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REVIEWS AND RECOMMENDATIONS

International Journal of Rheumatic Diseases

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Updated APLAR consensus statements on care for patients with rheumatic diseases during the COVID-19 pandemic

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Abstract

Aim: To update previous guidance of the Asia Pacific League of Associations for Rheumatology (APLAR) on the management of patients with rheumatic and musculoskeletal diseases (RMD) during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Research questions were formulated focusing on diagnosis and treatment of adult patients with RMD within the context of the pandemic, including the management of RMD in patients who developed COVID-19. MEDLINE was searched for eligible studies to address the questions, and the APLAR COVID-19 task force convened 2 meetings through video conferencing to discuss its findings and integrate

best available evidence with expert opinion. Consensus statements were finalized using the modified Delphi process.

Results: Agreement was obtained around key aspects of screening for or diagnosis of COVID-19; management of patients with RMD without confirmed COVID-19; and management of patients with RMD with confirmed COVID-19. The task force achieved consensus on 25 statements covering the potential risk of acquiring COVID-19 in RMD patients, advice on RMD medication adjustment and continuation, the roles of telemedicine and vaccination, and the impact of the pandemic on quality of life and on treatment adherence.

Conclusions: Available evidence primarily from descriptive research supported new recommendations for aspects of RMD care not covered in the previous document, particularly with regard to risk factors for complicated COVID-19 in RMD patients, modifications to RMD treatment regimens in the context of the pandemic, and COVID-19 vaccination in patients with RMD.

KEYWORDS

APLAR guidance, Asia Pacific, consensus, rheumatic disease, SARS-CoV-2

1 | INTRODUCTION

In May 2020, the Asia Pacific League of Associations for Rheumatology (APLAR) published a position statement on the care of patients with rheumatic and musculoskeletal diseases (RMD) during the coronavirus disease 2019 (COVID-19) pandemic.[1] The document was borne from the urgency to provide a preliminary rheumatology management guide for Asia Pacific practitioners as the rapid spread of COVID-19 generated challenges unique to the treatment of rheumatic disease.

The lack of data from quantitative research on COVID-19 before the May publication of the APLAR statement, especially data that centers on patients with RMD, precluded our guideline working group, the APLAR COVID-19 task force, from providing specific recommendations. Since then, new information from both quantitative and qualitative research has emerged from globally conducted dynamic research efforts. We aimed to review all available new and pertinent evidence, and to update our preliminary statement by developing consensus recommendations for the management of patients with RMD during the COVID-19 pandemic.

This document presents our findings and the resultant 25 consensus statements. The recommendations together aim to provide a much-needed practical guide to clinical decision-making of the healthcare practitioner caring for RMD patients during this time. They do not include recommendations on the specific management of COVID-19 infection.

2 | METHODS

The APLAR COVID-19 task force consisted of 21 members including specialists in the fields of rheumatology, pulmonology, and infectious disease, and a patient representative. Most members are internationally recognized rheumatologists with many years of clinical and scientific experience, who fulfill or have fulfilled official positions in the APLAR organization. Task force leaders compiled a list of key RMD topics and formulated questions that reflected clinically relevant issues in RMD management in the context of COVID-19, namely: (a) screening for or diagnosis of COVID-19 in patients with RMD; (b) the management of patients with RMD but with no COVID-19; and (c) the management of patients with RMD and COVID-19 (Table 1). To address the questions, eligible studies involving adult patients were identified in the archives of MEDLINE (through PubMed) published from December 2019 to August 2020. Medical subject headings (MeSH) for "rheumatic diseases" and "COVID-19" were used in the search strategy, along with the appropriate MeSH terms for the concepts of prevention, diagnosis, screening, and treatment. For drug therapy, the following key words and their related terms were included in the search: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). With the understanding that controlled trials may have not yet been completed, searches were not limited to randomized controlled trials but also included other study types such as non-controlled trials, cohort studies, other comparative studies, case series, and case reports. Other consensus documents and abstracts were also retrieved and reviewed. Searches were also not limited to the English language to broaden the yield of studies from across the globe.

The members were grouped according to the identified core RMD topics and their corresponding research questions. Each group was instructed to review the evidence, then draft relevant consensus

TABLE 1 Research questions

Screening for/diagnosis of COVID-19
1. Do patients with RMD have a higher risk of COVID-19 compared to the general population?
2. How can COVID-19 risk be mitigated in patients with RMD?
3. Should patients with RMD be screened for COVID-19 differently than the general population?
Management of RMD patients without COVID-19
4. In newly diagnosed patients, should treatment be initiated differently during this pandemic period compared with prior to the pandemic?
5. What is the evidence on continuing/de-escalating/discontinuing treatment in patients with RMD who are close contacts of individuals with SARS-CoV-2 infection?
6. What has been the effect of the pandemic on treatment adherence?
7. What is the role of telemedicine in the management of patients with RMD in the setting of COVID-19?
8. Which vaccines should be recommended for patients with RMD during the pandemic period?
Management of RMD patients with COVID-19
9. What are the rheumatic manifestations of COVID-19?
10. Is the clinical presentation of COVID-19 in patients with RMD different from that in patients without RMD?
11. Can patients with RMD continue their medication once diagnosed with COVID-19?
12. What is the evidence for de-escalating/discontinuing treatment in patients with RMD with COVID-19?
13. What is the evidence on glucocorticoids in the treatment of COVID-19?
14. What is the evidence on continuing/re-initiating treatment in patients with RMD post-COVID-19?
15. What is the effect of COVID-19 on the quality of life of patients with RMD post-COVID-19?

Abbreviations: COVID-19, coronavirus disease 2019; RMD, rheumatic and musculoskeletal disease.

statements, all for presentation and discussion during pre-planned video conferences.

The first meeting was held on 10 October 2020 to discuss, refine, and vote on the statements. The quality of evidence supporting each statement was evaluated using the evidence-assessment frameworks prescribed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[2,3] Using the modified Delphi approach to achieve expert group consensus, the meeting attendees provided feedback on the evidence presentation and the proposed statements. An online poll launched during the meeting allowed them to indicate their levels of agreement with the proposed statements by choosing among 5 options: 1, accept completely; 2, accept with some reservations; 3, accept with major reservations; 4, reject with reservations; and 5, reject completely. The draft statement was endorsed as a final consensus recommendation when the combined percentages for the responses of "accept completely" and "accept with some reservations" totaled ≥80% of votes among the attendees. The group agreed on a strength of recommendation where applicable, that is, for statements recommending a course of action.

Discussion of the research questions, their associated evidence, and proposed statements continued during the second meeting, which was held on 1 November 2020. Further clarifications on unresolved matters during the first meeting were carried over to the second meeting. The panel members were encouraged to review additional references that emerged during the interval between the 2 meetings. Grading of the statements and online voting proceeded for the remainder of topics and their draft statements. Consensus was again established at ≥80% agreement. Some proposed statements were considered at the time to have insufficient supporting evidence. These "expert opinion" statements were made available to the task force members online for final review and voting after the second meeting.

3 | RESULTS

The task force achieved consensus on 25 statements (Table 2). Nine of the statements were deemed "expert opinion" statements, given the paucity of supporting evidence on these topics.

3.1 | Screening for and diagnosis of COVID-19

3.1.1 | Risk of COVID-19 in RMD patients

C1. Patients with immune-mediated RMD may be at a higher risk of COVID-19 and of respiratory failure than the general population. (90% agreement, grade of evidence very low, strength-of-recommendation assessment not applicable).

C2. Those potentially at high risk include patients on glucocorticoids (≥10 mg prednisolone/d). (100% agreement, grade of evidence moderate, strength-of-recommendation assessment not applicable).

C3. Patients with RMD should be strongly advised to follow all preventive measures as stipulated by the healthcare authorities in their countries, as for patients without RMD. (94% agreement, grade of evidence low, strong recommendation).

In a meta-regression of 65 observational studies, patients with RMD had the highest rates of hospitalization (0.54; 95% CI 0.46-0.63) and mortality (0.113; 95% CI 0.098-0.13) due to COVID-19 among patients with autoimmune diseases.[4] Meanwhile, descriptive studies suggest that RMD and RMD-related factors may be associated with a more severe course of COVID-19. A higher risk of respiratory failure was shown in RMD patients when matched against non-rheumatic patients from a Wuhan, China cohort study (patients with respiratory failure: 38% of RMD patients vs 10% of those without RMD; $\chi^2 = 13$, $P < .001$).[5] A higher risk of mechanical ventilation was also seen for RMD patients in a Boston, Massachusetts cohort (multivariable odds ratio [OR] 3.11, 95% CI 1.07-9.05), but a follow-up

that extended the study period from 4 to 6 months showed similar risk between rheumatic and non-rheumatic patients (adjusted hazard ratio [HR] 1.51, 95% CI 0.93-2.44).[6,7] The presence of comorbidities, older age, and use of prednisone ≥10 mg/d have been suggested as risk factors for poor outcomes in SARS-CoV-2-infected RMD patients.[8-11] Also, according to primary care data from the UK, patients with the diagnosis of rheumatoid arthritis, systemic lupus erythematosus, or psoriasis, analyzed as a group, were more likely to die from COVID-19-related causes compared to patients without those conditions (adjusted HR 1.19; 95% CI 1.11-1.27).[12]

Initially, shielding, or strict quarantine and minimizing non-essential contact even with other household members, was recommended for certain high-risk RMD patients.[13] However, shielding may even be less important than self-education and adherence to general preventive measures.[14] RMD patients should thus be advised to follow locally stipulated guidance for transmission prevention as advised for the general population.

3.1.2 | Diagnosing COVID-19 in RMD patients

C4. There is no evidence to support a different diagnostic strategy for COVID-19 in patients with RMD from that of non-RMD patients. (100% agreement, expert opinion, strength-of-recommendation assessment not applicable).

C5. Patients with RMD should be tested as soon as they develop any symptoms of COVID-19 because of the potential increased risk of poorer outcomes. (100% agreement, expert opinion, strong recommendation).

The task force aimed to address whether the approach to test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with RMD should be modified from the current testing protocol for non-rheumatic patients. No evidence currently supports a different strategy. Despite this, owing to the risks for complicated COVID-19 discussed earlier, it is recommended that timely testing be performed, that is, upon symptom onset.

3.2 | Management of RMD patients without COVID-19

3.2.1 | Initiation of RMD therapies in patients with newly diagnosed RMD

C6. In the absence of contrary evidence, patients with newly diagnosed RMD without COVID-19 should be treated as per standard of care during the pandemic. (100% agreement, expert opinion, strong recommendation).

C7. Therapeutic options alternative to rituximab, sulfasalazine, and cyclophosphamide may be considered on a case-by-case basis. (82% agreement, grade of evidence very low, weak recommendation).

No publications have, as yet, reported on whether starting rheumatologic treatment during the pandemic influenced the clinical course or condition of a patient newly diagnosed with RMD. Therefore, it is recommended that management of newly diagnosed RMD without COVID-19 should be as indicated for each specific RMD, using established, guideline-based therapies.

Underpinning the decision to start RMD treatment during the pandemic is the risk of contracting COVID-19, which may be increased by use of immune-modulating medication. This may stem from a known risk of other infections with use of some DMARDs.[15] Furthermore, immunosuppression with some agents, including rituximab (RTX), sulfasalazine (SSZ) and cyclophosphamide (CYC), may have a role in altering the immune response to infection. The true risk of infection associated with RMD therapies is still uncertain, but caution stemming from a registry-reported risk of COVID-19-related death with RTX, SSZ, and CYC[16] prompted our group's proposal to use good but safer alternatives, if available. Our votes were almost equally divided between accepting statement C7 completely and accepting with some reservations. Nevertheless, the members agreed that the decision to use alternatives should always be individualized. It was considered that the high risk for COVID-19 exposure in endemic areas may be a contributing and confounding factor to the development of COVID-19; thus, starting treatment with alternative options in these locations may be appropriate. On the other hand, to manage acute, critical conditions such as vasculitis and myositis, established therapies may be more beneficial than alternatives. The urgency to control disease in these critical conditions will need to be prioritized over the potential risk of acquiring SARS-CoV-2 infection.

3.2.2 | Modification of RMD treatment of patients who are close contacts of SARS-CoV-2 -infected individuals

C8. For patients with RMD who do not have COVID-19 symptoms and do not have documented COVID-19, but who have had close contact with a highly suspected or documented COVID-19 case, the recommendations for RMD medications vary depending on risk. (84% agreement, expert opinion, weak recommendation).

C9. For asymptomatic RMD patients without documented infection, antirheumatic medications, if stopped after exposure, may be resumed once a negative test has been certified, or after approximately 2 weeks of symptom-free observation from the day of exposure, if a test was not performed. (84% agreement, expert opinion, weak recommendation).

Exposure to SARS-CoV-2 through close contact implies a risk of contracting the infection, raising the question of modifying treatment even in the absence of confirmed COVID-19. “Close contact” is described by the Centers for Disease Control and Prevention (CDC) as being within 6 feet of the infected individual for a total of 15 minutes over 24 hours.[17] Some groups recommend modifying

TABLE 2 Summary of consensus statements

Consensus statements	Grade of evidence	Agreement	Strength of recommendation
C1. Patients with immune-mediated RMD may be at a higher risk of COVID-19 and of respiratory failure than the general population.	Very low	90%	Not applicable
C2. Those potentially at high risk include patients on glucocorticoids (≥10 mg prednisolone/d).	Moderate	100%	Not applicable
C3. Patients with RMD should be strongly advised to follow all preventive measures as stipulated by the healthcare authorities in their countries, as for patients without RMD.	Low	94%	Strong
C4. There is no evidence to support a different diagnostic strategy for COVID-19 in patients with RMD from that of non-RMD patients.	Expert opinion	100%	Not applicable
C5. Patients with RMD should be tested as soon as they develop any symptoms of COVID-19 because of the potential increased risk of poorer outcomes.	Expert opinion	100%	Strong
C6. In the absence of contrary evidence, patients with newly diagnosed RMD without COVID-19 should be treated as per standard of care during the pandemic.	Expert opinion	100%	Strong
C7. Therapeutic options alternative to rituximab, sulfasalazine, and cyclophosphamide may be considered on a case-by-case basis.	Very low	82%	Weak
C8. For patients with RMD who do not have COVID-19 symptoms and do not have documented COVID-19, but who have had close contact with a highly suspected or documented COVID-19 case, the recommendations for RMD medications vary depending on risk.	Expert opinion	84%	Weak
C9. For asymptomatic RMD patients without documented infection, if stopped after exposure, antirheumatic medications may be resumed once a negative test has been certified, or after approximately 2 wk of symptom-free observation from the day of exposure, if a test was not performed.	Expert opinion	84%	Weak
C10. Rheumatologists should explore the perceptions of patients and address their concerns to ensure treatment adherence during the COVID-19 pandemic.	Moderate	100%	Strong
C11. The use of telemedicine should be strongly encouraged, especially in areas of high community transmission levels, for follow-up of appropriate patients with RMD if implementing such an intervention is feasible and accepted by patients.	Moderate	100%	Strong
C12. It is recommended that patients with RMD receive an approved SARS-CoV-2 vaccine as soon as it becomes available to them.	Expert opinion	100%	Strong
C13. RMD patients with normal or altered immunocompetence should receive vaccination based on current country, regional and/or international guidelines for vaccinations.	Expert opinion	100%	Strong
C14. Immunization schedules of RMD patients should be maintained while adhering strictly to the safety protocols of COVID-19 prevention.	Expert opinion	100%	Strong
C15. Clinical manifestations mimicking RMDs, laboratory reports of positive antinuclear antibodies, antiphospholipid antibodies, and lupus anti-coagulant have been reported with COVID-19 patients. These patients should be followed for the possibility of persistent intermediate- to long-term immune dysregulation.	Expert opinion	95%	Strong
C16. The clinical presentation of COVID-19 in patients with RMD is similar to that in patients without RMD. Nonetheless, RMD patients who experience worsening of respiratory symptoms should immediately seek further healthcare advice of an expert in treating COVID-19 (eg, pulmonologist, infectious diseases specialist, or general internist) according to local recommendations.	Low	100%	Strong
C17. HCQ, NSAIDs, and ACEi/ARBs may be continued but should be individualized based on disease condition.	Moderate	100%	Strong
C18. The clinician should consider stopping or withholding csDMARDs (other than HCQ), tsDMARDs, and bDMARDs, on a case-by-case basis.	Moderate	94%	Weak
C19. RMD patients with COVID-19 should be treated according to the standard of care.	Low	92%	Strong
C20. Glucocorticoids should be used at the lowest possible dose to control RMD and should not be abruptly stopped.	High	94%	Strong
C21. Immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus) should be discontinued in patients with COVID-19.	Low	82%	Strong

(Continues)

TABLE 2 (Continued)

Consensus statements	Grade of evidence	Agreement	Strength of recommendation
C22. In general, RMD treatments may be re-introduced at least 2 wk after recovery from acute COVID-19. They may need to be individualized based on the clinical scenario and the physician's judgment.	Low	100%	Weak
C23. For asymptomatic individuals, RMD treatment may be re-introduced approximately 10 d after diagnosis of COVID-19.	Low	100%	Weak
C24. SARS-CoV-2 infection has a negative impact on the QoL of RMD patients, particularly the mental health component.	Expert opinion	95%	Not applicable
C25. Social isolation or shielding has a negative impact on the QoL (both mental and physical) of RMD patients during the COVID-19 pandemic.	Expert opinion	90%	Not applicable

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; bDMARDs, biologic disease-modifying antirheumatic drugs (DMARDs); COVID-19, coronavirus disease 2019; csDMARDs, conventional synthetic DMARDs; HCQ, hydroxychloroquine; NSAIDs, non-steroidal anti-inflammatory drugs; QoL, quality of life; RMD, rheumatic and musculoskeletal disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tsDMARDs, targeted synthetic DMARDs.

treatment based on the patient's confirmation of COVID-19 status and clinical condition, thus requiring that patients be tested for SARS-CoV-2 upon known exposure. The European League Against Rheumatism (EULAR) guidelines recommend testing even if the patient does not have COVID-19 symptoms, while the German Society of Rheumatology advises this only for symptomatic persons.[18,19] We suggest that the decision to test for SARS-CoV-2 in these close contacts should be based on local protocols.

Votes were divided among the responses for acceptance and rejection for C8 and C9, which seems to indicate that the topic of withholding RMD medication in unconfirmed COVID-19 remains debatable; nevertheless, consensus was reached for these statements. A change in administration of RMD therapies may be determined by the patient's risk of poor outcomes with use of specific agents during a presumed COVID-19 infection.

The association of specific RMD therapies with poor COVID-19 outcomes is described in detail for COVID-19-afflicted individuals in a later part of this document. For asymptomatic RMD patients with no COVID-19 but who are close contacts, we recommend that, pending testing results, antimalarials and NSAIDs may be continued, which is aligned with the American College of Rheumatology (ACR) guidelines.[20] SSZ may be continued at the discretion of local COVID-19 experts and according to guidance from APLAR rheumatology member national organizations. In agreement with similar guidance from ACR and EULAR, we recommend that immunosuppressants (eg, CYP, azathioprine [AZA], mycophenolate mofetil [MMF], tacrolimus, Janus kinase inhibitors [JAKi]), and all biologics, especially RTX, should be stopped or avoided except when necessary in managing critical RMD conditions. Glucocorticoids should be used at the lowest possible dose to control RMD. Finally, methotrexate (MTX) should be discontinued unless considered indispensable for a specific RMD by the treating rheumatologist.

With the confirmation of a negative SARS-CoV-2 test, asymptomatic individuals may resume RMD medications that were suspended. Recognizing that testing may not be easily available or accessible in some countries, resumption of RMD medication is recommended after approximately 2 weeks from contact if the patient with no confirmatory test remains asymptomatic.

3.2.3 | Impact of COVID-19 on treatment adherence

C10. Rheumatologists should explore the perceptions of patients and address their concerns to ensure treatment adherence during the COVID-19 pandemic. (100% agreement, grade of evidence moderate, strong recommendation).

Surveys reported on patient feedback about their RMD medications during the early part of the pandemic. These were conducted by rheumatologic treatment centers in the US, Germany, Greece, Italy, Mexico, Iran, and Saudi Arabia through email or telephone interviews. Rates of non-adherence (self-change or self-discontinuation of regimen) ranged 2.2%-15%. Possible reasons for non-adherence included: lack of availability of medications; inability to travel to the dispensing facility; fear of contracting COVID-19; perception of worsening RMD activity; and fear of immunosuppression.[21-26] An Australian survey found that patients were worried that RMD medications may increase their risk of contracting COVID-19 or increase COVID-19 severity, and the concern for contracting COVID-19 was increased when RMD regimens with combination csDMARDs or bDMARDS/tsDMARDs were used.[27]

From the reasons cited above for non-adherence, it appears that perceptions about the immune-modulating effects of rheumatologic drugs influenced patients' understanding of their susceptibility to contracting COVID-19 and to having a complicated course if infected. Physicians are encouraged to elicit feedback from their patients and help them address any challenges to continuing their current treatment regimen.

3.2.4 | Role of telemedicine in RMD management during the COVID-19 pandemic

C11. The use of telemedicine should be strongly encouraged, especially in areas of high community transmission levels, for follow-up of appropriate patients with RMD if implementing such an intervention is feasible and accepted by patients. (100% agreement, grade of evidence moderate, strong recommendation).

Before the pandemic, telemedicine for consultation, disease activity monitoring, and delivery of self-management programs for RMD were reported to have high feasibility and patient satisfaction rates.[28] During the pandemic, a rheumatology unit in Italy recently reported on its experience of using telemedicine, thus demonstrating its feasibility. In the unit, outpatient consultations, except for urgent cases, were conducted as tele-consults. Assessments of disease activity were carried out through questionnaires, and considering the changes brought about by the pandemic, patients were also asked about infection symptoms and psychological well-being. Medications were accordingly adjusted.[29] Survey respondents in Hong Kong indicated a high acceptance of use of telemedicine for follow-up. They agreed that disease activity assessment through telemedicine is accurate and that telemedicine reduces the risk for infection during the pandemic.[30]

More descriptive studies on telemedicine are expected given the adjustments made by both practitioners and patients during the pandemic. Future research evaluating the effectiveness of telemedicine for rheumatology care is much desired. In the context of the COVID-19 pandemic, telemedicine can minimize potential exposure to COVID-19 in stable RMD patients.[18,20] We recognize this is particularly important in areas with high community transmission; follow-up through telemedicine can provide treatment guidance safely while helping to ensure treatment continuity.

3.2.5 | Vaccination

C12. It is recommended that patients with RMD receive an approved SARS-CoV-2 vaccine as soon as it becomes available to them. (100% agreement, expert opinion, strong recommendation).
C13. RMD patients with normal or altered immunocompetence should receive vaccination based on current country, regional and/or international guidelines. (100% agreement, expert opinion, strong recommendation).
C14. Immunization schedules of patients with RMD should be maintained while adhering strictly to the safety protocols of COVID-19 prevention. (100% agreement, expert opinion, strong recommendation).

SARS-CoV-2 vaccines have been in development since the start of the pandemic and several vaccine candidates are in Phase 3 evaluation.[31] In the US and EU, messenger RNA (mRNA) SARS-CoV-2 vaccines have been granted emergency use authorization by the US Food and Drug Administration and European Medicines Agency, respectively, and the initial vaccination phase has begun for healthcare personnel and residents of long-term healthcare facilities in the US as recommended by the Advisory Committee on Immunization Practices.[32-36] While no data are currently available on the safety of mRNA or other SARS-CoV-2 vaccines in patients with RMD or who are otherwise immunocompromised, based on vaccine clinical trial results, there is no reason to expect that these vaccines are any less safe in these patient subgroups than in the general population.[37] Moreover, while there is a theoretical possibility that these vaccines are less effective in those taking immunosuppressant medications, there are, as yet, no data to support this. In the context of the ongoing COVID-19 pandemic, it is recommended that patients with RMD receive a SARS-CoV-2 vaccine approved for use by their national health authority, as soon as it becomes available to them; however, they must be counseled about the paucity of safety and efficacy data on these vaccines in the RMD population.

There are no live vaccines currently available for COVID-19. Should one become available, it should generally be avoided in immunocompromised persons with RMD until such time that vaccine data on safety and efficacy have been reviewed. A revised recommendation should then be considered based on its merits.

If disease activity allows, immunosuppressive therapy should be initiated in patients with newly diagnosed RMD at least 2 weeks after the completion of SARS-CoV-2 vaccination with the minimum recommended interval between 2 successive vaccine doses, in order to allow the immune system to mount an adequate immune response to the vaccine and also to minimize the delay in the administration of immunosuppressive therapy.[38] Given prior evidence of improved immunogenicity of the influenza vaccine upon temporary discontinuation of MTX for 2 weeks post-vaccination without an increase in rheumatoid arthritis disease activity, a similar strategy may be considered for MTX in patients with well-controlled rheumatoid arthritis receiving a SARS-CoV-2 vaccine.[39,40]

Because of physical distancing requirements, important preventive services such as routine vaccination may be delayed.[41] The CDC and World Health Organization (WHO) underscore the need to maintain the recommended schedule of routinely administered vaccines for all individuals during the pandemic.[41,42] For persons with suspected or confirmed COVID-19, the CDC recommends deferment until completion of isolation (for suspected cases, and for asymptomatic individuals) or after recovery from acute illness (for symptomatic cases).[42] Vaccine administration should be safely undertaken while following protocols to prevent the spread of COVID-19.[41,42] Appointments should be scheduled to ensure that all required vaccinations can be given, including catch-up doses, to minimize unnecessary healthcare visits and potential exposure to SARS-CoV-2.[42]

At this time no published studies can provide information on whether specific routine vaccines should be recommended for patients with RMD during the pandemic. C13 and C14 are based on the current advice of maintaining and updating the appropriate vaccination schedule, with precautions for immunocompromised individuals and patients with autoimmune inflammatory RMD.[18,43,44]

3.3 | Management of RMD patients with COVID-19

3.3.1 | Clinical manifestations of COVID-19 in RMD patients

C15. Clinical manifestations mimicking RMD, laboratory reports of positive antinuclear antibodies, antiphospholipid antibodies, and lupus anti-coagulant have been reported with COVID-19 patients. These patients should be followed for the possibility of persistent intermediate- to long-term immune dysregulation. (95% agreement, expert opinion, strong recommendation).

C16. The clinical presentation of COVID-19 in patients with RMD is similar to that in patients without RMD. Nonetheless, RMD patients who experience worsening of respiratory symptoms should immediately seek further healthcare advice of an expert in treating COVID-19 (eg, pulmonologist, infectious diseases specialist, or general internist) according to local recommendations. (100% agreement, grade of evidence low, strong recommendation).

Acute SARS-CoV-2 infection triggers hyperinflammatory and autoimmune processes that manifest similarly to RMD, including a cytokine release syndrome seen in critical patients with SARS-CoV-2 infection.[45,46] Musculoskeletal, skin, and central nervous system manifestations similar to those in RMD have been reported. Specific examples include: arthralgias, myalgias, and myositis; "COVID toes" or pseudo-chilblains, transient urticarial or maculopapular rash, livedoid or necrotic lesions, punctiform or diffuse purpura, and erythema elevatum diutinum-like rash; and large-vessel stroke in the young.[47-49] Features of giant cell arteritis such as headache, cough, fever, and fatigue can also be mimicked by COVID-19.[50] After the acute phase, post-viral autoimmune manifestations in the form of Guillain-Barré syndrome and Kawasaki-like disease have also been reported.[51-53]

Furthermore, laboratory results positive for antinuclear antibodies, antiphospholipid antibodies, lupus anti-coagulant assay, and increased levels of D-dimer associated with RMDs, erythrocyte sedimentation rate, and C-reactive protein have been documented with COVID-19.[50,54] In patients with established RMD, the identification of RMD-like COVID-19 manifestations should prompt close monitoring for immune dysregulation.[45]

The clinical presentation of COVID-19 among RMD patients is generally similar to its presentation in non-rheumatic patients. Fever, cough, sore throat, and dyspnea manifest in the same manner.[6,55,56] Laboratory parameters were also found to be similar, except for higher white blood cell count at presentation and lower peak ferritin levels in RMD patients.[6,56] Because RMD patients are more likely to develop complicated COVID-19, worsening of respiratory symptoms should prompt a consult with an expert in treating COVID-19.

3.3.2 | Modification of RMD treatment in patients with COVID-19

C17. Hydroxychloroquine (HCQ), NSAIDs, and angiotensin-converting enzyme inhibitors (ACEi) / angiotensin receptor blockers (ARBs) may be continued but should be individualized based on disease condition. (100% agreement, grade of evidence moderate, strong recommendation).

C18. The clinician should consider stopping or withholding csDMARDs (other than HCQ), tsDMARDs, and bDMARDs, on a case-by-case basis. (94% agreement, grade of evidence moderate, weak recommendation).

C19. RMD patients with COVID-19 should be treated according to the standard of care. (92% agreement, grade of evidence low, strong recommendation).

C20. Glucocorticoids should be used at the lowest possible dose to control RMD and should not be abruptly stopped. (94% agreement, grade of evidence high, strong recommendation).

C21. Immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus) should be discontinued in patients with COVID-19. (82% agreement, grade of evidence low, strong recommendation).

High-quality studies to directly address adjustment (de-escalation, discontinuation, re-initiation) of RMD medication regimens upon confirmed COVID-19 diagnosis are lacking. The risk of developing COVID-19 complications with these regimens is also uncertain. Our recommendations are mainly based on guidance from regulatory bodies and other specialty organizations, extrapolations from studies that included patients who developed other infections while using RMD therapies, and information from registries and case series. Votes garnered for this topic were divided between complete acceptance and acceptance with some reservations despite achieving consensus. Generally, our task force agreed that modifying current RMD therapies should be individualized, and potential benefits and risks should be discussed with patients and family.

NSAIDs, ACEi and ARBs, and HCQ may be continued but with consideration of the patient's clinical condition. No association was found between NSAID use in non-SARS-CoV-2 viral respiratory infections and poor clinical outcomes.[57,58] Recently, a retrospective cohort study in primary care did not find an increased risk in COVID-19-related mortality among osteoarthritis patients treated with NSAIDs versus comparator drugs (paracetamol plus codeine/hydrocodeine).[59]

The WHO presented low-certainty evidence that patients on long-term ACEi/ARB therapy are not at a higher risk of poor outcomes from COVID-19.[60] In addition, the only randomized trial data to date did not show clinical benefit with discontinuing long-term ACEi/ARB treatment for hospitalized, COVID-19-positive patients. The BRACE CORONA trial was a phase 4, randomized study evaluating 2 approaches in hospitalized patients with confirmed COVID-19 taking long-term ACEi/ARB: temporarily stopping the ACEi/ARB for 30 days versus continuing ACEi/ARB. The study found no significant difference in the number of days alive and out of hospital, the primary outcome, between approaches.[61]

Chloroquine and HCQ were initially thought to be useful in COVID-19 because they have been shown to inhibit SARS-CoV-2 in vitro; however, to date there is no convincing evidence of clinical

efficacy for either agent.[62] Their use in the treatment of COVID-19 per se is beyond the scope of this document. In the management of RMD, observational studies, primarily of registry data, did not show an association between HCQ use and poor outcomes from COVID-19,[11,55,63,64] except that a case series suggested a link with higher hospitalization rate. [65] One retrospective study suggested overall reduced mortality with HCQ use.[66]

Similar to the list of agents to consider for a treatment pause upon known COVID-19 exposure, our group suggests temporarily discontinuing csDMARDs (other than HCQ, such as SSZ, MTX, leflunomide), tsDMARDs (eg, JAKi, other than baricitinib), and bDMARDs (eg, tumor necrosis factor inhibitors [TNFi], rituximab, tocilizumab) upon diagnosis of COVID-19. RMD patients already on baricitinib may be maintained on it, and ideally paired with remdesivir in the context of COVID-19 treatment – a randomized controlled trial showed that baricitinib plus remdesivir was superior to remdesivir in improving outcomes in confirmed COVID-19;[67] however, use of baricitinib in an RMD patient with COVID-19 should be within the context of approved COVID-19 management guidelines in the clinician's country. Case series, case reports, and observational studies showed mixed results: while some immune-modulating therapies were not associated with poor outcomes, others were linked to a more severe COVID-19 course, particularly rituximab and SSZ.[13,68-76] The results of the meta-analysis by Akiyama et al. should also be considered: meta-regression analysis according to RMD therapeutics revealed that studies with a greater percentage of patients using csDMARDs and the bDMARD/tsDMARD–csDMARD combination had a higher rate of hospitalization or death from COVID-19.[4] Use of bDMARD/tsDMARD monotherapy, particularly TNFi monotherapy, was associated with lower COVID-19 hospitalization or mortality rates.[4] TNFi use appears to be protective in some studies,[77,78] but this benefit needs to be replicated in further studies before a specific recommendation can be proposed. For treatment of SARS-CoV-2 infection in hospitalized patients, the use of interleukin (IL)-6 inhibitor tocilizumab has been evaluated in a randomized controlled trial but did not lead to significantly different clinical outcomes compared with placebo.[79]

Glucocorticoids, specifically dexamethasone, may be useful for severe COVID-19.[80,81] It is expected that glucocorticoids may confer additional benefit in terms of managing COVID-19 in infected RMD patients, but observational data suggest a likelihood toward a more severe course. The meta-analysis by Akiyama et al. showed a trend for higher rates of hospitalization and death with glucocorticoid use.[4] From the registry-based observational studies, glucocorticoid use was associated with poor COVID-19 outcomes, including hospitalization, mortality, intensive care unit admission, and ventilator use.[11,55,63,66,76] In terms of dose, the GRA-19 study showed that prednisone ≥10 mg/d was associated with a higher risk of hospitalization (OR 2.05, 95% CI 1.06-3.96, $P = .03$).[11] Therefore, it is recommended to reduce the dose to <10 mg daily if the underlying RMD disease activity permits. However, in severe or life-threatening autoimmune disease, a higher dose of glucocorticoid may be needed for disease control. Thus, dosage of glucocorticoid for control of the underlying RMD should be determined on a case-by-case basis according to disease activity and patients' COVID-19 status.

As with the use of other RMD therapies, the need to control RMD activity should be weighed against preventing severe COVID-19. Currently, only low-quality evidence suggests a predisposition toward poor COVID-19 outcome with glucocorticoid use; thus, RMD patients should receive standard care, and continue glucocorticoids with the appropriate dose adjustment as indicated to control flares. The use of the lowest possible doses to manage disease activity is considered as good clinical practice.[18,20]

3.3.3 | Restarting RMD medication

C22. In general, RMD treatments may be re-introduced at least 2 weeks after recovery from acute COVID-19. They may need to be individualized based on the clinical scenario and the physician's judgment. (100% agreement, grade of evidence low, weak recommendation).

C23. For asymptomatic individuals, RMD treatment may be re-introduced approximately 10 days after diagnosis of COVID-19. (100% agreement, grade of evidence low, weak recommendation).

The optimal time to resume RMD medication that was discontinued in the context of COVID-19 infection is uncertain. Limited evidence from observational studies on the course of viral shedding and clearance may guide the decision to re-start RMD treatment.

Viral shedding has been noted 2-6 days before symptom onset; up to 10 days after symptom onset in mild COVID-19; and up to a median of 8 days after symptom onset in immunocompromised patients with severe COVID-19 (range of 0-20 days).[82-85] The time frame for viral shedding was not described for mild COVID-19 in immunocompromised individuals, although the CDC suggests that prolonged viral shedding may be present in immunocompromised patients even with mild SARS-CoV-2 infection.[86] Extrapolating the data for RMD patients, and depending on COVID-19 severity, it may be reasonable to wait for at least 2 weeks after symptom onset or after a positive reverse-transcription polymerase chain reaction (RT-PCR) test before re-introducing RMD therapy. Similarly, the ACR guidance recommends a waiting period of 7-14 days after symptom resolution in mild COVID-19, or 10-17 days after a positive RT-PCR test for asymptomatic patients.[20]

This time frame for medication re-start is compatible with the CDC's 10-day wait after symptom onset prior to discontinuing transmission-based precautions (eg, quarantine).[86] Based on viral clearance studies, this interval was proposed as viral load had presumably declined, and transmission likelihood had been reduced. In mild to moderate COVID-19, the CDC suggests waiting 10 days; for severe disease or immunocompromised individuals this wait can be up to 20 days. The CDC further requires that the last fever incident should have occurred at least 24 hours prior, with no anti-pyretic use, and symptoms such as cough should have improved.[86] When

restarting RMD therapy, assessment of the patient's condition can use a similar symptom-based approach as the CDC's approach to de-isolation. In cases of acute conditions, the need to control flares urgently may also affect the timing of re-introduction. SARS-CoV-2 re-testing, if feasible, may be warranted in severely immunocompromised individuals.

3.3.4 | Impact of COVID-19 on the quality of life (QoL) of RMD patients

C24. SARS-CoV-2 infection has a negative impact on the QoL of RMD patients, particularly the mental health component. (95% agreement, expert opinion, strength-of-recommendation assessment not applicable).

C25. Social isolation or shielding has a negative impact on QoL (both mental and physical) of RMD patients during the COVID-19 pandemic. (90% agreement, expert opinion, strength-of-recommendation assessment not applicable).

Surveys have shown lower QoL while coping with the life changes borne from the pandemic among the general populations in Europe.[87] Understandably, lower QoL was also reported after being infected with COVID-19.[88]

The pandemic has also impacted the QoL of RMD patients. Individuals in New York City surveyed during the heightened phase of implementing transmission prevention measures reported worsening of their RMD with the changes to their daily lives regardless of SARS-CoV-2 infection status. Fatigue from multitasking and adherence to isolation measures may have directly contributed to disease flares.[89] Stress from uncertainties in finances, exposure to infection, and changes to RMD medication, among other issues, were indirect contributors.[89] One study which used the Short Form 12-item Health Survey to specifically measure QoL in a UK cohort of RMD patients, showed a worsening of physical and mental functioning during the pandemic. Mental component scores of the survey were significantly lower for the group infected with SARS-CoV-2 compared with those of the non-infected group (mean difference: −3.3; 95% CI −5.2-1.4, $P < .001$). In the non-infected group, those who were in strict isolation had significantly lower mental (−2.1; 95% CI −2.9-1.4, $P < .001$) and physical component scores (−2.2; 95% CI −3.8-2.5, $P < .001$) than those not in isolation.[90]

Mindful of the known negative impact of COVID-19 on patients' QoL, rheumatologists caring for RMD patients during the pandemic should be ready to ask about life changes and mental well-being. They should provide or recommend support for mental and physical functioning, in addition to managing RMD.

4 | CONCLUSIONS

To update the initial APLAR position statement, the COVID-19 task force was mandated to address important concerns in the care of the patient with RMD that arose from the rapid changes to healthcare due to the pandemic. Patients with RMD have also been coping with the challenges of adhering to infection prevention directives while working with their treating rheumatologists to control their disease.

Based on currently available best evidence, our group has updated previous APLAR guidance by:

- noting the potential risk of RMD patients for complicated COVID-19 and listing probable risk factors
- describing the clinical manifestations of COVID-19 that are similar to RMD features
- reviewing the initial findings of potential risks associated with specific RMD therapies and providing some guiding principles for medication adjustment, and
- highlighting the role of vaccination, the role of telemedicine, changes in RMD treatment adherence, and the importance of changes to QoL during the pandemic.

The vibrant research landscape has, to date of this publication, produced a great volume of descriptive research that has helped to provide a better understanding of COVID-19. Importantly, numerous studies have also covered how aspects of RMD management are impacted by the pandemic. However, most of the data from publications summarized here were considered as low-quality to moderate-quality evidence. Our audience should regard this guidance judiciously and continue to monitor for more robust, definitive data from randomized controlled trials and larger, population-based studies; the APLAR COVID-19 task force will do the same, updating this document in 2021 as new evidence becomes available.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

L-S Tam, Y Tanaka, R Handa and SA Haq planned the meeting and prepared the clinical questions. All task force members contributed

to the development of the manuscript by drafting, reviewing, and discussing the statements and supporting evidence, voting to refine and finalize statements, and reading and approving the manuscript.

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REVIEWS AND RECOMMENDATIONS

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Recommendations for COVID-19 vaccination in people with rheumatic disease: Developed by the Singapore Chapter of Rheumatologists

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Abstract

Aim: People with rheumatic diseases (PRD) remain vulnerable in the era of the COVID-19 pandemic. We formulated recommendations to meet the urgent need for a consensus for vaccination against SARS-CoV-2 in PRD.

Methods: Systematic literature reviews were performed to evaluate: (a) outcomes in PRD with COVID-19; (b) efficacy, immunogenicity and safety of COVID-19 vaccination; and (c) published guidelines/recommendations for non-live, non-COVID-19 vaccinations in PRD. Recommendations were formulated based on the evidence and expert opinion according to the Grading of Recommendations Assessment, Development and Evaluation methodology.

Results: The consensus comprises 2 overarching principles and 7 recommendations. Vaccination against SARS-CoV-2 in PRD should be aligned with prevailing national policy and should be individualized through shared decision between the healthcare provider and patient. We strongly recommend that eligible PRD and household contacts be vaccinated against SARS-CoV-2. We conditionally recommended that the COVID-19 vaccine be administered during quiescent disease if possible. Immunomodulatory drugs, other than rituximab, can be continued alongside vaccination. We conditionally recommend that the COVID-19 vaccine be administered prior to commencing rituximab if possible. For patients on rituximab, the vaccine should be administered a minimum of 6 months after the last dose and/or 4 weeks prior to the next dose of rituximab. Post-vaccination antibody titers against SARS-CoV-2 need not be measured. Any of the approved COVID-19 vaccines may be used, with no particular preference.

Conclusion: These recommendations provide guidance for COVID-19 vaccination in PRD. Most recommendations in this consensus are conditional, reflecting a lack of evidence or low-level evidence.

KEYWORDS
COVID-19, immunosuppression, people with rheumatic diseases, SARS-CoV-2, vaccination

1 | INTRODUCTION

The global novel coronavirus disease 2019 (COVID-19) pandemic has posed many uncertainties among physicians treating people with rheumatic diseases (PRD). Such patients are considered high risk due to their diseases and the immunosuppressive nature of their medications. A recent meta-analysis demonstrated that PRD had a 2-fold risk of COVID-19 compared to control patients.[1] In addition, PRD with COVID-19 had a higher fatality rate and were at significant risk of suffering poor outcomes such as the need for hospitalization, care in the intensive care unit (ICU) and mechanical ventilation.[2,3]

Various candidate vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are in development. The first 3 COVID-19 vaccines to receive Emergency Use Authorization (EUA) from the United States Food and Drug Administration (US FDA), the Pfizer-BioNTech® COVID-19 vaccine (BNT162b2), the Moderna® COVID-19 vaccine (messenger RNA [mRNA]-1273) and the Johnson & Johnson® vaccine (JNJ-78436735), reported good vaccine efficacy at 95%, 94.1% and 66.9%, respectively.[4-6] However, patients on immunosuppressive therapy were excluded from all 3 trials. Additionally, patients with autoimmune diseases were excluded from 2 of the trials, and only 62 PRD (0.3% of the total study population, but without detailed information) were included in the treatment arm of the Pfizer-BioNTech® trial. Thus, there is a paucity of evidence for PRD and their managing physicians to guide COVID-19 vaccination in this population.

The Singapore Health Sciences Authority (HSA) has approved the Pfizer-BioNTech® and Moderna® COVID-19 mRNA vaccines via the Pandemic Special Access Route, and the Ministry of Health, Singapore (MOH) Expert Committee on COVID-19 Vaccination (EC19V) has published recommendations for their use[7,8] with other vaccines to be evaluated at a later date. Worldwide, 4 additional vaccines, namely from Gamaleya Research Institute of Epidemiology and Microbiology (Gam-COVID-Vac or Sputnik V®),[9] Oxford-Astra-Zeneca® (AZD1222),[10] Novartis (Novavax® or NVX-CoV2373)[11] and Bharat Biotech (BB-152 or Covaxin®),[12] have so far published or announced interim Phase 3 efficacy data and are either already authorized or expected to apply for EUA in several countries. In this consensus recommendation, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore seeks to address questions regarding the suitability of COVID-19 vaccination in PRD and provide consensus recommendations on COVID-19 vaccination among PRD.

2 | METHODS

A Core Working Group (CWG) was established (AS, CX, WF, ML). Members of the CWG reviewed published primary clinical trials and performed a systematic literature review to answer 4 research questions. Where appropriate, in lieu of a systematic review of the primary literature, international best practice guidelines and recommendations from rheumatology societies on vaccinations in PRD were reviewed. Other academic bodies' recommendations for COVID-19 vaccination and other non-live, non-COVID-19 vaccinations in PRD and / or immunocompromizing conditions were also considered. The CWG developed draft recommendations for rating by an invited task force panel (TFP). A modified Delphi approach, similar to what has been applied by other organizations, was used.[13,14] The TFP (TA, KOK, AL, THL, KHL, AHLL, MKS, TCT, GGT, BYT) comprised 8 locally recognized adult rheumatologists from public and private healthcare institutions in Singapore, 1 pediatric rheumatologist and 1 infectious diseases specialist. A conflict-of-interest declaration was required from all members of the CWG and TFP prior to the consensus process. All members declared no conflicts of interest.

2.1 | Review of the literature

The CWG sent out preselected topics to the TFP and sought their input on additional clinically important topics. Considering the TFP's input, the CWG selected the following core topics relevant to clinical decision-making for COVID-19 vaccination:

1. Are PRD at increased risk of adverse outcomes from COVID-19?

A recent systematic review and meta-analysis of global data showed that PRD remain vulnerable, with substantial rates of severe outcomes.[3] The overall rates of hospitalization, oxygen support, ICU admission and fatality among COVID-19 infected patients with rheumatic diseases were 58% (95% CI 48%-67%), 33% (95% CI 21%-47%), 9% (95% CI 5%-15%) and 7% (95% CI 3%-11%), respectively, which are comparable with data from the COVID-19 Global Rheumatology Alliance (GRA) physician registry. The fatality rate was higher both in this meta-analysis and the COVID-19 GRA (7.0% and 6.7%, respectively) than that (3.4%) of general population infected with COVID-19 in the WHO database, although age, gender and comorbidities were not matched.[3] D'Silva et al reported a higher risk of hospitalization, ICU admission, mechanical ventilation, acute kidney injury, renal replacement therapy and death based on TriNetX, a multi-center research network with real-time electronic health record data across 35 healthcare organizations in the US.[15] The authors concluded that these outcomes were likely mediated by a higher comorbidities burden in PRD, such as hypertension, diabetes mellitus, chronic kidney disease and asthma.

2. Are existing approved vaccines against SARS CoV2 safe, immunogenic and efficacious in PRD?

TABLE 1 Primary COVID-19 vaccine trials

	Pfizer-BioNTech® 4	Moderna® 5	Sinovac® 19	Oxford-Astra Zeneca® 10
Trial sites	US, Brazil, Argentina, South Africa, Germany, Turkey	US	China	UK, Brazil, South Africa
MOA	Lipid nanoparticle–formulated, nucleoside-modified mRNA		Adsorbed SARS-CoV-2 (inactivated) vaccine	Replication deficient viral vector with SARS COV2 spike protein
Storage	Freezer −70°C	Freezer −15 to −25°C	Refrigerator 2 to 8°C	Refrigerator 2 to 8°C
Dosing	Two 30 μg (0.3 mL) IM doses 21 d apart	Two 100 μg (0.5 mL) IM doses 28 d apart	Two doses 2 wk apart	Two doses 4-12 wk apart
Inclusion	Adults (>16 y)	Adults (≥18 y)	Adults (≥18 y)	Adults (≥18 y)
Relevant Exclusions	Immunodeficient state and use of immunosuppressant medication.	Autoimmune disease Immunodeficient state and use of immunosuppressant medication within the past 6 mo	Autoimmune disease Immunodeficient state and use of immunosuppressant medication within the preceding 3 mo	Autoimmune disease Immunodeficient state and use of immunosuppressant medication within the past 6 mo
N[a]	37 706	28 207	13 060	11 636
Follow-up (median) after last dose	2 mo	64 d	NA	2 mo
Asian participants	1608 (4.3%)	1382 (4.6%)	NA	517 (4.4%)
Comorbidities	20.5%	22.3%	NA	24.7%
PRD	62 (0.3%)	Excluded	NA	Excluded
Elderly	>55 y (42.2%)	>65 y (25.3%)	NA	>55 y (12.2%)
Outcomes	8 vs 162 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 95%	11 vs 185 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 94.1%	NA	30 vs 101 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 70.4%
Common adverse events	Expected reactogenicity: fatigue, headache. Rare anaphylaxis, lymphadenopathy	Expected reactogenicity: injection site pain, fatigue, headache, muscle pain, joint pain and chills. Rare lymphadenopathy and hypersensitivity.	NA	Not different from placebo arm. No anaphylaxis

Abbreviations: MOA, mechanism of action; NA, not available; PRD, patients with rheumatic disease.

[a]Patients included in published interim analysis

Two mRNA vaccines are currently approved by the US FDA and Singapore HSA. It is known that selected DNA and RNA molecules have the unique property to activate the immune system, through activation of Toll-like receptors.[16] It has been shown that the innate immune response would be suppressed by nucleoside modification of RNA, as the innate immune system detects RNA lacking nucleoside modification as a means of selectively responding to bacteria or viruses.[17,18] Both mRNA COVID-19 vaccines from Pfizer/BioNTech® and Moderna® are nucleoside-modified RNA. Thus, the risk of autoimmune disease flare after receiving mRNA COVID-19 vaccine may more likely result from the adaptive immune response to spike protein synthesized by mRNA, rather than the innate immune response to nucleoside-modified RNA. Theoretically, this is no different from the risk from other protein / conjugate vaccines, which have been in use for many years and have been confirmed to be safe in PRD.

There were 62 (0.3%) participants who had rheumatic disease and received BNT162b2 mRNA COVID-19 vaccine in the Pfizer/BioNTech® trial.[4] No flare of autoimmune disease was reported. Certainly, larger sample size and long-term follow-up studies are needed to further ascertain the risk of flares in autoimmune diseases.

Other vaccine strategies, including inactivated virus vaccines (such as the CoronaVac developed by Sinovac®[19] and Covaxin® developed by Bharat Biotech[12]), virus vector vaccines (such as the COVID-19 vaccines by AstraZeneca®,[10] the Johnson & Johnson® vaccine[6] and the Sputnik V® Russian vaccine by Gamaleya[9]) and protein subunit vaccines (such as the Novavax® vaccine[11]) similarly provide little data in PRD. Pertinent information from primary COVID-19 vaccine trials to date are summarized in Table 1.[4-6,9,10,12,19,20]

There are currently no available data on the immunogenicity and efficacy of COVID-19 vaccination in PRD.

Gamaleya® 9	Johnson & Johnson® 6	Novartis 20	Bharat Biotech12
Russia	US, Central and South America, South Africa	UK, South Africa	India
		Adjuvant recombinant protein particle	Whole-virion inactivated SARS-CoV-2 vaccine with a Toll-like receptor 7/8 agonist molecule adsorbed to alum
Refrigerator 2 to 8°C	Refrigerator 2 to 8°C	Refrigerator 2 to 8°C	Refrigerator 2 to 8°C
Two (0.5 mL) IM doses 21 d apart	Single dose	Two (0.5 mL) IM doses 21 d apart	Two 6 μg IM doses 28 d apart
Adults (≥18 y)	Adults (≥18 y)	Adults (18-84 y)	Adults (18-98 y)
Immunodeficient state and use of immunosuppressant medication within the past 3 mo	Immunodeficient state and use of immunosuppressant medication.	Autoimmune disease Immunodeficient state and use of immunosuppressant medication within the preceding 3 mo	NA
19 866	43 783	15 000	25 800
27 d	8 wk	NA	NA
286 (1.4%)	3.5%	NA	100%
24.8%	41% (including obesity)	NA	17.4%
Likely excluded	Allowed, likely none included	NA	NA
>60 y (10.8%)	>65 y (20.4%)	>65 y (27%)	>60 y (9.4%)
16/14 964 vs 62/4902 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 91.6%	116/19 514 vs 348/19 544 moderate / severe PCR confirmed COVID-19, vaccine efficacy 66.9%	6 vs 56 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 89.3%	7 vs 36 cases of symptomatic and PCR confirmed COVID-19, vaccine efficacy 80.6%
Injection site reactions, flu-like illness, headache, asthenia. No anaphylaxis	Expected reactogenicity: injection site pain, fatigue, headache, myalgia and fever. No anaphylaxis	NA	Not different from placebo arm. No anaphylaxis

3. Are other (non-COVID-19) recommended non-live vaccines safe, immunogenic and efficacious in PRD?
4. What is the effect of various drugs used in PRD on immunogenicity of (non-COVID-19) vaccines in PRD?

To review the evidence in non-live, non-COVID-19 vaccinations in PRD, a systematic review of international best practice guidelines and recommendations from rheumatology societies on vaccinations in PRD was performed, in lieu of a systematic review of the primary literature. We searched PubMed for publications using the Medical Subject Headings (MeSH) terms ("Consensus" [MeSH] OR "Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus Development Conferences, NIH" [MeSH] OR "Consensus Development Conferences" [MeSH]) OR ("Guidelines as Topic" [MeSH] OR "Practice Guidelines as Topic" [MeSH] OR "Guideline" [Publication Type] OR "Health Planning Guidelines" [MeSH] OR "Standard of Care" [MeSH] OR "Practice Guideline" [Publication Type] OR "Clinical Protocols" [MeSH] AND ((vaccine [MeSH Terms]) OR (vaccination [MeSH Terms])) OR (active immunization [MeSH Terms]) AND (autoimmune disease [MeSH Terms]) OR (rheumatology [MeSH Terms]) OR (host, immunocompromised [MeSH Terms]) OR (immunocompromised host [MeSH Terms]) OR (immunocompromised patient[MeSH Terms]). The filters English (language) and Humans were applied. This search yielded 191 citations. One member of the CWG (ML) screened through the titles and/or abstracts and excluded those that were not a practice guideline, not targeted to PRD, only addressed live vaccines, were only targeted to childhood vaccines, did not undertake a systematic literature review, were duplicates, or were outdated recommendations from the same body. Four additional citations were added from manual search. We then reviewed the remaining 21 full text articles and excluded best practice guidelines that did not undertake

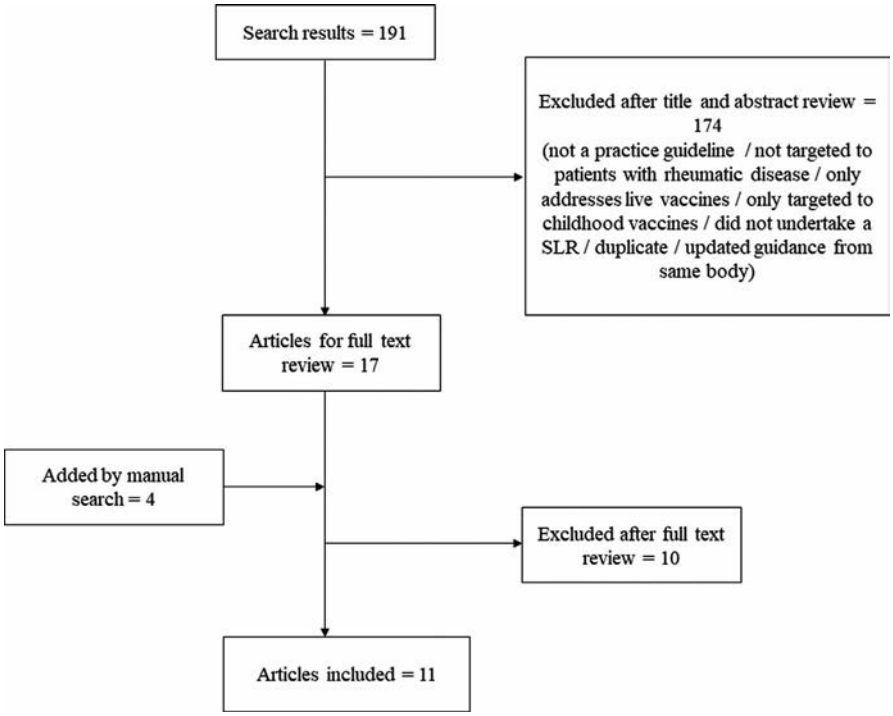

FIGURE 1 Flowchart for study selection

a consensus methodology and evidence grading or strength of recommendations. Eleven full text articles were finally included (Figure 1, Table 2).[21-31] The definitions of PRD and immunomodulatory drugs considered in this recommendation are summarized in Table 3.

2.2 | Creation of preliminary statements and rating

The CWG met to formulate and finalize preliminary statements for rating by the TFP, which was conducted on an online survey platform. The TFP were provided with summarized evidence from the reviewed trials and guidelines, a link to an online rating form and rating instructions. Based on their expertise and the provided literature, each TFP member independently rated each statement on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree); an agreement was defined as a score of 4 or 5. A consensus was obtained if there was ≥70% agreement. The CWG and the TFP convened via a teleconferencing platform, where the aggregated findings were presented and discussed. Definitions were clarified and statements were reworded, if needed. As there was consensus on all statements following the online voting round, no further round of voting was conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[32] was used to determine the strength of recommendations. In determining the strength of recommendations, the TFP considered the level of evidence available, as well as the balance between the potentially expected benefits and risks from COVID-19 vaccination/ omission of vaccination in PRD. Recommendations were categorized as "strong" when benefits/risks clearly outweighed the other, and "conditional" when benefits/risks were closely balanced or uncertain.

2.3 | Finalizing consensus statements

The final consensus statement was circulated to the TFP after the consensus meeting and was approved by all members.

3 | RESULTS

The final consensus statements consist of 2 overarching principles and 7 recommendations. They are summarized in Table 4.

3.1 | Overarching principles

1. Vaccination in PRD should be aligned with prevailing national policy.

The knowledge on COVID-19 vaccination is rapidly evolving with various candidate vaccines still undergoing clinical trials. As new evidence becomes available, the landscape of vaccine availability in each country will likely differ. It is important that healthcare professionals align their recommendations to prevailing national policy, to ensure consistency of messages to patients and maintain streamlined safety workflows. Vaccine safety monitoring systems, such as the vaccine adverse event reporting system are in place to detect possible safety signals in the vaccinated population.

Locally, the HSA reviews all reports of post-vaccination reactions, to inform national policy of vaccine eligibility, monitoring and precautions.

2. The decision for vaccination should be individualized, and should be explained to the patient, to provide a basis for shared decision-making between the healthcare provider and the patient.

Rheumatologists' decision for offering vaccinations to their patients should take into account the individual patient's disease state, medications, as well as their risk profile and preferences. Patients should be provided with evidenced-based information to enable them to participate in a shared decision-making process. Information should include the potential risks and benefits from vaccination (or its omission), the vaccination schedule and a discussion of the various available vaccines.

3.2 | Recommendations

1. We strongly recommend that eligible patients be vaccinated against SARS-CoV2.

PRD are a vulnerable patient population at increased risk of acquiring COVID-19[1] and suffering severe outcomes.[3,15] While there are little data on mRNA vaccination in PRD, there are no reports of autoimmune disease flares in the small group of PRD included in the Pfizer/BioNTech® trial.[4] There is an isolated report of a healthy individual who was diagnosed with fatal immune thrombocytopenia 6 days after COVID-19 vaccination with no clear evidence of the development of a new autoimmune disease. While there was temporal association, it could not be fully concluded that the vaccine was definitely the cause for the patient's presentation.[33] To our knowledge, there are no other published reports of autoimmune disease induction or flare after COVID-19 vaccination in the more than 300 million people vaccinated worldwide to date. COVID-19 vaccination should therefore be strongly recommended for PRD given the vulnerability of PRD along with good efficacy, immunogenicity and favorable safety profile of COVID-19 vaccination in healthy patients. This is in line with recommendations endorsed by the British Society of Rheumatology for clinically extremely vulnerable patients,[34] which includes PRD and the recent press release from the American College of Rheumatology (ACR).[35] The United States Centers for Disease Control and Prevention (US CDC) similarly places immunocompromised persons at an increased risk for severe COVID-19 and recommends that these patients receive vaccination as long as there are no contraindications.[36]

2. We conditionally recommend that the COVID-19 vaccine be administered during quiescent disease, if possible.

This recommendation is extrapolated from other vaccine recommendations in PRD, and is largely based on expert opinion, hence the conditional strength of recommendation. Vaccination studies in PRD have been largely conducted during quiescent disease state[28,29] and thus have limited generalizability to the PRD population with active disease, although isolated studies have shown similar vaccine immunogenicity regardless of disease state.[37] The decision for vaccination in patients whose disease is not quiescent should be considered on an individual patient level.

3. We conditionally recommend that immunomodulatory drugs, other than rituximab, can be continued alongside COVID-19 vaccination.

Vaccination studies in PRD on immunomodulatory drugs (other than B cell depleting therapy) have shown sufficient protective efficacy with common non-live vaccines including influenza and pneumococcal vaccines, despite somewhat reduced immunogenicity, particularly with methotrexate and abatacept.[22,26,30]

4. We conditionally recommend that the COVID-19 vaccine be administered prior to commencing rituximab, if possible. For patients on rituximab, the vaccine should be administered a minimum of 6 months after the last dose, and/or 4 weeks prior to the next dose of rituximab.

B cell depleting therapy with rituximab is associated with significant reduction in immunogenicity. Despite reduced humoral immune response, cellular immune response is still preserved after influenza vaccination in patients who were treated with rituximab.[38] Satisfactory immunogenicity has been shown in rituximab treated patients when influenza and pneumococcal vaccines were administered 6 months after a previous dose[21,23,29] and at least 4 weeks prior to a subsequent dose,[24,28] forming the basis of this conditional recommendation. Of note, the British Arthritis and Musculoskeletal Alliance recommends that vaccination should not be delayed in patients on or planned for rituximab, with an ideal interval of vaccination 4-8 weeks after the last dose of rituximab or 2 weeks prior to a planned dose of rituximab, if possible.[34]

5. We conditionally recommend that post-COVID-19 vaccination antibody titers need not be measured.

Outside of pediatric care,[27] post-vaccination antibody titer measurement is not part of routine clinical practice and is not part of other vaccination guidelines in adult PRD. As the correlation between antibody titers post-COVID-19 vaccination and clinical protection is not well established at present, we conditionally recommend that titers not be measured.

6. We strongly recommend that household contacts be vaccinated against SARS-CoV-2.

TABLE 2 Reviewed practice guidelines citations, with focus on non-live vaccinations

Article	Vaccine type	Patient population	Safety	Immunogenicity
Furer V, et al.[29]	Non-live	PRD on IS/ DMARD/ GC	Influenza (LOE[a] 2b-4) and PCV (LOE 4) deemed safe	Good for influenza (LOE 1b-4) and PPSV23 (LOE 1b-4) Influenza: reduced by RTX, ABA PPSV23: reduced by RTX, ABA, TOF, GOL PCV13: reduced by MTX
Seo YB, et al.[22]	Non-live	PRD on IS/ DMARD/ GC	Similar risk as general population (Influenza LOE:[b] mod; pneumococcal LOE : low)	Similar or slightly lower than that of healthy individuals. Pneumococcal: reduced by MTX, RTX, ABA
Guerrini G, et a.[28]	Influenza and pneumococcal	PRD on IS/ DMARD/ GC	Influenza and pneumococcal deemed safe (LOE[c] 2)	Pneumococcal: reduced by MTX, RTX, ABA, TOF, MMF, AZA, CyC, high dose GC (LOE 2) Influenza: reduced by RTX, ABA, high dose GC (LOE 2)
Papp KA, et al.[24]	Non-live	PRD on IS/ DMARD/ GC	-	-
Holroyd CR, et al.[26]	Non-live	RA, PsA, axSpA	No flare of RA with Influenza	Influenza: reduced by ETN and INF, RTX, ABA Pneumococcal: reduced by MTX, RTX, ABA (LOE[d] 1C)
Keeling SO, et al.[25]	Influenza	SLE	Trivial number of SLE flares with influenza (LOE[e] mod)	-
Singh JA, et al.[21]	Non-live	RA on DMARD/ GC	-	Reduced by RTX and possibly MTX (LOE[d] very low)
Bühler S, et al.[30]	Non-live	PRD on IS/ DMARD/ GC	No flare nor trigger of rheumatic disease, (LOE[d] low)	Reduced by DMARD/ GC especially MTX, RTX, ABA (LOE mod)
Rubin LQ, et al.[23]	Non-live	IC	-	Influenza: reduced within 6 mo of RTX (LOE[5] mod)
Centers for Disease Control & Prevention [31]	Pneumococcal	IC	-	-
Heijstek MW, et al.[27]	Non-live	PRD on DMARD /GC	No flare of rheumatic disease or serious adverse events in comparison to healthy subjects	Influenza: reduced by GC > 10 mg/d (LOE[c] 3), AZA, HCQ, CYC (LOE 2), RTX (LOE 2) Pneumococcal: reduced by MTX (LOE 2), RTX (LOE 1b)

Abbreviations: ABA, abatacept; axSpA, axial spondyloarthritis; Aza, azathioprine; CYC, cyclophosphamide; DMARD, disease modifying anti-rheumatic drugs; dx, disease; GC, glucocorticoid; IC, immunocompromised; IS, immunosuppression; JAKi, inhibitors of Janus kinase; LOE, level of evidence; MMF, mycophenolate mofetil; mod, moderate; mo, months; MTX, methotrexate; NA, non-available; PCV, pneumococcal vaccination; PRD, people with rheumatic diseases; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus; TNFi, tumor necrosis factor inhibitors; TOC, tocilizumab; wk, weeks.

[a]Oxford Centre for Evidence-Based Medicine – levels of evidence.[45]

[b]Level of evidence as defined: High – very unlikely to change confidence in the estimate of effect by an additional study; Moderate – likely to change confidence in the estimate of effect by an additional study; Low – highly likely to change confidence in the estimate of effect by an additional study; Very low – not sure about confidence in the estimate of effect

[c]Level of evidence as defined: 1a – meta-analysis of randomized controlled trials (RCT); 1b – RCT; 2 – prospective controlled intervention study without randomization; 3 – descriptive/analytic study (including case-control, cross-sectional, case series); 4 – expert committee reports or opinion or clinical experience of respected authorities or both

[d]GRADE level of evidence.[32]

[e]Level of evidence as defined: High – consistent evidence from well performed RCTs or exceptionally strong evidence from unbiased observational studies; Moderate – evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies; Low – evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence; Very low – evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence.

Efficacy	Timing /DMARD cessation	Post-vaccination antibody testing	Vaccination of household contacts
Influenza (LOE 2a-5), PPSV23 (LOE 1b-4) No data for MTX, TNFi, B cell depletion, belimumab, tocilizumab, abatacept, tofacitinib, glucocorticoids	Quiescent dx Prior to IS, in particular B cell depleting therapy (6 mo post-RTX, 4 wk before next dose of RTX) No DMARD cessation	-	Yes, except for oral polio (LOE NA)
Influenza and pneumococcal	Stable dx (LOE: very low) Prior to IS (LOE : very low) Before ABA and ≥4 wk before RTX No DMARD cessation	-	Yes
-	Stable dx (LOE 2) Pneumococcal: before IS and ≥4 wk before RTX (LOE 2)	-	-
-	2 wk before IS (LOE[4] mod) RTX: 5 mo post-RTX and ≥4 wk prior to RTX (LOE low)	-	-
-	-	-	-
Influenza (LOE mod)	-	-	-
Killed vaccine (LOE very low)	No DMARD cessation needed (LOE very low)		
-	When the IS lowest (LOE low) Before ABA RTX: 6 mo post-RTX for revaccination, 12 mo post-RTX for primary vaccination	4-6 wk post vaccine (LOE NA)	Yes (LOE NA)
-	≥2 wk before IS (LOE mod)	-	Yes (LOE high)
-	-		
-	Before RTX (LOE 1b-2)	Influenza and pneumococcal: on RTX (LOE 1b-2), GC ≥ 2 mg/kg or 20 mg/d for ≥2 wk (LOE 3), ±TNFi (LOE 2) PPSV23: On MTX (LOE 2)	-

TABLE 3 Definition of PRD (people with rheumatic diseases) and immunomodulatory treatment

PRD include, but are not limited to, those diagnosed with:

1. Chronic inflammatory arthritides (eg rheumatoid arthritis, psoriatic arthritis, spondyloarthritides, juvenile idiopathic arthritis, adult onset Still's disease)
2. Connective tissue diseases (eg systemic lupus erythematosus, immune-mediated inflammatory myositis, Sjögren's syndrome, systemic sclerosis)
3. Primary systemic vasculitides
4. Autoinflammatory diseases

Immunomodulatory drugs considered for this guidance include:

1. Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) (methotrexate, sulphasalazine, leflunomide, hydroxychloroquine)
2. Biologic DMARDs (anti-tumor necrosis factor, tocilizumab, rituximab, abatacept, secukinumab, ixekizumab, anakinra, belimumab)
3. Targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib[a])
4. Immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin A, tacrolimus)
5. Glucocorticoids

[a]Not included in any of the searched literature on vaccines, hence recommendation is by extrapolation.

Vaccination of household contacts has been advocated by societies such as European Alliance of Associations for Rheumatology (EULAR)[29] and Infectious Diseases Society of America (IDSA)[23] for a variety of inactivated and live vaccines (except for the oral polio vaccination[22,23,29]). Increasingly, epidemiologic studies have demonstrated SARS-CoV-2 transmission in close contacts due to asymptomatic and presymptomatic infections,[39-41] highlighting the importance of extending vaccinations to household contacts in order to protect vulnerable patients.

7. We conditionally recommend that any of the approved COVID-19 vaccines may be used, with no particular preference.

The various SARS-CoV-2 vaccines in development are non-live vaccines. The anticipated risk-benefit ratio should therefore be similar for vaccinations to be recommended without preference for any particular vaccine. However, long-term follow-up in PRD will be needed to ascertain longer term efficacy and safety of the various vaccines.

4 | DISCUSSION

The consensus recommendations for COVID-19 vaccination in PRD presented in this article were based on review of the limited currently available literature with these vaccines, supplemented by the more extensive knowledge that is available for other non-live vaccines in PRD. It is noteworthy that the absence of evidence is not evidence of absence, and practical recommendations for PRD need to be made despite the scarcity of literature in these vulnerable patients. Experts in the specialty were consulted, in order to synthesize the available literature into clinically meaningful recommendations. Available evidence on the risk of COVID-19 in PRD was weighed against the potential risks / benefits of vaccination with a new vaccine technology, borrowing from the principles of vaccination with non-live viruses in PRD and the available knowledge on mRNA drug delivery systems.

In formulating these recommendations, the TFP were cognizant of the heightened risk of COVID-19 in our patients. Therefore, recommendations were formulated to aid practicing rheumatologists in their decision-making without being overly restrictive, while allowing individualized decision-making for each patient. These should take into account patient's disease status, ongoing treatment, risk profiles, preferences and local community transmission risk.

Our consensus recommendations for COVID-19 vaccinations in PRD were developed employing a systematic literature review and Delphi method. The process of recommendation development incorporated all components of the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument,[42] other than patient/ allied health involvement, for practicality. The AGREE framework was developed to ensure the rigor of guideline formulations which are feasible for clinical practice. The only other consensus recommendations developed using a standardized Delphi method for COVID-19 vaccination in PRD were recently announced in a press release by the ACR.[35] Importantly, the broad principles for COVID-19 vaccination in PRD in our recommendations are similar to what the ACR has outlined, in spite of the vastly different pandemic situations (and therefore the balance of risk / benefit of the vaccine) in Asia vs North America. Vaccination is strongly encouraged, may be given while on immunomodulatory therapy, preferably during quiescent disease, and without the need for testing for post-vaccination antibody titers. The ACR recommended that COVID-19 vaccination should be timed according to the dosing of certain immunomodulatory treatments (rituximab, intravenous abatacept and intravenous cyclophosphamide) and that treatment with methotrexate, Janus kinase inhibitors and abatacept should be temporarily interrupted prior to or after COVID-19 vaccination. However, as discussed, while there may be reduced vaccine immunogenicity in patients on these medications, sufficient protective efficacy has been demonstrated,[22,26,30] thus forming the basis of our recommendation to vaccinate without treatment interruption or consideration for timing of doses.

As of the latest WHO update on March 5 2021, 79 candidate vaccines are in clinical development, with a further 182 in pre-clinical development.[43] Since the rollout of vaccination campaigns in various regions in mid-December 2020 up to March 9 2021, more than 312 million vaccine doses have been administered worldwide[44] and our collective experience with the new vaccines continues to evolve. It is important that governing institutions and healthcare providers continue to keep abreast of the latest evidence, so that recommendations can be reviewed and/or revised as new knowledge emerges. Particularly, data on safety and efficacy of vaccination in PRD are

TABLE 4 Final consensus statements

	Median Likert score	% agreement	Strength of recommendation
Overarching principles			
Vaccination in people with rheumatic diseases should be aligned with prevailing national policy.	4.5	100	-
The decision for vaccination should be individualized, and should be explained to the patient, to provide a basis for shared decision-making between the healthcare provider and the patient.	5	100	-
Recommendations			
1. We *strongly* recommend that eligible patients be vaccinated against SARS-CoV2.	5	100	Strong
2. We *conditionally* recommend that the COVID-19 vaccine be administered during quiescent disease, if possible.	4.5	100	Conditional
3. We *conditionally* recommend that immunomodulatory drugs, other than rituximab, can be continued alongside COVID-19 vaccination.	5	80	Conditional
4. We *conditionally* recommend that the COVID-19 vaccine be administered prior to commencing rituximab, if possible. For patients on rituximab, the vaccine should be administered a minimum of 6 mo after the last dose, and/or 4 wk prior to the next dose of rituximab.	4	90	Conditional
5. We *conditionally* recommend that post-COVID-19 vaccination antibody titers need not be measured.	4	90	Conditional
6. We *strongly* recommend that household contacts be vaccinated against SARS-CoV2.	4.5	100	Strong
7. We *conditionally* recommend that any of the approved COVID-19 vaccines may be used, with no particular preference.	4	70	Conditional

urgently needed to update recommendations in this vulnerable population.

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REVIEWS AND RECOMMENDATIONS

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Update on pregnancy in Takayasu arteritis—A narrative review

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Abstract

Takayasu arteritis (TA) is a chronic, idiopathic large-vessel vasculitis that affects women of reproductive age, and has significant maternal and fetal implications. Although there are contrasting data on the effect of TA on fertility, most studies have shown that fertility outcomes remain unaffected. The disease activity of TA usually either remains stable or decreases during pregnancy. The important feto-maternal complications are maternal hypertension, pre-eclampsia, prematurity, and intrauterine growth restriction. To reduce maternal and fetal morbidity, controlling the disease before conception is important. This review article discusses the various implications, challenges, and medical and endovascular management of TA during pregnancy.

KEYWORDS

aortoarteritis, fertility, obstetrical outcomes, pregnancy, Takayasu arteritis

1 | INTRODUCTION

Takayasu arteritis (TA) is a large-vessel vasculitis of unknown etiology that involves the aorta and its branches, and may rarely involve the pulmonary and coronary arteries.[1] It is more common among young women, less than 40 years of age. Vessel wall inflammation eventually leads to fibrosis, stenosis, and thrombus formation. These lesions are often discovered after many years of the disease. However, when inflammation is acute and severe, it can compromise the arterial media, leading to loss of vessel wall integrity and aneurysm formation.[2] These lesions are often asymptomatic unless they cause ischemic symptoms, dissection, rupture, or produce aortic regurgitation. Most of the autoimmune rheumatic diseases occur in women of childbearing age, which raises important concerns for fertility as well as maternal and fetal implications of disease during pregnancy. Most of the vasculitic disorders, however, occur beyond the childbearing age groups.[3] In contrast, the onset of TA is usually in the age bracket below 40 years. There are contrasting reports of the effect of TA on fertility.[4,5] Some data show that pregnancy does not affect the disease activity of TA,[6] but women with TA are at increased risk of adverse pregnancy outcomes like maternal hypertension, premature delivery, and intrauterine growth restriction (IUGR) of the fetus.[7] A study in France showed a 13-fold increased risk of maternal complications during pregnancy in TA.[8] However, some studies have reported no significant maternal or fetal concerns in pregnancy.[9] Although single-center reports from Japan,[10] Europe,[11] and North America[5] show favorable pregnancy outcomes, cohorts from India show adverse pregnancy outcomes.[12-14] This may be due to the increased prevalence of Type 4 and Type 5 TA in the Indian population, which may be an important contributor to hypertension and related complications.[15] Hence, the management of TA deserves special attention. However, the optimum management has not been well established and this poses a challenge to rheumatologists, obstetricians, and other concerned clinicians. This review article addresses the issues of risks of infertility, pregnancy and fetal outcomes, medical management as well as vascular interventions, intrapartum care, and other interventions needed to improve the outcomes.

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2 | SEARCH STRATEGY

The existing literature on the subject was searched using electronic databases of PubMed and Scopus using the terms "Takayasu arteritis", "aortoarteritis", "pregnancy", "obstetric outcomes", "cesarean delivery", "infertility" over the last 20 years, to identify relevant publications of patients with TA and obstetrical outcomes. A few items of relevance were included even if published earlier.

A total of 181 articles were found, of which 22 articles were relevant to this review. Small series of patients (<15 pregnancies) were excluded.

3 | IMPLICATIONS OF TAKAYASU ARTERITIS FOR FERTILITY

Systemic vasculitis may affect male and female reproductive organs leading to infertility. Both ovarian failure and testicular failure have been reported widely in autoimmune diseases, including vasculitic diseases. Mechanisms that lead to infertility in systemic vasculitic conditions include inflammation of vessels in reproductive systems and the formation of autoantibodies against the placental tissues. This has been documented in polyarteritis nodosa, and necrotizing small and medium-sized vasculitis.[16]

Many reports have been published stating the presence of anti-endothelial antibodies and anti-phospholipid antibodies in the sera of patients with TA.[17] In patients with lupus and antiphospholipid antibody syndrome, these antibodies are known to cause early ovarian failure and pregnancy loss.[18,19] However, there is a lack of evidence demonstrating the association of female infertility with anti-endothelial antibodies in TA. Medications like cyclophosphamide, aging, surgery, and hypothalamic-pituitary-gonad axis dysfunction due to steroids have also been found to influence the follicles in ovaries and eventually the ovarian reserve.[20,21]

In a small case-control study, reduced ovarian reserve was noted in patients with TA as measured by anti-Müllerian hormone.[22] In that study, they also found that diminished follicular reserve was not related to therapy of TA. Moreover, in contrast to systemic lupus erythematosus, where the reproductive function is also affected by disease activity, the same finding was not seen in TA.[23] Therefore, family planning must be discussed with all patients, especially young patients with low ovarian reserve. A recent study showed that healthy women over the age of 40 years with extremely low levels of anti-Müllerian hormone still had a chance of pregnancy.[24] In an Italian cohort study comprising 104 patients with TA, the incidence of pregnancy decreased from 8.2% before onset to 2.8% after the onset of disease.[4] However, in this regard, we need to consider other aspects, like voluntary delaying of pregnancy or fear of maternal/fetal complications, which would have led to a reduction in the incidence of pregnancies after diagnosis of TA.

A study performed in Sweden showed that TA may be an infrequent cause of infertility.[5] Subsequently, however, multiple studies, including a few systematic reviews, have shown that there is no decrease in fertility rates due to TA[10,12,13] (Table 1).

4 | EFFECT OF PREGNANCY ON TAKAYASU ARTERITIS

Pregnancy is a state that mandates the female immune system to tolerate the semi-allogenic fetus. A successful pregnancy is achieved by perfect interaction among maternal immune cells, decidua stromal cells, and placental trophoblast. Various immune cells accumulate in the decidua including uterine natural killer cells, macrophages, mast cells, dendritic cells, and T cells, whereas B cells are undetectable.[25] A reduced number of uterine natural killer cells leads to recurrent spontaneous abortions by contributing to increased local inflammation in decidua.[26] Altered immune cell subsets, cytokines, chemokines, and hormones disturb the maternal-fetal interface throughout pregnancy (Figure 1). There are contrasting reports on the effect of pregnancy on the disease activity of TA. Although, several studies have observed that the inflammatory activity of TA decreases during pregnancy, suggesting that pregnancy does not exacerbate the disease course, a few of studies have shown findings contrary to this.[6,13,27] In a recent study, out of 20 patients, only two of them required escalation of immunosuppression because of worsening disease activity during pregnancy.[28] However, one other study has shown relapse of TA in 22.7% (5/22) of patients during pregnancy.[29] Few other studies have also reviewed disease flare during pregnancy in TA, and reported its range to be 5%-40%.[30] A possible postulate of decrease in disease activity could be due to the T helper type 2 cytokine polarization at the fetomaternal interface and the systemic level, as well as the immunomodulatory effect of progesterone in pregnancy, similar to the situation in rheumatoid arthritis.[6,27,31] Progesterone modulates the immune response during pregnancy by conversion of dendritic cells to tolerogenic phenotype, differentiation of uterine natural killer cells, upregulation of Treg cells, and suppression of T helper type 17 cells.[32,33] The immunologic profile of TA is not well studied in pregnancy and postpartum. Detailed studies on regulatory T cells, measurement of cytokine levels, and sex hormones are required to obtain greater insights into the effects of pregnancy on TA.

5 | IMPLICATIONS OF TAKAYASU ARTERITIS ON PREGNANCY

Physiologic adaptive changes of the cardiovascular system, such as increased circulating blood volume and increased cardiac load, which occur in a normal pregnancy, may contribute to the deterioration of vascular lesions in a pregnant woman with TA. Pregnancy in TA can also lead to vascular injury, and to cardiovascular and cerebrovascular accidents. The risk of stroke and myocardial infarction has been shown to increase in pregnant women compared with non-pregnant women of similar age.[34] Therefore pregnant women with TA have a high risk of vascular complications that could negatively affect

TABLE 1 Summary of studies showing fetomaternal outcomes in TA

Study	Number of pregnancies	Effect on Fertility	Maternal implications	Fetal implications
Kirshenbaum et al 2017 [28]	6 patients, 20 pregnancies	Not mentioned	Abortions 30% Hypertension in 65% of pregnancies	SGA 23%
Assad et al 2015[27]	38 patients, 38 pregnancies	Does not affect	Abortion 7% Hypertension 31%	SGA 31% Premature 8%
Comarmond 2015[8]	96 patients, 240 pregnancies	Not mentioned	Hypertension 39% Abortion 9%	IUGR 5%
Mandal 2011[13]	16 patients, 29 pregnancies	Not mentioned	Abortions 3% Maternal hypertension 100% Placental abruption 6% PPH 17%	Prematurity 17% IUGR 51%
Gupta L, 2020[39]	20 patients, 38 pregnancies	Not mentioned	Abortions 26% Hypertension 40%	LBW 16%
Alpay-Kanitez et al 2015[56]	36 patients, 84 pregnancies	Tubal obstruction and azoospermia in 3 patients	Abortions 5% Hypertension 14%	Prematurity 10%
Singh 2015[47]	12 patients,18 pregnancies	No effect on fertility	Hypertension 66% Abortion 27%	IUGR 33%
Suri et al 2011[14]	37 pregnancies, 16 patients	Not mentioned	13.9% abortions Hypertension 91%	IUGR 16.7% IUD 11% Preterm 19%
David et al 2019[48]	16 pregnancies	Not mentioned	Live births 100% Hypertension 43%	IUGR 33% Preterm 25%
Tanacan et al, 2018[29]	11 patients, 22 pregnancies	Not mentioned	Abortions 22.7% Hypertension 36.7%	Preterm 18% IUGR 14%
Abisror 2020[46]	43 pregnancies, 33 patients	Not mentioned	Hypertension 35%	IUGR 14% Preterm 21%

Abbreviations: IUD, intrauterine death; IUGR, intrauterine growth restriction; LBW, low birthweight; PPH, post partum haemorrhage; SGA, small for gestational age.

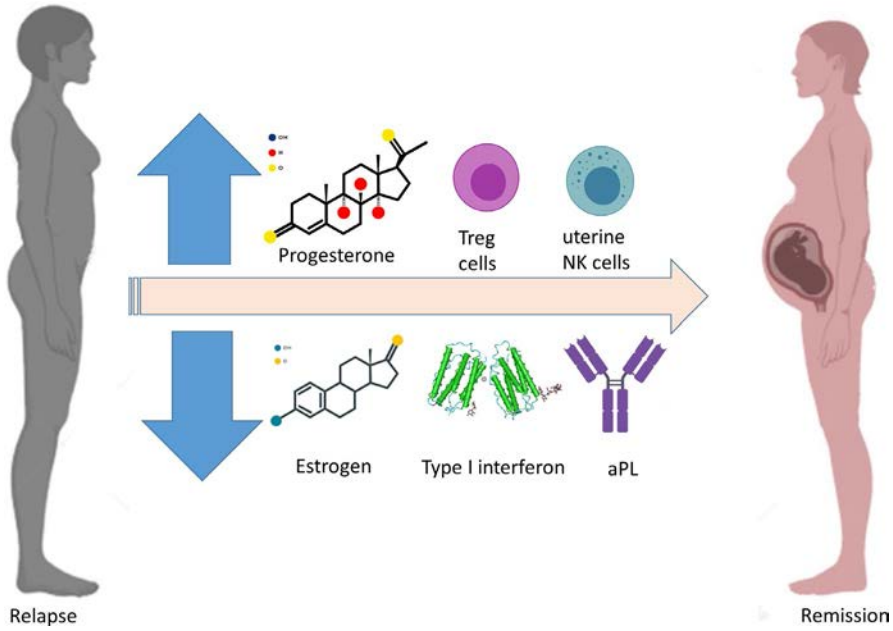

FIGURE 1 Pathophysiologic mechanisms explaining the effect of pregnancy on Takayasu arteritis

fetal and maternal outcomes.[35] It was seen in a nationwide French study that pregnancies concomitant with or after the diagnosis of TA had a 13-fold higher rate of obstetrical complications compared with pregnancies before the diagnosis of TA (odds ratio [OR] 13, 95% confidence interval [CI] 5-33, P <0.0001).[8] There seems to be an increased prevalence of uncontrolled hypertension during pregnancy

in TA patients compared with normal pregnancies, as depicted by the following citations. The overall incidence of maternal hypertension gathered from various studies is around 54% (ranging from 11% to 100%).[12] The worst fetomaternal outcomes in TA might be associated with hypertension. A study by Assad et al showed that cesarean rates, low birthweight, prematurity, and abortion rates were statistically more prevalent in those with hypertension during pregnancy.[27] It is also prudent to differentiate between accelerated hypertension of TA during pregnancy and pregnancy-induced hypertension as the management differs (Table 2).

Increased blood volume leads to increased cardiac load during pregnancy, which may eventually lead to complications like worsening of aortic regurgitation, congestive heart failure, renal insufficiency, antepartum hemorrhage, pulmonary embolism, and ischemic heart disease.[6,10,13]

No differences were noted in the fetomaternal outcomes in those with abdominal aortic involvement compared with those without.[27] Table 1 summarizes the published studies with maternal and fetal outcomes in TA. Cardiovascular and cerebrovascular events are the major causes of mortality and they constitute 5%-19% of all maternal deaths in TA during pregnancy.

Women with TA may have antiphospholipid antibody positivity, which may affect the pregnancy outcome. A retrospective study by Jordan et al showed that persistently positive Antiphospholipid (aPL) antibodies / a diagnosis of concurrent antiphospholipid syndrome was present in 41% (9/22) of patients.[36] However, the rates of vascular complications or the need for interventions did not differ between the two groups. Misra et al reported that 41% (14/34) of patients with TA had an increased IgG Anticardiolipin antibody (aCL) level and none had features suggestive of antiphospholipid antibody syndrome.[37] This highlights the possible role of aspirin in management.

6 | FACTORS AFFECTING FETOMATERNAL OUTCOMES IN TAKAYASU ARTERITIS

1. *Disease activity:* Controlling the disease activity before conception is of utmost importance. A French study of 98 pregnancies showed National Institutes of Health activity score >1 could be an independent risk factor for obstetrical and maternal complications.[8] Smoking (OR 6.15, 95% CI 1.31-28.8) and disease activity of TA (OR 28.7, 95% CI 7.89-104.7) were independently associated with bad obstetrical outcomes.[8] The same study also found that the maternal complications (hypertension), but not fetal complications, increased when the disease was active during pregnancy.[8]
2. *Hypertension and vascular involvement:* Pregestational hypertension is another important factor determining the fetomaternal outcomes.[10,12,27] A study by Suri et al showed that patients with angiographic Class IIb and Class III had a numerically higher incidence of superimposed pre-eclampsia (18/22), preterm labor (7/7), and IUGR (4/6) than those with milder disease belonging to class IIa; but this difference was not statistically significant ($P > 0.05$).[14] Patients with involvement of two or more vessels were also found to have a higher complication rate during pregnancy. Complications during pregnancy were three times more likely to occur in women with active disease, especially in the second and third trimesters of pregnancy. A prognostic scoring has been devised by Wong et al, for assessing the neonates at high risk for IUGR [38] (Table 3). A score of 4 or more identifies the neonates at high risk for IUGR. However, one study showed that involvement of the abdominal aorta or renal arteries did not have any effect on pregnancy outcomes.[8]
3. *Timing of diagnosis:* The timing of the diagnosis of TA also affects the fetomaternal outcomes. In a study by Gupta et al, conception

TABLE 2 Comparison between worsening of pre-existing hypertension of Takayasu arteritis in pregnancy and preeclampsia

Clinical features	Worsening of pre-existing hypertension of Takayasu arteritis	Pregnancy-induced hypertension/ pre-eclampsia
Onset	Anytime during pregnancy	After 20 wk of gestation
Proteinuria	Rare. Unless, hypertension is longstanding	Common
Hyperuricemia	Less common	More common
Liver enzymes	Normal	Abnormal
Thrombocytopenia	Absent	Common
Creatinine elevation	Present	Absent
Neurologic symptoms	Present	Absent

TABLE 3 Wong's prognostic scoring system for neonates born to mothers with Takayasu arteritis

Score	0	1	2
Involvement of abdominal aorta	No	Yes	Yes + renal
Trimester when treatment started	1st	2nd	3rd
Highest mean arterial pressure in third trimester	<100	101-130	>130
Superimposed pre-eclampsia	None	3rd trimester	1st-2nd trimester

after the diagnosis of TA was more likely to result in abortion compared with conception before the diagnosis of TA (relative risk 3.6, $P < 0.0001$).[39] These negative outcomes of the active disease can be explained by the inflammation occurring in the placenta leading to injury of the syncytiotrophoblasts, endovascular trophoblasts, endothelial cells of the spiral veins, and superficial/glandular epithelial cells of the decidua resulting in impaired implantation and disturbed fetal perfusion in these patients.[40]

7 | MANAGEMENT OF TAKAYASYU ARTERITIS IN PREGNANCY

Pregnant women diagnosed with TA at the same time as or before conception may have more aggressive vasculitis compared with women who are pregnant before a late TA diagnosis.[35]

Delay in the diagnosis of TA is very common, and women may conceive without knowing the diagnosis of TA. Treatment of the disease can also either positively or negatively influence pregnancy outcomes. More favorable outcomes are expected in patients in whom disease activity is controlled, but the adverse effects of the drugs used could also influence the outcome.[27]

7.1 | Pre-conceptional management

Planning of conception, pre-pregnancy counseling, and risk assessment for existing comorbidities are of paramount importance and are among the foremost steps to achieve good pregnancy outcomes. Indeed, it may be among the most difficult roles on the part of the physician to advise against conception in certain situations. Remission of vasculitic activity at the time of conception is an important determinant for a successful pregnancy. Immunosuppression should be changed to pregnancy-compatible agents before conception, according to the British Society for Rheumatology and American College of Rheumatology guidelines.[41,42] Managing the preconception and antenatal phases should be undertaken in a multidisciplinary fashion.[43] Severe aortic valvular disease and aortic aneurysm, chronic kidney disease, severe pulmonary artery hypertension, and congestive cardiac failure are risk factors for maternal morbidity and fatality; therefore, patients with these complications should be discouraged from pregnancy and, if pregnancy unexpectedly occurs, termination of pregnancy may have to be considered.[44,45]

7.2 | Pre-conceptional management—Is a vascular intervention needed?

Considering the nature of the disease, TA can cause stenosis of the vessels leading to organ damage. As we have already seen in the earlier sections, maternal hypertension is the single most important complication and factor that determines neonatal outcomes. In the current era, where endovascular procedures have picked up the pace and are being performed in most institutions with almost negligible complications, a valid question arises as to whether patients need a vascular intervention before planning a pregnancy? As seen in the preceding section, the involvement of renal or abdominal vessels did not have any effect on pregnancy outcomes.[8,39] In contrast, other studies have shown poor obstetrical outcomes with vascular involvement.[1,14] A French multicentre group showed that adverse obstetrical events were more common in TA with infra-diaphragmatic artery involvement and renal artery stenosis.[46] In an observational study published recently, it was seen that renal artery intervention before conception was associated with better fetomaternal outcomes.[47] A study performed in southern India, in a tertiary care center, carried out vascular interventions in around half of the patients before pregnancy. This series of patients had improved maternal (pre-eclampsia 12%) and fetal (IUGR 31%) outcomes with no mortality.[48] Considering these limited data, it may be reasonable to consider vascular intervention for critically stenosed arteries (renal artery, abdominal aorta, and carotids) in selected patients.

7.3 | Diagnosis of Takayasu arteritis in pregnancy

Diagnosis and monitoring of TA in pregnancy is a challenge because angiography is not recommended during pregnancy given the effect of contrast agents and radiation on fetuses. Color Doppler ultrasonography is a useful non-invasive means for assessing vasculitis and can explore stenoses or occlusions in the aorta and its main branches (carotid artery, subclavian artery, or renal artery).[49] Magnetic resonance angiography can also be used instead of computed tomography angiography for the assessment of aortic lesions.[50]

7.4 | Challenges with the assessment of disease activity of Takayasu arteritis in pregnancy

- Blood pressure measured in a limb with arterial occlusion may be lower than the actual pressure.[51]
- Blood pressure in lower limbs is not very accurate and is very difficult to assess because of positioning during labor.
- Mechanical stress-related symptoms like back pain and extremity pain may mimic ischemic symptoms in Takayasu arteritis.
- The erythrocyte sedimentation rate also increases during pregnancy and therefore, it cannot be used as a reliable marker for assessing the disease activity; instead, C-reactive protein may be used.
- C-reactive protein level can be monitored during pregnancy; meanwhile, the effect of other factors, such as trauma or infection, on the C-reactive protein level should also be excluded.[49]
- Doppler to assess renal arteries becomes difficult as gestational weeks progress.

TABLE 4 Grades of severity of aortoarteritis by Ishikawa

Grades	Features
Group 1	Uncomplicated aortoarteritis
Group 2	Aortoarteritis associated with one of the following—hypertension, retinopathy, aortic regurgitation, or aneurysm formation
Group 2A	Mild or moderate severity of the complication
Group 2B	Severe complication
Group 3	Aortoarteritis with two or more complications

8 | ANTEPARTUM MANAGEMENT

Antenatal evaluation should entail a detailed history and clinical examination. Each antenatal visit includes blood pressure and pulse recordings in four limbs and the detection of any change in symptoms and signs, with 3- to 4-weekly visits till 28 weeks and then twice in a month till 37 completed weeks of pregnancy. Growth surveillance of the fetus should be performed every 4 weeks through a serial growth scan and fetal Doppler.

Control of blood pressure is of paramount importance. Proven success has been shown with labetalol, hydralazine, and α-methyldopa, which can be safely used in pregnancy. Despite aggressive medical treatment, uncontrolled hypertension may require termination of pregnancy.

Immunosuppression compatible with pregnancy, i.e. steroids, azathioprine, or cyclosporine, needs to be continued to control the disease activity. Regular blood pressure monitoring must be done if the patient is on cyclosporine, which can be more problematic if patients have occluded arteries in the upper limb. Some biologicals can be considered if there are flare-ups during pregnancy. Tumor necrosis factor inhibitors are compatible during pregnancy as per the latest guidelines.[42] There is also one case report of active disease in pregnancy being treated successfully with IL-6 blocker tocilizumab.[52] Certolizumab pegol was tried in three patients during pregnancy refractory to conventional therapy and was found effective in two patients in terms of laboratory and clinical remission and in one patient in terms of angiographic remission.[53]

9 | REGARDING MODE OF DELIVERY—VAGINAL OR CESAREAN?

Ishikawa in a study of 23 pregnancies found that the blood pressure rises significantly during the second stage of labor and intracerebral hemorrhage can occur.[1] Those with aortic arch involvement are more prone to this serious complication. There is also a concern of strain-induced cerebral hypoperfusion during vaginal delivery. Ishikawa and Matsuura in their paper recommend cesarean delivery in (a) group 2B and 3 (using Severity of Aortoarteritis, Ishikawa), especially in patients with marked retinopathy and markedly increased blood pressure, (b) in group 2B and 3 if blood pressure measurement is unrecordable in arms, and (c) in group 1 and 2 if pressure is markedly increased in the first stage of labor despite multiple medications (Table 4).[54,55] However, multiple studies have shown favorable outcomes with normal spontaneous delivery.[10,56] In a series of 137 cases, 40.8% of patients had a spontaneous vaginal delivery with good outcomes.[7] In an older publication, vaginal delivery at term has been recommended as an expert consensus.[57] However, we should not disregard the fact that systolic blood pressure rises significantly during the second stage of labor.[12] Hence curtailing the second stage of delivery is suggested.[13] In a study by Kirshenbaum, preterm induction of labor was needed because of uncontrolled disease or obstetrical indication in 4/13 patients (30%).[28]

In a series of cases presented by Aso et al, 13 patients underwent cesarean section for severe hypertension.[58] However, in a single-center study from northern India, a majority (58.3%) of pregnancies ended in spontaneous vaginal delivery without any adverse events.[14] A total of 9.7% of patients in a series had a forceps or vacuum delivery to expedite the second stage of delivery because of hypertension.[7] So we may conclude that cesarean delivery may be reserved for specific obstetrical indications and if there is severe hypertension or risk of severe hypertension (depending on the arterial territory involved) during pregnancy, or the risk of aortic dissection or severe aortic regurgitation, and not for all cases.

10 | PERIPARTUM MANAGEMENT

Peripartum management should include optimization of intravascular volume and appropriate monitoring, which may be difficult in pregnant women with TA for the reasons mentioned earlier.

Incremental rises in blood pressure values during the first and second stages of labor are much higher in TA than in normal controls, so the second stage of labor should be assisted and expedited, as described above.

Epidural analgesia is considered ideal because it prevents the wide fluctuation in blood pressure levels that occur in the second stage of labor.

Epidural analgesia is also suitable for cesarean section if indicated. If general anesthesia is employed, then hyperextension of the neck during intubation must be avoided, as this may severely compromise cerebral blood flow in cases of carotid artery involvement.[59] The use of ergometrine needs to be avoided because these patients can have an increased incidence of dyspnoea or cyanosis. Instead, oxytocin infusion can be given for the prevention of postpartum hemorrhage.[14]

11 | CONCLUSION

Despite some reports of adverse fetomaternal outcomes, the overall prognosis of TA in the vast majority of pregnancies is good. The outcomes may be improved by achieving disease remission before conception and tight control of blood pressure during pregnancy. The disease activity of TA remains stable or decreases during pregnancy more often than producing a flare-up. Although the data on recanalization before pregnancy are limited, there may be a benefit in the setting of critically stenosed vessels of vital organs, which needs to be studied in the future.

CONFLICTS OF INTEREST

The authors did not have any conflicts of interests.

AUTHOR CONTRIBUTIONS

DD produced the concept and idea for this study. Manuscript writing and preparation was performed by SP, MP, JK, SR, and DD.

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ORIGINAL ARTICLE

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Frailty in relation to psycho-social factors in elderly patients with rheumatoid arthritis: A cross-sectional mixed qualitative-quantitative study

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Abstract

Aim: The aim of the study was to explore in patients with rheumatoid arthritis (RA) ≥55 years: (1) whether the occurrence of frailty as measured by the Groningen Frailty Indicator (GFI) increases with age (survey 1); and (2) to gain insight into which frailty characteristics (eg, loneliness) contribute to frailty (survey 2).

Methods: The GFI was assessed in 3 age groups (55-64/65-74/≥75-years), ensuring equal representation. GFI-subdomains that discriminated most between those classified as frail were further studied in a subset of patients using validated domain-specific questionnaires (eg Hospital Anxiety and Depression Scale [HADS]) and semi-structured interviews. Questionnaires were filled out twice: for current age and the recalled situation at age 40, to see whether psychiatric symptomatology might be misinterpreted for frailty.

Results: Of 90 patients included, frailty prevalence on the GFI across age groups was 43.3%-40.0%-43.4%, respectively. Frail patients often reported depressive (73.7% vs. 11.5%) and anxious (57.9% vs. 15.4%) feelings. There were 32/90 patients who filled out the psycho-social questionnaires twice. More frail patients had signs of an anxiety disorder on the HADS (missing data 4 patients), both at current age (5/11 frail patients vs. 0/17 non-frail patients, $P = .01$) and age 40 (7/11 frail patients vs. 0/0 non-frail patients, $P < .01$). During the interviews, especially frail patients reported gloomy feelings, although none confirmed depression or anxiety.

Conclusions: Frailty is highly prevalent in RA patients ≥55 years. As frail patients were characterized by symptoms of anxiety both at current age but (recalled) also at age 40, this finding suggests that pre-existing psychiatric symptomatology may confound assessment of frailty.

KEYWORDS

elderly, frailty, qualitative research, questionnaire, rheumatoid arthritis

1 | BACKGROUND

Accelerated population aging in the European Union is expected in the coming years, leading to a rise in the proportion of people aged 65 and over from 87.5 million in 2010 to 152.6 million in 2060.[1] As a consequence, the number of elderly rheumatoid arthritis (RA) patients will also increase.

Geriatric syndromes (GS) are common in older people and include among others immobility, instability, incontinence, intellectual impairment, sarcopenia and frailty.[2] GSs often occur concomitantly and have a significant effect on quality of life, disability, hospitalization and use of healthcare resources.[2]

Frailty is a common GS and is defined as an age-associated decline in physiologic reserve and function across multi-organ systems, leading to inability to cope with new stressors.[3] Based on this conceptual framework, 2 major definitions with proposed assessment tools were developed. The most widely known is the frailty phenotype, also known as Fried's definition. Fried et al. defined frailty as a purely physical condition, including weakness, slowness, low level of physical activity, self-reported exhaustion and unintentional weight loss.[3] The second definition is the Frailty Index, which defines frailty as cumulative deficits identified in a comprehensive geriatric assessment.[4,5] Several validated tools to measure frailty are available. One of these is the Groningen Frailty Indicator (GFI), a questionnaire that also addresses social and emotional aspects of frailty, such as loneliness, depression and anxiety.[6]

In a systematic review in community-dwelling people aged >65 years, the average pooled prevalence of frailty, defined by a variety of approaches, was 10.7%.[7] However, this prevalence is highly varied across studies included in this review (range 4%-59%), mainly due to different definitions of frailty status.[7] Measurement of frailty in RA patients, is extra complicated, since several frailty characteristics are part of the RA disease construct, for instance lower grip strength and slower walking speed due to sarcopenia.[8] In a recent study by our group, we found that 55% of 80 RA patients >65 years who visited our outpatient clinic could be classified as frail when applying the GFI, but surprisingly no association with age was seen. It was felt that more data among younger patients would be needed, as we might have missed the inclination point for becoming frail. In addition, patients in our study were often classified as frail because of positive answers on items that report on depressive feelings (53.8%), anxiety (40.0%), missing people around (32.5%) and emptiness (23.8%).[8] As the domains for loneliness, depression and anxiety are assessed with single items with a dichotomous answer in the GFI, this observation requires confirmation by validated domain-specific questionnaires. Last, to confirm whether these subdomains were characteristic for older and frail patients, we were interested whether these psycho-social domains are a cause or consequence of frailty. Therefore, the objective of this mixed qualitative-quantitative study was to gain insight into the occurrence of frailty across increasing age categories (55 years and older) and to explore whether poor psycho-social health might be a longitudinal predictor of frailty.

2 | METHODS

2.1 | Design and participants

Two cross-sectional surveys and a qualitative exploration were conducted. All studies were approved by the Ethics Committee of the Maastricht University Medical Center (MUMC+).

The first survey was conducted in RA patients aged ≥55 years visiting the outpatient clinic of the MUMC+, Maastricht, The Netherlands. Consecutive patients visiting the outpatient rheumatology clinic of the MUMC+ between July 2017 and December 2017 were considered for inclusion while ensuring equal representation of patients in 3 pre-defined age groups (55-64, 65-74, and ≥75 years). Patients were included if they were ≥55 years and were able to understand the study information. The rheumatologist informed all patients after a regular visit to the outpatient clinic about the study. Patients received an information letter, an informed consent form, and several questionnaires. Patients were included if they returned the informed consent form and questionnaires. No reminders were sent. Next to demographic characteristics, patients rated their overall health on a visual analog scale (0-100; 100 very bad health) and completed the GFI. The GFI is a validated, 15-item questionnaire with a score range from 0 to 15 which assesses the physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive dysfunction), social (emotional isolation), and psychological (depressed mood and feelings of anxiety) domains. Items have various scales that are dichotomized and "1" indicates a problem or dependency. A total GFI score of ≥4 is considered the cut-off point for frailty.[6] Information about healthcare consumption in the past 3 months was also collected. Rheumatologists recorded the number of comorbidities and the number of medications (polypharmacy was defined as the use of at least 5 medications).

A second survey was performed in October 2018 among patients who participated in the first survey. As the first survey revealed that the distinction between frail and non-frail patients was almost exclusively determined by psycho-social factors, we aimed to ascertain this by using 4 validated questionnaires among a subpopulation of the RA patient group of the first survey. The 11-item De Jong Gierveld Loneliness Scale measures loneliness. The total score ranges from "0" (not lonely) to "11" (extremely lonely), with a score of "3" or higher indicating loneliness.[9] The 34-item Social Support List – Interactions (SSL-I) measures the number of supportive interactions the respondents receive from their social support network. The 34 items are subsequently repeated to measure the amount of (dis)satisfaction with that support (SSL-D).[10] The 14-item Hospital Anxiety and Depression Scale (HADS) consists of 2 7-item subscales measuring depression and anxiety. A 4-point response scale ("0", absence of symptoms, to "3", maximum symptomatology) is used, with scores per subscale ranging from 0-21. A cut-off score ≥8 indicates a possible presence of anxiety or depression.[11] The 15-item Geriatric Depression Scale (GDS) assesses depressive symptoms and screens for depression among older people. A cut-off score ≥6 indicates symptoms of depression.[12]

Further, to understand whether these determining psycho-social domains were actually a personality trait of consequence, patients filled out 4 questionnaires twice, once for current age and once for the recalled situation at age 40.

In addition, responders to the second survey were invited for semi-structured interviews to explore whether loneliness, depression and anxiety are actually personality traits already present at younger age or are a characteristic of aging. An interview guide that included both open-ended and closed questions was developed to secure uniform data quality and comparability (Table S1).

2.2 | Statistical testing

Patient characteristics, total GFI, and domain scores of participants in the first survey were compared between the 3 age groups using analysis of variance or Kruskal–Wallis tests. Data of patients classified as frail or non-frail were compared using a Chi-square test for categorical data or the independent samples *t* test for continuous data. For the follow-up survey, presence of loneliness, depression and anxiety between frail and non-frail and between current age and age 40 were compared using the Chi-square test. The qualitative interviews were audio-taped, transcribed, read and annotated by 2 readers (FC and AvM). Content analyses were conducted using NVivo12 software to uncover themes related to symptoms of loneliness, depression and anxiety and the role of RA in the development or aggravation of these symptoms. Coding was performed to structure themes further into categories and to create groups.

Statistics were analyzed using SPSS 24.0 (IBM, Armonk, NY, USA). Probability values of $P < .05$ were considered to be statistically significant.

3 | RESULTS

3.1 | Frailty across age groups (first survey)

Out of 172 invited RA patients, 90 (52%) completed the first survey; 30 (33%) were men and 38 (42%) out of 90 patients were classified as frail on the GFI. Across age groups, the median frailty score was 3.0 (interquartile range 1.0-5.0) and prevalence rates of frailty (respectively 43% [age group 55-64 years], 40% [age group 65-74 years] and 43% [≥ 75 years], $P = .80$) were remarkably similar (Table 1).

Frail compared to non-frail patients indicated on the GFI feelings of emptiness (63.2% vs. 3.8%), missing the presence of people around (65.8% vs. 7.7%), feelings of loneliness (55.3% vs. 0%), depression (73.7% vs. 11.5%) and anxiety (57.9% vs. 15.4%; Table S2). These percentages did not differ between the age groups (Table S3). No differences between frail and non-frail patients and between the different age categories were found with regard to number of comorbidities and polypharmacy (Tables 1 and S2).

Remarkably, independent of frailty, younger patients often indicated having memory complaints (33.3% vs 13.3%). Elderly patients more often experienced difficulties with grocery shopping (20% vs. 0%; Table S3).

3.2 | Domain-specific questionnaires: psycho-social health at current age and recalled at the age of 40 (second survey)

Of the 90 initial patients, 32 (36%) participated in the follow-up study and this subsample was representative for the total study population with regard to age and gender (mean age 70.5 years, 12 [37.5%] men, Table 2). Twelve out of 32 patients (37.5%) were classified as frail on the GFI. The domain-specific questionnaires revealed that frail patients more often had symptoms of depression and anxiety (Table 2). On the GDS at current age, 6/12 frail patients had signs of depression compared to 2/17 non-frail patients ($P = .04$, missing data on 3 patients). On the GDS retrospectively at age 40, 3/12 frail patients had signs of depression compared to 0/17 non-frail patients ($P = .06$; Table 2).

More frail patients had signs of an anxiety disorder on the HADS, both at current age and age 40 (current age: 5/11 frail patients vs. 0/17 non-frail patients; age 40: 7/11 frail patients vs. 0/17 non-frail patients, $P < .01$, missing data on 4 patients; Table 2). Results on the individual level were more blurred (kappa values 0.17 [GDS], 0.29 [HADS-anxiety]). For instance, 3 (42%) out of 7 frail patients were anxious at age 40, but not at current age. The loneliness, social support (data not shown) and HADS-depression questionnaires showed no difference between frail and non-frail patients, both at current age and age 40.

3.3 | Semi-structured interviews (survey 2)

Ten RA patients who participated in both studies (6 male, median age 66.5 [10.8] years) were interviewed and 5 patients (50%) were frail. Illustrative quotes are presented in Table 3. All frail RA patients reported having gloomy feelings. Main reason for these feelings was being limited in activities due to RA (quote 1). In general, non-frail patients had a more positive outlook on life (quote 2). Non-frail patients did not specifically experience symptoms of anxiety (quote 3). When asked whether anxiety or depression played a role at younger age, before the RA diagnosis, none of the patients reported to have these feelings in the past. However, compared to the questionnaires, 3 patients (all frail) had a positive score on the HADS-anxiety questionnaire at current age and at age 40. Main reasons for feeling lonely were not being able to participate in all activities anymore. The majority, but especially all frail patients, addressed this problem and thus felt lonely from time to time (quote 4). The majority of the

TABLE 1 Demographics, clinical characteristics, and resource utilization of the study population (survey 1)

	Total group (N = 90)	Age 55-64 (n = 30)	Age 65-74 (n = 30)	Age ≥75 (n = 30)	*P* value
Demographic characteristics					
Male	30 (33.3)	8 (26.7)	12 (40.0)	10 (33.3)	.55
Age, mean (SD)	69.7 (7.9)	61.0 (2.4)	69.6 (2.7)	78.7 (3.8)	<.01
Marital status					
Married or living together	67 (74.4)	22 (73.3)	25 (83.3)	20 (66.7)	.64
Educational level					
None or elementary school	6 (6.7)	3 (10.0)	2 (6.7)	1 (3.3)	.30
Secondary school	58 (64.4)	15 (50.0)	20 (66.7)	23 (76.7)	
Academic	26 (28.9)	12 (40.0)	8 (26.7)	6 (20.0)	
Smoking status					
Smoker	13 (14.4)	8 (26.7)	5 (16.7)	0 (0.0)	<.01
Never smoker	29 (32.2)	7 (23.3)	5 (16.7)	17 (56.7)	
Alcohol use					
Never	19 (21.1)	7 (23.2)	4 (13.3)	8 (26.7)	.48
Clinical characteristics					
Disease duration, y, median (IQR)	9.0 (4.0-20.5)	5.5 (2.8-10.5)	12.5 (6.0-21.8)	17.0 (4.0-25.0)	<.01
Patient global health, 0-100, median (IQR)	63.5 (46.9-74.0)	59.9 (45.8-70.3)	57.8 (48.8-80.2)	65.1 (45.1-74.2)	.83
Polypharmacy reported by rheumatologist, ≥5 medications	49 (54.4)	14 (46.7)	14 (46.7)	21 (70.0)	.11
Comorbidities, median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.3)	.76
Classified as frail on GFI	38 (42.2)	13 (43.3)	12 (40.0)	13 (43.3)	.96
GFI total score, median (IQR)	3.0 (1.0-5.0)	3.0 (1.0-5.3)	3.0 (1.0-4.3)	3.0 (1.8-6.0)	.80
Resource utilization					
Non-rheumatologic appointments with specialist within the past 3 months, median (IQR)	3.0 (1.0-10.5)	3.0 (1.0-11.8)	2.0 (0.0-4.0)	4.5 (2.0-11.3)	.01
Medical/social services h within the past 3 mo	15 (17.0)	3 (10.0)	2 (6.9)	10 (34.5)	.01
Biological infusion treatment of at least 4 h during the past 3 mo	14 (15.7)	7 (23.3)	2 (6.9)	5 (16.7)	.24
Hospitalization during the past 3 mo	6 (6.7)	2 (6.7)	1 (3.3)	3 (10.0)	.87

Note: Data are presented as number (percentage) of patients unless stated otherwise. Two patients had incomplete data.
Abbreviations: GFI, Groningen Frailty Indicator; IQR, interquartile range; SD, standard deviation.

interviewed patients expressed being worried about the prognosis of RA and their future (quote 5).

4 | DISCUSSION

This study showed that the prevalence of frailty as measured by the GFI was 42% in a cohort of RA patients. Frailty was remarkably not related to increasing age or presence of polypharmacy and co-morbidity. Patients were often classified as frail on the GFI due to positive answers on items related to poor psycho-social health. The higher frequency of depressive and anxious feelings in frail people was confirmed with more domain-specific questionnaires including the GDS-15 and HADS. More frail patients had signs of an anxiety disorder on the HADS, both at current age and (recalled) at age 40. During the interviews, signs of poor psycho-social health were also more prevalent in frail patients. However, most patients expressed during the interviews that they did not experience these anxious or depressive feelings at the age of 40.

In a study by Andrews et al., including 124 RA patients (mean age 58.0 ± 10.8 years), a prevalence of frailty of 13% was found.[13] In another study by our group, we found that 55% of 80 RA patients ≥65 years could be classified as frail.[6] Although all frailty researchers agree that frailty is a multidimensional concept, consensus on a definition of frailty is lacking. Some researchers mainly put emphasis on the physical aspects, other researchers also include psycho-social aspects of health in the frailty concept.[5] The lack of consensus on the frailty definition is reflected in availability of various instruments that claim to measure the "frailty construct". Differences in study populations, methodology and use of different definitions to define

TABLE 2 Comparison between frail and non-frail elderly patients with rheumatoid arthritis (RA) (survey 2)

	Total RA (N = 32)	Frail (n = 12)	Non-frail (n = 20)	*P* value
Demographical characteristics				
Male	12 (37.5)	5 (42)	7 (35)	.72
Age, mean (SD)	70.5 (6.3)	67.4 (5)	72.4 (6.4)	.03
Marital status				
Married or living together	26 (81.3)	10 (83.3)	16 (80)	.65
Educational level				
Academic	12 (37.5)	5 (41.7)	7 (35)	1.00
Smoking status				
Smoker	18 (56.3)	3 (25)	1 (5)	.05
Never smoker	4 (12.5)	1 (8.3)	9 (45)	
Alcohol use				
Never	8 (25.0)	2 (16.7)	6 (30)	.96
Clinical characteristics				
Disease duration, y, median (IQR)	13 (5.0-22.0)	19.5 (6.0-22.0)	10.5 (4.3-20.8)	.30
RA at age 40	4 (12.5)	1 (8.3)	3 (15)	1.00
Patient global health, 0-100, median (IQR)	65.1 (51.8-78.1)	54.4 (38.4-65.1)	68.2 (54.4-86.2)	.01
Polypharmacy reported by rheumatologist, ≥5 medications	21 (65.6)	10 (83.3)	11 (55)	.14
Comorbidities, median (IQR)	2.0 (1.0)	2.0 (2.0-2.0)	1.0 (1.0-2.0)	.09
Classified as frail on GFI	12 (37.5)			
GFI total score, median (IQR)	2.5 (1.0-5.8)	6.0 (5.0-7.8)	2.0 (1.0-2.0)	<.01
Domain-specific questionnaires				
GDS-15 (current age, data N = 29)				
No depressive symptoms	21	6	15	.04
Mild depressive symptoms	8	6	2	
Moderate to severe depressive symptoms	0	0	0	
GDS-15 (recalled situation age 40, data N = 29)				
No depressive symptoms	26	9	17	.06
Mild depressive symptoms	3	3	0	
Moderate to severe depressive symptoms	0	0	0	
HADS-anxiety (current age, data N = 28)				
No indication anxiety	23	6	17	.01
Indication anxiety	5	5	0	
HADS-anxiety (recalled situation age 40, data N = 28)				
No indication anxiety	21	4	17	<.01
Indication anxiety	7	7	0	
HADS-depression (current age, data N = 28)				
No indication depression	27	11	16	1.00
Indication depression	1	0	1	
HADS-depression (recalled situation age 40, data n = 28)				
No indication depression	27	11	16	1.00
Indication depression	1	0	1	
Resource utilization				
Non-rheumatologic appointment with specialist within the past 3 mo, median (IQR)	4.0 (2.0-13.0)	9.0 (3.3-16.5)	2.0 (1.0-6.0)	.04

(Continues)

TABLE 2 (Continued)

	Total RA (N = 32)	Frail (n = 12)	Non-frail (n = 20)	*P* value
Medical/social services ho within the past 3 mo	4 (12.9)	2 (16.7)	2 (10.5)	.63
Biological infusion treatment of at least 4 h during the past 3 mo	3 (9.7)	2 (16.7)	1 (5.3)	.54
Hospitalization during the past 3 mo	2 (6.3)	1 (8.3)	1 (5.0)	1.00

Note: Data are presented as number (percentage) of patients unless stated otherwise.

Abbreviations: GDS, Geriatric Depression Scale; GFI, Groningen Frailty Indicator; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; SD, standard deviation.

TABLE 3 Illustrative quotes made by patients (survey 2)

	Frail	Quotes
Quote 1 (F, 69 years)	Yes	"I used to travel a lot, sometimes even for weeks, on city trips. I used to go to friends. That is a lot less after the diagnosis."
Quote 2 (M, 65 years)	No	"It is what it is. From that perspective you try to live, think and act."
Quote 3 (M, 77 years)	No	"No, in everyone's life something bad happens. If you worry or are afraid then you can't live your life anymore."
Quote 4 (M, 65 years)	Yes	"They do not ask me to help anymore because they know I have RA. Then you experience a form of loneliness that I cannot handle. When they do not ask you anymore for help but somebody else, that makes me unhappy."
Quote 5 (M, 63 years)	Yes	"If you end up in a wheelchair. Then what? Then it is over."

Abbreviations: F, female; M, male; RA, rheumatoid arthritis.

frailty may explain the differences of observed prevalence rates in RA patients. Our prevalence rates may be higher due to the fact that we included patients directly from our outpatient clinics as compared to the study by Andrews et al., who included selected younger patients who were also enrolled in another cohort study.[13] These latter patients might not resemble the spectrum of patients treated in the "real world", that is, elderly patients with polypharmacy and comorbidities. In our study, we used the GFI which includes many items related to psycho-social health; in the study by Andrews et al., an adapted version of the Fried criteria was used, that mainly focuses on the physical frailty phenotype. When selecting a frailty assessment tool for clinical practice, consideration should be given to aspects such as feasibility, setting, purpose and added value of the tool.[14] For example, the use of GFI might not be appropriate in all cases, as criteria such as low grip strength (ie, weakness) are not incorporated. Recently, a Comprehensive Rheumatologic Assessment of Frailty (CRAF) algorithm was developed and validated in RA patients.[15] The CRAF index includes 10 major frailty domains: nutritional status, weakness, falls, comorbidity, polypharmacy, social activity, pain, fatigue, physical function, and depression. Further validation studies are necessary to see whether the CRAF can be implemented in daily rheumatology care.[15]

Patients in our study who were frail according to the GFI were strikingly characterized with symptoms of poor psycho-social health. As it is unclear whether poor psycho-social health was a symptom of frailty, a longer existing comorbidity or patient characteristic, we explored whether poor psycho-social health might be a longitudinal predictor of frailty. Although it is difficult to disentangle the causal conundrum between psycho-social health and frailty, frail patients were on a group level more anxious at younger age on the HADS in our study. A first step to elucidate this relationship might be to investigate psycho-social health in a sample of frail individuals, whose frailty was confirmed during a comprehensive geriatric assessment.

Prospective studies in which psycho-social health is studied as a risk factor for onset of frailty are very scarce. In a secondary analysis of the Women's Health Initiative Observational Study (N = 27 652 women, aged 65-79 years), it was found that depressive symptoms in combination with antidepressant use were associated with development of frailty 3 years later (odds ratio 3.64 [2.41-5.53]).[16] On the other hand, several studies also focused on frailty as a predictor of depression over time and found that presence of frailty appears to contribute to development, persistence or worsening of depressive symptoms.[17,18] As (1) the prevalence of frailty in our study was stable over the 3 age categories, (2) patients were often classified as frail on the GFI due to positive answers on items related to poor psycho-social health and (3) frail patients were on a group level more anxious at younger age on the HADS, our results suggest that psychiatric symptomatology might indeed be misinterpreted for frailty.

RA might be an extra complicating factor in the interplay between poor psycho-social health and frailty, as patients expressed during the interviews that RA disease activity made them worry about participation in daily activities and their future health.

This study has several limitations. Selection bias may reduce the generalizability of our results. Patients with RA living in nursing homes or severely disabled patients who are not visiting outpatient clinics were not included. Reasons for non-participation were not documented, as rheumatologists recruited patients during their daily outpatient clinics.

In addition, we did not record information about RA disease activity. Disease activity might be a potential confounder of the relation between psycho-social health and frailty. There was significant loss to follow-up in the second part of the study. Also, since patients in the second part of the study had to fill out questionnaires retrospectively at age 40, there is a high risk of recall bias. Furthermore, it is possible that patients tend to be more positive about life events in the past (the "positivity effect").[19-21] Last, we did not confirm our findings using another set of frailty criteria (eg, Fried criteria) that mainly includes physical items.

5 | CONCLUSIONS

Frailty is highly prevalent in all RA patients older than 55 years. Frailty seems to be a distinctive health construct which is not necessarily related to increasing age, polypharmacy or comorbidity in RA patients. Frail patients are characterized by lower physical fitness but also with symptoms of depression and anxiety. This might suggest that pre-existing psychiatric symptomatology may confound assessment of frailty. It is therefore debatable whether psycho-social items should be included in frailty criteria sets. Defining what frailty actually constitutes in RA patients and subsequently developing a valid measurement method to screen for frailty are important steps to improve management of elderly RA patients.

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CONFLICT OF INTERESTS

Marloes van Onna: consultancy fees Novartis, Pfizer. Research grant: Pfizer. Annelies Boonen: has received to her department research grants from Abbvie and Celgene and consultancy fees from UCB, Lilly, Novartis, Sandoz and Galapagos. The other authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

FC, AB and MO contributed to the study design, interpretation of findings and writing of the manuscript. AM analyzed the data of both surveys, with MO as supervisor. FC interviewed all the participants and performed the analysis with AM, with MO as supervisor. All authors approved the final version of the manuscript for submission.

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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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Prevalence of chronic obstructive pulmonary disease in patients with rheumatoid arthritis: A cross-sectional study

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Abstract

Objective: Rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD) are both chronic inflammatory diseases; the prevalence of COPD in RA patients is known to be high. However, the prevalence of both RA and COPD differs according to sex; the relationship between RA and COPD may also vary according to sex. Therefore, we investigated the prevalence of COPD and its association in patients with RA in Korea by sex.

Methods: We conducted a nationwide cross-sectional study using data from the Korea National Health and Nutrition Examination Survey. A total of 12 417 men and 15 878 women were included. In this study, RA was defined as physician diagnosed or currently under RA treatment. COPD was defined based on spirometry results, chronic symptoms, and smoking history. Multivariable logistic regression models were employed and we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for COPD prevalence in patients with RA.

Results: The prevalence of COPD was 15.5% in men with RA, 3.5% in women with RA, 7.8% in men without RA, and 2.2% in women without RA. After adjustment for potential confounding variables, including smoking status, RA was significantly associated with COPD in men (OR 2.16, 95% CI 1.06-4.40), but not in women (OR 1.58, 95% CI 0.81-3.10).

Conclusions: In Korea, the prevalence of COPD was high in patients with RA of both sexes; RA and COPD was significantly likely to be associated in men, but not in women.

KEYWORDS

chronic obstructive pulmonary disease, prevalence, rheumatoid arthritis, sex

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease; its occurrence and progress are strongly influenced by genetic and environmental factors. Genetic regions, including genes for protein tyrosine phosphatase non-receptor type 22 (PTPN22), and interleukin-6 receptor (IL6R), are associated with RA occurrence; environmental factors such as smoking and air pollution are associated with

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an increased risk of RA.[1] In addition, the presence of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) is important in the development of RA, and smoking or air pollution affects the generation of ACPAs.[1,2] Citrullination of proteins can occur not only in the synovial membrane but also in any inflamed tissues, and smoking increases the peptidyl deiminase enzyme expression in the lungs, leading to the citrullination of proteins.[3]

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lungs and distal airway caused by noxious gases or particles, which are mainly inhaled due to smoking; it is characterized by persistent airflow restriction and respiratory symptoms.[4] ACPAs are more likely to be produced when the lungs are chronically exposed to smoking and inflammation of tissues, such as in COPD. Therefore, the prevalence of RA is likely to be higher in patients with COPD. In addition, RA and COPD are both chronic inflammatory diseases, and pro-inflammatory cytokines such as IL-1β, tumor necrosis factor (TNF)-α, and IL-6 play a role in the progression of both diseases.[5,6] Previous epidemiological studies have shown that the presence of RA increases the risk of COPD.[7-12] However, each study reported different prevalence rates of COPD; moreover, each study used different definition for COPD, using only pulmonary function test results or International Classification of Diseases (ICD) codes. The Korea National Health and Nutrition Examination Survey (KNHANES) is a national survey conducted by the Korea Centers for Disease Control and Prevention (KCDC).[13] In the KNHANES, pulmonary function tests (PFTs) are performed in the participants, and symptoms of chronic cough and sputum as well as smoking history are examined. Using KNHANES data, in this study, COPD was defined as per the definition provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which is based on smoking exposure, respiratory symptoms, and PFT results.[4]

RA and COPD are chronic inflammatory diseases, and smoking is a major risk factor for both these diseases, but the prevalence of both diseases varies according to sex. The prevalence of RA is higher in women, but the positive rates for serum RF or ACPAs are lower in women than in men.[14] COPD has a higher prevalence and mortality rate in men but exacerbations are more common in women.[15] Thus, the prevalence of COPD in patients with RA and the relationship between RA and COPD are expected to be different according to sex. The aim of this study was to investigate the prevalence of COPD in patients with RA and the relationship between RA and COPD by stratification according to sex using KNHANES data. Since both RA and COPD can cause irreversible structural changes through a chronic course and since these patients can have various comorbidities, investigating the prevalence of and the association between the two diseases is important for the management of patients with one or both conditions.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This was a cross-sectional study performed using KNHANES data from 2008 to 2016. The KNHANES is a nationally representative cross-sectional survey administered to a sample of the non-institutionalized civilian population of Korea.[13] Households were randomly selected for participation and sampled using multistage stratifications based on geographical areas. The study design was approved by the Institutional Review Board of the KCDC.

2.2 | Participants

In the 2008-2016 KNHANES, participants aged 40-80 years were surveyed for health status, including smoking history, chronic respiratory symptoms, and diagnosis and treatment of RA; PFTs were also performed. A total of 31 003 participants completed RA-related questionnaires and underwent PFTs; the participants who did not complete the health survey were excluded. The final sample size of our study was 28 295 participants, of which 12 417 were men and 15 878 were women.

2.3 | Main variables and covariates

The RA group included participants diagnosed with RA by a physician who were currently taking medications for RA. Among the participants who responded questionnaires about RA, those who were not defined as RA participants were defined as non-RA participants. COPD was defined as follows: (a) a pre-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio of <0.7, (b) chronic cough or sputum for more than 3 months, and/or (c) smoking history of ≥10 pack-years. Rolling dry seal spirometry was performed using the Vmax series SensorMedics Type 2130 (SensorMedics, Yorba Linda, CA, USA) in a controlled environment (temperature 10-34℃, humidity 15%-95%, altitude <2000 m, ambient pressure 700-1060 hPa) by trained medical personnel, and the results were transferred to a connected computer. The initial extrapolated volume was <5% or <150 mL of the FVC, the exhalation time was at least 6 s, and the test was performed at least three times and at most eight times.

Sex, age, obesity, smoking status, occupation, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, alcohol consumption, and household income and education levels were considered as potential confounding variables affecting the prevalence of RA and COPD. According to the guidelines of the KCDC, we classified the low-weight group to include patients whose body mass index (BMI) was <18.5 kg/m^2; the normal weight group, patients whose BMI was ≥18.5 kg/m^2 and <25 kg/m^2; and the overweight group, patients with a BMI ≥25 kg/m^2. Regarding smoking status, patients were categorized as: never smokers, past smokers, or current smokers. Past smokers were defined as those who had smoked in the past, but had not smoked for more than 1 year from the date of the survey. Among current smokers, participants who smoked <10 cigarettes/day were defined as light smokers, those who smoked 10-20 cigarettes/day were defined as moderate smokers, and those who smoked >20 cigarettes/day were defined as heavy smokers.

Occupations were clustered into the following categories: white-collar for managers and professionals; pink-collar for clerks and service and sales workers; blue-collar for craft/trade workers, machine operators and assemblers, and elementary manual workers; green-collar for agricultural/fishery workers; and soldier, based on the International Standard Classification of Occupations.[16] The diagnosis of DM, dyslipidemia, and HTN was based on objective laboratory test results or measurements and subjective medication histories. DM was defined as a > 8 h fasting plasma glucose level ≥126 mg/dL, with a diagnosis of DM made by a clinician, or prescription of an oral hypoglycemic agent or insulin. Impaired fasting glucose (IFG) was defined as a fasting plasma glucose level ≥100 mg/dL and ≤126 mg/dL without a diagnosis of DM. Blood pressure was measured for a total of three times after resting for 5 minutes or more, and was based on the average value. HTN was defined as an average systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or prescription of antihypertensive drugs; pre-HTN was defined as an SBP of ≥120 mm Hg or a DBP ≥ 80 mm Hg without HTN. The diagnosis of dyslipidemia was based on the following: >8 h fasting figures for, total cholesterol level ≥200 mg/dL, triglyceride level ≥150 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women, or current use of any anti-dyslipidemia drugs for the purpose of controlling blood lipid concentrations. Alcohol consumption status was defined according to the amount of alcohol consumed. Heavy drinkers were defined as those consuming an average of ≥7 units of alcohol for men and ≥5 units for women on ≥2 days/wk; moderate drinkers were defined as those consuming more than one glass of alcohol per month over the past year; and non-drinkers were defined as those who had never consumed alcohol or had consumed less than one glass of alcohol per month over the past year. Household income levels were divided into quartiles based on monthly income, and education level was classified as primary school or lower, middle school, high school, and university or higher.

2.4 | Statistical analysis

The prevalence of COPD was determined using descriptive statistics. Chi-square tests and Fisher's exact tests were used to examine differences between the RA and non-RA groups with regard to general characteristics and COPD. The odds ratios (ORs) and 95% confidence intervals (CIs) for COPD in accordance with the presence of RA were calculated. In this study, four different logistic regression models were used to assess the association between RA and COPD: Model I was adjusted for age and BMI; Model II was adjusted for age, BMI, smoking status, and occupational cluster; Model III was adjusted for age, BMI, smoking status, occupational cluster, DM, HTN, and dyslipidemia; and Model IV was adjusted for age, BMI, smoking status, occupational cluster, DM, HTN, dyslipidemia, alcohol consumption, and household income and education levels. SPSS ver. 23.0 (SPSS Inc) was used for all statistical analyses, and a *P* value of ≤.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 shows the demographics of the study sample according to the presence of RA with stratification according to sex. In men, there were significant differences in age, occupational cluster, DM, alcohol consumption, and household income and education levels between the RA and non-RA groups. The most common age group was 50-60 years in the RA group and 40-50 years in the non-RA group. In the RA group, more than 40% of participants were unemployed, and the participants with jobs belonged mainly to the green-collar group. The prevalence of DM was higher in the RA group than in the non-RA group; however, the prevalence of IFG was lower in the RA group than in the non-RA group. The level of alcohol consumption was higher in the non-RA group than in the RA group, and approximately 40% of participants in the RA group were included in the lower quartiles of both household income and education levels. In women, there were significant differences in age, obesity, occupational cluster, HTN, dyslipidemia, alcohol consumption, and household income and education levels between the RA and non-RA groups. Those in the RA group were mostly aged over 50 years, and participants in the non-RA group were relatively young compared to participants in the RA group. The prevalence of obesity was higher in the non-RA group than in the RA group. Unemployment was more common in the RA group than in the non-RA group, and there was a smaller percentage of participants with white- and pink-collar jobs in the RA group. In the RA group, the prevalence of HTN, pre-HTN, and dyslipidemia was higher than that in the non-RA group, but the level of alcohol consumption was lower. Household income and education levels were relatively lower in the RA group than in the non-RA group.

3.2 | Prevalence of RA and COPD

The prevalence of RA among the participants in this study was 1.1%. Fifty-eight out of 12 417 men were defined to have RA (0.5%), and 260 of 15 877 women were defined to have RA (1.6%). The prevalence of COPD was 4.7% in the total sample, 7.9% in men, and 2.2% in women, 4.7% overall. The prevalence of COPD was 15.5% in men with RA, and 3.5% in women with RA, and 7.8% in men without RA, and 2.2% in women without RA.

3.3 | Association between RA and COPD

In the crude model and Models I and II, men had a higher OR for COPD in the RA group than in the non-RA group, but the difference was not significant. However, in Models III and IV, the OR for COPD was significantly higher in the RA group than in the non-RA group among men (OR 1.83, 95% CI 1.00-3.82; OR 2.16, 95% CI 1.06-4.40). In women, there was no significant difference in OR between the crude and logistic regression models (Table 2).

TABLE 1 Demographic characteristics of the study participants according to the presence of rheumatoid arthritis

	Male (n = 12 417)					Female (n = 15 877)				
	RA (n = 58)		Non-RA (n = 12 359)			RA (n = 260)		Non-RA (n = 15 618)		
	n	%	n	%	*P*	n	%	n	%	*P*
Age (y)										
40-50	6	10.4	3943	31.9	<.001	33	12.7	5138	32.9	<.001
50-60	22	37.9	3451	27.9		74	28.5	4659	29.8	
60-70	14	24.1	3091	25.0		79	30.3	3639	23.3	
70-80	16	27.6	1874	15.2		74	28.5	2181	14.0	
Mean ± SD	61.4 ± 10.29		55.6 ± 12.82			62.2 ± 11.26		54.9 ± 12.43		
BMI (kg/m^2)										
Underweight	0	0.0	242	2.0	.597	13	5.0	347	2.2	.006
Normal weight	35	60.3	7509	60.7		169	65.0	9862	63.2	
Overweight	23	39.7	4608	37.3		78	30.0	5408	34.6	
Mean ± SD	24.0 ± 2.62		24.3 ± 2.95			23.7 ± 3.36				
Smoking status										
Never	10	17.2	2312	18.7	.693	239	91.9	14 552	93.2	.567
Past	31	53.5	5605	45.3		11	4.3	413	2.6	
Light	3	5.2	628	5.1		5	1.9	292	1.9	
Moderate	13	22.4	3250	26.3		5	1.9	347	2.2	
Heavy	1	1.7	564	4.6		0	0.0	13	0.1	
Occupational cluster										
None	25	43.1	2969	24.0	<.001	157	60.4	7819	50.1	<.001
White-collar	9	15.5	2924	23.7		8	3.1	1654	10.6	
Pink-collar	1	1.7	1230	9.9		23	8.8	2468	15.8	
Blue-collar	9	15.5	3629	29.4		38	14.6	2396	15.3	
Green-collar	12	20.7	1584	12.8		34	13.1	1280	8.2	
Soldier	2	3.5	23	0.2		0	0.0	0	0.0	
Diabetes mellitus										
Normal	36	62.1	6508	52.7	.041	167	64.2	10 515	67.3	.112
Impaired fasting glucose	9	15.5	3786	30.6		52	20.0	3295	21.1	
Diabetes mellitus	13	22.4	2065	16.7		41	15.8	1807	11.6	
Hypertension										

(Continues)

TABLE 1 (Continued)

	Male (n = 12 417)					Female (n = 15 877)				
	RA (n = 58)		Non-RA (n = 12 359)			RA (n = 260)		Non-RA (n = 15 618)		
	n	%	n	%	*P*	n	%	n	%	*P*
Normal	20	34.5	3440	27.8	.516	60	23.1	6259	40.1	<.001
Prehypertension	14	24.1	3515	28.5		71	27.3	3660	23.4	
Hypertension	24	41.4	5404	43.7		129	49.6	5698	36.5	
Dyslipidemia										
Normal	55	94.8	11 495	93.0	.633	234	90.0	14 549	93.2	.049
Dyslipidemia	3	5.2	864	7.0		26	10.0	1068	6.8	
Alcohol consumption										
None	6	10.4	699	5.7	.039	83	31.9	3664	23.5	.004
Moderate	43	74.1	8111	65.6		173	66.6	11 496	73.6	
Heavy	9	15.5	3549	28.7		4	1.5	457	2.9	
Household income										
Lowest	23	39.7	2309	18.7	<.001	100	38.5	3648	23.4	<.001
Lower middle	10	17.2	3141	25.4		65	25.0	3963	25.4	
Upper middle	6	10.3	3265	26.4		52	20.0	3767	24.1	
Highest	19	32.8	3644	29.5		43	16.5	4239	27.1	
Education										
Primary school or lower	25	43.1	2690	21.8	<.001	161	61.9	6040	38.7	<.001
Middle school	8	13.8	1960	15.9		42	16.2	2297	14.7	
High school	13	22.4	3991	32.3		37	14.2	4720	30.2	
University or higher	12	20.7	3718	30.1		20	7.7	2560	16.4	
COPD										
None	49	84.5	11 389	92.2	.045	251	96.5	15 271	97.8	.051
COPD	9	15.5	970	7.8		9	3.5	346	2.2	

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; SD, standard deviation.

4 | DISCUSSION

In this study, the prevalence of RA is 1.1%; it is approximately three times higher in women than in general Korean men. The prevalence of RA in this study was similar to that obtained based on the ICD-10 code of RA using the Korean National Health Insurance database (1.2%-1.4%),[17] and similar to that in previous studies; three to four times higher in women than in men.[18] The prevalence of COPD is increasing; in 2010, a meta-analysis reported that the global prevalence was 11.7%, and the prevalence in East Asia was 9.7%, which is lower than the global prevalence.[19] The prevalence of COPD in this study was 4.7%, which is lower than that previously reported. Most previous studies have defined COPD using only spirometry-based criteria (FEV1/FVC < 0.7),[20] but we propose symptoms of chronic cough and sputum as well as a history of smoking be included in the definition of COPD; the use of this definition, lowered the prevalence in this study. The prevalence of COPD was approximately 3.5 times higher in men than in women. A reason for the difference in COPD prevalence between the sexes was that 81.3% of men had a smoking history, while only 6.8% of women had a smoking history; thus, the number of women diagnosed with COPD was small.

In men, the prevalence of COPD was more than two times higher in the RA group than in the non-RA group after adjustment. Smoking is a common risk factor for both COPD and RA. Smoking induces the release of intracellular antigens due to hypoxia or toxin-mediated cellular necrosis, enhances the proliferation of B cells, and stimulates the proliferation of peripheral T cells.[21] Exposure to toxins inhaled via smoking increases the incidence of autoimmune diseases, including RA, by inducing gene mutations. Smoking also has a direct effect on COPD development, causing inflammation and airflow limitation. Thus, the prevalence of COPD may be higher in the RA group than in the non-RA group. However, other than smoking, various factors, including cytokines and free radicals, have a common effect on RA and COPD. In this study, there was no significant difference in smoking history between the RA and non-RA groups, and there was a significant correlation between the prevalence of COPD and RA even after adjusting for smoking history. Thus, it can be suggested that there is an independent association between RA and COPD in men.

In contrast, among women, the RA group had a higher OR for COPD prevalence than the non-RA group, but this difference was not significant. In patients with COPD, an increase in the citrullination of proteins is seen in the lungs,[22] but in female patients, seronegativity of ACPAs is more likely to have a weaker effect on airway inflammation. In this study, COPD was defined only if there was a smoking history of 10 pack-years or more, and the number of women that could be defined to have COPD was too small. In addition, half of the women were unemployed; therefore, they were less likely than men to continuously inhale toxic substances at work. Therefore, the prevalence of COPD was low in women, possibly resulting in the lack of a significant association between RA and COPD.

Pulmonary lesions, as well as vascular, airway, pleural and parenchymal diseases, appear in approximately 70% of patients with RA.[23] RA-related pulmonary diseases involving the airways such as COPD, asthma, bronchiectasis, and cricoarytenoid arthritis, are known to be frequent, but interstitial lung disease (ILD), a parenchymal disease, is also common, and it has been reported that up to 58% of RA patients have ILD.[24] Parenchymal pulmonary diseases that occur in RA include ILD, rheumatoid nodules, fibrosis, drug-induced pneumonitis, and pneumonia. Vascular diseases in RA include rheumatoid vasculitis, pulmonary hypertension, and thromboembolism; pleural diseases include pleuritic and pleural effusion.[25] These pulmonary diseases are caused by various genetic and environmental factors and usually share a common risk factor smoking. In addition, they have similar respiratory symptoms, and when the disease progresses, both obstructive and restrictive patterns appear simultaneously on PFT appear.[23,26] Therefore, in this study, pulmonary diseases other than COPD having mixed pattern on PFT may be included; further investigations such as radiological findings may be used to distinguish pulmonary diseases more accurately.

This study investigated the association between RA and COPD using representative nationwide data and showed the recent status of both diseases in Korea. In addition, sexes is an important factor in the development of both RA and COPD, and the study used sex stratification to show the relationship between these two diseases. However, this study has some limitations. First, the cross-sectional study design can show the association between RA and COPD but cannot show a causal relationship. Second, the current diagnostic status of RA was based on a self-report survey. Consequently, these data may have been influenced by systematic errors in individuals' consideration, which may have led to non-differential misclassification. However, RA was defined as a diagnosis by a physician and current use of treatment, similar to the definitions used in previous studies that diagnosed RA based on the ICD-10 code.[17] In addition, the results of RF and ACPA tests were not examined and RF and ACPA levels were not measured; thus, we could not determine the seropositivity status or levels of RF or ACPA. Third, COPD was defined based on prebronchodilator data. Since KNHANES was conducted in the general population, drugs such as bronchodilators could not be used. However, to increase the accuracy of the PFT results, spirometry was

TABLE 2 Odds ratios and 95% confidence intervals for chronic obstructive pulmonary disease in patients with rheumatoid arthritis

	Male		Female	
	OR	95% CI	OR	95% CI
Crude	1.68	0.81-3.52	1.03	0.52-2.03
Model I	1.68	0.81-3.21	1.08	0.55-2.14
Model II	1.74	0.84-3.62	1.10	0.56-2.17
Model III	1.83	1.00-3.82	1.13	0.57-2.22
Model IV	2.16	1.06-4.40	1.58	0.81-3.10

Note: Model I: adjusted for age and BMI. Model II: adjusted for age, BMI, smoking status, and occupational cluster. Model III: adjusted for age, BMI, smoking status, occupational cluster, DM, HTN, and dyslipidemia. Model IV: adjusted for age, BMI, smoking status, occupational cluster, DM, HTN, dyslipidemia, alcohol consumption, and household income and education levels.

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio.

performed repeatedly using the same machine in a controlled environment by trained medical personnel. Fourth, pulmonary diseases other than COPD may have been defined as COPD, as RA is associated with various pulmonary diseases having similar symptoms and a mixed pattern on PFT. Fifth, the disease duration, activity or severity of RA and COPD were not considered, and the medications used were not examined. Finally, interstitial lung disease (ILD) is known to be associated with RA, and the presence of ACPAs also affects ILD development, which was not investigated.[27]

In conclusion, the prevalence of COPD was higher in participants with RA than in those without RA among both men and women. After adjusting for various confounding variables, including smoking status, the prevalence of COPD was more than two times higher in men with RA than in men without RA, but there was no significant difference in prevalence between the two groups in women. Although the presence of ACPAs and the disease severity were not considered, the association between RA and COPD differed according to sex, and further studies on this topic are needed.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Limited utility of novel serological biomarkers in patients newly suspected of having giant cell arteritis

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Abstract

Aim: Diagnosing and monitoring vascular activity in giant cell arteritis (GCA) is difficult due to the paucity of specific serological biomarkers. We assessed the utility of 8 novel biomarkers in an inception cohort of newly suspected GCA patients.

Method: Consecutive patients were enrolled between May 2016 and December 2017. Serum was collected within 72 hours of commencing corticosteroids and at 6 months. It was analyzed for levels of intra-cellular adhesion molecule 1, vascular endothelial growth factor (VEGF), pentraxin 3, von Willebrand factor and procalcitonin (5-plex R&D Systems multiplex assay) and interleukin (IL)6, IL12 and interferon-γ (high-sensitivity 3-plex ProcartaPlex multiplex assay). A GCA specific positron emission tomography / computed tomography (PET/CT) scan was performed at enrolment with uptake in each vascular territory graded and summed to derive a total vascular score (TVS).

Results: For the 63 patients enrolled, 12 (19%) had a final diagnosis of biopsy-positive GCA and a further 9 had a clinical diagnosis of biopsy-negative GCA. None of the 8 biomarkers was significantly higher in GCA patients compared with those with alternative diagnoses, or demonstrated a positive correlation with the PET/CT TVS. This was in contrast to the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) which were higher in the biopsy-positive GCA cohort ($P < .04$) and showed weak positive correlations with the TVS (correlation coefficient 0.34, $P < .01$). Procalcitonin did not distinguish between GCA and infection. Concentrations of CRP, ESR, VEGF and pentraxin 3 decreased between diagnosis and 6 months in GCA patients.

Conclusion: This study did not identify new serological biomarkers to assist in diagnosing or assessing the vasculitis burden in GCA.

KEYWORDS

enzyme-linked immunosorbent assay, giant cell arteritis, immunoassay, interleukin-6, vasculitis

1 | INTRODUCTION

Giant cell arteritis (GCA) is a medium to large vessel vasculitis of the elderly that requires prompt recognition and management due its propensity to cause sudden vision loss. Clinicians may be alerted to the diagnosis by the presence of one or more of the classical manifestations of GCA: headache, polymyalgia rheumatica, constitutional upset, jaw claudication and vision disturbance. However, none of these features are sufficiently sensitive or specific to confirm the condition in their own right.[1,2]

Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly obtained by clinicians as part of the diagnostic pathway. Around 96% of patients with biopsy-positive GCA have elevation in either the CRP or ESR and elevation of both markers increases the likelihood of a positive temporal artery biopsy.[3] Unfortunately, many mimicking conditions including infection and malignancy also present with elevated CRP and ESR and thus while normal markers can help to exclude the diagnosis, elevation does not discriminate GCA from important differential diagnoses. Furthermore, patients with more concerning ischemic presentations may have less marked elevations in CRP and ESR levels than their non-ischemic peers.[3,4]

A range of newer serological markers have been examined in GCA to help diagnose GCA and distinguish subsets of patients at risk of ischemic events. These markers are closely linked to the pathogenesis of GCA[5,6] and can be broadly grouped into 3 domains.

1. Systemic inflammatory response markers. These are focused around the interleukin (IL)6 /IL17 cytokine cluster and are associated with T helper (Th)17 cells and hepatic production of inflammatory mediators.[7] Key markers include IL6, IL1, IL17, IL23 and CRP.
2. IL12/interferon (IFN)γ cytokine cluster. These cytokines are linked with Th1 cells and contribute to the sustained vascular inflammation in GCA. They include IL12, IFNγ, IL2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).[5]
3. Vascular injury and growth factors. These stimulate and/or are released from endothelial and vascular smooth muscle cells in response to vascular injury or chronic inflammation.[8] They include vascular endothelial growth factor (VEGF),[9] von Willebrand factor (vWF),[10-12] soluble intra-cellular adhesion molecule (ICAM)1[13] and pentraxin 3.[14]

While some studies have reported promising results with specific markers, their clinical utility remains questionable due to assay variability and lack of validation in large prospective cohorts. Of all markers, IL6 is the best studied and has most consistently been shown to be elevated in active disease.[15,16] Studies to date have not rigorously assessed how the timing of collection in relation to commencement of corticosteroid may affect reproducibility. Nor have they assessed a range of serological markers against an imaging-assessed vasculitis burden.

Our study had 3 aims. First was to examine serum concentrations of biomarkers from each of the 3 domains and assess if they could assist in differentiating GCA from mimicking conditions. Second was to assess if the markers correlated with a position emission tomography / computer tomography (PET/CT) determined vasculitis burden. Finally, we aimed to examine how these markers changed between diagnosis and 6 months for the sub-cohort of patients with a final diagnosis of GCA.

2 | METHODS

2.1 | Patients

Patients newly suspected of having GCA were referred to the study from 13 centers in Sydney, Australia between 2016 and 2017 and enrolled if they met the Giant Cell Arteritis and PET Scan entry criteria which have been published in detail elsewhere.[17] In brief, patients had to fulfill at least 2 of the 1990 American College Rheumatology Classification criteria for GCA[18] and have received less than 72 hours of corticosteroids at the time of enrolment and PET/CT scan. The project was approved by the local health district human ethics committee (HREC/16/HAWKE/68).

2.2 | GCA clinical assessment

Patients underwent a standardized clinical survey and examination at the time of enrolment. Temporal artery biopsies (TAB) were reported as positive if they had diffuse inflammation in one or more layers of the main artery wall (intima, media and/or adventitia). The clinical diagnosis was confirmed after a minimum of 6 months follow-up based on the biopsy result, the use (or not) of corticosteroids at 3 months, treating clinician and external reviewer diagnoses.[17] The clinical diagnoses were grouped into 6 categories of biopsy-positive GCA, biopsy-negative GCA, infection (viral or bacterial), malignancy, other inflammatory diseases (eg, polymyalgia rheumatica, spondylarthritis), and alternative diagnoses (eg, cervicogenic headache, thyroiditis, self-limited ophthalmological disease). The full list of clinical diagnoses has been previously reported.[17]

2.3 | PET/CT scans

The baseline PET/CT scan was performed prior to TAB on a single Siemens Biograph™ mCT time-of-flight scanner. Patients were scanned from the vertex of the head to diaphragm with 1 mm CT reconstruction. Arms were positioned by the side to allow better visualization of the head and neck vessels.[17] Fluorine-18 fluoro-2-deoxyglucose tracer (FDG) uptake was scored from 0 (no uptake) to 3 (very marked uptake) as previously described.[17] Eighteen artery segments were scored: the bilateral temporal, occipital, maxillary, vertebral, carotid, subclavian, axillary arteries, the brachiocephalic artery, ascending, arch and

descending aorta. A total vascular score (TVS) was calculated as a sum of the vascular grades across the 18 artery segments.

2.4 | Serological biomarker analysis

Patients had study blood collected at a maximum of 72 hours from starting corticosteroids. This was generally at enrolment or at the time of the baseline PET/CT scan. Collection took place between 8 AM to 5 PM and timing was not standardized across the cohort. Blood was immediately transported to the laboratory and centrifuged. Serum was aliquoted and transferred to a −80°C freezer within 4 hours of collection and stored until the day of analysis. It did not undergo repetitive freeze-thaw cycles. Patients were also invited to undergo blood collection at 6 months follow-up.

Serum was analyzed in 3 batches in February, July and October 2019 using 2 multiplex systems. An R&D Systems Human Magnetic Luminex Assay was used to measure ICAM1, vWF (A2 domain), pentraxin 3, VEGF-A and procalcitonin. A ProcartaPlex high-sensitivity multiplex panel was used to measure IL6, IFNγ and IL12 (p70 subunit). All samples were tested in duplicate and assays were conducted according to manufacturer instructions. Three identical patient samples were included in each of the 3 batches to serve as internal controls.

2.5 | Data analysis

Data were analyzed in SPSS version 25. Median biomarker levels were compared using the Mann-Whitney *U* test. Clinical features were compared using the Fisher exact test. Differences between baseline and 6 months biomarker levels were assessed using Wilcoxon signed ranks test. Correlations between biomarkers and the PET/CT vascular score were assessed using Spearman Rho test. We did not apply a correction factor for multiple comparisons.

3 | RESULTS

Sixty-three patients were enrolled in the study and had serum available for analysis. At the time of thawing and multiplex analysis, serum had been stored for a median of 27 months (range 20-44 months).

The final clinical diagnosis for the 63 patients was categorized as biopsy-positive GCA (19.0%), biopsy-negative GCA (14.3%), infection (17.5%), malignancy (4.8%), other inflammatory diseases (14.3%) and alternative diagnosis (30.2%). As presented in Table 1, GCA patients had similar clinical characteristics to the other groups but had higher median PET/CT vascular scores.

In contrast to CRP and ESR levels, which were higher in biopsy-positive GCA patients, there was no difference in median ICAM1, procalcitonin, vWF-A, pentraxin 3, IL6, IL12, IFNγ and VEGF-A serum concentrations between GCA patients and those with other diagnoses (Table 2). IL12 and IFNγ concentrations were less than 1 pg/mL for all but 1 patient who had a final clinical diagnosis of pneumonia and with an elevated IFNγ of 24 pg/mL. Forty-nine (78%) patients had undetectable IL6 at less than 1 pg/mL and 9 had a borderline concentration of between 2 and 5 pg/mL. Six (10%) patients had levels greater than 5 pg/mL. The final diagnosis for these 6 patients was

TABLE 1 Baseline characteristics of patients based on final diagnosis

	Biopsy-positive GCA (n = 12)	Biopsy-negative GCA (n = 9)[a]	Infection (n = 11)	Malignancy (n = 3)	Inflammatory disease (n = 9)	Alternative diagnosis (n = 19)	P1	P2
Age in y, median (range)	74 (58-85)	73 (56-88)	68 (60-83)	62 (59-74)	62 (57-85)	67 (50-90)	0.17	0.04
Female gender (%)	75%	56%	54%	67%	89%	74%	1.0	0.77
Jaw claudication (%)	50%	11%	27%	33%	20%	21%	0.09	0.57
Polymyalgia rheumatica symptoms (%)	58%	22%	27%	33%	67%	16%	0.09	0.58
Headache (%)	92%	78%	100%	100%	89%	90%	1.0	0.39
Vision disturbance (%)	42%	11%	9%	33%	33%	47%	0.50	0.78
Temporal arteries: tender or reduced pulse (%)	42%	56%	55%	67%	44%	63%	0.52	0.59
PET/CT Total Vascular Score, median (range)	14 (2-32)	7 (0-22)	1 (0-14)	4 (0-7)	1 (0-3)	0 (0-6)	< 0.01	<0.01

Note: P1, biopsy-positive GCA vs other patients. P2, clinically diagnosed GCA (both biopsy-positive and biopsy-negative) vs other patients.
Abbreviations: CT, computed tomography; GCA, giant cell arteritis; PET, positron emission tomography.
[a]One patient refused temporal artery biopsy as she had unequivocal CT aortitis.

TABLE 2 Serological biomarkers based on final diagnosis

	Biopsy-positive GCA (n = 12)	Biopsy-negative GCA (n = 9)[a]	Infection (n = 11)	Malignancy (n = 3)	Inflammatory disease (n = 9)	Alternative diagnosis (n = 19)	P1	P2
CRP, median, (range), mg/mL	74 (7-280)	12 (1-41)	28 (2-186)	31 (3-69)	7 (1-141)	3 (1-72)	<0.01	0.02
ESR, median, (range), mm/h	65 (10-116)	41 (9-99)	35 (3-130)	30 (30-32)	28 (2-64)	21 (5-82)	0.04	0.06
ICAM-1, median (range), ng/mL	203 (88-410)	184 (99-588)	244 (146-1117)	263 (262-567)	140 (49-249)	211 (96-706)	0.99	0.80
Procalcitonin, median (range), ng/mL	0.03 (0.01-0.10)	0.04 (0.01-0.08)	0.03[b] (0.01-0.16)	0.02 (0.01-0.04)	0.02 (0.01-0.04)	0.02 (0.01-0.36)	0.51	0.37
vWF, median (range), pg/mL	65 (26-258)	69 (42-146)	82 (21-252)	39 (21-191)	46 (22-152)	84 (23-243)	0.99	0.96
Pentraxin 3, median (range), ng/mL	2.3 (1.3-13)	4.6 (1.5-9.4)	3.3 (0.8-18)	2.8 (2.3-4.2)	2.5 (1.2-3.7)	2.1 (1.1-9.1)	0.67	0.46
VEGF-A, median (range), pg/mL	138 (25-487)	115 (35-339)	151 (22-292)	81 (56-158)	76 (31-297)	97 (28-297)	0.28	0.39
IFNγ, median (range), pg/mL	0.0 (0-0.18)	0.0 (0-0)	0.0 (0-24)	0.0 (0-0)	0.0 (0-0.49)	0.0 (0-0.79)	0.80	0.68
IL12p70, median (range), pg/mL	0.0 (0-0.4)	0.0 (0-0.31)	0.28 (0-0.5)	0.0 (0-0.21)	0.0 (0-0.21)	0.11 (0-0.44)	0.63	0.49
IL6, median (range), pg/mL	0.0 (0-109)	1.2 (0-5.9)	8.9 (0-172)	0.0 (0-5.5)	0.0 (0-3.7)	0.0 (0-3.4)	0.67	0.67

Note: P1, biopsy-positive GCA vs other patients. P2, clinically diagnosed GCA (both biopsy-positive and biopsy-negative) vs other patients.

Abbreviations: CRP, C-reactive protein; GCA, giant cell arteritis; ICAM, intra-cellular adhesion molecule; IFN, interferon; IL, interleukin; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; ESR, erythrocyte sedimentation rate.

[a] 1 patient refused temporal artery biopsy as she had unequivocal CT aortitis.

[b] For the subset of 7 patients with bacterial infections, median procalcitonin was 0.66 (range 0.14-1.56).

GCA (2 patients), pneumonia (2 patients), cervical discitis (1 patient) and metastatic lung cancer (1 patient). Five of these 6 had serum collected before commencing corticosteroids.

Twelve (19%) patients, including 1 with biopsy-positive GCA had serum collected prior to commencing steroids. The remaining 51 had serum collected in the subsequent 72 hours. There was a significant difference in IL6 levels between those who had serum collected before and after starting corticosteroids (mean 27 vs 0.59 pg/mL, median 1 vs 0 pg/mL, $P < .01$). Compared with their peers, these 12 patients also had higher median levels of CRP (48 vs 11 mg/mL, $P = .11$), ESR (41 vs 32 mm/h, $P = .19$), procalcitonin (0.037 vs 0.023 ng/mL, $P = .06$) and ICAM1 (249 vs 189 ng/mL $P = .11$) but none of the differences reached statistical significance.

Twenty patients with a final diagnosis of GCA had serum collected at both diagnosis and 6 months. Between these 2 time-points there were significant reductions in the median VEGF (132 to 87 pg/mL $P < .01$), pentraxin 3 (2.96 to 2.02 ng/mL $P = .05$), CRP (33 to 4 mg/L $P < .01$) and ESR (43 to 16 mm/h $P < .01$). Results are presented in Figure 1. At 6 months, IL6 was undetectable (<1 pg/mL) for 15 patients, low range positive (4-6 pg/mL) for 4 patients and was not assessable for the single patient who was taking an IL6 inhibitor. None of the 4 patients with low-positive IL6 levels experienced a clinical flare in the subsequent 6 months.

Fifty-eight (92%) patients had normal procalcitonin levels less than or equal to 0.1 ng/mL and none had levels exceeding 0.5 ng/mL. The median concentration of 0.03 ng/mL was similar for biopsy-positive GCA patients and those with infection. The 7 patients with bacterial infection had a non-significantly higher median procalcitonin of 0.07 ng/mL.

None of the serological markers correlated strongly with the baseline PET/CT TVS. A weak positive Spearman's Rho correlation coefficient of 0.34 was found between the CRP and TVS and the ESR and TVS ($P < .01$) but no other marker demonstrated a statistically significant positive correlation.

Three patients had serum tested on each of the 3 multiplex runs to determine intra-batch consistency. The intraclass correlation coefficient for the pooled markers was 0.97.

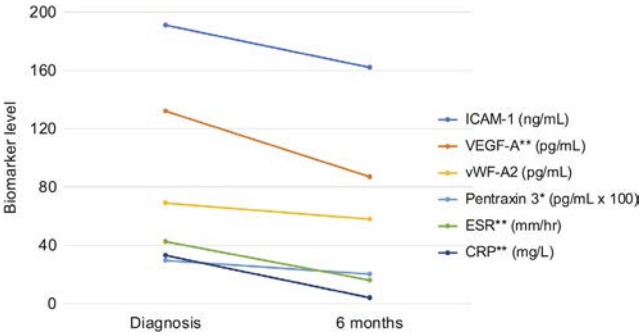

FIGURE 1 Median biomarker levels at diagnosis and 6 mo for 20 patients with a clinical diagnosis of GCA. Significant reductions between diagnosis and 6 mo indicated by **($P < .01$), *($.01 < P < .05$)

4 | DISCUSSION

This study examined the clinical utility of a range of experimental biomarkers in patients newly suspected of having GCA. We assessed if the markers could distinguish GCA patients from those with alternate diagnosis and how closely they correlated with the PET/CT detected vasculitis burden. We also examined their performance compared with CRP and ESR, which are currently used for diagnosing and monitoring patients with GCA.

Patients had serum collected prior to (19%) or within 72 hours (81%) of starting corticosteroids. This reflects real-world practice whereby corticosteroids are commenced as soon as the condition is suspected to minimize the risk of vision loss.[19,20] This collection methodology differed from many other studies which required blood draws prior to the commencement of steroids.[21-23]

We found that CRP and ESR, which are both well validated and utilized in clinical practice were able to discriminate between biopsy-positive GCA patients and those with alternative diagnoses. Both markers were also found to demonstrate a weak positive correlation with PET/CT detected vasculitis burden. In contrast, we did not find a significant difference in ICAM1, pentraxin 3, VEGF or vWF, IL6, IL12 or IFNγ between GCA patients and those with other diagnoses. Nor did we find these markers to correlate positively with the PET/CT detected total vascular score. Our findings differ from many prior published reports and prompt a discussion of comparisons and contrasts between studies.

Prior to this negative study, 2 groups had reported ICAM1 to be 25%-33% higher in active GCA patients compared with healthy controls and those with episodic cluster headache.[21,22] ICAM1 is an adhesion molecule which promotes leucocyte and endothelial cell interactions. Methodological differences include the fact that serum in both of these studies was collected prior to commencement of corticosteroids and controls did not have mimicking inflammatory or infective conditions.

Pentraxin 3 has been proposed as a useful biomarker in GCA due to the fact that it is both an acute phase reactant and is elevated in non-inflammatory vascular injury states and atherosclerosis.[14,24] Our negative results are in keeping with the findings of Goodfellow et al. which required serum to be collected within 7 days of corticosteroids.[9] It contrasts with the positive findings of an earlier cohort of long-term GCA patients where pentraxin 3 levels were higher for GCA than healthy controls and rheumatoid arthritis patients.[14]

A number of studies have found VEGF to be elevated in GCA patients and those with rheumatic diseases[25] compared with normal controls.[9,14] VEGF is a growth factor that stimulates angiogenesis in chronic inflammatory states and promotes the migration of monocytes and lymphocytes into the extracellular matrix.[8,26] In contrast to previously reported positive findings, our GCA patients had similar VEGF-A (the predominant form of VEGF in adults[9]) levels to those

with other diagnoses. In addition, our average VEGF concentrations were 5-fold lower (median 138 pg/mL) than those previously reported (ranging from 680[14] to 880 pg/mL[25]). Differences may be explained by detection methodology with previous studies using enzyme-linked immunosorbent assay (ELISA) rather than multiplex assay platforms.

We also found vWF levels to be similar in patients with GCA and those with other diagnoses. vWF, a glycoprotein produced by megakaryocytes and endothelial cells, is released from Weibel Palade bodies in response to endothelial vascular injury.[10] Our results differ from a number of older studies which reported elevated plasma and serum vWF levels in GCA patients compared with normal controls.[10-12] Notably, these studies have not been validated in contemporary cohorts with modern commercial assays.

IL6 is a key component of the GCA cytokine milieu and IL6 inhibition with tocilizumab has been shown to be an effective treatment.[27] Our results were somewhat discordant with most contemporary series[23,28-30] with only 1/12 biopsy-positive GCA patients having elevated levels above 5 pg/mL. IL6 is exquisitely responsive to high dose corticosteroids and levels drop by more than 50% within a few hours of administration.[31] The biopsy-positive GCA patient with high IL6 had serum collected prior to commencing corticosteroids. The other biopsy-positive GCA patients were taking high dose prednisone or methylprednisolone at the time of collection. Most other studies have collected serum prior to initiating corticosteroids and the discrepancy in results would argue in favor of measuring IL6 prior to corticosteroids. Two corticosteroid-treated GCA cohorts that measured IL6 levels on prednisone treated patients prior to commencing tocilizumab also found low IL6 levels in keeping with our findings.[32,33] The extreme sensitivity of IL6 to corticosteroid therapy combined with the fact that none of the patients with low-positive IL6 levels at 6 months experienced a subsequent clinical flare would argue against its routine use in clinical practice.

IL12 and IFNγ promote leukocyte vascular invasion in GCA. A landmark study in 2010[23] showed that these cytokines are elevated in GCA and that levels remain high despite treatment with corticosteroids, perhaps explaining persistence of vascular activity even during clinical remission.[6] In contrast to these findings and in keeping with a 2015 report,[29] we found that IL12 and IFNγ were not elevated in GCA patients. Our GCA patients had levels in the normal range (<1 pg/mL). The concentrations in our cohort were lower than in the 2015 study which reported a median concentration of 804 pg/mL for IL12 and 132 pg/mL for IFNγ.[29] The discrepancy may be due to differences in the assay reference ranges.

In this study we also assessed how the biomarker levels changed between diagnosis and 6 months for patients with a clinical diagnosis of GCA. We expected levels to be lower at 6 months as all patients were in clinical remission at this timepoint. This theory was validated with significant reductions seen in CRP, ESR, VEGF and pentraxin 3 concentrations. There were also non-significant reductions for ICAM1 and vWF. We were unable to assess changes in biomarker levels in non-GCA patients as many of them elected not to undergo the 6-month blood collection.

In addition to evaluating markers known to be associated with GCA, we also assessed procalcitonin as a potential marker to distinguish those patients with infection mimicking GCA. Procalcitonin has been validated as a clinical tool to identify patients with bacterial infections requiring antibiotics.[34,35] Values below 0.1 ng/mL are considered normal and values greater than 0.5 ng/mL indicate a need for antibiotics. In keeping with a previous report, we found that procalcitonin was in the normal range for GCA patients with all having levels less than or equal to 0.1 ng/mL. Procalcitonin was not significantly higher in patients with infection and thus did not appear to help discriminating between the conditions. Furthermore, while the 7 patients with established bacterial infection had a numerically higher median procalcitonin level than those with GCA, none had a clearly elevated level of greater than 0.5 ng/mL which could serve as a diagnostic cut-point.

This study had a number of limitations which may account for the discrepancy between our results and other studies. First, the timing of serum collection was not standardized with respect to corticosteroid administration. While this reflects clinical practice where patients are often commenced on corticosteroids once GCA is suspected, it may have confounded the results. It also meant we are not able to definitively exclude these markers being important in untreated disease and the pathogenesis of the GCA. The influence of corticosteroid treatment was most clearly illustrated by the difference in IL6 concentrations in patients who had serum collected before and after initiation of steroids.

Second, our samples had been stored for up to 40 months at the time of analysis. While cytokine levels can fall in serum stored for longer than 2-3 years,[36] we do not believe this contributed significant error to our results. Storage was at −80°C which should have minimized cytokine degradation. In addition, we added a freshly collected and stored serum sample from a newly treated GCA control patient to our final multiplex batch and found similar biomarker concentrations to our larger study cohort.

Another limitation of the study was the fact that we did not standardize blood collection times. It is thus possible that diurnal variations in cytokines may have confounded our results. Levels of IL6 have been shown to peak in the early morning in patients with rheumatoid arthritis.[37,38]

The discrepancies between our results and those previously reported may also relate to differences in assays. We used commercial multiplex assays while most other groups have reported results from ELISA assays. All of our assays had appropriate standard curves indicating good performance. Furthermore, a subset of patients had IL6, IL12 and IFNγ tested on 2 multiplex assay platforms with similar results. While we believe that assay variability may have contributed to the absolute concentration differences between our study and other reports, it should not have affected the relative difference between patients with GCA and those with alternate diagnoses.

Another important factor which may account for the discrepancy between our results and those described in the literature is publication bias. Negative studies may have failed to reach publication, thereby providing an overly optimistic view of the utility of these markers. While there have been mixed reports of the utility of pentraxin 3, IL12 and IFNγ in GCA, there have been no recent published literature describing vWF levels in GCA, questioning the reproducibility of positive findings in the 1980s and 1990s.

It is worthwhile noting a key strength of our study when comparing results to the published literature. We compared GCA patients to the most clinically relevant control group, patients initially suspected of having GCA but who were ultimately shown to have an alternative diagnosis. Many other groups have compared GCA biomarker levels to normals and/or patients with other rheumatic diseases.

A limitation of our study was the modest sample size. While the cohort of 63 patients is comparable with many other biomarker studies[23,29] it was prone to type 2 error and was not designed with the statistical power to detect differences in each biomarker for GCA cases and controls.

5 | Conclusions

In summary, this study did not find utility in a panel of serological markers in differentiating GCA patients from those with mimicking conditions. None of the markers correlated closely with the PET/CT detected vasculitis burden or outperformed the CRP or ESR. Based on these results, we would not recommend the use of these markers in the routine workup of patients suspected of having GCA. CRP and ESR should remain the standard of care.

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ORIGINAL ARTICLE

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Serum VEGF-A and VEGFR-1 levels in patients with adult immunoglobulin A vasculitis

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Abstract

Aim: Immunoglobulin A vasculitis (IgAV) is classified as a leukocytoclastic vasculitis characterized by immune deposits in endothelial walls of small vessels causing vascular endothelial injury. The aim of the present study is to evaluate levels of vascular endothelial growth factor-A (VEGF-A) and VEGF receptor-1 (VEGFR-1) levels in adult IgAV patients.

Method: Thirty-seven adult IgAV patients admitted to the Rheumatology Clinic meeting the IgAV American College of Rheumatology (ACR) criteria and 32 control subjects were enrolled in the study. Disease activity was categorized as "remission" or "active" according to Birmingham Vasculitis Activity Score (BVAS). Serum VEGF-A, VEGFR-1 levels and VEGFR-1/VEGF-A ratio were evaluated in patient and control groups.

Results: Serum median VEGF-A, VEGFR-1 and VEGFR-1/VEGF-A ratios were significantly higher in the patient group when compared to controls (235.9 [155-308.4] pg/mL vs. 78.8 [29.7-210.3] pg/mL, 400 [277.2-724.3] pg/mL vs. 31.5 [12.5-214.4] pg/mL and 1.85 [0.57-2.97] vs. 0.46 [0.38-0.63] respectively, all P values <.001). VEGFR-1 had the strongest predictive value with a cut-off value of 0.6 with 75% sensitivity and 73% specificity ($P < .001$).

Conclusion: This study is the first report indicating elevated serum VEGF-A, VEGFR-1, and more importantly VEGFR-1/VEGF-A ratio can be good representatives of the inflammatory processes together with vascular endothelial injury in adult IgAV patients. VEGFR-1 seems to be a more important indicator of the ongoing inflammation.

KEYWORDS

IgA vasculitis, vascular endothelial growth factor receptor 1, vascular endothelial growth factor-A

1 | INTRODUCTİON

Immunoglobulin A vasculitis (IgAV; formerly called Henoch-Schönlein purpura), first described in the late 1800s, is an immunocomplex vasculitis which mostly affects small vessels. The disease is characterized as a leukocytoclastic vasculitis with characteristic IgA1 dominant immune deposits. The clinical spectrum of the disease includes cutaneous purpura, arthralgias and/or arthritis,

acute enteritis and glomerulonephritis.[1,2] IgAV is the most common childhood vasculitis. Although the disease is manifested mostly in children, rare adults having the disease show worse prognosis than pediatric patients. The incidence of renal involvement is 45%-85% of all cases in adult patients and around 30% of the cases progress to renal insuffiency.[3,4] The etiopathogenesis of the disease is not yet clearly understood. A number of studies have been carried out in children but studies carried out in adults for highlighting the pathophysiology of the disease are limited.[5,6] Search for new prognostic markers is of crucial importance to identify patients with risk of damage. Immune complex accumulation in IgAV is known to trigger inflammation through polymorphonuclear leukocytes, monocytes and macrophages. Vascular endothelial growth factor (VEGF), is a potent endothelium-specific cytokine which is primarily produced by neutrophils, macrophages and vascular endothelial cells and the main driving force for VEGF production is inflammation. VEGF also has critical roles in the regulation of angiogenesis of blood vessels and lymphatic vessels, wound healing and tumor progression.[7,8] In mammals, the VEGF family consists of 5 secreted proteins (VEGF-A, B, C and D and placental growth factor [PGF]), which have different binding affinities for 3 tyrosine kinase receptors VEGFR-1, 2 and 3. Among the different VEGF ligands, the role of VEGF-A in the vascular endothelium is understood best as it modulates such proliferation and migration of endothelial cells (ECs) and vascular permeability.[9-11] The effect of VEGF-A can best be observed when it binds to VEGFR-2 but VEGF-A is also known to have high affinity for receptor VEGFR-1.[12]

Vascular endothelial injury seems to be the key factor in IgAV and as VEGF promotes functional changes in endothelial tissue, it is very likely that VEGF may play a role in disease pathogenesis. There are a few studies evaluating VEGF-A levels in IgAV showing either increased VEGF-A levels or increased incidence of VGEF-A gene polymorphisms in this patient group.[13-15]

The aims of the present study are: (a) to determine and compare the levels of VEGF-A and VEGFR-1; and (b) to evaluate the possible role of the VEGFR-1/VEGF-A system on progression and activity of disease among adult patients with IgAV.

2 | MATERİALS AND METHODS

2.1 | Study population

Thirty-seven adult IgAV patients meeting the IgAV American College of Rheumatology (ACR) criteria[16] and 32 healthy control subjects were included in the study. ACR criteria classifies patients as IgAV according to 4 basic criteria, which are: (1) palpable purpura; (2) age ≤20 years at disease onset; (3) acute abdominal pain; and (4) wall granulocytes on small arterioles and venules on biopsy (leukocytoclastic vasculitis). For purposes of classification, a patient is said to have IgAV if at least 2 of these 4 criteria are present. Demographic features of all participants were recorded. Subjects being <18 or >65 years, having any chronic metabolic diseases, acute or chronic infections, hematological disorders, malignancy, and also pregnant and lactating subjects and also individuals taking any medication that can interfere with the measurement of VEGF, VEGFR-1 were excluded from the study. The study was approved by the local ethics committee (approval number: E1-20-378) and written informed consent was obtained from all participants according to the principles of the Declaration of Helsinki.

2.2 | Clinical examination

The patient group fullfilled the "classic triad" of IgAV having purpura, arthralgia and abdominal pain. Skin biopsies revealed either leukocytoclastic vasculitis (LCV) or vasculitis with IgA deposition. Disease activity was categorized as "active" or "remission" according to Birmingham Vasculitis Activity Score (BVAS) criteria which is a composite score made of 59 items organized into 9 different groups, expressing possible organ involvement.[17] BVAS ≥1 was accepted as "active." Disease severity is evaluated by the involvement of different organs/systems and increased with increasing scores. Disease activity was defined as the presence of new or worsening symptoms attributable to active vasculitis in the last 28 days or on the day of examination.[18]

2.3 | Sample collection and quantification

Venous blood samples were collected from the participants into red-capped serum tubes after 12 hours of fasting. Blood samples collected for analysis were centrifuged at 3500 × *g* for 10 minutes. Separated sera were aliquoted into Eppendorf tubes and stored at −80°C until the time of analysis of VEGF-A and VEGFR-1.

Serum VEGF-A (Lot. no. E-EL-H0111), and VEGFR-1 (E-EL-H1087) levels were measured by using quantitative enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, Wuhan, China). Measurements were carried out with ELISA plate reader Bio-Tek Synergy HT (Biotek Instruments Inc.). Intra-assay coefficients of variation (CV) and inter-assay CV were 4.69% and 4.2%, respectively with sensitivity 18.75 pg/mL for VEGF-A, and 5%, 4%, and 75 pg/mL for VEGFR-1. Complement C3, C4 and C-reactive protein (CRP) levels were detected with immunoturbidimetric method and erythrocyte sedimentation rate (ESR) was measured with Westergren Method.

2.4 | Statistical analysis

The Statistical Package for Social Science v 22.0 software (SPSS) was used for statistical analyses. Anthropometric and biochemical features were categorized as categorical variables or continuous variables. Continuous variables were expressed as mean ± SD, median (range) and categorical variables as numbers and percentages. Kolmogorov-Smirnov test was used to detect whether the

distribution of groups was homogeneous. Analysis for numerical variables was performed by Mann-Whitney *U* test and by Spearman correlation coefficient. Chi-square and Fisher's exact tests were used for categorical variables as appropriate. Multivariate logistic regression analysis was performed to identify significant factors associated with disease activity. *P* values lower than .05 were considered as significant.

3 | RESULTS

The patient group consisted of 26 males and 11 females while the control group consisted of 23 males and 9 females. Mean age of the patient group was 44.4 (±14.9) years while for the control group it was 45.1 ± 14.8 years. There was no significant difference between age and gender distribution of patient and control groups (*P* values were .26 and .68 respectively). Demographical and clinical features of the patient group are shown in Table 1. Disease duration was 43.62 ± 7.68 months. The most common symptoms were cutaneous palpable purpura, arthritis and/or arthralgia and abdominal pain in 37 (100%), 21 (56.7%), 23 (62%) and 17 (42%) patients, respectively. Cumulative median doses and median duration of glucocorticoid (GC) were 3.9 g (0-18 g) and 7.5 months (0-72 months), respectively. Sixteen out of 37 patients (43.2%) were active with BVAS scores ≥1, and 21 (56.8%) were inactive. Skin biopsies revealed leukocytoclastic vasculitis (LCV) in 24 (68.6%) and LCV with IgA deposition in 9 (25.7%) patients. Two patients had renal biopsies confirming IgA deposition in the glomerulus. The most common treatments were systemic steroids and steroids in combination with immunosuppressants and median treatment duration was 8 months (5-16 months).

Median VEGF-A levels were 235.9 (155-308.4) pg/mL in patients and 78.8 (29.7-210.3) pg/mL in the control group. VEGFR-1 levels were 400 (277.2-724.3) pg/mL in patients and 31.5 (12.5-214.4) pg/mL in healthy controls, and VEGFR-1/VEGF-A ratio was 1.85 (interquartile range [IQR]: 0.57-2.97) in patients while it was 0.46 (IQR: 0.38-0.63) in the control group. VEGF-A, VEGFR-1 and VEGFR-1/VEGF-A ratios were significantly higher in the patient group when compared to controls ($P < .001$ for all). All data are shown in Table 2.

TABLE 1 The characteristics of patients with immunoglobulin A vasculitis/ Henoch-Schönlein purpura

Feature	All patients (N = 37)
Age, y, mean (SD)	44.4 (±14.9)
Disease duration, mo, mean (SD)	43.6 (±7.68)
Gender, n (%)	
Female	11 (30.6)
Male	26 (69.4)
Disease activity (Birmingham Vasculitis Activity Score), n (%)	
Active	16 (43.2)
Inactive	21 (56.8)
Skin involvement, n (%)	35 (97.2)
Renal involvement, n (%)	19 (52.8)
Gastrointestinal involvement, n (%)	14 (38.9)
Vascular involvement, n (%)	3 (4.3)
Arthritis, n (%)	21 (56.7)
Arthralgia, n (%)	23 (62)
Hypertension n (%)	3 (4.3)
Extremity edema, n (%)	1 (1.4)
Abdominal pain, n (%)	17 (47.2)
Weight loss, n (%)	5 (7.2)
Myalgia or muscle weakness, n (%)	9 (25)
Purpura, n (%)	37 (100)
Proteinuria n (%)	12 (31.9)
Hematuria, n (%)	6 (15.9)
Presence of biopsy, n (%)	34 (97.1)
Site of biopsy	
Skin	27 (77.1)
Renal	2 (5.7)
Skin + renal	5 (14.3)
Pathological diagnosis	
Immunoglobulin A vasculitis	9 (25.7)
Leukocytoclastic vasculitis	24 (68.6)
Treatment	
Steroid	18 (48.6)
Steroid + immunosuppressant	16 (43.2)
Nonsteroidal anti-inflammatory drugs	1 (2.7)
No treatment	2 (5.4)
Treatment duration, median (interquartile range)	8 (5-16)

3.1 | Receiver operating characteristic (ROC) analyses

ROC analysis was made to evaluate the predictive capacity of levels of VEGF-A, VEGFR-1, VEGFR-1/VEGF-A for IgAV. VEGFR-1 levels seemed to be the most predictive parameter for IgAV with higher sensitivity and specificity (Figure 1). Sensitivity and specificity at the cut-off level 215 pg/mL for VEGFR-1 were 81.1% and 75% respectively. Cut-off values, sensitivity, specificity, statistical significance and area under curve values for VEGFR-1, VEGF-A and VEGFR-1/VEGF-A are summarized in Table 3.

3.2 | Evaluation of the relationship between serum VEGF-A, VEGFR-1 and VEGF-A/VEGFR-1 levels and disease characteristics

Serum VEGF-A, and VEGFR-1 levels were similar between active and inactive patients while VEGFR-1/VEGF-A levels were higher in the active patient group ($P = .69$; $P = .54$; $P = .042$), and in patients with and without renal involvement ($P = .91$; $P = .59$; $P = .46$), with and

without hypertension ($P = .47$; $P = .71$; $P = .14$) and patients with and without gastrointestinal involvement ($P = .12$; $P = .24$; $P = .72$).

No correlation was observed between serum VEGF-A, VEGFR-1 and VEGFR-1/VEGF-A levels and age, age at diagnosis, disease duration and treatment duration.

Median VEGF-A and VEGFR-1 levels were significantly higher in patients with arthritis and arthralgia 302.8 (IQR: 234.7-430.9) versus 199.7 (IQR: 142.2-282) and 727.1 (IQR: 318.6-1352.9) versus 372 (IQR: 212.2-592.2) respectively ($P = .010$ and $P = .015$). VEGFR-1/VEGF-A levels were similar in the 2 groups ($P = .12$).

VEGF-A levels were significantly higher in patients with myalgia or muscle weakness ($P = .030$) but VEGFR-1 and VEGFR-1/VEGF-A ratios were similar in the 2 groups (P values were .12 and .27 respectively).

In patients with abdominal pain, serum VEGF-A and VEGFR-1 levels were significantly higher (P values .010 vs. .024 respectively).

TABLE 2 Serum median (interquartile range) VEGF-A, VEGFR-1 levels and VEGFR-1/VEGF-A ratio in patient and control groups

	IgAV patients (n = 37)	Controls (n = 33)	*P*
VEGF-A, pg/mL	235.9 (155-308.4)	78.8 (29.7-210.3)	<.001
VEGFR-1, pg/mL	400 (277.2-724.3)	31.5 (12.5-214.4)	<.001
VEGFR-1/VEGF-A	1.85 (0.57-2.97)	0.46 (0.38-0.63)	<.001

Abbreviations: IgAV, immunoglobulin A vasculitis; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

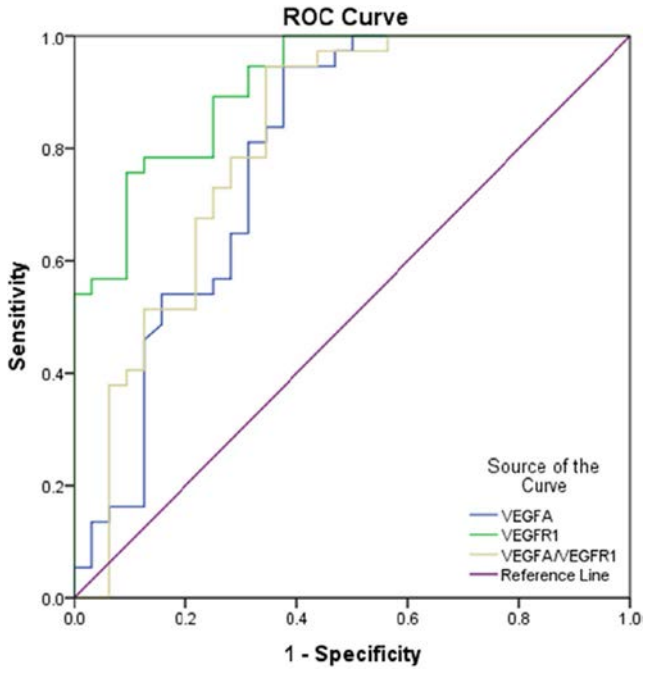

FIGURE 1 Receiver operating characteristic (ROC) analysis

4 | DISCUSSION

The aim of the present study was to investigate the association between serum VEGF-A and VEGFR-1 levels and their ratio (VEGFR-1/VEGF-A) in adult IgAV patients. This study is the first report which demonstrates a significant increase in VEGFR-1 levels which is about 10 times higher, increases in both VEGF-A levels and VEGFR-1/VEGF-A ratio in serum samples of IgAV patients.

As previously clarified, IgAV is an immunoinflammatory small vessel vasculitis, with immune complex deposition due to endothelial dysfunction.[5,19] Various markers of endothelial dysfunction and/or injury like thrombomodulin, intercellular adhesion molecule 1, E-Selectin and von Willebrand factor have previously shown to be elevated in IgAV.[20,21] VEGF is known as a key vascular permeability factor, and it stimulates functional changes in ECs. It is involved in the transendothelial migration of monocytes and also activates major serine proteases functioning in tissue remodeling.[10,22] Although being limited, there are several studies in the literature evaluating the role of VEGF in IgAV patients. Topaloglu et al. found that plasma VEGF levels were higher in the acute phase of the disease than the resolution phase.[13] Rueda et al. and Zang et al. declared that VEGF gene polymorphisms in the promoter region make IgAV patients more susceptible to nephritis development and frequency of VEGF-634 C allele is increased in these patients causing VEGF overexpression.[23,24] And in a more recent study by Mohammadian et al., it was shown that together with angiotensin-converting enzyme and C-C motif chemokine ligand 2 polymorphisms, VEGF gene polymorphisms are common in IgAV patients. In our study, we found that levels of VEGF-A are elevated in adult IgAV patients. Since VEGF is known as not specific for a particular disease, it is assumed as a non-specific marker for vascular disorders in which endothelial damage/repair occurs. Although C3 and C4 were within the reference range, CRP and ESR levels were higher than the upper reference limit. However, there was no correlation between these parameters and VEGF-A levels. Therefore, although VEGF-A

TABLE 3 AUC, cut-off points, sensitivity, specificity, and statistical significance of VEGF-A, VEGFR-1 and VEGFR-1/VEGF-A in predicting IgAV

	Cut-off value	Sensitivity	Specificity	*P* value	AUC
VEGF-A	157.8	70.3	69	<.001	0.79
VEGFR-1	215	81.1	75	<.001	0.91
VEGFR-1/VEGF-A	0.6	75	73	<.001	0.81

Abbreviations: AUC, area under the curve; IgAV, immunoglobulin A vasculitis; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

elevation is associated with vasculitis in itself, it is hard to rule out the possibility that the increased VEGF levels resulted from inflammation. Also, VEGF-A expression may change during transition from early to late stage disease. Our patient group had a mean of 43.62 months as disease duration but for a more detailed understanding of the changes in VEGF with disease progression, a larger patient group is needed for statistical grouping within patient groups. In addition, considering the previous literature indicating VEGF production by numerous cell types, including macrophages and T cells, these cells are predominantly present in the inflammatory infiltrates and thus may be a source of increased VEGF.[25] Even so, vascular endothelium may be regarded as the victim of vasculitis in IgAV and ECs play an initiating role in vascular damage. On the other hand, augmentation of VEGF may lead to increase in vascular permeability and may contribute to the transmigration of the inflammatory cells through the vessel walls as the results. Even though it is not evaluated in the present study, this situation leads to an increase in vascular cell adhesion molecules. Besides these, the composition of inflammatory infiltrates are quite important in diseases like IgAV, as they are assumed to be rich in T cells and macrophages playing key roles in VEGF release. Although the major cell composition of the infiltrates is not evaluated in our study, VEGFR-1 levels besides VEGF-A levels are evaluated. This in turn brought us the possibility of measuring VEGFR-1/VEGF-A ratio and therefore the advantage of evaluating receptor levels counterbalancing VEGF increase.

As mentioned before, VEGFR-1 is the main VEGF transmembrane receptor with tyrosine kinase activity which modulates the biological activity of VEGF upon binding to it.[26] In addition to the increase in VEGF-A levels, we detected a significant increase in VEGFR-1 levels up to 10 times, in our study. This shows us that VEGFR-1 levels are as important as VEGF-A levels in IgAV pathogenesis, which was not considered in previous studies. Also supported by ROC analysis, VEGFR-1 has the highest sensitivity and specificity with the highest predictive value. Previous studies have shown that VEGFR-1 is also expressed on monocytes,[27] indicating that the rise in the levels of this molecule is not only caused by endothelial disfunction, but also with the inflammatory process. One of the drawbacks of this study can be accepted as the levels of the other receptor, VEGFR-2 are not evaluated. Although the affinity of VEGF-A to VEGFR-1 is almost 10 times higher than its affinity for VEGFR-2; VEGFR-2 is known to be the principal VEGF-A receptor in exerting angiogenetic affects in the endothelium and is found almost 10-fold higher than VEGFR-1 in the endothelium. It is known that membrane-bound VEGFR-1 homomeric receptor serves as a decoy receptor for VEGF-A, by binding excess VEGF-A to compensate its uncontrolled expression. Besides this, VEGFR-1 is also known to regulate the activity of VEGFR-2, which in turn is the principal VEGF receptor in the endothelium to prevent cell proliferation and angiogenesis. Recent studies have shown that heterodimerization between VEGFR-1 and VEGFR-2 ($VEGFR_{1\text{-}2}$), rather than VEGFR-1 homodimers, inhibits VEGFR-2 receptor phosphorylation under VEGF stimulation in human ECs.[28,29] In these aspects, evaluation of VEGFR-2 levels together with VEGFR-1 and VEGF-A levels will be more enlightening in understanding the role of VEGF and its receptors in IgA vasculitis. Besides this, Hiratsuka et al. revealed that Flt-1 tyrosine kinase activity is important for the VEGF-induced cell migration of macrophages in mice.[30] In previous studies, VEGF and its soluble receptor sVEGFR-1 and VEGF/sVEGFR-1 ratio have been evaluated together in understanding the function of VEGF in angiogenic imbalance and/or endothelial dysfunction. In the present study, we evaluated the VEGF increase caused by the vasculitis underlying IgAV with its direct membrane-bound receptor VEGFR-1. Our findings have shown that the increase in VEGFR-1 levels are much higher than the increase in VEGF levels. This reveals that although the main determinant seems to be VEGF in progression of the vascular pathology, the role of the endothelium is more important as the levels of the membrane receptor are increased in great manner. Increased VEGFR-1 levels might also exert an impact on the downregulation of VEGFR-2, to counterbalance the endothelial effects of VEGF-A. This brings out the fact that in cellular composition basically the immune system cells are very important in vasculitis progression. The distribution of cells may lead us in treatment and/or classification of pathogenesis of these diseases. All these findings support the idea that only inflammation and inflammatory markers are not enough to enlighten disease pathogenesis although they give information about disease activity; but they need to be co-evaluated with cells taking part in the immune response. Our data also clarified that while VEGF-A and VEGFR-1 levels are similar in active and inactive patients, VEGFR-1/VEGF-A ratio is higher in the active patient group. This finding in turn supports the hypothesis that VEGF-A exerts its effects in progression of vascular pathologies through VEGFR-1.

On the other hand, contrary to expectations, no significant correlation between VEGF and VEGFR-1 serum levels and age of IgAV patients or duration of disease was observed. This might be due to the relatively small number of the study group. And since endothelial dysfunction is a complex, multi-step mechanism, VEGF does not seem to be specific for a particular clinical manifestation, but it most likely is a non-specific marker for vascular disorders in which endothelial dysfunction occurs and may contribute to the pathophysiology of endothelial injury in IgAV.

Only 2 participants in the patient group included in the study were not taking any kind of medications like steroids and immunosuppressants. These drugs might exert some effects on levels of VEGF and its receptors. But since IgAV is a chronic disease with long disease durations, it is not possible to include patients without taking any kind of treatment. For detailed understanding of the effects of steroids and other immunosuppressant drugs on VEGF levels, larger study populations will be needed.

As the first report in the literature co-evaluating VEGF-A and its receptor VEGFR-1 in adult IgAV patients, our study has revealed that these molecules and their ratio (VEGFR-1/VEGF-A) play important roles in disease pathogenesis; for more detailed understanding of the progression of vasculitis, VEGF and its receptors are needed to be evaluated together with the cells taking place in inflammation and endothelial injury. In evaluation of endothelial dysfunction, VEGFR-1 and VEGFR-1/VEGF-A ratio can be candidate non-invasive biomarkers in follow-up of progression in patients after these findings are combined

with clinical monitoring of patients together with long-term correlation of measurements with outcomes to be planned as future studies.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

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Secukinumab and metformin ameliorate dermal fibrosis by decreasing tissue interleukin-17 levels in bleomycin-induced dermal fibrosis

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Abstract

Although the pathogenesis of systemic sclerosis is not exactly known, it is thought that immune activation has prominent roles in pathogenesis. Secukinumab is a monoclonal antibody against interleukin (IL)-17A. Metformin, a widely used antidiabetic medication, has anti-proliferative, immunomodulating and anti-fibrotic activities. The purpose of our study is to determine the therapeutic efficacy of secukinumab and metformin on bleomycin (BLM) induced dermal fibrosis. Fifty Balb/c female mice were divided into 5 groups: (group 1 control, 2 sham, 3 secukinumab, 4 metformin and 5 secukinumab + metformin). The mice in the control group received 100 μL phosphate-buffered saline (PBS), while the mice in other groups received 100 μL (100 μg) BLM in PBS subcutaneously (sc) every day for 4 weeks. In addition, mice in groups 3 and 5 received secukinumab at a dose of 10 mg/kg/wk sc, and mice in the groups 4 and 5 received oral metformin 50 mg/kg/d for 28 days. All groups of mice were sacrificed at the end of the 4th week and tissue samples were taken for analysis. In addition to histopathological analysis, skin tissue messenger RNA (mRNA) expressions of IL-17 and collagen 3A were measured by real-time polymerase chain reaction. Repeated BLM injections had caused dermal fibrosis. In addition, the mRNA expressions of IL-17 and collagen 3A were increased in the BLM group. Secukinumab and metformin ameliorated dermal fibrosis. They decreased dermal thickness and tissue IL-17A and collagen 3A mRNA levels. Secukinumab and metformin exhibit anti-fibrotic effects in the BLM-induced dermal fibrosis.

KEYWORDS

experimental scleroderma, metformin, secukinumab

1 | INTRODUCTION

Systemic sclerosis (SSc) is a chronic, systemic, complex autoimmune connective tissue disease of unknown etiology, starting with microvascular damage and inflammation in the tissues and progressing to fibrosis with a progressive course. It is an important cause of morbidity and mortality among rheumatic diseases.[1] Especially with the discovery of new pathogenetic pathways specific to the disease, new treatment agents that may be effective come to the agenda. The pathogenesis of SSc has not been fully illuminated; however, a complex relationship between T and B cells, monocyte/macrophage, and fibroblasts is emphasized in the pathogenesis.[2,3] These cells

normally work in balance. This balance deteriorates in SSc according to the type and stage of the disease. This complex structure of pathogenesis is because the immune response is dynamic. This dynamic process causes heterogeneity and clinical tables consisting of variable treatments are formed.

It is known that CD4+ T cells play an important role in the pathogenesis of SSc. T helper (Th)1, Th2, Th17, and Treg are subtypes of CD4+ T cells. Th17/Treg balance plays an important role in the pathogenesis of SSc. The fibrotic process is triggered by this balance shifting toward the Th17 pathway. Th17 cells mainly secrete interleukin (IL)-17. IL-17 also triggers inflammation by stimulating the production of proinflammatory cytokines such as IL-1, IL-6, and IL-8. It has also been shown that IL-17 stimulates the proliferation of fibroblasts responsible for collagen synthesis. The results show that IL-17 is an important cytokine that causes inflammation and fibrosis in SSc.[2-8] Anti-inflammatory and anti-fibrotic efficacy can be achieved with treatments targeting IL-17. Secukinumab, which selectively binds to IL-17A, blocks IL-17 released from Th17 cells.[9] Thus, it can be a potential treatment agent in SSc by showing anti-inflammatory and anti-fibrotic effects.

Metformin is used as an antidiabetic treatment agent and has been shown to have effects such as anti-proliferative, anti-fibrotic, and immune system modulation.[10] In addition, metformin inhibits the mammalian target of rapamycin (mTOR). mTOR plays an important role in initiating inflammation by changing the balance of Th17/Treg cells toward the Th17 pathway.[11,12] On the other hand, mTOR plays a critical role in the proliferation and activation of B cells.[13] Metformin, which reduces Th17 formation with mTOR inhibition, may be effective in the treatment of SSc.

In our study, we used the bleomycin (BLM)-induced experimental scleroderma model to demonstrate the effect of secukinumab and metformin treatments on inflammatory and fibrotic pathways in SSc.

2 | MATERIALS AND METHODS

Fifty Balb/c female mice, aged 6 weeks and weighing 20-25 g, were included in the study. The mice were housed in specially prepared cages in a room with 12 hours of sunlight. In the feeding of the mice, standard mouse feed from Elazig Feed Factory was used and water was given by using special bottles placed in special sections in cages and droppers at the ends. A region designated in the back region of all mice was shaved for sc applications. The Animal Care and Ethics Committee of Fırat University approved the care of mice and the experimental procedures.

Fifty Balb/c female mice were divided into 5 groups: (group 1 control group, 2 sham group, 3 secukinumab group, 4 metformin group and 5 secukinumab + metformin group). One hundred microliters of phosphate-buffered saline (PBS) was applied to the mice in the control group, and 100 μg of BLM (in 100 μL of PBS) was administered to the mice in the other groups sc daily for 4 weeks. In addition, 10 mg/kg dose of secukinumab was administered once a week to mice in groups 3 and 5, and metformin (oral) at a dose of 50 mg/kg daily for 28 days to the mice in groups 4 and 5.

At the end of the experiment, mice in all groups were decapitated under anesthesia by intraperitoneal administration of ketamine (75 mg/kg) + xylazine (10 mg/kg) at the end of the 4th week. After decapitation, the tissues of the mice were rapidly removed, fixed with appropriate fixatives, then passed through histological follow-up series and embedded in paraffin blocks. In addition, tissue messenger RNA (mRNA) expressions were evaluated by real-time polymerase chain reaction (PCR). Tissue samples taken for this were stored at −80°C until the working day.

2.1 | Histopathological and immunohistochemical analysis

Paraffin blocks were prepared from tissue samples in formalin solution on the same day. The sections taken from the blocks were stained with hematoxylin-eosin and Masson-trichrome, and the degree of inflammatory cell infiltration and the degree of fibrosis under light microscope (Olympus BX-50) ×40, ×100, ×200 and ×400 magnification (examined by a qualified pathologist) were determined. For dermal thickness (length between epidermo-dermal junction and dermis-subcutaneous adipose tissue component), at least 2 different preparations in each subject, at ×100 magnification, at least 5 different measurements, were averaged.

For immunohistochemical evaluation, determining the number of fibroblasts was done by determination of anti-alpha-smooth muscle actin (α-SMA) activity after the application of a monoclonal α-SMA antibody commercial kit (1:800, MS-113-P; Thermo) to deparaffined sections.

2.2 | Determination of tissue mRNA levels

IL-17A and collagen 3A mRNA expressions were determined from the tissue homogenates collected for real-time PCR analysis, using the appropriate RNA isolation kit.

Trizol (Invitrogen) was used for RNA isolation from skin tissues obtained from mice. RNA measurements were done with the Qubit® RNA Assay Kit for use with the Qubit® 2.0 Fluorometer (Invitrogen). The amount of RNA was measured as μg/mL. For the complementary DNA (cDNA) synthesis, to equalize the RNA amounts the lowest RNA value read was taken as standard. For cDNA synthesis, the RNA pool was prepared from the samples in each group. cDNA synthesis was performed with the High-Capacity cDNA Reverse Transcription Kit. (Applied Biosystems). The cDNAs obtained by reverse transcription were amplified in the presence of sequence-specific primers using the Tag Man Master Mix (Applied Biosystems) on the ABI Prism 7500 Fast Real-Time PCR device (Applied Biosystems). The temperature conditions were adjusted as 2 minutes at 50°C, 10 minutes at 95°C, ×40 cycles, 15 seconds at 95°C and 1 minute at 60°C. Real-time PCR was performed repeatedly three times. In the study, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as

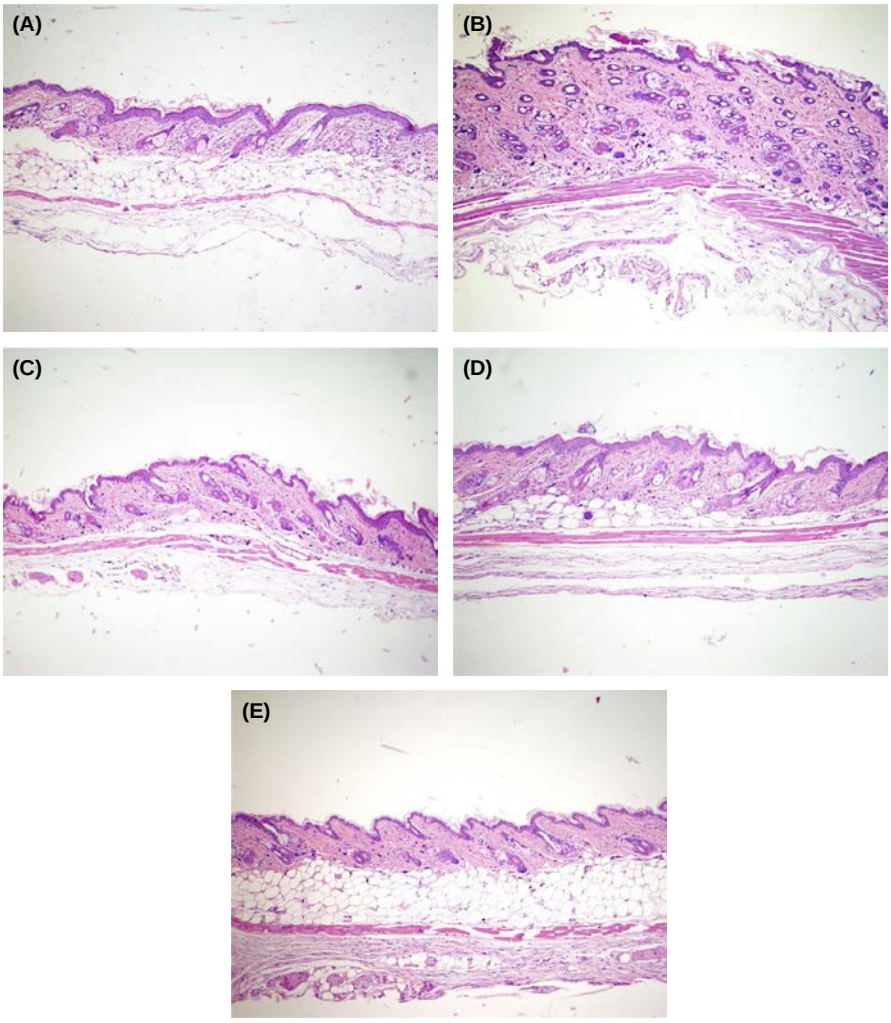

FIGURE 1 Histopathological appearances of skin sections in the study groups (hematoxylin and eosin staining, ×100). Normal histopathological view of mice immunized with PBS in control group (A). Increased dermal thickness, infiltration of inflammatory cell, and fibrosis in the BLM-injected sham group (B). Secukinumab (C), metformin (D), and secukinumab + metformin (E) applications decreased the dermal thickness, infiltrations of inflammatory cells, and fibrosis in the BLM-injected mice. BLM, bleomycine; PBS, phosphate-buffered saline

a control gene (housekeeping). Gene expression levels were determined by the comparative Ct (ΔCt) method.

2.3 | Statistical analysis

After the study was completed, the statistical analyses of the data obtained were made in the IBM SPSS statistics program (IBM SPSS Statistics for Windows, IBM Corp.). The significance of possible differences between the groups was evaluated by Kruskal-Wallis and post hoc Mann-Whitney *U* tests. The *P* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Secukinumab and metformin protect skin thickness and dermal fibrosis

Dermal fibrosis did not occur in the skin tissue histopathological evaluation of mice in group I which received only PBS injection (Figures 1A and 2A). However, BLM applications caused inflammatory cell infiltration and dermal fibrosis in dermal and subcutaneous areas (Figures 1B and 2B). Dermal fibrosis was more prominent in the sham group to which BLM was applied (Figures 1B and 2B).

Dermal fibrosis regressed with both secukinumab and metformin treatment (Figures 1C-E and 2C-E). Compared with the BLM group, dermal thickness decreased significantly in the groups treated with secukinumab and metformin (Table 1).

3.2 | Secukinumab and metformin reduced the count of skin myofibroblast

Compared to the control group, BLM applications increased the mean myofibroblast (α-SMA positive cell) count (Figure 3A,B). α-SMA positive cell counts were decreased in the secukinumab and metformin treatment groups (Figure 3C,D). However, the added benefit of adding metformin to secukinumab therapy could not be observed in terms of histopathological findings (Figure 3C,E; Table 1).

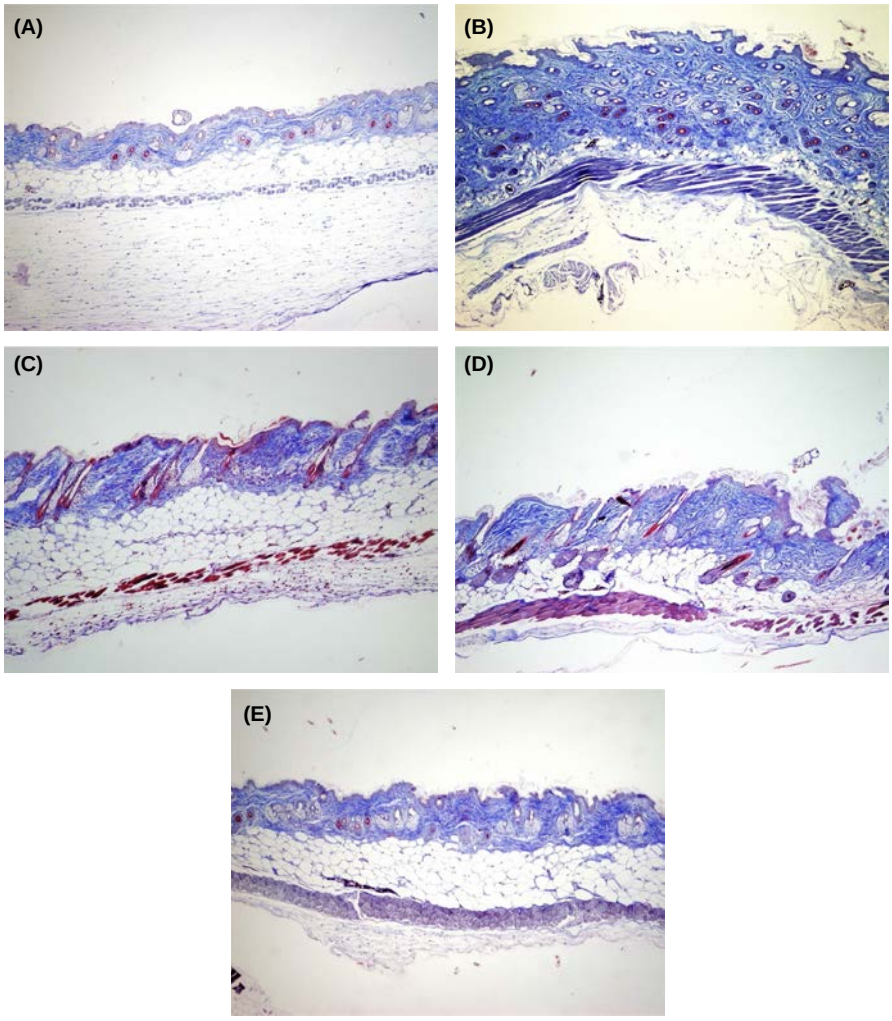

FIGURE 2 Dermal fibrosis in the study groups (Masson's trichrome staining, ×100). Normal histopathological view of mice immunized with PBS in control group (A). Increased dermal thickness, infiltration of inflammatory cell, fibrosis in the BLM-injected sham group (B). Secukinumab (C), metformin (D), and secukinumab + metformin (E) applications decreased the dermal thickness, infiltrations of inflammatory cells, and fibrosis in the BLM-injected mice. BLM, bleomycin; PBS, phosphate-buffered saline

3.3 | Secukinumab and metformin reduced collagen 3a1 and IL-17 mRNA expressions

Both secukinumab and metformin applications reduced collagen 3A1 (Figure 4) and IL-17 mRNA expressions (Figure 5). However, the added benefit of adding metformin to secukinumab treatment has not been observed for collagen 3A1 and IL-17 mRNA expressions.

4 | DISCUSSION

In this study, the possible therapeutic efficacy of secukinumab and metformin treatments in the BLM-induced experimental scleroderma model were investigated. BLM applications cause increase in dermal inflammatory cell infiltration, myofibroblastic cell activity and dermal thickness. Moreover, it was observed that tissue IL-17 mRNA levels were increased in mice with dermal fibrosis. Secukinumab and metformin applications prevent the development of inflammatory cell infiltration, myofibroblastic cell activity, and dermal fibrosis in this experimental scleroderma model.

It is known that T cells play an important role in the pathogenesis of SSc. Th17 cells have been shown to play roles in the pathogenesis of many autoimmune diseases, including systemic lupus erythematosus, psoriasis, inflammatory bowel diseases, rheumatoid arthritis, ankylosing spondylitis, and multiple sclerosis.[14-17] Recent data have also shown that Th17 cells play a central role in the pathogenesis of SSc.[18,19] Th17 cells secrete many different cytokines. The most important of these cytokines is IL-17A.[20] IL17 is released not only from Th17 cells but also from different cells such as natural killer cells, type 3 innate lymphoid cells, polymorphonuclear cells, and macrophages.[21]

In the literature, there are divergent results related to IL-17 levels in SSc. This difference may be due to the design of the studies and the heterogeneous nature of the disease. Kurasawa et al.[22] have found that IL-17 is highly expressed in the skin and bronchoalveolar fluid of SSc patients. Yang et al.[23] have documented that Th17 cells are associated with disease activity in patients with SSc, and that IL-17 levels augment fibroblastic activity and thus increases collagen production. Radstake et al.[24] have found that circulating Th17 and intracellular IL-17 expression increased in patients with SSc. In addition, Fenoglio et al.[25] have showed that Th17 cells are increased and immune response is shifted toward the Th17 pathway, in SSc patients compared to healthy controls. Similarly, Almanzar et al.[26] have found that circulating Th17 cell

TABLE 1 Histopathological findings in the study groups

	PBS	BLM	SEC	MET	SEC + MET	*P*
Dermal thickness (μm)	138.8 ± 26.9	314.1 ± 99.1[a]	200.1 ± 18.1[b]	215.6 ± 23.5[b]	188.6 ± 27.3[b]	<.001
Myofibroblast (n/HPF)	1.75 ± 1.17	8.20 ± 2.34[a]	2.56 ± 0.73[b]	2.89 ± 0.78[b]	2.71 ± 0.76[b]	<.001
Lymphocytes (n/HPF)	1.63 ± 0.52	2.10 ± 0.57	1.33 ± 0.50[b]	2.22 ± 0.67	2.01 ± 0.82	.023
Mast cell (n/HPF)	3.25 ± 1.38	5.92 ± 2.34[a]	3.72 ± 1.19[b]	4.06 ± 1.27[b]	3.84 ± 1.66[b]	.013

Abbreviations: BLM, bleomycin; HPF, high-power field; MET, metformin; PBS, phosphate-buffered saline; SEC, secukinumab.
[a]$P < 0.05$ when compared to the PBS group.; [b]$P < 0.05$ when compared to the BLM group.

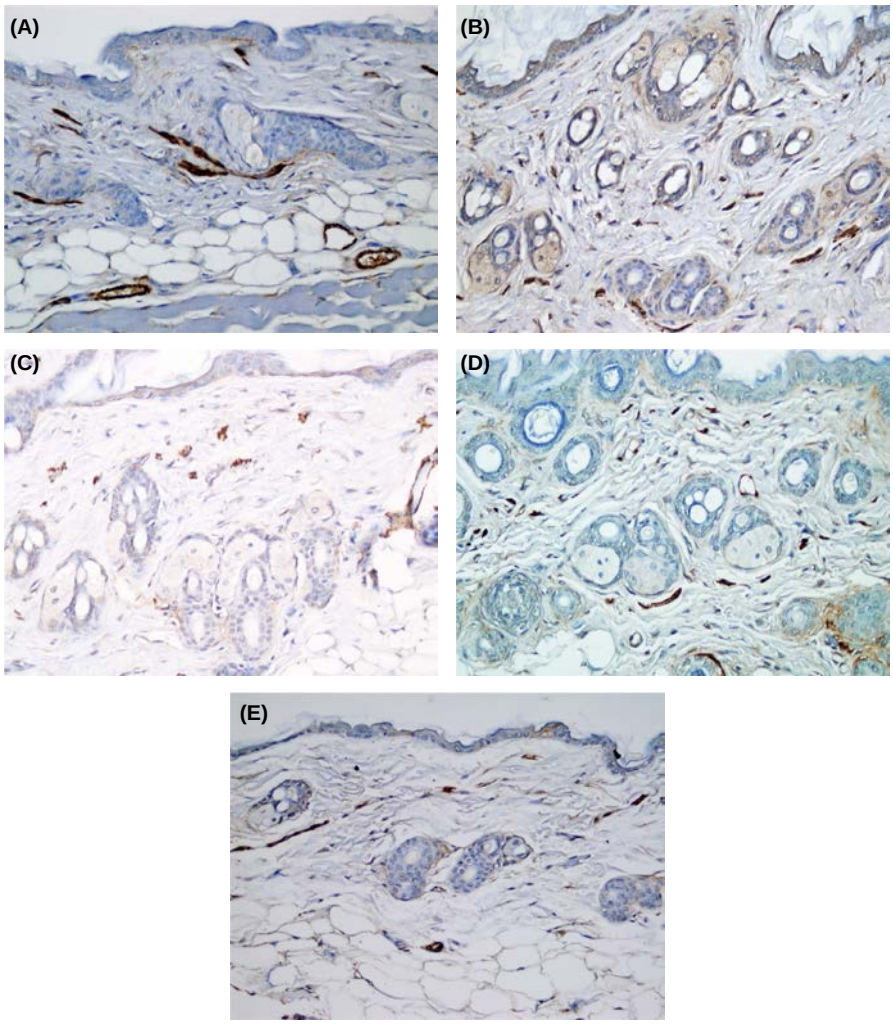

FIGURE 3 Fibroblastic activity in the study groups (α-SMA staining, ×400). Normal histopathological view of mice immunized with PBS in control group (A). Increased expression of α-SMA in the BLM-injected sham group (B). Secukinumab (C), metformin (D), and secukinumab + metformin (E) applications decreased the expression of α-SMA in the BLM-injected mice. BLM, bleomycin; PBS, phosphate-buffered saline; α-SMA, alpha-smooth muscle actin

count and intracellular IL-17 expression are increased in a study on 135 SSc patients. In addition, Zhou et al.[27] have documented a positive correlation between IL-17A level and modified Rodnan score in patients with SSc. Truchetet et al.[28] have reported that IL-17 level is higher in SSc patients with interstitial lung disease compared to healthy controls. In our study, mice with skin fibrosis had higher tissue IL-17 mRNA levels.

It has been demonstrated that BLM-induced pulmonary fibrosis is restricted in experimental animals with IL-17 deficiency.[29] Park et al.[19] have showed that mice with IL-17A gene defects have less severe skin fibrosis. In the other way it has been observed that IL-17 stimulates the synthesis of monocyte chemoattractant protein (MCP)-1, IL-8, and matrix metalloproteinase (MMP)-1 from skin fibroblasts harvested from SSc patients. However, there are different (reverse) opinions regarding the effects of high IL-17 levels on SSc disease. In a study made by Nakashima et al.,[30] IL-17A was found to show anti-fibrotic effects by decreasing collagen synthesis in SSc. However, interestingly, it was found that IL-17 reduced collagen synthesis in patients diagnosed with SSc less than the healthy control group.[31] In another study, it was observed that IL-17 stimulates fibroblasts, but the amount of collagen synthesized from these stimulated fibroblasts did not increase.[22] In our study, tissue IL-17A

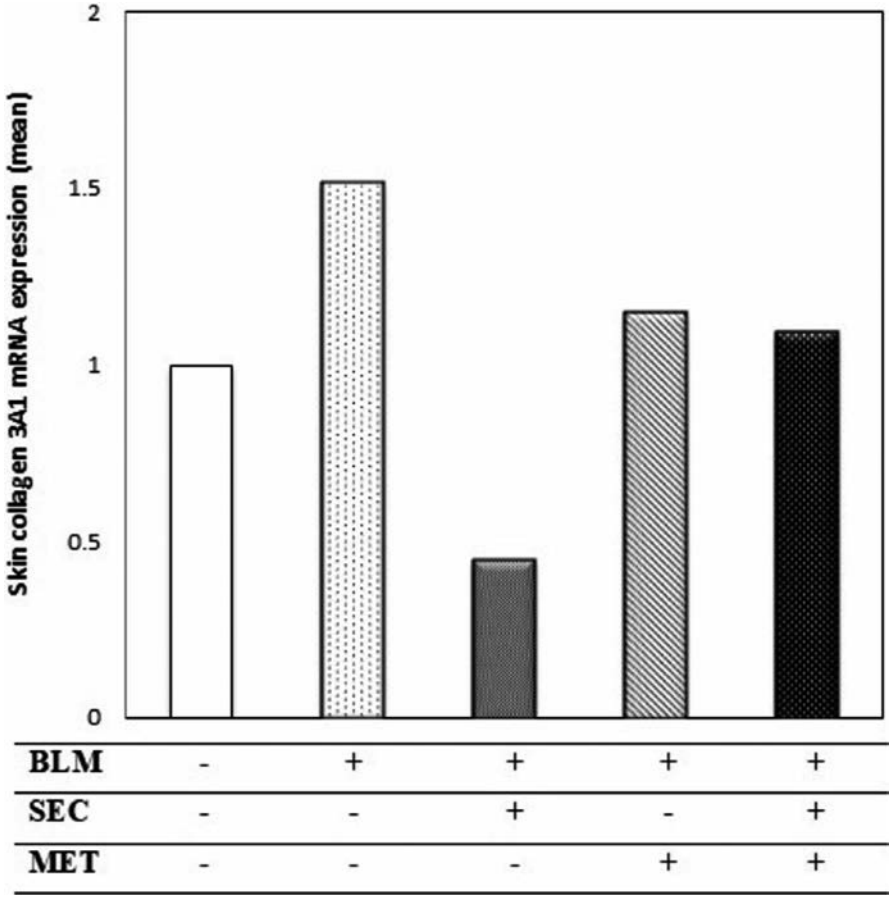

FIGURE 4 Skin collagen 3A1 messenger RNA expression in the study groups. BLM, bleomycin; MET, metformin; SEC, secukinumab

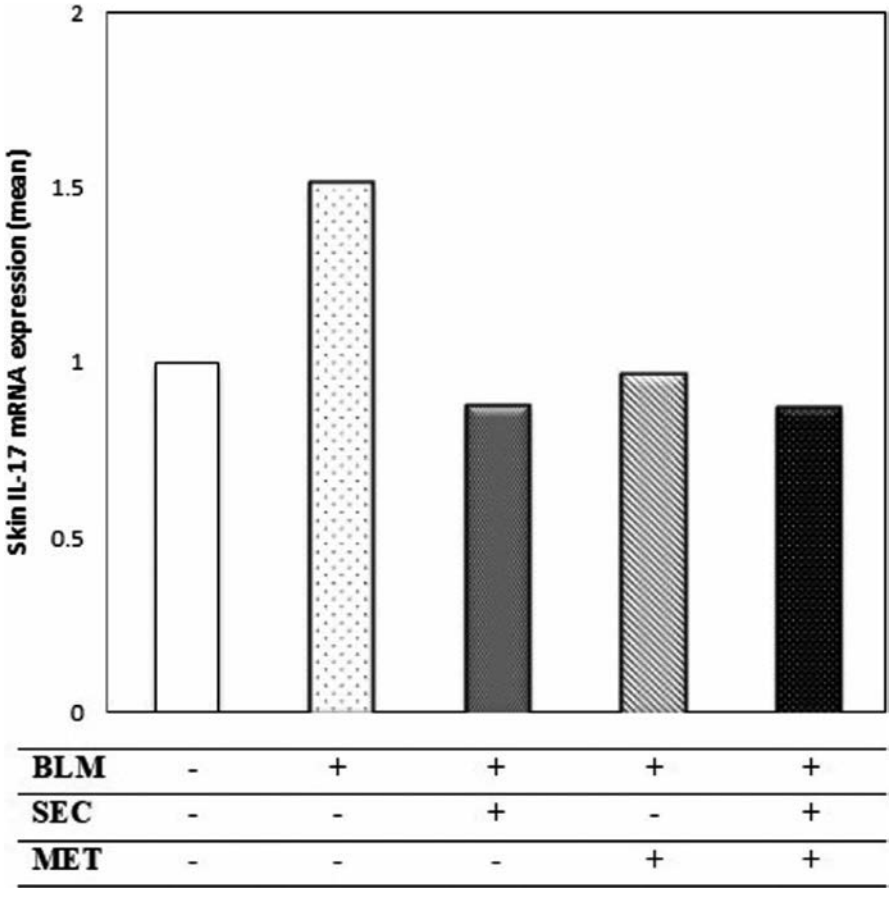

FIGURE 5 Skin interleukin (IL)-17 messenger RNA expressions in the study groups. BLM, bleomycin; MET; metformin; SEC; secukinumab

mRNA expression was detected to be increased and anti-IL-17A applications ameliorate dermal fibrosis induced by BLM.

Vasculopathy is an important step in the pathogenesis of SSc.[1,2] IL-17 has been shown to cause proliferation of vascular smooth muscle cells.[32] In addition, IL-17 has been shown to lead to endothelial inflammation[33] by increasing the production of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and chemokine (CXC motif) receptor 4 (CXCR-4) in SSc patients. In our study, collagen synthesis and skin fibrosis were suppressed with secukinumab treatment in the BLM-induced experimental scleroderma model.

Metformin, used in the treatment of diabetes mellitus, has additional effects such as anti-inflammatory, anti-oxidant, and anti-proliferative activities.[10,34,35] Metformin displays regulatory effects in energy metabolism by activating 5′AMP-activated protein kinase (AMPK).[36] While AMPK suppression is associated with fibrosis, metformin is known to activate AMPK and thus suppress the activation of fibroblasts.[37] Increased collagen synthesis as a result of activation of fibroblasts is an important step in the fibrotic process in SSc. Transforming growth factor (TGF-β) is an important cytokine involved in the activation of fibroblasts through intracellular SMAD proteins.[38] Metformin treatment has been shown to decrease fibrosis by reducing fibroblast differentiation and extracellular matrix formation via the TGF-β/SMAD3 signaling pathway.[39,40] Metformin has been shown to prevent BLM-induced pulmonary fibrosis in 2 different studies.[41,42] Kim et al.[43] demonstrated that orally administered metformin suppresses radiation-induced dermal fibrosis in experimental animals. Similarly, Ursini et al.[44] reported that oral metformin suppressed skin fibrosis in the BLM-induced experimental scleroderma model. In our study, metformin ameliorates BLM-induced skin fibrosis.

Activation of mTOR is one of the other important steps in the proliferation of fibroblasts. Phosphorylated mTOR levels in fibroblasts were found to be increased, in patients diagnosed with SSc.[45] In another study, it has been shown that fibroblasts are suppressed by mTOR inhibition.[46] In a study conducted on patients diagnosed with SSc, it has been found that collagen production synthesized from fibroblasts is increased by activation of mTOR.[47] In the experimental scleroderma study, it has been shown that skin fibrosis is decreased after mTOR inhibition by rapamycin.[48] The mTOR pathway also plays a role in the activation and differentiation of T cells. Activation of mTOR leads to Th17 activation and shifts Th17/Treg balance to the Th17 pathway. With the inhibition of mTOR, the Treg pathway becomes dominant.[11,49] In a study, it has been found that metformin treatment decreases the level of IL-17 and increases the number of Tregs.[50] In our study, it was found that metformin treatment reduced IL-17 level and suppressed collagen synthesis and skin fibrosis, in the BLM-induced experimental scleroderma model.

As a result, in our study, secukinumab and metformin decreased tissue IL-17 levels, suppressed myofibroblastic activity and collagen production, and histopathologically suppressed inflammatory cell infiltration and fibrosis in the BLM-induced experimental scleroderma model. Thus, it has been demonstrated that both secukinumab and metformin have anti-inflammatory and anti-fibrotic effects by affecting inflammatory and fibrotic pathways in the pathogenesis of SSc. These findings encourage these 2 drugs to be tested for SSc treatment in further studies.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE

Characteristics of Japanese patients with systemic sclerosis complicated with calcinosis

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Abstract

Aim: Calcinosis is often observed in systemic sclerosis (SSc), but its pathogenesis remains unclear. The aim of the present study was to explore the association of clinical features with calcinosis in patients with SSc.

Methods: A retrospective cohort study was performed analyzing 416 SSc patients from our SSc database. We examined the clinical features with relation to calcinosis and SSc.

Results: Calcinosis was observed in 24.0% of patients with SSc. The group with calcinosis comprised more female patients ($P < 0.05$) and diffuse cutaneous types ($P < 0.001$) than the group without calcinosis. Complications of Raynaud's phenomenon ($P < 0.05$), nail fold bleeding (NFB) ($P < 0.001$), peripheral bone resorption ($P < 0.001$), myositis ($P < 0.001$), and pulmonary hypertension ($P < 0.05$) were more frequently observed in patients with calcinosis compared with those without calcinosis. The group with calcinosis had a higher modified Rodnan total skin-thickness score (mRSS) than the group without calcinosis ($P < 0.001$). The factors that affected calcinosis in multivariable analysis were peripheral bone resorption (partial correlation coefficient 0.46, 34%), anti-Scl-70 antibody (partial correlation coefficient 0.29, 20%), diffuse type (partial correlation coefficient 0.34, 16%) and NFB (partial correlation coefficient 0.23, 11.2%).

Conclusions: Calcinosis in SSc is associated with Raynaud's phenomenon, NFB, and pulmonary hypertension, so peripheral circulatory insufficiency seems to be one of the causes of calcinosis. Furthermore, as it is related to mRSS and the diffuse cutaneous type, common factors related to skin fibrosis are considered to be involved.

KEYWORDS

autoantibody, calcinosis, skin ulcer, systemic sclerosis

1 | INTRODUCTION

Calcinosis cutis is the accumulation of insoluble calcium deposits in the skin and subcutaneous tissues. The condition is classified as metastatic (characterized by hypercalcemia or hyperphosphatemia), dystrophic (without abnormalities in calcium or phosphate metabolism), idiopathic, related to administration of calcium preparations, subepidermal calcified nodules, and calciphylaxis. Calcinosis

associated with rheumatic diseases is classified as dystrophic calcification, in which blood calcium and phosphate levels are normal.[1] By tightly binding to the surface of hydroxyapatite crystals and impeding their growth, inorganic pyrophosphate has a strong inhibitory effect on calcification, and this pathway is disturbed in ectopic calcification.

Calcinosis in systemic sclerosis (SSc) has been reported to occur in approximately 40% of patients with limited cutaneous SSc, but the pathogenesis is unknown.[2] The significant component of calcinosis in SSc is calcium hydroxyapatite.[3] Several mechanisms of calcinosis in SSc have been reported: chronic hypoxemia,[4] repetitive injury due to peripheral circulatory insufficiency, impaired limb extension caused by skin sclerosis, local tissue structural damage,[5] genetic factors,[6-9] increased production of tumor necrosis factor-α, interleukin-1, interleukin-6, and other inflammation-induced cytokines,[10] and imbalance between hypoxia-induced angiogenic factors (such as vascular endothelial growth factor and platelet-derived growth factor) and anti-angiogenic factors (such as angiostatin and endostatin).[11] Clinically, risk factors for calcinosis in SSc have been reported to be associated with longer duration of morbidity,[12] anticentromere antibody positivity,[2] limited-type SSc,[2] and skin ulcers.[13] However, reports are conflicting. A Canadian cohort study reported anti-RNA polymerase antibody positivity and diffuse type as risk factors for calcinosis.[14] An international cohort study of 5218 patients reported that calcinosis was associated with hand ulcers, telangiectasia, and osteoporosis.[15]

Transforming growth factor-β acts on dermal fibroblasts to enhance collagen production and inhibit vascular endothelial cell proliferation, promoting skin hardening in SSc. Similarly, an increase in transforming growth factor-β superfamily ossification regulators such as activin and bone morphogenetic protein (BMP) occurs in SSc.[16]

As mentioned above, the calcinosis that occurs in SSc is heterotrophic calcification. However, it remains unclear how calcinosis occurs in SSc. For this reason, the pathophysiology is unknown, and treatment is evidence-based for the calcinosis that occurs in SSc. To promote understanding of the pathogenesis of calcinosis in SSc, a retrospective study collecting factors associated with calcinosis in SSc was conducted.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a retrospective cohort study that analyzed 416 SSc patients using the Systemic Sclerosis Database at our hospital. All patients with SSc met the 2013 classification criteria of the American College of Rheumatology and the European Society of Rheumatology. The patients in this group also had complications of other collagen diseases, such as rheumatoid arthritis, polymyositis, systemic lupus erythematosus, and Sjögren syndrome. Calcinosis was diagnosed by clinical symptoms and imaging (X-ray). Interstitial lung disease was confirmed by high-resolution chest CT scan and pulmonary hypertension by right heart catheterization and echocardiography. The covariates analyzed in this study were as follows: age; sex; clinical presentation; disease type; complications; Raynaud's phenomenon; joint pain/swelling; reflux esophagitis; fingertip ulcers; modified Rodnan total skin thickness score (mRSS); complications of the lung, kidney, and gastrointestinal tract; periungual erythema; anti-nuclear antibody; SSc-specific autoantibodies (anti-Scl-70 and anti-centromere, anti-U1 RNP, anti-SS-A, and anti-RNA polymerase III antibodies) and radiological imaging. The present study was approved by the Institutional Review Board of Tokyo Women's Medical University.

2.2 | Statistical analysis

The percentage of each categorical variable for all patients is described by descriptive statistics. Continuous variables are described as the mean ± SD in the case of a normal distribution; nonparametric variables are described as the median and are estimated by Mann-Whitney *U* test. Categorical variables were tested using Fisher's direct probability test. We also calculated the odds ratio (OR) to estimate the risk of calcification. Statistical significance was defined as a *P* value less than or equal to 0.05. If the results were significant by univariate analysis, we performed multivariable analysis (by quantitative II analysis) to further examine these variables. Statistical analysis was performed using the Excel software.

3 | RESULTS

3.1 | Clinical manifestations in patients with SSc and calcinosis

A total of 416 patients with SSc were included in this study. One hundred patients (24.0%) had calcinosis, and 316 did not (Table 1).

TABLE 1 Patients characteristics

Variates	
Age, mean ± SD	62.8 ± 12.9
Sex (female), n (%)	389 (93)
Diffuse cutaneous type, n (%)	156 (37.5)
mRSS, mean ± SD	8.4 ± 7.6
Raynaud's phenomenon, n (%)	275 (89.2)
Digital ulcer, n (%)	20 (4.8)
Interstitial lung disease, n (%)	73 (17.5)
GERD, n (%)	223 (53.6)
Arthritis, n (%)	52 (12.5)
Pulmonary hypertension, n (%)	47 (11.3)
Anti-Scl-70 antibody, n (%)	86 (20.7)
Anti-CENP antibody, n (%)	168 (40.3)
Anti-U1 RNP antibody, n (%)	59 (14.2)

Abbreviations: GERD, gastroesophageal reflux disease; mRSS, modified Rodnan total skin thickness score; SD, standard deviation.

TABLE 2 Demographic and clinical data with univariate analyses

	With calcinosis n = 100	Without calcinosis n = 316	Univariable analysis		
Variates	**n (%)**	**n (%)**	***P* value**	**OR**	**95% CI**
Age (mean ± SD)	62.5 ± 12.7	62.9 ± 12.9	1		
Female	98 (98)	291 (92)	<.05	4.21	0.98-18.10
Diffuse cutaneous type	57 (57)	99 (31)	<.001	3.01	1.83-4.61
Raynaud's phenomenon	96 (96)	275 (87)	<.05	2.86	1.10-7.45
Interstitial lung disease	14 (14)	59 (19)	.36528	0.71	0.38-1.33
Pulmonary hypertension	17 (17)	30 (10)	<.05	1.95	1.03-3.72
GERD	7 (7)	44 (14)	.0796	0.47	0.20-1.07
Myositis	48 (48)	68 (22)	<.001	3.37	2.09-5.42
Digital ulcer	8 (8)	12(4)	.10628	2.2	0.87-5.55
Nail fold bleeding	84 (84)	131(42)	<.001	7.41	4.15-12.24
Peripheral bone resorption	60 (60)	50(16)	<.001	7.98	4.83-13.17
Anti-Scl-70 antibody	29 (29)	57(18)	<.05	1.86	1.11-3.12
Anti-Centromere antibody	33 (33)	135 (43)	.1047	0.66	0.41-1.06
Anti-U1RNP antibody	16 (16)	43 (14)	.62171	1.21	0.645-2.26
Anti-Polymerase III antibody	9 (9)	16 (5)	.15289	1.85	0.79-4.34
Comorbidity					
Rheumatoid arthritis	4 (4)	31 (9.8)	<.05	0.25	0.09-0.73
SLE	2 (2)	13 (4)	.1579	0.32	0.07- 1.44
Sjögren syndrome	7 (7)	30 (22)	.09	0.47	0.20-1.10
Vasculitis	2 (2)	2 (0.6)	.5937	2.18	0.30-15.73
PM/DM	5 (5)	7 (5)	.5288	1.57	0.49-5.08

Abbreviations: CI, cumulative interval; DM, dermatomyositis; GERD, gastroesophageal reflux disease; OR, odds ratio; PM, polymyositis; SD, standard deviation; SLE, systemic lupus erythematosus.

Among the patients with calcinosis, there were higher proportions of female patients ($P < 0.05$, OR 4.2) and diffuse cutaneous type disease ($P < 0.001$, OR 3.0) than in the control group. Complications of Raynaud's phenomenon ($P < 0.05$, OR 2.9), nail fold bleeding (NFB) ($P < 0.001$, OR 7.4), external bone resorption ($P < 0.001$, OR 8.0), myositis ($P < 0.001$, OR 3.4), and pulmonary hypertension ($P < 0.05$, OR 2.0) were also significantly associated with calcinosis (Table 2). We also found that higher mRSS values were associated with significantly more calcifications ($P < 0.001$, Figure 1). A review of concomitant diseases revealed rheumatoid arthritis to be a protective factor for calcinosis in SSc ($P < 0.05$, OR 0.25). Examination of disease-specific antibodies showed an association with anti-Scl-70 antibody positivity ($P < 0.05$, OR 1.9), as shown in Table 2.

Multivariable analysis was performed for the following factors: female, diffuse type, Raynaud's phenomenon, NFB, peripheral bone resorption, pulmonary arterial hypertension, myositis, and anti-Scl-70 antibody positivity. The factors that affected calcinosis in multivariable analysis were peripheral bone resorption (partial correlation coefficient 0.46, 34%), anti-Scl-70 antibody (partial correlation coefficient 0.29, 20%), diffuse cutaneous type (partial correlation coefficient 0.34, 16%), and NFB (partial correlation coefficient 0.23, 11.2%) (Figure 2).

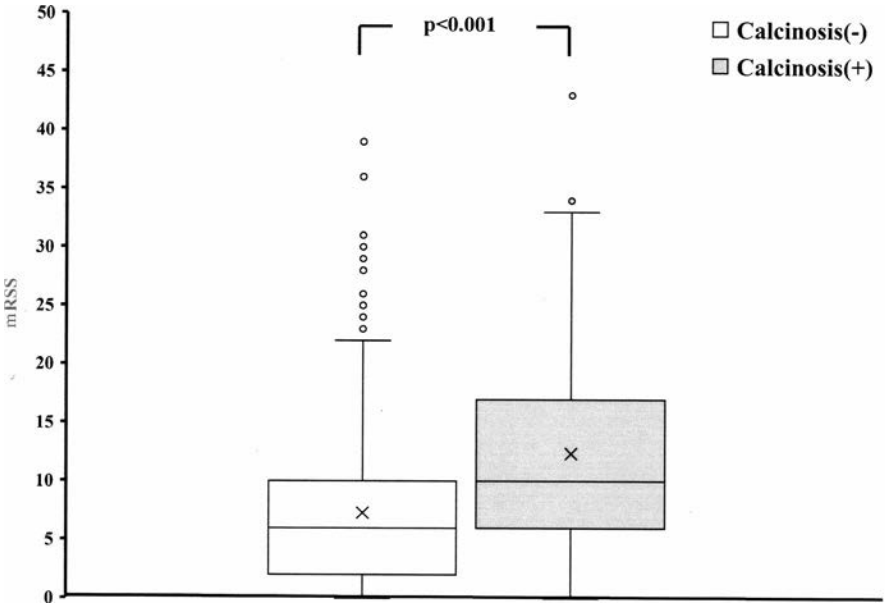

FIGURE 1 Comparison of modified Rodnan total skin thickness score (mRSS) value between with calcinosis and without calcinosis. The mRSS of the cases with calcinosis (gray circle) or without calcinosis (open circle) are shown as a box plot. Mean values of mRSS are statistically significant ($P < 0.001$, Mann-Whitney U test)

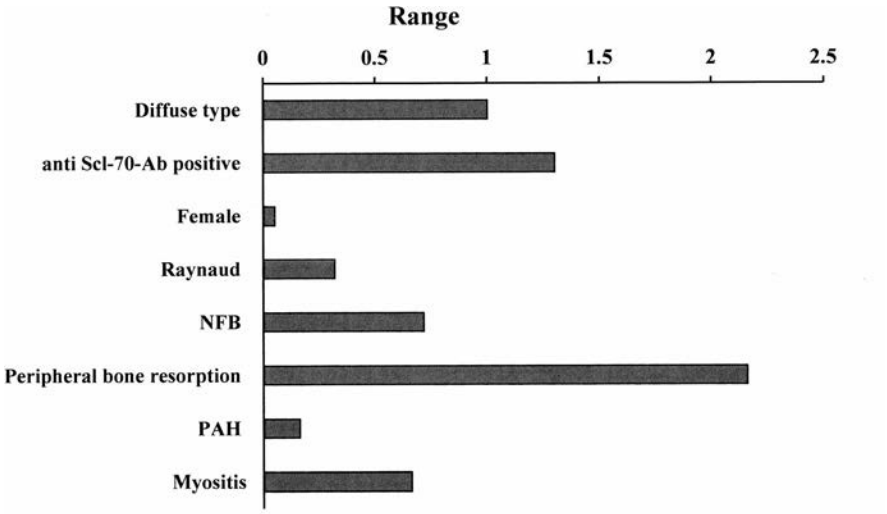

FIGURE 2 Demographic and clinical data of multivariable analysis. NFB, nail fold bleeding; PAH, pulmonary arterial hypertension

variates	Contribution rate (%)	Partial correlation coefficient
Diffuse type	16	0.34
anti Scl-70-Ab positive	20	0.29
Female	0.8	0.008
Raynaud	5	0.06
NFB	11.2	0.23
Peripheral bone resorption	34	0.46
PAH	3	0.05
Myositis	10	0.25

4 | DISCUSSION

In our study, 100 (24.0%) of 416 patients with SSc had calcinosis. Although it has been reported that calcinosis is more common in patients with the limited cutaneous type, our study revealed that calcinosis is more common in the diffuse cutaneous type and was associated with higher mRSS values and anti-Scl-70 antibody positivity, which are more commonly observed in the diffuse type. Our observation is also supported by the report by Valenzuela and Baron.[17] It has been reported that calcinosis is more common in individuals with disease of long duration. However, there were no data on the disease onset or duration of the disease in the database used for this study; therefore, we could not assess the relationship between calcinosis and disease duration. Additionally, this study was a

longitudinal retrospective observation, and the number of cases at the single center was small, which may be a limitation of this study.

Several mechanisms involved in calcinosis have been proposed, and especially the transforming growth factor-β superfamily, including BMPs, also plays a crucial role in the pathogenesis of calcinosis and systemic sclerosis.[17,18] Ectopic expression of BMP2 in subcutaneous or muscle tissue may lead to the formation of cartilage and subsequent bone tissue in SSc.

The factors associated with calcinosis in SSc mainly involve peripheral circulatory insufficiency, Raynaud's phenomenon, NFB, and pulmonary arterial hypertension. SSc tissues are chronically in a hypoxic state. Several studies suggest that the presence or history of finger ulcers is predictive of the development of calcification.[14,15,19] Several studies focused on the genetic factors. Associations of HLA *DRB104* and single nucleotide polymorphisms of matrix metalloprotease 3 that involve extracellular matrix protein deposition have been reported, as have single nucleotide polymorphisms of the plasma protein α-2-HS-glycoprotein displaying interaction with calcium phosphate, with ectopic vascular calcification inhibition and calcinosis in SSc.[9]

The frequency of calcinosis in our cohort is lower than that of the previous report.[2] There are no reports focusing on ethnicity, although it is known that susceptibility to a variety of diseases varies with ethnicity. A French study reported that the *HIF1A* rs12434438 G allele increases susceptibility to SSc development.[20] However, similar results were not obtained in our previous study of a Japanese cohort.[21] We think it important to describe the factors involved in pathogenicity in different races for further genetic analysis. In addition, there are limited reports focusing on the molecular biological process of calcinosis in SSc. Hence, further molecular biological studies are required to understand calcinosis in SSc.

There are reports that warfarin, diltiazem, bisphosphonates, minocycline, intravenous immunoglobulin, colchicine, rituximab, and extracorporeal shock waves have beneficial effects on calcinosis in SSc. However, these reports were case reports,[22-26] and there are no reports of randomized controlled studies. Further clinical research for therapeutic intervention based on etiology and risk factors is needed.

In conclusion, calcinosis in SSc is associated with Raynaud's phenomenon, NFB, peripheral bone resorption, and pulmonary hypertension. We speculate that peripheral circulatory insufficiency is one of the causes of calcinosis in SSc. Furthermore, mRSS, the diffuse type and anti-Scl-70 autoantibody positivity are associated with calcinosis, and common factors involved in skin fibrosis may also be involved in the etiology. Calcinosis in SSc leads to joint contractures, skin ulcers, and infections, greatly reducing activity of daily living. Further studies are required to ameliorate the complications identified in this study that are associated with calcinosis.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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ORIGINAL ARTICLE

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Health-related quality of life and work impairment in idiopathic inflammatory myopathies in South Australia

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Abstract

Aim: The idiopathic inflammatory myopathies (IIM) are rare autoimmune diseases that are usually chronic and often present with skeletal muscle inflammation and weakness. We sought to examine the impact of IIM in a cohort of 50 South Australian patients on health-related quality of life (HRQOL) and work productivity (WP). We uniquely categorized patients across gender, IIM subtypes, employment status, and also whether there was extramuscular involvement from IIM.

Methods: Multiple modalities were used, as recommended by the International Myositis Assessment and Clinical Studies Group (IMACS), to assess the impact of IIM, including manual muscle strength testing (MMT-8), the Physician and Patient Global Activity Assessments (PHGAA, PTGAA), Myositis Disease Activity Assessment Tool (MDAAT), and serum creatinine kinase (CK) levels. The impacts of IIM on HRQOL and WP were analyzed using the Medical Outcomes Study 36-items Short Form (SF-36) and Work Productivity and Activity Impairment (WPAI) questionnaires, respectively.

Results: We found significantly lower HRQOL outcome scores in most of the SF-36 domains when compared to the most recent population norms ($P \leq .01$). Physical health was predominantly affected with relative preservation of emotional health. There were also significant associations between MMT-8, PHGAA and PTGAA scores and HRQOL and WP.

Conclusions: Our findings highlight the significant impact of IIM on HRQOL and WP in a well-characterized cohort of patients with IIM within Australia, and therefore the importance of a holistic approach to the management of these patients.

KEYWORDS

life, myositis, productivity, quality, work

1 | INTRODUCTION

The idiopathic inflammatory myopathies (IIM) are a heterogenous group of rare autoimmune diseases, characterized by chronic and progressive skeletal muscle inflammation and weakness.[1] The annual incidence of IIM in the South Australian population is approximately 8 cases per million.[2] The current classification includes polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM) and immune-mediated necrotizing myopathy (IMNM), with each of these disease subsets producing characteristic histological changes in skeletal muscle. Our laboratory also recognizes myositis-not otherwise specified (MNOS), where skeletal muscle inflammatory infiltrates are visualized, but lack sufficient features for a histological diagnosis of other subtypes. A small proportion of patients have cutaneous manifestations of disease without overt muscle involvement and are referred to as amyopathic DM.

Progressive muscle weakness and organ involvement can adversely affect health-related quality of life (HRQOL) and work productivity (WP).[3-8]

Measuring the impact of chronic conditions on a patient's life requires validated tools which encompass both the impact of the condition on physical and psychological well-being, and employment. Even though there are validated tools designed to capture disease activity in IIM, there are none officially slated to assess HRQOL and WP in IIM. The Outcome Measures in Rheumatology Group (OMERACT) Working Group has sought to address this area and international efforts have enabled identification of pertinent domains important in the assessment of HRQOL.[9]

Many prior studies have demonstrated the impact of IIM on HRQOL on a number of international populations, with results showing lower Medical Outcomes Study 36-items Short Form (SF-36) scores/HRQOL in IIM groups compared to the general population.[10-15] Factors such as patient age at time of the study, gender and disease subset have often been incorporated, with varying results. Despite this, other possible associations, such as the duration of IIM, serum creatine kinase (CK) levels and the use of other analogs such as the use of manual muscle strength testing in 8 groups (MMT-8) have not often been employed. Additionally, only scant literature has studied the impact of extramuscular disease on HRQOL.[4]

Data and literature on the effects of IIM on WP have also not been extensively studied to date, with some literature suggesting that there are impacts.[5-7] Herein we examined the impact of IIM on HRQOL and WP in a group of South Australian patients.

2 | METHODS

The study was approved by the Human Research Ethics Committee. The patient cohort was selected from a group of adult patients with IIM under the care of the Rheumatology Unit at the Royal Adelaide Hospital in South Australia. All patients with a diagnosis of IIM attending a routine clinic appointment were considered eligible. Eligible patients were approached with a patient information sheet, along with SF-36 and Work Productivity and Activity Impairment (WPAI) questionnaires, at their routine rheumatology outpatient appointments between 15/1/2019 and 11/2/2020. The return of completed questionnaires was taken as consent.

We uniquely categorized patients across gender, IIM subtypes, employment status, and also whether there was extramuscular involvement from IIM.

The impact of IIM was measured by different tools recommended by International Myositis Assessment and Clinical Studies Group (IMACS). These included MMT-8, the Physician and Patient Global Activity Assessments (PHGAA, PTGAA), Myositis Disease Activity Assessment Tool (MDAAT), and serum CK levels.[16,17] The PTGAA and PHGAA are visual analog scales of disease activity, scored 0–100, with higher scores reflecting worse outcomes. The MDAAT captures the physician's assessment of extramuscular disease activity, and was used in this study to identify patients with cardiopulmonary or gastrointestinal involvement. As this study sought to investigate HRQOL and WP in IIM, and as the extramuscular manifestations pertaining to the cardiorespiratory and gastrointestinal systems are most likely to impact on these measures, our analysis was limited to these organ systems. In addition to CK, duration of IIM was also used as a surrogate marker for cumulative damage. Other numerical and categorical predictor variables, such as patient age and gender were also included in the study, outlined in Table 1. Cohort characterization also included histological diagnosis.

TABLE 1 Baseline characteristics

Female n (%)	29 (58)
Employed n (%)	16 (32)
Organ involvement	
Cardiorespiratory n (%)	17 (34)
Gastrointestinal n (%)	10 (20)
Subtypes of IIM	
DM n (%)	9 (18)
PM n (%)	11 (22)
IBM n (%)	9 (18)
NM n (%)	11 (22)
MNOS n (%)	10 (20)
Age at diagnosis, y, mean (SD)	56.4 (12.7)
Age at survey, y, mean (SD)	61.9 (12.6)
CK at diagnosis, U/L, median (IQR)	911 (203, 3761)
CK at survey, U/L, median (IQR)	143 (75, 387)
Duration of IIM, y, median (IQR)	5 (2.5, 7.4)
MMT-8 median (IQR)	75 (66, 80)
PHGAA median (IQR)	16.5 (5, 31)
PTGAA median (IQR)	29 (11, 49)

Abbreviations: DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; MMT-8, manual muscle testing; MNOS, myositis-not otherwise specified; NM, necrotizing myositis; PHGAA, physician's global activity assessment; PM, polymyositis; PTGAA, patient's global activity assessment.

The impacts of IIM on HRQOL and WP were analyzed using the SF-36 and WPAI questionnaires, respectively.

The SF-36 has often been employed to evaluate HRQOL in patients with chronic conditions.[3,16,18] It includes 36 questions which produce a score 0–100 in 8 domains (with 100 representing the best possible health). The domains cover a range of physical and psychological categories, including physical function (PF), physical role limitations (PRL), emotional role limitations (ERL), vitality (V), mental health (MH), social function (SF), bodily pain (BP) and general health (GH). HRQOL outcomes were determined by scores derived from all 8 domains of the SF-36, and the Mental Component Summary (MCS) and Physical Component Summary (PCS). The MCS and PCS were calculated by standardizing the SF-36 scores against Australian population means, standard deviations, and factor coefficients.[19] The PCS and MCS are summary measures, where the PCS encompasses PF, PRL, BP and GH, while the MCS captures V, SF, ERL and MH.

The WPAI is widely used by clinicians to assess work impairment, and is felt to have clinical and research usability.[20] It involves 6 undemanding questions which yield 4 outcome scores relating to different aspects of a patient's experience in the workforce.[20,21] WP outcomes were calculated from the WPAI scores, and include absenteeism (percentage of work time missed), presenteeism (percentage of impairment while working), work productivity loss (overall percentage of work impairment), and life impairment (overall percentage of life impairment), all of which were due to IIM.

Statistical tests performed included correlation via Pearson and Spearman's tests, comparison via the independent *t*, Mann-Whitney *U* and Kruskal-Wallis tests, based on a number of normally and non-normally distributive data. SF-36 scores from our study were compared against the means derived from the most recently published SF-36 1995 Australian Bureau of Statistics Population Norms, which incorporated unweighted data (not matched for age or gender) collected from approximately 18 000 adult respondents.[19] Statistical software used was IBM SPSS Statistics, Version 26.

3 | RESULTS

Fifty patients returned the survey from 61 who were approached; of these 29 (58%) were female. The mean age at study recruitment was 61.9 years (SD 12.6) and the median duration since IIM diagnosis was 5 years (interquartile range [IQR] 2.5, 7.4) (Table 1).

Testing for myositis-specific and myositis-associated antibodies had been performed in all 50 patients and antibodies were detected in 30/50 (60%) patients. Specifically, the following autoantibodies were detected: anti-Ro52 (n = 10), anti-HMGCR (n = 9), anti-Jo1 (n = 7), anti- Mi-2 (n = 2), anti-PL7 (n = 3), anti-NXP2 (n = 2), anti-SRP (n = 2), anti-PMSCL (n = 2) and anti-RNP (n = 1).

Only 16 (32%) participants were employed at the time of survey completion, equating to an unemployment rate of 68 percent.

Among the employed cohort, there were impacts of IIM on WP, with an overall median work impairment of 20.8% (IQR 10, 50) (Table 2). When compared to the unemployed cohort, the employed cohort had higher HRQOL in the PCS ($P = .032$, median 43.9, IQR 38.4, 50.6 vs median 32.9, IQR 25.1, 45.4), PF ($P = .023$, median 70, IQR 46.3, 88.8 vs 47.5, IQR 23.8, 71.3) and PRL domains ($P = .038$, median 50, IQR 25, 100 vs median 12.5, IQR 0, 75) (Mann-Whitney *U* test). There were no other significant differences in the other SF-36 domains between those employed and not employed (data not shown). There were no significant differences for SF-36 domains between genders (data not shown).

When compared with Australian population norms, our cohort showed significantly lower SF-36 scores in 7 of the 8 domains ($P \leq .01$), indicating the widespread effects of IIM (Table 3). In particular, the PCS was over 10 points lower in our cohort (37.2, SD 11.1) than the general Australian population (49.8, SD 10.2), representing differences over 1 SD, indicating significant physical impairments. In contrast, the study cohort MCS score (48.9, SD 12.0) was similar to the Australian population (50.1, SD 10.0), indicating the relative preservation of emotional health.

In our cohort, PTGAA scores were significantly inversely associated with HRQOL in all 8 domains and positively associated with WP life impairment, whereas PHGAA scores were significantly inversely associated with the PCS, PF, PRL and SF only, and positively associated with WP life impairment (Table 4). MMT-8 scores were significantly positively associated with the PCS, PF, PRL, ERL, SF and BP domains, and inversely associated with WP life impairment (Table 4).

Patients with cardiopulmonary involvement compared with those without cardiopulmonary involvement, also showed statistically significant differences in the MCS ($P = .031$, median 41.5, IQR 33.5, 56.1 vs median 55.7, IQR 44.3, 59.9) and V domain ($P = .013$, median 45, IQR 30, 55 vs median 60, IQR 37.5, 75) (Mann-Whitney *U* test). The *t* test showed significance in the PF domain ($P = .018$, mean 40.6, SD 25.7) compared to those with no cardiopulmonary involvement (mean 60, SD 27.1).

There were no statistically significant effects of CK levels, duration of IIM, age and IIM subtype on HRQOL.

4 | DISCUSSION

In this South Australian study reporting HRQOL and WP outcomes in IIM patients, we demonstrate the significant physical impacts of IIM on patients' HRQOL and WP.

TABLE 2 WPAI descriptive statistics

WPAI outcome scores	
Absenteeism %, n = 16, median (IQR)	0 (0, 9.7)
Presenteeism %, n = 16, median (IQR)	20 (10, 50)
Work productivity loss %, n = 16, median (IQR)	20.8 (10, 50)
Life impairment %	
Employed only, n = 16, median (IQR)	22.5 (10, 47.5)
All patients, n = 50, median (IQR)	30 (13.8, 50)

Note: Absenteeism, percentage of work time missed due to IIM; Presenteeism, percentage of impairment while working due to IIM; Work productivity loss, overall percentage of work impairment due to IIM; Life impairment, overall percentage of life impairment due to IIM; IIM, idiopathic inflammatory myopathy; IQR, interquartile range; WPAI, Work Productivity and Activity Impairment.

TABLE 3 Comparison of study means against the 1995 Australian Population Norms for SF-36

SF-36 domains	Study mean (SD) n = 50	1995 Australian population mean (SD)[a]	*P*-value (95% CI)
Physical function	53.40 (27.95)	83.46 (23.23)	<.001 (−38.00, −22.12)
Physical role limitations	44.00 (42.43)	80.28 (34.84)	<.001 (−48.34, −24.22)
Emotional role limitations	66.66 (42.60)	83.19 (32.15)	.008 (−28.63, −4.42)
Vitality	52.50 (22.23)	64.48 (19.77)	<.001 (−18.30, −5.66)
Mental health	74.08 (21.22)	75.98 (16.96)	.530 (−7.923, 4.13)
Social function	69.75 (24.10)	85.06 (22.29)	<.001 (−22.16, −8.46)
Bodily pain	62.70 (25.69)	76.94 (24.84)	<.001 (−21.54, −6.94)
General health	51.60 (21.27)	71.82 (20.35)	<.001 (−26.26, −14.17)

Note: (One sample *t* test). SF-36, Medical Outcomes Study 36-items Short Form.

[a]ABS, National health survey Australia, 1995: SF-36 population norms. Australian Bureau of Statistics, 1997.

Using the SF-36 as a measure of HRQOL, we showed that patients with IIM demonstrated lower mean scores in all domains measured (except mental health), when compared with Australian population norms. These findings have not, to our knowledge, been established in other Australian cohorts to date. Similarly, studies of other international populations also showed reduced HRQOL in all domains except mental health, suggesting a stronger impact of IIM on physical than emotional health.[10,11] Conversely, other studies have published data highlighting low mood and illness perception as determinants of poor mental health and the importance of psychological therapy.[4,10,12-15,22] Many of these studies used specific questionnaires addressing mental health, including the Hospital Anxiety and Depression Scale, which may account for this.[10,22] Additionally, the discrepancy may reflect different emotional reserves of populations studied and the readiness to disclose impairments in mental health may vary according to cultural norms. Furthermore, changes are compared with the population-based norms, and in some populations in which mental health is poorer, it may be difficult to ascertain additional impacts of a chronic disease such as IIM.

There was a strong statistical relationship between higher MMT-8 scores and the physical domains, indicating patients whose power is relatively preserved have a greater HRQOL. Prior data also suggest similar findings.[14] This supports the clinical utility of testing MMT-8; furthermore, targeted therapies to restore muscle power, such as immunomodulatory therapies and resistance training programs, should have a significant impact on HRQOL. Prior literature has demonstrated that patients with IIM with impaired endurance may have these improved with endurance training.[23,24] It would thus be of interest to perform sequential assessments of HRQOL from disease onset and ascertain the relationship between MMT-8 and HRQOL within individual patients.

Patients who assessed their disease as more active (as determined by a higher PTGAA), had poorer HRQOL. The PTGAA measures the patient's perception of disease activity, which may be subjectively influenced by their emotional state, and as such, it is not surprising that this correlates with poorer scores on the SF-36. The PTGAA may thus be a surrogate marker reflective of patients' emotional well-being. Conversely, higher PHGAA scores showed correlations with lower physical scores only, and had no relationship with mental scores, suggesting that the PHGAA may not adequately capture the impact of IIM on the patient's mental well-being.

Our study did not establish gender or age as strong predictors for poorer HRQOL, and prior literature has varying evidence. Ponyi et al. showed stronger negative links between female gender and physical domains.[4] However, other studies have denied such links.[11,12,25] Conflicting evidence may be explained by discrepancies in HRQOL in gender groups and age even in healthy subjects.[25] In our cohort, patients with cardiopulmonary disease showed poorer outcomes in several domains including the MCS, suggesting a degree of impact by extramuscular disease. Published data are limited regarding the presence of extramuscular disease and HRQOL, with some research suggesting association of features, such as Raynaud's phenomenon and polyarthritis with poorer HRQOL.[4] Measures of characterizing extramuscular disease have also varied which may account for differences in results.

As IBM is often considered treatment-refractory and progressive, it would perhaps have been anticipated that this subgroup of patients may have shown poorer HRQOL; however, we and prior research have found no differences between the IIM subgroups.[4,11,12]

CK levels and duration of IIM, both considered surrogate markers for disease severity, did not show correlations with outcome variables. These variables have not been studied extensively to date in prior literature; however, Graham et al.[25] also describes inconsistent evidence regarding this.

Only 32% of our study population was employed at the time of the study, which is lower than previous reports.[5,7] Data from the Australian Bureau of Statistics estimate the rate of unemployment in a similar age group to be 4.3 percent (as of January 2020).[26]

Literature on WP in patients with IIM remains limited to date.[5-7] Bradford et al. demonstrated an increased amount of work loss, with increased absenteeism and presenteeism, when compared to a control group. In our study, employed patients showed better physical

TABLE 4 Correlations between functional assessments and measures of health-related quality of life and WP outcomes (n = 50)

	MMT-8	PHGAA	PTGAA
Variable	***r* (*P*-value)**	***r* (*P*-value)**	***r* (*P*-value)**
Physical component summary	**.48 (<.001)**	−.39 **(<.01)**	−.69 **(<.001)**
Mental component summary	.17 (.25)	.11 (.47)	−.28 **(.05)**
Physical function	.57 **(<.001)**	−.38 **(<.01)**	−.63 **(<.001)**
Physical role limitations	.37 **(<.01)**	−.30 **(.03)**	−.52 **(<.001)**
Emotional role limitations	.33 **(.02)**	−.03 (.84)	−.35 **(.01)**
Vitality	.27 (.06)	−.06 (.67)	−.49 **(<.001)**
Mental health	.13 (.36)	.09 (.52)	−.34 **(.02)**
Social function	.46 **(.001)**	−.34 **(.02)**	−.60 **(<.001)**
Bodily pain	.30 **(.03)**	−.14 (.35)	−.62 **(<.001)**
General health	.26 (.07)	.01 (.93)	−.57 **(<.001)**
WP absenteeism	−.03 (.93)	.18 (.51)	.44 (.087)
WP presenteeism	−.28 (.29)	.27 (.31)	.40 (.12)
WP work-related impairment	−.22 (.41)	.29 (.28)	.46 (.07)
WP life impairment, employed only, n = 16	−.39 (.14)	.21 (.43)	.73 **(.001)**
WP life impairment, all patients, n = 50	−.61 **(<.001)**	.28 **(.05)**	.69 **(<.001)**

Note: (Spearman correlation test).

Abbreviations: MMT-8, manual muscle testing score; PHGAA, physician global activity assessment; PTGAA, patient global activity assessment; WP, work productivity.

The bold values were used to indicate statistically significant *P*-values

health, suggesting targeting improved physical health may result in improved employability and WP. Higher PTGAA tended to correlate with worse outcomes, also highlighting a link between the patients' perceived degree of disease activity and impairment on WP.

There are limitations to this study. Our cohort was studied 25 years after the 1995 Australian population norms. Ideally, data should be compared against more recent norms, or perhaps our own control cohort. In addition, our sample size of 50 participants is limited and inevitably has potential for bias. Recruiting and approaching patients at outpatient appointments, yielded a very high response rate (50/61); however, those patients who are more severely affected or immobile may not attend hospital appointments as readily. Furthermore, the small numbers of our patients who were in employment at the time of the study limits the ability to draw meaningful conclusions. Certainly, it is difficult to ascertain the numbers who are unemployed as a result of their disease or due to age-related retirement. We also need to be mindful that although the SF-36 has been widely used in previous research and recommended by IMACS as a patient-reported outcome (PRO), it has not been entirely validated for use in IIM populations per se.

Additionally, the WPAI is only limited to the 7 days prior to the survey, and does not specify if unemployment is due to the health condition or retirement, making comparison to control data difficult. The use of different WP questionnaires may have produced data that were more inclusive and significant.

These limitations acknowledged, our study nonetheless demonstrates that even at a median of 5 years after diagnosis of IIM, these patients have significantly poorer HRQOL, are less often in employment, and have significant impairments even in those who remain employed. We have reported these findings for the first time in a well-characterized cohort of patients with various histological subsets of IIM. Further research in larger patient cohorts, and investigating the effect of race and socioeconomic status is needed, as are longitudinal studies of different patient cohorts. The findings of this study should be a reminder to treating clinicians of the far-reaching and diverse effects of IIM on patients' HRQOL and WP, and to encompass a multidisciplinary and holistic approach to address the impacts of IIM.

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CONFLICT OF INTEREST

There are no conflicts of interest from this article.

AUTHOR CONTRIBUTIONS

AX, CS, RM and VL were all major contributors in the production of this manuscript. CS and VL participated in the study design, research proposal and patient recruitment. AX and CS participated in data collection. AX and RM participated in data analyses and AX, CS, RM and VL all contributed to the writing and editing of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

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Analysis of risk factors of interstitial lung disease and mortality rates in Chinese patients with idiopathic inflammatory myopathy

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Abstract

Aim: To investigate the risk factors for interstitial lung disease (ILD) and prognosis in patients with idiopathic inflammatory myopathy (IIM).

Methods: A retrospective longitudinal study was performed in patients diagnosed with IIM between January 2012 and December 2018.

Results: The study cohort included 91 men and 195 women who were classified as having dermatomyositis (DM, n = 183), polymyositis (PM, n = 77), or clinical amyopathic DM (CADM, n = 26). ILD was identified in 46.5% (n = 133) of patients with IIM. The independent risk factors for ILD were age at disease onset, presence of anti-Ro-52 antibody, Gottron's papules, elevated serum immunoglobulin M levels and hypoalbuminemia. Older age at disease onset, ILD, malignancy, and increased serum aspartate aminotransferase and neutrophil-to-lymphocyte ratio (NLR) were identified as the independent predictors for mortality, whereas elevated serum albumin level was associated with a better prognosis. A total of 73 deaths (25.5%) occurred after a median follow-up time of 33 months. Infection (49.3%) was the leading cause of death. In the overall cohort, the 1-year, 5-year and cumulative survival rates were 83.2%, 74.2% and 69.4%, respectively. The receiver operating characteristic curve indicated that the optimal cut-off value of NLR for predicting death in IIM was 6.11.

Conclusion: IIM patients have a poor prognosis with substantial mortality, especially in patients who have older age at onset, ILD, malignancy and higher NLR. Close monitoring and aggressive therapies are required in patients having poor predictive factors.

KEYWORDS

dermatomyositis, idiopathic inflammatory myopathy, interstitial lung disease, polymyositis, prognosis

1 | INTRODUCTION

Idiopathic inflammatory myopathy (IIM) is a heterogeneous group of autoimmune diseases mainly characterized by weakness in proximal extremities and elevated muscle enzyme levels, accompanied by the involvement of organs such as the lung and heart in addition to the joints and skin. Despite aggressive treatments, some refractory IIM patients have substantial morbidity and mortality, leading to increased risk of death and long-term disability. The 10-year mortality rate for IIM patients has been reported to range from 28.6% to 60.1%.[1-3] Myositis with pulmonary involvement is a main factor which affects the mortality of IIM patients and interstitial lung disease (ILD) is now a major cause of death in IIM patients.[4] Results from recent studies showed that age at disease onset, malignancy, infection, anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody, pneumomediastinum and Gottron's papules are the risk factors related to poor prognosis.[5-7] However, most of these studies focused on predictive indicators of mortality or ILD, whereas few multivariate survival analyses have investigated risk factors for ILD and death together. Moreover, data on the mortality rates of patients with IIM living in mainland China are limited. In the present study, a retrospective analysis was performed to assess mortality rates and causes of death across different clinical subsets, and determine prognostic factors related to ILD and mortality in a large cohort of Chinese patients diagnosed with IIM in a tertiary university hospital between 2012 and 2018. Due to the high heterogeneity of this autoimmune disorder, the prognosis of patients with IIM among different clinical subsets can widely vary. To obtain a comprehensive interpretation of the prognosis of IIM, patients having different myositis subtypes including dermatomyositis (DM), polymyositis (PM), and clinical amyopathic DM (CADM) were included. Data obtained from analysis of a relatively large sample cohort that includes more subclasses of myositis and longitudinal follow-up can contribute to a better understanding of the clinical characteristics that are associated with poor prognosis for patients with IIM.

2 | MATERIALS AND METHODS

2.1 | Patients

We consecutively selected 286 patients diagnosed with IIM who were hospitalized at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2012 and December 2018. The inclusion criteria were: (a) age ≥16 years; (b) diagnosed with definite or probable DM/PM based on the criteria of Bohan and Peter;[8,9] (c) diagnosed with CADM based on the criteria of Sontheimer;[10] and (d) at least one follow-up visit to our center. The exclusion criteria included: (a) patients with muscle involvement due to infections, neuromuscular disease, metabolic endocrine disorders and myotoxic drugs; (b) inclusion body myositis; (c) patients diagnosed with another type of connective tissue disease; and (d) patients with incomplete primary data. All patients underwent high-resolution computed tomography (HRCT) at their first admission. Written informed consent was waived due to the retrospective nature of this study. The study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology in accordance with the principles of the Declaration of Helsinki (approval number: 2020-S105).

2.2 | Definitions

The diagnosis of ILD was based on the following criteria: (a) the presence of hallmark manifestations of disease including reticular, honeycombing, irregular linear or ground-glass opacities or patchy clouding on chest HRCT as judged by professional radiologists, pulmonologists or physicians;[11,12] (b) patients with ILD arising in response to definite exposure (eg, environmental, drugs) were excluded. The radiologic patterns of ILD were categorized into usual interstitial lung pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP) and undefined forms that were independently evaluated by 2 professional radiologists based on the American Thoracic Society/European Respiratory Society statement.[13,14] Patients were defined as having pulmonary infection according to distinctive infectious lesions in the lung as evaluated by radiologists or pulmonologists, positive etiological evidence (eg, sputum culture, bronchoalveolar lavage, blood culture, or pleural biopsy) as well as a good response to anti-infective treatments. Fever was documented as recurrent temperature >38°C without alternative explanations other than the primary disease. Antinuclear antibodies were considered positive at titers ≥1:100. Malignancies were defined as occurrence within 3 years before or after the diagnosis of IIM. Duration of disease was defined as the time from the date of the appearance of any symptoms associated with the primary disease to the date of the first visit to the rheumatology department. Methylprednisolone pulse therapy was defined as intravenous methylprednisolone ≥200 mg/d for 1-3 days.

2.3 | Methods

We retrospectively retrieved the medical records of 286 IIM patients to collect clinical data including demographic information, clinical features, laboratory parameters and therapeutic regimens and obtained the survival outcome of patients through follow-up. The patients were divided into an ILD group and non-ILD group according to the comprehensive evaluation by physicians at the first admission. To identify the mortality-related factors for IIM, the 286 patients were further divided into a survival group and deceased group. Clinical characteristics and laboratory parameters were compared between different subgroups. The data on survival outcome were obtained through telephone follow-up, and we attempted to contact cases who were lost to follow-up via correspondence or email. For patients who died at our hospital, the causes of death were identified via tracing of the medical records. To ascertain the date and cause of death for cases that were lost to

follow-up, family members were contacted by telephone or email. The antinuclear antibody profile for 6 autoantibodies was assessed by an immunoblotting assay using a EUROIMMUN kit (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany).

2.4 | Outcomes and follow-up

The primary end-point for this study was the all-cause mortality rate. Follow-up began at the index date, which was identified as the date of the first visit to our hospital. Follow-up ended at death, 30 November 2019, or the date the subject was lost to follow-up for any reason (eg, emigration), whichever date came first. The observation period was defined as the time from the index date to the last day of follow-up.

2.5 | Statistical analysis

Continuous variables are presented as mean ± standard deviation or as the median (quartile) depending on the normality of variables distribution. Continuous numerical variables of subgroups were compared with Mann-Whitney *U* test or Student's *t* test. Categorical variables were analyzed with Fisher's exact test or Chi-square test. Logistic regression analysis was conducted to investigate the risk factors for ILD. The survival rates of IIM patients were evaluated using Kaplan-Meier survival curves with log-rank test. The predictors associated with mortality were analyzed with Cox regression analysis. A receiver operating characteristic (ROC) curve was used to determine the best diagnostic threshold of the clinical index and evaluate the diagnostic efficacy. All data were analyzed using SPSS version 25.0 (IBM) and GraphPad Prism version 8.4 (GraphPad Software). A 2-tailed $P < .05$ was considered to indicate a statistically significant difference.

3 | RESULTS

3.1 | Epidemiologic characteristics and clinical manifestations

A total of 286 hospitalized patients diagnosed with IIM were enrolled. Of these, 183, 77 and 26 had DM, PM, and CADM, respectively. Among this patient group, 69% (195) were female and the mean age at disease onset was 49 ± 14 years with a median disease course of 4 months (range, 2-12 months). Nearly all (284/286) had at least one follow-up visit with a median duration of follow-up of 32 months (range, 1-103 months). Two patients were lost to follow-up. Baseline clinical characteristics of the ILD group and non-ILD group as well as the deceased group and survival group were compared (Table 1). The follow-up time of patients with ILD and the deceased group was significantly shorter than that of the control groups. Compared to the non-ILD group, patients with ILD exhibited a larger number of constitutional symptoms such as fever. The proportion of patients with pulmonary infection, arthralgia and Gottron's papules was significantly higher in the ILD group than the non-ILD group. Meanwhile, patients without ILD had a higher frequency of malignancy, myalgia and V sign compared with the ILD group. Out of the 133 patients with ILD, 127 could be assessed by HRCT. The distribution of radiologic patterns was: 43.3% NSIP (n = 55), 43.3% UIP (n = 55), 5.5% AIP (n = 7), 3.9% LIP (n = 5), 2.4% OP (n = 3) and 1.6% not defined (n = 2). There was no significant difference in ILD type in terms of clinical features and IIM subsets (Table S1). Pulmonary infection and ILD were predominantly observed in the deceased group (56% vs. 33% and 63% vs. 41%, respectively). A significant difference was observed in age at onset between the deceased group and survival group (54 ± 13 vs. 47 ± 13 years; $P < .001$). In terms of IIM subsets, the proportion of patients with DM in the deceased group was significantly higher than the survival group ($P = .001$). Patients in the deceased group exhibited a higher proportion of dysphagia (30% vs. 18%), heliotrope rash (58% vs. 32%), and Gottron's papules (59% vs. 43%) than the survival group. Compared with the survival group, the incidence of comorbidities such as hypertension and malignancy was significantly higher in the deceased group (Table 1).

3.2 | Laboratory features and treatment regimens

Baseline laboratory features and initial treatment modalities between different subgroups were compared (Table 2). The percentages of anti-Ro-52 antibody and anti-Jo-1 antibody were significantly higher in the ILD group than the non-ILD group. The levels of serum globulin, serum immunoglobulin G (IgG) and serum IgM in the ILD group were significantly higher than those in the non-ILD group, whereas the serum albumin level of patients with ILD was significantly lower. Compared to the survival group, the presence of anti-Jo-1 antibody, platelet count, lymphocyte count, serum total protein level and serum albumin level were significantly lower in the deceased group. Meanwhile, serum aspartate aminotransferase (AST) level, neutrophil-to-lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) were significantly higher in patients who died. In terms of initial therapy modalities, 81% of all the enrolled patients treated at our center received a combination treatment of glucocorticoids and immunosuppressants, with the most frequent being cyclophosphamide (32.2%), followed by methotrexate (29.0%), calcineurin inhibitors (19.2%), hydroxychloroquine (17.8%), intravenous Igs (16.1%), plasma exchange (15.4%) and azathioprine (9.8%). The proportion of patients treated with cyclophosphamide in the ILD group was significantly higher than the control group. Subgroup analysis by a Kaplan-Meier curve indicated that in the ILD group (n = 133), patients treated with methylprednisolone pulse appeared to show a higher mortality than those who did not receive methylprednisolone pulse (Figure 1A).

3.3 | Causes of death

Among the 73 deaths in the study group, no cause of death was known for 4 patients. The most common cause of death in our

TABLE 1 Baseline clinical characteristics between different subgroups, X ± SD, median (interquartile range) or n (%)

Characteristics	ILD group (N = 133)	Non-ILD group (N = 153)	*P* value	Deceased group (N = 73)	Survival group (N = 213)	*P* value
Gender (M/F)	44/89	47/106	.669	26/47	65/148	.419
Mean age at disease onset, y	50 ± 11	47 ± 15	.029*	54 ± 13	47 ± 13	<.001***
DM/PM/CADM	86/32/15	97/45/11	.353	59/8/6	124/69/20	.001**
Median duration of disease, mo	5 (2,12)	4 (2,12)	.669	4 (2,12)	4 (2,12)	.844
Median time of follow-up, mo	26 (13,54)	37 (20,61)	.007**	6 (2,16)	42 (25,66)	<.001***
Fever	54 (42)	43 (28)	.013*	29 (40)	70 (33)	.288
Pulmonary infection	65 (49)	47 (31)	.002**	41 (56)	71 (33)	.001**
ILD	133 (100)	0	/	46 (63)	87 (41)	.001**
Myalgia	60 (45)	88 (58)	.036*	36 (49)	112 (53)	.630
Muscle weakness	106 (80)	123 (80)	.884	61 (84)	168 (79)	.387
Arthralgia	69 (52)	61 (40)	.042*	34 (47)	96 (45)	.824
Dysphagia	22 (17)	38 (25)	.086	22 (30)	38 (18)	.026*
Heliotrope rash	47 (35)	62 (41)	.368	42 (58)	67 (32)	<.001***
Gottron's papules	72 (54)	63 (41)	.029*	43 (59)	92 (43)	.020*
V sign	28 (21)	49 (32)	.037*	20 (27)	57 (27)	.916
Shawl sign	24 (18)	30 (20)	.736	18 (25)	36 (17)	.144
Comorbidity						
Arterial hypertension	22 (17)	35 (23)	.181	21 (29)	36 (17)	.029*
Diabetes mellitus	16 (12)	23 (15)	.460	11 (15)	28 (13)	.679
Coronary heart disease	3 (2)	9 (6)	.127	5 (7)	7 (3)	.190
Malignancy	4 (3)	14 (9)	.033*	12 (16)	6 (3)	<.001***

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; M/F, male/female; PM, polymyositis.
*$P < .05$.; **$P < .01$.; ***$P < .001$.

cohort was infection (49.3%), followed by ILD (19.2%) and malignancy (11.0%), while other less frequent causes were, in descending order, heart failure (6.8%), cerebral hemorrhage (2.7%), sudden death (1.4%), pulmonary embolism (1.4%), rhabdomyolysis (1.4%) and renal failure (1.4%) (Table 3). No significant differences in the leading causes of death were observed among the DM, PM and CADM subsets. Pneumonia was the most frequent condition in patients who died from infection (n = 32). Lung cancer was the leading condition in the group of patients who died from malignancies (n = 4).

3.4 | Survival analysis

Across the median follow-up time of 33 months, 73 (25.5%) deaths were observed in our cohort. The 1-year, 5-year and cumulative survival rates of the entire IIM cohort were 83.2%, 73.3% and 68.3%, respectively. After stratification by age, the Kaplan-Meier analysis revealed significantly lower survival rates in patients with disease onset at ≥60 years old than those who were younger than 60 years at disease onset (68.5% vs. 86.6%,, 49.1% vs. 78.4% and 36.9% vs. 74.1% for 1, 5 and cumulative years, respectively). Significant differences were also observed in patients with and without ILD (75.2% vs. 90.2%, 62.9% vs. 82.1% and 60.5% vs. 74.6% for 1, 5 and cumulative years, respectively) (Table 4). For IIM subsets, there were significant differences in survival rates among DM, PM, and CADM in 1, 5 and cumulative years ($P = 0.005$, $P = .001$ and $P = 0.001$, respectively). PM had the highest cumulative survival rate of up to 86.0%, followed by patients with CADM (76.9%) and DM (59.2%) (Figure 2H). Univariate analysis with the log-rank test demonstrated that the mortality rates of patients with pulmonary infection, malignancy, hypertension, dysphagia, heliotrope rash, Gottron's papules and absence of anti-Jo-1 antibody were significantly higher than the controls (Figure 2). For the classifications of ILD, the cumulative survival rates were 73.1% for NSIP, 58.6% for UIP, 0% for AIP, 60.0% for LIP, 100.0% for OP and 50.0% for the undefined, with a significant difference in log-rank test ($P < .001$) (Figure 1B).

3.5 | Prognostic factors for ILD and mortality

Univariate analysis showed there were 14 predictors related to the occurrence of ILD at the significance level of $P < .05$ (Table S2).

TABLE 2 Baseline laboratory features and treatment modalities between different subgroups, X ± SD, median (interquartile range) or n (%)

Baseline laboratory examinations	ILD group (N = 133)	Non-ILD group (N = 153)	*P* value	Deceased group (N = 73)	Survival group (N = 213)	*P* value
ANA	55 (43)	50 (34)	.132	26 (38)	79 (38)	.993
Anti-dsDNA antibody	1 (1)	1 (1)	.918	0	2 (1)	1.000
Anti-SSA antibody	26 (20)	20 (13)	.132	8 (12)	38 (18)	.222
Anti-SSB antibody	4 (3)	3 (2)	.564	2 (3)	5 (2)	.798
Anti-Ro-52 antibody	68 (53)	40 (27)	<.001***	24 (35)	84 (40)	.489
Anti-Jo-1 antibody	24 (19)	9 (6)	.001**	2 (3)	31 (15)	.009**
WBC, $\times10^9$/L	7.17 (5.09,10.99)	7.51 (5.52,10.00)	.530	7.96 (5.24,11.29)	7.39 (5.24,10.21)	.605
RBC, $\times10^9$/L	4.18 ± 0.55	4.14 ± 0.59	.548	4.08 ± 0.64	4.19 ± 0.55	.181
PLT, $\times10^9$/L	218 (164,282)	214 (162,274)	.692	188 (146,249)	227 (175,283)	.010*
Hb, g/L	121 ± 15	122 ± 19	.470	119 ± 18	123 ± 17	.116
Neutrophil count, $\times10^9$/L	5.61 (3.50,8.88)	5.64 (3.87,8.33)	.715	5.86 (4.17, 9.44)	5.52 (3.50, 8.38)	.172
Lymphocyte count, $\times10^9$/L	1.01 (0.73,1.56)	1.10 (0.76,1.65)	.337	0.84 (0.63, 1.23)	1.11 (0.83, 1.72)	<.001***
NLR	5.28 (3.21,8.79)	5.04 (3.18,8.28)	.605	6.88 (3.83, 12.76)	4.54 (2.86, 7.92)	<.001***
Total protein, g/L	65.7 (61.5,71.7)	66.7 (61.9,73.5)	.201	63.7 (59.7, 68.5)	66.8 (63.1, 74.4)	<.001***
Albumin, g/L	32.7 (29.5,35.4)	36.2 (32.6,40.3)	<.001***	31.8 (28.1, 34.2)	35.2 (32.0, 39.5)	<.001***
Globulin, g/L	33.6 (29.6,37.3)	31.1 (26.6,34.7)	.001**	32.5 (28.7, 35.6)	31.8 (27.6, 36.2)	.690
ALT, U/L	45 (23,96)	48 (23,107)	.750	48 (28,111)	46 (23,98)	.399
AST, U/L	56 (32,129)	65 (30,154)	.543	85 (35,174)	55 (27,137)	.031*
CK, U/L	376 (63,1610)	402 (64,2565)	.529	344 (67,1913)	442 (61,2371)	.451
LDH, U/L	402 (286,570)	394 (261,627)	.724	423 (303,661)	392 (270,566)	.212
ESR, mm/L	28 (15,49)	22 (10,39)	.021*	32 (16,49)	22 (12,40)	.018*
IgG, g/L	13.4 (11.0,17.5)	11.0 (8.8,14.0)	<.001***	12.1 (10.0,16.3)	12.0 (9.7,15.7)	.440
IgA, g/L	2.3 (1.6,3.1)	2.2 (1.5,2.8)	.194	2.3 (1.9,3.1)	2.1 (1.5,2.8)	.074
IgM, g/L	1.5 (1.0,2.1)	1.2 (0.9,1.8)	.023*	1.3 (0.9,2.1)	1.3 (1.0,2.0)	.968
C3, g/L	0.93 (0.80,1.16)	0.93 (0.83,1.16)	.831	0.91 (0.80,1.17)	0.94 (0.83,1.16)	.332
C4, g/L	0.27 (0.20,0.33)	0.27 (0.22,0.35)	.473	0.27 (0.22,0.33)	0.27 (0.21,0.33)	.931
Initial treatment regimens						
PE	21 (16)	23 (15)	.860	10 (14)	34 (16)	.644
High-dose glucocorticoid therapy	8 (6)	6 (4)	.413	5 (7)	9 (4)	.370
IVIG	24 (18)	22 (14)	.400	12 (16)	36 (16)	.924
GC alone	20 (17)	37 (24)	.048*	18 (25)	39 (18)	.374
GC+CTX	62 (47)	30 (20)	<.001***	25 (34)	67 (32)	.660
GC+FK506/CsA	28 (21)	27 (18)	.466	9 (12)	46 (22)	.083
Initial dose of oral glucocorticoid, mg	40 (40,50)	32 (40,50)	.266	40 (40,50)	40 (32,50)	.245

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase / glutamic-oxalacetic transaminase; CK, creatine kinase; CsA, cyclosporin; CTX, cyclophosphamide; ESR, erythrocyte sedimentation rate; FK506, tacrolimus; GC, glucocorticoid; Hb, hemoglobulin; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PE, plasma exchange; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

Variables with $P < .05$ in univariate logistic analysis were considered as candidates for entry into multivariate logistic regression. In the multivariate model, age at disease onset (odds ratio [OR] = 12.593 and OR = 21.211), the presence of anti-Ro-52 antibody (OR = 2.560), Gottron's papules (OR = 2.342) and the serum IgM level (OR = 1.930) were the independent risk factors for ILD, whereas baseline serum albumin level presented a protective effect (OR = 0.915) (Table 5).

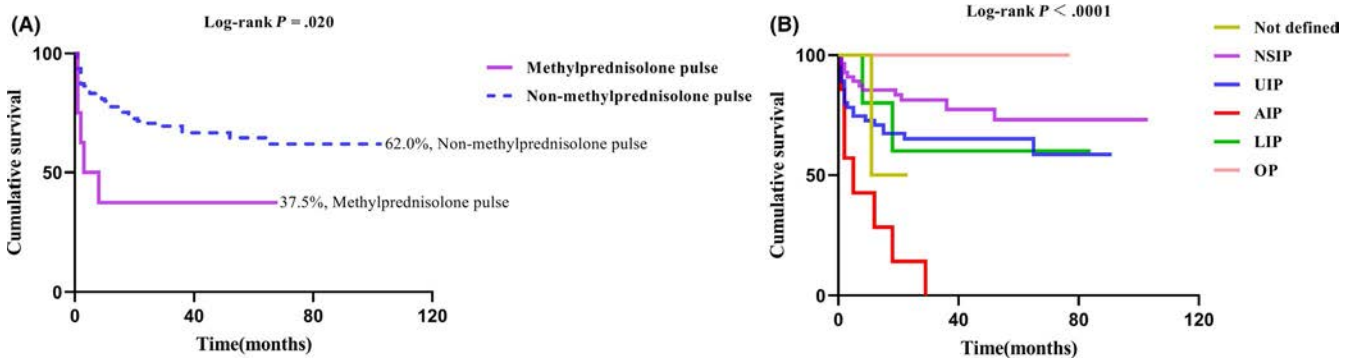

FIGURE 1 (A) Kaplan-Meier survival curves of patients in the interstitial lung disease (ILD) group treated or not with methylprednisolone pulse; (B) ILD group mortality rates according to radiologic classifications of interstitial lung disease. UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; AIP, acute interstitial pneumonia; OP, organizing pneumonia; LIP, lymphocytic interstitial pneumonia

Univariate Cox regression identified 16 mortality-related factors for IIM (Table S3). After adjusting for gender, age, comorbidities, laboratory parameters and IIM subsets, ILD (hazards ratio [HR] = 2.215) and malignancy (HR = 3.889) were independently associated with a poor prognosis. Mortality increased slightly with higher serum AST level (HR = 1.002), higher NLR (HR = 1.029) and higher age at disease onset (HR = 1.024), whereas the baseline serum albumin level (HR = 0.933) was associated with a favorable prognosis (Table 6). As displayed above, baseline NLR was identified as an independent risk factor for mortality. Therefore, the ROC curve analysis of NLR was performed to evaluate the predictive value of this factor for mortality. The ROC curve suggested the best diagnostic cut-off value of NLR for predicting death in IIM patients was 6.11 (Figure 3A). Kaplan-Meier curves further indicated that the survival rate of patients with NLR >6.11 was significantly lower than that of patients with NLR ≤6.11 (log-rank test <0.001) (Figure 3B).

4 | DISCUSSION

Although multiple studies have reported on predictors associated with prognosis and ILD in patients with IIM, the data regarding mortality of IIM subsets DM/PM/CADM in a relatively large study population in mainland China were limited. The present study investigated independent risk factors for ILD and poor prognosis of IIM patients. The 1-year, 5-year and cumulative survival rates of the overall cohort and the subgroups stratified by age, IIM subsets and ILD were also examined. To the best of our knowledge, our study represents the most comprehensive patient cohort comprising of 3 clinical subsets of IIM to determine both the risk factors for ILD and mortality.

Previous studies indicated that the frequency of IIM patients with accompanying ILD varied from 20% to 75%.[15-17] The ILD occurrence rate in this study, 46.5%, fell in the mid-range of this series. Similar to the meta-analysis by Hiroyuki et al.,[18] our study demonstrated that age at disease onset was an independent risk factor for ILD. This relationship is likely associated with the higher likelihood of comorbidities as well as reduced tolerance to disease due to diminished basal pulmonary function with age. Our data indicated that patients aged between 30 and 60 years and those over 60 years had 12.6-fold and 21.2-fold higher risk, respectively, for developing ILD than patients younger than 30 years. Our data also suggested that Gottron's papules are an independent risk factor for patients complicated with ILD, which is consistent with previous studies.[19] Therefore, careful screening for pulmonary parenchyma involvement should be performed, particularly for those patients who were over 30 years at disease onset and those who have Gottron's papules.

The myositis-associated autoantibody, anti-Ro-52 antibody was previously shown to be associated with ILD in IIM patients,[20,21] which is consistent with finding for this study. Our cross-sectional data demonstrated that the presence of anti-Ro-52 antibody could be a potential marker for ILD with an OR of 2.560. Anti-Jo-1 antibody was considered to be the strongest predictor of pulmonary fibrosis, although this possibility has become increasingly controversial in recent years.[21] In our cohort, multivariate analysis showed that anti-Jo-1 antibody was not an independent predictor of ILD, although the prevalence of anti-Jo-1 antibody was significantly higher in patients with ILD. These results suggest that anti-Ro-52 antibody has a higher predictive value relative to the anti-Jo-1 antibody in predicting ILD occurrence in IIM.

In our study, we revealed several serum biomarkers that were associated with increased risk for ILD and that were not analyzed in previous studies. Data from our cohort suggested that a higher level of serum IgM (OR = 1.930) was an independent predictor for ILD in IIM patients. The role of B cells in myositis pathogenesis has been supported by the presence of autoantibodies and favorable treatment responses to rituximab.[22] Thus, the elevated serum IgM levels seen in IIM patients with ILD may be indicative of inflammatory activation in B cells that could drive development of ILD, although prospective studies are needed to confirm whether IgM is simply an indicator of inflammation or whether IgM-producing B cells are directly affecting this condition. Multivariate analysis suggested that a reduction in serum albumin levels correlated with occurrence of ILD. According to a prior study, albumin, as a protective factor, can

TABLE 3 Comparisons of cause of death according to different idiopathic inflammatory myopathy subsets

Cause of death	DM N = 58 (%)	PM N = 9 (%)	CADM N = 6 (%)	Overall N = 73 (%)
Infection	30 (51.7)	4 (44.4)	2 (33.3)	36 (49.3)
ILD	10 (17.2)	1 (11.1)	3 (50.0)	14 (19.2)
Malignancy	7 (12.1)	0	1 (16.7)	8 (11.0)
Heart failure	4 (6.9)	1 (11.1)	0	5 (6.8)
Unknown	3 (5.2)	1 (11.1)	0	4 (5.5)
Cerebral hemorrhage	1 (1.7)	1 (11.1)	0	2 (2.7)
Sudden death	1 (1.7)	0	0	1 (1.4)
Pulmonary embolism	0	1 (11.1)	0	1 (1.4)
Rhabdomyolysis	1 (1.7)	0	0	1 (1.4)
Renal failure	1 (1.7)	0	0	1 (1.4)

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; PM, polymyositis.

TABLE 4 Survival rates in subgroups and overall idiopathic inflammatory myopathy cohort

Group	Total (n=)	Death (n=)	1-year survival rates (%)	5-year survival rates (%)	Cumulative survival rates (%)	*P* value[a] (1 year)	*P* value[b] (5 year)	*P* value[c] (cumulative)
IIM	286	73	83.2%	73.3%	68.3%	-	-	-
The subgroups of age								
<60 years	232	48	86.6%	78.4%	74.1%	.002**	<.001***	<.001***
≥60 years	54	25	68.5%	49.1%	36.9%			
The subgroups of ILD								
ILD	133	46	75.2%	62.9%	60.5%	.001**	<.001***	.001**
Non-ILD	153	37	90.2%	82.1%	74.6%			
The subsets of IIM								
DM	183	59	78.1%	65.2%	59.2%	.005**	.001**	.001**
PM	77	8	94.8%	90.0%	86.0%			
CADM	26	6	84.6%	76.9%	76.9%			

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; PM, polymyositis.

[a]*P* values for comparison of survival rates among different subgroups at 1 year of follow-up.

[b]*P* values for comparison of survival rates among different subgroups at 5 year of follow-up.

[c]*P* values for comparison of cumulative survival rates among different subgroups.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

inhibit endothelial cell apoptosis, prevent the generation of oxygen free radicals and reduced platelet aggregation.[23] A large number of cytokines and inflammatory mediators are produced during the course of ILD that could lead to a decline in albumin synthesis in the liver. Consequently, pulmonary fibrosis could progress due to the weakened protective action of albumin and activation of fibroblasts. Moreover, in a study of 1269 patients with idiopathic interstitial pneumonia, David et al. found that hypoalbuminemia was independently associated with higher mortality.[24] Hence, close attention and effective treatments are necessary for IIM patients with hypoalbuminemia to avoid progression to ILD.

Earlier studies reported the mortality of IIM patients ranged from 10% to 45%.[25-28] In our study, the mortality of IIM patients was 25.5% across 7 years, which is in the mid-range of previously reported rates. In addition, previous studies showed that survival rates of IIM patients ranged from 79.3%-96%, 69.9%-93% and 67%-92% at 1, 5 and 10 years, respectively.[2,3,26,29,30] The 1-year, 5-year and cumulative survival rates of IIM patients in our cohort were 83.2%, 73.3% and 68.3%, respectively, which are on the lower end of these ranges. This discrepancy could be explained in part by ethnic differences among populations and different treatment regimens. Thus, multicenter studies are needed to determine the mortality rate of IIM patients from different regions.

In terms of predictors that influence survival, our study confirmed several clinical prognostic factors that were previously reported to be associated with mortality in IIM patients, such as age at onset, ILD and malignancy.[28,31,32] Malignancy is considered to be a severe complication of IIM patients and closely related to poor prognosis.[3]

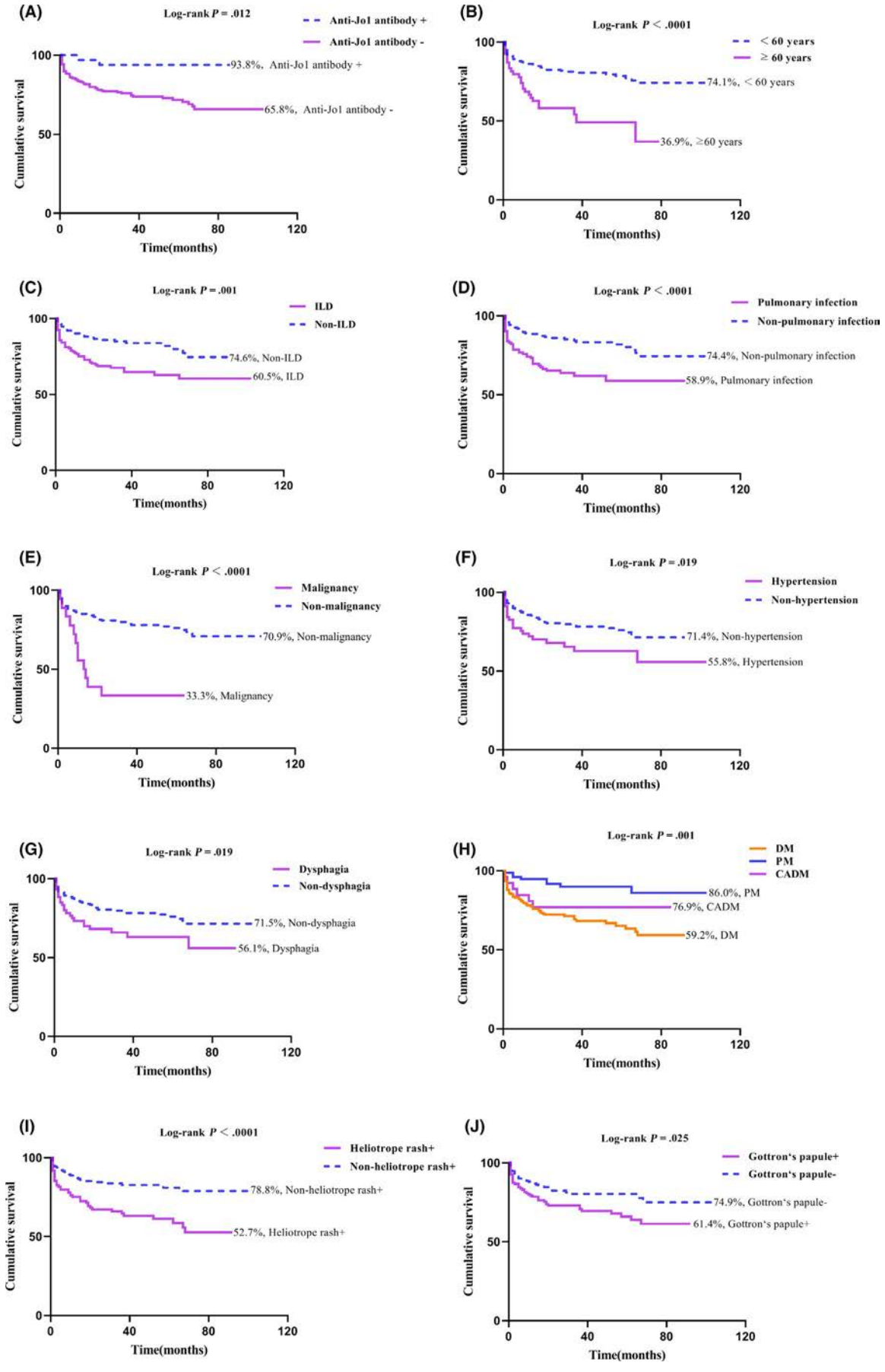
(A)
Log-rank P = .012
Anti-Jo1 antibody +
Anti-Jo1 antibody -
93.8%, Anti-Jo1 antibody +
65.8%, Anti-Jo1 antibody -
Cumulative survival
Time(months)
(B)
Log-rank P < .0001
< 60 years
≥ 60 years
74.1%, < 60 years
36.9%, ≥60 years
Cumulative survival
Time(months)
(C)
Log-rank P = .001
ILD
Non-ILD
74.6%, Non-ILD
60.5%, ILD
Cumulative survival
Time(months)
(D)
Log-rank P < .0001
Pulmonary infection
Non-pulmonary infection
74.4%, Non-pulmonary infection
58.9%, Pulmonary infection
Cumulative survival
Time(months)
(E)
Log-rank P < .0001
Malignancy
Non-malignancy
70.9%, Non-malignancy
33.3%, Malignancy
Cumulative survival
Time(months)
(F)
Log-rank P = .019
Hypertension
Non-hypertension
71.4%, Non-hypertension
55.8%, Hypertension
Cumulative survival
Time(months)
(G)
Log-rank P = .019
Dysphagia
Non-dysphagia
71.5%, Non-dysphagia
56.1%, Dysphagia
Cumulative survival
Time(months)
(H)
Log-rank P = .001
DM
PM
CADM
86.0%, PM
76.9%, CADM
59.2%, DM
Cumulative survival
Time(months)
(I)
Log-rank P < .0001
Heliotrope rash+
Non-heliotrope rash+
78.8%, Non-heliotrope rash+
52.7%, Heliotrope rash+
Cumulative survival
Time(months)
(J)
Log-rank P = .025
Gottron's papule+
Gottron's papule-
74.9%, Gottron's papule-
61.4%, Gottron's papule+
Cumulative survival
Time(months)

FIGURE 2 Kaplan-Meier survival curves of idiopathic inflammatory myopathy (IIM) patients with different clinical characteristics and subtypes. Survival curves for IIM patients (A) with and without anti-Jo-1 antibody; (B) of different age groups (<60 years and ≥60 years); (C) with and without interstitial lung disease (ILD); (D) with and without pulmonary infection; (E) with and without malignancy; (F) with and without arterial hypertension; (G) with and without dysphagia; (H) having different myositis subsets (DM, dermatomyositis; PM, polymyositis; CADM, clinical amyopathic DM); (I) with and without heliotrope rash; (J) with and without Gottron's papules

TABLE 5 Univariate and multivariate logistic regression analyses of risk factors for ILD in IIM patients

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Gender (F/M)	0.897	0.545-1.476	.669	1.053	0.516-2.147	.887
Age at disease onset						
<30 years	-	-	.004**	-	-	**.004****
30-60 years	6.288	2.339-16.910	<.001***	**12.593**	**2.454-64.631**	**.002****
>60 years	5.000	1.682-14.863	.004**	**21.211**	**3.552-126.653**	**.004****
Fever	1.860	1.137-3.045	.014*	0.799	0.389-1.639	.540
Pulmonary infection	2.156	1.330-3.495	.002**	1.466	0.745-2.884	.268
Myalgia	0.607	0.380-0.970	.037*	1.541	0.782-3.038	.212
Arthralgia	1.626	1.017-2.600	.042*	1.059	0.554-2.024	.863
Heliotrope rash	0.802	0.496-1.297	.368			
Gottron's papule	1.686	1.055-2.695	.029*	**2.342**	**1.112-4.935**	**.025***
V sign	0.566	0.331-0.969	.038*			
Malignancy	0.308	0.099-0.959	.042*	0.386	0.092-1.620	.193
Anti-Ro-52 antibody	3.038	1.841-5.012	<.001***	**2.560**	**1.321-4.964**	**.005****
Anti-Jo-1 antibody	3.556	1.587-7.967	.002***	2.083	0.699-6.208	.188
Albumin	0.895	0.855-0.938	<.001***	**0.915**	**0.857-0.978**	**.009****
Globulin	1.045	1.009-1.083	.014*			
IgG	1.111	1.051-1.174	<.001***			
IgM	1.627	1.132-2.339	.009*	**1.930**	**1.203-3.096**	**.006****
LDH	1.000	0.999-1.000	.499			
ESR	1.009	0.999-1.019	.083			
NLR	0.999	0.969-1.030	.959			
Clinical subsets of IIM						
DM	-	-	.357	-	-	.319
PM	0.802	0.468-1.374	.422	1.165	0.449-3.024	.753
CADM	1.538	0.670-3.529	.310	2.443	0.766-7.795	.131

Abbreviations: CADM, clinical amyopathic dermatomyositis; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; F/M, female vs. male; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PM, polymyositis.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

According to several recent studies, the incidence rate of myositis-associated malignancy was about 4.25%-17.2%.[32-34] In our patient cohort, the prevalence of malignancy in association with IIM was relatively low (6.3%) compared to reports from other countries.[32-34] The rate we observed could be an underestimation, since patients in our cohort were not systematically screened for this complication. The prevalence of malignancy in our study was similar to a study by Chang et al. which reported a rate of 8.83% among a cohort of 736

TABLE 6 Univariate and multivariate Cox regression analyses of risk factors for death of IIM patients

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Gender (F/M)	0.853	0.528-1.377	.514	0.914	0.525-1.592	.751
Age at disease onset	1.045	1.025-1.065	<.001***	**1.024**	**1.001-1.047**	**.040***
Pulmonary infection	2.450	1.539-3.898	<.001***	1.406	0.802-2.466	.235
ILD	2.218	1.379-3.569	.001**	**2.215**	**1.261-3.891**	**.006****
Dysphagia	1.795	1.088-2.961	.022*	1.358	0.738-2.498	.325
Heliotrope rash	2.410	1.515-3.835	<.001***	1.565	0.889-2.754	.120
Gottron's papules	1.684	1.056-2.684	.029*	1.089	0.616-1.923	.770
Arterial hypertension	1.808	1.089-3.001	.022*	1.206	0.647-2.247	.556
Malignancy	4.083	2.178-7.654	.001**	**3.889**	**1.589-9.517**	**.003****
Anti-Jo-1 antibody	0.200	0.049-0.816	.025*	0.276	0.064-1.190	.084
PLT	0.997	0.994-1.000	.038*	0.999	0.996-1.002	.522
Lymphocyte count	0.509	0.328-0.790	.003**			
NLR	1.037	1.019-1.056	<.001***	**1.029**	**1.004-1.055**	**.025***
Total protein	0.947	0.920-0.974	<.001***			
Albumin	0.897	0.861-0.935	<.001***	**0.933**	**0.881-0.988**	**.018***
AST	1.001	1.000-1.002	.009*	**1.002**	**1.001-1.003**	**.001****
CK	1.000	1.000-1.000	.721			
LDH	1.000	0.999-1.001	.891			
ESR	1.007	0.999-1.016	.091			
Clinical subsets of IIM						
DM	-	-	.002**	-	-	.287
PM	0.273	0.130-0.571	.001**	0.471	0.174-1.279	.140
CADM	0.659	0.284-1.527	.331	1.185	0.469-2.995	.720

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CADM, clinical amyopathic dermatomyositis; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; F/M, female vs. male; Hb, hemoglobulin; HR, hazard ratio; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; PM, polymyositis.

The variables in bold are those that were statistically significant in the multivariate analysis.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

DM patients (8.83%).[35] Nevertheless, malignancy was the strongest predictor of mortality in our cohort with a HR of 3.889. Malignancy was also the third leading cause of death behind ILD and infection in our cohort. Together, these results indicate that a comprehensive whole-body examination to detect insidious malignancies in patients with IIM should be performed during the early stage of disease.

ILD was identified as a risk predictor for higher mortality of IIM in previous studies,[28,31] which was consistent with findings from our cohort. Similar to other cohorts,[19,28] we found that infection, particularly pulmonary infection, was the predominant cause of death at our center. Indeed, a higher proportion of pulmonary involvements including ILD and infections would increase the risk of respiratory failure despite aggressive treatments, particularly in patients with refractory conditions, such as rapidly progressive ILD (RPILD) with positive anti-MDA5 antibodies. A retrospective study from China focusing on DM/PM patients in the intensive care unit highlighted a substantially poor prognosis of patients with this condition, and noted that the complicated pathogenesis of acute respiratory failure including pulmonary infection and RPILD distinguished IIM as a distinct entity compared with other rheumatic diseases.[36] Our results also revealed that mortality was higher for ILD involving AIP compared to other ILD classifications, although overall there was no difference in clinical features based on radiologic classification of ILD. Therefore, close monitoring and aggressive treatments are

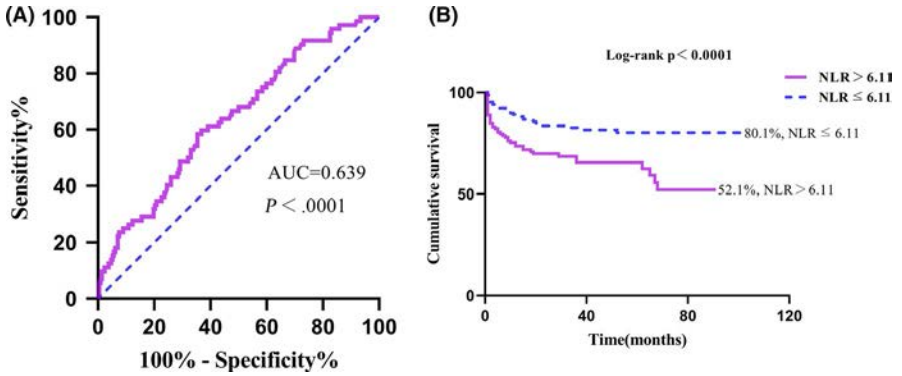

FIGURE 3 (A) Receiver operating characteristic curve for death in idiopathic inflammatory myopathy patients during the follow-up period determined based on NLR; (B) Kaplan-Meier survival curves for patients in the group with NLR ≤6.11 and NLR >6.11. AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio

particularly needed for patients with ILD, especially for those diagnosed with AIP.

Several serum biomarkers such as hypoalbuminemia, NLR and increased levels of AST tended to be associated with poor prognosis in our study, although the relationship was not strong. Our results showed that hypoalbuminemia was independently associated with increased mortality in IIM patients, which was similar to data from other studies.[7,37] As described above, albumin has a number of essential physiological effects for normal health.[23] Persistent inflammation activity and substantial consumption contribute to the increased risk of infections and even malignancy,[35] that can lead to increased mortality. However, the results of continuous data such as serum albumin and AST levels seem to lack substantial clinical implications and may be considered to be less meaningful as they are difficult for clinicians to apply in clinical practice. Therefore, the implications of these findings should warrant attention and be verified by further studies.

NLR has been suggested to be a useful and valuable prognostic biomarker in various disorders, such as cardiovascular and malignant diseases.[38,39] In our study, both univariate and multivariate analyses noted a significant association between NLR and increasing mortality. Thus, we further investigated the predictive value of NLR in the overall survival of IIM patients. In a cohort of 225 PM/DM patients, Ha et al. reported that the optimal threshold for predicting mortality in PM/DM by NLR was 4.775,[7] whereas the cut-off value in our cohort was 6.11. This difference may be caused by different characteristics of the study population and examinations. The Kaplan-Meier curve revealed that mortality of patients with NLR ≥6.11 was significantly higher than that in the control group. Although our data showed that the sensitivity and specificity of NLR for predicting death in IIM patients were comparatively low, measurement of NLR may nonetheless be a useful prognostic biomarker considering its cost-effective value.

Although multivariate analysis did not verify that dysphagia, hypertension, IIM subsets, heliotrope rash and Gottron's papules were independent predictors for mortality in IIM patients, the Kaplan-Meier curve demonstrated that patients with those characteristics did carry a higher risk of death. Several studies noted that dysphagia was an independent predictor of poor prognosis and associated with increased risk for malignancy in IIM patients.[35,40] Dysphagia contributes to an increased risk of infections in IIM patients due to the risk for aspiration and malnutrition. Thus, intensive treatments for patients with dysphagia should be undertaken to increase the quality of life and improve prognosis.

Pairwise comparisons showed a significant difference in mortality between DM and PM subgroups, although no such difference was seen between DM and CADM subsets. A Chi-square test indicated that the proportion of patients in the DM group with baseline NLR ≥6.11 was significantly higher than that in the other 2 groups (46.7% vs. 31.6% for DM vs. PM and 46.7% vs. 30.8% for DM vs. CADM, P =.042). Additionally, the percentage of DM patients who died from infections appeared to be higher than that for the other groups (51.7% vs. 44.4% for DM vs. PM and 51.7% vs. 33.3% for DM vs. CADM). A potential reason for higher risk of death in DM patients may be that these patients have a higher risk of infection compared to PM and CADM patients. The 5-year survival rates in the DM group were significantly lower than that for the PM patients (65.2% vs 90.0%, P < .001), which was similar to results from other cohorts.[2,3,29,41] An earlier study involving a cohort of Swedish patients also indicated that the survival curve descended most rapidly within 1 year of diagnosis.[3] Therefore, careful monitoring and aggressive interventions, particularly for DM patients, are needed during the early stage of disease.

Glucocorticoids (GCs) remain a mainstay for treatment of IIM. However, the infection risk secondary to high-dose GC therapy for primary disease warrants additional attention. Our study suggested that patients treated with methylprednisolone pulse therapy had a higher mortality rate than the controlled for ILD group and there were no significant differences in radiologic classifications of ILD between the 2 groups. Thus, we speculated that the higher mortality rate in patients treated with methylprednisolone pulse was not only related to disease severity, but also to the increased risk of infection secondary to intensive immunosuppressive therapy. Several retrospective studies demonstrated that application of GCs and/or immunosuppressive agents were risk factors for infection in IIM patients.[16,19,42] These results underscore that the need for comprehensive consideration of precautions to prevent secondary infections and the need to control primary disease should be taken into account for clinicians before using high-dose GCs, especially when treating IIM patients with ILD. Further randomized controlled trials

are needed to clarify the efficacy of glucocorticoids in management of IIM.

Our study had several limitations. Due to the retrospective nature of the study, information bias and recall bias were inevitably present. Further, treatment modalities of the entire follow-up periods were not obtained due to the retrospective analysis such that evaluation of the impact of therapies on prognosis was not possible. Data on myositis autoantibody profiles were not available since examinations of microaggregates of albumin were not widely performed until 2018. Last, there was some truncated data in survival analysis and the survival outcomes for several patients needed to be further tracked. Thus, calculating the median survival time of patients was difficult. Future prospective and multicenter studies in which patients are grouped according to the subsets of myositis autoantibody, such as anti-MDA5 antibody, are needed to determine the risk factors associated with ILD and mortality in IIM patients.

5 | CONCLUSION

In summary, this retrospective study enhanced our understanding of the features of IIM-associated ILD and identified patients having high risk for mortality based on clinical characteristics. Age at onset, Gottron's papules, anti-Ro-52 antibodies and elevated serum IgM, as well as hypoalbuminemia were identified as risk factors for IIM-associated ILD. Furthermore, we confirmed age at onset, ILD, malignancy, elevated serum AST and NLR and hypoalbuminemia as predictors for higher mortality in IIM patients. These findings highlight that close surveillance and aggressive treatments may be required for IIM patients having unfavorable predictive factors, especially patients with ILD and malignancy. For future studies, our study might be helpful to provide longitudinal information on the outcome of IIM patients, as well as survival and mortality rates.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, to the interpretation of the results and to the writing of the manuscript. Lingli Dong mainly contributed to the conception and design. Zhiqian Bai analyzed the data and wrote the first draft of the manuscript. Guifen Shen critically revised the article for important intellectual content. All authors read, commented upon and edited various drafts and approved the final version of the manuscript.

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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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Enthesis lesions are associated with X-ray progression in psoriatic arthritis

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Abstract

Objective: To analyze the relationship among enthesis ultrasound (US) lesions and radiological structural damage in psoriatic arthritis (PsA) patients.

Methods: Consecutive PsA patients with swelling of at least 1 of the 2nd to 5th metacarpophalangeal joints were included. Clinical and demographic data were collected. The Madrid Sonographic Enthesitis Index (MASEI) was selected to evaluate the enthesis, with its total score and MASEI-activity and MASEI-structural damage subscores. The modified Sharp van der Heijde method for PsA and the New York criteria for sacroiliitis were selected to evaluate cumulative bone damage on X-rays.

Results: Twenty-seven patients were included. Male gender, older age, longer PsA duration and acute reactant factors were associated with greater bone cumulative damage. Enthesis tendon thickening, enthesophytes, total MASEI and the MASEI-structural damage subscore showed significant correlations with radiographic peripheral and sacroiliac damage scores. Tendon thickening and enthesophytes were the enthesis lesions more frequently associated with radiographic damage in PsA.

Conclusion: The enthesis MASEI score was associated with axial and articular radiographic structural damage in PsA patients. The MASEI-structural damage subscore correlated better with cumulative bone damage in PsA than the MASEI-activity subscore.

KEYWORDS

enthesis, psoriatic arthritis, tendon, ultrasound, X-rays

1 | INTRODUCTION

Psoriatic arthritis (PsA) is a chronic rheumatic inflammatory disease with musculoskeletal and systemic involvement which, due to its potential ankylosing, erosive and deforming behavior, has possible consequences that produce a functional deterioration in quality of life and even a reduction in life expectancy in these patients.[1]

The assessment of PsA disease has improved significantly over the last decade due to the need for reliable measures for clinical trials. However, currently, the evaluation of PsA remains complex since it is a multidomain disease including joint, enthesis, dactylitis, spine, skin and nail involvement, with all of these elements having different behaviors in each patient and at different times throughout their follow-up. These facts make the assessment of PsA disease activity a difficult challenge.

One of the cornerstone domains in the pathogenesis of PsA is enthesis,[2-4] but, to date, it is probably the least used domain. Several clinical enthesitis scoring measures have been developed[5-10] based

on a standard enthesis palpation approach, but all of them have shown a lack of sensitivity, specificity and reliability.[11] In patients with PsA, among all these clinical scoring measures, the Leeds Enthesitis Index (LEI)[8] is the unique index that has been developed and validated specifically for this disease[4] and the index that correlates most consistently with clinical parameters of disease activity,[12] but it has the limitation of low number of explored entheses (6), and it is not validated compared to objective outcomes.

The clinical limitations of enthesis evaluation have led to the emerging importance of imaging techniques such as ultrasound (US), which seems to be the preferred imaging method for the detection of enthesitis as it is feasible and allows an accurate morphostructural assessment of entheses, including the identification of new bone formation, erosions, enthesis tendon structural changes, as well as enthesis vascularization.[13] However, the use of US in the assessment of PsA enthesis involvement still has to gain positions in clinical practice, and to achieve this it is necessary to increase its validity evidence in front of other clinical and imaging measures accepted as being representative of the condition of the patients. Consequently, the aim of this study was to explore in PsA patients the relationship among the presence of active and structural damage enthesis lesions by US examination, and the radiological structural damage of peripheral and sacroiliac joints by X-rays.

2 | PATIENTS AND METHODS

2.1 | Study population

This study is a post hoc analysis of a previous study from our group[14] in which consecutive non-selected PsA patients fulfilling Classification Criteria for Psoriatic Arthritis[15] with clinical swelling of at least 1 of the 2nd to 5th metacarpophalangeal joints (MCPj) were included. In addition to the MCPj assessment, we performed an enthesis US exam using the Madrid Sonographic Enthesitis Index (MASEI).[16] Clinical examination was performed by a rheumatologist before US assessment. Patients <18 years and those with explanations other than PsA for MCPj swelling were excluded. Demographic, clinical, radiographic and laboratory data were collected. The study was approved by the local ethics committee (Hospital Clínico Valladolid, PI 15-275). Written informed consent was obtained from all patients according to the Declaration of Helsinki.

2.2 | Ultrasound settings

Ultrasound enthesis examinations were performed by an expert rheumatologist blinded to the clinical data. A MyLab 70 XVG machine (Esaote SpA) with a 13 MHz linear transducer was used. Power Doppler (PD) settings were as follows: pulse repetition frequency 750 Hz, wall filter 3, persistence 4 and Doppler frequency 7.1 MHz. Color gain was set just below the level of noise. Three- to 5-second videos were recorded for a posterior reliability assessment.

2.3 | Enthesis ultrasound assessment

As previously reported,[14] the 6 entheses included in the MASEI (bilateral triceps, quadriceps, proximal and distal patellar and Achilles tendons and the proximal insertion of the plantar aponeurosis) and the elementary lesions included (structure, thickening, erosion, enthesophyte, PD and bursa) were evaluated in longitudinal and transverse views. In addition to the MASEI PD item (defined as PD signal in the cortical bone profile, intratendon or bursa on the enthesis insertion area), the Outcome Measures in Rheumatology (OMERACT) definition for PD in entheses (PD signal at enthesis ≤2 mm to the cortical bone profile insertion)[17] was also evaluated as being present or absent. Reliability assessment was performed among 3 readers, finding[14] good to excellent MASEI inter-reader reliability (intraclass correlation coefficient [ICC] 0.918, 95% CI 0.846-0.960), and the PABAK (prevalence-adjusted and bias-adjusted kappa) values for each elemental enthesis lesion were as follows: 0.547 for structure, 0.699 for thickening, 0.950 for erosion, 0.399 for calcification, 0.888 for bursa, 0.860 for PD MASEI and 0.864 for PD OMERACT.

In addition, we added to the analysis 2 subtypes of MASEI based on previous publications:[18-20] the MASEI-activity (structure, thickening, PD and bursa) and MASEI-structural damage (erosion and enthesophyte) subscores.

2.4 | Radiographic joint and sacroiliac damage assessment

Peripheral joint damage was assessed by an expert rheumatologist (ACV) with hand and foot X-rays using the modified Sharp van der Heijde (SvdH) method for PsA.[21,22] According to this method, the maximum score for erosions in the hands is 200 points and in the feet is 120 points, and the maximum score for joint space narrowing in the hands is 160 points and in the feet is 48 points; thus, the possible maximum score is 528.

Radiographic sacroiliitis was scored by an expert rheumatologist (EDM) with sacroiliac X-rays according to the modified New York (NY) 1984 criteria.[23]

2.5 | Statistical analysis

Quantitative variables are given as the mean (SD). Student's *t* test for independent samples was used to compare continuous variables, and the Chi-squared test was used for qualitative variables. Correlations were calculated with Spearman's rho test. SPSS version 20 (SPSS Inc.) was used for statistical analysis.

3 | RESULTS

3.1 | Baseline characteristics

Twenty-seven PsA patients were included. Demographic, clinical and radiological characteristics are summarized in Table 1. The mean MASEI score was 30.62 ± 13.89. The most prevalent enthesis lesions in our sample were detected for the structure, enthesophytes and thickening items (in descending order). All patients had available hand and foot X-rays from the last year. Twenty-six (96%) had available sacroiliac X-rays.

TABLE 1 Characteristics of the patients

Demographics	
Patients	27
Men (%)	17 (63)
Women (%)	10 (37)
Age, y ± SD	56 ± 11
Disease information	
Disease duration, mo ± SD	109 ± 101
Peripheral PsA (%)	21 (78)
Axial and peripheral PsA (%)	6 (22)
Swollen MCPj, mean ± SD	2.2 ± 1.4
CRP mg/L, mean ± SD	8.3 ± 8.2
ESR mm/h, mean ± SD	21.9 ± 19.3
DAS28 CRP, mean ± SD	3.6 ± 0.9
DAS28 ESR, mean ± SD	3.9 ± 1.2
MASEI, mean ± SD	30.6 ± 13.9
Current treatment	
Steroids n (%)	6 (22.2)
NSAIDs n (%)	12 (44.4)
DMARDs n (%)	19 (70.4)
Biologics n (%)	3 (11.1)
Radiographic evaluation	
Sacroiliitis NY criteria n (%)	7 (26.9)
Modified SvdH score (mean ± SD)	104.9 ± 73.2
Hand space narrowing score	55.5 ± 23.7
Feet space narrowing score	9.7 ± 9.9
Total narrowing score	65.2 ± 29.7
Hand erosion score	24.2 ± 33.1
Feet erosion score	11.6 ± 14.8
Total erosion score	35.8 ± 44.1

Note: Sacroiliac X-rays were available in 26 patients. CRP, ESR and their respective DAS28 calculations were available in only 18 patients.

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MCPj, metacarpophalangeal joint; NSAID, nonsteroidal anti-inflammatory drug; NY, New York; PsA, psoriatic arthritis; SD, standard deviation; SvdH, Sharp van der Heijde.

3.2 | Association between radiographic sacroiliitis and clinical, US and radiographic items

Radiographic sacroiliitis based on NY criteria in PsA patients was associated with male gender ($P = .014$). The rest of the results are shown in Table 2.

Radiographic sacroiliitis in PsA was associated with enthesis involvement in terms of total MASEI, 3 of its lesions (structure, thickening and enthesophytes) and both of its subtypes (the MASEI-activity and MASEI-structural damage subscores). The association of radiographic sacroiliitis with peripheral joint damage was found with the modified SvdH hand erosion score and total erosion score. Radiographic sacroiliitis did not show any association with any clinical item.

3.3 | Association and correlation analysis between peripheral radiographic damage and clinical and US items

Joint space narrowing was associated and positively correlated with age, acute reactant factors, total MASEI, 2 MASEI elemental lesions (thickening and enthesophytes), and the MASEI-structural damage subtype.

Joint erosion was associated and positively correlated with PsA duration, male gender, and in terms of entheses with total MASEI, 4 MASEI items (structure, thickening, erosion and enthesophytes) and the MASEI-structural damage subtype. Some items were only correlated with the modified SvdH foot erosion score (PD OMERACT, MASEI-activity and age) and other items with the modified SvdH hand erosion score (swollen MCPj).

The total modified SvdH score was positively correlated with age, PsA duration, total MASEI, 4 MASEI components (structure, thickening, erosion and enthesophytes), and the MASEI-structural damage subscore.

The results are shown in Table 3.

4 | DISCUSSION

In PsA patients, tendon thickening and enthesophytes are the enthesis lesions most frequently associated with radiographic peripheral and sacroiliac damage, followed by tendon structure and erosions. However, PD, being the hallmark of inflammation in entheses, is scarcely related.

Multiple publications point out enthesis as having a key role in the pathogenesis of PsA. Today, the main evaluation of enthesis is the clinical approach despite the emerging utility of imaging techniques such as US. However, entheseal clinical scores used in medical practice do not have good correlation with disease activity and structural damage measures at the patient level. This was the starting point of this study, trying to explore the construct validity

TABLE 2 Association between radiographic sacroiliitis and clinical and peripheral (joint and enthesis) ultrasound and radiographic items

	Radiographic sacroiliitis (New York criteria)		
	Present	Absent	*P* value
Age	57.85 ± 11.20	56.16 ± 10.47	.734
PsA duration	149.28 ± 101.63	95.16 ± 101.55	.254
CRP	5.57 ± 3.31	8.63 ± 9.17	.223
ESR	22.43 ± 20.03	21.31 ± 20.07	.902
DAS28 CRP	3.59 ± 0.33	3.61 ± 1.15	.962
DAS28 ESR	4.02 ± 0.77	3.78 ± 1.51	.666
Swollen MCPj	1.86 ± 0.69	2.26 ± 1.59	.375
MASEI	45.00 ± 15.92	25.21 ± 9.10	.016*
Structure MASEI	9.14 ± 2.54	6.47 ± 2.69	.039*
Thickness MASEI	8.14 ± 2.61	4.37 ± 2.89	.008*
Erosion MASEI	5.57 ± 7.63	0.79 ± 1.68	.150
Enthesophytes MASEI	8.86 ± 2.41	5.94 ± 2.55	.021*
Bursa MASEI	0.57 ± 0.79	0.26 ± 0.45	.358
PD MASEI	8.14 ± 6.87	6.31 ± 5.09	.538
PD OMERACT	2.00 ± 1.82	1.05 ± 1.02	.233
MASEI-activity	26.00 ± 8.50	17.42 ± 7.66	.042*
MASEI-structural damage	14.43 ± 7.87	6.74 ± 3.62	.042*
Hand joint space narrowing score	62.57 ± 27.56	51.57 ± 22.07	.367
Feet joint space narrowing score	16.28 ± 12.13	7.79 ± 8.20	.124
Total joint space narrowing score	78.86 ± 35.46	59.37 ± 27.13	.221
Hand erosion score	55.57 ± 47.54	10.58 ± 12.96	.046*
Feet erosion score	21.86 ± 17.41	8.31 ± 12.54	.094
Total erosion score	77.43 ± 62.24	18.89 ± 22.13	.048*
Modified Sharp van der Heijde score	163.43 ± 98.74	81.16 ± 49.73	.072

Note: The results are expressed as the mean ± standard deviation. A *P* value <.05 was considered statistically significant and is marked with a star and bold values. Only 8 bursae were found in the sample. Sacroiliac X-rays were available in 26 patients.

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; MASEI, Madrid Sonographic Enthesitis Index; MCPj, metacarpophalangeal joint; OMERACT, Outcome Measures in Rheumatology; PD, power Doppler; PsA, psoriatic arthritis.

of enthesis US examination in front of another imaging technique, X-rays. The increase in the modified SvdH score is accepted in PsA patient clinical trials and clinical follow-up as a defined damage progression measure, in the same way that it is accepted for the NY score for sacroiliac joints.

To date, 5 studies[18,20,24-26] have explored the relationship between entheses and radiographic damage in SpA, 2 of which are focused on PsA.[20,24] The study performed by Polachek et al.[20] is similar to ours in terms of patients (long-duration PsA), enthesis US index (MASEI), and X-ray evaluation (in terms of locations, but they selected the modified Steinbrocker score). The results of both studies are similar, as both demonstrate that in PsA, the MASEI and its activity and structural damage subscores are associated with a peripheral joint damage score. But one difference is that we found an association between sacroiliitis and both inflammatory and chronic enthesis damage subscores, while Polachek et al.[20] found an association only with the latter items. A possible explanation is that our sample had greater peripheral involvement than theirs.

El Miedany et al.[24] identified potential early PsA structural joint damage prediction factors using the GUESS (Glasgow Ultrasound Enthesitis Scoring System) index, articular US, the modified SvdH score and sacroiliac X-rays. They found an increased probability for structural progression over 1 year related to PD at entheses and total GUESS score.

Cobo et al.[25] and Falcao et al.[26] evaluated on early SpA the association of the BASRI (Bath Ankylosing Spondylitis Radiology Index) with the MASEI, only on the Achilles enthesis in the Falcao et al. study. None of them found any association, but Cobo et al. found greater BASRI progression over a year in patients with a basal MASEI score ≥18.

Finally, in ankylosing spondylitis patients, in contrast to our findings on PsA, Alcalde et al.[18] did not find any association between enthesis chronic lesions (erosions and calcifications) and sacroiliitis but the structural damage enthesis subscore in this case was different.

The existence of local inflammation is probably the cause of joint and enthesis structural damage in PsA. However, in our study we found that PD, even being the hallmark of inflammation in entheses, was barely related with structural damage in sacroiliac joints and with the modified SvdH PsA score. Our explanation of this finding is that enthesis and joint Doppler signal are indicators of current active inflammation, in contrast to structural damage that is the result of an accumulated injury resulting from previous inflammation. In our opinion, this is the explanation of the better correlation of enthesophytes and the MASEI-structural damage subscore with radiographic peripheral and sacroiliac damage seen in our series, also supported by the findings of El Miedany et al.[24] It is possible that in early PsA patients, like the ones of their sample, the initial enthesis changes could be related with recent inflammatory activity, a different pattern than seen in patients with a longer disease evolution with greater structural damage.

As previously reported,[27-29] male gender, older age, longer PsA duration and higher acute reactant factors also demonstrated a relationship with higher structural damage scores in our series.

Our study has some limitations. One of them was that the stratification of enthesis US lesions into inflammatory lesions (enthesis structure, thickening, bursa, and PD) and chronic/structural lesions (enthesis erosion and enthesophyte/calcification) is not totally

TABLE 3 Correlation analysis between modified Sharp van der Heijde score for PsA and clinical and peripheral (joint and enthesis) ultrasound items

	Modified Sharp van der Heijde score for PsA						
	Hand joint space narrowing score	Feet joint space narrowing score	Total joint space narrowing score	Hand erosion score	Feet erosion score	Total erosion score	Total score
MASEI Rho/*P* value	+.314/.111	+.502/.008*	+.405/.036*	+.508/.007*	+.540/.004*	+.584/.001*	+.538/.004*
MASEI structure Rho/*P* value	+.296/.134	+.343/.080	+.358/.067	+.464/.015*	+.444/.020*	+.522/.005*	+.493/.009*
MASEI thickness Rho/*P* value	+.370/.058	+.311/.114	+.406/.036*	+.567/.002*	+.459/.016*	+.612/.001*	+.532/.004*
MASEI erosion Rho/*P* value	+.299/.130	+.223/.263	+.307/.119	+.404/.036*	+.310/.116	+.414/.032*	+.426/.027*
MASEI enthesophytes Rho/*P* value	+.559/.002*	+.607/.001*	+.676/.001*	+.612/.001*	+.573/.002*	+.692/.001*	+.754/.001*
MASEI bursa Rho/*P* value	−.333/.090	+.099/.624	−.237/.234	−.166/.407	−.115/.568	−.169/.399	−.170/.396
PD MASEI Rho/*P* value	−.076/.708	+.092/.649	−.072/.722	−.047/.817	+.199/.319	+.011/.957	−.042/.836
PD OMERACT Rho/*P* value	+.024/.906	+.182/.363	+.031/.879	+.091/.651	+.406/.036*	+.173/.389	+.088/.662
MASEI-activity Rho/*P* value	+.171/.394	+.378/.052	+.245/.218	+.305/.122	+.439/.022*	+.398/.040*	+.346/.077
MASEI-structural damage Rho/*P* value	+.498/.008*	+.580/.002*	+.589/.001*	+.539/.004*	+.539/.004*	+.613/.001*	+.677/.001*
CRP Rho/*P* value	+.359/.066	+.386/.047*	+.428/.026*	+.104/.605	+.078/.698	+.137/.496	+.287/.146
ESR Rho/*P* value	+.196/.326	+.268/.177	+.243/.222	+.031/.880	+.045/.822	+.060/.768	+.199/.320
DAS28 CRP Rho/*P* value	+.079/.757	−.097/.702	+.094/.711	−.094/.709	−.174/.491	−.029/.909	+.144/.570
DAS28 ESR Rho/*P* value	+.032/.900	+.049/.847	+.053/.836	−.094/.709	−.069/.785	−.044/.861	+.128/.612
Swollen MCPj Rho/*P* value	+.309/.117	−.127/.527	+.202/.313	+.396/.041*	+.170/.398	+.359/.066	+.270/.173
Age Rho/*P* value	+.364/.062	+.533/.004*	+.455/.017*	+.225/.259	+.460/.016*	+.341/.081	+.428/.026*
PsA duration Rho/*P* value	+.358/.067	+.135/.503	+.331/.091	+.512/.006*	+.316/.109	+.478/.012*	+.428/.026*

Note: Rho is the Spearman rho value. A *P* value <.05 was considered statistically significant and is marked with a star and bold values. Only 8 bursae were found in the sample.

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; MASEI, Madrid Sonographic Enthesitis Index; MCPj, metacarpophalangeal joint; OMERACT, Outcome Measures in Rheumatology; PD, power Doppler; PsA, psoriatic arthritis.

validated but based on 3 previous publications[18-20] and another that showed that only inflammatory enthesis lesions respond to anti-tumor necrosis factor therapy.[30] Another limitation was the small sample size, but having achieved significant results with this sample makes us think that the results could probably improve with a bigger cohort. Finally, clinical enthesis data were not available, and the percentage of patients with sacroiliitis was fair.

In conclusion, in PsA patients, an association between enthesis involvement and sacroiliac joint structural damage was found. The association between hand and foot X-ray joint space narrowing and erosions and the enthesis MASEI-structural damage subscore showed in this study could support the central pathophysiological role of entheses in the assessment of a multidomain disease like PsA.

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ORIGINAL ARTICLE

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The infrapatellar fat pad produces interleukin-6-secreting T cells in response to a proteoglycan aggrecan peptide and provides dominant soluble mediators different from that present in synovial fluid

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Abstract

Objective: The purpose of this study was to investigate the effects of osteoarthritis (OA) peripheral blood mononuclear cell (PBMC) -stimulating proteoglycan aggrecan peptides on T cells present in infrapatellar fat pads (IPFPs) and synovial tissues, and to correlate these findings with mediators present in synovial fluid of OA patients.

Methods: We tested for interleukin-6 (IL-6) -producing T cells in IPFPs of patients with knee OA using ELISPOT. Cytokine and cytotoxic mediator production from OA PBMCs, IPFPs, synovial tissues, and synovial fluids in response to proteoglycan aggrecan peptides were quantified by cytometric bead array. Patterns of cytokine and cytotoxic mediator production were analyzed and compared.

Results: T cells from IPFPs elicited strong responses towards the p263-280 peptide by secreting IL-6. In addition, there was a trend that the p263-280 peptide stimulated higher production of cytokines/cytotoxic mediators than other proteoglycan aggrecan peptides, although this was not statistically significant. In patients with knee OA, a group of cytotoxic mediators (sFas, perforin, granzyme A, and granulysin) and IL-6 were detectable at high levels from the synovial fluid. In addition, inflammation in patients with knee OA was more pronounced in joint-surrounding tissues than levels in circulating peripheral blood.

Conclusion: Our data suggest that T cells responding to the p263-280 peptide contribute to the secretion of various soluble mediators that are found within the synovial fluid. We also identified potential new candidates that may serve as biomarkers of knee OA.

KEYWORDS

inflammation, infrapatellar fat pad, osteoarthritis, proteoglycan aggrecan peptides, synovial tissue

1 | INTRODUCTION

Osteoarthritis (OA) is a disease accompanied by inflammation of the joint and surrounding tissues that debilitates the quality of life with chronic pain and decreased mobility.[1-3] Disease pathology includes cartilage destruction, osteophyte formation, joint space narrowing, and immune cell infiltration.[4]

Evidence of adaptive immune response involvement in OA arises from the presence of T-cell infiltration in synovial fluid, synovial membrane linings, and infrapatellar fat pads (IPFPs) in OA patients.[5] Both $CD4^+$ and $CD8^+$ T cells have been shown in anterior cruciate ligament-transection mouse models to have a role in the development and progression of OA.[6-10] T cells respond to antigens through clonal selection and expansion, resulting in antigen-specific T-cell clones.[11] An oligoclonal pattern of T-cell receptor-β-chain usage in the synovial membrane has been described, suggesting an antigen-driven response by these T cells.[12,13] Proposed antigens include type II collagen and proteoglycan (PG) aggrecan.[14,15]

Proteoglycan aggrecan is a macromolecule synthesized by chondrocytes of the cartilage and is prone to degradation in response to catabolic stimuli of arthritic conditions.[16] The increase in PG aggrecan degradation results from increased matrix metalloproteinases (MMPs and ADAMTS4/5) in the joint.[17,18] The structure of PG aggrecan that stimulated peripheral blood mononuclear cells (PBMCs) was confined to the (bovine) G1 domain of which the keratin sulfate portion had been enzymatically removed.[14] Recently, de Jong et al tested PG aggrecan-specific peptides that were previously predicted from experiments with human HLA-transgenic mice on an arthritis-susceptible background[19] and showed that PBMCs from OA patients significantly responded to certain peptide fragments of PG.[15] These OA PBMC-stimulating PG peptides include the p16-31 and p263-280 peptide fragments.[15]

The IPFP is an adipose tissue situated beneath the patella and resides adjacent to the knee joint space within the capsule, which is infiltrated by immune cells, eg T cells, in patients with knee OA.[5,20] The synovial tissue lines the non-articulating surfaces of the joints and is in direct contact with the synovial joint.[21] The IPFP and synovial tissue are tissues that encapsulate the knee joint and function as a morpho-functional unit, in that there is mutual interaction between the two tissues in OA pathology.[22] OA IPFPs exhibit increased inflammation, and higher vascularity and fibrosis than their control groups.[23,24] In addition, it was observed that both IPFPs and synovial membranes showed increased inflammatory features simultaneously and IPFPs can secrete mediators to the cartilage and synovial membrane in an endocrine-paracrine/autocrine-like fashion; and subsequently may affect the quality of synovial fluid secreted by the synovial membrane.[22]

Therefore, in our study, we investigated how these OA PBMC-stimulating PG aggrecan peptides (p16-31 and p263-280 peptide fragments including a control p2379-2384 peptide fragment) affect T cells that were present in IPFPs and synovial tissues and correlated these findings with mediators present in synovial fluid of OA patients.

2 | MATERIALS AND METHODS

2.1 | Patient recruitment and sample collection

Infrapatellar fat pads, synovial tissues, synovial fluids, and peripheral blood were collected from patients with knee OA undergoing total knee arthroplasty at King Chulalongkorn Memorial Hospital. All selected patients were aged over 60 years with unilateral or bilateral knee effusion and had been evaluated to have moderate to severe OA. Patients with other joint diseases, such as rheumatoid arthritis, were excluded. All samples were obtained after patients provided informed consent in accordance with the ethical standard and approval of the Faculty of Medicine, Chulalongkorn University Institutional Review Board (IRB no. 497/60) and the Declaration of Helsinki. Demographic characteristics and clinical data of OA patients used in the study are shown in Table S1. Demographic and clinical data of OA patients (n = 30) showed mean ±SD of age, weight, height, and body mass index, while gender, treatment methods, and co-morbidities of the patients were shown as percentage or frequency (Table S1).

2.2 | Mononuclear cell isolation

The PBMCs were isolated from peripheral blood using density gradient centrifugation. Whole blood was diluted with RPMI-1640 (ratio 1:1) (Gibco, Life Technologies, Paisley, UK) and layered on to Ficoll-Paque (GE Healthcare, Uppsala, Sweden). Samples were centrifuged at 524 *g* without deceleration for 30 minutes at room temperature. Cells were collected and washed twice with RPMI-1640 supplemented with 10% fetal bovine serum (FBS) (Gibco, Life Technologies). PBMCs were cryopreserved in freezing media (10% dimethylsulfoxide [DMSO; PanReac AppliChem, An ITW Company, Darmstadt, Germany] in 90% FBS [Gibco, Life Technologies]) until experiments were performed. For mononuclear cell isolation from IPFPs and synovial tissues, tissue samples were soaked in phosphate-buffered saline (PBS) buffer (Gibco, Life Technologies), cut into 2×2 mm^2 pieces and digested with type IV collagenase (3 μg/mL) (Worthington Biochemical Corporation, Lakewood, NJ, USA) and DNase I (0.1 μg/mL) (Worthington Biochemical Corporation) in PBS containing 5% FBS with shaking at 600 *g*, 37°C for 90 minutes. Supernatant was filtered through a 40-μm filter and washed with RPMI-1640-containing 10% FBS. Cells were cryopreserved in freezing media (10% DMSO in 90% FBS) until experiments were performed.

2.3 | Magnetic bead T-cell enrichment

T cells were magnetically purified from peripheral blood using positive selection with anti-human CD3 microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany) according to the manufacturer's instructions. Briefly, 5×10^6 PBMCs were labeled with anti-human

CD3 microbeads for 15 minutes at 4°C. Cells were washed with buffer and applied onto a magnetic column (LS) (Miltenyi Biotec). PBS buffer was added to the column to elute unbound cells. The magnetically labeled T cells were eluted after removal of the magnet from the column and collected for further experiments. Enrichment of T cells was validated by cell surface labeling with anti-human CD3-fluorescein isothiocyanate, anti-human CD4-allophycocyanin/Cychrome7 and anti-human CD8-AlexaFluor700 antibodies (BioLegend, Hercules, CA, USA) at 4°C for 20 minutes. Cells were washed with FACS buffer (PBS buffer containing 2% FBS), fixed with 1% formaldehyde and acquired on the BD LSRII flow cytometer (BD Biosciences, San Jose, CA, USA). Data were analyzed using the FlowJo software (Tree Star Inc., Ashland, OR, USA).

2.4 | Peptide preparation

Proteoglycan aggrecan peptides including p16-31 (QPSPLRVLLGTSLTIP), p263-280 (TTGHVYLAWQAGMDMCSA), p2379-2394 (LQKRSSRHPRRSRPST) and ovalbumin (OVA p323-p339: ISQAVHAAHAEINEAGR), based on De Jong et al,[15] was purchased from Genscript company (Piscataway, NJ, USA). CEF peptide (cytomegalovirus, Epstein-Barr virus and influenza virus peptide pool) were purchased from CTL (Cellular Technology Limited, Shaker Heights, OH, USA). Peptides were synthesized by solid-phase peptide synthesis method at 95% purity. Lyophilized peptides were resuspended in DMSO (PanReac AppliChem) and diluted to 10 μg/μL in concentration with RPMI-1640 medium. Possible endotoxin contamination was tested before using in experiments. All peptides confirmed negative endotoxin contamination.

2.5 | Interleukin-6 ELISPOT

Interleukin-6 (IL-6) production was determined using Human IL-6 Elispot Antibody Pair kit (Merk Millipore, Billerica, MA, USA). Plates were coated with IL-6 capture antibody (10 μg/mL) overnight at 4°C and blocked with RPMI-1640 containing 10% FBS for 2 hours at 37°C. After washing the plate with PBS buffer, IPFP isolated cells (1×10^5 cells/well) were added and treated with 10 μg/mL of PG peptides (p263-280 peptide or control p2379-2394 peptide) (GenScript) or 50 ng/mL of phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich, St. Louis, MO, USA) and 500 ng/mL ionomycin (Thermo Fisher Scientific, Eugene, OR, USA) for 48 hours. Cells were washed with PBS containing 0.01% Tween-20 (Anatrace, Maumee, OH, USA) six times and incubated with biotinylated detection antibody (2 μg/mL) for 2 hours. Streptavidin-conjugated alkaline phosphatase enzyme was added and incubated for 45 minutes. Afterwards, BCIP/NBT (5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium (Mabtech, Nacka Strand, Sweden)) substrate was added to the wells. Spot development was stopped after 10 minutes using distilled water and plates were analyzed using an Immunospot S6 analyzer (Cellular Technology Limited).

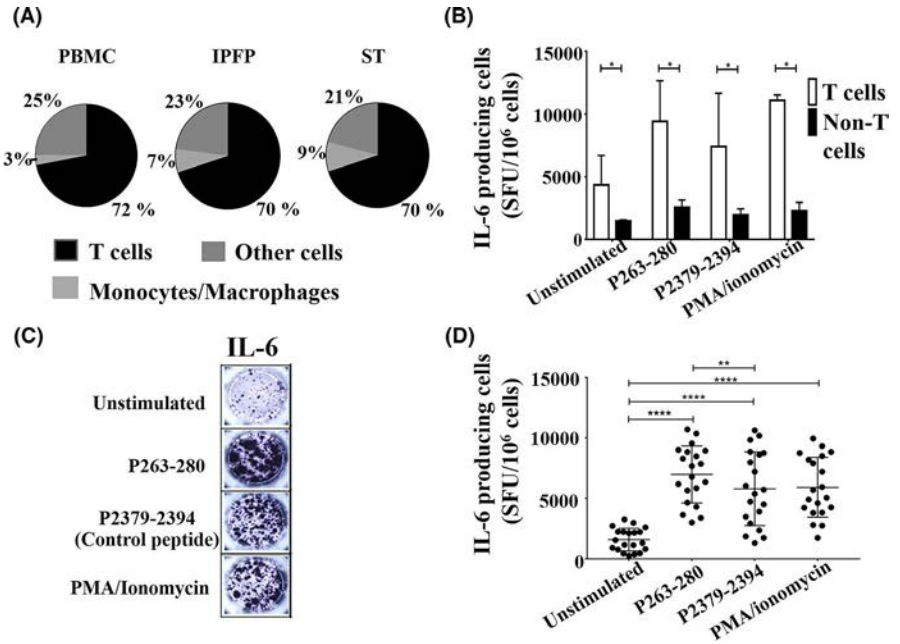


FIGURE 1 Infrapatellar fat pad (IPFP) T-cell responses to proteoglycan aggrecan peptides (A) Pie charts comparing the proportion of T cells, macrophages and other cell compartments in peripheral blood mononuclear cells (PBMC), IPFPs, and synovial tissues (ST) of individuals; (B) Bar graphs showing interleukin-6 (IL-6) production from sorted T cells (white bars) and non-T cells (black bars) isolated from a sample of pooled IPFPs (N = 5) in response to proteoglycan aggrecan peptides; (C) ELISPOT showing IPFP cell responses (unsorted) to proteoglycan aggrecan peptides (p263-280 and p2379-2394) and phorbol 12-myristate 13-acetate (PMA)/ionomycin; (D) Dot plot showing IL-6 production of IPFP cells (unsorted) of patients with knee osteoarthritis in response to proteoglycan aggrecan peptides (p263-280 and p2379-2394) and PMA/ionomycin (N = 20); Error bars are shown as mean ±SEM; ****$P < 0.0001$; ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$

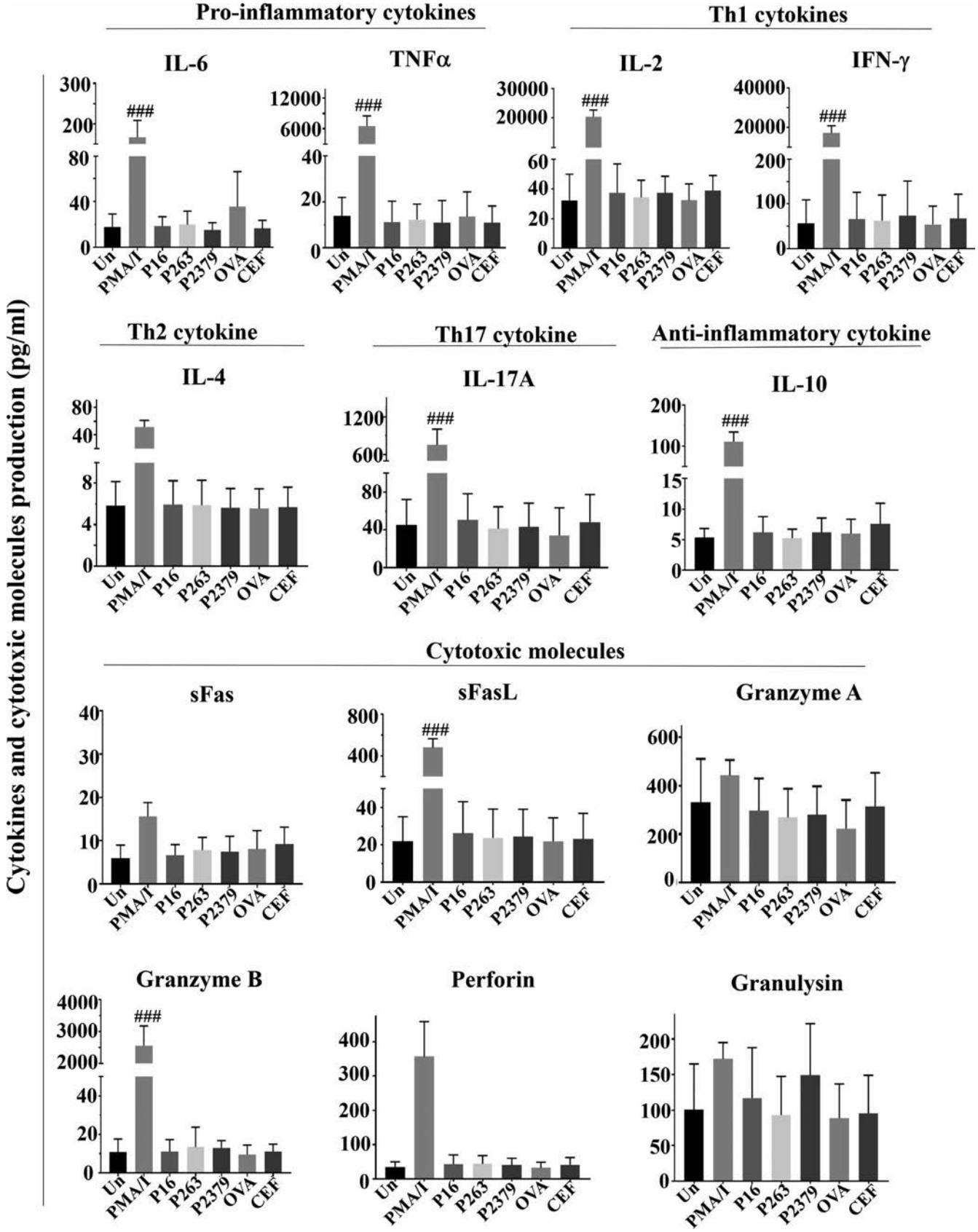


FIGURE 2 Cytokine and cytotoxic molecule levels from peripheral blood mononuclear cells (PBMCs) of patients with knee osteoarthritis (OA) in response to proteoglycan aggrecan peptides. Bar graphs showing levels of cytokines and cytotoxic molecules from PBMCs stimulated with proteoglycan aggrecan peptides (p16-31, p263-280, and p2379-2394), ovalbumin peptide (OVA), CEF peptides, and phorbol 12-myristate 13-acetate/ionomycin (PMA/I) (N = 11). Cytokines and cytotoxic molecules production were determined using cytometric bead array (CBA) and error bars are shown as mean ±SEM (****$P < 0.0001$; ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$) (### indicates significant difference with all conditions at $P < 0.001$)

2.6 | Proteoglycan aggrecan T-cell stimulation

Cells (8×10^4 cells/well) were treated with 10 μg/mL of PG aggrecan peptides (p16-31, p263-280, or p2379-2394); OVA p323-339 (10 μg/mL) (PG peptides and OVA peptide from GenScript); CEF peptide (5 μg/mL) (Cellular Technology Limited); and 50 ng/mL of PMA (Sigma-Aldrich) and 500 ng/mL of ionomycin (Thermo Fisher Scientific) for 48 hours. Supernatant was collected to further determine cytokine concentration via cytometric bead array (CBA) (BioLegend).

2.7 | Ex vivo determination of cytokines and cytotoxic mediators

PBMCs, IPFP cells or synovial tissue cells (8×10^4 cells/well) were cultured in a 96-well plate for 48 hours without adding any stimuli. Supernatant was collected to further determine cytokine concentration via CBA (BioLegend).

2.8 | Cytometric bead array

The human CD8/NK cell (13-plex) LEGENDplex™ panel kit (BioLegend) was used to determine the concentrations of IL-2, IL-4, IL-6, IL-10, IL-17A, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), granzyme A, granzyme B, perforin, granulysin, soluble Fas (sFas), and sFas ligand (sFasL). Briefly, supernatant was mixed with assay buffer at a ratio of 1:1 and incubated with antibody-coated beads with shaking at 84 *g* for 2 hours at room temperature. Streptavidin-phycoerythrin was added and incubated with shaking for 30 minutes at room temperature. Beads were then washed twice with wash buffer and centrifuged at 1000 *g* for 5 minutes. Samples were acquired on the BD FACSCalibur flow cytometer (BD Biosciences) and analyzed with LEGENDPLEX software (BioLegend).

2.9 | Statistical analyses

All statistical analysis was calculated using GRAPHPAD PRISM 8 statistical software (GraphPad Software Inc., San Diego, CA, USA). The continuous data were summarized using descriptive statistics and were expressed in mean ± SD or percentage and frequencies (%, (n)). Comparisons of cytokine production between T cells and non-T cells were performed using paired *t* test. Response to peptides between two groups of samples was compared by unpaired *t*-test. One-way or two-way analyses of variance with post hoc Bonferroni's multiple comparison tests were used to compare cytokine production or peptide response between multiple groups. Statistical significance was indicated by a *P* value less than 0.05. Data were shown as mean ± standard error of the mean.

3 | RESULTS

3.1 | The PG aggrecan p263-280 peptide induced IPFP T cells to secrete IL-6

Interleukin-6-producing T cells have been reported in adipose tissue and IPFPs.[25,26] In order to investigate T-cell responses within the knee joint, we first tested our system for IL-6-secreting cells isolated from IPFPs of 20 patients with knee OA in response to representative PG aggrecan peptides, the stimulating p263-280 peptide and a control p2379-2394 peptide.[15] We tested for the proportion of T cells in cells isolated from IPFPs, synovial tissues, and PBMCs and show that the compositions were similar (Figure 1A). Due to the limited number of cells in each sample, we sorted T cells and non-T cells from a mixed pool of IPFPs from five patients with knee OA to test for their IL-6 production in response to the peptides. IL-6 responses were found in both the T-cell and non-T-cell compartments with significantly higher IL-6 production from T cells (Figure 1B). Hence, in our experiments, we used whole cell isolates from IPFPs and synovial tissues without further purification to represent IPFP and synovial tissue T cells, respectively. IPFP cells stimulated with the p263-280 peptide had significantly higher levels of IL-6-producing cells than when stimulated with the p2379-2394 peptide (Figure 1C,D). The PG aggrecan p263-280 peptide induced higher T-cell responses than the PG aggrecan control peptide, p2379-2394.

3.2 | The p263-280 PG aggrecan peptide stimulates IPFP cells, but not peripheral blood and synovial tissue cells, to secrete IL-4, IL-10, IL-17A, sFas, granzymes A and B, perforin, and granulysin

Previously, de Jong et al demonstrated T-cell proliferation when PBMCs of OA patients were stimulated with the p16-31 and p263-280 peptides.[15] For this reason, to investigate systemic inflammation and cytotoxicity that may occur in patients with knee OA in response to these PG aggrecan peptides, we sorted peripheral blood T cells from patients with knee OA and stimulated these cells with the peptides (p16-31, p263-280, and p2379-2394). We measured IL-2, IL-4,

FIGURE 3 Cytokine and cytotoxic molecule responses from infrapatellar fat pad (IPFP) cells and synovial tissue cells in response to proteoglycan aggrecan peptides. (A) Bar graphs showing levels of cytokines and cytotoxic molecules from IPFP cells and (B) synovial tissue cells. Cells were stimulated with proteoglycan aggrecan peptides (p16-31, p263-280, and p2379-2394), ovalbumin peptide (OVA), CEF peptides, and PMA/ionomycin (PMA/I) (N = 11) and cytokine and cytotoxic molecule production were determined using cytometric bead array (CBA). Black arrows indicate a trend of higher production of mediators in the presence of p263-280 peptide. Data are shown as mean ±SEM (****$P < 0.0001$; ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$)

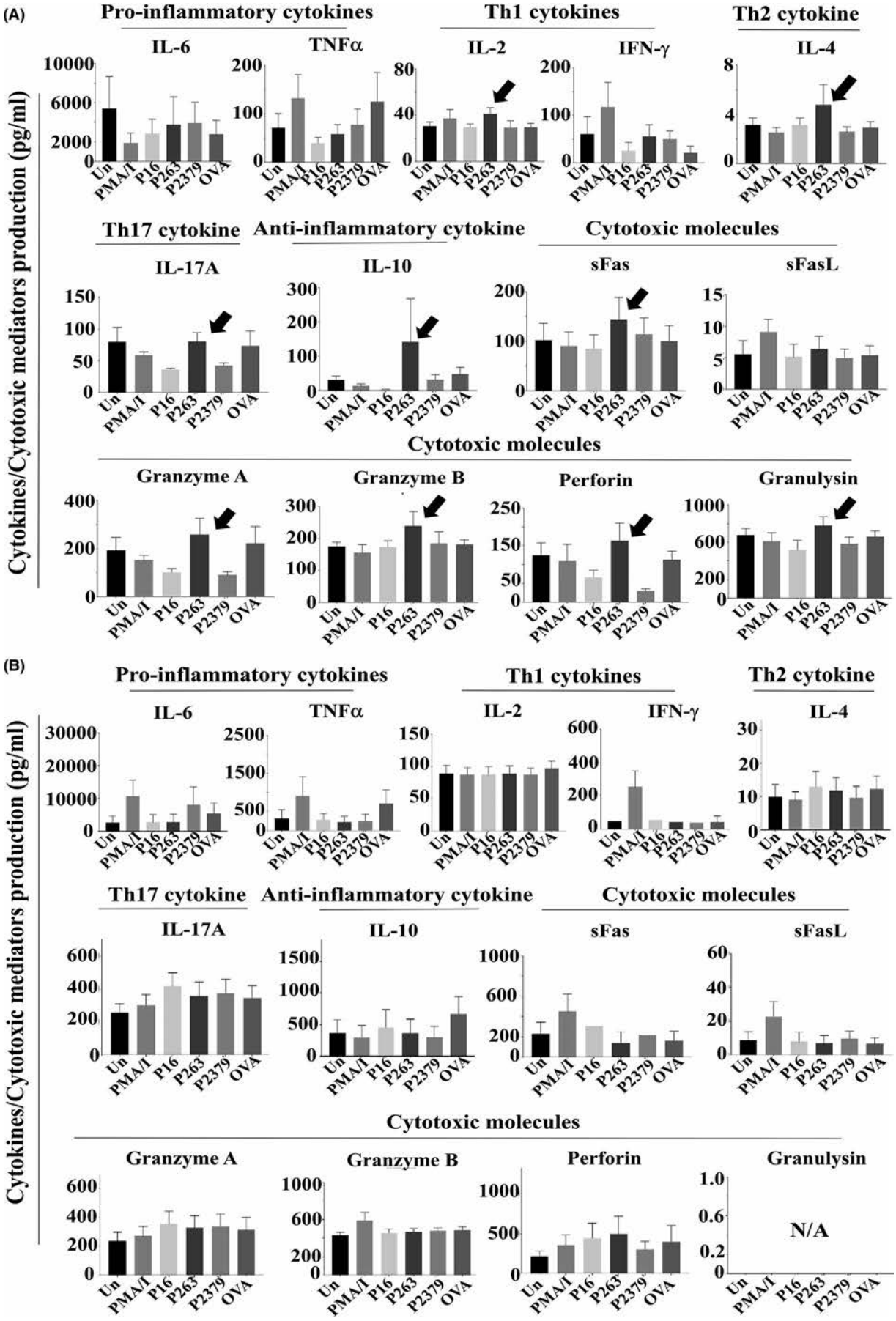

(A)
Cytokines/Cytotoxic mediators production (pg/ml)
Pro-inflammatory cytokines
IL-6
TNFα
Th1 cytokines
IL-2
IFN-γ
Th2 cytokine
IL-4
Th17 cytokine
IL-17A
Anti-inflammatory cytokine
IL-10
Cytotoxic molecules
sFas
sFasL
Cytotoxic molecules
Granzyme A
Granzyme B
Perforin
Granulysin
Un
PMA/I
P16
P263
P2379
OVA
(B)
Cytokines/Cytotoxic mediators production (pg/ml)
Pro-inflammatory cytokines
IL-6
TNFα
Th1 cytokines
IL-2
IFN-γ
Th2 cytokine
IL-4
Th17 cytokine
IL-17A
Anti-inflammatory cytokine
IL-10
Cytotoxic molecules
sFas
sFasL
Cytotoxic molecules
Granzyme A
Granzyme B
Perforin
Granulysin
N/A

TABLE 1 Levels of cytokines/cytotoxic molecules and percentage of detectable cytokines/cytotoxic molecules in synovial fluid from patients with knee osteoarthritis (OA) (N = 40)

Cytokines (pg/mL)	Synovial fluid of OA (pg/mL) (n = 40)	Detectable (%)
Interleukin-4	0 ± 0	0
Soluble Fas ligand	0 ± 0	0
Granzyme B	272.63 ± 216.13	7.5
Interleukin-2	12.23 ± 6.23	25
Tumor necrosis factor-α	14.97 ± 27.63	37.5
Interferon-γ	6.50 ± 4.51	50
Interleukin-10	3.392 ± 1.80	60
Interleukin-17A	10.92 ± 10.34	67.5
Perforin	102.98 ± 86.83	90
Interleukin-6	130.91 ± 239.01	92.5
Granzyme A	23.05 ± 18.00	92.5
Granulysin	210.77 ± 177.46	95
Soluble Fas	835.91 ± 370.86	97.5

IL-10, IL-6, IL-17A, TNF-α, sFas, sFasL, IFN-γ, granzyme A, granzyme B, perforin, and granulysin levels using CBA. Magnetic bead-enriched T cells resulted in 95% purity of T cells (data not shown). Our results show that there were no significant increases in cytokine and cytotoxic mediator production from T cells when stimulated with the PG aggrecan peptides (Figure 2). Stimulation with PMA/ionomycin resulted in a significant boost in cytokine and cytotoxic molecule production (Figure 2). We observed granulysin production when cells were stimulated with the p263-280 peptide; this was comparable to levels when stimulated with PMA/ionomycin (Figure 2).

We further tested the extent of cytokine and cytotoxic mediator production in the IPFPs and synovial tissues. Cells isolated from IPFPs and synovial tissues from patients with knee OA were stimulated with PG aggrecan peptides (p16-31, p263-280, and p2379-2394), OVA (p323-339), and PMA/ionomycin. Supernatant was collected and tested for the presence of cytokines and cytotoxic mediators. Our results show that stimulation with PG aggrecan peptides did not result in statistically significant increases in any cytokine nor in cytotoxic mediator production in either IPFPs or synovial tissues. Interestingly, we observed that there was a trend that the p263-280 peptide stimulated a higher production of mediators in nearly all cytokines/cytotoxic mediators tested, despite not being statistically significant, when compared with the p16-31 peptide and the control p2379-2394 peptide (Figure 3A). However, we did not observe this trend with synovial tissues (Figure 3B). These results suggest potential responses to the PG aggrecan p263-280 peptide in IPFPs and a potential role of this peptide in inflammation found in knee OA.

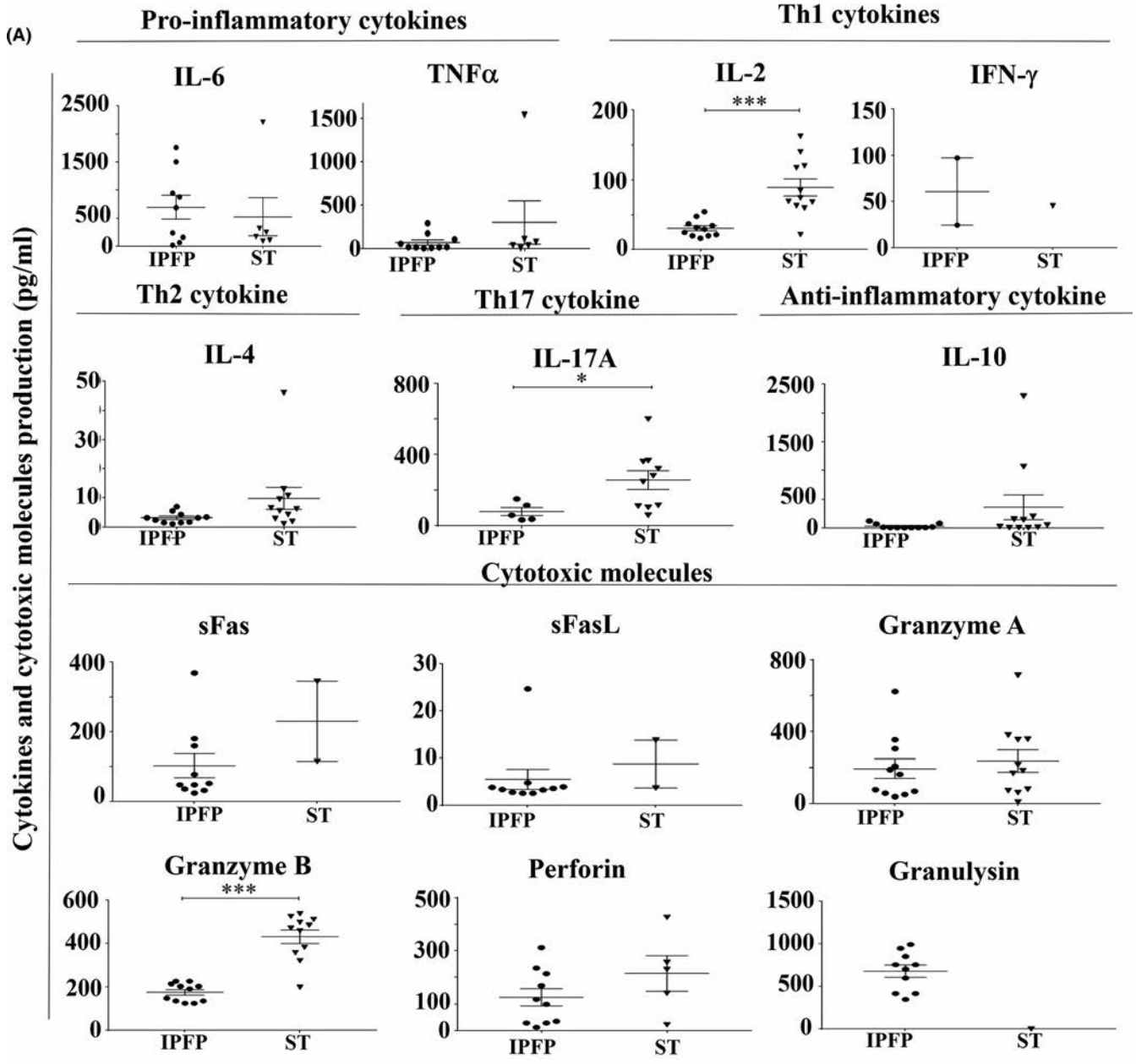
3.3 | Cytotoxic mediators were highly detectable and present predominantly in synovial fluid of patients with knee OA

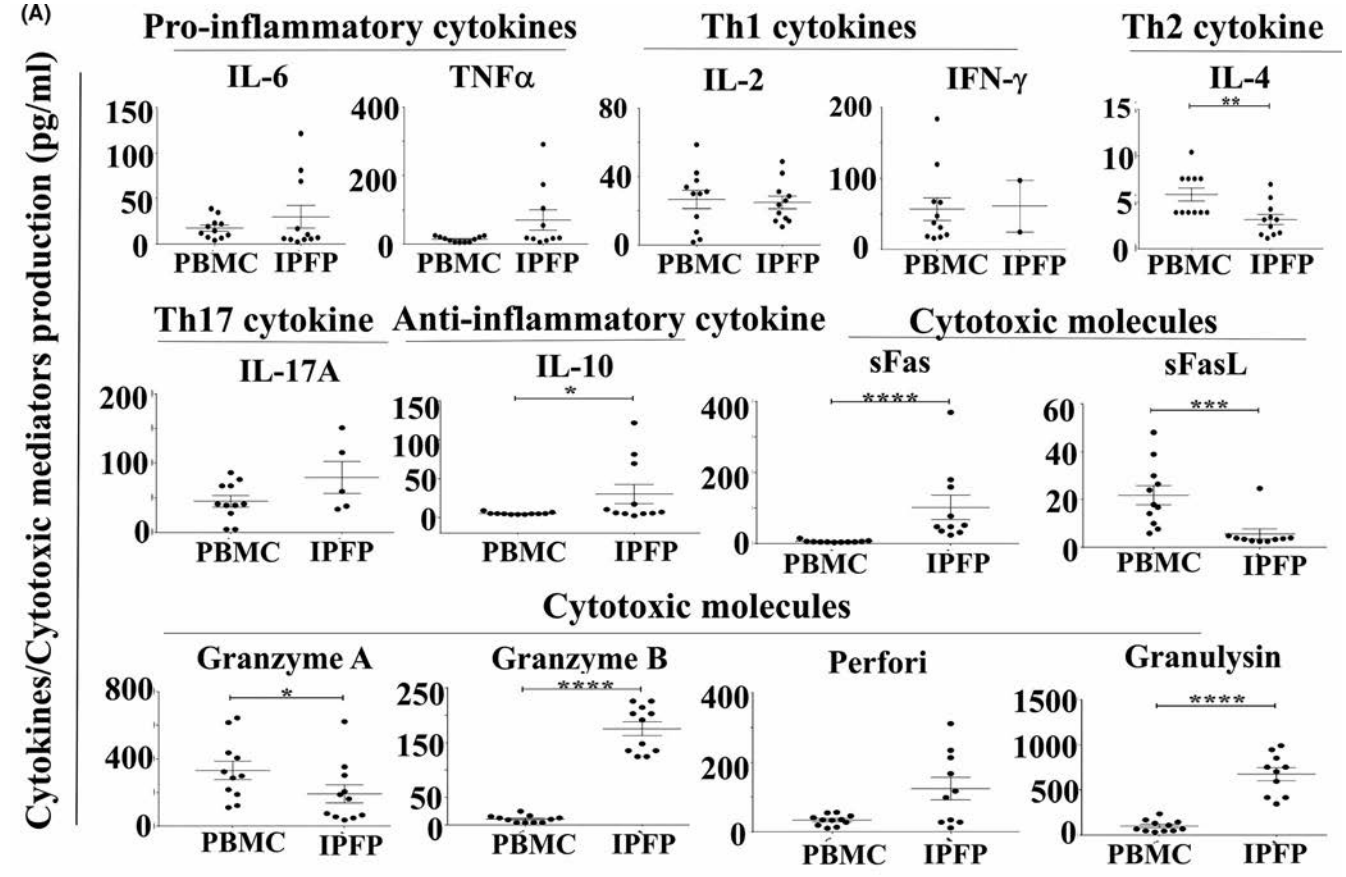
The synovial fluid acts as a lubricant and a cushion to forces exerted on the knee.[27] Many cytokines are also present and can be detected in the synovial fluid.[28] Therefore, in order to phenotype the cytokine and cytotoxic mediator profile of knee OA synovial fluid, we tested for IL-2, IL-4, IL-10, IL-6, IL-17A, TNF-α, sFas, sFasL, IFN-γ, granzyme A, granzyme B, perforin, and granulysin concentrations in 40 patients with knee OA. Our results show that certain mediators were highly detectable, but others were either undetectable or detectable at a low percentage (Table 1). sFas, granulysin, IL-6, granzyme A, and perforin were among the highly detectable mediators (≥90% detection rate) with detection rates of 97.5%, 95%, 92.5%, 92.5%, and 90%, respectively (Table 1). The absolute concentrations of sFas, granzyme B, and granulysin were among the highest and these cytotoxic mediators were present at levels higher than the pro-inflammatory prototypic cytokine for OA, IL-6 (Table 1). Despite most cytotoxic mediators tested being highly detectable, granzyme B had levels similar to granulysin (272.63 ± 216.13 vs 210.77 ± 177.46 pg/mL, respectively), but had strikingly different detectable percentages (7.5% vs 95%, respectively). These results suggest that cytotoxic mediators may play a crucial role in knee OA pathology and that these mediators may serve as good predictors of the inflammatory status within the knee joint because of their high abundance and easily detectable rate.

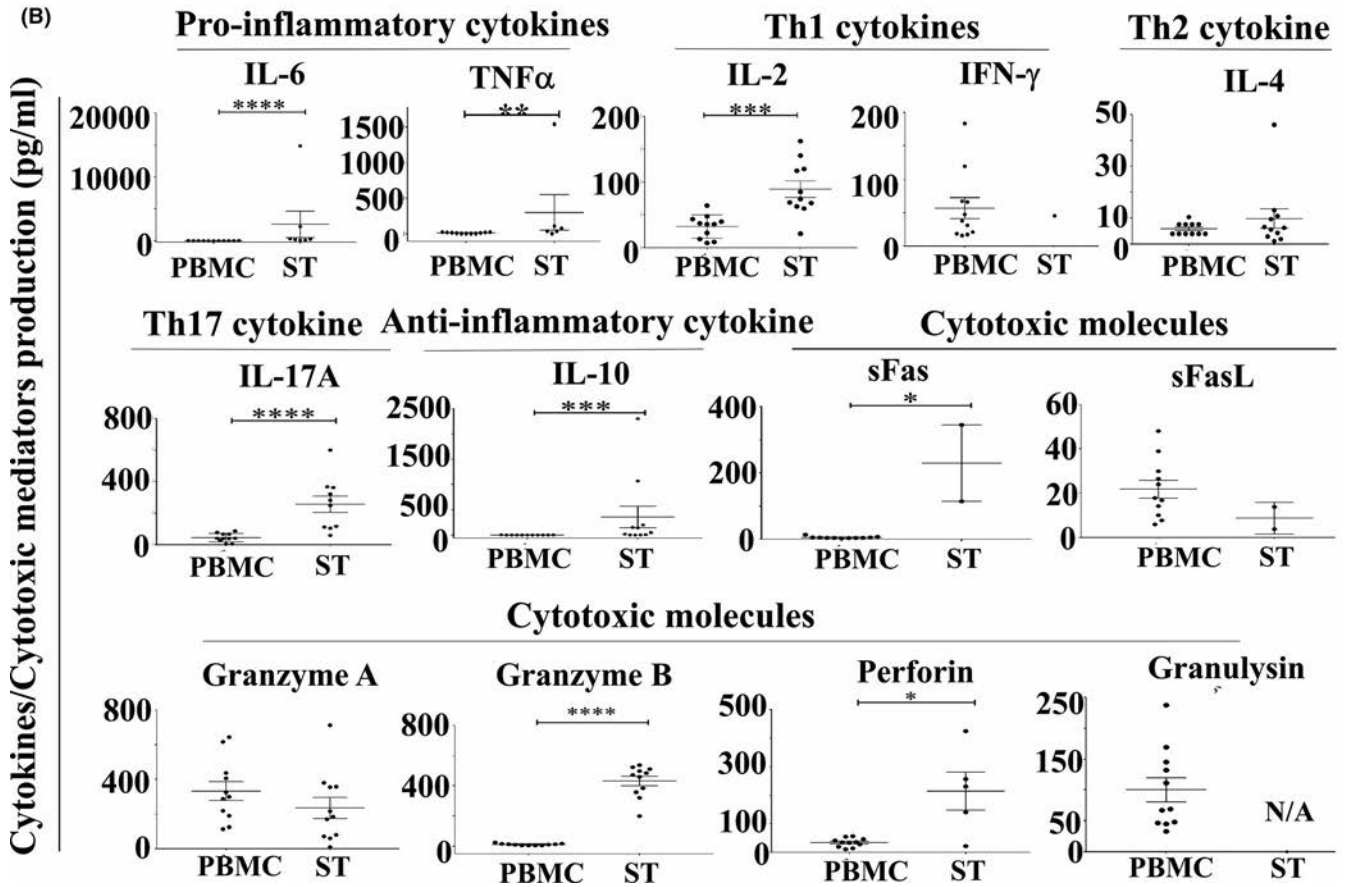
3.4 | Synovial tissues and IPFPs are sites of various cytokine and cytotoxic mediator production

The synovial tissues and IPFPs are tissues adjacent to the knee joint and may be a site of cytokine and cytotoxic mediator production.[26,29,30] We compared the levels of cytokines and cytotoxic mediators released from ex vivo synovial tissue and IPFPs. There were significantly higher levels of IL-2, IL-17A, and granzyme B production from synovial tissues than IPFPs (Figure 4A). All other mediators (IL-6, IL-4, TNF-α, IFN-γ, IL-10, sFas, sFasL, granzyme A, and perforin) were found to have similar levels in both tissues (Figure 4A). Unfortunately, we were not able to detect granulysin from synovial tissues for technical reasons and comparison between the two

FIGURE 4 Comparison of each cytokine and cytotoxic molecule level in infrapatellar fat pad (IPFPs), synovial tissue and synovial fluid. (A) Dot plots comparing levels of cytokines and cytotoxic molecules present in ex vivo IPFP cells and synovial tissue cells (N = 11); (B) Bar graphs depicting patterns of cytokine/cytotoxic mediator abundance in ex vivo IPFP cells (N = 11), ex vivo synovial tissue cells (N = 11) and synovial fluid from patients with knee osteoarthritis (N = 40). *y*-axis represents cytokine/cytotoxic molecule levels and data are shown as mean ±SEM (****$P < 0.0001$; ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$) (#### indicates significant difference with all cytokines and cytotoxic molecules at $P < 0.0001$)


(A)
Pro-inflammatory cytokines
Th1 cytokines
IL-6
TNFα
IL-2
IFN-γ
Th2 cytokine
Th17 cytokine
Anti-inflammatory cytokine
IL-4
IL-17A
IL-10
Cytotoxic molecules
sFas
sFasL
Granzyme A
Granzyme B
Perforin
Granulysin
IPFP
ST
Cytokines and cytotoxic molecules production (pg/ml)
(B)
Fad pad (IPFP)
Synovial tissue (ST)
Synovial Fluid (SF)
Cytokines/Cytotoxic molecules production (pg/ml)
IL-2
IL-4
IL-10
IL-6
IL-17A
TNFα
sFas
sFasL
IFN-γ
Granzyme A
Granzyme B
Perforin
Granulysin
N/A


(A)
Cytokines/Cytotoxic mediators production (pg/ml)
Pro-inflammatory cytokines
IL-6
TNFα
Th1 cytokines
IL-2
IFN-γ
Th2 cytokine
IL-4
Th17 cytokine
IL-17A
Anti-inflammatory cytokine
IL-10
Cytotoxic molecules
sFas
sFasL
Granzyme A
Granzyme B
Perfori
Granulysin
PBMC
IPFP


(B)
Cytokines/Cytotoxic mediators production (pg/ml)
Pro-inflammatory cytokines
IL-6
TNFα
Th1 cytokines
IL-2
IFN-γ
Th2 cytokine
IL-4
Th17 cytokine
IL-17A
Anti-inflammatory cytokine
IL-10
Cytotoxic molecules
sFas
sFasL
Granzyme A
Granzyme B
Perforin
Granulysin
N/A
PBMC
ST

tissues was not performed. Next, to assess the contribution of each source of cytokines and cytotoxic mediators, we compared the patterns of cytokine and cytotoxic mediator production found in ex vivo IPFPs and ex vivo synovial tissue with synovial fluid. The patterns of cytokine and cytotoxic mediator profiles differed among the three sources (Figure 4B). We observed that synovial tissues produced a broader range pattern of cytokines than IPFPs, whereas the IPFPs produced strikingly high levels of IL-6 and granulysin (Figure 4B). Interestingly, the mediator profile of the synovial fluid had a unique profile with a predominant level of sFas and high levels of granzyme B, granulysin, perforin, and IL-6 (Figure 4B). This did not fit the profiles of either synovial tissues or IPFPs. Hence, from our results, it is suggested that certain soluble products, such as sFas, may originate from other additional sources or may have an underlying mechanism that drives the predominant abundance of sFas found in synovial fluid of patients with knee OA.

3.5 | Inflammation in patients with knee OA is more pronounced at joint-surrounding tissues than in peripheral blood

Next, we compared systemic inflammation with local inflammation within the knee joint by comparing the cytokines and cytotoxic mediators produced from PBMCs with those produced from IPFPs and synovial tissues. We isolated knee OA PBMCs, IPFP cells, and synovial tissue cells; and determined the levels of cytokines and cytotoxic mediators ex vivo, using CBA. Our results showed that IL-10, sFas, granzyme B, and granulysin were produced from IPFPs at significantly higher levels than from PBMCs, but IL-4 and granzyme A were produced at significantly lower levels (Figure 5A). IL-10, IL-2, IL-6, IL-17A, TNF-α, sFas, granzyme B, and perforin were produced from synovial tissues at significantly higher levels than from PBMCs, with other cytokines and cytotoxic mediators produced at similar levels (Figure 5B). These significant differences in cytokine and cytotoxic mediator production between PBMCs and tissues surrounding the knee joint reflect the degree of inflammation of local knee joint tissues. The cytokine and cytotoxic mediator profile reflects a T helper type 1 (Th1) cytokine profile and cytotoxicity profile.

4 | DISCUSSION

In this study, we tested for T-cell responses to PG aggrecan peptides (p16-31, p263-280, and p2379-2384 fragments). The p16-31 and p263-280 PG aggrecan peptides are known to stimulate PBMCs of OA patients, but not the p2379-2384 peptide.[15] IPFPs are positioned in close contact with the intra-articular knee joint space,[31] providing a possibility that IPFPs may be a source of inflammation. We first tested for T-cell responses towards PG aggrecan peptides from IPFP T cells by looking at IL-6 production in response to peptide stimulation. IL-6-secreting T cells have been described previously in OA and adipose tissue.[26] We found that p263-280 peptide stimulation resulted in a significantly higher IL-6 response, suggesting specificity of IPFP T cells to the p263-280 peptide. Moreover, comparison of cytokine and cytotoxic mediator production in response to PG aggrecan peptides revealed a trend towards being stimulated by the p263-280 peptide in IPFPs rather than peripheral blood or synovial tissues. A result of IPFPs being responsive to the p263-280 peptide is higher cytokine and cytotoxic mediator production than when stimulated with PMA/ionomycin. These results underscore the IPFP as a potential source of local inflammation in the knee joint. It is also worth noting that both T cells and other IPFP cells secreted IL-6. T cells express major histocompatibility complex (MHC) class I and are, therefore, capable of being antigen-presenting cells themselves.[32,33] Whether these IL-6 responses are due to activation of the antigen processing and presentation cascades or T-cell stimulation cascades is still unclear. PG aggrecans are macromolecules synthesized by the host.[16] A T-cell stimulation response to PG aggrecan would suggest that IPFP T cells have a recall response to a "self-antigen". T-cell selection in the thymus is a process by which T cells that recognize self-antigens of the host are deleted by induced cell death.[34,35] Due to the cartilage being avascular and perhaps not exposed to any immune surveillance, we could assume that PG aggrecan is not presented to the T cells in the thymus; thus, providing the opportunity for PG aggrecan-specific T-cell clones to be generated and survive the T-cell selection process. Moreover, in knee OA pathology, there is an increase in MMPs.[36-38] The degradation of PG aggrecan by MMPs could possibly generate neoepitopes that are candidates for T-cell recognition. Also, in the elderly, immunosenescence tends to occur and increases the probability for autoimmunity to develop.[39,40] It is worth noting that the PG aggrecan peptides that were used in this study were based on prediction models with human HLA-transgenic mice and tested on peripheral blood of OA patients.[15] However, no studies have yet reported these exact sequence peptides in synovial fluid or other joint tissues. Nonetheless, the G1 domain of PG aggrecan, in which the p16-31 and p263-280 peptides reside, is prone to cleavage by MMPs and aggrecanases at the Asn341-Phe342 and Glu373-Ala374 bonds, respectively,[41] and these degradation products are found in synovial fluid of various joint diseases, including OA.[42] These degradation products have been shown to increase with age.[42] Cleavage of core proteins on PG aggrecan structures leads to increased uptake (endocytosis) by cells.[43] Another factor to be taken into account is the antigen-processing machinery

FIGURE 5 Comparison of each individual cytokine and cytotoxic molecule production from ex vivo peripheral blood mononuclear cells (PBMCs) of patients with knee osteoarthritis with ex vivo infrapatellar fat pad (IPFP) cells and ex vivo synovial tissue cells. (A) Dot plots comparing levels of cytokines and cytotoxic molecules present in ex vivo PBMCs and ex vivo IPFP cells (N = 11); and ex vivo PBMCs and ex vivo synovial tissue cells (N = 11) (B). *y*-axis represents cytokine/cytotoxic molecule levels and data are shown as mean ±SEM (****$P < 0.0001$; ***$P < 0.001$; **$P < 0.01$; * $P < 0.05$)

in cells. This governs how structural proteins are digested within the cells and which epitopes are presented on MHC molecules to T cells.[44,45] Further studies combining immunopeptidomics and mass spectrometry are required to investigate the nature of these PG aggrecan epitopes.

An analysis of soluble mediators in the synovial fluid of patients with knee OA revealed high levels of many cytotoxic mediators. We also observed different detectable rates for each mediator: high detectable rates of cytotoxic mediators and lower detectable rates for Th 1, Th2, and Th17 and anti-inflammatory cytokines. IL-6 has been reported to be a biomarker of OA.[46-48] Nonetheless, IL-6 levels in synovial fluid were not the most prominent, but detectable rates were still high, at 92.5%. However, sFas, granzyme B, and granulysin, all of which are cyototoxic, had levels exceeding IL-6 levels, with sFas and granulysin having detectable rates as high as 97.5% and 95%, respectively. In contrast, granzyme A was found at low levels, but had exceedingly high detectable rates of 92.5%. These data suggest that not only may IL-6 serve as a biomarker of patients with knee OA, but that cytotoxic mediators may also serve as biomarkers to predict disease severity and prognosis of patients. In addition, cytotoxicity may be more involved in the pathogenesis of knee OA than has been appreciated. Ligation of MHC and antigen-specific T cells induces the canonical apoptosis cascade of target cells by perforin/granzyme release and Fas/FasL (CD95/CD95L) pathway activation, resulting in caspase activation and cell apoptosis.[49,50] The Fas/FasL pathway is partially regulated by soluble forms of Fas and FasL (sFas and sFasL, respectively).[50,51] In knee OA, cartilage destruction is pivotal to the disease's pathological findings. Chondrocytes produce cartilaginous matrix (collagen and PG) and may serve as target cells because of their ability to present antigens to T cells.[52,53] Our current findings that p263-280 peptide stimulation results in cytotoxic mediator increase and the abundant presence of cytotoxic mediators in synovial fluid both suggest a potential role for cytotoxicity in mediating the pathology of knee OA.

The surrounding tissues that encapsulate the knee joint play both protective and pathologic roles in knee OA development.[3,30,54] Therefore, a comparison of potential sources of inflammatory mediators with mediator profiles within the synovial fluid would provide additional understanding of how joint-surrounding tissues play a role in the pathogenesis of knee OA. We found that the mediator profiles from IPFPs, synovial tissues and synovial fluids all had different profile patterns, with some mediators highly produced from synovial tissues and others from IPFPs. The most striking observation was the high abundance of sFas in synovial fluid. sFas is a molecule generated by cleavage of the membrane form of Fas (mFas) via MMPs and prohibits the activation of the Fas/FasL system by competing with mFas to bind to mFasL.[51] Thus, the presence of high sFas would prevent activation of the Fas/FasL cascade. Fas is cleaved by MMP-7,[55] which is overexpressed in human OA cartilage and is highly specific for cartilage PG cleavage.[56] Digestion of the cartilage PG could result in peptide fragments that could be potential T-cell epitopes that stimulate T cells of OA patients. Moreover, OA IPFP stem cells may also serve as a source of sFas because of their strikingly high cell surface expression of Fas and FasL (up to 98% in both molecules).[57] This high expression of Fas and FasL is due to phenotypic reprogramming by the inflamed environment in OA.[57] It is also interesting to speculate that Fas promotes Th9 and Th17 cell differentiation, that Fas ligation exacerbates inflammatory bowel disease, and that Th17 cell-specific deletion of Fas protects mice from autoimmunity.[58,59] Perhaps the increase in MMPs and ADAMTS in OA patients may contribute to the abundance of sFas in synovial fluid. It could be that sFas is a direct result of MMP proteolysis or an increase in mFas followed by subsequent cleavage by MMPs. The Fas/FasL pathway plays a crucial role in immune homeostasis, especially in central tolerance by inducing the death of autoreactive T cells.[51] Individuals with system lupus erythematosus, a systemic autoimmune condition, have been reported to have high levels of sFas,[60,61] and in multiple sclerosis patients, there are high levels of Fas/FasL interaction that explain the pathology of the disease.[51,62] The effects of high levels of sFas in synovial fluid of patients with knee OA on the Fas/FasL system and whether it causes immune tolerance breakage in OA needs to be further investigated.

In conclusion, we investigated T-cell responses to PG aggrecan peptides. Our results demonstrate that T cells can recognize and respond to these PG aggrecan peptides. These responses were augmented in tissues adjacent to the knee joints and evidence of cytotoxicity was prominent. The findings of many cytotoxic mediators that were highly detectable in patients with knee OA also provide alternate options for novel potential biomarkers of knee OA. The strikingly high presence of sFas demands further investigation into the origins of this mediator.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

TS, NL, and NC performed the experiments, and collected and analyzed the data. SN and PY collected clinical samples for processing. AT collected clinical samples for processing and gave intellectual input. NH gave substantial intellectual input for manuscript preparation. NL, PS, and RR prepared, wrote and revised the manuscript. All authors approved the final version of the manuscript.

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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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A multicenter longitudinal study of the prevalence and mortality rate of systemic lupus erythematosus patients in Oman: Oman Lupus Study

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Abstract

Aim: This study is a longitudinal multicenter study which aims to find the prevalence, the demographic data, survival and mortality rates of patients with systemic lupus erythematosus (SLE) in Oman.

Method: All Omani patients, pediatrics and adults diagnosed with SLE, who fulfill either the 1997 American College of Rheumatology or Systemic Lupus International Collaborating Clinics classifications criteria for SLE were included from January 2006 till February 2020.

Results: In total 1160 patients were included in this cohort. Data analysis showed that patient's ages ranged from 2-82 years with female predominance and female-to-male ratio of 7:1 (87.7% female,12.3% male). The mean prevalence of SLE among different age groups was 38.8 (range 5-63 per 100 000 inhabitants). The mortality rate was found to be 5%. Male patients had significantly higher mortality rate than females (7.6% vs 5.4%, *P* value = .04). Sepsis was the commonest cause of mortality (34%). The coexistence of systemic sclerosis correlates significantly with death (*P* = .002). Survival analysis in our data showed 5, 10, 20, 40-year survival rates of 100%, 100%, 99% and 90% respectively for antinuclear antibody (ANA) positive patients and lower survival rate for ANA negative patients with 5,10, 20, 40-year survival rates of 100, 99%, 99% and 75%, respectively.

Conclusion: This study showed that the mean prevalence of SLE in Oman to be 38.8 (range 5-63) per 100 000 inhabitants. The 40-year survival rate among patients with positive ANA was found to be 90%, while patients with negative ANA had worse survival outcomes.

KEYWORDS

clinical aspects, epidemiology, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematous (SLE) is a multi-systemic autoimmune disease which is associated with significant morbidity and mortality. It generally exhibits different phenotypic expressions and severities among different ethnic groups as was found in numerous observational studies, which illustrated for instance that SLE is more common in Blacks who tend to display more severe forms of the disease and higher frequency of antibodies to Smith (Sm) and ribonucleoprotein (RNP) antigens.[1,2]

The reported worldwide incidence and prevalence of SLE vary considerably, which may be attributed to ethnic and geographic differences in the populations being studied, the definition of SLE applied and the methods of case identification.[3,4] Also, lupus in Arab countries is quite common.[5]

In Arabs, renal manifestations are reported in 54% of lupus patients which is significantly more frequent than in Europe but similar to Latin America.[5] Data from Oman showed that oral ulcers are less frequent at initial presentation (10.7%) than other reports from the Arab region.[4,6-9] Multiple other factors may impact disease severity in lupus populations, including income level, education, health insurance status, and medication compliance.[10]

Several studies describing the clinical and serologic features of SLE in Arab countries and few from Oman have been published; however, the data about the prevalence of this disease are scarce.[11] This study is the first multicenter study in the region conducted to estimate the prevalence of the disease in Oman and describe the mortality and survival rates in the Omani lupus population. It will provide the basis for future therapeutic and genetic trials in the Arab world in addition to developing a national lupus registry with a large cohort of patients that may aid survival analysis and better understanding of the disease outcomes in the region compared to international data.

2 | METHODS

This is a longitudinal observational study of SLE patients, conducted throughout the country including the Royal Hospital and all regional hospitals of the Ministry of Health (MOH), as well as the Sultan Qaboos University Hospital. MOH has an internationally recognized electronic medical record system called Al Shifa which uses the International Classification of Diseases and all clinical, laboratory and radiological data are collected prospectively. Hence, we performed an analysis of prospectively collected data. This observational study was ethically approved by the research and ethical review and approval committee, MOH (MoH/CSR/17/6785). All Omani pediatric and adult SLE patients who fulfilled at least 4 of the 1997 ACR (American college of Rheumatology) classification criteria[12] or SLICC (Systemic Lupus International Collaborating Clinics) classification criteria,[13] and were seen in all rheumatology centers in the Sultanate of Oman over a 14-year period between January 2006 and February 2020 were included in this study. Exclusion criteria were: non-Omani patients, patients with no sufficient clinical details, and patients who did not fulfil classification criteria for SLE. After applying the inclusion and exclusion criteria we ended up with 1160 patients on which statistical analysis was performed.

Each value is expressed as number and percentage (%). Also, continuous variables were expressed as mean ± SD. Descriptive analyses were used to assess patient characteristics including distribution plots, means for normally distributed data, medians, and interquartile ranges. Chi-square statistic was used to compare categorical variables, Student's *t* test compared means between 2 groups, one sample test of proportions was used to establish the proportion of one outcome within a population, and Wilcoxon rank sum statistics to compare data that were not normally distributed. We used the Kruskal-Wallis rank test to assess differences in more than 2 groups of non-normally distributed data. Statistically significant findings of these tests were defined by a P value ≤.05. All analyses were performed using STATA version 13 (StataCorp LP, College Station, TX, USA).

Prevalence was estimated by collecting the total number of Omani lupus cases present in Oman at a given time divided by the total population. This was done by including all lupus patients who fulfilled ACR/SLICC criteria from all major centers that treat lupus patients in Oman. The total population in the Sultanate during the electronic census of population and housing in 2020 reached 4.5 million persons, and the total of Omani citizens were around 2.7 million persons. Patients were further subdivided according to their age group and prevalence analysis of each age group was calculated.

3 | RESULTS

In the Oman Lupus Study, 1160 patients fulfilled the inclusion criteria and were included in this lupus cohort. Data analysis showed a female predominance with female-to-male ratio of 7:1 (87.7% female, 12.3% male). The mean (SD) age was 33 (12) years. Around 33% of patients were from Muscat (the Capital) and 25% from the Al Batinah region. The remaining 42% of patient were distributed over other governances in the Sultanate. This finding reflects the population distribution in Oman as these 2 regions, Muscat and Al Batinah, are heavily populated in comparison to other regions.

3.1 | Prevalence of different clinical manifestations of the disease

The clinical characteristics of the cohort are shown in (Table 1). Arthralgia and arthritis were reported in 70% of the patients. Malar rash was documented in 29% of patients, whereas photosensitive rash and alopecia were reported in 31% and 30% of the patients, respectively. Discoid rash was the least common cutaneous manifestation seen in only 8% of the patients. Female patients were more prone to develop arthralgia/arthritis, malar rash and alopecia compared to male patients (P score of .00, .03 and .00 respectively).

TABLE 1 Patients clinical characteristics and laboratory parameters of Oman lupus cohort

Clinical characteristics total (N = 1160)		Laboratory parameters from available data	
Variable	**No. (%)**	**Variable**	**Frequency (%)**
Average age, y	33 ± 12	Hemolytic anemia	442 (38)
Min	2 y	Thrombocytopenia	262 (23)
Max	82 y	Leucopenia	366 (32)
Gender		Positive direct Coomb's test	381 (33)
Male	143 (12.3)	Thyroid dysfunction	223 (19)
Female	1017 (87.7)	Antinuclear antibodies	1121 (96.5)
Average age at diagnosis	24 ± 12	Anti-double-stranded DNA	833 (72)
Overlapping syndromes	169 (15)	Anti-Smith	350 (30)
Rheumatoid arthritis	38 (22)	Anti-Ro/SSA	450 (39)
Scleroderma	22 (13)	Anti-La/SSB	173 (15)
Myositis	17 (10)	ACL IgM	38 (3.2)
SS	39 (23)	ACL IgG	178 (15)
Mixed connective tissue diseases	24 (14)	ß2-glycoprotein I	151 (13)
Others	30 (18)	Lupus anticoagulant	224 (19)
Arthritis/ arthralgia	819 (70)	Complement C3	731 (64)
Discoid rash	92 (8)	Complement C4	812 (71)
Malar rash	340 (29)	Renal involvement	607 (52)
Photosensitive rash	364 (31)	**Availability of kidney biopsy**	376 (33)
Alopecia	343 (30)	Class I/II	44 (12)
Mucosal ulcers	230 (20)	Class III	81 (21)
Lymphadenopathy	211 (18)	Class IV	182 (48)
Cardiac involvement	238 (21)	Class V	49 (13)
Neuropsychiatric involvement	242 (21)	Class VI	3 (0.8)
Respiratory involvement	215 (19)	Difficult to classify	21 (5.5)
Gastrointestinal involvement	91 (8)	**Lupus nephritis class of repeated kidney biopsy:**	55 (9)
Eye involvement	42 (4)	Class I/II	3 (5)
Regions		Class III	6 (10)
Muscat	377 (33)	Class IV	35 (58)
Al Batinah	286 (25)	Class V	11 (18)
Al Dhakhilia	133 (11.6)	Class VI	3 (5)
Al Sharqiyah	167 (14.6)	Difficult to classify	2 (3)
Al Buraimi	41 (4)		
Al Wasta	5 (0.4)		
Dhofar	82 (7)		
Musandam	5 (0.4)		
Al Dhaira	41 (4)		

Abbreviations: ACL Ig, anti-cardiolipin immunoglobulin; SS, Sjögren's syndrome.

Overlap syndromes were identified in 15% of the cohort. Rheumatoid arthritis and Sjögren's syndrome (SS) were the most common overlap diseases. There was a significant association between female gender and the occurrence of the overlap syndromes in general ($P = .09$). No significant gender difference in the occurrence of specific overlap syndromes was illustrated.

Lymphadenopathy was found in 18% of the patients. The frequency of lymphadenopathy was significantly more among male patients than female patients ($P = .01$).

Lupus nephritis was identified in 52% of the patients. Renal biopsy was performed in 33% of lupus nephritis patients. The most common pathological classes were class IV (48%) and class III (21%). Further analysis revealed that lupus nephritis was more frequent in male patients (male 68% and female 50%, $P < .001$) and therefore renal biopsy was performed more frequently in male patients than female patients ($P \leq .001$), but there was no gender difference among different lupus nephritis classes ($P = .39$, .27, .38, and .15).

Cardiovascular involvement was present in 21% of patients. Pericardial effusion and/or pericarditis were the most common cardiac manifestations (52%) followed by valvular heart diseases (39%). Neuropsychiatric involvement was present in 21% of patients with seizure disorder being the most common neurological manifestation (40%) followed by stroke and neuropathy in 20% of the patients. Psychosis was found in 13% of the patients and depression was reported in 14% of the patients.

Nineteen percent of patients in this cohort had pulmonary involvement out of which 50% developed pleural effusion during the disease clinical course, 22% had interstitial lung disease and 20% had pneumonitis (diffuse alveolar hemorrhage).

Gastrointestinal involvement and ophthalmological involvement were less common than other manifestations (8% and 4% respectively). Ischemic colitis (16%) and enteritis (13%) were the most common manifestations in patients with gastrointestinal involvements. Keratoconjunctivitis sicca (29%) and retinopathy (17%) were the commonest ophthalmological involvement.

Interestingly there was a significant association between male gender and internal organ involvement. Male gender had significantly more cardiac involvement ($P = .03$), pulmonary involvement

with pneumonitis (P = .03) and spleen and liver infarction ($P \leq$ .001).

3.2 | Laboratory parameters

Thyroid disorders were documented in 19% of patients, of which hypothyroidism was present in 15% and hyperthyroidism in 4% of patients. Thyroid dysfunction in general was significantly more common in female patients (20%) than in male patients (13.2%) (P = .001). Hyperthyroidism was more common in males (5.6%) than females (4%), whereas hypothyroidism was more common in female patients (16%) than male (7.7%).

Serological evaluation of this cohort showed that 96.5% of the patients had positive antinuclear antibodies (ANA), 72% had positive anti-double-stranded DNA and 30% had positive anti-Smith antibodies. Anti-Ro/SSA was positive in 39% of patients and anti-La/SSB was positive in 15% of the patients, while lupus anticoagulant was positive in 19% of patients, anti-cardiolipin immunoglobulin G (ACL IgG) was positive in 15% of patients and B2-glycoprotein antibodies were positive in 13% of patients in our cohort.

There were gender differences in the occurrence of some antibodies in which it was found that anti-Ro/SSA and anti-La/SSB were significantly more common in females than males ($P \leq$ .001 and .04 respectively). In contrast, male patients had significant association with B2-glycoprotein antibodies (P = .05) and lupus anticoagulant antibodies (P = .02).

3.3 | SLE prevalence among different age groups

The mean prevalence of SLE among different age groups was 38.8 (range 5–63 per 100 000 inhabitants). The mean prevalence for all adult lupus patients was 46 per 100 000 inhabitants. The highest prevalence was found among the 30-49 age group with a prevalence of 62 per 100 000 inhabitants. The lowest incidence was among the pediatric age group (age up 12 years), with a prevalence rate of 5.1 per 100 000 inhabitants. The disease prevalence in adolescents was 5 times higher than pediatrics with prevalence rate of 31.6 per 100 000 inhabitants. Moreover, SLE was still prevalent in patients above the age of 50 (39.8 per 100 000 inhabitants, Table 2).

TABLE 2 The prevalence rate of systemic lupus erythematosus patients of different age group in the Oman lupus cohort

Age group	Lupus patients/total population	Prevalence (per 100 000 inhabitants)
Pediatric patients up to 12 y	39/771 780	5.05
Adolescence patients 13-18 y	90/284 826	31.6
Adult patients		
Adult 19-24 y	136/387 448	35.1
Adult 25-29 y	154/475 403	32.4
Adult 30-39 y	403/639 636	63.01
Adult 40-49 y	212/352 632	60.12
Adult >49 y	103/262 192	39.28
Mean for all adult patients	45.96	
Oman lupus cohort overall mean	38.08	

3.4 | Mortality rate and survival rate

There were 54 reported patient deaths in this lupus cohort. The mortality rate was found to be 5%. Male patients had significantly higher mortality rate than female patients (7.6% vs 5.4%; P = .04). Sepsis was the commonest cause of mortality (34; 63%) followed by renal involvement (19; 35%), respiratory diseases (17; 31%), central nervous system (CNS) involvement (13; 24%) and cardiovascular diseases (12; 22%). CNS diseases as a contributing cause of mortality were significantly more in male patients than female (P = .04). There was no gender difference between other causes of mortality (Table 4).

All internal organ involvement including renal, pulmonary, neuropsychiatric, gastrointestinal and cardiovascular involvement correlate significantly with death in our lupus patients (P = .00).

Lupus nephritis was found in 74% of the deceased group. The most prevalent lupus nephritis pathological classes in this group were class IV followed by class V. Interestingly, none of the lupus nephritis classes or hypocomplementemia correlated significantly with mortality (Table 3).

The presence of systemic sclerosis and SLE overlap syndrome correlated significantly with death (P = .002). Hematological abnormalities including hemolytic anemia, thrombocytopenia and leucopenia correlated significantly with death (P < .001, < .001, .020, respectively). In addition, the presence of lymphadenopathy showed significant correlations with mortality (P = .014).

Serological analysis of this group showed that 92% of cases had positive ANA and 7.5% had negative ANA. All patients with positive ANA had reported mortality of around 5.4%. On the other hand, a 20% death rate occurred in the ANA negative group. Correlation analysis showed significant association of positive levels of ANA with patients' mortality (P= .038). Other antibodies including anti-dsDNA, anti-Smith antibodies, anti-Ro/SSA, anti-La/SSB, lupus anticoagulant, ACL IgM, ACL IgG and B2-glycoprotein antibodies all did not correlate with mortality (Table 3).

Survival analysis in our data showed 5, 10, 20, 40-year survival rates of 100%, 100%, 99% and 90%, respectively for ANA positive patients and lower survival rates for ANA negative patients with 5,10, 20, 40-year survival rates of 100%, 99%, 99% and 75%, respectively.

TABLE 3 The correlation between death and different clinical and immunological manifestations in the Oman lupus cohort

Clinical manifestations	Odds ratio	95% CI	*P* value	Adjusted *P* value	Laboratory parameters	OR	95% CI	*P* value	Adjusted *P* value
Gender	0.709	0.33-1.54	.385	.500	Hemolytic anemia	2.693	1.53-4.72	.000	.001
Average age at diagnosis	0.999	0.97-1.02	.687	.957	Thrombocytopenia	3.808	2.18-6.63	.000	.000
Overlapping syndromes	1.810	0.94-3.46	.066	.061	Leucopenia	1.910	1.09-3.32	.020	.031
Rheumatoid arthritis.	1.667	0.49-5.63	.405	.710	Direct Coomb's test	0.870	0.66-1.12	.640	.474
Scleroderma	4.928	1.58-15.39	.002	.003	Thyroid dysfunction	1.336	0.97-1.85	.094	.141
Myositis	2.541	0.56-11.47	.209	.219	Antinuclear antibodies	2.108	1.02-4.33	.013	.038
SS	2.210	0.74-8.73	.137	.012	Anti-double-stranded DNA	0.855	0.51-1.44	.834	.711
Mixed connective tissue diseases	1.767	0.40-7.76	.445	.370	Anti-Smith	2.049	0.91-5.15	.077	.278
Others	1.531	0.35-6.67	.567	.493	Anti-Ro/SSA	1.938	0.76-4.89	.366	.865
Arthritis/ arthralgia	0.815	0.45-1.47	.500	.719	Anti-La/SSB	1.438	0.59-3.49	.516	.474
Discoid rash	0.402	0.10-1.68	.197	.115	ACL IgM	1.009	0.81-1.26	.923	.908
Malar rash	0.989	0.54-1.80	.972	.876	ACL IgG	0.798	0.48-1.29	.549	.653
Photosensitive rash	0.539	0.27-1.06	.070	.089	ß2-glycoprotein I	0.895	0.62-1.44	.407	.941
Alopecia	0.713	0.38-1.35	.298	.303	Lupus anticoagulant	0.707	0.45-1.11	.186	.075
Mucosal ulcers	0.951	0.48-1.87	.886	.720	Complement C3	1.339	0.97-1.84	.073	.170
Lymphadenopathy	2.078	1.14-3.77	.014	.015	Complement C4	1.241	0.88-1.74	.212	.320
Cardiac involvement	8.618	4.81-15.44	.000	.000	Renal Involvement	36.83	24.42-45.14	.000	.066
Neuropsychiatric involvement	2.959	1.67-5.21	.000	.000	Lupus nephritis class	0.586	0.09-5.11	.610	.499
Pulmonary involvement	6.870	3.89-12.10	.000	.000					
GI involvement	4.563	2.32-8.96	.000	.000					
Eye involvement	0.937	0.22-3.99	.931	.934					

Abbreviations: ACL Ig, anti-cardiolipin immunoglobulin; SS, Sjögren's syndrome.

TABLE 4 Mortality rate and different risk factors that led to death in the Oman lupus cohort (N = 54)

Mortality rate	(5%)			
Common causes of death	No. (%)	Odds ratio (95% CI)	*P* value	Adjusted *P*
Sepsis	34 (63)	2.13 (1.15-4.31)	.000	.008
Cardiovascular diseases	12 (22)	8.62 (4.81-15.41)	.000	.000
Lung diseases	17 (31)	6.87 (3.90-12.11)	.000	.000
Renal diseases	19 (35)	3.73 (2.66-5.22)	.000	.003
Neurological diseases	13 (24)	2.96 (1.68-5.22)	.000	.000
Others	12 (22)	4.47 (1.23-6.09)	.000	.011

4 | DISCUSSION

SLE is a disease with many facets and presentations, and it may differ among different patients in different regions.[13,14] This heterogenicity in the presentation of the disease is caused by several factors that contribute to the evolution of lupus, including the genetic composition of the person, epidemiological and environmental factors, infections, microbiome, hormonal changes and psychological stresses that person may undergo. Lupus is known to affect females more than males with ratio of 9:1. In our cohort we found that this ratio is 7:1 with 12.3% of our patients being males and this ratio was reported in several other cohorts as well. Guillermo et al. in his review described that males were affected at different percentages among different countries, ranging from 2.5% to 33.3%. The highest reported frequency was in Brazil (33.3%).[15]

Analyzing different patient clinical characteristics, we found that discoid rash was less common, and it had occurred in only 8% of patients. Marwan et al. reported the frequency of discoid rash to range between 2.5% and 20.3% with an average of 12.7%.[5] Discoid rash frequency was higher in Egypt and lower in Sudan cohorts.[16] In Europe, the average frequency of discoid rash was found to be around 10%. Wengen Li et al. described discoid rash frequency of 14% in his lupus cohort in China.[17]

We reported the occurrence of anti-Ro in 39% of our patients, which was slightly lower than what is usually commonly reported in Arab cohorts.[5] Al Arfaj et al. reported anti-Ro in 53% of lupus patients in Saudi Arabia[18] and Al Saleh report 55% in his cohort in

the United Arab Emirates.[19] But the frequency of occurrence of anti-Ro was similar to what was reported in another cohort in Oman by Al-Maini et al., in which they found frequency of 41% of anti-Ro in their cohort.[20]

Overlapping syndromes were found in 15% of our lupus patients. Rheumatoid arthritis and SS were the commonest overlap diseases. Scleroderma was found to overlap with lupus in 22% of the patient and the presence of scleroderma was associated with increased risk of mortality (P score = .002). There are few reports describing this topic. Al Harbi et al. reported in 2018 in a cohort of 1252 lupus patients, scleroderma was found as an overlapping syndrome with lupus in 6.8% which is very low in comparison to what is reported in this cohort and they also found no risk of increasing mortality in this subgroup which is, as well, opposite to the present study findings.[21]

The percentage of renal involvement in our patients was around 52% which is similar to what is reported worldwide (21%-65%).[22] The commonest lupus classes on biopsy were class IV (48%) and class III (21%). Further analysis showed that lupus nephritis was more frequent in male patients ($P \leq .001$). This finding was also reported in other cohorts worldwide.[23] Male patients with lupus are usually at higher risk of mortality in comparison to female patients and usually they have higher disease activity.[24] In addition, we found that male gender had high significant correlation with internal organ involvement. Moreover, they had significant association with B2-glycoprotein antibodies ($P = .05$) and lupus anticoagulant antibodies ($P = .02$). These antibodies may put them at risk of having thrombosis in different organs.

The mean prevalence of SLE among different age groups varies according to different regions. It was found in our cohort that the mean prevalence in Oman was around 38.8 (range 5-63 per 100 000 inhabitants). The highest prevalence was found for the age group between 30 and 49 years (the average prevalence in this group is around 62 per 100 000 inhabitants), which is expected as SLE usually starts during this period of time. It was also found that the mean prevalence for all adult lupus patients was around 46 per 100 000 inhabitants. While trying to find literature about the prevalence of lupus in Arab countries, we found very limited data in the Middle East region. Al Arfaj et al. reported a prevalence of 19 per 100 000 inhabitants in Saudi Arabia[18] and Al Dhanhani et al. reported a higher prevalence in the United Arab Emirates of around 103 per 100 000 inhabitants.[14] We need more data about the prevalence of lupus in the Middle East region.

A comprehensive systemic review conducted by Rees et al. reported worldwide different prevalence rates around different countries, for example in Spain the prevalence ranged from 17 to 34, in the UK it ranges from 26 to100, in Germany around 36, in France around 40.8, in Canada around 22-45, in the US around 15-149, in China from 10 to 30 and in Argentina around 58.6 per 100 000 inhabitants.[3,24-26] But in a recent 2020 paper by Gonzalez et al., he reported a prevalence of 24.3 cases/100 000 inhabitants in Argentina, which is lower than the previous report in Argentina.[27] On the other hand, Cortes Verdu et al. described in their recent 2020 report that SLE prevalence was of 210 cases per 100 000 inhabitants (95% CI: 110-400) in Spain. This was one of the highest reported prevalences in most international epidemiological studies.[28]

Mortality rate of lupus is reported by different literature to range between 1.4%–5%.[29] Our lupus cohort had mortality rate of around 5%. Sepsis was the commonest cause of mortality (34; 63%) followed by renal involvement (19: 35%), respiratory diseases (17; 31%), CNS involvement (13; 24%) and cardiovascular diseases (12; 22%). It appears from the data presented that each patient may have more than one contributing cause for mortality (Table 4).

Several reports showed no difference in mortality between males and females.[29] But in our cohort male patients had higher rate of mortality in comparison to female patients (7.6% vs 5.4%) with significance level of $P = .04$).[30] This can be explained that our male patients had more internal organ involvement including renal involvement ($P \leq .001$), cardiac involvement ($P = .03$), pulmonary involvement with pneumonitis ($P = .03$) and spleen and liver infarction ($P \leq .001$). They had significant association with B2-glycoprotein antibodies ($P = .05$) and lupus anticoagulant antibodies ($P = .02$).

Survival rates of patient with SLE have improved remarkably in recent years, ranging between 60% and 90% in the early 1900s to a rate ranging between 80% and 97% in the 2000s.[5,14] It is worth mentioning that in the late 1990s, mycophenolate was introduced as an alternative to cyclophosphamide for the treatment of severe SLE, and in 2006 rituximab, a biologic agent that targets B-cells and inhibits antibodies formation was introduced and was used in the management of SLE. These 2 events reflect the advances in the therapeutic management of SLE and in turn have improved the survival rate of lupus patients. In addition, the increased awareness about the disease among physicians and caregivers and early detection of the disease has definitely played an important role. Moreover, the appearance of many other new therapeutic options including biologics has led to the improvement of disease outcome.

In the Gulf region, Al Saleh et al. reported a 5-year survival of 94% in United Arab Emirates lupus patients.[19] In Saudi Arabia, Heller et al. reported 5-year survival of 92%,[31] and Al Arfaj et al. reported a 10-year survival rate of 98%.[18] Our data showed 5, 10, 20, 40-year survival rates of 100%, 100%, 99% and 90%, respectively for ANA positive patients and lower survival rates for ANA negative patients with 5,10, 20, 40-year survival rates of 100%, 99%, 99% and 75%, respectively. This can be explained by higher disease activity in patients with negative ANA. Furthermore, the diagnosis is usually challenging and there may be a delay in diagnosing such cases, and some patients in remote areas may not be captured early in view of ANA negativity. In addition, we have good numbers of lupus nephritis patients with negative ANA, and lupus nephritis on its own is a risk factor for increasing mortality in this group. Furthermore, clinical trials are required to study this special group and analysis of their unique clinical features needs to be performed.

Finally, this is an important study which included large centers in Oman. Its importance relies in that it has provided us with the prevalence of lupus and its different clinical features and immunological background especially in this part of the world. It has helped us in

having a good insight about the nature of this disease in this region and to explore its unique difference and similarities in comparison to other regions. Furthermore, this study will provide the basis for future therapeutic and genetic trials in addition to a national registry that will involve larger numbers of patients than exists in current literature.

There are few limitations of this study including that some patients had no sufficient clinical details, and other patients did not fulfill the classification criteria for SLE. Also, most of the patients included in this study either were seen in the clinic or admitted in the hospital, so data of patients who may have been followed up at private clinics were missed. In addition, the challenges associated with collecting accurate data from the electronic system is another drawback of the present study. However, there are strengths associated with the present study including that it is whole-country data and the specificity of the national identity card as part of patient identification of their medical records. The study will continue to collect data and follow up of this cohort prospectively for future analysis and utilization for possible conducting of clinical trials in the future with collaboration at regional and international levels.

5 | CONCLUSION

Lupus will remain a disease with multiple facets. This study has shed some lights on the epidemiological and clinical characteristics of our patients. We found high occurrence of anti-Ro antibodies in this cohort. The mortality rate was similar to what is reported by other groups. Patients with positive ANA had 100% 10 years and 90% 40 years survival rates, but patients with negative ANA had lower survival outcomes in comparison to ANA positive patients. The health system, in view of a predominant young child-bearing female disease, needs to implement further improvement in the health care of the lupus population throughout its structures from primary to tertiary health care. This can be done through improvement in awareness about this disease among the public and physicians, and also improvements in screening methodology and early rheumatology referral. This study setting up future directions to follow this longitudinal cohort and to carry on other observational and clinical trials.

CONFLICT OF INTEREST

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COCHRANE CORNER

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Is Tai Chi beneficial for rheumatoid arthritis?—A Cochrane Review summary with commentary

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The aim of this commentary is to discuss the published Cochrane Review "Tai Chi for rheumatoid arthritis" [1] by Amy S Mudano, Peter Tugwell, George A Wells and Jasvinder A Singh,[a] under the direct supervision of the Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with the *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

1 | BACKGROUND

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disease.[2] It is often progressive and can result in pain, stiffness, swelling of the joints, and, in the long term, joint deformity and immobility of the musculoskeletal system that often impair patients' ability to work.[3,4] Currently, there is no cure for RA; however, with correct treatment, symptoms can be reduced and disease progression can be slowed. Treatment has a few major goals: to relieve pain, reduce inflammation, slow down or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function. In order to attain those goals, many treatments have been proposed or used. Pharmacological intervention is widely used, mainly in the form of both conventional synthetic disease-modifying antirheumatic drugs and biological disease-modifying antirheumatic drugs to slow the progression of the disease, nonsteroidal anti-inflammatory drugs for symptom-relief, or glucocorticoids to improve signs and symptoms and slow disease progression; but non-pharmacological interventions may also be important for RA treatment.[5] Patients with RA can suffer from reduced joint range and mobility that can result over time in reduced mobility and even immobility. A consequence of this reduced mobility is muscular atrophy, which can reduce mobility further, creating a vicious cycle. Specific exercises to improve strength, balance, flexibility, endurance, and aerobic capacity may improve functional capabilities and autonomy in activities of daily living. A Cochrane Review of dynamic exercise therapy demonstrated significant benefits on muscle strength, aerobic capacity, and range of motion, but it excluded studies of Tai Chi.[6] Tai Chi is a traditional Chinese martial art, that combines deep breathing and relaxation with slow and gentle movements.[7] Previous studies documented benefits of Tai Chi on health-related outcomes, namely it seems to reduce stress, increase muscle strength in the lower body, and improve balance, posture, and the ability to move.[8,9]

2 | TAI CHI FOR RHEUMATOID ARTHRITIS

Mudano AS, Tugwell P, Wells GA, Singh JA, 2019.

2.1 | What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to assess the benefits and harms of Tai Chi as a treatment for people with rheumatoid arthritis (RA).

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 9, Art. No.: CD004849, https://doi.org/10.1002/14651858.CD004849.pub2 (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 and do not represent the Cochrane Library or Wiley.

2.2 | What was studied in the Cochrane Review?

The population addressed in this review was adults with RA. The interventions studied were exercise programs with Tai Chi instruction or incorporating principles of Tai Chi philosophy. The interventions were compared with control groups who received either no therapy or alternative exercise therapy. The major outcomes studied were pain (measured on a visual analog scale at 12 weeks), disease activity (measured with the Disability Activity Scale (DAS-28-ESR) at 12 weeks), function (measured by the Health Assessment Questionnaire at 12 weeks), overall withdrawals at 12 weeks, radiographic progression, short-term or long-term adverse events, and withdrawals due to adverse events.

2.3 | What was the search methodology and search date of the Cochrane Review?

The review authors searched for studies in: MEDLINE (1946 to September 2018), Embase (1947 to September 2018), Cochrane Central Register of Controlled Trials (to August 2018), search of trial registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) portal (apps.who.int/trialssearch), Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases (1982 to September 2002), Beijing Chinese Academy of Traditional Medicine (to December 2003), the Chinese Biomedical Database (to December 2003), the Allied and Complementary Medicine (AMED) database (1985 to May 2013), and the Conference Proceedings Citation Index-Science (CPCI-S) (1990 to May 2013).

2.4 | What are the main results of the Cochrane Review?

The review included seven studies with 345 participants.

The review shows that:

- Participants included in the Tai Chi group assessed their pain 2.15 points lower (better) on a scale of 0 to 10, in comparison with the change in the control group (22% absolute improvement, 95% confidence interval [CI] 11%-32% improvement). Evidence quality was very low, because of low number of patients and concerns about study design (two studies, 81 participants).
- Participants included in the control group described a mean change in pain that ranged from 0.5 points lower to 1.6 points higher.
- Patients included in the Tai Chi group scored 0.4 points lower (better) on a scale of 0 to 10 for disease activity in comparison with the control group (4% absolute improvement, 95% CI 11% improvement to 3% worsening). Evidence quality was very low, because of issues about study design and a high number of withdrawals (one study, 43 participants).
- Participants included in the control group reported no change in disease activity.
- Patients included in the Tai Chi group scored 0.33 points lower (better) on a scale of 0 to 3 for function in comparison with the control group (11% absolute improvement, 95% CI 26% to 4% improvement). Evidence quality was very low, because of issues about study design and an elevated number of withdrawals (two studies, 63 participants).
- Participants included in the control group reported a mean change in function ranging from no change to 0.1 points higher.
- 17/100 fewer patients included in the Tai Chi group withdrew from their intervention at 12 weeks (17% absolute improvement in comparison to control group, 95% CI 30% to 3% fewer). Evidence quality was low, because of the small number of patients and issues about study design (seven studies, 289 participants).
- No studies that looked specifically at radiographic progression, or short-term or long-term adverse events were found. However, two studies narratively reported some joint and muscle soreness and cramps in the text.

2.5 | What did the authors conclude?

The authors concluded that it was still uncertain if Tai Chi was beneficial for disease activity in patients with RA, namely in terms of self-reported pain, disease activity, and physical function. The authors did not find any studies that investigated radiographic progression or short- or long-term adverse events of Tai Chi, even though it was possible to find in the text of two studies narrative description of some joint and muscle soreness and cramps in a small number of participants. Fewer participants withdrew in the Tai Chi group compared with the control groups; this may be important but was based on low-quality evidence.

3 | WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN RHEUMATOLOGY?

Pharmacological interventions are widely used in RA because of their efficacy in relieving symptoms and slowing the progression of the disease, but the possible short- and long-term benefits of non-pharmacological interventions should not be underestimated.[5] An already published Cochrane Review showed that there is already enough evidence to support the use of a dynamic exercise program not based on Tai Chi principles.[6] Unfortunately, because of the availability of very-low-quality to low-quality evidence, we are uncertain whether Tai Chi improves pain, disease activity, or function in people with RA, so we cannot recommend exercise programs based on Tai Chi in everyday clinical practice. From a biological and biomechanical standpoint, and considering the evidence already gathered about exercise for muscle strengthening and aerobic training, a practice like Tai Chi that focuses on balance, coordination, proprioception,

and in general accurate body control,[7] seems likely to be beneficial. Given these factors, further studies of higher quality are needed to assess the possible benefits, and their eventual magnitude, also in comparison with different types of exercise strategies.

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

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CORRESPONDENCE

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WILEY

Explaining the natural course of gout to people living in the tropics

Dear Editor,

We read with great interest the article by Shimizu and Rooks entitled "Slowly melting the urate snow in joints: Explaining gout attacks to patients", in which they described a method of explaining the natural course of gout to patients in order to improve their adherence to long-term urate-lowering therapy (ULT).[1] We commend the authors for their simple and accurate description of gout. In this description, snow falling on a roof represents the continuous accumulation of monosodium urate (MSU) crystals in the joints. The sunlight slowly melting the snow cover clearly represents the dissolution of MSU crystals by ULT. However, the use of this method could have limited success in explaining gout to people living in tropical areas who have never encountered snowfall. For people with gout in the tropics, different analogies may be more relatable.

We would like to share other methods of explaining the natural course and treatment of gout that we have used in our practice. The first method is a modification of the "dirty dish" hypothesis, described by Perez-Ruiz et al[2] In this analogy, the dish represents the joints in which the MSU crystals (the food residue) are continually building up. The longer the dirty dish is left unattended, the more effort and time are needed to clean it properly, similar to people with advanced gout requiring more intensive and longer duration of ULT before tophus disappearance. Large chunks of food residue may slough off if the dish is scrubbed too vigorously, similar to MSU crystal shedding and subsequent gout flares that are common during the early phase of ULT.[3]

The second method is a more literal explanation of the MSU crystal deposition in gout. We ask gout patients to imagine a glass of salty fluid with coarse grains of salt within. The grains keep growing as long as the liquid is saturated with salt. The salty fluid must be exchanged with fresh water to make the grains of salt disappear. This is similar to what happens in people with gout; MSU crystals keep growing inside the joints as long as the body is saturated with urate (hyperuricemia). ULT reduces the urate concentration in the blood, and drives the dissolution of MSU crystals. Gout flares occurring soon after initiation of ULT can be explained using the same analogy; an abrupt refilling of the glass with water (ULT) causes turbulence that stirs up the grains of salt from the bottom of the glass (crystal shedding and gout flare).

For people with gout, accurate understanding of the underlying pathology of gout is essential to ensure successful control of serum urate levels. Interventions that put emphasis on patient education lead to improved adherence to ULT, more patients achieving target serum urate levels, and better clinical outcomes.[4] Explaining gout to patients is more art than science. It depends on each patient's level of health understanding, as well as geographical and cultural factors. Explaining gout using the snowfall method may be suitable for people living in countries with colder climates. The dirty dish or grain of salt analogies may be more relatable to people with a wider range of geographical and cultural backgrounds. Regardless of the methods used to explain gout, the key message that must be effectively delivered is that gout is a chronic condition that needs regular long-term treatment to keep serum urate at a target level.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KJ and ND planned and drafted the manuscript. Both authors have reviewed and given approval to the submitted version of the manuscript.

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

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

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

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

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

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