a]				
Yes	1.40 (0.93-2.13)	.112	1.46 (1.01-2.13)	.043
Self-rated health status in the past year				
Excellent[a]				
Very good	0.47 (0.16-1.97)	.219	0.59 (0.23-2.29)	.348
Good	1.24 (0.50-4.84)	.702	1.26 (0.58-4.59)	.655
Fair	1.84 (0.66-7.52)	.305	1.32 (0.54-4.98)	.612
Poor	3.48 (1.26-14.08)	.033	1.72 (0.71-6.48)	.310
Depressive symptoms				
Normal[a]				
Borderline case	1.00 (0.58-1.64)	.990	0.93 (0.57-1.46)	.768
Case	2.10 (1.27-3.36)	.003	1.09 (0.68-1.68)	.700
Insomnia				
No[a]				
Yes	1.38 (0.90-2.07)	.134	1.40 (0.96-2.01)	.071

Abbreviations: APR, adjusted prevalence ratio; LBP, low back pain; PR, unadjusted prevalence ratio; the models to compute the APR for each variable were adjusted for intensity of pain, while the model to compute the ARP for intensity of pain was adjusted for pain spreading down the leg(s) and presence of additional spinal pain.

[a]Reference category.

Australian study,[21] which indicated that 17.6% of individuals with LBP, who presented to emergency departments, were admitted to hospital for 6 (3-12) days overall median (IQR) LOS. Alternatively, a study in the USA showed that only 4.5% of LBP patients presenting to emergency departments were admitted to hospital,[32] which is lower than the findings of the current study. This observed discrepancy in the rate of hospital admission following presentation to healthcare facilities for LBP across countries could be attributed to the variations in the healthcare and referral systems between countries. This difference could also be attributed to multiple other factors as discussed elsewhere.[33]

4.2 | Surgical and non-surgical management of LBP patients admitted to hospital

In this study, 21 (26.9%) of the hospitalized LBP patients who received surgical interventions made only 3.9% of the total LBP patients who presented to healthcare facilities in the past year. This finding fits with the argument that because of the side effects of surgical interventions of LBP, conservative treatment is often preferable to a surgical procedure.[34] In addition, Olafsson et al[35] found that in treatment pathways, most LBP patients receive conservative care, while only a few utilize high-cost care such as surgery. It should be noted that even the small proportion of patients who underwent surgical interventions, account for a large portion of LBP healthcare costs.[36] For example, in a study investigating expenditures and healthcare utilization among adults with newly diagnosed low back and lower extremity pain, only 1.2% underwent a surgical procedure, but accounted for 29.3% of the total 12-month healthcare costs associated with the pain.[37] This may reflect more severe symptoms among individuals with LBP eventually undergoing operative treatment, which may not rapidly resolve.[38]

In this study, the profile of surgical interventions was observed to be similar in males and females. This finding is in keeping with another study which reported that the proportion of surgical

procedures performed for the management of LBP patients was similar between the genders.[24]

4.3 | Factors associated with hospital admission for LBP

The rate of hospital admission was significantly higher in females than males, which is concordant with the findings of previous studies in Argentina[24] and England.[23] This gender-based differential rate of hospitalization for LBP may reflect the difference between the low back morbidity profile of both genders, as argued in the literature.[4,39] The participants' ages were also associated significantly with hospital admission for LBP. There was a nonlinear increase in the prevalence ratio of hospitalization with an increasing age cohort (test for trend $P = .009$). This finding is comparable with another study that observed a greater increase in the annual rate of hospital admission for LBP in older age groups.[23] This increase in the rate of hospitalization with increasing age supports the argument that the epidemiology of LBP, including hospitalization and healthcare resource utilization, is a function of age.[11,40,41] In addition, Nunn et al[42] argued that more comorbidities often require more medical attention with increasing age.

In a previous study,[27] the prevalence ratio of healthcare utilization for LBP was higher in participants living in rural settings than those living in urban settings. The same study showed that a significantly greater number of rural than urban residents were presenting to the lower levels of the Ethiopian healthcare system to deal with their pain. In contrast, a greater proportion of urban than rural residents were found to be presented to the middle and upper levels of the healthcare system. In this study, the prevalence ratio of hospital admission for LBP was 45% lower in the rural residents than the urban residents. This may not reflect the lower burden of LBP in the rural population compared with the urban population. Rather it shows that hospital admissions occur at the middle and upper levels of the Ethiopian healthcare system, where more urban than rural populations were found to be presented to get health services for their pain. This variation in point of healthcare utilization was suggested to be a product of the difference in socio-economic status between the rural and the urban populations.[27] In addition, the availability of health services also explains the observed difference in point of healthcare utilization for LBP. However, in settings with relatively improved access to the healthcare systems, such as Poland, it has been shown that a significantly greater proportion of rural than urban residents were hospitalized for LBP.[43]

A previous study documented that living in a non-nuclear family increased the hazard of hospitalization for LBP among adolescents.[31] In this study, a statistically significant difference was not observed between participants living with their nuclear and non-nuclear families. However, the rate of hospitalization was 2.54 times higher in individuals living alone than those living with their nuclear family. This could be because people living alone may suffer loneliness, which has been shown to be associated with increased ill-health,[44] which in turn exacerbates the effects of the pain and leads to hospital admission.

Previous studies demonstrated that alcohol consumption,[31] smoking, and being overweight,[45] were associated with an increased risk of hospitalization for LBP. These findings partly match the current study which showed that being currently non-consumer of alcohol reduced the prevalence ratio of hospital admission, while smoking and khat chewing status were not associated with hospitalization for LBP. In general, these health-compromising behaviors should not be overlooked as evidence is also mounting that they are associated with increased risk of LBP.[45-47]

In this study, a strong association was observed between intensity of pain and hospitalization. Increased intensity of pain was associated with a significantly higher profile of hospital admission. This finding matches with another study which showed that pain was the major reason for hospitalization in workers with herniated lumbar disks.[25] Because a higher intensity of pain adversely affects general health, which causes hospital admission, a comprehensive plan is needed to address it while providing health services to individuals with LBP. Borys et al[48] suggested that multimodal therapy is effective for the management of intensity of pain and depression among patients with LBP. Presence of additional spinal pain was also associated with the higher rate of hospitalization. This could be explained by the fact that further spinal pain may worsen general health status with subsequent hospital admission. For example, Konstantinou et al[49] showed that patients with both low back and leg pain experience worse outcomes than those with only LBP. In the current study, despite pain spreading down the leg(s) being found to be associated with a 2.46-fold increased rate of hospital admission in the unadjusted log-binomial regression model, the association did not remain statistically significant on adjustment for intensity of pain. This finding does not fit a previous longitudinal study which documented that radiating LBP down to the leg(s) was found to increase the risk of hospitalization 3-fold.[50] The inconsistency of the findings of these 2 studies could be linked to the difference in the reference population. While the reference cohort in this study was individuals with LBP whose pain did not spread down the leg(s), the previous study used LBP-free individuals as a reference cohort.

4.4 | Strengths and limitations of the study

The strength of this study lies in its relatively large sample size, which is highly likely to reflect the true burden of LBP on the individual patients and healthcare system in terms of hospitalization and associated consequences. Nonetheless, the directionality of the associations between the reported covariates and hospitalization for LBP could not be identified due to the cross-sectional nature of the study.

5 | CONCLUSIONS

This study demonstrated that 14.4% of individuals presenting to healthcare facilities for LBP in the past year reported a history of

hospitalization for the pain. This indicates the burden of LBP on the individual patients and the already overloaded Ethiopian healthcare system. A range of factors, such as gender, age, living conditions, residential environment, alcohol consumption status, intensity of pain, and comorbidity with additional spinal pain, were found to be independently associated with hospital admission following presentation to healthcare facilities for LBP.

Ineffective management approaches for LBP may lead to an increased burden of pain, and decreased motivation among healthcare providers, and non-compliance in the patients. Further research is, therefore, needed on LBP in relation to referral procedures in the Ethiopian healthcare system to inform health policy makers regarding appropriate management strategies capable of dealing with the increasing epidemiology of LBP.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS APPROVAL

Ethics approval for this study was obtained from the Human Research Ethics Committee (Tasmania) Network, ethics reference number H0017128. Approval for data collection was obtained from Oromia Regional State Health Bureau, South-west Shewa Zone Health Office, and health officials of the selected districts. Informed consent was also obtained from all study participants prior to their inclusion. Participation in the study was voluntary and confidentiality maintained at all times.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Cross-cultural adaptation and validation of the Turkish version of Centrality of Pain Scale in patients with fibromyalgia syndrome

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Abstract

Aim: The purpose of this study was to perform a cross-cultural adaptation of the Turkish version of the Centrality of Pain Scale (COPS) and to evaluate its psychometric properties in patients with fibromyalgia syndrome (FMS).

Methods: Centrality of Pain Scale was translated and culturally adapted according to guidelines. Clinical and demographic data of the patients were recorded. In addition to the Turkish version of the COPS (COPS-TR), fibromyalgia impact questionnaire (FIQ), Pain Catastrophizing Scale (PCS), Brief Pain Inventory-Short Form (BPI-SF), Beck Depression Inventory (BDI), Generalized Anxiety Disorder 7-item (GAD-7) scale and Short Form-36 were applied. Internal consistency and test–retest methods were used for reliability analysis. Convergent validity was assessed by analyzing the correlations between COP-TR and functional parameters. Divergent validity and responsiveness were also evaluated.

Results: One hundred and four patients (90 female and 14 male) were included. The mean age was 44 years. Good internal consistency (α = .84) and high test–retest reliability (intraclass correlation coefficient = 0.95) were determined. Highest correlations were detected between COPS-TR and BPI-SF pain interference score (r = .64), COPS-TR and PCS (r = .61). There was no significant correlation with non-functional parameters (body mass index, disease duration). It showed high responsiveness (effect size and standardized response mean were 1.66 and 1.94, respectively). The patients filled out COPS-TR in 2 minutes.

Conclusions: COPS-TR is a reliable and valid instrument that shows good psychometric properties. It can be used in clinical practice and scientific research.

KEYWORDS

Centrality of Pain Scale, cross-cultural adaptation, fibromyalgia, validation

1 | INTRODUCTION

Fibromyalgia syndrome (FMS), with prevalence of 2%-8%, is characterized by widespread pain and several symptoms including fatigue, sleep disturbances, and cognitive problems.[1,2] It is diagnosed with a set of criteria; according to the American College of Rheumatology (ACR) 2016 revision criteria, patients should have generalized pain which is defined as pain in at least 4 of 5 regions (left upper, left lower, right upper, right lower, and axial regions). Jaw, chest, and abdominal pain are not included in this definition.[3]

Pain is the core symptom of FMS which has a complex pathogenesis. Central sensitization, hypothalamic–pituitary–adrenal axis abnormalities, increased levels of substance P, neurotrophins, and psychological factors including depression and anxiety, are responsible for the pathogenesis.[4,5] Since chronic pain is the major symptom of FMS, it is important to evaluate how patients perceive pain and how their life is affected by pain. The term "centrality" is a distinct concept from pain mechanisms (central sensitization). It refers to what extent pain dominates or takes over the patients' lives. The Centrality of Pain Scale (COPS) is a 10-item self-report questionnaire which assesses how individuals with chronic pain perceive pain in their lives. It has been developed and validated in patients with chronic non-malignant pain and mixed chronic pain diagnoses.[6,7]

The aim of is this study is to investigate the psychometric properties of a Turkish version of COPS (COPS-TR) in patients with FMS.

2 | METHODS

The study protocol was approved by the Hamidiye local ethics committee of the University of Health Sciences. Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.1 | Patients

Patients with the diagnosis of FMS according to ACR 2016 revision criteria who were older than 18 years were included in the study.[3] Exclusion criteria were the diagnosis of psychiatric disorders or severe systemic diseases, such as heart or renal failure, and the inability to read and write in Turkish. The sample size was determined according to Nunnally who recommended a 10:1 respondent-to-item ratio.[8] COPS has 10 items and 100 (10 × 10) participants should therefore be included.

2.2 | Measures

2.2.1 | Fibromyalgia impact questionnaire

This is an instrument which assesses the health status of patients with FMS. Physical function, work status, morning tiredness, stiffness, fatigue, and depression are some measures evaluated by the FIQ. The lowest score is zero and the maximum possible score is 100.[9] Higher scores reflect a worse health status. It has been translated and validated for the Turkish population.[10]

2.2.2 | Centrality of Pain Scale

This is a 10-item questionnaire in which each item is rated on a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: neither agree nor disagree, 4: agree, 5: strongly agree). Items 2, 4 and 9 are reversely scored. The total score is the sum of all item scores. Higher scores reflect more "centralized" pain. The maximum possible score is 50 and the minimum score is 10.[6,7]

2.2.3 | The Pain Catastrophizing Scale

This is a 13-item self-reported questionnaire with 3 dimensions including rumination, magnification, and helplessness. Each item is rated on a 5-point Likert scale (0: not at all, 4: all the time) and its score ranges from 0 to 52.[11] It has been validated for the Turkish population.[12]

2.2.4 | Brief Pain Inventory-Short Form

This is a 9-item self-administered questionnaire which evaluates the severity of pain and the impact of the pain on an individuals' daily life. Patients were asked to rate their least, worst, average, and current pain, and by calculating the mean of these 4 items we get the pain severity score. Patients were also asked to rate the degree to which pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. The pain interference score is the mean of these 7 items and is a valid and reliable tool for the evaluation of musculoskeletal pain.[13]

2.2.5 | Beck Depression Inventory

This is a 21-item self-administered questionnaire in which each item is rated 0 to 3. The total score ranges from 0 to 63. It has been validated for the Turkish population.[14]

2.2.6 | Generalized Anxiety Disorder 7-item scale

This is a 7-item instrument that assesses the severity of anxiety. Each item is scored 0 to 3 (0: not at all, 1: several days, 2: over half the days, and 3: nearly every day). The total score is the sum of all item scores.[15] Its reliability and validity has been studied in the Turkish population.[16]

2.2.7 | Short Form-36

This evaluates health-related quality of life. It has 8 domains including physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The validity and reliability of the instrument has been studied and normative data is available for the Turkish population.[17,18]

TABLE 1 Demographic and clinical features of the participants (N = 104)

	n (%)
Gender	
Female	90 (86.5%)
Male	14 (13.5%)
Education	
Primary-secondary school	63 (60.6%)
High school	25 (24%)
University	16 (15.4%)
Work status	
Employed	30 (28.9%)
Unemployed	72 (69.2%)
Retired	2 (1.9%)

	Mean ± SD	Min-Max
Age	44 ± 9.5	19-66
BMI	28.7 ± 5.4	15.4-45.4
Symptom duration (mo)	41 ± 39.6	3-240
Disease duration (mo)	5.6 ± 7.6	0-36
Widespread pain index	12 ± 2.3	7-19
Symptom severity index	10.1 ± 1.7	5-12

Abbreviations: BMI, body mass index; Min-Max, minimum-maximum; SD, standard deviation.

2.3 | Translation process

The COPS scale was translated and adapted to Turkish according to standard guidelines.[19-21] Forward translation was performed by 2 independent bilingual translators whose native language is Turkish. A consensus was derived after discussion between the translators and the researchers. Backward translation was performed by 2 other bilingual translators who had not seen the original version of COPS and who were native English speakers, fluent in Turkish. An expert committee, composed of 2 physiatrists, 4 translators, a physiotherapist, and a psychiatrist, compared all versions and discussed the problems and discrepancies. The committee approved a pre-final version of COPS-TR and a pilot test was then performed on a lay group (n = 20) to test its clarity. Finally the committee assessed all the findings and approved the final version of COPS-TR.

2.4 | Statistical analysis

The IBM SPSS Statistics 22 (IBM Corp) was used for statistical analysis. The results were evaluated at a significance level of $P < .05$.

2.5 | Reliability

Test–retest reliability and internal consistency analysis were performed. COPS-TR was applied to the participants twice, with a 2-week interval between each undertaking. Intraclass correlation coefficients (ICCs) were used for the determination of test–retest reliability. ICC values between 0.75 and 0.9 represent good reliability and values greater than 0.90 indicate excellent reliability.[22] Cronbach's alpha was calculated for the assessment of internal consistency, with values >0.70 indicating good internal consistency.[8]

2.6 | Validity

The face validity of the COPS-TR was assessed via cognitive debriefing interviews with 20 lay participants. They were asked if there was any ambiguity or difficulty in understanding questions.

Correlation analysis was performed between COPS-TR and PCS, FIQ, BPI-SF, BDI, GAD-7, and SF-36 for convergent validity. The correlation between COPS-TR, body mass index (BMI) and disease duration was assessed for divergent validity. Spearman's correlation coefficient (ρ) was used to assess convergent and discriminative validity.

2.7 | Responsiveness

Patients who were treated for the first time were evaluated with the COPS-TR and PCS for responsiveness 12 weeks after treatment. The standardized response mean (SRM) and effect size (ES) were calculated. The values between 0.2 and 0.4 indicate a small effect, between 0.5 and 0.7 express a medium effect and values >0.8 point out a greater effect.[23]

3 | RESULTS

A total of 104 FMS patients (90 female and 14 male) were recruited into this study. The demographic and clinical characteristics of the patients are given in Table 1. The mean age of the patients was 44 ± 9.5 years, and the mean duration of the disease was 5.6 ± 7.6 months. The pre-final version of COPS was tested in FMS patients with cognitive interviews. Each subject completed the questionnaire and was interviewed to learn what the patient thought was meant by each questionnaire item and the chosen response. All of the questions were well understood by the patients. There were no unclear questions or missing data. According to the expert committee, no further cultural adaptations were needed. The final version of COPS was tested in 104 FMS patients. The COPS-TR took an average of 2 minutes (±30 seconds) to complete. The mean COPS-TR score was 33.1 and PCS was 28.7 in FMS patients (Table 2).

3.1 | Reliability

The internal consistency (Cronbach's alpha) of COPS-TR was found to be 0.84. Fifty-two FMS patients completed the questionnaire twice. The test–retest reliability of COPS-TR was 0.95 ($P < .005$) indicating low random measurement error for scale.

TABLE 2 Descriptive analyses of functional parameters (N = 104)

	Mean ± SD	Min-Max
FIQ	64.5 ± 14.1	30-92.1
BPI-pain severity	5.7 ± 2	1-10
BPI-pain interference	5.2 ± 2	0.1-10
PCS	28.7 ± 10.5	4-52
COPS-TR	33.1 ± 7.8	10-49
BDI	15.7 ± 8.2	0-41
GAD-7	13.4 ± 5.1	0-21
SF36 physical function	45.5 ± 25.2	0-95
SF36 physical role limitations	17.7 ± 30.5	0-100
SF36 bodily pain	41 ± 20.6	0-90
SF36 general health	40.1 ± 16.1	0-75
SF36 vitality	31.3 ± 15	5-75
SF36 social functioning	57.7 ± 24.3	0-100
SF36 emotional role limitations	33.7 ± 41.8	0-100
SF36 mental health	49.7 ± 18.9	6-96

Abbreviations: BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; COPS-TR, Turkish version of Centrality of Pain Scale; FIQ, Fibromyalgia Impact Questionnaire; GAD-7, Generalized Anxiety Disorder 7-item; Min-Max, minimum-maximum; PCS, Pain Catastrophizing Scale; SD, standard deviation; F36, Short Form-36.

TABLE 3 Relation of the COPS-TR scores with demographic, clinical and functional parameters (N = 104)

	Spearman's correlation coefficient (rho)	*P* value
Age	.21	.03*
BMI	.07	.47
Disease duration (mo)	.11	.25
FIQ	.54	<.0005*
BPI-pain severity	.41	<.0005*
BPI-pain interference	.64	<.0005*
PCS	.61	<.0005*
BDI	.36	<.0005*
GAD-7	.27	.006*
SF36 physical function	−.49	<.0005*
SF36 physical role limitations	−.27	.006*
SF36 bodily pain	−.32	.001*
SF36 general health	−.55	<.0005*
SF36 vitality	−.42	<.0005*
SF36 social functioning	−.45	<.0005*
SF36 emotional role limitations	−.32	.001*
SF36 mental health	−.57	<.0005*

Note: Abbreviations: BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; COPS-TR, Turkish Version of Centrality of Pain Scale; FIQ, Fibromyalgia Impact Questionnaire; GAD-7, Generalized Anxiety Disorder 7-item; Min-Max: minimum-maximum; PCS, Pain Catastrophizing Scale; SD, standard deviation; SF36: Short Form-36.
*$P < .05$ accepted as significant.

3.2 | Validity

For the face validity analysis, cognitive debriefing interviews were performed with 20 lay participants. The patients understood all of the questions easily and no further changes were needed. The COPS-TR had moderate-strong correlation with most of the functional and clinical parameters (convergent) and an insignificant correlation with non-clinical parameters (divergent validity; Table 3). The COPS-TR had the strongest correlation with BPI-pain interference scores (rho = 0.64, $P < .0005$) and PCS scores (rho = 0.61, $P < .0005$). The mean COPS-TR scores of female patients was significantly higher than male patients (33.8 ± 7.6 and 28 ± 7.6, respectively, $P = .012$).

Both the floor and ceiling effects were calculated at 1.9% which means that the floor or ceiling effect were not present.

3.3 | Responsiveness

The responsiveness of the COPS-TR was analyzed in 37 patients. The ES and the SRM of the COPS-TR were 1.66 and 1.94, respectively. The ES and the SRM of the PCS were 1.60 and 1.68, respectively (Table 4).

4 | DISCUSSION

The current study shows that the Turkish version of COPS is a valid and reliable instrument to evaluate how pain dominates patients' lives. The items are clear and the scale was filled out in 2 minutes.

Pain beliefs, cognitions, and behaviors are important for the diagnosis and treatment of chronic pain. Better functional outcome and treatment adherence can be ensured by adjusting these concepts.[24] Fibromyalgia patients feel more affected by their illness in their daily lives and have maladaptive coping strategies compared to patients with other rheumatic diseases. Among the coping strategies, catastrophizing is used more, and distancing from pain and ignoring pain sensations are used less by patients with FMS.[25] Taking all of this into account, in FMS it is very important to assess how "central" the pain is and how the patients' lives are affected by pain. The COPS scale aims to evaluate how pain takes over the patients' lives. The overall effect of multiple physical, psychological, and social factors on patients' perceptions of how much pain is dominating their lives is measured by COPS.

The mean score of COPS-TR was 33.1 (range: 10-49) in our study compared with 31.8 (range: 13-49) in the original study, which was performed on patients with chronic non-malignant pain.[6] In another study, conducted on patients with the hepatitis C virus who had

TABLE 4 Responsiveness of COPS-TR and PCS in FMS patients (N = 37)

	Mean change ± SD	ES	SRM
COPS-TR	12.21 ± 6.28	−1.66	−1.94
PCS	13.94 ± 8.29	−1.60	−1.68

Abbreviations: COPS-TR, Turkish Version of Centrality of Pain Scale; ES, effect size;PCS, Pain Catastrophizing Scale; SD, standard deviation; SRM, standardized response mean.

chronic pain, the mean score was 28.8.[7] In this study, the most common pain-related diagnoses were neck or joint pain (77.0%), low back pain (64.2%), and arthritis (59.7%).

COPS-TR has a good reliability with a Cronbach's alpha coefficient of 0.84, which refers to a sufficient internal homogeneity. The Cronbach's alpha value was 0.9 in the original study and 0.943 in a study where psychometric properties were studied in a Chinese population.[6,26] Test–retest reliability was performed with 2-week intervals in our study and was found to be very good (ICC: 0.95), indicating a low random measurement error for scale. Consistent with our findings, the ICC was found to be 0.929 in the Chinese version of COPS.[26]

The COPS-TR has a significant correlation with PCS, FIQ, BPI-SF pain severity and interference scores, BDI, GAD-7 and SF-36, which indicates a good convergent validity. On the other hand, it has no significant correlations with BMI and disease duration, which refers to a divergent validity. Taking these into consideration, COPS-TR has adequate construct validity among patients with FMS. Wang et al studied convergent validity with PCS and a Pain Self-Efficacy Questionnaire (PSEQ); they found moderate correlation with the PCS (r = .57) and the PSEQ (r = −.42).[26] In the original study, COPS was negatively correlated with physical health function (r = −.48), mental health function (r = −.38), quality of life (r = −.35), and provider assessment of pain control.[6] In another study, where psychometric properties were studied, COPS total scores were highly and positively correlated with measures of pain severity (r = .61), pain interference (r = .68), pain catastrophizing (r = .69), depressive symptoms (r = .47), and anxiety symptoms (r = .37).[7] Consistent with these findings, in our study the strongest correlation was with pain interference (r = .64) and pain catastrophizing (r = .61) scores. In addition, we found significant moderate correlation with SF-36 mental health (r = −.57), general health (r = −0.55), physical function (r = −.49), social function (r = −.45), vitality domain scores (r = −.42), pain severity scores (r = .41), and depressive symptoms (r = .36). A strong correlation was also observed with FIQ (r = .54). The FIQ measures the health status of patients with FMS and the COPS assesses how patients were affected by their pain. The strong correlation detected shows that it is a good outcome measure for FMS. Since it has good convergent validity and it has no floor or ceiling effect, it is a valid instrument. Responsiveness is evaluated to define the capacity of the scale to detect the change over time. In our study, the patients who were treated for the first time were evaluated 12 weeks after the treatment in order to assess the responsiveness of COPS-TR. The ES and SRM of the COPS-TR were 1.66 and 1.94, respectively, which suggests high responsiveness. There are a limited number of studies evaluating the psychometric properties of COPS and neither of these studies evaluated the responsiveness of COPS.

To the best of our knowledge, this is the first study in which psychometric properties were studied in fibromyalgia patients and cross-culturally adapted to the Turkish population. The strengths of this study include the use of standardized methods for both translation processes and the evaluation of the psychometric properties of the COPS-TR. We also performed a comprehensive analysis, including pain severity, interference, depressive and anxiety symptoms, quality of life, and how the patients perceived their pain. Furthermore, in addition to reliability and validity, we also evaluated the responsiveness of the COPS-TR. The study has some limitations, the most important being that there were only 14 men, because FMS is more frequent in the female gender.

In conclusion, COPS-TR is a valid and reliable instrument in patients with FMS in the Turkish population. It can be used to evaluate how the lives of patients with FMS are affected by their pain. It may have influence on treatment decisions and follow-up.

CONFLICT OF INTEREST

Both authors declare no conflict of interest to declare.

ETHICAL STANDARDS

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by local Hamidiye ethics committee of University of Health Sciences. The manuscript has 2 authors and each author is responsible for the content and writing of the paper.

INFORMED CONSENT

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

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ORIGINAL ARTICLE

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Intra-articular delivery of umbilical cord-derived mesenchymal stem cells temporarily retard the progression of osteoarthritis in a rat model

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Abstract

Aim: Mesenchymal stem cell (MSC)-based therapy is being explored in treating osteoarthritis (OA). Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) are least reported. In this study, we investigated the effects of single intra-articular injections of hUC-MSCs on a rat OA model.

Method: hUC-MSCs were isolated from the Wharton's jelly of the human umbilical cord and identified. Eighteen Sprague-Dawley rats were used for the OA model. All rats were divided into 3 groups: hyaluronic acid (HA)+MSCs (n = 6), HA (n = 6), and control group (n = 6). One by 10^6 hUC-MSCs in 100 μL HA, 100 μL HA or 100 μL saline were injected into the knee joint 4 weeks post-surgery as a single dose. Cartilage degeneration was evaluated at 6 and 12 weeks after treatment with macroscopic examination, micro-computed tomography analysis, behavioral analysis, and histology.

Results: At 6 weeks, the HA + MSCs group had a significantly better International Cartilage Repair Society score in the femoral condyle compared to the HA and control groups. Histological analysis also showed more proteoglycan and less cartilage loss, with lower modified Mankin score in the HA + MSCs group. However, at 12 weeks there were no significant differences between groups from macroscopic examination

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and histological analysis. Subchondral bone sclerosis of the medial femoral condyle and behavioral tests showed no significant differences between groups at 6 and 12 weeks.

Conclusion: These findings indicate that single injection of hUC-MSCs can have temporary effects on decelerating the progression of cartilage degeneration in OA rats, but may not inhibit OA progression in the long-term.

KEYWORDS

animal study, cartilage regeneration, intra-articular injection, mesenchymal stem cells, osteoarthritis

1 | INTRODUCTION

Osteoarthritis (OA) is a debilitating and highly common chronic musculoskeletal disorder that involves cartilage damage, subchondral bone sclerosis, and osteophyte formation.[1] It is estimated that at least 10% of people over 60 years of age are suffering from OA worldwide.[2] The prevalence of OA is constantly increasing due to the world's aging population. Risk factors for OA include age, gender, ethnicity, trauma, physical activity and occupation.[3,4] Other than these, causes of OA are reported to be a combination of genetic factors, mechanical stresses, including joint structure/alignment, and dedifferentiation of chondrocytes,[5-8] but the exact mechanism is still under debate.[9] Current mainstream treatments for OA include non-pharmacological, pharmacological, and surgical approaches.[10,11] However, all of these interventions can only provide transient relief of symptoms, such as short-term pain relief, but have no effect in stopping or slowing OA progression.

Over the last decade, mesenchymal stem cells (MSCs) have brought new hope as a potential regenerative therapy for treating OA.[12] The rationale for using these cells originally arose from extensive evidence of their applications in tissue regeneration, with the beneficial properties of being easily harvested, isolated and expanded in culture, and potential for multilineage (including chondrogenic and osteogenic) differentiation.[13,14] More importantly, MSCs have unique paracrine functions that can reduce inflammation and induce self-repair at the site of injection due to their secretory products.[15,16] Several preclinical studies have recently demonstrated some favorable effects on cartilage repair when MSCs were injected into OA joints in small animals.[17,18] However, from our previous systematic review on animal studies involving intra-articular injection of MSCs for knee OA, we do not have absolute confidence to recommend the use of MSCs for OA clinical trials based on the current evidence.[19] There is a limited number of high-quality clinical studies on using stem cells to treat OA in patients.[20] We have identified this as a key limitation in the current clinical evidence that gives low confidence in the efficacy of MSC therapy for treating knee OA.[21] Therefore, more animal studies are still required to confirm the effectiveness of different types of MSCs before proceeding to clinical studies.

The majority of animal studies investigating the effects of MSCs applied by intra-articular injection to treat knee OA involved MSCs derived from the bone marrow, adipose tissue, and joint tissues (including synovium, meniscus, and intrapatellar fat pad).[19] Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) are derived from the Wharton's jelly of the umbilical cord, and constitute an alternative MSC source with many advantages over adult cell sources. For instance, hUC-MSCs have greater proliferative capacity, are easy to isolate without being subjected to ethical controversies, and have been applied in both cartilage and bone tissue engineering.[22] The primary purpose of this study is to determine the efficacy of hUC-MSCs when applied for treating knee OA in xenogeneic recipients. We evaluated the therapeutic potential of a single intra-articular injection of hUC-MSCs co-injected with hyaluronic acid (HA), compared to HA alone in a rat OA model.

2 | MATERIALS AND METHODS

2.1 | Isolation and culture of hUC-MSCs

This study was approved by the Ethics Committee of the Institute of Zoology, Chinese Academy of Sciences and Peking University Biomedical Ethics Committee. All procedures involving human participants were conducted in accordance with the ethical standards of the Institute of Zoology, Chinese Academy of Sciences. After prior informed consent, the human umbilical cords were obtained from healthy donors following full-term cesarean section. The hUC-MSCs were isolated from the Wharton's jelly of the human umbilical cord. The cells were cultured in flasks containing Dulbecco's modified Eagle's medium/F12 (DMEM/F12; Hyclone) supplemented with 10% fetal bovine serum (Gemini) at 37°C under 5% CO_2. The culture medium was replaced every 3 days. The hUC-MSCs were passaged at approximately 80%-90% confluence using 0.25% trypsin. Cell proliferation ability was evaluated according to Cell Counting Kit-8 assay.

2.2 | Flow cytometry

The hUC-MSCs were digested from flasks and suspended in phosphate-buffered saline (PBS). The anti-human antibodies CD29,

CD73, CD105, CD34, CD90, CD45, human leukocyte antigen (HLA)-DR and HLA-ABC (BioLegend) were used for flow cytometry according to the manufacturer's instructions. Antibody incubations were conducted on ice for 30 minutes. Then, the hUC-MSCs were washed and resuspended in PBS for flow cytometry.

2.3 | Trilineage differentiation assay

For all differentiation assays, hUC-MSCs were cultured in basal medium for 48 hours before changing to differentiation medium. The hUC-MSCs were then cultured for 2 weeks in differentiation medium, with medium change performed every 3 days. Cells were washed in PBS and fixed before performing the differentiation assay.

For adipogenic differentiation, Fatty Acid-Binding Protein 4 (FABP4) was detected in the differentiated cells using human FABP4/A-FABP antibody (AF3150, R&D Systems) at 3 μg/mL overnight at 4°C. Cells were stained using immunoglobulin G (IgG) secondary antibody (red; HAF007, R&D Systems). For chondrogenic differentiation, aggrecan was detected in the differentiated cells using human aggrecan antibody (AF1220, R&D Systems) and IgG secondary antibody (red; HAF007, R&D Systems). Hoechst 33342 was used to stain the cell nuclei. For osteogenic differentiation, osteocalcin was detected in the differentiated cells using an osteocalcin monoclonal antibody (MAB1419, R&D Systems) at 10 μg/mL for 3 hours at room temperature. Cells were stained using IgG secondary antibody (red; HAF007, R&D Systems).

2.4 | OA animal model

The animal experiment was performed with approval from the Peking University Biomedical Ethics Committee. Eighteen Sprague-Dawley rats (10 weeks old; 180 g) were randomly divided into three groups (n = 6 per group): control group, HA group and HA + MSCs group. Bilateral knee OA was induced by anterior cruciate ligament (ACL) transection and medial meniscectomy. Briefly, the rats were anesthetized, and surgery was performed to transect the ACL. The full thickness of the medial meniscus was cut to induce destabilization of the knee joint (Figure 2B). After surgery, each rat was administrated penicillin once a day for the first 3 days. The control group was injected with 100 μL saline into the articular space. For the HA and HA + MSCs groups, 100 μL HA or hUC-MSCs (1×10^6/knee) in 100 μL HA, respectively were injected into the articular space of both knee joints at 4 weeks after surgery. The duration from surgery to intervention was determined according to a previous report and evidence.[19]

2.5 | Behavioral analysis

Rearing (standing on rear limbs) was counted before the injection, and at 6 and 12 weeks after injection.[17,23] A box (70 × 30×30 cm^3) was placed in a room without noise. The bottom of the box was covered with foam stamp pads. The 4 sides of the box were covered with white paper. The paws of the rats were stained with ink from a foam stamp pad. The rats left footprints on the white paper when they stood on their hind limbs and touched the walls of the box with their forelimbs. To distinguish rearing from incomplete standing actions, the reliable rears were defined as being at a height of at least 5 cm from the bottom. Each rat was left in the box for 10 minutes. The number of rears was manually counted.

2.6 | Micro-computed tomography (μ-CT) analysis

The rats were sacrificed at 6 and 12 weeks after treatment. The intact knee samples were imaged using a μ-CT system (Inveon MM CT, Siemens AG, Munich, Germany). A scanning time of 0.21 seconds with settings of 80 kVp, 500 μA, and 30 calibrations was used. Axial and transaxial fields of view of 30 mm were acquired. Three-dimensional (3D) reconstructions were generated from 2D images by using multimodal 3D visualization software (Inveon Research Workplace, Siemens). For the medial femoral condyle, the region of interest was acquired from subchondral bone. An appropriate threshold was adjusted to define the mineralized bone phase. Bone mineral density (Bone Volume/Total Volume) (BV/TV) was calculated three times for each sample.

2.7 | Macroscopic examination

Following μ-CT analysis, the surface of the distal femur was exposed. Macroscopic evaluation was conducted according to the cartilage repair assessment instrument of the International Cartilage Repair Society (ICRS).[24] The assessment was performed based on macroscopic examination of the cartilage surface, which was scored from 4 to 0 (4: intact smooth surface, 3: fibrillated surface, 2: small, scattered fissures or cracks, 1: several, small or few but large fissures and 0: total degeneration of surface area).

2.8 | Histological analysis

The knee joints were collected and fixed in 4% paraformaldehyde overnight. Decalcification was conducted in 4% ethylenediaminetetraacetic acid for 1 month, with the decalcifying solution changed every 3 days. Decalcified joints were embedded in paraffin. Sections (4 μm) of the medial femoral condyle of the knee joints were stained using hematoxylin and eosin (HE), safranin O and toluidine blue.

2.9 | Modified Mankin score

The severity of cartilage degeneration was assessed using the modified Mankin score[25] based on histological analysis, namely: (a) surface integrity (score 0-10); (b) cellularity (score 0-4); (c) cell clones (score 0-4); and (d) safranin O staining (score 0-5). A higher score indicated a greater level of cartilage degeneration.

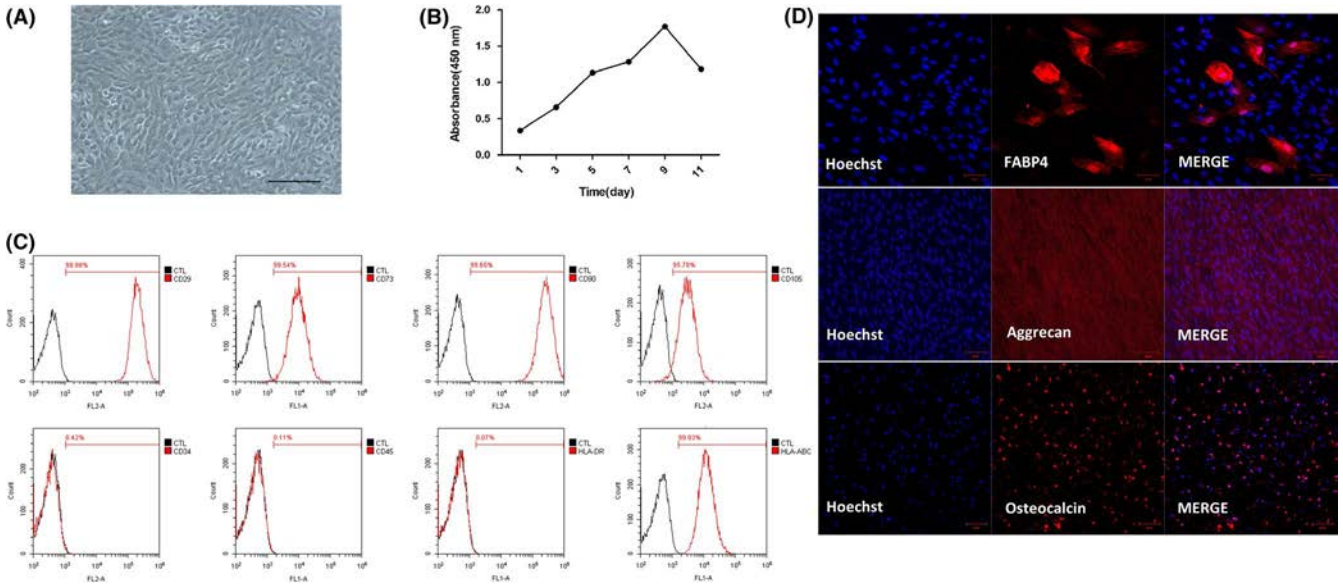

FIGURE 1 Characterization of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs). A, Morphology of cultured hUC-MSCs in passage 4. B, Cell Counting Kit-8 (CCK8) assay was conducted to evaluate the proliferation capability of hUC-MSCs. C, Flow cytometry analysis of CD29, CD73, CD90, CD105, human leukocyte antigen (HLA)-ABC, CD34, CD45 and HLA-DR of hUC-MSCs in passage 4. D, Adipogenic, chondrogenic and osteogenic differentiation of hUC-MSCs

2.10 | Statistical analysis

All data were presented as mean ± standard deviation. Multigroup comparisons of the means were carried out by one-way analysis of variance (ANOVA) test with post hoc contrasts by Student-Newman-Keuls test. $P < .05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Isolation and identification of hUC-MSCs

After initial isolation and expansion, hUC-MSCs with spindle-shaped morphology growing in a monolayer were observed (Figure 1A). Cell proliferation assay confirmed that hUC-MSCs proliferated in the first 7 days following the initial passage (Figure 1B). In addition, hUC-MSCs displayed flow cytometry standard (FCS) positive staining for the MSC surface markers CD90, CD29, CD73, CD105 and HLA-ABC, but were negative for CD45, CD34 and HLA-DR (Figure 1C). Differentiation assays confirmed the trilineage differentiation capacity of hUC-MSCs at 2 weeks (Figure 1D).

3.2 | Macroscopic evaluation of the knee joint

Following intra-articular injection of rat knee joints with HA alone or HA + MSCs, macroscopic observations of the distal femur were compared with the control group at 6 and 12 weeks (Figure 2A). At 6 weeks, the joint surface of the distal femur in the control and HA groups showed marked macroscopic signs of OA progression, including cartilage surface roughness and osteophyte formation, compared to the preserved cartilage surface in the HA + MSC group (Figure 2C). The ICRS macroscopic score for the HA + MSC group was significantly higher than other groups at 6 weeks ($F = 15.83$, $P < .01$; HA + MSCs vs HA: MD = 1.00, 95% CI 0.23-1.77, $P < .05$; HA + MSC vs control: MD = 1.67, 95% CI 0.90-2.44, $P < .01$) (Figure 2D). However, at 12 weeks after treatment, the joint surface showed significant OA progression in all 3 groups (Figure 2E), and the ICRS macroscopic scores showed no significant differences among groups ($F = 3.09$, $P = .08$; HA + MSC vs HA: MD = 0.17, 95% CI −0.77 to 1.09, $P > .05$; HA + MSC vs control: MD = 0.83, 95% CI −0.09 to 1.76, $P > .05$; HA vs control: MD = 0.67, 95% CI −0.26 to 1.59, $P > .05$) (Figure 2F). These findings suggested that a single injection of hUC-MSC was effective in suppressing OA changes during the early stages after treatment.

3.3 | Histological analysis of the medial femoral condyle

Representative histological images of the medial femoral condyle are shown for all groups at 6 and 12 weeks post-treatment (Figure 3). At 6 weeks, the articular cartilage in the control and HA groups showed surface irregularity, loss of cellularity and reduced area of safranin O staining, indicating significant OA changes. In contrast, the medial femoral condyle of the HA + MSC group showed abundant proteoglycan and reduced cartilage loss, and did not display significant features of OA progression (Figure 3A). Furthermore, the modified Mankin score was significantly reduced in the HA + MSC group compared to the control and HA groups ($F = 83.73$, $P < .01$; HA + MSCs vs HA: MD = 4.67, 95% CI 3.45-5.88, $P < .01$; HA + MSCs vs control: MD = 5.67, 95% CI 4.45-6.88, $P < .01$) (Figure 3B).

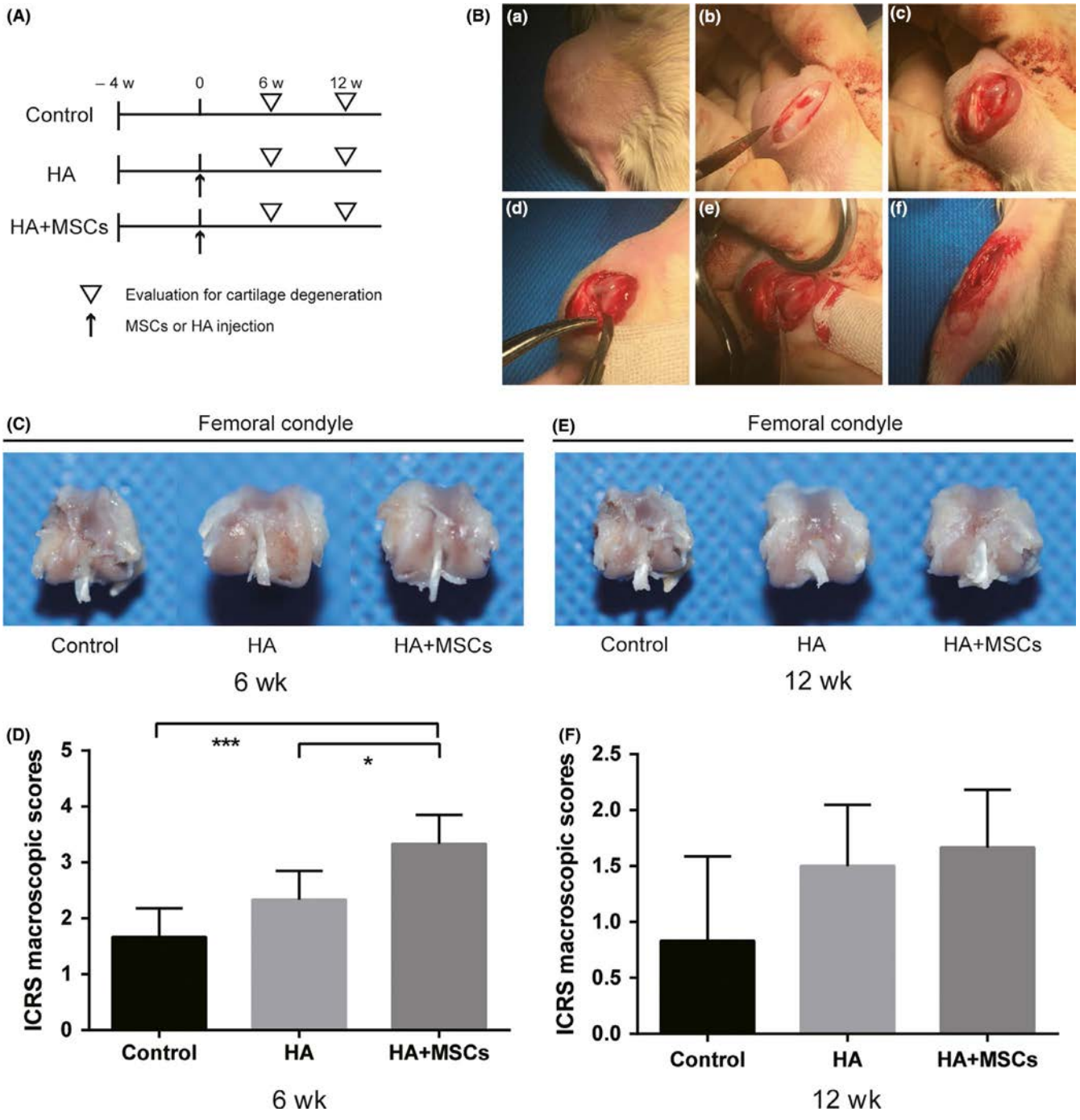

FIGURE 2 Rat osteoarthritis (OA) modeling procedures and macroscopic features in OA model. A, Schematic of the study timeline. B, Surgical procedure for the rat OA model. a, The anterior surface of the hind limb was shaved with an electric clipper, and the skin around the incision area was cleansed with Betadine. b, The skin and fascia on the kneecap region of the hind limb were vertically incised in the midline for a distance of approximately 4 cm. c, The patella was retracted laterally to expose the articular cavity. d, The synovial membrane was excised, and the knee joint was bent to expose the anterior cruciate ligament. e, The anterior cruciate ligaments were transected, and the medial meniscus was completely removed with surgical scissors. f, The patella was relocated back to its original position, and the fascia and skin were closed with sutures. C, Representative macroscopic features of the femoral condyle from 3 specimens at 6 weeks after injection. D, International Cartilage Repair Society (ICRS) macroscopic score for morphology of the femoral condyle (n = 6). E, Representative macroscopic features of the femoral condyle from 3 specimens at 12 weeks after injection. F, ICRS macroscopic score for morphology of the femoral condyle (n = 6). Error bars represent 95% confidence intervals.*P < .05 and ***P < .001. HA, hyaluronic acid; MSCs, mesenchymal stem cells

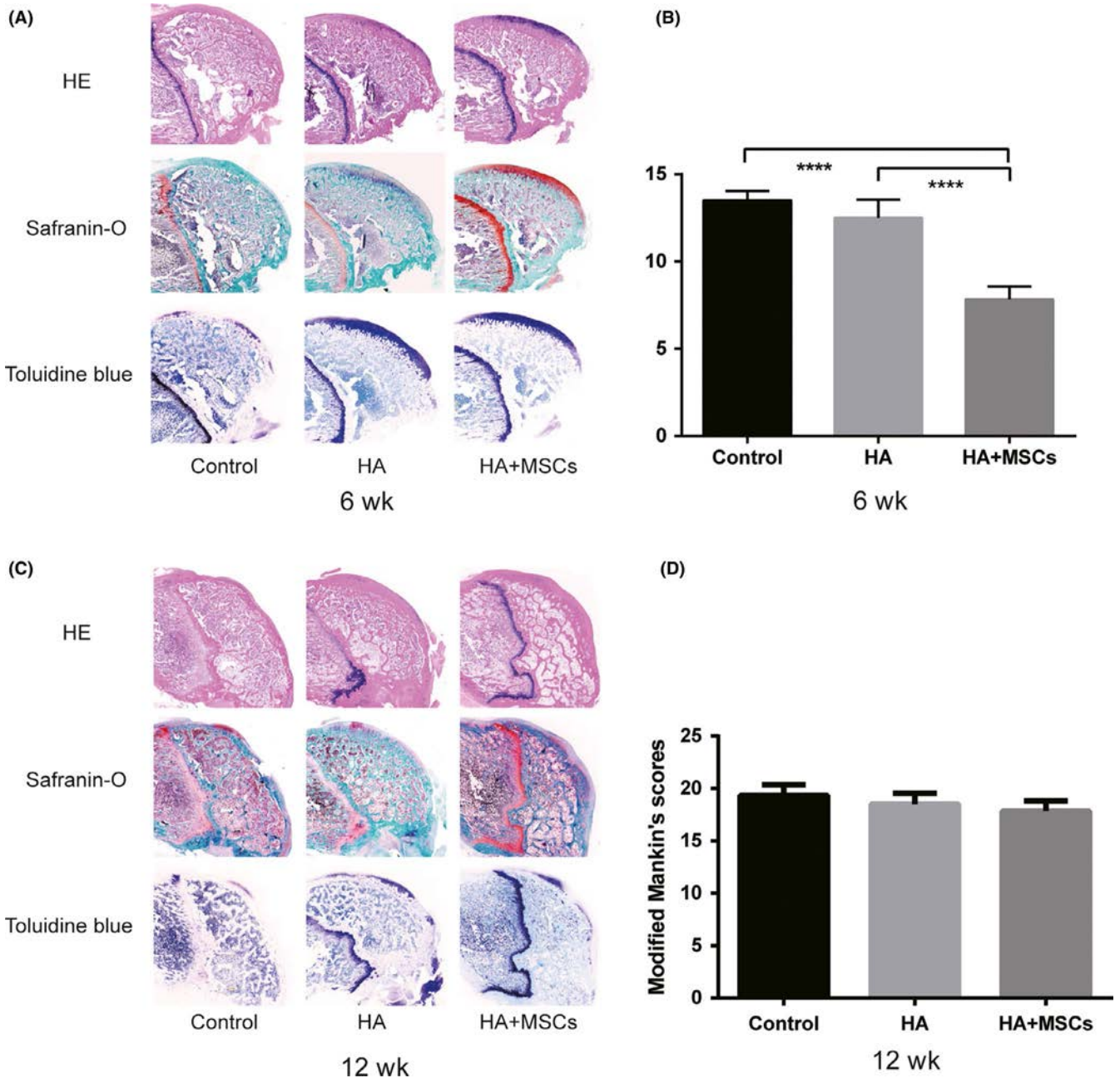

FIGURE 3 Histological analysis of medial femoral condyle of the knee joint. A, Histological images (hematoxylin and eosin [HE], safranin O and toluidine blue staining) of articular cartilage in all groups, and B, their modified Mankin score (n = 6) at 6 weeks after injection. C, Representative features of articular cartilage stained with HE, safranin O and toluidine blue at 12 weeks after injection. D, Modified Mankin score for histology of the articular cartilage (n = 6) at 12 weeks at post-treatment. Error bars represent 95% confidence intervals. ****P < .0001. HA, hyaluronic acid; MSCs, mesenchymal stem cells

At 12 weeks, safranin O staining was significantly reduced in the HA + MSCs group compared to at 6 weeks. Knee joints in all groups showed surface irregularity or cleft, loss of cellularity and tidemark integrity, and no proteoglycan (Figure 3C). Moreover, there was no difference in modified Mankin score among all groups (F = 3.25, P = .07; HA + MSCs vs HA: MD = −0.67, 95% CI −2.20 to 0.87, P> .05; HA + MSCs vs control: MD = −1.50, 95% CI −3.03 to 0.03, P> .05; HA vs control: MD = −0.83, 95% CI −2.37 to 0.70, P> .05) (Figure 3D). This data was consistent with the macroscopic findings and indicated that a single injection of hUC-MSC in HA rather than HA alone was effective in retarding OA histological changes at the early stages of OA induction.

3.4 | μ-CT analysis

Representative μ-CT images of knee samples are shown for all groups at 6 and 12 weeks post-treatment (Figure 4). μ-CT imaging at both 6 and 12 weeks after injection showed radiological osteophyte formation around the knee joint in all groups (Figure 4A,C). Subchondral

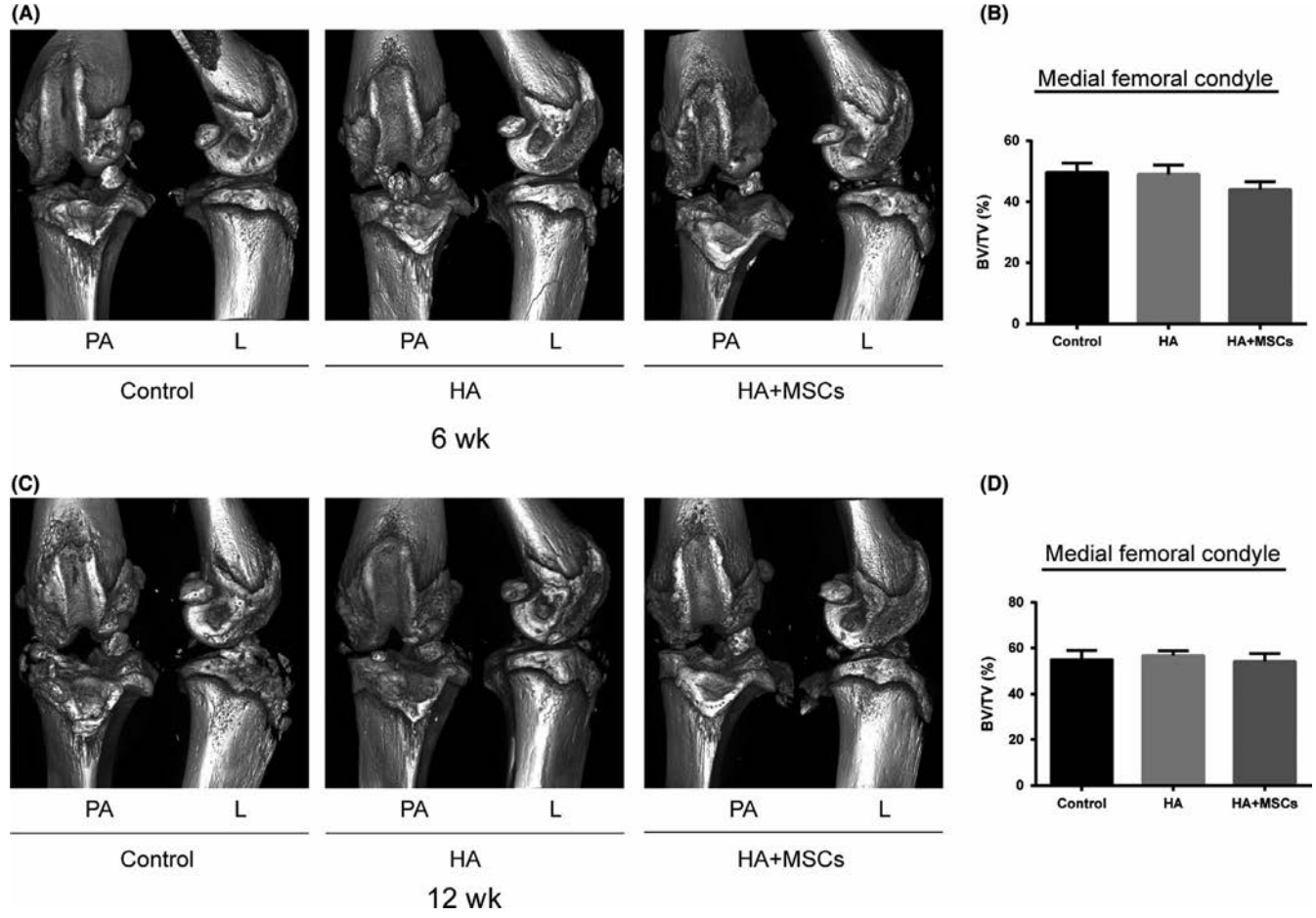

FIGURE 4 Micro-computed tomography (μ-CT) images of the knee and bone mineral density of subchondral bone. A, Post-anterior and lateral views of the knee joint by μ-CT at 6 weeks after injection. PA, post-anterior view. L, lateral view. B, Bone mineral density of subchondral bone of the medial femoral condyle at 6 weeks (n = 6). C, Post-anterior and lateral views of the knee joint by μ-CT at 12 weeks after injection. PA, post-anterior view. L, lateral view. D, Bone mineral density of subchondral bone of the medial femoral condyle at 12 weeks (n = 6). HA, hyaluronic acid; MSCs, mesenchymal stem cells; BV/TV, bone volume/total volume.

bone sclerosis of the medial femoral condyle was quantitatively analyzed. There were no significant differences in bone mineral density among all 3 groups at 6 and 12 weeks (Figure 4B,D).

3.5 | Behavioral analysis

The number of rears performed by animals in the control, HA and HA + MSC groups at 6 and 12 weeks post-treatment, shortly before euthanasia are shown (Figure 5). Rearing in all groups showed a non-significant rise from before injection to 6 weeks after injection. However, the difference in number of rears was not significant between groups at any of the time points or within the same group at different time points.

4 | DISCUSSION

Chronic and irreversible degeneration in OA joints creates significant pain and greatly limits the mobility of patients, leading to substantial reductions in quality of life and also increased risks of mortality due to co-morbidities such as cardiovascular disease.[26] The increasing prevalence of OA worldwide and the lack of effective therapies to stop disease progression has propelled the development of new treatment approaches inspired by regenerative medicine, such as cell and gene therapy. Recently, MSCs have been used in several preclinical studies and early-stage clinical trials to treat OA, with some reporting promising outcomes.[27-29] However, our previous systematic reviews on the current evidence of using intra-articular injections of MSCs to treat knee OA in animal studies and clinical trials showed inconclusive benefits, and indicated low confidence in recommending MSCs as a therapy for OA.[19,21] Further animal studies involving different types of MSCs, such as those derived from different sources or applied in different models of OA, are still necessary before the translation of MSC-based cell therapy should be made. In this study, we validated the efficacy of hUC-MSCs, as a rarely investigated source of MSCs in the OA space, in their ability to ameliorate disease progression following OA induction in a rat model.

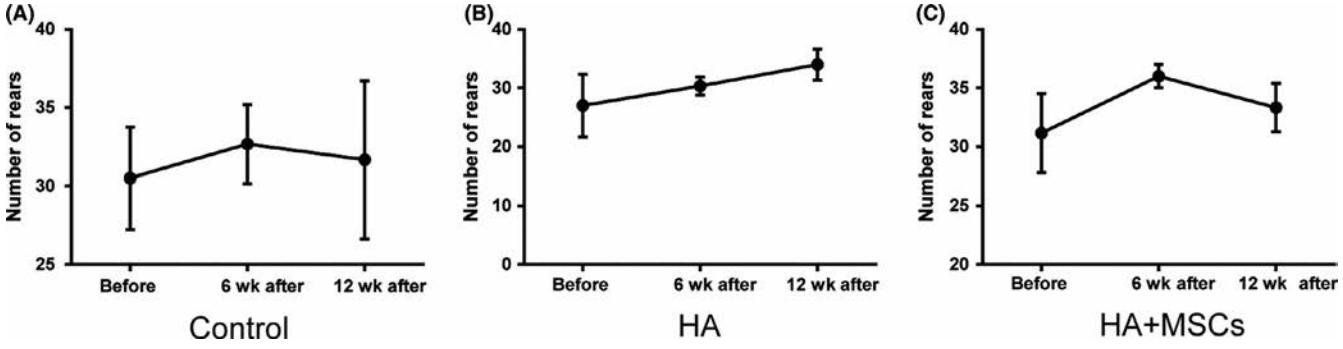

FIGURE 5 Behavioral analysis. The number of rears before, 6 weeks after, and 12 weeks after injection for all groups (n = 6). HA, hyaluronic acid; MSCs, mesenchymal stem cells

At the early stages following OA induction (6 weeks), histological analysis of the HA + MSCs group showed relatively normal cartilage features, with very mild irregularity in the surface layer, normal distribution of cells, appropriate cartilage thickness, and consistent safranin O staining. In comparison, the control and HA groups showed structural disorganization in the cartilage and significant OA progression. These results corroborated the macroscopic findings, and suggested that the hUC-MSCs can exert short-term effects in protecting joint cartilage from degradation during OA progression. However, the differences in the extent of joint pathology between groups at 6 weeks were not reflected in the behavior of the animals.

At later stages following OA induction (12 weeks), no significant differences were noted among groups for any of the outcome measures, with all groups showing a similar extent of cartilage damage, especially in histological evaluation. In particular for the HA + MSC group, the cartilage pathology in the OA joint significantly worsened at 12 weeks compared to at 6 weeks, reaching similar levels as the control and HA groups as reflected by the macroscopic and histological scores. At 12 weeks, the ICRS of all samples in 3 groups were only ranged from 0 to 2. Due to the limited sample size of studies and interindividual variabilities among the groups, the standard deviation may be statistically larger in ICRS score at 12 weeks. Thus, the reliable results for cartilage degeneration mostly depend on the histological evaluation. The inability of hUC-MSCs to achieve long-term cartilage protection during OA progression from a single injection may indicate that repeated injections are necessary to maintain beneficial effects. As reported in some studies, the number of injected MSCs could decrease rapidly following a single dose injection,[30,31] leaving insufficient numbers to counteract the long-term pathological progression of OA. Periodic injections of synovial MSCs can inhibit OA progression more effectively by sustained secretion of paracrine factors when compared with a single injection.[32] In the same study, a single treatment of MSCs only had minimal effects. These studies may provide an explanation for the lack of sustained improvements in cartilage pathology for the HA + MSC group beyond 6 weeks, since a single injection of hUC-MSCs could only have temporary effects due to limited long-term survival of MSCs in the joint following injection. In addition to this, the surviving MSCs may be adversely responding to the diseased joint environment during OA progression due to their unique "environmentally responsive" characteristics,[33] causing them to cease the secretion of beneficial factors and adopt a pro-inflammatory phenotype that reflects the diseased state of the surrounding tissues. This may explain the more significant deterioration in cartilage quality between 6 and 12 weeks for the HA + MSC group when compared to other groups. To clarify these observations, future studies should compare the effects of single and repeated injections of MSCs, as well as the effects of injecting the MSC secretome against direct cell injection.

Although hUC-MSC injection provided short-term improvement of macroscopic and histological appearance in the knee joint following OA induction, these findings were not substantiated by the μ-CT analysis that showed similar radiographic appearances and bone mineral densities in all three groups. One possible explanation is that joint instability following surgical induction may require compensation by bone hyperplasia or osteophytosis. Although the hUC-MSCs could temporarily ameliorate structural changes in the joint tissues following OA induction, they were unable to restore joint stability or lead to biomechanical changes that can be detected by radiographic analysis. As reported, alterations of the subchondral bone are pathological features associated with spontaneous cartilage repair following an acute injury and with articular cartilage repair procedures.[34] In our previous study,[35] a subchondral bone lesion model was developed to confirm that subchondral bone had a protective role with regard to the upper cartilage. Currently, there is a lack of imaging techniques that can directly evaluate subtle changes in subchondral bone microarchitecture during OA progression.[36] Although this study did not show differences in the subchondral bone between groups through μ-CT analysis, future studies utilizing magnetic resonance imaging with high resolution and advanced post-processing algorithms may be able to detect subtle changes in the trabecular bone structure in OA joints.[37] Another possibility is that the loss in cartilage thickness at the medial femoral condyle during OA progression may shift the loading force from the femur to the tibia, or from the whole joint to only the medial part of the joint, causing complex biomechanical changes that were not evaluated in this study but will be of interest to investigate in future studies.

In this study, no significant differences in behavior were found between time points in any of the treatment groups. This is not unexpected, because the number of rears in rats with OA is mainly affected by the decreased proprioception and pain symptoms evoked by knee OA.[23] Injections of hUC-MSCs with HA or HA alone are not likely to have direct effects in reducing pain or improving proprioception. Although MSCs are reported to have anti-inflammatory effects through the secretion of factors that inhibit inflammatory processes in OA joint tissues,[15] pain in OA is caused by a complex combination of mechanisms that may or may not be attributable to structural tissue changes and inflammatory processes.[38] A combination of regenerative therapies such as MSC injection and pharmacological therapies to target pain may be necessary to achieve substantial therapeutic benefits in the treatment of OA. Although several outcomes including macroscopic assessment, histological evaluation, μ-CT and behavioral analysis were investigated in the present study, the results of histological evaluation could be of considerable clinical significance due to our goal which is to restore hyaline cartilage in the clinic.

5 | CONCLUSION

A single injection of hUC-MSCs can have temporary effects that decelerate the progression of cartilage destruction in a rat OA model. hUC-MSCs may be a promising cell source for cell therapy approaches to treat OA, but a single dose may be insufficient to counteract long-term OA progression. Further animal studies are required to investigate multiple administrations of hUC-MSCs or their secretory products before moving to clinical trials.

ETHICS APPROVAL

All animal procedures used in this study were approved by the ethics committee of Peking University People's Hospital.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All of the experimental procedures involving animals were conducted in accordance with Institutional Animal Care guidelines of Peking University People's Hospital, China and approved by the Administration Committee of Experimental Animals of Peking University, Beijing, China.

STATEMENT OF INFORMED CONSENT

There are no human subjects in this article and informed consent is not applicable.

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ORIGINAL ARTICLE

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Altered protein levels in bone marrow lesions of hip osteoarthritis: Analysis by proteomics and multiplex immunoassays

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Abstract

Aim: To assess tissue level changes of proteome and cytokine profiles of subchondral bone in hip osteoarthritis (OA) affected by bone marrow lesions (BMLs). We compared significant protein level differences in osteoarthritic bone with BMLs to control bone without bone marrow lesions.

Methods: Subchondral bone biopsies were taken from femoral heads of end-stage osteoarthritis patients with (BML, n = 21) and without (CON, n = 9) BMLs. Proteins were extracted through a standardized Trizol protocol and used in the subsequent analyses. Angiogenesis and bone markers were assessed using multiplex immunoassays (Luminex). Liquid chromatography tandem mass spectrometry (LC-MS/MS) was performed to detect significant differences in proteome and peptide profiles between BML and CON.

Results: Multiplex immunoassays revealed increased tissue contents of vascular endothelial growth factors (VEGF-A/C/D), endothelin-1, angiopoietin-2 and interleukin-6 (IL-6) in bone with BMLs compared to control bone, whereas osteoprotegerin levels were reduced. Mass spectrometry demonstrated pronounced increase in the levels of hemoglobin (73-fold), serum albumin (30-fold), alpha-1-antitrypsin (9-fold), apolipoprotein A1 (4.7-fold), pre-laminin-A/C (3.7-fold) and collagen-alpha1-XII (3-fold) in BMLs, while aggrecan core protein (ACAN) and hyaluronan and proteoglycan link protein 1 (HAPL1) decreased 37- and 29-fold respectively.

Conclusion: Reduced osteoprotegerin, ACAN and HAPL1 are consistent with osteoclastic activation and high remodeling activity in BMLs. The pronounced increase in angiogenesis markers, hemoglobin and serum albumin support the presence of increased vascularity in subchondral bone affected by BMLs in OA. VEGFs and IL-6 are known nociceptive modulators, and increased levels are in keeping with pain being a clinical feature frequently associated with BMLs.

KEYWORDS
angiogenesis, bone marrow lesions, bone proteomics, multiplex immunoassays, osteoarthritis pain

1 | INTRODUCTION

Substantial challenges in early diagnosis and treatment of osteoarthritis (OA) still prevail. This is partly due to continued dispute regarding the relative roles of bone and cartilage in OA pathogenesis and limitations of diagnostic tools, including relevant imaging modalities (radiography and magnetic resonance imaging [MRI]).[1,2] These limitations have led to the search for new biomarkers, including markers of bone, cartilage and synovial metabolism.[3] Despite evidence of differential expression of a number of genes between early and late OA, there is considerable overlap in the activated biological pathways.[4] Therefore, combined use of several markers seems to be necessary to facilitate early detection and improve the prediction of disease progression.[1]

Significant research activity has centered around identifying different phenotypes of OA and several clinical phenotypes have been described, including chronic pain, inflammatory mechanisms, metabolic disturbances of bone and cartilage local to the joint, metabolic syndrome, mechanical overload, and other phenotypes have been suggested.[5,6] OA affects the change of every articular tissue over time, leading to different clinical phenotypes depending on the most damaged tissue at any given time. When subchondral bone injury is the main event, bone pain due to bone marrow lesions (BMLs) is the prominent manifestation and is expressed as the typical water signal on MRI.[7] Classification based on the underlying disease process in bone, might therefore be valuable to further elucidate OA pathophysiology and to optimize patient selection for treatment.

Using MRI, BMLs have been observed in a wide range of non-inflammatory and degenerative pathologies, prompting the notion that BMLs may represent a universal response to injury.[8] BMLs are seen in up to 80% of symptomatic hip and knee OA patients[9,10] and their association with OA pain and progression is well established, making BMLs an imaging biomarker for OA.[11] This prompted us to look for other, molecular biomarkers of OA progression in BMLs. The purpose of this study was therefore to compare osteoarthritic samples with and without bone marrow lesions with respect to protein levels using shotgun proteomics and the bone and angiogenesis multiplex panels in the Luminex system.

2 | METHODS

2.1 | Study population

The study population consisted of cases (BML) and controls (CON), and the characteristics of the subjects in each group are presented in Table 1. In brief, 30 patients with end-stage primary hip OA were recruited. This study population had a mean age of 64.2 (±9.9) years and met American College of Rheumatology criteria for OA.[12]

Among the 30 patients recruited, nine femoral heads were found to be without BMLs. These participants had a mean age of 62.2 (±12) years and were considered as controls. Comparison of mean age and body mass index between BML and CON revealed no significant differences. The study was approved by the Regional Committees for Medical and Health Research Ethics in south-east Norway (2011/1089/REK). All patients were given oral and written information, and written informed consent was obtained from each of the participant patients, in accordance with the Declaration of Helsinki.

2.2 | Sample preparation

Protein fractions were extracted from pulverized and homogenized subchondral bone biopsies taken out of the femoral heads. The extraction site for the biopsies was determined by visual evaluation of MRI (Figure 1) in coronal and axial planes as described elsewhere.[13] In brief, regions of subchondral bone affected by BMLs were demarcated in pairs of images from each plane prior to excision of the core biopsies. Articular cartilage was removed, and the bone tissue samples were snap-frozen with liquid nitrogen and ground manually using mortar and pestle. For each patient sample, proteins from two samples of 100 mg of homogenized bone were extracted using Trizol (Thermo Fisher Scientific) according to the manufacturer's instructions. Total protein content in each sample was measured using the BCA-assay (BCA Protein Assay kit; Thermo Fisher Scientific).

2.3 | Quantification of cytokines and angiogenesis markers

The levels of dickkopf-related protein 1 (DKK-1), fibroblast growth factor 23 (FGF-23), interleukin-1β (IL-1β), IL-6, insulin, leptin, osteocalcin (OC), osteopontin, (OPN), osteoprotegerin (OPG), sclerostin (SOST),

TABLE 1 Characteristics of the study population

Patients with hip OA	Without BMLs (n = 9)	With BMLs (n = 21)
Age, y	62.1 (±12.1)	65.3 (±9.1)
Female, %	67	52
Body mass index, kg/m^2	27.8 (±5.0)	25.9 (±4.3)

Abbreviations: BMLs, bone marrow lesions; OA, osteoarthritis.

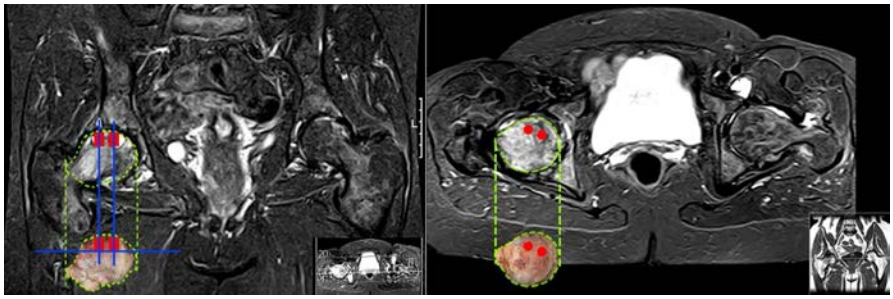


FIGURE 1 Biopsy site. The excision site of the biopsies (red circles) was determined by visual evaluation of MRI in coronal and axial planes. Regions of subchondral bone affected by BMLs were demarcated in three sequential images from each plane prior to excision of the core biopsies

parathyroid hormone (PTH), angiopoietin-2, endoglin, endothelin-1, vascular endothelial growth factor (VEGF)-A, VEGF-C and VEGF-D were quantified using a human bone (HBNMAG-51K) and angiogenesis panel (HAGP1MAG-12K) in the Luminex-200 system (Luminex). Assays were performed according to the manufacturers' instructions.

2.4 | Proteomics by liquid chromatography - tandem mass spectrometry (LC-MS/MS)

2.4.1 | Precipitation

Protein extracts from individual samples in each group, CON and BML, were pooled prior to precipitation with 4 volumes of cold (−20°C) acetone. Next, the samples were centrifuged at 13 000 *g* for 25 minutes, and the protein pellets were dissolved in 250 µL of denaturing buffer (8 mol/L urea in 50 mmol/L tetraethylammonium bromide [TEAB], pH 8.5). Total protein concentrations were measured by a colorimetric protein assay using a microplate absorbance reader (Tecan Austria GmbH). Dilutions of γ-microglobulin (Bio-Rad) were used as standards.

2.4.2 | Digestion

The protein extracts were reduced by adding 25 µL of 100 mmol/L dithiothreitol (DTT) solution to a final concentration of 10 mmol/L, and incubated for 1 hour at 37°C. Alkylations of free sulfhydryl groups were done by adding 22 µL of 250 mmol/L iodoacetamide (IAA) solution to a final concentration of 20 mmol/L, and incubated at 25°C for 45 minutes in the dark. Urea concentration was reduced in the samples by adding 750 µL of 50 mmol/L TEAB (pH 8.5) buffer, prior to digestion. Enzymatic digestion was performed with Lys-C/trypsin for 6 hours at 37°C. The digested samples were dried under nitrogen stream.

2.4.3 | Dimethyl labeling

Protein extracts were dimethyl labeled using isotopomers of formaldehyde (CH_2O) and sodium cyanoborohydride ($NaBH_3CN$).[14] Briefly, digested samples from each group were dissolved in 250 µL of 100 mmol/L TEAB buffer (pH 8.5). One hundred and forty microliters of 4% (v/v) CH_2O (light label) were added to the control group and 140 µL of CD_2O (intermediate label) were added to the stimulated group. Then, 140 µL of 0.6 mol/L $NaBH_3CN$ were added and the samples were incubated under rotation for 1 hour at 22°C. The labeling reaction was quenched by adding 560 µL of 1% (v/v) ammonia solution, mixed, followed by brief centrifugation. Further quenching and acidification were performed by adding 280 µL of 5% formic acid. The labeled samples were then mixed in 1:1 ratio, evaporated and dissolved in 0.1% formic acid before nano-LC-MS/MS analysis.

2.4.4 | Nano-LC-MS/MS

Tryptic digest separation of protein extracts was performed on a PepMap RSLC EASY-Spray C18 column (2 µm, 100 Å, 75 µm × 150 mm) using the EASY-neck 1000 nano ultra-high-performance LC system (ThermoFisher Scientific) connected to an LTQ-Orbitrap XL hybrid MS (Thermo Fisher Scientific) equipped with a nano EASY-Spray source (Thermo Fisher Scientific). The analytical separation was run for 180 minutes using a multi-step gradient of 0.1% formic acid in water as solvent (A), and 0.1% formic acid in acetonitrile as solvent (B). From 0% to 25% eluent B was used in 150 minutes and 25%-60% B in 20 minutes followed by 60% B in 10 minutes at a flow rate of 300 nL/min and a column temperature at 45°C. The mass spectrometer was operated in positive mode with a spray voltage set at 2.0 kV and the heated capillary temperature was kept at 200°C. The LTQ-Orbitrap XL was operated in data-dependent mode in which 1 cycle of experiments consisted of one full-MS survey scan using the Orbitrap mass analyzer and subsequently 5 sequential MS/MS events of the most intense peaks using collision-induced dissociation in the LTQ. The MS survey scans were performed on the high-resolution Orbitrap (R = 30 000) with a m/z range of 350-2000. Precursor ions with charge 1 or unassigned charge were rejected, and the isolation width was set to 3 m/z.

2.4.5 | Data analysis

Raw files were evaluated against a UniProt human database (June 2015) using Sequest HT in Proteome Discoverer 1.4 (Thermo Scientific). Precursor and fragment mass tolerances were set to

10 ppm and 0.6 Da, respectively. Only the peptides resulting from the tryptic cleavages were used, and 2 missed cleavage sites were allowed. Carbamidomethylation of cysteine (+57.021 Da) was selected as a fixed modification. The variable modifications were as follows: +15.995 Da for methionine oxidation, +28.031 for dimethyl (K and N-term) light label and +32.056 for dimethyl (K and N-term) intermediate label. Peptide and protein false discovery rates were set to 1% using default filters. Dimethyl datasets were quantified using peak area with the precursor ions quantifier node integrated in Proteome Discoverer with RT tolerance of isotope pattern multiplets set to 1 minute. To correct for possible experimental bias, protein ratio distribution was normalized on protein median. The cut-off ratio for up- and downregulated proteins was set at ≥2.0 and ≤0.5, respectively. Abundance ratios for proteins reported as differentially expressed in this study were confirmed by manual inspection of the MS spectra intensities of the labeled peptide pairs. Briefly, the criteria for passing the manual inspection were as follows: (a) signal-to-noise ratios of both light and intermediate labeled peptide pairs ≥20; (b) light and intermediate labeled peptide ion spectra must show similar isotope patterns and expected mass shift between doublet clusters. Only unique peptides were considered for protein quantification.

2.5 | Statistics

Patient age, body mass index and Luminex results were compared between BML and CON using one-way analysis of variance followed by Šídák's test for multiple comparisons. Normality was checked using D'Agostino-Pearson omnibus and Shapiro-Wilk tests. Values are presented as mean (SD) unless stated otherwise. In all instances, significance was assigned to $P < .05$.

2.6 | Bioinformatics

In order to find known and predicted functional associations between differentially expressed proteins in the dataset, we used STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins).[15,16] Each set of differentially upregulated/downregulated proteins where uploaded individually using the UniProt accession number, the number of K-clusters was set to 6 and stringency was set to high to correlate detailed biological information from the genes encoding the differentially expressed proteins. Gene Ontology term enrichment analysis was modified with Fisher exact P value ($P = 0$ [perfect enrichment] and $P < .05$ [strongly enriched]) was performed.

3 | RESULTS

3.1 | Cytokines and angiogenesis marker levels

Luminex multiplex immunoassays demonstrated reduced tissue levels of OPG (Figure 2A), and increased levels of IL-6 and the angiogenesis markers VEGF-A, VEGF-C, VEGF-D, endothelin-1 and angiopoietin-2 (Figure 2B), in hips with BMLs compared to those without. No statistically significant differences were found for endoglin, leptin, DKK-1, OPN, SOST, PTH, FGF-23 or insulin between the 2 groups (Figure 2A). For many of the samples within both groups, the values for OC and IL-1β were found to be above and below the upper and lower values of the standard curve ranges of the assay, respectively. Therefore, no meaningful interpretation could be made for these factors.

3.2 | Significant differential changes in BML proteomic profiles

In total, 106 proteins were differentially expressed in BMLs; 23 proteins were significantly ($P < .05$) upregulated while 20 were downregulated in BML compared to CON (Figure 3). Several proteins were markedly upregulated in the BML group, with hemoglobin subunit beta, serum albumin and immunoglobulin G1 (IgG1) chain C region exhibiting the highest upregulation, with 73- and 30- and 12-fold increases, respectively. The remaining upregulated proteins in BML showed fold-changes between 12 and 2. On the other hand, fibromodulin and the cartilage-derived proteins, hyaluronan and proteoglycan link protein 1 (HAPL1) and aggrecan core protein, were downregulated 27-, 29- and 37-fold in BML compared to CON (Figure 3).

Bioinformatic analysis of differentially expressed proteins in BMLs indicated that most upregulated proteins were derived from red blood cells, serum, and plasma (Figure 4D-G). Moreover, upregulated peptides in BMLs had several biological functions. This included immunoglobulin kappa variable 3-20 (IGKV3-20), immunoglobulin kappa constant (IGKC), serine (or cysteine) peptidase inhibitor, clade F, member 1 (SERPINF1), apolipoprotein A-I (APOA1), apolipoprotein A-II (APOA2), transthyretin (TTR) and collagen type VI, alpha 3 (COL6A3) as signal peptides (Figure 4D). Some of the upregulated proteins were membrane components, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), profilin 1 (PFN1), ribosomal protein SA (RPSA), hemoglobin alpha 1 (HBA1) (Figure 4F). Others were associated with extracellular region, that is immunoglobulin lambda constant 2 (IGLC2), immunoglobulin heavy chain (gamma polypeptide 2) (IGHG2) and albumin (Figure 4D). Few of the upregulated proteins were part of the extra cellular matrix (ECM), that is COL6A3, collagen type XII alpha 1 (COL12A1) and SERPINA1 (Figure 4G). Some peptides were significantly ($P < .01$) associated with phagocytosis, proteolysis, receptor-mediated endocytosis (Figure 3E). Downregulated proteins were mainly components of the ECM, including versican, collagen type I alpha 2 chain (COL1A2), clusterin (CLU), azurocidin 1 (AZU1), cathepsin G (CTSG), elastase, neutrophil expressed, heat shock factor binding protein 1 (HSBP1) (Figure 4A), signal peptides such as HSBP1, HtrA serine peptidase 1 (HTRA1), calgranulin A (S100A8) (Figure 4B), regulators of apoptosis, including S100 calcium binding protein A8 (calgranulin A) (S100A8), CLU and HSBP1 (Figure 4B) and participants in epigenetic regulation

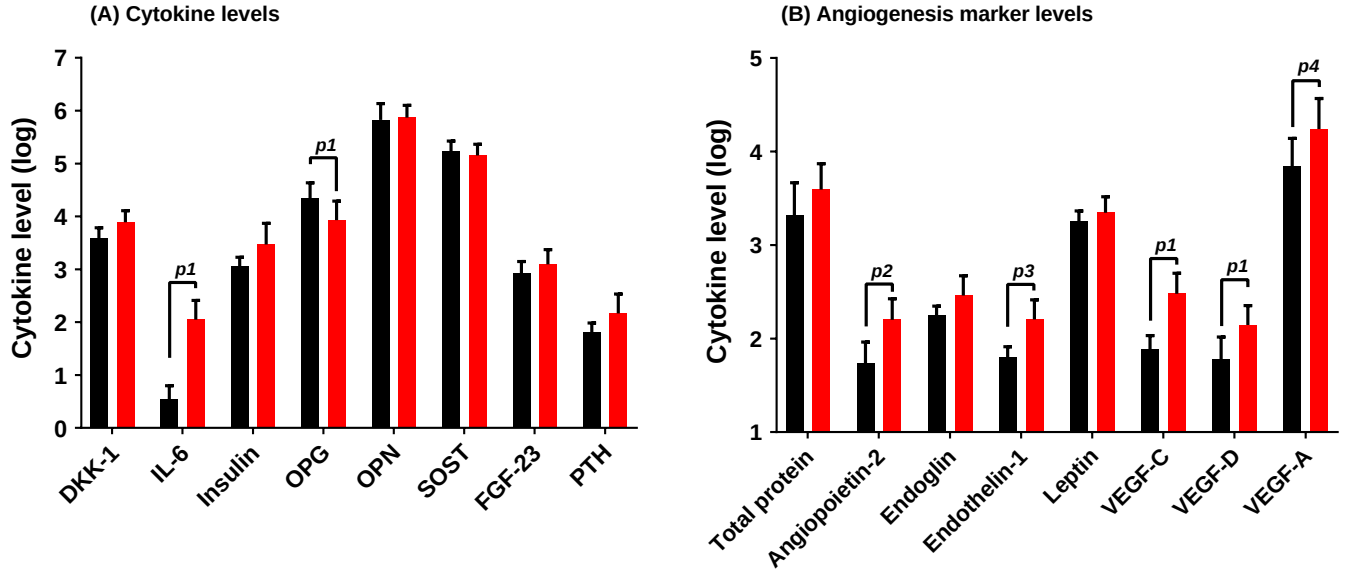


FIGURE 2 Cytokine and angiogenesis marker levels. Biomarker levels are assessed by Luminex in hips with (red) and without (black) BMLs. Total protein is given by logarithmic transformation of µg/mL protein. Cytokine and angiogenesis marker levels are given by logarithmic transformation of pg/mg bone tissue. DKK-1, dickkopf-related protein 1; FGF-23, fibroblast growth factor 23; IL-6, interleukin-6; OPG, osteoprotegerin; OPN, osteopontin; PTH, parathyroid hormone; SOST, sclerostin; VEGF, vascular endothelial growth factor. Multiplicity-adjusted *P*-values: P_1 = <.001, P_2 = .006, P_3 = .007, P_4 = .002

of transcription: histone cluster 1, H1c (HIST1HC), histone cluster 1, H1b (HIST1HB), H3 histone family member 3A (H3F3A) and HSPB1 (Figure 4C). An overview over networks of protein-protein interactions and the biological or cellular processes associated with upregulated and downregulated proteins in this study are listed in Figure 5A,B respectively.

4 | DISCUSSION

Bone plays an essential role in OA pathophysiology and the presence of BMLs in the subchondral bone is associated with pain, disease progression and important disease outcomes such as cartilage loss and joint replacement surgery.[7,17] These outcomes may be a consequence of dysregulated repair mechanisms associated with increased remodeling due to microdamage of subchondral bone tissue with BMLs. Our proteomics and multiplex data demonstrate significant differences in protein levels in hip bone affected by OA and BMLs. These differences indicate a central role for BMLs in the overarching context of OA pathogenesis. Biological pathways for angiogenesis, nociception and cartilage degeneration implicated by our findings are discussed in the two sections below.

4.1 | Markers of angiogenesis and pain

Biomarkers in subchondral bone with osteoarthritic BMLs have not been measured previously. Despite the absence of directly comparable studies, our finding of increased expression of IL-6 in bone tissue with BMLs is in line with previous clinical research indicating its involvement in OA pain[18] and several key elements of OA pathogenesis. IL-6 has been suggested to be as potent as VEGF in inducing vessel-sprouting.[19] The pro-inflammatory role of IL-6 in OA has been demonstrated in animal models, and increased levels have been found in non-calcified joint tissue.[20-22] Serum levels of IL-6 are associated with increased knee BMLs in both women and men with OA.[23] Our results are in line with other studies by demonstrating that levels of IL-6 are also increased in subchondral bone of the affected joints contributing to pathological angiogenesis and pain (Figure 6). IL-6 induces angiogenesis and activation of the Janus-activated kinase—Signal transducer and activator of transcription 3 signaling pathway, which is also activated by VEGF.[19,24,25] IL-6 also induces matrix metalloproteinases, which play a role in ECM degradation.[26,27] In arthritis, IL-6 signaling in sensory neurons plays a role in nociception by increasing inflammatory swelling.[28] Similarly, increased levels of IL-6 are related to pain caused by bone metastasis.[29] Molecular mechanisms related to angiogenesis and pain, therefore, share common pathways, which may exert synergistic effects in arthritis. The role of IL-6 in serum as a biomarker for pain and progression of OA and cartilage loss has been demonstrated.[30,31] However, longitudinal studies are still needed to determine possible correlations between cytokine levels and measures of disease progression or severity. Interactions between the structural changes seen in the advanced states of the disease and the inflammatory response in the subchondral bone also need further investigation.

In the VEGF family, VEGF-A is the most widely studied and targeted isoform in the context of OA pathogenesis. Increased VEGF levels have been observed in osteoblasts from patients undergoing

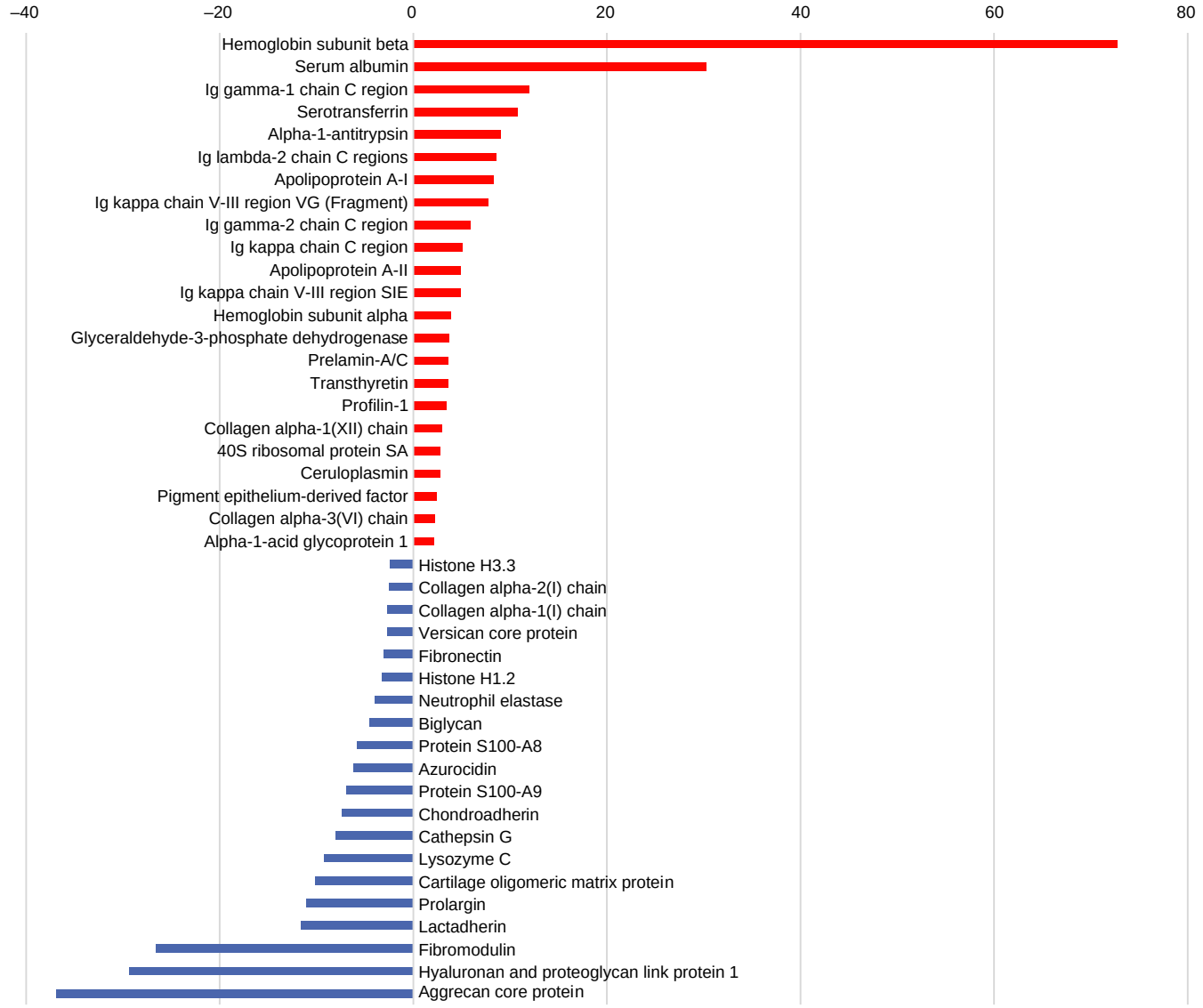


FIGURE 3 Differentially regulated proteins. Protein levels in BML are illustrated as fold-changes compared to CON. Upregulated proteins are represented by the rows in red and the downregulated ones in blue

total hip replacement,[32] cartilage, synovial fluid, serum and meniscus of OA patients.[33] Our observation of increased levels of all major isoforms of the VEGF family is therefore in agreement with previous studies, and supports our earlier findings of increased angiogenesis in BMLs. The proteins and growth factors involved in blood vessel growth, for example angiopoietins and the VEGF family, may contribute to inflammation.[34,35] Delivery of progenitor cells via blood vessels plays a central role in endochondral ossification and perturbation of blood vessel growth, potentially through inflammatory pathways which may lead to structural disease progression. Neovascularization may also be linked to pain, because it is accompanied by the growth of sensory nerves that penetrate non-calcified articular cartilage, osteophytes and the inner regions of menisci[36] The influence of VEGF on pain may occur indirectly from VEGF-mediated stimulation of angiogenesis and sensory neurogenesis or inflammation. Additionally, VEGF may be acting directly on sensory neurons to produce nociceptive sensitization. VEGF, VEGFR1, and VEGFR2 signaling have been directly associated with hyperexcitability of sensory neurons, and inhibition of VEGF signaling led to reduction of pain sensitivity.[33] Therefore, angiogenesis is associated with OA pain and represents a possible therapeutic target.[37] Mice with increased expression of VEGF-C in bone exhibit increased osteoclast number, bone loss, lymphatic vessels in bone and a similar phenotype to Gorham-Stout disease. Individuals with this disease demonstrate massive bone loss associated with a profound angiomatosis of blood/lymphatic vessels in their bones.[38] VEGF-D is closely related to VEGF-C, and both have N- and C-terminal extensions that are not found in other VEGF family members. VEGF-D is a ligand for the tyrosine kinases VEGFR-2 (Flk1) and VEGFR-3 (Ftl4). However, specific biological effects of increased levels of VEGF-D in bone are unknown, and the molecular effects of anti-VEGF antibody targeting nociceptive signaling sensitized by VEGF in OA pain remain to be established.

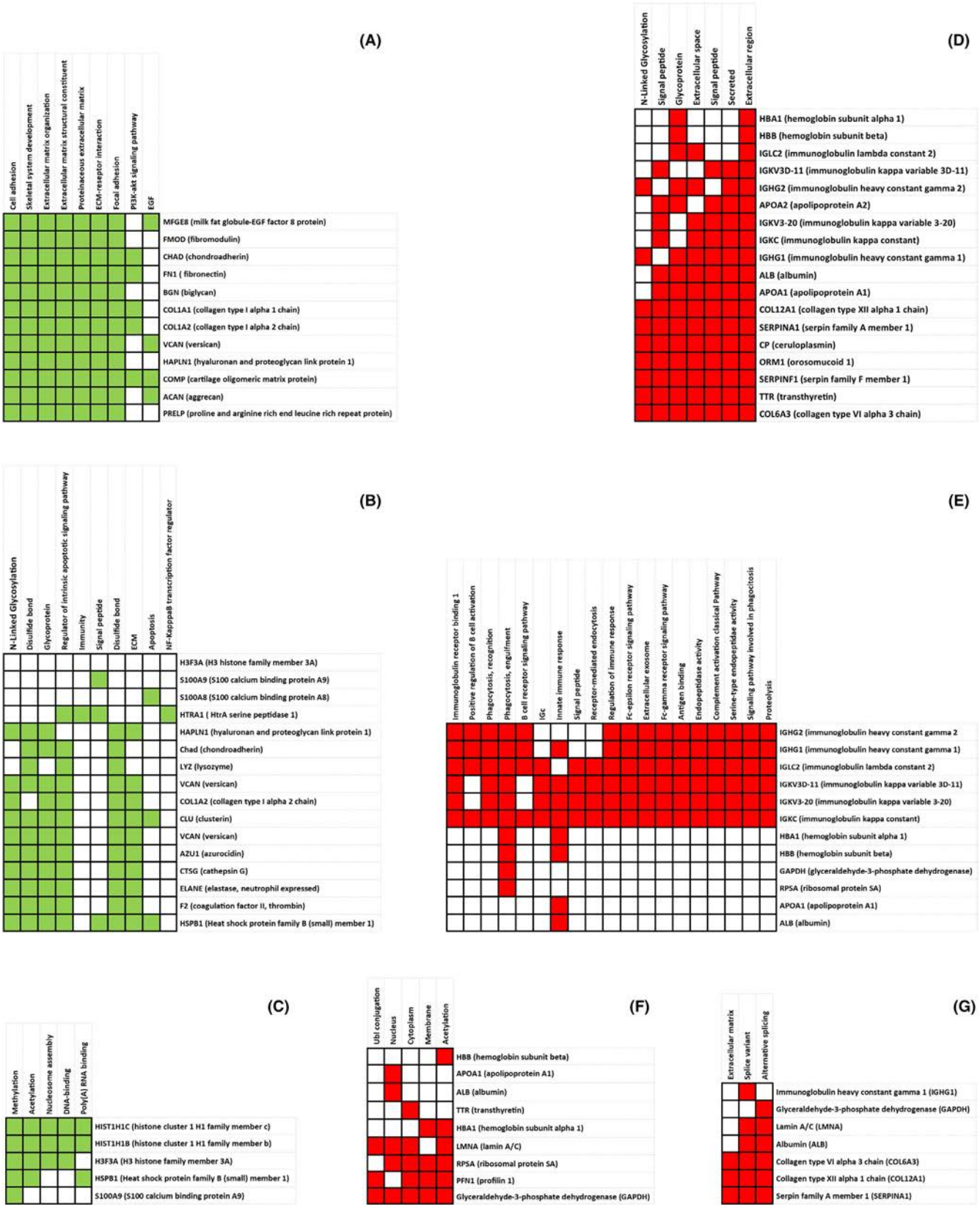
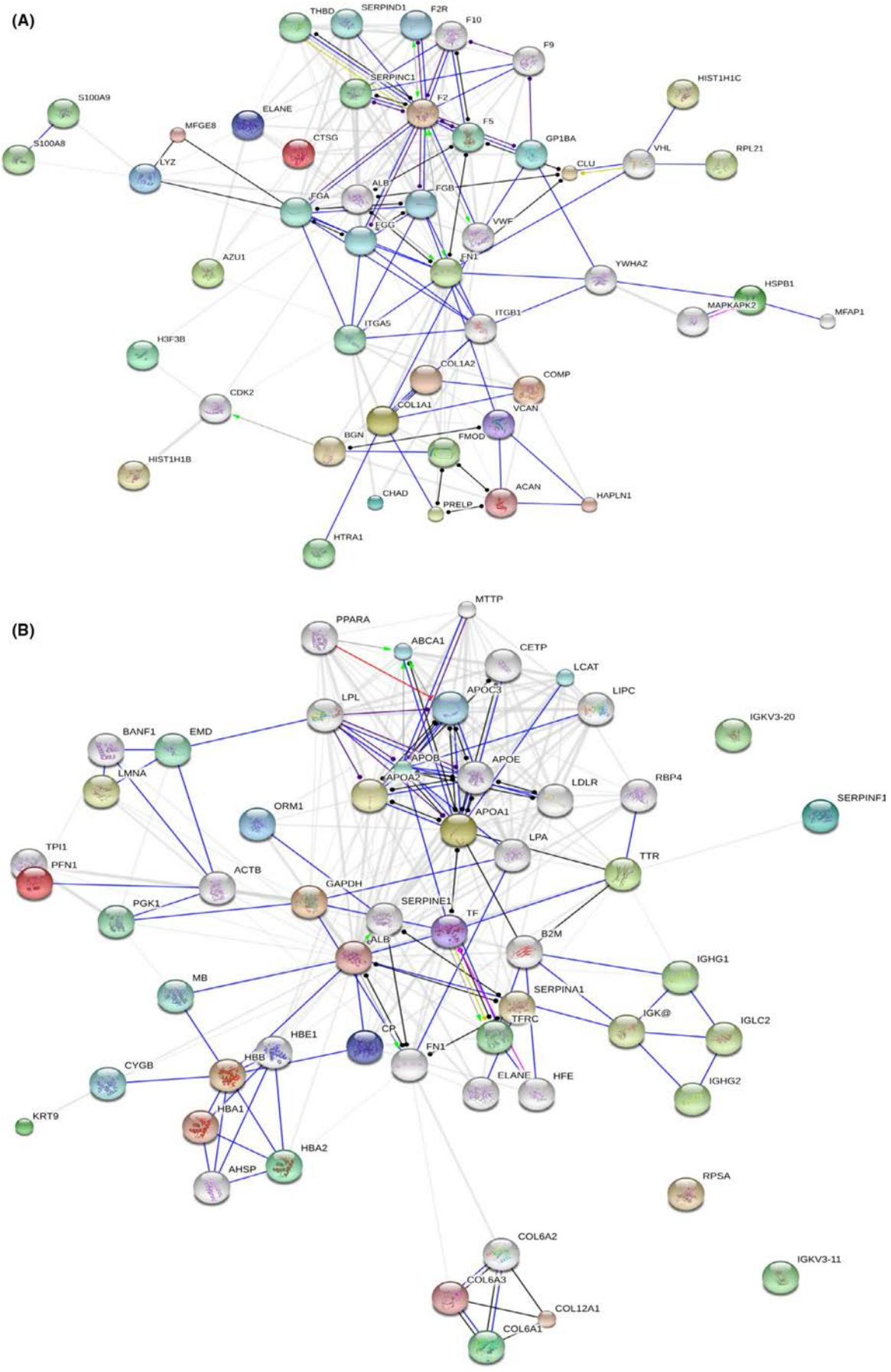


FIGURE 4 Functional annotation clustering of differentially regulated proteins in BML compared to CON. The heat map shows the protein-coding genes and their significant associated annotation term for the upregulated (red) or downregulated (green) proteins. Red/green squares: corresponding gene term association positively reported in the literature. White squares: corresponding gene-term association not reported yet


(A)
THBD
SERPIND1
F2R
F10
F9
SERPINC1
F2
HIST1H1C
S100A9
ELANE
MFGE8
F5
S100A8
CTSG
GP1BA
VHL
RPL21
LYZ
CLU
ALB
FGB
FGA
FGG
VWF
AZU1
FN1
YWHAZ
HSPB1
MAPKAPK2
MFAP1
ITGB1
ITGA5
H3F3B
COL1A2
COMP
CDK2
COL1A1
VCAN
BGN
FMOD
HIST1H1B
ACAN
CHAD
PRELP
HAPLN1
HTRA1
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ABCA1
CETP
LCAT
APOC3
LIPC
LPL
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GAPDH
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ALB
IGHG1
MB
SERPINA1
IGK@
IGLC2
TFRC
HBE1
CP
FN1
CYGB
HBB
ELANE
HFE
IGHG2
KRT9
HBA1
HBA2
AHSP
RPSA
COL6A2
IGKV3-11
COL6A3
COL12A1
COL6A1

FIGURE 5 Protein-protein interaction networks. The network nodes represent the downregulated (A) and upregulated (B) proteins. The edges show protein-protein interactions with predicted functional partners. Blue lines represent known protein-protein interactions from curated databases. Purple lines represent experimentally determined interactions. Green lines represent gene neighborhood, while fading, grey lines represent protein homology. Black lines represent co-expression

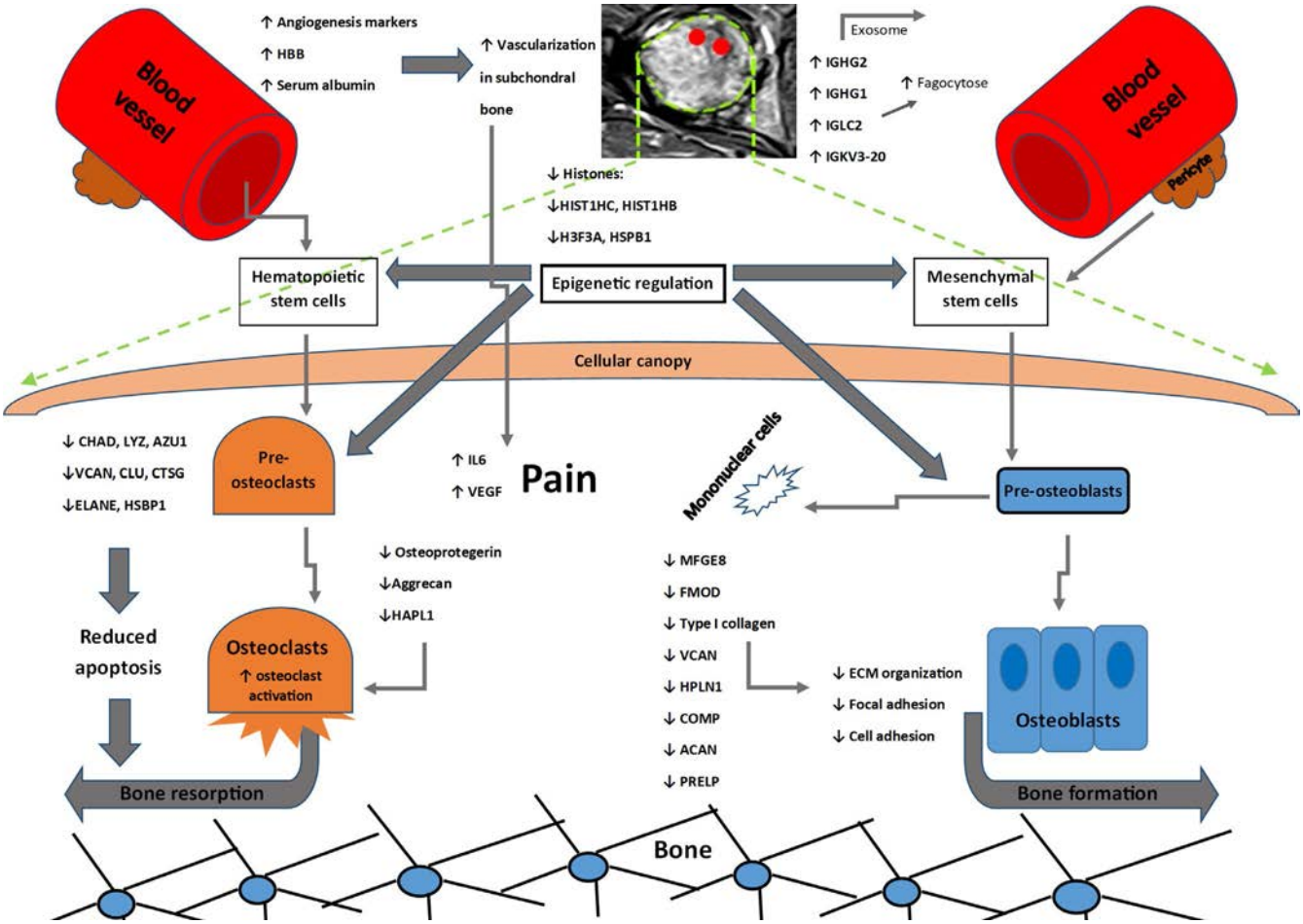

FIGURE 6 The biological role of differentially regulated cytokines and proteins in BMLs. The figure represents an overview of the differentially regulated cytokines and proteins in the biological context of angiogenesis, pain and bone remodeling

4.2 | Markers of extracellular matrix turnover

Previous attempts to identify changes in protein levels associated with OA and BMLs have relied on standard biochemical assays measuring markers of bone, cartilage, and synovium turnover in serum and/or urine,[39,40] without direct measurements of protein levels in bone tissue. These studies have shown increases in serum hyaluronan (HA) (+233%),[40] serum cartilage oligomeric matrix protein (COMP; +16%)[40] and increases in urinary N-terminal telopeptide of collagen I (NTx).[39] However, the observed increase in NTx contradicted the observed decline in other bone turnover markers, including C-terminal collagen crosslinks in both serum and urine and decreased serum osteocalcin, in patients with knee OA.[40] Therefore, direct measurement of the bone protein content as performed in the current study may more accurately reflect tissue level changes of the proteome and underlying molecular mechanisms in bone affected by BMLs.

Detection of some upregulated proteins usually present in blood in high concentrations (hemoglobin, serum albumin, IgG) is consistent with previous findings using immunohistochemical methods where there is a 4-fold increase of vascularity within BML compared to CON bone.[13] IL-6 may also be implicated in the crosstalk between bone and cartilage, as it has been shown that it induces a phenotype in normal osteoblasts similar to what is observed in osteoblasts from sclerotic subchondral bone of OA patients. These osteoblasts downregulated aggrecan but upregulate metalloproteinase expression by chondrocytes in vitro.[41] IL-6 also alters expression of different chemokines, such as regulated and normal T cell expressed and secreted, and monocyte chemoattractant protein-1.[42] Our observations of reduced aggrecan core protein and increased IL-6 levels

in BMLs would be in keeping with BMLs being involved in cartilage degradation.

Our bioinformatics results suggest that many downregulated proteins (collagen I alpha 1 and alpha 2, biglycan, aggrecan core protein, COMP, chondroadherin [CHAD]) probably reflect the loss of bone extracellular matrix. We observed for instance a 10-fold decrease of COMP in the BML compared to CON bone samples. COMP plays a role in the structural integrity of cartilage via its interaction with other extracellular matrix proteins such as collagens and fibronectin. This interaction of chondrocytes with the extracellular matrix of cartilage is mediated through interaction with cell surface integrin receptors.[43] Downregulation of COMP in BMLs may play a role in the pathogenesis of OA as COMP is a potent suppressor of apoptosis in primary chondrocytes by blocking the activation of caspase-3 and by inducing the Inhibitor of Apoptosis family of proteins. Previous studies show increased serum COMP in OA and indicate increased cartilage turnover, potentially leading to the elimination of cartilage matrix proteins through the increased vascularity. CHAD promotes attachment of chondrocytes, fibroblasts, and osteoblasts. CHAD-deficient mice show altered cartilage biomechanical properties[44] and bone turnover,[45] indicating its potential role in OA.

Collagen I was also decreased in bone with BMLs, while collagen type XII was increased. Type XII interacts with type I collagen-containing fibrils via the COL1 domain and may be associated with the surface of the fibrils, and the COL2 and NC3 domains may be localized in the perifibrillar matrix. These finding are in agreement with increased bone resorption as reflected in elevated urinary NTx levels.[39] The decrease in cartilage-associated proteins[46] is consistent with the previous reports[40] where loss of proteins controlling HA levels in cartilage and bone is a possible mechanism underlying the increase in serum HA.

Endochondral bone formation as a response to microdamage in subchondral bone has been suggested to be associated with OA initiation and progression.[47] Proteins primarily associated with cartilage may have shared functions in bone. The cartilage-associated protein HAPL1, for instance, stabilizes aggregates of aggrecan and HA, giving cartilage its tensile strength and elasticity. Mutations in HAPL1 of developing mice resulted in defects in cartilage development and delayed bone formation.[48] The observed downregulation of HAPL1 and other proteins shared by cartilage and bone matrix in the current investigation may therefore reflect altered cartilage properties and pathological endochondral bone formation. Enhanced angiogenesis, as observed histologically in advanced hip OA[13] may contribute to the observed reduction in ECM-derived proteins and promote alterations of the mechanical properties of the newly formed bone.

Small leucine-rich proteoglycans (SLRP) like biglycan and fibromodulin are essential in ECM turnover. They interact with collagen fibrils and limit the access of the collagenases to their cleavage sites. SLRP have been shown to be involved in OA pathogenesis, with the evidence mostly coming from knockout mouse models.[49] Biglycan deficiency increases osteoclast differentiation and activity due to defective osteoblasts[50] and fibromodulin affects the rate of fibril formation in collagen fibrillogenesis.[51] Our observation of a pronounced downregulation of fibromodulin and biglycan supports increased collagenase activity in BMLs, and is also in agreement with the histological observation of increased bone turnover[13] suggesting altered ECM composition. Peptides or proteins that are associated with programmed cell death, for example CLU (clusterin), that interact with APOA1 and PON1 were also downregulated.[52,53]

Monitoring or targeting SLRPs may offer new prognostic or therapeutic modalities for OA.[49] Downregulation of histones (HIST1HC, HIST1HB, H3F3A and HSPB1) indicate a perturbation in epigenetic regulation of transcription. Nucleosomes are the basic units of chromatin and are connected to one another by linker DNA which are bound by H1. These histone variants play significant roles in modulating the chromatin architecture, thereby influencing important biological processes. Serine peptidase 1 (HTRA1) is a highly conserved family of serine proteases found downregulated in many pathologies by epigenetic mechanisms.[54] It is also known that the loss of HTRA1 function in cells causes increased rates of proliferation, delayed onset of senescence, centrosome amplification, and polyploidy that suggest HTRA1 implication in regulation of the cell cycle.[55]

It is a strength of this study that bone samples from the same hips were previously characterized using immunohistochemistry and bone histomorphometry and compared to results from the present study. The correlation between results of the different analysis methods may add to the validity and reliability of the findings from the current study. Another strength of this study is the tissue level analysis of the subchondral bone compared to previous studies which were based on serum, urine or soft tissue samples. However, this study also has several shortcomings. It would have been advantageous to include samples from less severe stages of OA. Another limitation is the inability to compare the levels of proteins detected using Luminex to the proteins detected by the proteomic analysis.

5 | CONCLUSION

Our results support the notion that BMLs in advanced OA cause pronounced alternations in the proteome and cytokine profile of the subchondral bone. The alterations in protein levels in BMLs demonstrated in the present study may partly explain the association between the repair response to biomechanical injury in subchondral bone, progression of cartilage loss and the development of OA pain. Further research is required to verify these findings and to explore the temporal and spatial relation between the reported changes and the progression of osteoarthritis in the affected joint.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

MS and EFE made substantial contributions to the conception and design of this study. MS, YRS and MP conducted the experiments. MS, YRS, ML, MP, TCP analyzed and interpreted the data, and drafted the manuscript. JER and EFE participated in the interpretation of the data and coordination of the study. All the co-authors were involved in drafting the manuscript or revising it critically for important intellectual content and all approved the submitted and final versions.

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ORIGINAL ARTICLE

Comparison of safety, efficacy and cost between oral pulse cyclophosphamide versus intravenous cyclophosphamide pulse therapy in severe systemic lupus erythematosus

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Abstract

Objectives: The aim of this study is to compare efficacy, toxicity and cost between oral and intravenous cyclophosphamide (CYC) pulse therapy in inducing remission (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] <3) in severe SLE.

Methods: We retrospectively checked the hospital records of patients between the years 2000 and 2018, who had been administered oral cyclophosphamide pulse and intravenous (IV) cyclophosphamide pulse. SLEDAI at baseline and after 6 months of therapy were noted. The statistical analysis was done using Mann-Whitney *U* test. The cost was also calculated.

Results: We included 45 patients in this study, 21 in the oral pulse group and 24 in the IV group. The median age of patients in the oral and IV groups were 29 (interquartile range [IQR] 22-37) and 26 (IQR 19.25-0.75) years respectively. Median SLEDAI at baseline was comparable between the 2 groups (oral 18.0 [IQR 15.0-26.0]; IV 14.5 [IQR 11.0-20.0] $P = .151$). At the end of 6 months of treatment, it was 0.0 (IQR 0.0-4.0) in the oral group, as against 2.0 (IQR 0.0-5.5) in IV group ($P = .676$). There was no major adverse event in either group. Oral cyclophosphamide pulse therapy was more economical as compared to IV cyclophosphamide [630 Indian National rupees(INR)/ 8.85 US dollars(USD) in the IV arm and 50 INR/0.7 USD in the oral arm] ($P < .001$).

Conclusion: This study concludes that oral cyclophosphamide pulse therapy is an economical option and there was no difference in efficacy and safety between oral cyclophosphamide pulse therapy and IV pulse cyclophosphamide therapy.

KEYWORDS

oral cyclophosphamide, pulse, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease.1 The spectrum of presentation varies from minor skin manifestation to life-threatening disease.2 Among the manifestations, renal and central nervous system involvement are major causes of morbidity and mortality. Renal involvement is a major complication, occurring in approximately 50% of patients.2 Patients with nephritis are at higher risk for progressive renal insufficiency.3 There is over 3 decades of clinical experience with cyclophosphamide (CYC)

in severe SLE including proliferative nephritis.4 There is unequivocal evidence that the drug modifies the long-term course of the disease in lupus nephritis.5,6

Cyclophosphamide, in combination with glucocorticoids, is used for induction and maintenance of remission in severe lupus nephritis.7 The National Institute of Health protocol till recently was considered the standard treatment and for developing nations it is still economical compared to other options like mycophenolate. It consists of intravenous (IV) CYC (0.5-1.0 g/m^2, adjusted to white blood cell nadir), given monthly for the first 6 months, followed by quarterly for 24 months.8 CYC is an alkylating agent that substitutes alkyl radicals into other molecules. It was originally developed for oral administration. It is rapidly absorbed by the gut, and has a bioavailability of 75%.9 Daily oral CYC therapy has also been used in antineutrophil cytoplasmic antibody vasculitis, lupus nephritis and giant cell arteritis.10-12 However, previous studies suggest that intravenous pulse CYC regimens are safer and provide less cumulative CYC exposure than daily oral regimens.11,12

Although daily oral regimens have been in use, there is not much data on the efficacy of pulse oral CYC. Pulse oral CYC therapy is used widely in oncology practice, but there is sparse data on its use in the setting of autoimmune diseases.13 Oral pulse CYC can be useful in situations where the patient cannot be fluid-overloaded or when repeated hospital admissions are difficult. Also, in a cost-constrained set up as in South Asia, oral CYC is economical. IV therapy also involves additional costs related to short hospitalization, nursing and physician services, IV fluids and canula, in addition to risk of hospital-acquired infections through the IV route. In this study, we attempted to study the safety, efficacy and compare the costs of pulse oral CYC vs pulse intravenous CYC in severe SLE. Severe SLE was defined as those cases of lupus with major organ involvement or requiring hospitalization.

2 | AIMS AND OBJECTIVES

- To compare oral CYC pulse with IV CYC pulse in achieving induction remission (SLE Disease Activity Index [SLEDAI] <3) in severe SLE.
- To study the adverse events of oral CYC pulse as compared to IV CYC pulse.

3 | MATERIALS AND METHODS

We retrospectively reviewed hospital case sheets and electronic medical records of patients with SLE fulfilling American College of Rheumatology 1997/ Systemic Lupus International Collaborating Clinics criteria who were administered pulse oral CYC for induction therapy between 2000 and 2018 at our tertiary care teaching hospital in southern India. All the patients on IV and oral CYC during this period were included continuously and they were already randomly age- and gender-matched. The baseline variables between the 2 groups did not statistically differ. Efficacy was defined as attainment of SLEDAI of <3 at the end of treatment with 6 doses of monthly pulse CYC.14 SLEDAI was retrospectively entered from prospectively documented clinical data from the patient charts.

TABLE 1 Baseline characteristics

Baseline variables	IV group (N = 24) n (%)	Oral group (N = 21) n (%)
Clinical variables		
Photosensitivity	12 (50)	4 (19.04)
Fever	13 (54.16)	11 (52.3)
Myalgia	1 (4.1)	1 (4.7)
Skin rash	11 (45.8)	13 (61.9)
Oral ulcers	14 (58.3)	11 (52.3)
Hypertension	5 (20.83)	8 (38.09)
Arthritis arthralgia	14 (58.3)	13 (61.9)
Serositis	4 (16.6)	4 (19.04)
NPSLE	5 (20.8)	5 (23.8)
Laboratory variables		
Proteinuria[a]	18 (75)	20 (93.3)
Nephrotic[b]	12 (50)	3 (14.2)
Hematuria[c]	12 (50)	14 (66.7)
Hematological (AIHA, leucopenia/ thrombocytopenia)	12 (50)	18 (85.7)
APS	7 (29)	6 (28.5)
Low C3	20 (83)	20 (95.2)
Elevated dsDNA	18 (75)	20 (95.2)
Lupus nephritis	21	20
Class II	3	0
Class III	2	2
Class IV	8	15
Class V	4	1
Not biopsied	4	2

Abbreviations: AIHA, autoimmune hemolytic anemia; APS, antiphospholipid syndrome; dsDNA, double-stranded DNA; IV, intravenous; NPSLE, neuropsychiatric systemic lupus erythematosus.
[a]24-h urinary protein more than 500 mg.
[b]24-h urinary protein more than 3 g.
[c]Urine microscopy ≥5 red blood cells.

3.1 | Drug administration protocol

Oral pulse CYC was administered at a dose of 15 mg/kg/body weight split into 3 divided doses over 3 consecutive days, once every 4 weeks. For example, a patient with 60 kg body weight requiring 900 mg of CYC was given 300 mg on day 1, day 2 and day 3 every 4 weeks for 6 months. These patients had been instructed to self-administer the treatment in a domiciliary basis and were advised regarding self-monitoring of blood counts, hydration (at least

TABLE 2 Indication for cyclophosphamide

Indication	Intravenous cyclophosphamide (N = 24)	Oral cyclophosphamide (N = 21)
Lupus nephritis and NPSLE	21	18
Vasculitis	2	1
Isolated NPSLE	1	1
Skin	0	1 (Rowell syndrome)

Abbreviation: NPSLE, neuropsychiatric systemic lupus erythematosus.

2-3 L/d) and other precautions especially regarding symptoms related to infection. Patients in the IV pulse CYC arm also received the same dose, but as a single dose as per standard recommendation in our hospital setting. Before administration of each pulse, the blood counts (hemoglobin, total and differential counts, platelet count), serum creatinine and urine routine examination were monitored. Ondansetron tablets of strength 4-8 mg thrice a day (as per body weight) from day 1 to day 5 were prescribed in both arms to prevent vomiting.

MESNA (2-mercaptoethane sulfonate sodium) was not used in either of the arms. Patients were informed about the possibility of hemorrhagic cystitis and appropriate monitoring by a physician for the same was advised in case the adverse event happened.

All patients received corticosteroids and hydroxychloroquine as per the standard recommendations.

Patient data including the details of symptoms, laboratory results and SLEDAI score were retrieved from the hospital records noted at baseline and 1 month after the last induction dose. Statistical analysis was done using SPSS software (version 17.0). The comparisons of median values were done using Mann-Whitney *U* test.

4 | RESULTS

4.1 | Demographics

There were 45 patients, 24 in the IV pulse arm and 21 in the oral pulse arm. The median age of patients in the oral and IV groups were 29 (interquartile range [IQR] 22-37) and 26 (IQR 19.25-30.75) years, respectively. The female: male ratios were 23:1 and 19:2 in the IV CYC group and oral CYC group respectively. The median duration of the disease was 12 (IQR 5.75-33.00) months and 24 (IQR 10-72) months in the IV and oral CYC groups respectively. The baseline variables in both groups are shown in Table 1.

The commonest indication for CYC in either of the groups was lupus nephritis (Table 2). In the IV CYC group, 2 patients had Class III lupus nephritis, 8 patients had Class IV, and 4 patients had Class V. In the oral CYC group, 2 patients had Class III lupus nephritis, 15 patients had Class IV, and 1 patient had Class V. Biopsy was not feasible

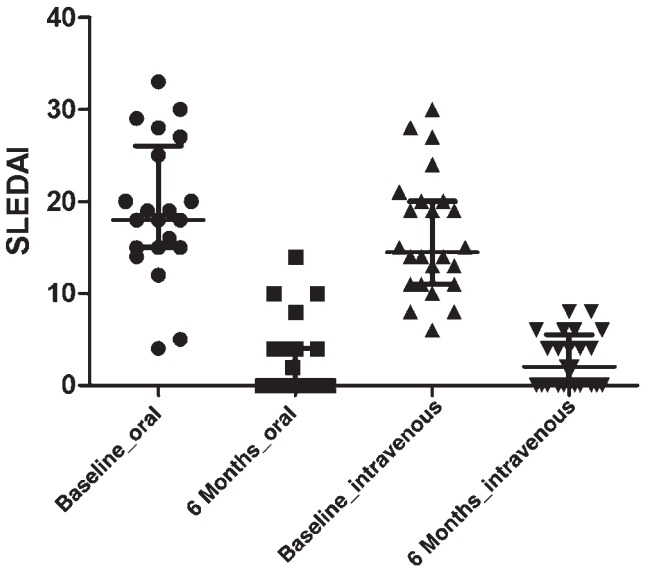

FIGURE 1 Comparison of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score between the oral and intravenous cyclophosphamide groups at baseline and after 6 mo of pulse therapy

in 4 patients in the IV group and 2 patients in the oral group. Of the 5 NPSLE (neuropsychiatric SLE) patients in the oral pulse CYC subset, 1 each had subarachnoid hemorrhage, cerebral infarction with left-sided hemiparesis, cortical venous thrombosis, generalized tonic-clonic seizure and the fifth one had psychiatric symptoms prior to pulse therapy. Of the 5 patients of NPSLE in the IV pulse subset, 1 each had psychiatric manifestations, mononeuritis multiplex and generalized tonic-clonic seizure. One patient in each group had vasculitis with digital gangrene. All except 1 patient completed the

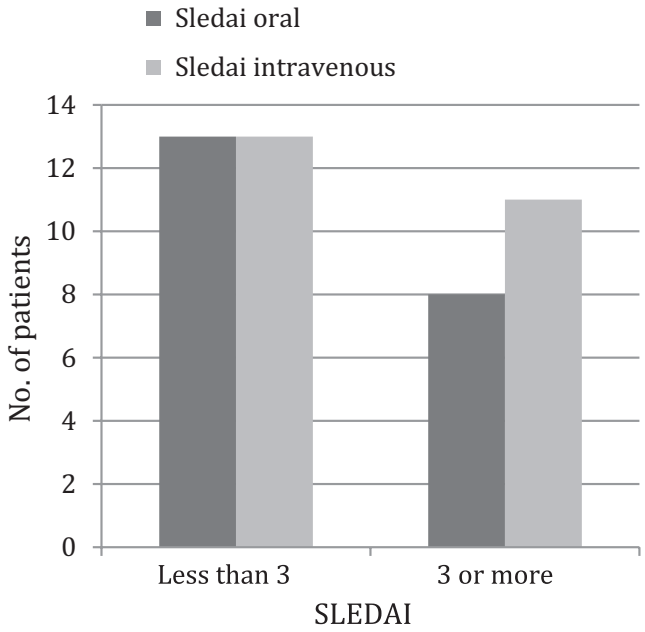

FIGURE 2 Number of patients with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) <3

TABLE 3 Cost projection for oral and IV CYC administration

	IV CYC (750 mg)	Oral CYC (750 mg)
Direct costs		
• Drug cost • IV set, Insyte, 3-way with extension, saline	130 INR (1.83 USD) 500 INR (7 USD)	50 INR (0.7 USD) NIL
Total INR	630 INR (8.85 USD)	50 INR (0.7 USD)

Abbreviations: CYC, cyclophosphamide; INR, Indian national rupees; IV, intravenous; USD, US dollars.

TABLE 4 Adverse events

Adverse events	IV group	Oral group
Total	5	2
Cutaneous fungal infection	1	0
Gastroenteritis	0	1
Lower respiratory infection	2	1
Urinary tract infection	2	0
Death	0	0

treatment course. One patient had resistant disease and received mycophenolate along with oral CYC pulse who subsequently developed skin infections and hence CYC had to be discontinued.

4.2 | Dose of immunosuppressants

The cumulative doses of CYC were 4488.6 ± 888.6 mg in the oral group and 4581 ± 1157.4 mg in the IV group. The cumulative dose of prednisolone (prednisolone equivalent dose of deflazacort) in the oral group was 6014 ± 2567 mg and it was 5615 ± 1465 mg in the IV CYC group (P = .532).

4.3 | Disease activity

SLEDAI were calculated at baseline and 1 month after 6 pulses of CYC. Median SLEDAI at baseline was comparable between the 2 groups (oral 18 [IQR 15-26]; IV 14.5 [IQR 11-20], P = .151). At the end of 6 months of treatment, it was 0.0 (IQR 0.0-4.0) in the oral group, as against 2.0 (IQR 0.0-5.5) in IV group (P = .676) (Figure 1). The median change in the SLEDAI between baseline and 6 months in the oral arm and IV arm were 16 (IQR 11.5-22.5) and 13.5 (IQR 7.25,-19.75) (P = .264). At the end of treatment, 8 patients in the oral group and 11 patients in the IV group had a SLEDAI of ≥3 (Figure 2).

4.4 | Costs

The direct costs of the patients in the IV and oral groups were calculated. The 6-month actual expenditure in the oral group for each patient was 630 Indian national rupees (INR) or 8.85 USD in the IV arm and 50 INR (0.7 USD) in the oral arm (P < .001). Being a retrospective study, the indirect costs could not be calculated. However, since IV administration implies hospitalization, oral CYC is obviously economical. The detailed projected costs as per the current state of both regimens can be calculated as in Table 3.

4.5 | Adverse events

The adverse events are mentioned in the Table 4. The adverse events were retrospectively noted from prospectively entered data. Both the groups did not have any major infection requiring hospitalization or parenteral antibiotics. In the IV group, there were 5 minor infections. These included 1 diffuse cutaneous fungal infection, 2 urinary tract infections and 2 lower respiratory infections; all of them were treated with oral antimicrobials without discontinuation of treatment. In the oral group, there were 2 minor infections; 1 had acute diarrheal disease, which was treated with antibiotics delaying the next dose of oral cyclophosphamide by a month. Another patient had a lower respiratory tract infection, which was again treated with oral antibiotics without discontinuation of oral pulse CYC.

5 | DISCUSSION

In this study we observed that pulse oral CYC had efficacy comparable to pulse IV CYC. The treatment was well tolerated. The choice of treatment option was made after discussion with the patients, keeping patient convenience, accessibility to health care, financial aspects and availability of local resources in mind. In addition, oral pulse therapy obviated the need for hospitalization, IV cannulation, related costs and complications. Minor infections were seen, but that did not affect the normal schedule of taking the oral pulse CYC. No patient developed major infection or cytopenias. Since the dose administered staggered over 3 consecutive days in the oral pulse regimen, chances of bladder toxicity were likely to be low; in fact, we did not observe any case of hemorrhagic cystitis in any of our cases. No patient had any major gastrointestinal side effects despite the oral administration. Furthermore, oral pulse CYC regimen has the advantage of being less costly in terms of the formulation itself and the associated costs of hospitalization incurred in the IV pulse regimen was also saved in the oral pulse group. Convenience of being at

home and self-administration of oral medication at home also cuts inconvenience of the hospital environment, travel time and related cost.

Hence our study shows that oral pulse CYC is a safe, convenient and economic therapeutic option in management of severe SLE with efficacy comparable to that of IV pulse CYC. To our knowledge, this is the first report related to efficacy, safety and economy of pulse oral CYC therapy in treatment of any systemic autoimmune disease.

Limitations of this study include single-center retrospective design of the study without a control arm with a small sample size. The compliance was assessed retrospectively by the medical records, but no formal pill count was feasible. Larger randomized controlled trials may generate stronger evidence and substantiate our findings.

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CONFLICT OF INTEREST

Nil.

AUTHOR CONTRIBUTIONS

Research and Study design: Conceptualised by Dr Danda; Research and study design by:Dr Shivraj, Dr Suvrat, Dr Ajit, Dr Vishad, Dr Danda. Data collection & analysis: Dr Shivraj, Dr Suvrat, Dr Ajit, Dr Vishad, Dr Danda. Interpretation and conclusion: Dr Shivraj, Dr Suvrat, Dr Danda. Preparation of Manuscript: Dr Shivraj, Dr Suvrat, Dr Danda. Review of Manuscript: Dr Shivraj, Dr Suvrat, Dr Ajit, Dr Vishad, Dr Danda. Guide and critical revision: Dr Danda. Administration: Dr Shivraj, Dr Suvrat, Dr Ajit, Dr Danda. Technical Support: Dr Shivraj, Dr Suvrat, Dr Danda.

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ORIGINAL ARTICLE

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Selection and perception of methotrexate treatment information in people with rheumatoid arthritis

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Abstract

Objective: To determine beliefs about methotrexate (MTX) in patients with rheumatoid arthritis (RA) in relation to utilized information sources.

Methods: RA patients, who were current participants in the Australian national biologic registry, completed an online questionnaire regarding their use and views about MTX (N = 1010). Participants who used MTX were asked about which MTX information sources they consulted, and whether positive or negative views were obtained. The Beliefs about Medicine Questionnaire (BMQ), was used to measure patient beliefs about MTX.

Results: The survey response rate was 804/1010 (80%). MTX survey data were analyzed for 742 RA participants (mean age 59 years, 76% female, mean disease duration 19 years) who had used MTX, with 494/742 (67%) reporting current use. Participants consulted multiple information sources (median 3, interquartile range 1-5). Rheumatologists (98%), general practitioners (GPs) (55%), internet searches (39%), educational websites (38%), and pharmacists (37%) were the most common information sources utilized. Positive MTX information was most often obtained from rheumatologists (92%), GPs (66%), and educational websites (56%). Negative information was most often obtained from relatives, social media, internet chat rooms and friends. Information from rheumatologists was the most influential on favorable BMQ MTX-specific scores, whereas information from educational websites also affirmed the need for MTX.

Conclusion: RA patients have significant concerns regarding MTX and consult a variety of sources for MTX information. However, the patient perception of this information varies widely. Rheumatologists and educational websites are the most important information sources in terms of a positive influence on the patient's perception of MTX.

KEYWORDS
drug treatment rheumatoid arthritis, methotrexate in rheumatoid arthritis, methotrexate treatment, treatment opinion

1 | INTRODUCTION

Uncontrolled rheumatoid arthritis (RA) activity results in significant morbidity, and increased mortality. Early initiation of treatment with a disease-modifying anti-rheumatic drug (DMARD), either as monotherapy or in combination, can prevent permanent joint damage. Methotrexate (MTX) is currently used as a first-line DMARD and remains the backbone of therapy. It has been demonstrated to reduce morbidity and mortality in this disease.[1] The low doses of MTX used for the treatment of RA have an established safety profile, hence, both the European League Against Rheumatism[2] and the American College of Rheumatology[3] recommend early initiation and optimizing treatment with MTX for RA. In Australia, MTX is commonly prescribed as the initial DMARD for the management of RA.[4]

However, fear of potential adverse effects may limit its use. Although serious adverse events including pancytopenia,[5] hepatotoxicity[6] and deaths have been reported with low-dose MTX (<30 mg weekly)[7] used to treat RA, it is generally considered safe if used and monitored as recommended.[6]

Qualitative studies have shown that patients seek available information from written, social media, and verbal sources to help with decisions regarding treatment.[8-10] The use of MTX for treatment of inflammatory disorders has generated negative publicity.[11,12] These misconceptions relate to documentation of misuse[13,14] or myths[15] obtained from other sources. Deaths due to MTX in Australia were commonly a result of dosing errors despite implementation of safety initiatives.[16]

We undertook this study to determine the range of information sources utilized by RA patients seeking information on MTX treatment, and whether this information was perceived to be positive or negative. We also sought to determine if this information influenced patient beliefs regarding MTX.

2 | METHODS

2.1 | Study participants

The Australian Rheumatology Association Database (ARAD) is a national Australian database, established in 2001, which collects longitudinal health information from individuals with RA, psoriatic arthritis, juvenile arthritis and ankylosing spondylitis.[17] It was originally set up to determine the long-term outcomes of biologic therapy. Participants can be referred to ARAD by rheumatologists or self-refer. Enrolled participants in ARAD complete self-administered surveys at 6-12-monthly intervals and provide information on their health status, arthritis treatments, function and quality of life. Each participant provides informed consent to be part of ARAD.[17]

Data for the current survey was collected using an online self-reported survey questionnaire, Survey Monkey (https://www.surveymonkey.com). A web link was emailed to patients with RA registered with ARAD who had completed an online ARAD questionnaire in the past 12 months.

2.2 | Survey data

The survey included:

1. MTX: patients were asked the question "Are you on methotrexate?" and were instructed to select 1 out of the following 4 options: "I am currently taking methotrexate", "I used to take methotrexate but it was stopped", "I was offered methotrexate but I declined" and "I was not offered methotrexate by my doctor". If MTX was suggested and the patient declined, then the reason for refusal was requested. Patients who had never used MTX were not asked any further MTX-specific questions.
2. The Beliefs about Medicine Questionnaire (BMQ),[18] which consists of MTX-specific questions, as well as questions about medicines in general. Two scores are derived from the MTX-specific questions, which assess a patient's beliefs about the necessity of MTX for controlling their disease (MTX necessity), and concern regarding adverse events (MTX concerns). Similarly, 2 scores are derived from the questions about medicine in general which indicate more generalized concerns about overuse (general medicine overuse) and harms (general medicine harm). Responses are measured using 5-point Likert scales, ranging from 1 strongly disagree to 5 strongly agree. Scores obtained for individual items within each scale are averaged. Thus, BMQ scores range from 1 to 5, with higher scores indicating stronger beliefs toward the need for the medicine
3. Sources of information: patients were asked where they sought advice and information regarding MTX, and how this advice was perceived. Sources of information could include healthcare practitioners (rheumatologist, general practitioner [GP], pharmacist), relatives, friends, other patients, and the internet (searches, social media, forums or patient educational websites such as the Australian Rheumatology Association and Arthritis Australia). Response categories were: not asked, strongly negative, negative, positive and strongly positive.

The following data were extracted for respondents from the most recently completed ARAD questionnaire (or baseline where relevant): gender, current age, and education level categorized as high school or less (secondary education) and university, vocational diploma, or certificate (tertiary education), RA medications, comorbidities, disability as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI); and quality of life as measured by Arthritis Condition Visual Analog Scale (Arthritis Condition VAS) and Pain VAS.

2.3 | Study procedure

An email explaining the study with a link to the survey was sent by ARAD staff to 1010 ARAD RA participants who met the inclusion criteria on 10 October, 2017. A reminder was sent to those who did not respond 2 weeks after the initial email and the survey link was closed 4 weeks after the initial email (10 November, 2017).

Australian Rheumatology Association Database has ethics approval from Monash University and other sites including Central Adelaide Local Health Network. Permission for this ARAD substudy was approved by the ARAD Steering Committee to conduct the survey. This study obtained ethics approval from both Cabrini Institute and Central Adelaide Local Health Network Human Research Ethics Committee with approval number HREC/17/TQEH/139.

2.4 | Statistical analysis

Analyses were performed in Stata v15.1 (StataCorp LLC). Univariate comparisons between survey responders/non-responders and MTX users/non-users were performed using Chi-square tests for categorical variables and *t* tests for continuous variables. Analysis of covariates for the number of information sources consulted was performed by multivariable Poisson regression. The self-reported influence of each information source on a patient's medication beliefs about MTX (MTX-specific BMQ) scores was examined by a seemingly unrelated regression model,[19] which allows for correlation between the error terms for regression models of different, but related, outcomes. Briefly, linear models were estimated for both MTX-specific BMQ necessity and concerns scores as outcome variables, with the responses for each information source included as multivariable predictors.[20] For this analysis, the results for each information source predictor variable were coded from −2 (strongly negative) to +2 (strongly positive) with 0 representing "not asked".

3 | RESULTS

3.1 | Study participants

The study flow chart is depicted in Figure 1. Eight hundred and four responded to the survey (response rate 79.6%). Survey responders were older (mean [SD] age 60 vs 56 years, $P = .001$), and more likely to be on biologic treatment (65% vs 53%, $P = .002$) compared to non-responders, but were otherwise comparable for other demographic, education, disease, and treatment variables including current MTX use (data not shown).

Of the 804 survey responders, 48 (6%) reported never using MTX, there was insufficient survey information from a further 14 for analysis, and therefore 742 patients were included in the analysis. Participant characteristics are summarized in Table 1. The mean age was 59 years, 76% were female, 75% were rheumatoid factor positive, and the mean disease duration was 19 years.

3.2 | MTX use

Of the 48 participants who had never used MTX, 14 had declined MTX treatment, and fear of potential adverse effects was the most

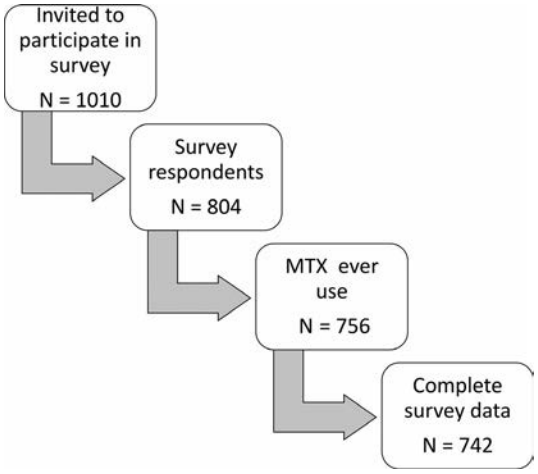

FIGURE 1 Study flow chart

common reason for this decision. Of those who reported having been exposed to MTX, a third had used it previously (248/742, 33%) and two-thirds were currently taking MTX (494/742, 67%). Those who previously used MTX (n = 248) reported feeling generally ill (n = 149), and specific adverse events included gastrointestinal (n = 27), hepatic (n = 26), pulmonary (n = 12), hematologic (n = 5), and severe mouth ulcers (n = 3). Just over half reported ceasing MTX due to adverse effects (n = 126, 51%), and MTX was withdrawn in almost a third of participants (77/248, 31%) because the treatment approach was changed, while a minority (n = 5) ceased due to planning pregnancy. Some participants (32/248, 13%) ceased MTX due to lack of improvement and perceived negative information. "My symptoms were not so severe. Also, I wasn't keen after the pharmacist told me about the possible side effects." Or negative experience. "Side effects from taking it. My call and not the specialist." "Because it destroys my immune system".

Comparisons between MTX current users (n = 494) and prior users (n = 248) are summarized in Table 2.

3.3 | MTX information sources

Most patients sought information on MTX from multiple sources. The median (interquartile range) number of sources consulted was 3 (1-5) (Figure 2A). Variables associated ($P < .05$) with seeking information from a greater number of sources were younger age, tertiary education, higher BMQ-specific MTX concerns and higher BMQ general medicine harms scores (Figure 2B).

The tabulations of responses by information source are summarized in Figure 3A. As anticipated, rheumatologists were the most frequent source of MTX information (98%), and just over a quarter of respondents (192/742, 26%) reported this as their only source of information. The next most common sources of MTX information were GPs (55%), internet searches (39%), educational websites such as Australian Rheumatology Association and Arthritis Australia (38%) and their pharmacist (37%), while less frequent sources were internet chat rooms (18%), friends (17%), relatives (16%) and social media (14%).

TABLE 1 Study participant characteristics (N = 742)

Measure	Summary
Age, y, mean (SD)	59 (11)
Age at diagnosis, y, mean (SD)	41 (14)
Disease duration, y, mean (SD)	19 (11)
ARAD duration, y, mean (SD)	7 (4)
Arthritis condition, VAS 0-100, mean (SD)	7.1 (4.0)
Pain, VAS 0-100, mean (SD)	38 (26)
HAQ, mean (SD)	0.77 (0.73)
Female, n (%)	562/742 (76)
Rheumatoid factor, n (%)	426/558 (75)
Anti-CCP, n (%)	63/106 (59)
Ever smoker, n (%)	320/718 (45)
Highest education level, n (%)	
High school or less	181/742 (24)
University, vocational diploma/certificate	451/742 (61)
Current medications, n (%)	
MTX	494/742 (67)
Other DMARDs	251/742 (34)
Biologics	485/742 (65)
NSAIDs	306/742 (41)
Prednisolone	239/742 (32)
Opioids	210/742 (28)

Abbreviations: Anti-CCP, anticyclic citrullinated peptide; ARAD, Australian Rheumatology Association Database; DMARDs, disease-modifying anti-rheumatic drugs; HAQ, Health Assessment Questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; VAS, visual analog scale.

TABLE 2 Univariate comparisons between current and previous users of MTX

Measure	MTX current	MTX prior	*P* value
N	494	248	
Age, mean (SD)	59.7 (11.3)	58.4 (11.3)	.13
Age at diagnosis, mean (SD)	41.6 (13.8)	40 (13.6)	.12
Females, n (%)	377/494 (76)	185/248 (75)	.61
Education, n (%)			
High school or less	198/494 (40)	93/248 (38)	.50
University, diploma/certificate	296/494 (60)	155/248 (63)	
Disease duration, mean (SD)	18.5 (11.1)	18.8 (11.5)	.75
ARAD duration, y, mean (SD)	7.1 (4.0)	7.1 (4.0)	.98
Arthritis condition, VAS 0-100, mean (SD)	32.8 (26.4)	37.7 (25.3)	.014
Pain, VAS 0-100, mean (SD)	37.1 (26.6)	41.0 (25.5)	.055
HAQ, mean (SD)	0.7 (0.7)	0.9 (0.7)	.015
Other medications, n (%)			
Other DMARDs	175/494 (35)	76/248 (31)	.19
Biologics	321/494 (65)	164/248 (66)	.76
NSAIDs	199/494 (40)	107/248 (43)	.56
Prednisolone	155/494 (31)	84/248 (34)	.49
Opioids	130/494 (26)	80/248 (32)	.09
BMQ: MTX necessity, mean (SD)	3.5 (0.7)	1.5 (0.7)	<.001
BMQ: MTX concerns, mean (SD)	2.5 (0.8)	2.6 (0.9)	.037
BMQ: general harms, mean (SD)	2.1 (0.6)	2.2 (0.6)	.62
BMQ: general overuse, mean (SD)	2.6 (0.9)	2.7 (0.9)	.19

Abbreviations: ARAD, Australian Rheumatology Association Database; BMQ, Beliefs about Medicine Questionnaire; DMARDs, disease-modifying anti-rheumatic drugs; HAQ, Health Assessment Questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; VAS, visual analog scale.

Most participants reported mainly positive MTX information from rheumatologists (671/726, 92%), GPs (269/405, 66%) and educational websites (157/278, 56%), while just under half reported receiving most positive information from pharmacists (128/272, 47%) (Figure 3B). Although accessed less frequently, participants perceived mostly negative MTX information from relatives (75/122, 61%), social media (64/106, 60%), internet chat rooms (74/125, 59%) and friends (65/124, 52%).

Multivariable analysis of all information sources as predictors of the 2 BMQ MTX-specific scales (Figure 4) revealed that information from rheumatologists appeared to be the most influential for both the patient's perception of the necessity of MTX treatment (BMQ MTX necessity), and alleviation of concerns of adverse events (BMQ MTX concerns). In contrast, information from internet chat rooms appeared to have an adverse influence on both scales. While information from other health professionals (such as GPs and pharmacists) may have contributed to a patient's view that MTX treatment was necessary, it did not appear to alleviate concerns of adverse events. Information from educational websites and other patients

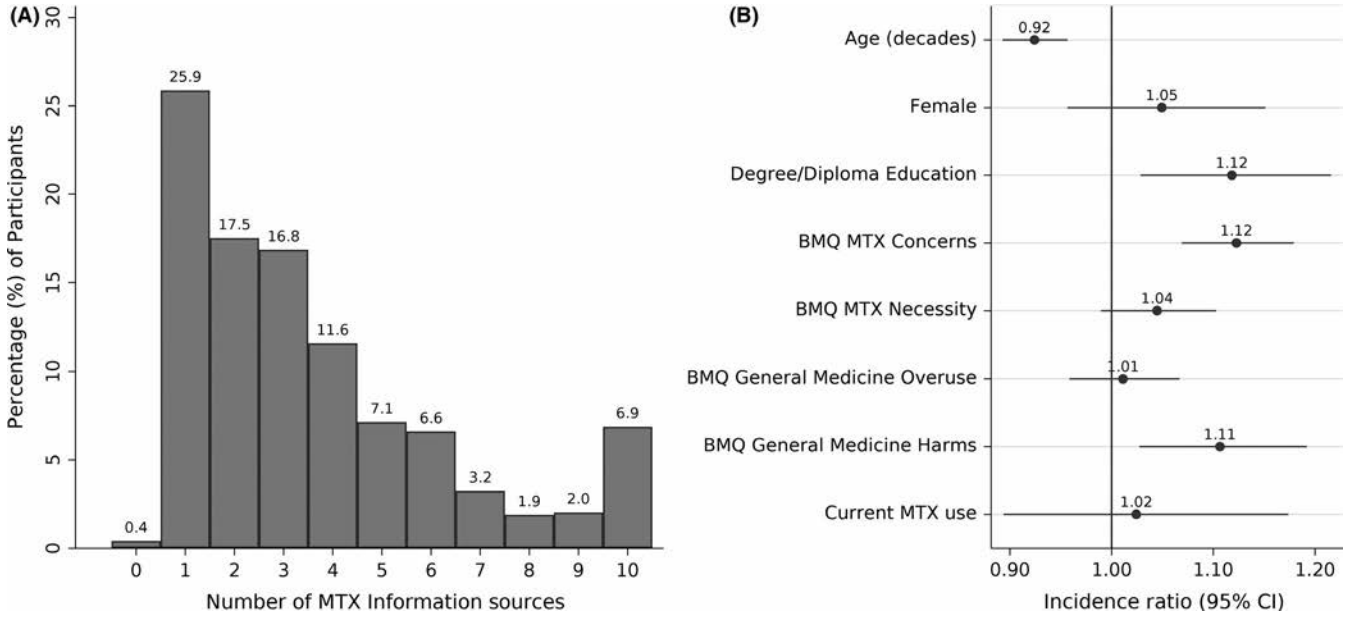

FIGURE 2 Number of Information Sources used A, Histogram showing the percentage of patients who reported consulting each number of possible methotrexate (MTX) information sources. The median (interquartile range) number of sources consulted was 3 (1-5). B, Coefficient plot (exponentiated) from a multivariable poisson regression analysis for predictors of the reported number of MTX information sources. The effect size is the incidence ratio for each covariate and error bars represent 95% confidence intervals. All continuous covariates were centered around their means, and age was scaled in 10-y units

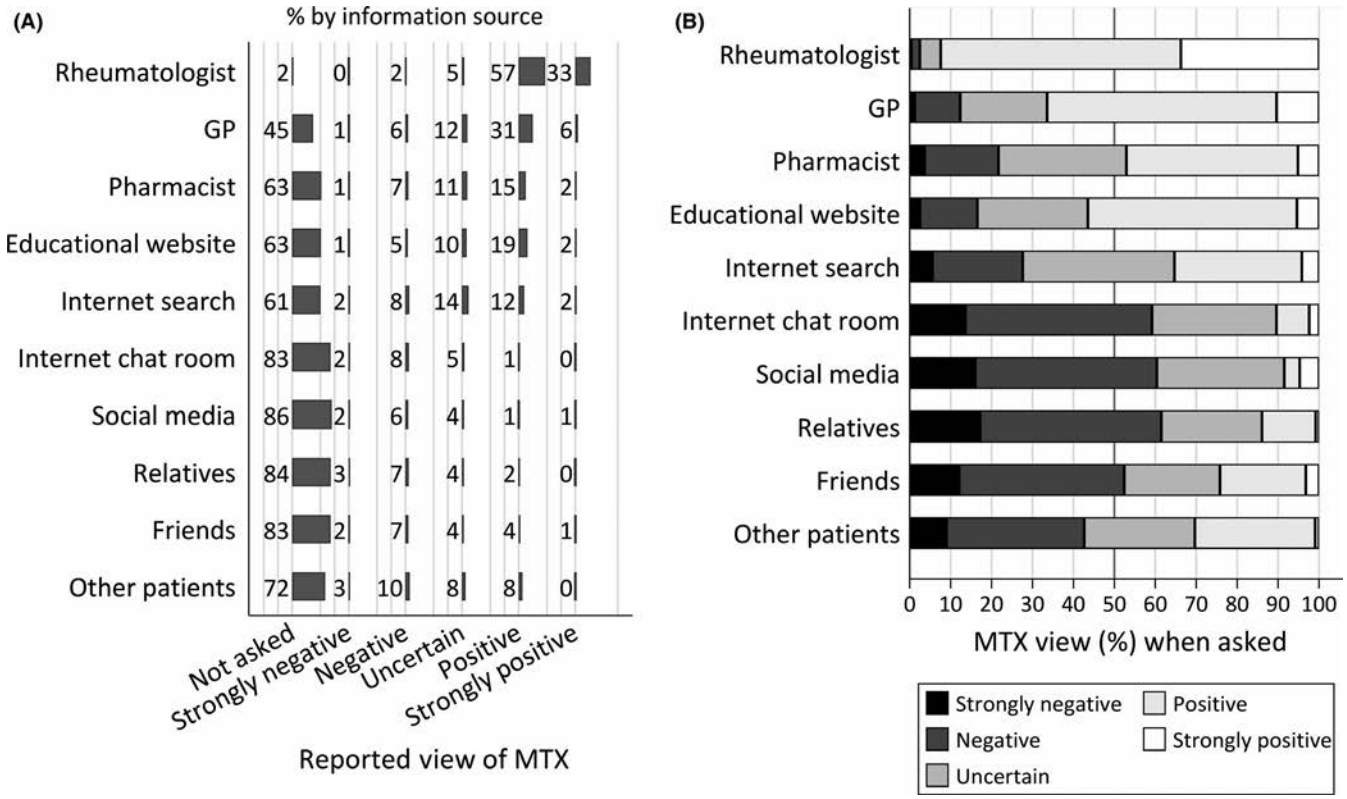

FIGURE 3 Methotrexate (MTX) views reported by patients, according to their information source. A, Cross tabulation of results, which are expressed as percentages (%) for each information source. B, Stacked bar chart of the percentage of each reported response, conditional on each information source being consulted

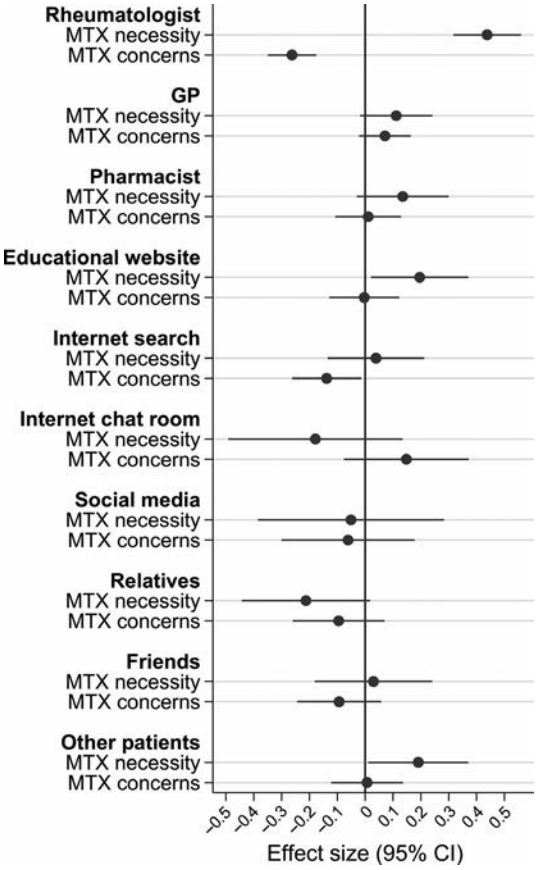

FIGURE 4 Coefficient plot for the association between positive/negative methotrexate (MTX) information from different sources as predictors of MTX-specific Beliefs about Medicine Questionnaires (BMQ). MTX information categories were coded as a linear variable for each source, with (−2, +2) representing the most strongly negative and positive views respectively. The effect size is the difference in each BMQ score for each covariate and error bars represent 95% confidence intervals

was associated with affirmative effects on the perceived necessity of MTX, and apart from rheumatologists, information from internet searches was the most effective for alleviation of concerns of adverse events.

4 | DISCUSSION

In this study we examined different MTX information sources sought by RA patients, the perception of the positive or negative nature of the information received, and the influence of this information on the patient view about necessity or harms associated with MTX treatment.

For a patient with RA, the decision whether to take DMARDs can be affected by multiple factors such as disease activity, anxiety regarding side effects, knowledge about the medications, emotional/psychological state, and health literacy.[21] A 4-phase decision-making process about DMARDs was described by Salt.[22] This begins with the decision to seek initial healthcare advice, followed by knowledge acquisition, where information regarding both RA and medications for treatment are sought. The third phase pertains to building a trusting relationship with the healthcare provider. Then finally, the decision whether or not to take the medication prescribed for their RA.

RA patients may seek information from other sources if their initial visit resulted in dissatisfaction, concern, conflicting information,[8] or for validation of what they have been told by their rheumatologist.[10] In general, multiple information sources are utilized[9]; in this study patients used a median of 3 sources. In addition to their rheumatologist, these information sources included allied health professionals (pharmacists), other healthcare providers such as their GP, as well as friends, family, the internet and other patients. Younger, more educated patients with higher BMQ-specific MTX concerns and higher BMQ general medicine harms scores utilized a greater number of information sources. It is not surprising that patients with higher BMQ MTX-specific concerns and general medicine harm scores seek more information to address the discordance between the need to take MTX and fear of harm.[9,10] However, it is also possible that multiple sources of information may increase confusion and concerns about MTX treatment.

In our study, as has been previously reported,[9] patients may commonly utilize the internet as a source of information about MTX. However, this can be unreliable.[23] In our study we specifically asked participants about their usage of educational websites, internet searches, social media and internet chat rooms, and the favorability of the reported information substantially varied. When consulted, a majority of participants reported receiving positive information about MTX from educational websites, while a majority also reported receiving negative information from social media and internet chat rooms. These latter information sources are predominantly unregulated, can disproportionately emphasize adverse unpleasant personal experiences, adverse events and other concerns about treatment,[9,23] and may have an adverse impact on a patient's treatment decisions. In our study, educational websites were influential to a patient's belief that MTX treatment was necessary, whereas information sourced from internet chat rooms appeared to be linked with both an underestimation of the necessity for MTX and a heightening of concerns about its use due to the adverse events.

As would be expected, rheumatologists were the most frequently identified source of information about MTX in our study, and most influential for patient views about the necessity, and concerns, of MTX treatment. Other health professionals, such as GPs and pharmacists, were less frequently identified as a source of information about MTX, and appeared to be less influential. Of some concern, the study identified that only a minority of patients who consulted pharmacists reported receiving positive MTX information. Previous studies have also shown that the treating rheumatologist helps the patient with decision-making, and has the most impact on their decision.[8-9,21,22] Information from the treating specialist can mold the RA patient's beliefs regarding MTX by alleviating concerns, reducing perceived barriers, and strengthening the belief that it is needed for optimal treatment.[9-10,22] Good-quality

multimedia information sources from treating specialists may also improve patient knowledge and help overcome fear.[24] It is therefore important for treating doctors to provide and/or direct patients to appropriate and accurate information sources,[23] such as the Australian Rheumatology Association patient information sheets and Arthritis Australia.

The strengths of our study are the high response rate in a large sample of RA patients from across Australia, which includes patients treated in different healthcare settings. The main limitation of this study is the cross-sectional design which precluded determination of the direction (causation) of the relationship between MTX information sources and medication beliefs. There was also the risk of imperfect recall of information sources in patients with a lengthy disease duration. Further, specialized rheumatology nurses were not included in the list of information sources utilized as not all RA patients, especially in private care, have access to this kind of service.

Our study demonstrates that patients with RA seek advice from a variety of sources. Both clinicians and pharmacists need to be aware of this and ideally should ask patients the sources of their advice regarding medication information. To provide safe and consistent messaging regarding MTX for RA in Australia, the data from this study was used in a program developed by the Australian National Prescribing Service (NPS), in collaboration with the Australian Rheumatology Association and Arthritis Australia to develop materials for consumers regarding MTX and RA.[25] This program also included education for GPs and pharmacists on safe and effective use of MTX.

5 | CONCLUSION

People with RA may seek information about MTX and other DMARDs from multiple sources, and these sources of information may provide conflicting information. Our study highlighted the important role of the rheumatologist in helping the patients make treatment decisions, and the importance of directing patients to appropriate and accurate additional information such as educational websites like Australian Rheumatology Association patient information, Arthritis Australia and the Australian NPS consumer guidelines.

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CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL ARTICLE

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Patient and clinician views on an app for rheumatoid arthritis disease monitoring: Function, implementation and implications

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Abstract

Aim: Best practice management for rheumatoid arthritis (RA) involves regular clinical assessment of RA disease activity. This is not achievable with current rheumatology systems of care. We aimed to use opinions from people with RA and their specialist rheumatology healthcare professionals to inform development of a mobile app for people with RA for recording their disease activity data for potential integration into clinical service, and assess usability of the app.

Method: In phase 1 we interviewed nine people with RA and seven healthcare professionals. In phase 2 we developed an app with professional software developers. In phase 3 we evaluated app usability for people with RA using the System Usability Scale (SUS).

Results: Interview data showed four themes regarding functionality and implementation of a patient-held app in RA care: (a) variable app acceptance and readiness; (b) app use to reduce barriers; (c) pros and cons of patient-reported outcomes; and (d) allocation of clinics by need. The app developed has high usability in people with RA using the app on their own device for a month (SUS 79.5, n = 16) or using the app on a study device for 10 minutes (SUS 83, n = 100).

Conclusion: People with RA and healthcare professionals have clearly identified features, benefits and risks of an app for self-assessment of RA and incorporation into clinical care. An app developed informed by these opinions has high usability. Next steps are development and validation of a method of patient-performed joint counts, and implementation, with evaluation, in the clinical setting.

KEYWORDS
mHealth, mobile applications, rheumatoid arthritis, telemedicine

1 | INTRODUCTION

The treat-to-target approach for rheumatoid arthritis (RA) achieves better outcomes for people with RA; however, rheumatology services may struggle to meet the service and care requirements.[1] Treat-to-target mandates initial monthly review for assessment of disease activity, using a composite disease activity (CDA) instrument, and optimization of treatment.[2,3] Once remission or low disease activity state is reached, review with CDA calculation is recommended every 3-6 months. Even high-income countries have insufficient

rheumatologists to meet this care need[4,5] with limited rheumatology services in regional and rural areas.[6,7] Current care does not consistently implement treat-to-target practices, with CDA scores recorded in less than half of clinic visits in real-world settings.[8-10] Even in rheumatology practices that have enrolled in the Rheumatology Informatics System for Effectiveness continuous quality registry, only 55% of care providers record CDA in at least 50% of clinic visits for RA.[11] To achieve widespread and effective adoption of the treat-to-target strategy in RA will require changes in models of care.[12]

New models of service delivery for people with RA, that include nurse-led clinics and patient-initiated review have been shown to be clinically and cost effective[13-19] but still require personnel and a face-to-face visits for assessment of RA disease activity. A Danish study followed people with established RA with low disease activity, who received telephone monitoring by a rheumatology nurse or rheumatologist. Follow up was informed by a computer-generated self-report RA flare tool, and showed non-inferiority of RA disease activity at 1 year compared to routine clinic visits.[20] These data suggest new models of care informed by patient report of disease activity measures may achieve good outcomes for people with RA, without the requirement for regular face-to-face clinical review. This could be implemented via mobile applications (apps) and the internet.[21,22]

Accumulating evidence suggests the goal of remote patient assessment of RA disease activity via mobile apps or web-based software is feasible, sufficiently accurate and desirable. Preliminary small studies with bespoke mobile apps confirm RA-related impairments do not hinder mobile app data entry[23] and self-reporting may increase empowerment and facilitate shared decision making.[24] Over the short term patient self-report of RA disease activity via a web-portal with the Routine Assessment of Patient Index Data (RAPID-3 or -4) has high correlation with rheumatologist-assessed Disease Activity Score of 28 joints (DAS-28) at baseline (r = .63) and 12 weeks (r = .66).[25] A UK-based rheumatology service has overcome the barrier of lack of suitable commercially developed mobile apps[26,27] by developing a bespoke mobile app for recording and transmission of patient-generated disease activity for people with RA and inclusion of these data in the electronic health record.[24] In a 3-month evaluation in a research clinic 20 people with RA and two clinicians found this approach feasible and viewed it as positive in enabling patient-centered consultations. Clinical outcomes were not evaluated and issues of technical implementation in real-world settings, impacts on workflow, and clinical processes were not addressed. Although remote app-based RA disease monitoring has promise, these factors will need consideration in any setting planning to implement RA disease monitoring via mobile technology.

In Aotearoa/New Zealand (NZ) the taxpayer-funded health system has long struggled to provide rheumatology specialist care to a growing, aging and geographically dispersed population.[5] As smartphone penetrance in NZ is high, even among low socio-economic status communities, and some geographic areas do not have easy access to rheumatology services, exploration of rheumatology service provision supported by patient-generated health data and needs-based appointment scheduling of RA management is of interest. Any remote monitoring patient management system is more than just software. The input of the users in software development and integration into redesigned services is of utmost importance. In the setting of developing an app for patient-generated health data reporting and needs-based appointment scheduling for follow up of people with RA, our research questions were: what are the requirements for an app for patient-generated health data reporting; what are the opinions and readiness of people with RA and members of healthcare teams caring for people with RA about using an app as part of needs-based service provision; and what are opinions of people with RA on an app developed informed by these data? In particular the aims of this study are to:

1. Assess the opinions of people with RA and healthcare professionals regarding (a) design and functionality, and acceptability and usefulness of an app to complement current service and (b) pros and cons of this approach for assessment of disease activity and organization of monitoring of patient-generated health data and face-to-face visits.
2. Develop an app, informed by information gained from interviews.
3. Assess the usability of the app.

We report a 3-stage study: phase 1 stakeholder interviews; phase 2 app development; and phase 3 evaluation of app usability in research and real-world clinic settings.

2 | METHODS

2.1 | Phase one: stakeholder interviews

2.1.1 | The setting and participants

The Wellington Regional Rheumatology Unit (WRRU) at Hutt Hospital, Hutt Valley, NZ is a referral rheumatology service for a population of approximately 500 000 people, in both urban and rural areas. WRRU employed six rheumatologists (all part-time, total full-time equivalent 2.6), one rheumatology registrar and four specialist nurses. People with RA who had attended WRRU in a 3-month period were phoned in sequence by a research assistant (FR, CAF) inviting participation in an interview about use of apps to monitor RA. Eligible participants were over 18 years of age, had a diagnosis of RA according to the American College of Rheumatology 2010 criteria[28] and spoke English. Exclusion criteria were cognitive impairment or inability to be available for a 1-hour interview. Four rheumatologists and three rheumatology nurses from the WRRU volunteered to participate and were individually interviewed.

2.1.2 | Interviews and data analysis

All eligible people with RA telephoned agreed to and completed an interview. Semi-structured interviews were undertaken in person

or by telephone/skype at the participant's preference. Interviews were based on a schedule developed by two rheumatologists (RG, WT) which focused on technology use, use of patient-reported outcomes measures in management of RA, mobile app functionality, barriers and facilitators to app use, and the potential impacts of app implementation on service provision and experience (Appendix 1). The interview schedule was not piloted. Of the nine people with RA interviewed, one research assistant interviewed the first five (FR, female medical student, Bachelor degree) and the remaining four were performed by a second research assistant (CAF, female research assistant previously trained as a dentist, Bachelor degree). Each underwent training with research lead (RG, female, rheumatologist, PhD, experienced in qualitative research). Both interviewers met with RG after the first interview to review the process. Participants were aware of RG's involvement and that interviewers were employed to undertake interviews. Open-ended prompts were used to explore participant opinions. All interviews were audio recorded and transcribed verbatim. Field notes were made at the time of interview to support interpretation of interviews. Interviews were ceased once no new ideas were being offered (ie, saturation reached). The interview schedule for people with RA was adapted for the health professional interviews to explore aspects of app development and how data would be handled at the WRRU and possible impacts on practice (Appendix 2). All interviews with healthcare professionals (HCPs) were undertaken by 1 researcher (CAF).

Data were managed in Microsoft Word documents Version 16.0 (Microsoft Corporation). Content analysis with latent meaning was used as methodological framework[29] and subject to thematic analysis.[30,31] Two researchers (RG, FR) coded the first five participant transcripts by reading the transcripts repeatedly, systematically coding each unit of information (a sentence or part of a sentence) using key words or phrases to set up the basic parameters of the analysis. Codes that clustered into themes were identified and themes reviewed and named. Where uncertainty or differences in coding occurred, a discussion was held to achieve convergence. A constant comparative approach was taken to ensure coding categories were consistently used. The codes were then grouped together to form categories which became the main themes of the analysis. One researcher (RG) coded the remaining transcripts. Once all the transcripts were coded, RG and CAF reviewed randomly selected transcripts to ensure consistency of coding. Transcripts were not returned to participants for checking or to provide feedback on themes. Data are reported according to the Consolidated Criteria for Reporting of Qualitative Research (COREQ) guidelines[32] and the COREQ checklist is provided (Appendix 3).

2.2 | Phase 2: app development

The interview data informed the required content and functionality of an app for patient-generated health data for people with RA in this NZ rheumatology service. A mobile app was developed for both Android and iOS by a commercial software development company (Codeflugel™) using agile project management approach with the design team including a rheumatologist (RG), a computer scientist with expertise in human-computer interface (TL) and a software developer from Codeflugel. The development team met weekly by Skype to review progress and provide feedback, which was incorporated in an iterative manner. User manuals for iOS and Android were prepared to describe how to download the app and instructions on how to download and navigate the app.

The app, called RAConnect, is designed to be held on the phone of a person with RA (Figure 1). Functionality includes: (a) data collection function for RA-relevant validated instruments (all detailed in Anderson et al[33]): Health Assessment Questionnaire II (HAQ-II), patient global assessment, 28 swollen and tender joint count,

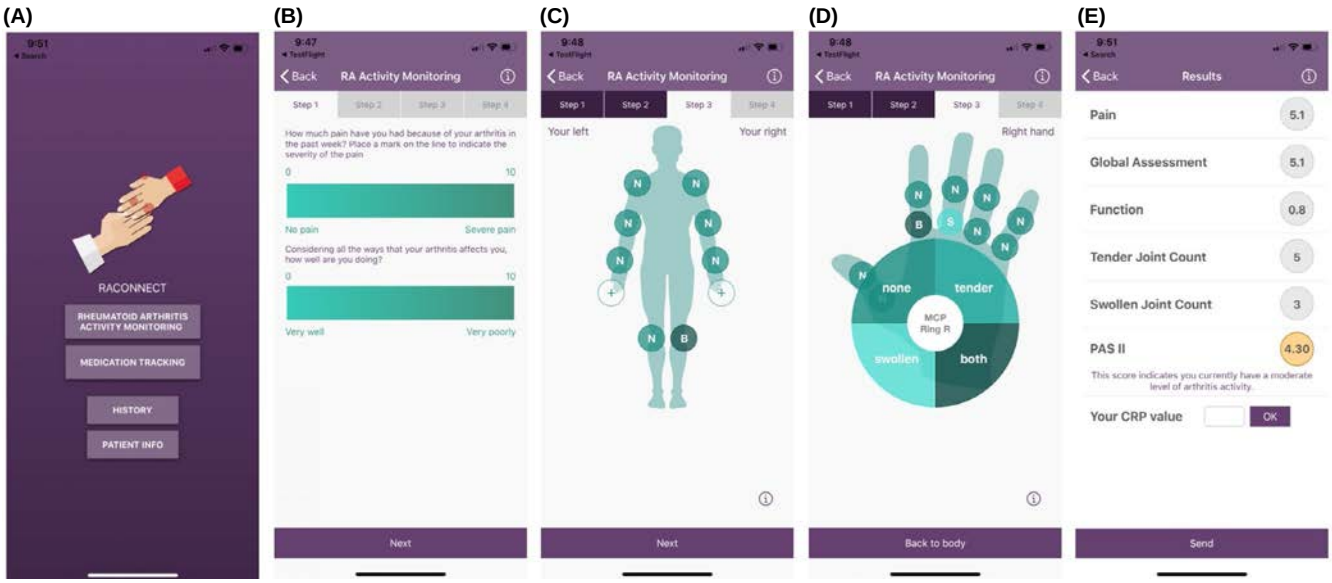

FIGURE 1 RA connect app screen shots. A, Menu. B, Health assessment questionnaire. C, Joint counts-body. D, Joint count-hand detail, E, Summary data

calculates CDA measures (Patient Activity Scale II [PASII], and the patient-reported DAS-28 C-reactive protein [DAS-28-CRP]), along with patient-generated free text comments; (b) medication recording for all commonly used conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs, including start date, dose, stop date and free text for reasons for stopping); and (c) generation of an email report of data to a designated email address, intended to be the treating rheumatologist or rheumatology service. The app supports direct integration with Hutt hospital electronic health records using a secure connection. Although it may have been desirable to have 2-way messaging incorporated into app functionality, this was not possible within the information technology infrastructure of the hospital. All data entered is stored on the phone, and can be accessed at any time by the app user. The clinical workflows, for example how healthcare professionals monitor and respond to patient-reported data, and patient data entry management, for example how often patients enter data and reminders for patient data entry, are outside the scope of this manuscript.

2.3 | Phase 3: usability testing

The appropriateness of RAConnect for RA patient-generated health data reporting (ie, usability in a specific context) was assessed with the Systems Usability Scale (SUS).[34] Each of the 10-item questions in the scale were contextualized to RAConnect and had a 5-point Likert scale with anchors 0 = strongly disagree and 4 = strongly agree. Mean scores and standard deviations were calculated for each item and overall score calculated.[34] SUS scores range from 0 (poor) to 100 (excellent).

Usability testing of the app with people with RA was undertaken in two ways: with people using the app on their own phone or tablet for 1 month and with people with RA using the app once immediately before their routine rheumatologist clinic visit.

2.3.1 | Testing on participants' devices

Participants in stakeholder interviews and people participating in a patient-opinion online platform coordinated by a rheumatologist at WRRU were invited to participate by email, and people attending the rheumatology clinic were invited to participate via a phone call from a research assistant (HT). Formal sample size calculation was not performed and the recruitment period limited to 1 month. After written informed consent was obtained, participants provided demographic and disease information. Participants were then emailed the user manual appropriate for their device and asked to download and install RAConnect. If participants had not been able to download RAConnect, downloading was completed via phone support. Participants were asked to use RAConnect at least once a week for 4 weeks by filling out the 'RA Activity Monitoring' section. This includes the HAQ-II, patient global assessment, 28 swollen and tender joint counts and automatic calculation of CDA. Participants were not prompted or reminded to use RAConnect. Reports of participant data were sent to a research email address. Participant reporting data frequency were analyzed using summary statistics. After 4 weeks, participants completed the RAConnect-contextualized SUS via an online survey.

2.3.2 | Testing before clinic visit

At rheumatology clinics in NZ public hospitals (WRRU, Christchurch hospital and Dunedin hospital) 100 people with RA were prospectively recruited to use RAConnect on a smartphone (Samsung Galaxy J1ace running Android) immediately before a scheduled clinic appointment. Participants completed data collection in RAConnect. A research assistant was present to answer questions but provided no prompting. Participants then completed a paper version of RAConnect-contextualized SUS.

2.4 | Ethics

The Central Health and Disability Ethics Committee approved the interview and longitudinal usability study (14/CEN/208) and the clinic visit usability study (which was part of a larger project to be reported separately, [16/NTB/102]). Participants provided written, informed consent.

3 | RESULTS

3.1 | Phase 1: stakeholder interviews with people with RA and healthcare professionals

Nine people with RA (seven female, two male) aged 27-79 years, with duration of RA of 1-26 years and current low or moderate RA disease activity were interviewed (Table 1). Seven HCPs (five female [three rheumatology nurses, two rheumatologists] and two male [rheumatologists]) were interviewed. Details of demographics of HCPs are not provided to avoid identification from publicly available information. Mean interview duration was 30 minutes with range from 14-46 minutes. No additional people were present at interviews.

Four main themes were identified in the interview data to inform the research questions: (a) variable app acceptance and readiness; (b) app use to reduce barriers; (c) pros and cons of patient-reported outcomes; (d) allocation of clinics by need. These themes are expanded below with illustrative quotes in Tables 2-5.

3.2 | Variable app acceptance and readiness

People expressed differing enthusiasm and interest for using an app as part of RA disease monitoring, management and health

TABLE 1 Characteristics of people with rheumatoid arthritis participating in interviews

Gender	Age, y	Duration of RA, y	DAS28-CRP[a]	DMARD	bDMARD	Smartphone ownership	Mode of interview
F	62	10	2.77	Y	Y	N	Phone
F	60	3	3.74	Y	Y	Y	Phone
M	79	1	1.71	Y	N	N	Phone
F	48	6	2.82	Y	Y	Y	Phone
M	58	26	3.51	y	y	Y	Phone
F	33	9	2.80	Y	Y	Y	Phone
F	27	12	1.89	Y	Y	Y	IP
M	48	8	2.21	Y	Y	Y	Phone
F	37	1	2.74	Y	N	Y	Phone

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drugs; DMARDS disease-modifying anti-rheumatic drugs; IP, in person.
[a]European League Against Rheumatism Disease Activity Score of 28 joints C-reactive protein (DAS-28-CRP)[33] criteria at most recent clinic visit, within 3 mo of interview.

care. Some people with RA were very enthusiastic, while others expressed interest moderated by concerns about sufficient technical skills or reduction in clinician contact. One person with RA had no interest in app use but acknowledged that younger people with RA were likely to have high interest. HCPs accepted that their patients, current and future, will expect use of apps as part of RA management. However, HCPs were concerned technical demands could exceed their own abilities, and those of their patient', especially in terms of app download and training. There was also concern about increased workload and change in workflow to monitor and respond to patient-generated health data.

3.3 | App use to reduce barriers

People with RA felt that having an intuitive app designed specifically for people with RA and integrated with their rheumatology service would enhance their engagement in care and reduce barriers to accessing care. An app was perceived as an easy method to seek information and reassurance from rheumatology nurses and rheumatologists via short messages. RA was not considered a barrier to data input on a smartphone by any people with RA, acknowledging that smartphone screens are small. People with RA required a simple mechanism for data input. People with RA were not concerned about the security of data or risk of privacy breaches.

3.4 | Pros and cons of patient-reported-outcomes

Two-thirds (6/9) of people with RA recalled completing paper-based patient-reported outcomes at rheumatology clinics. However, none were familiar with the concept of 28 tender and 28 swollen joint counts contributing to a composite disease activity instrument or indeed the existence of CDAs. Despite this, all people with RA saw some personal benefit to completing the RA-relevant health data instruments on an app on their smartphone, if this summarized their current RA disease activity as low, medium or high. Some participants were concerned that the proposed RA-related instruments failed to capture some pain and function aspects of their lived experience. They wished to have ability, within the app, to add free text to communicate the current impact of RA disease. HCPs expressed some ambivalence over the concept of patient-generated health data as they felt people with RA may report frequently, as often as daily,

TABLE 2 Quotes supporting variable app acceptance and readiness themes

Quotes	Age (y) and gender
I use my phone all the time…like every 5 minutes that I'm awake. I don't think anyone my age or under would have a problem doing that but… some older patients might not be interested.	33 female
I'm believing on…talking to humans on the phone instead of machines. That's preferred to me, cos you guys were born to this stuff.	79 male
Some patients will be freaked out by the technology aspect of the app. They will need good education on how to use the app and a good patient help desk where any questions could be answered by someone who spoke in lay person's language.	Nurse

TABLE 3 Quotes supporting app use to reduce barriers in interview data

Illustrative quotes	Age (y) and gender
I can…tap something twice without meaning to so…it will just require you to, you know, think about things for a minute	58 male
You can find the phone's a little bit small to do some things on	48 male
It's good to be able to email or text somebody because at the moment if something is not quite right you gotta go through the booking or usually I go to the GP and then another referral and…it's takes a bit of time	48 male
I think that would be useful as sometimes it's a bit scary for me, not understanding something properly, if you could send a text, that way it makes you feel more reassured	60 female
Cos sometimes I've had things to ask about and just a few texts back and forth can answer the problem and I didn't need to go all the way in and they didn't need to make a time to see me	48 female

TABLE 4 Quotes supporting app pros and cons of patient-reported outcomes in interview data

Illustrative quotes	Age (y) and gender
I think it's important to know where you are at quite honestly. The app would answer a lot of questions to know why you're feeling so rotten	60 female
Somewhere there should be some inclusion about feet though, but I don't know where they'd put it if it isn't part of that calculation. Because me feet are quite affected	33 female
Would there be any room for comment instead of just yes or no…because some of the questions are, just ah, don't quite suit. Well, like getting in and out of a car, that a good one for me because I am a mechanic so I have a lot of difficultly doing that. But also we work underneath cars and you're lying on the ground and getting up from the ground and things like that is very difficult also	48 male
If they came and said 'my DAS has changed it is getting better or worse, it means they have some feeling it is flaring. Them having some control over it I think would be brilliant.'	Rheumatologist

Abbreviation: DAS, Disease Activity Score.

which they felt would be excessive. Furthermore, HCPs had concern that people with RA seeing quantification of self-reported measures could have an increase in RA-related anxiety. Conversely, providing an app for self-reporting health data was considered a mechanism to empower self-management. Rheumatologists felt that this would give useful information about patients' disease between clinic visits to give a more comprehensive view of the patient lived experience.

3.5 | Allocation of clinic by need

People with RA highly valued face-to-face clinic visits with rheumatologists and nurses. However, they acknowledged that prioritizing allocation of clinic visits, according to patient-generated RA disease activity via an app, would be acceptable and fair when demand exceeded capacity. HCPs also valued face-to-face care but recognized that patient-generated health data reporting via an app could enable less frequent review in an equitable manner. In contrast, one rheumatologist felt that a remote reporting system could lead to people without smartphones or technical expertise being disadvantaged with respect to access to care.

3.5.1 | Usability testing

Sixteen people with RA were recruited, from various sources, to use RAConnect on their device for a 4-week period. Seven of the 46 people with RA enrolled in the patient-opinion online platform participated, a response rate of 15%. Four of the nine people with RA interviewed in phase 1 participated, a response rate of 44%. Five participants were recruited from rheumatology clinics held at WRRU. Most participants were female (11/16, 69%), mean age was 56.6 years (range 28-71 years); only one participant was under 40 years of age, nine were 41-60 years and six aged over 60 years old. Devices used were iPhone (n = 7), iPad (n = 2), Android smartphone (n = 5), and Android tablet (n = 2). All participants had completed secondary level education and 75% (12/16) had tertiary level education. Participants completed the RA Activity Monitoring

TABLE 5 Quotes supporting app use for allocation of clinic by need in interview data

Illustrative quotes	Age (y) and gender
I am very lucky with my rheumatoid as there are a lot of people that have got it much worse. So I would rather that they have the appointment that I have… this way (the app self-report) Dr X can see that I'm alright and somebody else can have that appointment	62 female
There would probably be less interaction with your specialist…but I'd like to think that you know, if things were bad enough I actually could still get to see her as often as I needed	60 female
I like the face-to-face appointments but great if it means that you wouldn't need to go in unless you needed to	33 female
I think it would probably streamline appointments a bit because they wouldn't need to sit there questioning you about the last 2 weeks when they've probably already seen what is going on	33 female
Yeah, just so they're not booking unnecessary appointments but also you're not falling under the radar if you are actually really in a lot of pain. Because I know some people with go, like nearly a year, you know, without an appointment but they haven't actually said they need one or rung up and said "Actually I'm pretty miserable. I do need an appointment sooner than a year"	33 female

component of RAConnect a mean of 3.5 times (SD = 1.26) in the 4 weeks. All participants used RAConnect at least twice, and one participant used RAConnect 6 times. The SUS score of RAConnect for the 16 participants was 79.5.

The 100 people recruited from clinics were predominantly female (77%), mean age 60.2 years (range 33-83 years), duration of RA 17.0 years (range 0.25-55 years) and 45% were using a biologic DMARD. The overall SUS score for RAConnect for the 100 people using RAConnect for 10 minutes before a clinic visit was 83.

4 | DISCUSSION

Our study reports that people with RA and their HCPs have similar, cautiously positive opinions regarding a mobile app for people with RA to record and report RA disease data. They offered similar potential benefits and risks, and challenges of using patient-generated health data in new models of care. An app developed, informed by these views, received high usability scores from people with RA, after use on their own device over the short term or brief use on a provided phone. These scores were above the mean (69.69) and median (70.91) SUS reported in its evaluation from inception in 1986-2008.[35] The RAConnect SUS scores are on or above the 90th centile (80) indicating high usability and are similar to the SUS reported for online RA disease self-reporting software.[25]

Patient and HCP opinions have been obtained in other settings to inform the development of web or mobile apps for children and adolescents with juvenile idiopathic arthritis[36,37] and adults with arthritis.[38,39] In a UK study young people with inflammatory arthritis were positive about an app for self-monitoring, but felt ambivalent about tracking symptoms at times of good disease control.[36] Security or privacy issues were not a concern and young people expressed a clear preference for social and peer support and engaging design, including gamification. Our older patient group did not request peer interaction via an app, with their design advice focusing on function over enjoyment, perhaps as this was outside the scope of an app proposed to them in the setting of service development. In our study HCP ambivalence about patient-generated health data reporting related to potential for increased anxiety about RA, not reporting burden; while rheumatologists identified potential benefit in gaining insight into daily lived experience of their patients. Indeed, a recent UK study has reported that reviewing daily RA symptom reporting in rheumatology clinics gave rheumatologists deeper insight into day-to-day RA impact and enabled more patient-centered consultations.[24] Recently a Belgian study that interviewed adults with inflammatory arthritis to inform self-management app development also reported varying opinions about personal value of an app for arthritis monitoring.[38] Our study participants clearly identified logs for reporting disease activity and medication reminders as key desirable features for an app. Again, even people who felt app features were not relevant to them personally acknowledged that other people with arthritis might find them useful. This was also found in a Swedish study engaging people with arthritis to inform development of web software for self-management.[39] This emphasizes an app for RA monitoring might be useful and of interest to anyone with RA, but not everyone with RA.

The findings of our study have some parallels with the key findings of a recent meta-synthesis of 43 qualitative studies of patient views on mHealth interventions for chronic diseases.[40] Key strengths of mHealth identified were patient empowerment and engagement, which was expressed by participants in our study in the theme of reduced barriers, with practical examples like the ability to send short messages to clinical team members. Limitations identified in the meta-synthesis included the technical and knowledge trustworthiness, personalization to the disease, appropriateness and accessibility. In our study we have addressed a priori trustworthiness as the developers are the HCPs for the participants, and disease personalization, and appropriateness as the scope and purpose of the

proposed app was carefully predefined. Our participants did identify accessibility as a potential disadvantage of an app for RA, expressing that not all people with RA would be interested in an app for RA disease monitoring and communication, which creates potential for inequitable service access. Interestingly our study identified potential challenges when incorporating mHealth into current healthcare services as concern for both patients and HCPs, which was not identified in the meta-synthesis of extant literature. This might be because literature to date has largely focused on chronic disease apps being considered as a patient-facing tool only, not as a mechanism for interaction with HCPs to supplement or assist clinical care. This is an important point as successfully leveraging of the potential of mobile health will require people to be pro-active in self-management of health conditions in partnership with HCPs.[41] Although recording of patient self-reported RA-related activity or impact is an accepted and encouraged component of high-quality clinical care, the assessment of tender and swollen joint counts is usually done by a rheumatologist. Therefore patient-self-reported joint counts, which people with RA and rheumatologists endorsed to be included in a patient-held app for RA, are not yet fully validated for use in evaluation of disease activity. A systematic review of the literature on joint counts reported high reliability for tender joint counts for HCPs and patients, while reliability for swollen joint counts was poorer for patients than HCPs.[42] However, previous work has confirmed that scores in CDA measures for RA are similar to those derived from ultrasound-determined joint inflammation.[43] Therefore sufficient data exist to support further research to evaluate the reliability of patient self-joint count as a component of disease activity measurement in RA, which would be required before implementation of patient reporting as a means for remote monitoring and allocation of clinic appointments. Furthermore, the frequency of app-reporting of RA disease activity by people with RA, and if this is sufficient for clinical purposes, will also need to be evaluated. In a feasibility study in the USA, people with RA using an app to report symptoms for research, showed a steady drop in use until only 11.3% of participants were engaging with the app after 12 weeks.[44]

The limitations of this study need to be acknowledged. This qualitative approach by necessity limited sampling to a smaller number. Although data saturation was reached, it is possible other participants may have provided different opinions. The participants also volunteered their time so may have biases about the topic of exploration, either favorable or unfavorable, that influenced the results. Furthermore, qualitative data from a single site study may not be generalizable. Interviews were chosen for logistic flexibility and to allow participation by telephone of people from across the geographic bounds of our service. It is possible that data collection by a focus group could have elicited more nuanced information or other ideas. It is possible that positive bias may have influenced the usability responses, as participants were patients of the service which developed the app. Results must be interpreted with these limitations in mind; however, this study still signposts major areas of concern for people with RA and their HCPs when considering implementation of mobile collection of patient-generated health data for monitoring and service allocation.

While these results can guide implementation of an app into rheumatology care, there are areas for further research. These include the accuracy of patient-performed joint counts, the most effective methods to teach patients to perform their joint counts, technical and logistical barriers to implementation of self-monitoring in the clinical setting. Although we have reported high usability and interest in incorporating apps in RA clinical care, it remains unknown if ongoing engagement in such apps would be sufficient to support triage for clinic or supplement care. Lastly, although this app was developed primarily for implementation into clinical care pathways, the utility of this app for data collection in research or for quality improvement could also be explored.

5 | CONCLUSIONS

People with RA and their healthcare providers have clear opinions about the content and functions for an app for remote self-monitoring of RA and how it could be incorporated into clinical care, including risks and benefits. An app developed with these considerations in mind demonstrates high usability for people with RA. Next steps are development and validation of a method of patient-performed joint counts, including training of patients, and careful implementation in the clinical setting with evaluation.

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AUTHOR CONTRIBUTIONS

RG, TL and WJT designed the overall study with HRT, CAF, FER also contributing to practical aspects of study design. RG, HRT, CAF and FER acquired the data. RG, HRT, CAF, FER, TL and WJT all contributed to data analysis. RG and HRT wrote first draft of the manuscript and critically revised it for intellectual content, with CAF, FER, TL and WJT all providing critical revision for intellectual content. RG, HRT, CAF, FER, TL and WJT all approved the final manuscript for publication and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX 1

SEMI STRUCTURED INTERVIEW SCHEDULE FOR PATIENTS AND PATIENT-ADVOCATES

The following questions are grouped by the topics that will be explored in the interview. The questions themselves are 'examples' because not all of these might be used, or the phrasing may vary from person to person. In addition to questions, generic prompts (such as, please tell me more about that, please could you give an example, could you please expand on that idea) will be used to elicit more detail. The interviewer will sometimes paraphrase what a participant has said in order to check understanding (eg, what I am hearing is that you think…….). The interviewer will aim to use neutral language and questioning strategies to attempt to avoid biasing participant responses. This document gives an outline of the interview with specific questions indicated in italics.

A. Introduction and consent

1. Interviewer introduces self and thanks participant for time.
2. Aims of interview outlined: to explore patient perspectives on an mobile software that can be used on smartphones for patient initiated monitoring of RA disease activity and communication with treating health care teams, including rheumatology team.
3. Logistical details outlined:
   - -. the interview will be recorded and transcribed,
   - -. the responses are confidential and will be de-identified and secure data storage will be used.
   - -. The study has ethical approval under 14/CEN/208. You can withdraw your consent and discontinue the interview at any time with no impact on you or your health care. Any questions can be answered by the research team with contact details on information sheet. Checks participant has information sheet and has signed consent form.
   - -. We expect the interview will take 30-45 minutes. Please indicate if you need a break at any time or wish to stop the interview.

B. Demographics and current technology access and use

Interviewer will collect basic demographic details and experience and exposure to relevant technology (hardware, applications and access) in interview sheet (attached).

Based on the collected data, the interviewer will tailor the questions to the technology access of the participant.

eg, Participant with smartphone, familiar with use and apps

How would you feel about using an app on your smartphone to self monitor your RA symptoms?

eg, Participant with no smartphone or experience in use but computer and internet access and use

How would you feel about having a smartphone and learning to using an app on this smartphone to self monitor your RA symptoms?

Would you be interested in using similar software on a computer (laptop or desktop)? How would computer access compare for you with smartphone access?

Are there any reasons why you would not want to use an app on a smartphone (privacy, intrusion, difficultly doing things with hands etc)?

C. Semi-structured interview

Thanks for the background information. It helps me frame the rest of the interview to match your current technology exposure.

We are interested in four main areas; 1. the software content, 2. how users might prefer to access the software, 3. how the software may need to function and 4. how the software will interact with the rheumatology service.

1. Software content and function

There are some basic groups of information and measurements of rheumatoid arthritis activity the RA software could include and want to get your feedback on this. Here is a list (shows sheet "Possible RA app content" [attached], an A4 page)

Take a moment to read through these. (waits) Are there any that you would like to ask about or understand better? I'd like to get your thoughts about each of these sections.

*First I'd like to know your thoughts on the **summary data**. This data would be entered by you and act as a portable health record that you could show to health care providers as you wished.*

Does this look right to you?

Is there any other information that you think is important that should be recorded in this section?

Any other comments?

Now I'd like to know about the **patient assessment section**. The patient assessments may not look familiar to you.

2. Joint counts

The tender or swollen joint count would be according to your own assessment and be entered on a body by tapping the area. Although many areas of your body could be affected by RA, rheumatologists standard assessments focus on a subset of joints. These are in the hands, arms and legs. We have three options of how this information could be entered on an app. It could look something like this (show GUI 1—hands) *and this* (GUI 2—other joints).

Takes a few minutes to explain—the app would feature use designs similar to A (Stick and box) B (body outline) *OR* C (body outline with skeleton). Date could be collected in two ways 1. There would be two screens for right hand (tender and swollen), two screens for left hand (tender and swollen) and two screens for body (tender and swollen). Joints on each diagram that were tender would be tapped, then same for swollen. 2. There are three screens (right hand, left hand, body). For each joint, one tap for tender, tap again, swollen, tap a third time tender and swollen).

Do you prefer one of the three GUI's (A, B or C)? Why do you say that?

Which of the two ways of entering data would most suit you?

How do you think it would be for you completing this? Are there any ways that RA might impact on you completing this data?

Are there any comments about how the body should look or about how the tender/swollen areas should be entered?

3. Patient self reports

If you have attended rheumatology clinics through Hutt Valley DHB you have completed a form that looks like this while you wait for the rheumatologist (Card 3—Hutt Valley DHB Rheumatology assessment form—patient global and HAQII). *You would enter these data on screens that might look like this* (GUI 3—Patient globals and HAQ II).

How do you think this might work for you? Do you have any concerns?

The composite scores are a measure of RA disease activity that incorporate the above data. Usually your rheumatologist will calculate these in clinic but may or may not share them with you. They are often grouped into low, medium and high RA disease activity. This is sometimes displayed using a traffic light system, green – low disease, orange – medium activity, red—high disease activity. Red is used for high as it reminds the rheumatologist that something needs to be done! Here is a way that these have been presented on a web site (shows attached DAS28 severity visuals).

How would you feel about seeing these?

If these scores showed that your RA was very active, or had got more active recently, the app could automatically send an email or text your rheumatology service. How do you feel about this?

How long would you be prepared to wait for a response when you have sent information?

How would you feel about the time frame if you received a generic acknowledgement of the receipt of the information? How long after that would you expect a personal/detailed reply?

Could the reply come via text alert to the app or would you expect to speak to a health professional on the phone?

This leads me on to a more general discussion of ***communication****. The app could have three communication capabilities. The first is the ability post reminders to you as an email or an alter that appeared within the app (like a text box, or little message within the app), for example, get a blood test, enter your data or attend appointments.*

Is this useful to you?

What are the advantages and disdavantages of these reminders for you?

The second is that you could write and send a text message or email to your treating rheumatology team from within the app.

Is this useful to you?

What are the advantages and disdavantages of this message function (email/text) of the app for you?

4. Interaction with specialist rheumatology team

Now I'd like to know a little about how you think use of this smartphone app might impact on your interaction with your rheumatology care team (rheumatologist and their nurses). What are your thoughts?

Further comments could be elicited around the following:

face to face appointments could be less frequent

- how the data may be incorporated into face to face appointments
- completing an assessment just before appointment (in waiting room, no need for paper review).
- How participant would feel if the rheumatologist or rheumatology nurse did not use the app data the patient had collected.

RA App interview data sheet

Section A Demographics

Interview number
Subject initials
Age
Gender
Years since RA diagnosis
DMARDS (y/n)
Biological DMARDs (y/n/)

Section B Technology familiarity/access

Smartphone

Do you own an internet capable smartphone (y/n)
If Y
What type of device (iPhone, Android, etc)
Do you use your device to access the internet? (y/n)
Do you use “apps” on your smartphone?
Do you use your device to access email?
Do you use your device to send or receive text messages?
Do you have a dataplan on your device?
Do you use wifi (when available) on your device?

Computer use and usage

Do you own a computer? (y/n)
If Y
Do you use your computer to access the internet? (y/n)

Do you use your computer to access email?

Do you own another internet capable device such as a tablet or iPad?

If N

Do you use computers to access the internet, for example at work or a public library?

Possible content of an RA app

1. Summary data

   -. Contact details of patient, next of kin and health care professionals
   -. Medical history and hospital admissions
   -. Medications (current and previous, including reasons for discontinuation and adverse effects)

2. Patient assessments
   - Tender and swollen joint count
   - Other patient assessed indices (eg, pain, global well-being, HAQ-II)
   -Generation of composite score measures of RA activity (eg, DAS-28, SDAI)
3. Communication

   - Reminders to user (appointments, tests, data input eg, laboratory data)
   - Alerts to user or health care provider if patient assessments fall outside pre-set parameters
   -Email or text message of patient assessments or patient concerns to health care providers.

APPENDIX 2

SEMI STRUCTURED INTERVIEW SCHEDULE FOR HEALTH CARE PROFESSIONALS

Version A. Rheumatologist

The following questions are grouped by the topics that will be explored in the interview. The questions themselves are 'examples' because not all of these might be used, or the phrasing may vary from person to person. In addition to questions, generic prompts (such as, please tell me more about that, please could you give an example, could you please expand on that idea) will be used to elicit more detail. The interviewer will sometimes paraphrase what a participant has said in order to check understanding (eg, what I am hearing is that you think…….). The interviewer will aim to use neutral language and questioning strategies to attempt to avoid biasing participant responses. This document gives an outline of the interview with specific questions indicated in italics.

A. Introduction and consent

1. Interviewer introduces self and thanks participant for time.
2. Aims of interview outlined: to explore health care professional's perspectives on an mobile software that can be used on smartphones for patient initiated monitoring of RA disease activity and communication with treating health care teams, including rheumatology team.
3. Logistical details outlined:
   -. the interview will be recorded and parts may be transcribed,
   -. the responses are confidential and will be de-identified and secure data storage will be used.
   -. The study has ethical approval under 14/CEN/208. You can withdraw your consent and discontinue the interview at any time with no impact on you or your health care. Any questions can be answered by the research team with contact details on information sheet. Checks participant has information sheet and has signed consent form.
   -. We expect the interview will take 20-30 minutes. Please indicate if you need a break at any time or wish to stop the interview.

B. Demographics and current technology access and use

Interviewer will review the details and completeness of the RA app interview data sheet (attached) that the rheumatologist has completed before the interview. This includes demographic and professional practice details and experience and exposure to relevant technology (hardware, applications and access).

C. Semi-structured interview

Thanks for the background information. It helps me frame the rest of the interview to match your current technology exposure

We are interested in three main areas; 1. the software content, 2. how the software may need to function and 3. how the software will interact with your rheumatology service

1. and 2. Software content and function

There are some basic functions that the app could have. These include a record of patient details including medical information, measurements of rheumatoid arthritis activity and means of communication or feedback to the user (the patient) and the health care team. I would like to get your feedback on this. Here is a list (shows sheet "Possible RA app content" (attached), an A4 page)

"Take a moment to read through these. (waits).

(Note Rheumatologists should be familiar with most of the patient reported indices.)

I'd like to get your thoughts about each of these sections."

First I'd like to know your thoughts on the ***summary data****. These data would be entered by the patient and act as a portable health record that they could show to health care providers as they wished.*

Does this look right to you?

Is there any other information that you think is important that should be recorded in this section?

Any other comments?

*"Now I'd like to know about the **patient assessment section***

A. Joint counts

The tender or swollen joint count would be entered by the patient according to their own assessment and be entered on a body by tapping the area. We have three options of how this information could be entered on an app. It could look something like this (show GUI 1—hands) *or these* (GUI 2—other joints and GUI 3)."

Takes a few minutes to explain—the app would feature use designs similar to A (Stick and box) B (body outline) *OR* C (body outline with skeleton). Data could be collected in two ways;

1. There would be two screens for right hand (tender and swollen), two screens for left hand (tender and swollen) and two screens for body (tender and swollen). Joints on each diagram that were tender would be tapped, then same for swollen.
2. There are three screens (right hand, left hand, body). For each joint, one tap for tender, tap again, swollen, tap a third time tender and swollen).

Do you prefer one of the three GUI's (A, B or C)? Why do you say that?

Are there any comments about how the body should look or about how the tender/swollen areas should be entered?

B. Patient self reports

Do you currently measure and/or record any patient reported indices in your clinical assessment of people with RA? These could include patient assessment of pain, patient global assessment of disease, the Health assessment questionnaire (the HAQ) or others?

If yes, how do you do this?)(paper, electronic etc)

In your current clinical management of people with RA, do you calculate any composite disease activity measures eg, DAS28 or CDAII?

What impact would it have on your practice if your patients with RA, arrived with completed patient reported outcomes, recorded at intervals, and calculated composite disease activity measures

The RA app we propose would send the data recorded data to the DHB and these data would be entered into the electronic medical record (concerto), much like the way blood tests are entered. We are proposing that disease activity would be calculated and "forced sign off" generated if the disease activity indices showed the patient had highly active RA (Probably signed off by rheumatology nurses). We are envisaging that this would trigger a phone call from the nurse to the patient to get more information and assist the patient in planning appropriate management (eg, see GP, appt with rheumatology). Would this have any impact on your practice? Would this be useful or create problems?

Would your practice have the ability to respond to these alerts? How would you respond – phone call, email, text, arrange and appointment? Who would do this? How long might it take to respond and how long do you think is reasonable?

*While on the **communication** functionality, the App could also have the ability to post reminders to the patient as an email or an alert that appeared within the app (like a text box, or little message within the app), for example, get a blood test, enter joint patient reported assessment data or attend appointments.*

Would this be useful to the RA patients in your practice?

What are the advantages and disdavantages of these reminders for your patients?

2. Interaction with specialist rheumatology team

Now I'd like to know a little about how you think use of this smartphone app might interact with your current patient management arrangements? We are interested how it may influence the way appointments are scheduled, change the way patients communicate with the rheumatology team between appointments, change work flows within the rheumatology team. What are your thoughts?

Further comments could be elicited around the following

face to face appointments could be less frequent

- how the data may be incorporated into face to face appointments
- do you see any issues with patients who were completing the data and want time to review it in the clinic visit (or how they may react if you are not seen to review the data?)
- completing an assessment just before appointment (in waiting room, no need for paper review).

RA App interview data sheet

Section A Demographics

Interview number
Subject initials
Age (decade is fine)
Gender
Practice setting (public, private, NGO)
Years of practice

Section B Technology familiarity/access

Smartphone

Do you own an internet capable smartphone (y/n)
If Y
What type of device (iPhone, Android, etc)
Do you use your device to access the internet? (y/n)
Do you use "apps" on your smartphone?
Do you use your device to access email?
Do you use your device to send or receive text messages?
Do you have a dataplan on your device?
Do you use wifi (when available) on your device?

Computer use and usage

Do you own a computer? (y/n)
If Y
Do you use your computer to access the internet? (y/n)
Do you use your computer to access email?

Do you own another internet capable device such as a tablet or iPad?

If N

Do you use computers to access the internet, for example at work or a public library?

Notes:

Possible content of an RA app

1. Summary data

   -. Contact details of patient, next of kin and health care professionals
   -. Medical history and hospital admissions
   -. Medications (current and previous, including reasons for discontinuation and adverse effects)

2. Patient assessments
   - Tender and swollen joint count
   - Other patient assessed indices (eg, pain, global well-being, HAQ-II)
   - Generation of composite score measures of RA activity (eg, DAS-28, SDAI)
3. Communication

   - Reminders to user (appointments, tests, data input eg, laboratory data)
   - Alerts to user or health care provider if patient assessments fall outside pre-set parameters

Email or text message of patient assessments or patient concerns to health care provider.

APPENDIX 3

COREQ (CONSOLIDATED CRITERIA FOR REPORTING QUALITATIVE RESEARCH) CHECKLIST

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349–357.

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	8
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	8
Occupation	3	What was their occupation at the time of the study?	8
Gender	4	Was the researcher male or female?	8
Experience and training	5	What experience or training did the researcher have?	8
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	8
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	8
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	8
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	9
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	8
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	8
Sample size	12	How many participants were in the study?	13
Non-participation	13	How many people refused to participate or dropped out? Reasons?	not reported
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	8
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	13
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	13, Table 1
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	8
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	No
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	8, 9
Field notes	20	Were field notes made during and/or after the inter view or focus group?	9
Duration	21	What was the duration of the inter views or focus group?	13
Data saturation	22	Was data saturation discussed?	9
Transcripts returned	23	Were transcripts returned to participants for comment and/or	9

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	9
Description of the coding tree	25	Did authors provide a description of the coding tree?	no
Derivation of themes	26	Were themes identified in advance or derived from the data?	9
Software	27	What software, if applicable, was used to manage the data?	9
Participant checking	28	Did participants provide feedback on the findings?	9
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	27,28,29,30
Data and findings consistent	30	Was there consistency between the data presented and the findings?	13,14
Clarity of major themes	31	Were major themes clearly presented in the findings?	13,14
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	n/a

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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APLAR GRAND ROUND CASE

International Journal of Rheumatic Diseases | WILEY

Anti-alanyl tRNA positive antisynthase syndrome with Kaposi sarcoma

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Abstract

We report a rare case of antisynthase syndrome (ASS) complicated with Kaposi sarcoma, analyze its clinical characteristics, and review the literature on the topic. An 80-year-old male patient developed fever, cough, and shortness of breath. Lung high-resolution computed tomography showed nonspecific interstitial pneumonia in both lungs, and myositis antibody examination showed strongly positive anti-alanyl tRNA synthase (PL-12) antibodies. Based on these findings, the patient was diagnosed with ASS. After full-dose glucocorticoid treatment, the symptoms of fever and cough were relieved, but skin thickening and pigmentation in both feet were observed. We confirmed Kaposi sarcoma through skin pathology and immunohistochemical examination of the bottom of the patient's feet, and the patient was transferred to a cancer hospital for radiotherapy. ASS presents with some skin changes that might lead to misdiagnosis. ASS complicated with Kaposi sarcoma is rare, and to our knowledge, this is the first case reported in China.

KEYWORDS

anti-alanyl tRNA, antisynthase syndrome, immunosuppressive therapy, Kaposi sarcoma, PL-12

1 | INTRODUCTION

Antisynthetase syndrome (ASS) is a type of idiopathic inflammatory myopathy (IIM), which is characterized by the presence of antibodies against aminoacyl-tRNA synthetases in serum, and is associated with multiple clinical syndromes. Clinical manifestations, serological indicators, and chest imaging findings differ for different clinical ASS subtypes. The association of myositis and cancer occurrence, in cancer-associated myositis (CAM), is well known. The correlation between myositis, cancer occurrence time, and CAM remission after cancer treatment indicates that in some cases, CAM might be a type of paraneoplastic myositis syndrome.[1] Kaposi sarcoma (KS) is a vasoproliferative disease caused by human herpes virus (HHV)-8 infections, which is associated with human immunodeficiency virus (HIV) infection and immunosuppression.

We report the first case of ASS complicated with KS during therapy in China, analyze its clinical characteristics, and review the relevant literature.

2 | CASE SUMMARY

An 80-year-old man was hospitalized in September 2019 with fever, cough, fatigue, skin pigmentation, and thickening in both feet. In May 2019, he had fever without an apparent cause (~39.2°C), cough, shortness of breath, fatigue, and rash. At this time he did not present symptoms of Raynaud's phenomenon or mechanic's hand, which are often associated with ASS. Laboratory test results were: white blood cells (WBC) 7.5 × 10^9/L; neutrophil (NE) 78.3%; C-reactive protein level (CRP) 67.9 mg/L; and creatine kinase level (CK) 44 U/L. Chest

Nan He and Dingqi Lu contributed equally to this work and should be considered co-first authors.

computed tomography (CT) showed exudation in both lungs and the lobular septum was thickened, the two lungs were frequently patchy and blurred, and the ground glass and honeycomb-like changes could be seen (Figure 1A). Pulmonary infection was diagnosed and moxifloxacin 0.4 g per day was administered orally. Since his symptoms were not significantly improved, he was hospitalized at the respiratory ward.

Laboratory test results after 2 weeks showed: WBC 7.2 × 10^9/L; NE 79.0%; CRP 40.7 mg/L; erythrocyte sedimentation rate (ESR) 43 mm/h; CK 76 U/L; procalcitonin 0.10 ng/mL; and immunoglobulin G (IgG) 18.9 g/L. Chest CT showed no significant change since the previous examination (Figure 1B). The antibiotic regimen was changed to cefoperazone sodium and sulbactam 2.0 g every 8 hours.

No other abnormalities, except for mucosal hyperemia and edema, were noted on bronchoscopy. Further, the alveolar lavage test for non-tuberculous *Mycobacterium*, *Aspergillus*, and *Cryptococcus* were negative. Antibody testing revealed anti-nuclear antibody titer was 1:100, and there was anti-Ro52 antibody positivity. Labial gland biopsy showed slightly atrophic salivary gland tissue and interstitial multifocal lymphocyte aggregation (>50/foci).

The myositis antibody spectrum included anti-signal repetition particle IgG(+), anti-PL-12 IgG(+++), and anti-Ro52 IgG(++); lung function parameters forced vital capacity 37.3, total lung capacity 43.5, diffusion capacity of carbon monoxide 48.1; and cellular immune function parameters $CD19^+$ B-cell 7, $CD4^+$ T-cell 672 (normal). Antisynthetase syndrome, and interstitial pneumonia were diagnosed.

He was transferred to the department of rheumatology and administered methylprednisolone 40 mg per day for 2 weeks. His symptoms were significantly relieved, and he was discharged from the hospital. Glucocorticoid dosage was gradually reduced to 8 mg per day; no immunosuppressants had been administered.

In July 2019, he developed bilateral foot swelling without obvious inducement, local skin darkening, and slight pain. He was treated with Chinese medicine foot soaking, but the symptoms did not improve. He gradually developed bilateral foot blackening, swelling, and obvious pain and was re-admitted to the hospital.

Physical examination showed no rash, Gottron sign, or mechanic's hand but a few Velcro rales were noted in both the lower lungs. Muscle strength and limb tension were normal. No swelling, tenderness, or joint dysfunction was noted. Skin of the double sole was black with some cracks (Figure 2A). Skin temperature was slightly lower than normal, and bilateral dorsalis pedis artery pulsation was normal. ESR and CRP were normal, and cellular immune function was normal (CD19 + B-cell 10/μL and CD4 + T-cell 1107/μL). Chest CT re-examination showed that nonspecific interstitial inflammation in both lungs was better than B (Figure 1C).

Arteriovenous B-ultrasound of the lower extremities indicated mild atherosclerosis. Lower-limb CT angiography showed no arterial stenosis or occlusion. Pathologic biopsy of the dorsal skin showed hyperkeratosis, irregular epidermis, mild hyperplasia, and endothelial cell proliferation in the dermis that was partly distributed in a lumpy pattern. Vascular fissures and a large number of dilated lumens filled with red blood cells were observed (Figure 3). Immunohistochemical staining revealed the following: smooth muscle antigen(−), vimentin(+), S-100(+), CD34(+), Fil(+) −1, ERG(+), D2-40 part(+), Ki-67 (15%-20% +), FX II(−), and HHV-8 part(+) (Figure 4). These results were consistent with the changes in KS.

He was transferred to a cancer hospital for local radiotherapy and regular chemotherapy. His skin on the feet gradually molted, exudation and pain were obvious, and new granulation tissue gradually grew (Figure 2B). No other changes were observed during follow-up. At present, his condition is better than that prior to treatment, and he is undergoing chemotherapy.

3 | DISCUSSION

In addition to ASS, IIM diseases include dermatomyositis (DM), polymyositis, immune-mediated necrotizing myopathy, and inclusion

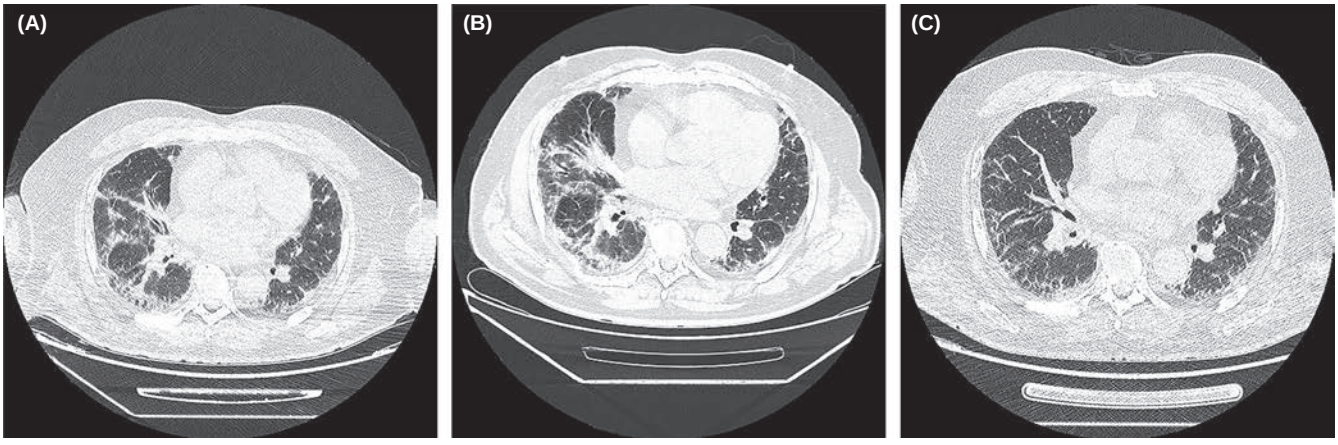

FIGURE 1 High-resolution CT scan of the chest of the patient: A, (2019-05-19) The texture of both lungs is increased and thickened, the lobular septum is thickened, the two lungs are frequently patchy and blurred, and the ground glass and honeycomb-like changes are made. B, (2019-05-27) No significant change compared with A. C, (2019-08-02) Nonspecific Interstitial inflammation of both lungs, better than B.

FIGURE 2 A, The patient's sole skin was dark, crusted, and partially cracked. B, After 7 months of radiotherapy and chemotherapy, the black part of the skin of the foot has faded, and new granulation tissue has grown on the surface.

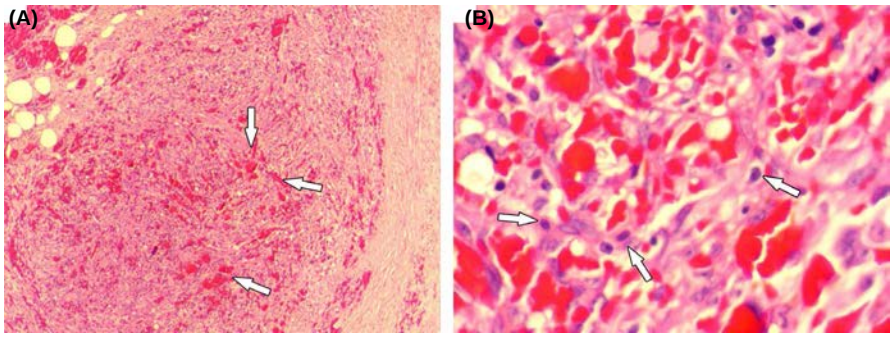

FIGURE 3 Light microscopic manifestations of foot dorsal skin pathology: A, Hyperplasia can be seen in the dermis, irregular branching into a network of blood vessels and cracks (arrow), red blood cells can be seen inside and outside the cavity, with spindle cells in between, fused with nodules. (Hematoxylin-eosin stain, original magnification, ×40). B, The spindle cells are intertwined (arrow), the cell heterosexuality is not obvious, and red blood cells can be seen inside and outside the blood vessel cavity (Hematoxylin-eosin stain, original magnification, ×400).

body myositis. DM shows the highest correlation with cancer development, with the incidence of about 5 times higher in DM patients than in the general population.[2] DM patients with cancer tend to exhibit higher levels of anti-transcriptional intermediate factor 1 (TIF1)-γ and anti-nuclear matrix protein 2 antibodies.[3-5] IIM itself may be a risk factor for cancer, and immunosuppressants administered for IIM treatment also increase malignancy risk.

Antisynthase syndrome has an annual incidence of approximately 0.6/100 000.[6] A retrospective study[7] showed that the morbidity of malignancy in Chinese ASS patients was 6.5%. The presence of anti-Jo1 antibodies was associated with a higher risk of cancer than other autoimmune antibodies such as anti-PL-7 and anti-PL-12 antibodies.[8] ASS patients with both anti-Jo1 and anti-Ro52 antibodies are more prone to cancer than those with anti-Jo1 antibodies alone (19.4% vs 5.7%), highlighting the significance of anti-Ro52 antibodies in ASS patients with cancer. In our case, blood tests revealed the presence of anti-Ro52 antibodies, consistent with Marie et al,[8] suggesting that anti-Ro52 positivity may be a risk factor for cancer.

Kaposi sarcoma is an endothelium-derived cancer, which can be classified into classic KS, endemic KS (found in African populations), iatrogenic KS caused by long-term immunosuppressive therapy, HIV-induced and immunodeficiency-associated epidemic KS, and KS in HIV-negative men who have sex with men.[9] Although these 5 types of KS are different, they mainly affect men and are related to HHV-8 infection, a highly carcinogenic human virus. HHV-8 can infect endothelial cells, induce angiogenic phenotypes in infected cells and promote neovascularization.[10] HHV-8 genome-encoded proteins inhibit the innate immune system by blocking pattern recognition receptors such as Toll-like receptor (TLR)2, TLR4, nucleotide-binding leucin-rich repeat Pyrin domain (NLRP)1, and NLRP3[11,12] and promote HHV8-related disease progression. Our patient was an older male with skin lesions on the feet and HHV-8 infection, consistent with the classic manifestations of KS.

Dantzig[13] first reported the occurrence of KS and polymyositis in 1974..Simeoni et al[14] reported a case of KS in a DM patient thought to be caused by immunosuppressive therapy; KS also occurred in an ASS patient after 2 months of glucocorticoid therapy without immunosuppressant drugs.[15] The number of glucocorticoid receptors increases in KS tissues, and glucocorticoids can induce HHV-8 replication and activate the lytic cycle.[16] This may be one of the mechanisms underlying KS development after glucocorticoid administration. Our patient did not receive immunosuppressive therapy, and CD4+/CD8 + T-cell proportion did not significantly decrease. Therefore, glucocorticoid-induced KS could not be ruled out.

Sellitto et al[17] reported a rare case of KS with ASS paraneoplastic syndrome in which ASS was stable during chemotherapy and

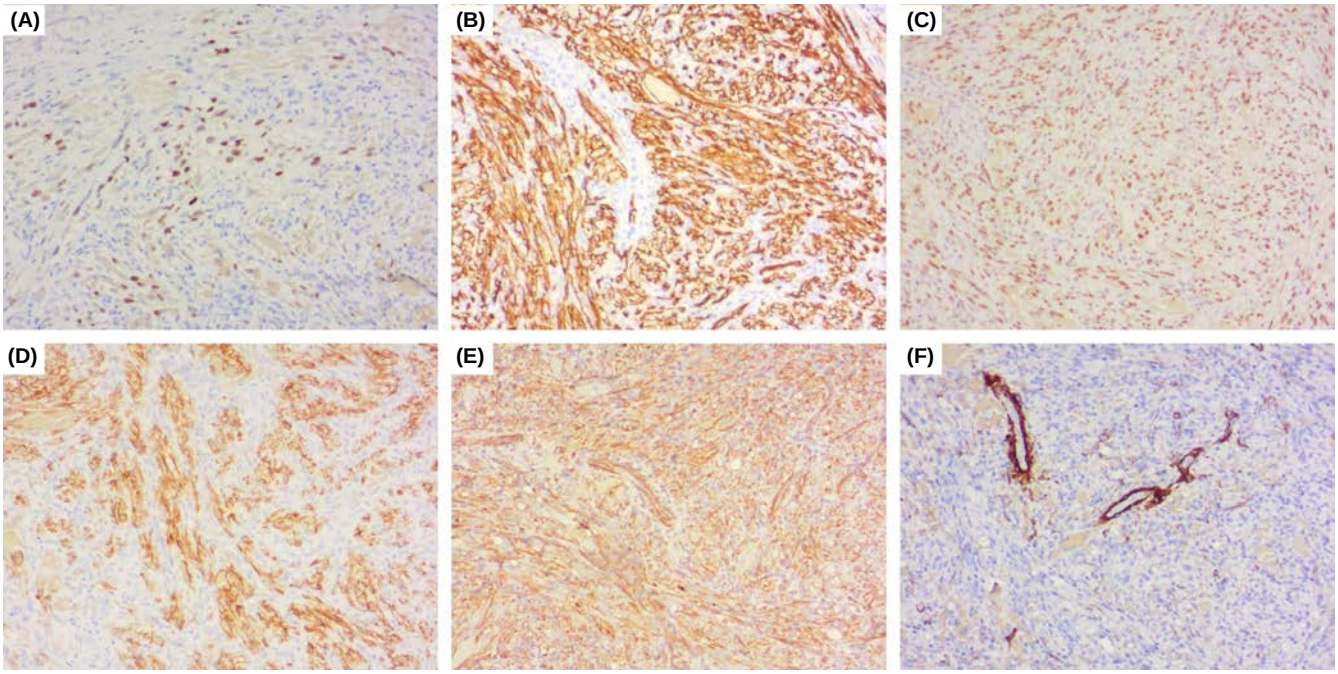

FIGURE 4 Immunohistochemical manifestations of foot dorsal skin pathology: A, HHV-8 (+); B, CD34 (+); C, Fil-1 (+); D, D2-40 (+); E, Vimitin (+); F, SMA (–). original magnifications × 100.

relapsed after chemotherapy discontinuation. Our patient developed skin lesions and was diagnosed with KS 2 months after being diagnosed with ASS. However, the possibility that KS development had started before ASS diagnosis cannot be excluded. Therefore, ASS may have also appeared as a secondary cancer manifestation in our patient. As in the case reported by Sellitto, our patient also tested positive for anti-Ro52 antibodies, which is suggestive of the link between anti-Ro52 antibodies and cancer risk in ASS patients.

Sufficient understanding of the pathophysiological relationship between ASS and KS is lacking. The number of genetic modifications in the tumor *TIF1* gene, including mutations and loss of heterozygosity, increases in patients with anti-TIF1γ-positive myositis,[18] suggesting that an induced immune response is associated with both cancer and inflammatory myopathy. Whether this response caused KS in our patient remains unclear.

This case provides some insights into ASS and its complications. Although very few cases of ASS with KS are reported. It is important for ASS patients who are involved with interstitial pneumonia to have early immunosuppressive therapy, and attention to their immunosuppression state at the same time. We recommend preventative cancer screening and follow-up for ASS patients, especially those who are anti-Ro52 antibody positive. Furthermore, in ASS patients treated with immunosuppressant drugs, once unexplained skin changes occur, skin biopsy should be performed as soon as possible.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Nan He and Dingqi Lu contributed equally to this paper, they were involved in the conception, design, data acquisition and write-up of the manuscript. Jing Xue and Xinchang Wang contributed to data acquisition, critical review of manuscript for important intellectual content and final approval of the manuscript.

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COCHRANE CORNER

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Are interventions for preventing falls in older people in care facilities and hospitals effective? A Cochrane Review summary with commentary

The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review "Interventions for preventing falls in older people in care facilities and hospitals"[1] by Cameron et al.[a]

2 | BACKGROUND

Falls are commonly described as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects".[2] About one-third of the population aged 65 or older falls each year[3] rising up to 50% for those living in long-term care institutions.[4] A systematic review has shown that in nursing homes and hospitals falls in older people have multifactorial etiologies, and risk factors include history of falls, use of walking aids and disability.[5] A retrospective study reported that almost 90% of external-cause deaths of residents of nursing homes in Victoria (Australia) were due to falls.[6] There are many interventions that are used to prevent falls in the elderly. The important question as to which interventions are effective for preventing falls in care facilities and hospitals in older people is addressed in a Cochrane Review.[1] The evidence for effectiveness of these interventions is of particular interest to physiatrists and other rehabilitation professionals.

3 | WHAT IS THE AIM OF THIS COCHRANE REVIEW?

The aim of this Cochrane Review was to assess the effects of interventions designed to reduce the incidence of falls in older people in care facilities and hospitals.

4 | WHAT WAS STUDIED IN THE COCHRANE REVIEW?

The population addressed included older people staying in care facilities or hospitals. The interventions studied were any intervention aimed to reduce falls. They were classified using the taxonomy developed by the Prevention of Falls Network Europe (ProFaNE) and grouped by combination (single, multiple, or multifactorial), and type or descriptors (exercises, medication, surgery, management of urinary incontinence, fluid or nutrition therapy, psychological interventions, environment/assistive technology, social environment, interventions to increase knowledge, other interventions).[7] The interventions were compared with placebo or "usual care", where "standard practices" for managing risk factors for falls were applied. The primary outcomes were rate of falls and risk of falling, secondary outcomes included number of participants sustaining a fall-related fracture, complications of the interventions, and economic outcomes.

5 | SEARCH METHODOLOGY AND UP-TO-DATENESS OF THE COCHRANE REVIEW?

This Cochrane systematic review is an update of a review first published in 2010[8] and updated in 2012.[9] Authors searched, without any language restriction, for studies that had been published up to August 3, 2017, on the Cochrane Bone, Joint and Muscle Trauma Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, the World Health Organization's International Clinical Trials Registry Platform Search Portal, and ClinicalTrials.gov.

[a]This summary is based on a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews* 2018, Issue 9. Art. No.: CD005465, DOI: 10.1002/14651858.CD005465.pub4. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in the summary with commentary are those of the Cochrane Corner author(s) and do not represent the Cochrane Library or Wiley. This review was produced with the support of the Cochrane Bone, Joint and Muscle Trauma Review Group. This Cochrane Corner is produced in agreement with the *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

6 | WHAT ARE THE MAIN RESULTS OF THE COCHRANE REVIEW?

The review included 95 studies (138 164 people). Thirty-five trials (77 869 people) were added to the previous review.[9] Authors reported the results by setting (care facilities or hospitals), combination of intervention (single, multiple, or multifactorial) and intervention type (categorized according to ProFaNE).[7] Table 1 summarizes the included studies with information on the number of studies and participants for the classified intervention and for each outcome studied.

The review shows the following according to settings and classification of interventions.

6.1 | Care facilities

Seventy-one trials included patients in care facilities and analyzed single (exercise, medication, environment/assistive technology, social and psychological interventions), multiple, or multifactorial interventions.

- For all interventions, there is uncertainty of their effects on fractures and on adverse events as the quality of the evidence for these outcomes was graded as very low.
- There is also uncertainty on the effects of exercise compared with usual care on the rate of falls (very low-quality evidence).
- Low-quality evidence suggests little or no difference of exercise on risk of falling.
- There is also low-quality evidence of little or no difference with medication review compared with usual care regarding the rate of falls and risk of falling.
- It is uncertain whether different types of exercise can influence any of the outcomes as the evidence quality is very low.
- Vitamin D supplementation probably reduces rate of falls but probably makes little or no difference to the risk of falling in those with low levels of vitamin D (moderate-quality evidence).
- Moreover, an education intervention aimed at increasing the prescription of vitamin D, calcium and osteoporosis medication may make little or no difference to the rate of falls or risk of falling (low-quality evidence).
- The very low-quality evidence from the single trial testing an environment/assistive technology intervention (wireless position-monitoring), means there is uncertainty of its effect on the rate of falls.
- Considering the quality of evidence on staff training interventions, there is uncertainty of any effect on the rate of falls, but the intervention may make little or no difference to the risk of fracture.
- Regarding service model change interventions, the use of a falls risk-assessment tool probably makes little or no difference to the rate of falls or risk of falling, while there is uncertainty on the effect of dementia care mapping on rate of falls. Evidence on the risk of fracture is also uncertain for the interventions in this category.
- Considering the very low quality of available evidence, there is uncertainty on the effectiveness of psychological interventions in reducing the rate of falls and the risk of falling.
- There is uncertainty whether multiple interventions influence the rate of falls, risk of falling, as quality of available evidence was very low.
- There is uncertainty on the effect of multifactorial interventions on rate of falls (very low-quality evidence). Low-quality evidence suggests these interventions may make little or no difference on risk of falling.

6.2 | Hospitals

Twenty-four trials examined patients in hospitals. The analyzed treatments were single (exercise, medication, environment/assistive technology, and social interventions), or multifactorial.

- There is uncertainty whether additional exercise has an effect on the rate or risk of falling, as available evidence is very low.
- It is also uncertain whether medication review and vitamin D supplementation are effective on rate or risk of falling.
- The evidence on any environment/assistive technology intervention (eg furnishing, communication aids such as bracelets for those at high risk for falls and bed exit alarms) and social environment (eg changes in service models) is also very low, indicating uncertainty of their effect on the rate or risk of falling.
- It is also uncertain whether an educational intervention based on the identification of risk factors and usual fall-prevention care in acute medical wards can be effective, but low-quality evidence shows that providing patients with educational materials alone may make little or no difference to the rate of falls or risk of falling.
- Multifactorial interventions may reduce rate of falls (low-quality evidence). However, there is uncertainty regarding their effects on risk of falling.

7 | HOW DID THE AUTHORS CONCLUDE?

There was evidence of effectiveness for some of the investigated interventions but most of the evidence were graded as low or very low quality. Further high-quality large randomized controlled trials on this topic would be necessary to clarify the effectiveness of the various interventions to prevent falls and fracture-related falls in patients staying in care facilities and hospitals.

8 | WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN REHABILITATION?

Falls are one of the most common causes of morbidity and mortality in the elderly, representing a major issue in care facilities and

TABLE 1 Summary of number of studies and participants available for 4 outcomes for each comparison, split by setting

Setting and intervention	Rate of falls		Risk of falling		Risk of fracture		Adverse events	
	No. trials	No. people	No. trials	No. people	No. trials	No. people	No. trials	No. people
Care facilities, single intervention, exercise (vs usual care)	10	2002	10	2090	1	183	4	1032
	4	130	1	110				
Care facilities, single intervention, comparisons of two different exercise programs	5	305	6	327	1	159	4	269
Care facilities, single intervention, medication review intervention	6	2409	6	5139	1	93	2	102
	1	716	1	716				
	1	36						
Care facilities, single intervention, vitamin D supplementation	4	4512	4	4512	3	4464	2	747
	1	91	1	91	1	583	1	91
	1	4017	1	4017	1	4017	1	583
			1	583				
			1	75				
Care facilities, single intervention, environment/assistive technology intervention	1	43					1	43
Care facilities, single intervention, staff training	1	5637	1	4017	1	5637		
	1	392						
	1	497 staff members 982 facility beds						
Care facilities, single intervention, service model change	1	1125	1	1125	1	1125		
	1	289						
	1	293						
	1	5391			1	5391		
Care facilities, single intervention, psychological intervention	1	114	1	114				
	1	49						
Care facilities, other single interventions	1	145	1	145	1	395	1	145
							1	395
Care facilities, multiple intervention	1	190	1	190	1	190		
	1	412	1	412	1	412		
	1	50						
Care facilities, multifactorial intervention	10	3439	9	3153	5	2160	3	312
	1	31	1	482				
Hospitals, single, exercise	2	215	2	83			1	161
Hospitals, single, medication review intervention	1	114	1	114				
Hospitals, single, vitamin D supplementation			1	205	1	205	1	205
Hospitals, single, furnishing adaptations	1	54	1	54				
	1	11 099						
Hospitals, single, communication aids	1	134	1	134				
	2	28 649	2	28 649			2	27 742
	1	70						

(Continues)

TABLE 1 (Continued)

Setting and intervention	Rate of falls		Risk of falling		Risk of fracture		Adverse events	
	No. trials	No. people	No. trials	No. people	No. trials	No. people	No. trials	No. people
Hospitals, single, service model change intervention	1	1122	1	5264	1	199		
	1	2201	1	71				
	1	5264						
	1	217						
	1	199						
Hospitals, single, knowledge intervention	1	1206	1	1206	1	1206		
	1	1822	1	1822				
Hospitals, multifactorial intervention	5	44 664	3	39 889	2	4615	4	39 763

Note: Many of the trials included in the review are cluster randomized controlled trials and thus the available evidence is substantially less than it might appear from the number of participants for these trials.

hospitals. The etiology of falls is multifactorial and therefore there are many interventions that might be successfully addressed to prevent them. The International Classification of Functioning, Disability and Health (ICF) is an ideal comprehensive framework for fall risk assessment and management.[10] An ICF core set comprising 34 fall risk categories (18 body functions, 2 body structures, 8 activities and participation, 4 environmental factors, and 2 personal factors) was developed[11] and tested.[12] Physiatrists need to be aware of the different treatment options, their effects on reducing the rate and risk of falling, the risk of fracture, and possible adverse events. Data on how these interventions can optimize functioning should also be provided. Evidence from this Cochrane systematic review and from future well-conducted randomized controlled trials on this topic can contribute to inform rehabilitation health professionals.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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CORRESPONDENCE

Successful treatment of adalimumab for older Behçet's disease complicated with pulmonary artery thrombosis: A case report

Behçet's disease (BD) is a chronic systemic disorder characterized by inflammation of multiple organs, such as eyes, mucosa, skin, brain, joints, and vessels.[1] Vascular manifestations, which consist of arterial involvements and venous involvements, affect 15%-40% of patients with BD.[2] Pulmonary involvements, including pulmonary thrombosis and pulmonary aneurysms, are less common, but associated with poor prognosis and severe cases and are most common among younger men.[3] Anti-tumor necrosis factor (anti-TNF) inhibitors have been recommended for the treatment of severe cases of vascular BD.[4] However, the use of TNF inhibitors has been reported to cause adverse effects such as infections, especially for older patients.[5]

Herein, we present a case of an older patient with BD, who developed refractory pulmonary artery thrombosis, improved with adalimumab (ADA), and sustained remission for 1 year without adverse effects.

1 | CASE REPORT

A 80-year-old man admitted to our hospital with fever, dyspnea and erythema nodosum. He had a history of recurrent erythema nodosum in lower limbs and recurrent oral aphthous ulcers for over 4 years. He was diagnosed with BD 6 months ago with oral aphthous ulcers, anterior uveitis, erythema nodosum, and arthritis. As treatment of colchicine and prednisolone (PSL) 30 mg/d was started, his clinical symptoms rapidly improved. The dose of PSL was decreased to 15 mg/d, but he suffered from dyspnea and fever 1 month later.

A physical examination at admission revealed a fever of 37.0°C, arthralgia, erythema nodosum in both legs, and left leg edema. Respiratory rate was 20 breaths/min, pulse rate was 108 beats/min, and oxygen saturation was 93% in room air. No dry cough, oral ulcers, inflammatory back pain, psoriasis, or abdominal pain were seen. Laboratory data showed C-reactive protein (CRP) of 8.33 mg/dL and erythrocyte sedimentation rate of 70 mm/h. D-dimer (D-D) was elevated to 2.3 μg/mL. White blood cell count was 6300/μL, hemoglobin was 11.7 g/dL and the platelet count was 23.8 × 10^4/μL. Human leucocyte antigen (HLA)-B26 was positive and HLA-B27 was negative. Anti-nuclear antibodies, anti-cardiolipin antibodies, and lupus anticoagulant were negative. Enhanced chest computed tomography (CT) showed multiple thrombi on right pulmonary artery (Figure 1). He was diagnosed as having pulmonary artery thrombosis complicated with BD. The dose of PSL was increased from 15 to 20 mg/d, and heparin was started. However, chest CT performed 1 week after the first scan showed exacerbation of thrombosis (Figure 1). He was administered subcutaneous ADA (160 mg at first week and from then 80 mg every 2 weeks; Figure 2). Immediately after treatment, his clinical symptoms improved. Four days after first injection of ADA, CRP and D-D was decreased. Chest CT revealed improvement of pulmonary thrombosis after 2 weeks. We could taper PSL dose from 20 to 4 mg/d without recurrence after a year. He had no adverse effect, such as injection site reactions or infections.

2 | DISCUSSION

We present a case of an older patient with vascular BD who received ADA treatment without adverse effect.

Pulmonary artery manifestation is rare, and affects mainly young man, but predicts a poor prognosis. Pulmonary artery aneurysms and pulmonary artery thrombosis are the two most common manifestations in pulmonary artery manifestations, the prevalence of which is <5%.[6] However, vascular involvement is the most common cause of morbidity and mortality in BD.[7] The underling pathogenesis of pulmonary involvements of BD has remained unknown. It has been reported that TNF-α, INF-γ and interleukin-8 are associated with disease activity and vascular involvement.[8]

Treatment of pulmonary artery thrombosis is mainly immunosuppressive drugs. Recommended treatment is pulse corticosteroid therapy followed by prednisolone of 1 mg/kg/d. Azathioprine, cyclophosphamide, cyclosporine A and mycophenolate mofetil are also recommended for thrombosis in BD. In refractory cases, anti-TNF-α inhibitors including adalimumab or infliximab might be useful[4,9] in addition to immunosuppressive drugs. Further, anti-TNF inhibitors have corticosteroid-sparing effect in vascular BD.[9]

In patients with rheumatoid arthritis, the most common adverse events were infections during anti-TNF-α inhibitors treatment, particularly in older patients.[5] In BD patients including vascular BD with anti-TNF-α inhibitors treatment, infections are also the most important issues.[10] However, previous reports about BD with anti-TNF-α inhibitors treatment included mainly those for younger patients. There are few reports of anti-TNF-α inhibitors treatment for BD patients older than 80 years. In this case, we reported successful treatment with ADA in a 80-year-old BD patient without adverse

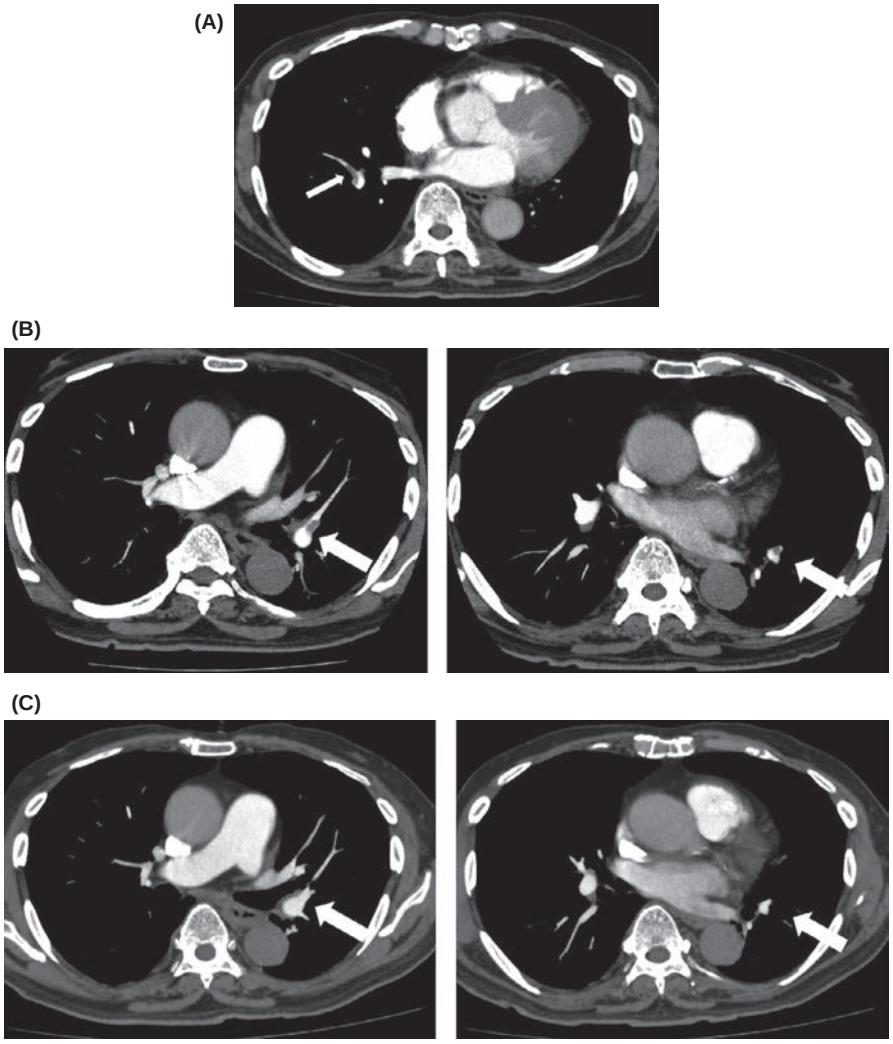

FIGURE 1 Pulmonary artery thrombosis. A, Enhanced computed tomography image demonstrating a filling defect (white arrow) in the right pulmonary artery on admission. B, Enhanced computed tomography image showing multifocal contrast filling defect (white arrow) in the left pulmonary arteries before adalimumab treatment. C, Pulmonary artery thrombosis is diminished after adalimumab treatment (white arrow)

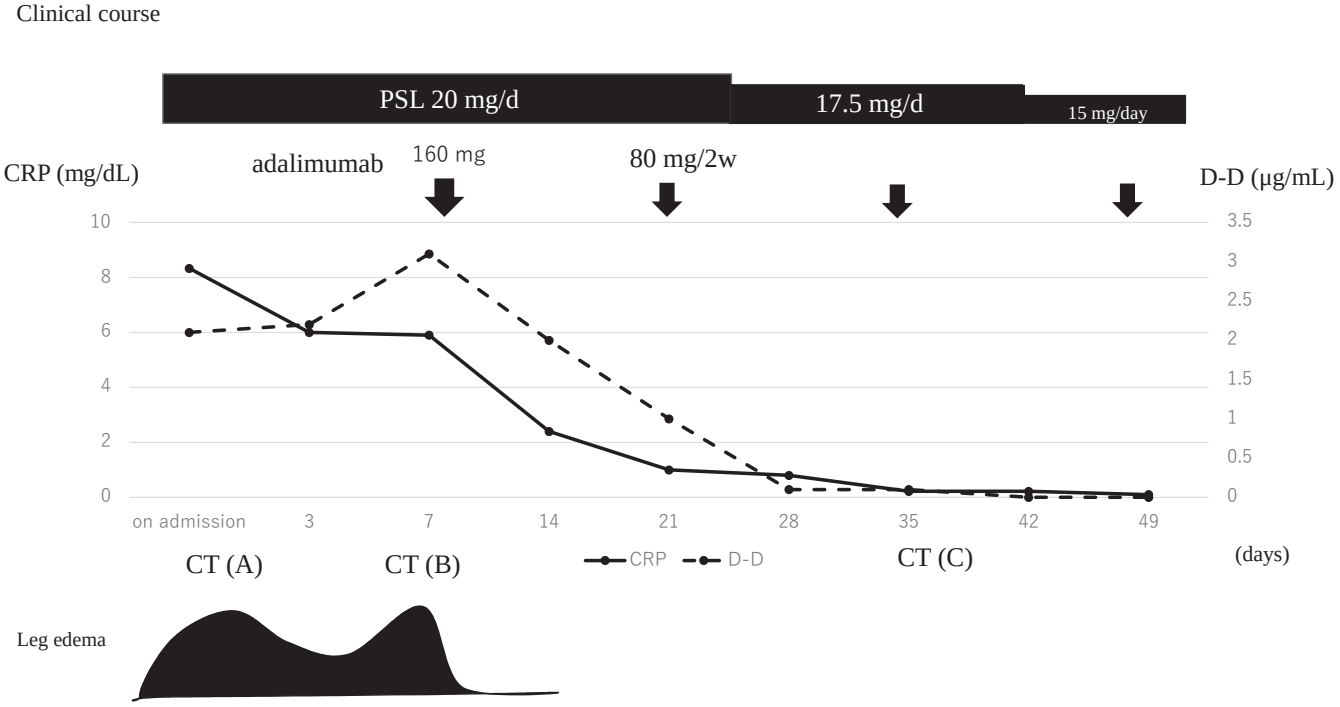

FIGURE 2 Clinical course. CRP, C-reactive protein; CT, computed tomography; D-D, D-dimer; PSL, prednisolone

events including infections. In conclusion, this case suggests that anti-TNF-α treatment is an effective and safe therapy for older vascular BD patients.

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None.

CONFLICT OF INTEREST

No potential conflict of interest is reported by the authors.

PATIENT CONSENT

The patient provided written informed consent for publication of his data.

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ERRATUM

The authors would like to draw the readers' attention to an error in the following article:

Negrini F, Negrini S. Is paracetamol better than placebo for knee and hip osteoarthritis? A Cochrane review summary with commentary. *Int J Rheum Dis*. 2020;23(4):595-596.
Affiliation 2 should read as: Department of Biomedical, Surgical and Dental Sciences, University of Milan "La Statale", Milan, Italy.

The publisher apologizes for this error and any confusion this may have caused.

The 2020 congress will be held on **31 August – 3 September** in Kyoto International Conference Center, Japan. Please do look out for updates by visiting the website.

APLAR aims to improve standards of clinical practice, teaching, and research in rheumatology across Asia Pacific. We are recognising the long-term efforts and dedication of centers in the region with a similar goal for excellence in the field. The certification programme we have initiated will award leading centers in Asia Pacific as Centers of Excellence based on three pillars (research, clinical practice, academia), pre-defined by a list of criteria set by APLAR.

We hope the centers in the region with an excellent track record in any of these pillars will participate in this programme as our goal is to establish reference centers that are best in class models for practice, teaching, and research in rheumatology. We believe this will enhance and enrich the 'best in class' experience for our trainees involved in the APLAR Fellowship programme. Further, this will also help us build a strong network of reference centers for collaborations and consultation within and among countries in the region.

APLAR awarded Centers of Excellence have been updated and information about these centers can be found on the website. Center of Excellence 2020 application will begin in March next year. Application information will be made available through the Member National Organisations of APLAR.

APLAR FELLOWSHIP GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 2 applicants for the Fellowship Grant of 2019. They are embarking on their fellowship programme in the coming months. Successful candidates must have a long-term commitment to continue research or clinical work in his/her own country at the conclusion of the Fellowship. The grant is awarded to cover accommodation and subsistence costs. We congratulate the awardees and wish them a fruitful journey in their career paths.

APLAR RESEARCH GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 2 applicants for the Research Grant of 2019. The grants are to assist the undertaking of research in either adult or paediatric rheumatology. The aims of the grant are to give the researcher an opportunity to start and do research within their own country of residence. In addition, we hope to promote and support basic and clinical research directed to the causes, prevention, and treatment of rheumatic diseases in the APLAR member society countries. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset. The awarded candidates are encouraged to publish their work in the APLAR official journal – International Journal of Rheumatic Disease (IJRD) as part of their contribution.

APLAR-COPCORD GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) did not have any applicant for COPCORD grant 2019. We encourage interested candidates to send in their application during the application period for COPCORD grant 2020. The aims of the grant are to give the researcher an opportunity to study rheumatic disease in the community of their own country of residence. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset.

All APLAR Grants are currently open for application. The closing date will be on 21 February 2020. APLAR Grants information on eligibility, criteria and application requirement can be found on the *website*.