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REVIEW

APLAR recommendations on the practice of telemedicine in rheumatology

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Abstract

Introduction: The COVID-19 pandemic led to rapid and widespread adoption of telemedicine in rheumatology care. The Asia Pacific League of Associations for Rheumatology (APLAR) working group was tasked with developing evidence-based recommendations for rheumatology practice to guide maintenance of the highest possible standards of clinical care and to enable broad patient reach.

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Materials and methods: A systematic review of English-language articles related to telehealth in rheumatology was conducted on MEDLINE/PubMed, Web Of Science and Scopus. The strength of the evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach as well as the Oxford Levels of Evidence. The recommendations were developed using a modified Delphi technique to establish consensus.

Results: Three overarching principles and 13 recommendations were developed based on identified literature and consensus agreement. The overarching principles address telemedicine frameworks, decision-making, and modality. Recommendations 1-4 address patient suitability, triage, and when telemedicine should be offered to patients. Recommendations 5-10 cover the procedure, including the means, data safety, fail-safe mechanisms, and treat-to-target approach. Recommendations 11-13 focus on training and education related to telerheumatology.

Conclusion: These recommendations provide guidance for the approach and use of telemedicine in rheumatology care to guide highest possible standards of clinical care and to enable equitable patient reach. However, since evidence in telemedicine care in rheumatology is limited and emerging, most recommendations will need further consideration when more data are available.

KEYWORDS
guidelines, remote consultation, rheumatology, telemedicine

1 | INTRODUCTION

Although telemedicine services have been used in various countries for some time, there was rapid and unplanned adoption of telemedicine globally during the COVID-19 pandemic due to the disruption to health services and the need for physical distancing. The World Health Organization (WHO) has defined telemedicine as: "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities".[1] The application of telemedicine in rheumatology – so-called telerheumatology – had previously and largely been used to extend care provision in rural and remote areas. As such, knowledge gaps remain about approaches to the organization and delivery of telerheumatology to achieve the best possible patient outcomes. The recent pandemic-precipitated uptake of telerheumatology offers the potential to increase access to rheumatology care and reach hitherto underserved areas of the Asia-Pacific region. Accordingly, it can be employed in the attainment of health equity, a state which has been described by the WHO as the "absence of unfair, avoidable, or remediable differences" among specific populations delineated by a dimension of inequality, such as geography.[2] The achievement of equitable access to rheumatology care within and between countries is an attractive goal that may be more achievable with appropriately deployed telehealth.

For telerheumatology to be truly equitable, the quality of care received by patients via telemedicine must be non-inferior to in-person care. In particular, patient-reported and clinical outcomes, quality of life measures, and patient satisfaction scores, would ideally be comparable between teleconsultations and in-person visits. As continuous effort is made in practice toward reaching the difficult goal of health equity via telemedicine, the delivery of non-inferior care through telemedicine remains the minimum standard. The literature to date may identify strengths and limitations of telemedicine and factors influencing the acceptance, access, and efficacy of telemedicine. To this end, an Asia Pacific League of Associations for Rheumatology (APLAR) working group undertook a systematic literature review to inform and develop this set of recommendations on telemedicine in rheumatology. The overall aim was to inform new approaches to rheumatology care via telemedicine that complement current in-person care and potentially extend affordable, high-quality care to underserved areas and patients. The recommendations do not cover infrastructure, data management systems, and other "how-to" steps for telemedicine.

2 | MATERIALS AND METHODS

All 34 APLAR Member National Organizations (MNOs) were invited to put forward a working group member as representative, and consequently a working group was formed with 18 members from volunteering MNOs. First the working group convened online on

8 April 2021 to discuss and identify areas of telemedicine practice most relevant to rheumatology practice. Through iterative editing of a document summarizing the areas identified, 14 discrete, clinically relevant questions related to telemedicine in rheumatology were formed in PICO (Patient/Population, Intervention, Comparison, Outcome) format. These research questions were then used to establish keywords for a systematic literature search across 3 databases: MEDLINE/PubMed, Web Of Science and Scopus. The search was limited to English language articles published from inception to May 2021, and the resulting articles were then matched according to their relevance with each clinical question, some articles informing more than one question. A detailed protocol for the literature search was registered with PROSPERO (registration number: CRD42021258712).

The working group members were divided into 4 sub-groups and assigned different sets of research questions, then tasked with reading and critically evaluating the articles and drafting preliminary guidance statements, which included generation of some overarching principles. The working group convened for 2 meetings via video-conferencing on 23 July 2021 and 13 October 2021 to review the guidance statements and supporting evidence and to undertake consensus voting. At the first meeting, 1 member from each subgroup presented the draft recommendations along with tables of the supporting evidence. The evidence from each article was graded according to 2 complementary grading systems (Tables S1 and S2): Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) and the Oxford Levels of Evidence (2011).[3-5] During the meeting the guidance statements were edited and refined as informed by the gradings to determine the strength of the wording for each recommendation statement. Where evidence was lacking, no grade was assigned, but the strength of the statement wording reflected this, and recommendations were then generated based on clinical expertise and experience of working group members, in order to provide practical guidance in the areas of telemedicine considered most relevant to rheumatology practice.

The voting process followed a modification of the Delphi method, in keeping with previous APLAR recommendations,[6,7] and was carried out by a voting group composed of working group members and representatives from the executive and scientific committees of APLAR. Voting took place after the presentation of each recommendation, the summary of the evidence, and the editing of the statement, as outlined earlier. Voting used a numeric rating scale from 1 to 5 where 1 corresponded to strongly disagree, 5 meant strongly agree, and 3 implied a neutral stance (neither agree nor disagree). The votes were then tallied up, and an average score was calculated based on the assigned values. A consensus was reached if there was an average score of ≥3.5, which equated to ≥70% agreement, as determined a priori. At the second meeting, all the recommendations were presented again, along with the results of the first round of voting. Following active discussion, there was further editing and refining of statements according to the members' increased understanding of the concepts and literature. Then a second vote took place for any recommendation statements that did not reach a consensus in the first voting round or that had been significantly re-worded. Thirteen recommendations were agreed upon, covering key aspects of rheumatology in telemedicine.

3 | RESULTS

We present 3 overarching principles and 13 recommendations for telemedicine in rheumatology with their corresponding levels of agreement, grades of evidence, and rationale for inclusion, along with a discussion of the supporting literature. Table 1 provides a summary of the 3 overarching principles and 13 recommendations.

3.1 | Overarching principles

These principles were developed by the working group as a pragmatic base to scaffold interpretation of the recommendations.

1. Development of telemedicine in rheumatology services should use a framework to ensure explicit consideration of the appropriateness of telemedicine with respect to the clinical effectiveness, safety issues, patient's perspective, economic, organizational, sociocultural, ethical, and legal aspects, with an aim for equitable healthcare access for all.

   Level of agreement: 89%
   Not graded.

2. There should be shared decision between rheumatologists and patients or caregivers before use of telemedicine, ensuring understanding of advantages and limitations.

   Level of agreement: 86%
   Not graded.

3. The telemedicine modality should be appropriate for the patient, considering the diagnosis, disease activity and severity, availability of technology, and appropriately trained practitioners.

   Level of agreement: 86%
   Not graded.

Telemedicine has the potential to increase equity in access and quality of healthcare services but requires careful planning for successful implementation. A variety of telemedicine frameworks and guidelines emphasize a holistic approach with multiple domains in the life-cycle phases of a telemedicine service, including technology, organizational structure, change management, economic feasibility, societal impacts, perceptions, user-friendliness, evaluation and evidence, legislation, policy and governance.[8] The 2016 WHO strategic framework included the Model for Assessment of Telemedicine Application (MAST), as well as steps in establishment of telemedicine services with an outline of key operational issues such as legal

TABLE 1 Overarching principles and recommendations on practice and use of telemedicine

	Overarching principle	GRADE of recommendation	Level of evidence	Percentage agreement
1	Development of telemedicine in rheumatology services should use a framework to ensure explicit consideration of the appropriateness of telemedicine with respect to the clinical effectiveness, safety issues, patient's perspective, economic, organizational, sociocultural, ethical, and legal aspects, with an aim for equitable health care access for all.	Not graded		89%
2	There should be shared decision between rheumatologists and patients or caregivers before use of telemedicine, ensuring understanding of advantages and limitations.	Not graded		86%
3	The telemedicine modality should be appropriate for the patient, considering the diagnosis, disease activity and severity, availability of technology, and appropriately trained practitioners.	Not graded		86%
	Recommendation	**GRADE of recommendation[a]**	**Level of evidence**	**Percentage agreement**
1	All patients can be assessed for suitability of telemedicine follow-up and, if suitable, offered teleconsultations over a period not exceeding 12 mo.	B	3	86%
2	In a new patient without a confirmed rheumatic disease diagnosis, telemedicine consultation should be limited to early guidance to a healthcare practitioner treating the patient regarding diagnostic work-up, interim management and appropriate timing of an in-person assessment by a rheumatologist.	C	4	83%
3	Having a pre-teleconsultation triage system may help in scheduling in-person visits earlier for patients unlikely to benefit from teleconsultation alone.	C	4	78%
4	When normal health services are disrupted, scheduled telemedicine consultations are recommended over unsupervised medication changes.	B	3	90%
5	The adoption of video consultation over other forms of teleconsultation such as telephone or asynchronous messaging via email, short message services and other internet-based services, is conditionally recommended.	C	4	84%
6	Scheduling of an in-person consultation with the patient at an earliest possible date if the consulting rheumatologist comes across unexplained symptoms or has difficulty in assessing the patient or if the rheumatologist or the patient perceives a gap in communication during the telemedicine consultation, is conditionally recommended.	C	4	87%
7	Teleconsultations with a healthcare professional adequately trained in rheumatology examination, co-located with the patient, is preferred when and if feasible.	C	4	86%
8	Patient data privacy, integrity and security should be protected according to local expectations and regulations.	B	3	94%
9	Routine patient-reported outcome (PRO) collection is suggested to ensure the quality of care and may be used for pre-consultation triage.	B	3	82%
10	In rheumatic diseases where a treat-to-target approach is recommended for in-person care, a similar approach for telemedicine should be practiced.	C	2	81%
11	Rheumatologists practicing telemedicine should be acquainted with the process and technology used. Training of rheumatologists in telemedicine is conditionally recommended.	N/A	5	83%

TABLE 1 (Continued)

	Recommendation	GRADE of recommendation[a]	Level of evidence	Percentage agreement
12	Beyond patient care, telemedicine may also include training of healthcare workers (general practitioners or nurse practitioners).	N/A	4	84%
13	The potential of telemedicine platforms may be developed to provide patient education and other activities to benefit patients.	N/A	5	86%

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development and Evaluations.
[a]N/A not applicable (due to a lack of any published evidence to support this topic).

and regulatory, technology and infrastructure, human resourcing, and financial.[1]

Nevertheless, the current literature identified some barriers to the acceptability and sustainability of telerheumatology, such as limited access to technology, absence of laboratory testing or physical examination, loss of travel-related or sick-leave benefits, and concerns about data privacy.[9-13]

Given the barriers and the limited evidence about outcomes, the risks and benefits of teleconsultations should inform the patient decision about choice of telemedicine services. Current circumstances, such as convenience and safety during the COVID-19 pandemic, will influence decisions. Overall, the "fitness for purpose" of telemedicine should be considered individually for each patient. The "shared decision" between physician and patient implies that both parties understand the potential advantages and possible limitations of telemedicine.

3.2 | Summary of literature

Three randomized controlled trials (RCTs)[13-15] and 8 observational studies[12,16-22] have been conducted in 7 countries (Australia, Canada, Denmark, Hong Kong, Italy, the UK, and the US). In most studies, the patient participants had an established rheumatic diagnosis at recruitment. All 3 RCTs, as well as majority of observational studies, involved patients with rheumatoid arthritis (RA) while the rest included inflammatory arthritides (eg, psoriatic arthritis, ankylosing spondylitis), lupus, or unspecified rheumatologic conditions. Two of the RCTs included people with RA with low disease activity;[13,14] the remaining trial exclusively enrolled patients with high disease activity.[15] In terms of the mode of telemedicine delivery, both telephone consultations (n = 5) and video consultations (n = 6) occurring between the rheumatologist and the patient were used. Across the trials, outcomes were assessed at 9-12 months.

The RCTs show some heterogeneity in results. In 2 trials, both including people with RA and low disease activity, telemedicine was either non-inferior to in-person visits or not significantly different, in terms of the following outcomes: disease control, quality of life, satisfaction rates, and self-efficacy.[13,14] In the RCT including patients with high disease activity, the telemedicine group achieved a significantly better disease control than the conventional group, which may be explained by the more intensive treatment protocol in the telemedicine group.[15] Conversely, a cross-sectional study of people with RA patients showed high disease activity correlated with prior telemedicine use.[21] It seems possible that high disease activity necessitates more intensive escalation of therapy and therefore, more frequent monitoring. This management plan may be difficult to negotiate with in-person visits alone and thus drives the utilization of telemedicine in such cases.

3.3 | Recommendations

1. All patients can be assessed for suitability of telemedicine follow-up and, if suitable, offered teleconsultations over a period not exceeding 12 months.

Level of agreement: 86%
Level of evidence: 3; GRADE: B

The working group considered that any patient may be suitable for telemedicine follow-up, yet not every patient will be suitable. The period for telemedicine follow-up was limited to 12 months, given potential for fluctuation in disease activity, and that duration is the maximum reported follow-up interval for telemedicine described in identified literature.[14,15,20,21]

2. In a new patient without a confirmed rheumatic disease diagnosis, telemedicine consultation should be limited to early guidance to a healthcare practitioner treating the patient regarding diagnostic work-up, interim management and appropriate timing of an in-person assessment by a rheumatologist.

Level of agreement: 83%
Level of evidence: 4; GRADE: C

In contrast to patients with established diagnoses, there were no studies that directly compared teleconsultation and in-person visits in people without confirmed rheumatologic conditions (ie, "new" patients), possibly because most trials excluded these new patients for safety purposes. In a survey of the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN), 19 lead representatives reported that during the COVID-19 pandemic, both new referrals and established patients were seen via teleconsultation

in their respective centers, and the majority of centers (79%) felt telemedicine could be safely used for new patients.[9] However, an Australian retrospective case-control study showed that after implementation of telemedicine, the odds of making an accurate diagnosis in new patients were reduced (28.6% vs 57.4%; odds ratio 0.30; 95% confidence interval: 0.16–0.53; $P < .001$).[22] This reduced diagnostic accuracy of telemedicine was also found in prospective cohort studies of new patients from rheumatology clinics in the UK and US.[23,24] Another study showed that telemedicine shortened the wait time for an in-person visit among patients referred for assessment of positive antinuclear antibody.[25] While noting the relatively low quality of this evidence, it does suggest that while telemedicine may not be as effective as conventional consultation in the diagnosis of new patients, it can provide benefit in terms of earlier access to a rheumatologist.

Therefore, in new patients, the teleconsultation should generally be for interim management until scheduling of the earliest possible in-person visit to a rheumatologist. The presence of another healthcare professional (HCP), such as a primary care physician, who is co-located with the patient during teleconsultation could facilitate accurate assessment and appropriate interim management. In the event that a rheumatologist has a telemedicine consultation with a patient who is not previously known to them but already has an established rheumatologic diagnosis, appropriate steps should be taken to verify the diagnosis.

3. Having a pre-teleconsultation triage system may help in scheduling in-person visits earlier for patients unlikely to benefit from teleconsultation alone.

Level of agreement: 78%
Level of evidence: 4; GRADE: C

The triaging process, a separate event preceding the actual teleconsultation, aims to identify patients who may need in-person visits instead of teleconsultation, with patient safety as the primary focus. Depending on the local context, triaging in telemedicine may be conducted by an HCP or a non-HCP and may use screening questions. We found no studies that directly compared the impact of triaging versus no triaging in telerheumatology. However, in several studies demonstrating the benefits of telemedicine over in-person visits, some form of triaging was applied.

In a prospective case-control study, rheumatology clinics prioritized inflammatory and autoimmune conditions over non-inflammatory conditions.[26] One RCT including people with RA for more than 2 years implemented pre-teleconsultation collection of patient-reported outcomes (PROs), wherein detection of a flare or raised C-reactive protein (CRP) prompted an in-person visit instead of teleconsultation.[14] Another study excluded those with comorbidities requiring hospitalization, for example, heart disease, chronic obstructive pulmonary disease, dialysis.[14,15] In a more recent cross-sectional study in India, conducted at the onset of the COVID-19 pandemic, a rheumatology nurse or physician assistant screened patients before a teleconsultation using the following criteria: prior in-person visit, no new complaints, not on biologics, and not planned for interventions (eg, intra-articular injection or biopsy).[27] These studies suggest that a triaging system prior to teleconsultation may lead to more appropriate scheduling although further studies specifically addressing triaging are warranted.

4. When normal health services are disrupted, scheduled telemedicine consultations are recommended over unsupervised medication changes.

Level of agreement: 90%
Level of evidence: 3; GRADE: B

None of the identified studies directly assessed the impact of telemedicine during disruption of health services, such as in a pandemic or war, with its impact on routine health services. However, 1 study carried out in New Zealand reported emergency use of the telephone for rheumatology clinics after an earthquake, finding that 13% of patients who were reachable by telephone needed urgent assessment, and importantly, despite many challenges, telemedicine enabled a continuation of care.[28] Three studies conducted during the COVID-19 pandemic comprise low to moderate quality evidence supporting the use of teleconsultation during times of irregular healthcare delivery. Findings from cross-sectional studies in India show that without telemedicine, the majority of rheumatology patients would have stopped their medications or self-medicated,[27] especially the socioeconomically marginalized,[29] while its presence would be cost saving and improve drug adherence.[29] Similarly, in the Australian case-control study, telemedicine reduced all-cause, disease-related, and total medical costs among rheumatology patients.[22] Therefore, in the context of disrupted health care, telemedicine can be seen as a "some care" versus "no care" option, and it was agreed that in these instances, the overall benefits would outweigh the limitations, particularly if advice regarding modification of medication is required.

5. The adoption of video consultation over other forms of teleconsultation such as telephone or asynchronous messaging via email, short message services and other internet-based services, is conditionally recommended.

Level of agreement: 84%
Level of evidence: 4; GRADE: C

Several identified studies describe various modes of delivery of teleconsultation, including synchronous (ie, video, telephone) and non-synchronous (ie, email, short message service), but none performed direct comparisons between different modes of delivery. Video and telephone consultations were the most utilized modes. In the Canadian RCT for RA patients in a rural clinic, video consultations were not significantly different from in-person visits in terms of clinical outcomes (eg, Disease Activity Score-28 for RA with CRP [DAS28-CRP], RA Disease Activity Index [RADAI]) and satisfaction rates.[13] These findings are corroborated by a number of observational studies in patients with rheumatologic conditions

(mostly RA).[20,26,30] However, 3 observational studies have shown that among new rheumatology referrals, telephone consultations exhibited lower diagnostic accuracy versus in-person visits or video consultations.[22-24] Video consultations have the added advantage of allowing a presenter or facilitator to join the patient during teleconsultation, as in the hub-and-spoke model.[13,20,30] Furthermore, cross-sectional surveys among rheumatology patients in Australia and the US during the COVID-19 pandemic revealed that satisfaction rates and future acceptability of telemedicine were higher with video than with telephone consultations, alluding to the value of visual cues in teleconsultation.[31,32]

Although preferred, video use in teleconsultation will principally depend on both availability and shared decision-making between the patient and rheumatologist. In a cross-sectional study of rheumatology patients in the US, patient satisfaction with video consultations correlated with previous exposure to the technology and concerns about privacy.[33] Another cross-sectional study in India revealed that willingness of rheumatology patients to use video consultations was influenced by confidence about the physician's abandonment of the physical examination, beliefs on social distancing during a pandemic, and satisfaction with the initial encounter.[27] Collectively, these factors represent some of the elements that should be included in the discussion with the patient to reach a shared decision about the use of telemedicine.

This evidence points to a potential advantage in adopting video consultation over other forms of teleconsultation. In a recent review to assess the extent that video consultations could replace face-to-face consultations in palliative care during the pandemic, it was concluded that video consultations broke down geographical and physical barriers, enabled other HCPs or family members to be present, and generally led to positive experiences among patients and caregivers.[34] Therefore, although the specific evidence for promoting video consultations over other modalities in rheumatology is limited, from a practical perspective, face-to-face interactions via video are closer to in-person consultations than any other mode of delivery and are therefore potentially preferable. However, this recommendation should not be interpreted as suggesting that other forms of teleconsultation should not be used.

6. Scheduling of an in-person consultation with the patient at an earliest possible date if the consulting rheumatologist comes across unexplained symptoms or has difficulty in assessing the patient or if the rheumatologist, or the patient perceives a gap in communication during the telemedicine consultation, is conditionally recommended.

Level of agreement: 87%
Level of evidence: 4; GRADE: C

There are multiple ways that telemedicine can fail to achieve its intended patient and process outcomes, including the delivery of clinical care with inherently non-ideal information.[35] Clinical issues may arise so that teleconsultation is no longer appropriate. So-called "fail-safe mechanisms" are the built-in processes to avoid unacceptable risk to patient safety. None of the identified studies directly compared telehealth services with and without fail-safe mechanisms. However, 2 of the RCTs,[13,15] including people with RA and one observational study[17] of patients with inflammatory arthritis, included some form of fail-safe mechanism in their methodology.

In the study by Taylor-Gjevre et al, the fail-safe mechanism was an urgent in-person visit to the rheumatologist for patients experiencing pressing concerns between scheduled telemedicine or in-person consultations.[13] In the trial by Salaffi et al, whenever the regularly collected, internet-based PROs failed to meet predefined levels, the telemedicine platform generated automated clinical management advice for both the patient and the clinical case manager.[15] The clinical case manager could then alert the rheumatologist, who may schedule an urgent in-person visit.[15] A retrospective cohort study described a mechanism within the actual teleconsultation, such that any perception of a disease flare, side effects, or general inadequacy of the session prompted scheduling of an urgent in-person visit.[17] In these studies, the fail-safe mechanism was triggered in 7%-45% of events. The highest fail-safe trigger represented the low threshold in the Italian study, where telehealth was urgently instituted for distribution of disease-modifying antirheumatic drugs at the height of the COVID-19 pandemic.[17]

Overall, there are few examples of fail-safe mechanisms in the literature, with only low-quality evidence to support fail-safe use. Nonetheless, since patient safety is a priority in the quality-and-safety framework for improving health services,[1,36] these mechanisms seem to be an essential part of telerheumatology. Although the mechanisms will ultimately depend on the local context, a sensible mechanism is early access to in-person rheumatology assessment triggered by predetermined criteria. Some criteria may include acute disease flare and symptoms that cannot be adequately assessed or explained or managed by co-located HCPs.

7. Teleconsultations, with a healthcare professional adequately trained in rheumatology examination, co-located with the patient, is preferred when and if feasible.

Level of agreement: 86%
Level of evidence: 4; GRADE: C

A number of studies described a hub-and-spoke model where an HCP was present with the patient during teleconsultation, including a variety of HCPs (nurses, physical therapists, or unspecified non-physician presenters) with or without training in rheumatology.[13,18,20,30] In 3 of these studies, teleconsultation with a facilitating HCP was not significantly different from in-person visits in terms of disease control, satisfaction rates, and medical costs among patients with RA and other unspecified rheumatologic conditions.[13,20,30] None of these studies directly compared the impact of teleconsultation with and without facilitation, but from a practical perspective, co-location of an appropriate HCP is more important for new patients or patients with active disease in a remote area.

Until further evidence becomes available, the presence of a facilitator during teleconsultation is encouraged where feasible. Nonetheless, we recognize that access to a non-rheumatologist HCP depends on the local setting. As an example, if the patient needs to travel excessive distances to be with a facilitator, then the purpose of telemedicine is defeated. The type of HCP qualified to perform this role will also vary on a case-to-case basis. For instance, with the appropriate training, primary care physicians, nurses, and nurse practitioners are generally suitable. Meanwhile, physical therapists or physiotherapists may require even more training to reasonably facilitate the evaluation of rheumatologic diseases outside of musculoskeletal conditions. Regardless of context, we emphasize the importance of adequate training of HCPs for this role.

8. Patient data privacy, integrity and security should be protected according to local expectations and regulations.

Level of agreement: 94%
Level of evidence: 3; GRADE: B

Evidence from an extensive review of telemedicine frameworks highlights the need for a system that accounts for ethical and legal aspects by ensuring data privacy, integrity, and security.[1] Cross-sectional surveys among rheumatology patients in the US as well as patients with lupus nephritis in Hong Kong, found that concerns about data privacy and security affected patient satisfaction and acceptability of teleconsultations.[12,33] As legislation on data privacy varies widely across countries, local regulations will apply to the practice of telerheumatology. Where local regulations are not available or unclear for the setting, the onus is on the rheumatologist to ensure patient data and confidentiality are protected. The legal status of recording of the teleconsultations, especially video consultations, may not yet be clearly addressed by legislation. Hence, recording should only be done when the purpose is clearly defined, and both patient and rheumatologist give consent.

9. Routine patient-reported outcome (PRO) collection is suggested to ensure quality of care and may be used for pre-consultation triage.

Level of agreement: 82%
Level of evidence: 3; GRADE: B

The utility of PROs for in-person visits is well-recognized.[37,38] PROs support clinician-patient communication through the process of patient self-reflection and can alert both the patient and clinician to symptoms and issues that may not have been previously identified.[39] Phone applications and web platforms have enabled systematic PRO collection in research and patient care settings.[40] These electronic PRO instruments appear to be well-received by patients, empowering them to adjust treatment and lifestyle in real time, as well as providing visual feedback to positively influence treatment adherence and improve disease control.[41-43]

We did not find any studies that directly compared the effect of PRO collection in telerheumatology with no PRO collection. However, as previously discussed, 2 RCTs determined the efficacy of PRO-informed teleconsultations versus in-person visits among RA patients.[14,15] In one RCT,[14] PROs on disease activity, functional disability, adherence, and side effects were used to triage patients needing urgent in-person visits, whereas the other study[15] utilized electronic PROs (Clinical Disease Activity Index [CDAI]) to regularly monitor the response of the telemedicine group to an intensive treatment protocol. In both trials, in-person visits were not superior to telemedicine in terms of disease control.[14,15] Based on the evidence from these studies, PROs may contribute to the efficacy and safety of teleconsultations in rheumatology.

As adoption of telemedicine increases, the reliability of PROs currently applied in rheumatologic conditions (eg, fibromyalgia, osteoarthritis, osteoporosis) should be tested across various modes of administration to detect potential bias by media. Nonetheless, since PROs enhance assessment in the absence of physical examination and facilitate clinical decision-making, educating patients on their use and relevance is essential. Lastly, the choice of the appropriate PROs should be supported by data demonstrating correlation with disease outcomes, as well as endorsement from professional groups.[44]

10. In rheumatic diseases where a treat-to-target approach is recommended for in-person care, a similar approach for telemedicine should be practiced.

Level of agreement: 81%
Level of evidence: 2; GRADE: C

The treat-to-target approach is a well-accepted strategy for RA that has been endorsed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[37,45] None of the identified studies directly compared the impact of its use in telemedicine versus no use of treat-to-target in telemedicine. Nevertheless, in the absence of physical examination findings, PROs when remotely monitored may potentially allow a treat-to-target approach via telemedicine, as they have performed in conventional in-person consultations. This strategy has been described in the study by Salaffi et al, where an intensive treat-to-target approach was implemented in the telemedicine group through the application of electronic PROs.[15] Compared to a conventional strategy with regular in-person visits, the intensive treat-to-target strategy with teleconsultations and electronic PROs resulted in greater improvements in function, less radiological progression, and shorter time to remission.[15]

Evidence for treat-to-target approaches may be limited for diseases such as psoriatic arthritis, lupus or other connective tissue diseases. Despite the limited evidence specific to telemedicine, the standards of care and desired patient outcomes for telemedicine should be the same standards of care as in-person visits. Therefore, a treat-to-target approach is recommended whenever applicable. However, it must also be recognized that telemedicine inherently imposes limitations to the successful conduct of this approach for certain objective targets, such as joint tenderness or swelling.

11. Rheumatologists practicing telemedicine should be acquainted with the process and technology used. Training of rheumatologists in telemedicine is conditionally recommended.

Level of agreement: 83%
Level of evidence: 5; GRADE: N/A.

No study directly compared the impact of training rheumatologists in telemedicine with no training. In the study by Taylor-Gjevre et al which included people with RA, the participating rheumatologists received training on aspects of the teleconsultation such as software and camera use, basic principles of video etiquette and telemedicine-specific workflows.[13] The role of training in patients' acceptability of telemedicine is reflected in a cross-sectional study of RA, wherein the rheumatologists' amount of experience with telemedicine was shown to be a predictive factor for telemedicine use by patients.[21] Another uncontrolled study showed high patient satisfaction after a 2-day training of physicians in telerheumatology.[16] One survey showed that only 25% of rheumatology specialty nurses had been trained in providing telephone advice to patients.[46] Studies based on Expanding Capacity for Health Outcomes have provided indirect evidence on the role of technology-enabled collaborative learning and capacity building models in improving outcomes in several chronic non-rheumatic diseases.[47-49]

Thus, there is limited evidence to suggest that training specialists as well as HCPs who are co-located with the patients will increase the efficacy of telemedicine-based treatment and result in comparable treatment outcomes with in-person rheumatology. Regardless of the limited evidence, rheumatologists undertaking telemedicine should, at a minimum, be versed with the video or telephone software and hardware. Pending further studies, training on steps in setting up a telemedicine practice and communication skills appropriate for teleconsultation is also desirable.

12. Beyond patient care, telemedicine may also include training of healthcare workers (general practitioners or nurse practitioners).

Level of agreement: 84%
Level of evidence: 4; GRADE: N/A.

There were no studies that evaluated the effect of training the facilitators or co-located HCPs in telerheumatology. One study evaluated the role of telemedicine in training family physicians and general practitioners in rheumatology care, with the aim to empower them to help fill unmet needs in access to musculoskeletal health care.[50] The investigators designed a standardized training module, based on the Rheum2Learn Modules developed by the ACR, spreading the training sessions over 9 months. The module was comprised of a multi-modal learning approach which was a combination of face-to-face/in-person sessions, online learning modules and reflective learning. The study reported successful training of 44 family physicians and 4 allied HCPs, as evaluated by a pre- and post-test questionnaire.

Further to training opportunities, and as suggested by the WHO definition of telemedicine, teleconsultations have the potential for networking, connectivity, and ensuring equity of care through the promotion of education in remote areas.[1] Despite the limited evidence, telemedicine may ultimately help strengthen primary care rheumatology through training of non-specialist HCPs in the community.

13. The potential of telemedicine platforms may be developed to provide patient education and other activities to benefit patients.

Level of agreement: 86%
Level of evidence: 5; GRADE: N/A.

Patient education has a well-recognized role in standard rheumatology care. However, no identified studies provided evidence on its adequacy and outcomes when delivered through telerheumatology. A cross-sectional survey of rheumatology patients in Australia revealed that not all aspects of the teleconsultation were understood by the patients, highlighting the need to integrate patient education in telemedicine.[18] In recent years, other asynchronous mobile health interventions that have been studied include SMS reminders to increase medication adherence and physical activity,[51,52] as well as web-based applications for physical activity intervention, social support or group activities, gamification (ie, the use of game design in another context to increase participation), and health education.[53-55] Similarly, telemedicine platforms can also be used for group education initiatives or supervised group exercise or physiotherapy, but there remains a need to systematically study several patient outcomes, including knowledge of the rheumatologic condition, clarity in seeking specialty health care in rheumatology, ability to self-identify side effects of medications, and compliance to therapy.

4 | DISCUSSION

We have proposed 3 overarching guidelines and 13 practice recommendations for the use of telemedicine in rheumatology. The extant literature provides scant high-quality evidence on many aspects of rheumatic disease assessment and management using telemedicine, so many of the recommendations are pragmatic. The literature emerging on telemedicine in rheumatology during and after the COVID-19 pandemic will provide more data on appropriate telemedicine practices and procedures, and therefore, as further data emerges, these recommendations are likely to need updating.

While telemedicine does provide opportunities, there may be challenges to adoption, including lack of infrastructure such as limited high-speed internet in some Asia-Pacific regions or patient or rheumatologist reluctance to adopt new practices. Although smart phones are now ubiquitous even in low-income countries, these devices may not prove ideal for telemedicine.

Avoiding unacceptable risk to patients and avoiding compromise of goals of patient care must remain a key driver of telemedicine

practices in rheumatology. Nevertheless, telemedicine provides an opportunity to extend the limited rheumatology workforce, access to underserved remote populations, and increased convenience of health care for patients. Rapid adoption of telemedicine in rheumatology can begin to address inequitable access to health care.

Patient and public involvement has a well-recognized role in the development, implementation, and dissemination of clinical practice guidelines. However, during the formulation of these recommendations, we encountered challenges in selecting a truly representative group of patients that could capture the inherent diversity of patient values and perspectives across all 34 MNOs. Accordingly, patient representation was lacking in the working group, posing a limitation to our recommendations. Notwithstanding, to provide a venue for patient feedback, we presented draft recommendations to both physician and patient attendees of the APLAR Annual Congress in August 2021, where the recommendations received no negative response. Following the adoption of these recommendations, we encourage efforts toward continuous and multinational evaluation of patient acceptability, experiences, and satisfaction with telerheumatology, so that these guidelines can be updated and refined.

5 | CONCLUSION

These recommendations may guide implementation or continuation of telemedicine with guidance on minimum essential elements and provide practical and relevant information on the practice and use of telemedicine, to meet the needs of patients and clinicians globally who are taking advantage of this fast-growing branch of rheumatology. The guidelines bring together evidence from the literature and expert consensus, in addition to incorporating educational aspects, and align with clinical experience and expertise, with the overall aim of bringing state-of-the-art rheumatology care to the most underserved areas.

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CONFLICTS OF INTEREST

SA has received honorarium as speaker from Pfizer, Dr Reddy's, Cipla and Novartis (outside of submitted work). RG has received honoraria as speaker for AbbVie Australia, Cornerstones, Janssen, consulting fees from Novartis, AstraZeneca and non-financial support from Janssen Australia and Pfizer Australia (outside of submitted work). AS has received honoraria as speaker for Pfizer, Janssen and Boehringer-Ingelheim and non-financial support from Pfizer (all outside of submitted work). AA, KA, YHC, CK, NSKK, AK, SEAK, BM, SN, FP, NR, HS, MGS, AST and LT declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the manuscript. Each contributed to the formulation of the research questions for the literature search and assessment of the literature as per GRADE and Oxford Level of Evidence. SA led and supervised the planning and execution of this APLAR project. SA, RG and AS had substantive roles in drafting the initial manuscript. All authors participated in critically revising the contents of the manuscript, approved the final version to be published and agree to be accountable for all content.

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SUPPORTING INFORMATION

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REVIEW

B7 immune checkpoint family members as putative therapeutics in autoimmune disease: An updated overview

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Abstract

Autoimmune diseases, especially among young people in the US, are one of the leading causes of morbidity and death. The immune responses are the fundamental pathogenicity of autoimmune disorders. The equilibrium between stimulatory and inhibitory signals is critical for the stimulation, migration, survival, and T cell-related immune responses. The B7 family can substantially regulate T cell-mediated immune responses. Nevertheless, recent breakthroughs in immune checkpoint blockade in cancer immunotherapy have facilitated autoimmune diseases, especially among the prone populations. In the current study, we tried to concisely review the role of the B7 family in regulating immune reactions and the influence of immune checkpoint inhibitors on autoimmunity development.

KEYWORDS
autoimmune disease, B7 family checkpoints, host immune response, immune checkpoint

1 | INTRODUCTION

The immune system consists of a large arsenal of effector mechanisms that can inflict catastrophic damage to attacking pathogens, but it can also cause a great deal of harm to the body itself.[1] A significant global health burden that affects about 5% of the population is autoimmune diseases (AID).[2] AID is one of the principal causes of mortality among young women in the US.[3] Autoimmunity occurs when extremely active immune responses act toward their own body's tissues.[4] Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), ankylosing spondylitis (AS), psoriasis, and inflammatory bowel disease are well-characterized AID.[5] The main symptoms and mechanisms of some common AID have been presented in Table 1. The regulated immune system coordinates immune homeostasis and self-tolerance by establishing robust immune responses to pathogens.[6,7] Dysregulated immune tolerance triggers immune responses and inflammation, which leads to tissue injury.[8] "Two signal theory" highlights the critical roles of co-inhibitory and co-stimulatory signals in mounting anti-tumoral immune responses.[8,9] Physiologically, co-stimulatory molecules pave the road for immune responses against foreign antigens, and co-inhibitory molecules are essential for peripheral tolerance to maintain self-tolerance. The co-stimulatory and co-inhibitory molecules have pivotal roles in the pathogenesis of AID.[10] The B7 family members have been documented to regulate T cell-mediated immunity.[11] Via the CD28-positive lymphocytes, B7 ligands deliver these co-stimulatory or co-inhibitory signals.[12] The best-known T cell ligands include B7-1 (CD80) and B7-2 (CD86), sharing 2 receptors, CD28 and cytotoxic T lymphocyte antigen-4 (CTLA-4) (CD152). To regulate T cell proliferation, differentiation, survival, and T cell-dependent B cell responses in many diseases, especially in autoimmunity, the balance between $CD28^{+}$, and CTLA-4

signals seems to be important.[13] Since then, the capacity to effectively attack checkpoint modulators has led to several clinical trials of antibodies attacking the B7 family members' cascades.[14] This review aims to demonstrate the role of certain CD28-B7 family immune checkpoints in AID pathogenesis.

2 | IMMUNE CHECKPOINTS

The activation of T cells depends on 2 separate signals; the first signal is that antigen-specific T cell receptor (TCR) cognate engagement with peptide antigens is presented on the surface of antigen-presenting cells (APC) by major histocompatibility complex class II (MHC II) molecules. The interaction of CD28 on T cells with the co-stimulatory agents like B7-1 and B7-2 on APCs provides the second signal.[15,16] In the same fashion, the co-inhibitory signals can impede developing immune responses.[17,18] The proliferation of T cells depends on the involvement of co-stimulative molecules, for example, CD28, along with antigen/MHC and TCR axis.[15,19] However, the participation of co-inhibitory molecules, for example, CTLA-4, blocks the subsequent stimulation of T cells.[15] In a physiological condition, immune homeostasis must also be adequately controlled by a mixture of activating and inhibitory immune signals identified as immune checkpoints.[20] For maintaining self-tolerance, inhibitory immune checkpoints are crucial for preventing tissues from immune system disruption and giving defensive immunity.[21] Inhibitory immune checkpoints substantially regulate T cells' aberrant activation and terminate the AID.[22] The B7 family belongs to immune checkpoints, which their interactions with different receptors can elicit both stimulatory and inhibitory signals.[23] These family members are pivotal health and disease modulators of immune function.[24] The expression of B7 ligands on lymphoid and non-lymphoid cells is indicative of their notable roles in directing immune responses in cancer and AIDs. Therefore, regulation of this interaction by different immunotherapy approaches is an essential instrument for the prevention and treatment of immune disorders.

3 | THE ROLE OF IMMUNE CHECKPOINTS IN AUTOIMMUNITY

Immune checkpoints have an important function in maintaining tolerance. A defect in the co-inhibitory molecules' negative signals can lower the autoreactive lymphocyte activation threshold and contribute to the development of AID.[22] Following the loss of T regulatory cells and tissue damages, dysregulated stimulation of T cells can pave the road for developing AID.[8,25] In human samples, CTLA-4 gene mutation gives rise to dysregulation of immunity,[26] and also PDCD1 gene polymorphisms are correlated with susceptibility to AIDs such as RA,[27] SLE,[28] MS.[29] Dysfunction of immune checkpoints in mice models led to a variety of autoimmunity conditions. For instance, deletion of PD-1 in the BALB/c animal model results in autoimmune cardiomyopathy.[30] Also, the disruption of the PD-1 gene in the C57BL/6 murine model promotes a late-onset lupus-like disease.[31] Additionally, several other immune checkpoints can be associated with autoimmunity. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a new immune control point, and vulnerability to experimental autoimmune encephalitis (EAE) has been recorded due to the absence of TIGIT in mice.[32] Mice without B and T lymphocyte attenuator (BTLA) develop multi-organ inflammatory infiltrates.[33] Further, LAG-3 knockout (KO) non-obese diabetic (NOD) mice develop diabetes. Lacking TIM-3 can also be correlated with RA, MS, and AS.[34-36] Therefore, different types of immune checkpoints have a pivotal role in autoimmunity (Figure 1).

Highlights

- Discovering novel approaches to manage autoimmune diseases (AID) is crucial.
- Numerous studies have described the role of immune checkpoint molecules in AID.
- Here, the molecular participation of the B7 immune checkpoint family in AID is reviewed.
- Targeting these checkpoint molecules is an efficient approach in AID therapy.

4 | THE CLASSIFICATION OF IMMUNE CHECKPOINTS

Among co-signaling molecules, the B7/CD28 family molecules have essential and special functions. These molecules are type 1 transmembrane proteins distinguished by an extracellular N-terminus.[37] The B7/CD28 axis was the first to be recognized and the most widely investigated ligand/receptor complex for T cell co-stimulation.[38] The B7 family includes 10 members, that is, B7.1, B7.2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6, and B7-H7[39] (Table 2). Neutralizing the co-stimulatory pathways to alleviate AID has led to various medicines being marketed.[37] The US Food and Drug Administration (FDA) approval of many drugs to treat cancer and AID by targeting the ligands or their receptors has demonstrated the relevance of these molecules.[14,40] The remarkable success in treating cancer and AID by B7 family members has attracted significant interest in recognizing other regulators of T cells.

4.1 | B7-1

B7-1 (also known as CD80[41]) is expressed on resting APCs at low levels and is up-regulated with extended contact with T cells.[42] While the TCR is involved, the B7-1 or B7-2 co-stimulatory signal via CD28 enhances the secretion of interleukin (IL)-2 in T cells, thereby preserving them from apoptosis and anergy.[43] CD28 expressed on APCs such as dendritic cells (DCs), B cells, and macrophages make

TABLE 1 The possible mechanisms by which B7 family molecules can control autoimmune disease activity and pathogenesis

Autoimmune disease	Molecules involved	Mechanism
Multiple sclerosis	B7-1 B7-2 B7-H3	Reactive astrocytes in chronic active lesions of multiple sclerosis express the co-stimulatory molecules B7-1 and B7-2
Systemic lupus erythematosus (SLE)	B7-1 B7-2 B7-H1 B7-H2 B7-H3 B7-H4	SLE-related defects in APC function in vitro can be explained by abnormalities in APC surface membrane molecules such as B7, IgG Fc receptors, and possibly others. Recently, the B7H1 gene was found to be located within the vulnerable locus of human SLE. ICOS indicates a higher frequency of circulating T follicular helper cells in SLE compared to healthy controls
Rheumatoid arthritis (RA)	B7-1 B7-2 B7-H1 B7-H2 B7-H3 B7-DC B7-H4	Cellular interaction between synovial infiltrating T lymphocytes and synovial cells via the B7/CD28 pathway is closely associated with the development and exacerbation of inflammation in RA synovial cells. Increased B7H3 expression is an indicator of RA's more severe activity and may be involved in disease progression through cytokine secretion. Expression pattern of B7H4 in synovial tissue and PBMC subsets of RA patients. This suggests that B7H4 is involved in the pathological changes in RA progression
Type-1 diabetes mellitus (T1DM)	B7-1 B7-2 B7H3	Decreased levels of B7.1 and B7.2 expression at DC may contribute to the development of T1DM, thereby through or more likely generations through decreased expression of inhibitory receptors. Hypothesis and regulation that may shift immune imbalance to self-reactive T cell phenotype by affecting CD4 + CD25 + T cell homeostasis taking into account the relationship between clinical characteristics of T1DM patients and sB7H3 levels, renal function (Cr, BUN, ACR) and sB7H3 were found to be positively correlated
Autoimmune thyroid diseases	B7-2	Co-stimulation is required at the effector stage of EAT, and B7.2 may play the opposite role in activation compared to the effector stage of autoreactive T cells

Abbreviations: APC, antigen-presenting cells; ACR, albumin-to-creatinine ratio; BUN, blood urea nitrogen; Cr, creatinine; EAT, experimental autoimmune thyroiditis; DC, dendritic cells; ICOS-L, inducible T Cell co-stimulatory; IgG, immunoglobulin G; PBMC, peripheral blood mononuclear cells

a homodimer on the cell membrane and bind to B7-1 and B7-2.[44] The TCR signal causes the tolerance of T cells to their cognate antigen without co-stimulation, instead of being activated.[43] B7-1 has a pivotal function in immune response propagation. T cells express CTLA-4 after activation, which has a higher affinity than CD28 for B7-1 and B7-2.[42,45] CTLA-4, a 188 amino acid glycoprotein, is expressed on activated T cells.[46] CTLA-4 is a cell surface molecule intimately associated with CD28. It has also been described to be a potent negative regulator of the activation of T cells.[47] The potential of anti-CTLA-4 antibodies to cause T cell activation first has also been reported CTLA-4 germline deletion has been identified to cause serious AID with early lethality.[48] Engagement of CTLA-4 delivers negative signaling to T cells, resulting in T cell responses being inhibited and/or terminated.[42] Using COS cells (COS; an abbreviation for CV-1 in Origin with SV40 genes) expression cloning, numerous pieces of evidence identified PD-L1 as a ligand for B7-1 that showed PD-L1-transfected cells bound to B7-1-Ig immobilized on anti-Ig-coated plates.[49] Different experiments have been conducted to determine the role of the B7-1/ PD-L1. PD-L1/ B7-1 blockade interaction breaks T cell anergy and oral tolerance and accelerates

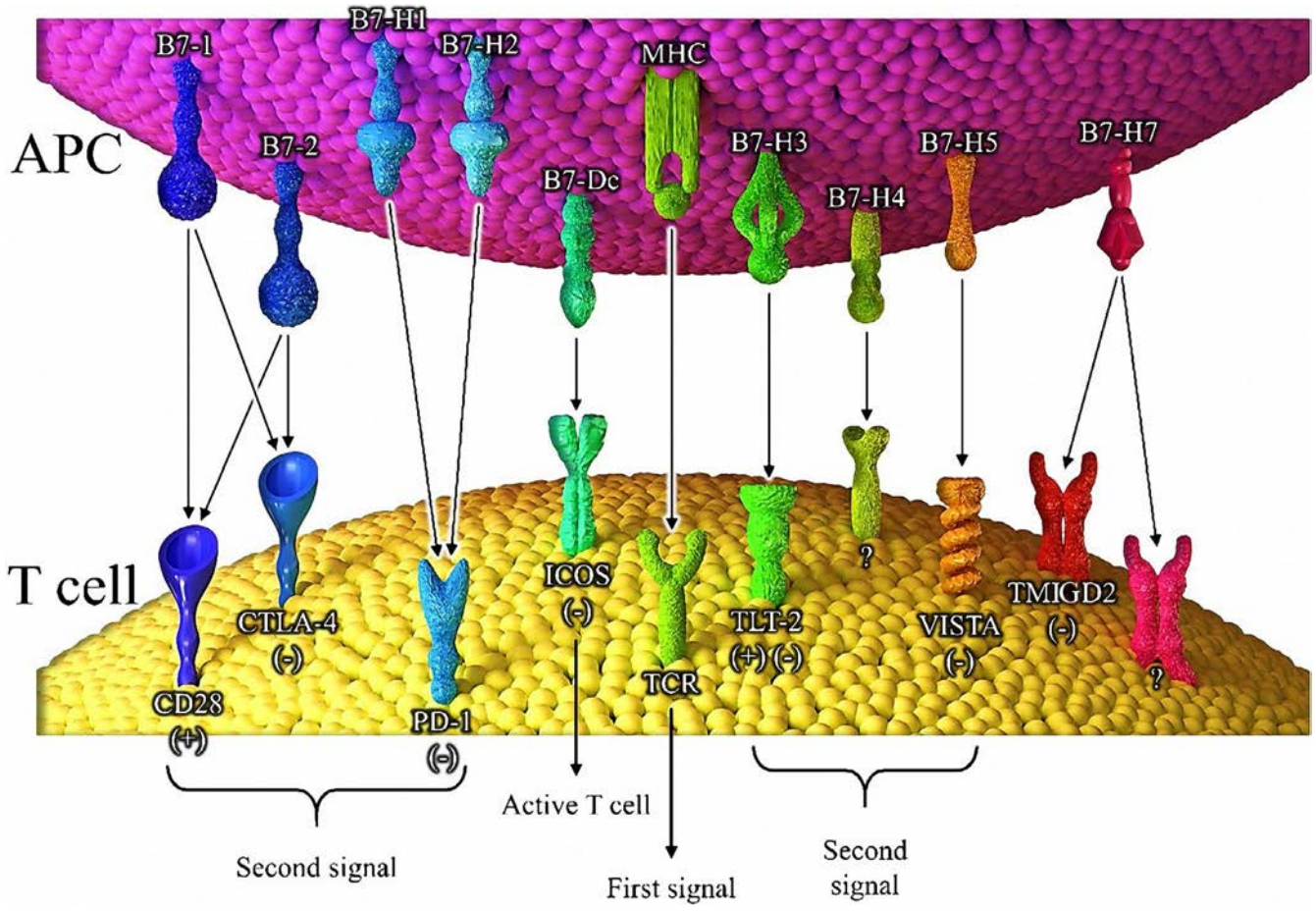

FIGURE 1 Overview of the B7 family checkpoints and their receptors. The B7 family and the application of antigens to T cells. Antigen-presenting cells (APC) or APC-like cells present a basic antigen to the T cell receptor (TCR) of T cells on major histocompatibility complex (MHC) molecules. The CD80/CD86 classically illustrates this. However, over the past few years further B7/CD28 family member proteins have been identified. They can be subdivided into novel B7s such as programmed death-ligand 1 (PD-L1), inducible costimulator of T cells (ICOS)/ICOS ligand (ICOS-L), B7-H3, and B7-H4, all of which can minimize CD4+ T cells' function and distorts the response of CD4+ T cells to a Th2 cell or Treg cell phenotype. In addition to these B7 family members, potential family members such as T-cell activation suppressor V-domain immunoglobulin are also newly identified (VISTA). CTLA-4, cytotoxic T lymphocyte antigen-4; TLT-2, trem-like transcript 2 protein; TMIGD2, transmembrane and immunoglobulin domain containing 2

TABLE 2 Common name, relative ligands, date of discovery of the family of B7 immune checkpoints

Immune checkpoint	Common name	Major receptor	Date of discovery	References
B7-1	CD80	CD28	1991	46,49,50,77,115
B7-2	CD86	CD28	1994	52,54,76,132,133
B7-H1	PD-L1	CD279 (PD-1)	1999	42,65,66,115,134
B7-H2	ICOS-L	CD278 (ICOS)	1999	65,72,132,135
B7-H3	CD276	TLT-2	2001	46-48,81,115,136
B7-H4	B7X	?	2003	8,73,115,137
B7-H5	VISTA	?	2011	31,66,69,91,92,115
B7-H6	NCR3LG1	NKP30	2009	93,94
B7-H7	HHLA2	TMIGD2, KIR3DL3	1999	95,96

Abbreviations: BTLA, B and T lymphocyte associated; ICOS-L, inducible T Cell costimulator ligand; MS, multiple sclerosis; PD-L1, programmed death-ligand 1; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, Type 1 diabetes mellitus; TLT-2, trem-like transcript 2 protein; VISTA, V-domain immunoglobulin suppressor of T cell activation.

progression to autoimmune diabetes in NOD mice.[49] This promotes an inhibitory role in the activation of T cells. In collagen-induced arthritis (CIA), the pivotal role of CD28 in RA pathogenesis was first demonstrated in a mouse model using the recombinant CTLA-4Ig recombinant experiment.[50]

4.2 | B7-2

B7-2 (also known as CD86[41]) is expressed constitutively and up-regulated rapidly on APCs.[42] B7-2 is likely to be primarily implicated in mediating the activation of initial T cells.[42] In the association between B7-1 / B7-2 and CTLA-4 molecules expressed in T cells, an inhibitory signal for down-regulation of T cells' functions was induced.[41,46] On resting T cells, CTLA-4, one of the CD28 homologs, does not exist but is expressed following T cell stimulation.[41] CD28-B7-1/B7-2 binding inhibitor and CTLA4-Ig may be used to treat AID.[41] Previous findings showed that B7-1/B7-2 molecules' binding in their ligand to APCs generate modulation safety response and APC activation suppression.[46,51] The CTLA-4 gene has been shown to influence alternate splicing and is associated with susceptibility or tolerance to AIDs. Accelerating autoimmune pathology has been shown to increase the expression of a soluble splice type (CTLA-4), lacking the transmembrane domain encoded by exon 3.[52] Further results support the fact that alternative splice forms of CTLA-4 influence the susceptibility of diabetes in NOD mice and indicate the clinical benefits of antisense-mediated splice-switching to modulate immune reactions.[52] NOD mice deficient in the co-stimulatory molecule B7-2 (NOD-B7-2KO mice)[53] were shown to be safe from autoimmune diabetes and sialadenitis, but autoimmune peripheral polyneuropathy was spontaneously formed[52,54]. As seen by several groups determining the function of B7 association of CD28/CTLA-4 in the induction and perpetuation of experimental allergic encephalomyelitis, co-stimulation of B7 was found to be a significant factor for encephalitogenic encephalomyelitis in the animal model for MS.[54] Moreover, Kinoshita and colleagues have declared both B7-1 and B7-2 related co-stimulatory pathways are involved in the pathogenesis of SLE.[55] B7-1 and B7-2 deficient MRL-Faslpr have shown improved survival in comparison to MRL-Faslpr mice with B7-1 and B7-2 positive kidney-infiltrated leukocytes.[55]

4.3 | B7-H1

B7-H1, also referred to as programmed death-ligand 1 (PD-L1),[56] is an inhibitory molecule, which is a member of the B7-CD28 family.[57,58] The B7-H1 molecule is involved in TCR-mediated proliferation inhibition and cytokine formation.[59] The B7-H1 cascade contributes to the negative modulation of specific immune responses. It may have an essential impact in controlling peripheral tolerances.[59] Owing to the lack of peripheral resistance of self-reactive T cells, the genetic removal of PD-1 (also referred to as CD279[60]) results in severe autoimmunity.[43] PD-1 is a co-inhibitory protein that regulates the balance of activation, resistance, and functional exhaustion of T cells.[61] The PD-1 checkpoint struggles to avoid autoimmune degradation in T1DM, MS, SLE, and RA.[62] The therapeutic role of interferon (IFN)-β in MS patients tends to be due to the PD-L1 expansion of myeloid cells.[63] The activated $CD4^+$ and $CD8^+$ T cells express this molecule, which subsequently binds to its ligand on APC and inhibits T cells. Since PD-L1 controls peripheral tolerance, tumoral cells express PD-L1 and suppress anti-tumoral immune reactions.[49,60] Consistent with this, the axis protects the pancreatic islets from self-reactive T cells in patients with T1DM.[65] Moreover, the up-regulated expression of PD-L1 is correlated with lymphocyte infiltration and disease progression. Although PD-L1 can protect the cells from autoreactive T cells, NOD female mice have been prone to develop autoimmunity. This is consistent with the recent observation in diabetic human samples of T1DM. Besides T1DM, PD-L1 deficiency can promote the development of MS in mice models. To attenuate the inflammation, there has been an increased expression of B7-H1 in the affected tissue of SLE and RA subjects.[66] In murine models, some approaches have been developed for targeting this critical interaction between PD-1/PD-L1. For instance, for treating EAE, transferring DCs which express PD-L1 can be useful.[67] In autoimmune BXSB mice, overexpressing PD-L1 by recombinant adenovirus can engage PD-1 and hinder lupus nephritis.[68] Therefore, PD-1/PD-L1 interaction can be beneficial for AID therapy.

4.4 | B7-H2

A significant member of the inducible costimulator of T cells (ICOS)/ICOS ligand (ICOS-L) signaling cascade along with its receptor ICOS is ICOS-L, also called B7-H2, B7h, GL50, B7RP-1, ICOSLG, CD275, ICOS-L, or LICOS[69,70] acts as the ICOS ligand and promotes differentiation of T cell activation and effector responses. Induction of both Th1 and Th2 cytokines, including IL-4, IL-10, and INF-γ, can be increased by co-stimulation via ICOS.[71] Inflammatory response, transplant rejection, and AID are associated with the ICOS / ICOS-L signaling cascade.[69] A variety of AID have been related to the ICOS gene region, for example, T1DM, autoimmune thyroid diseases, MS, and coeliac disease.[72] ICOS is significantly increased on activated T cells in RA and SLE subjects.[73,74] Also, for inducing CIA in the murine model, ICOS signaling is required. Moreover, an antibody against ICOS-L impedes T follicular helper (Tfh) cells which have high expression of ICOS.[75] In SLE patients, Tfh cells enhance with increased ICOS expression and IFN-γ production gives rise to autoantibody secretion.[74]

4.5 | B7-H3

B7-H3, also known as CD276, is a type I membrane protein sequence similar to the extracellular domain of B7-H1.[14,76] B7-H3 has a single domain identical to IgV and IgC with a transmembrane and intracellular tail in humans and mice.[76] This type I transmembrane glycoprotein

encoded by chromosome 15 in humans shares its 20%–27% amino acid sequences with other B7 family members.[77] Although this molecule is rarely found in lymphoid tissues, other tissues commonly express B7-H3 on their cell surface.[17] B7-H3 is not expressed substantially on freshly isolated lymphocytes; however, the expression level of B7-H3 may be up-regulated on DCs and monocytes/macrophages upon developing immune responses.[47] B7-H3 was reported to be a co-stimulatory molecule expressed by a wide variety of cells, such as activated T cells, epithelial cells, and natural killer (NK) cells.[56] While initially established as a T cell function activator, other investigations have shown that B7-H3 can contribute to T cell activity down-regulation.[78] There is a controversy regarding the role of B7-H3 in the activation of T cells; some reports have indicated the stimulatory role of B7-H3 in the activation of T cells.[47] Either genetic KO or antibody blockade ablation of B7-H3 increased autoantibodies production, followed by more severe kidney impairment. Studies confirm that intrinsic B7-H3 suppresses the development of autoantibodies and disease progression in this SLE model.[47] Since B7-H3 expression is enhanced by inflammatory cytokines in human monocytes and DCs, its possible immunoregulatory role at inflammation sites has been suggested. In the pathophysiology of complex inflammatory diseases, including AID, monocytes play a crucial role.[79] Earlier studies showed that B7-H3 upregulation provided an indication of more extreme RA activity and may be involved in the progression of the disease through inflammatory cytokine production, such as TNF-α.[80] In addition to membrane B7-H3 (mB7-H3), its soluble form (soluble B7-H3, sB7-H3) could be identified in the serum of healthy volunteers and suggested a functional impact in controlling the mB7-H3 / B7-H3R cascade.[81] High levels of B7-H3 expression in macrophages in RA tissues have been shown to increase macrophages' ability to promote an inflammatory response. The inflammatory response was reduced by blockade with anti-B7-H3, indicating that B7-H3 may be used as a drug target for RA treatment.[48] In MS, myelin basic protein (MBP)-stimulated $CD14^+$ and $CD19^+$ cells from relapsing MS were found to have the highest expression levels of mB7-H3.[81] Although the expression of mB7-H3 was up-regulated on T cells from the cerebrospinal fluid (CSF) of MS subjects, it is unclear if the proportion of activated T cells is reflected by $mB7\text{-}H3^+$ T cells.[81] The expression levels of mB7-H3 and sB7-H3 were finely associated with the clinical characteristics and outcomes of MS subjects.[81]

4.6 | B7-H4

B7-H4, also known as B7x, B7S1, and VTCN1, was initially established as a negative T cell regulator.[8] Human B7x (hB7x) is on chromosome 1p12/13.1 and inhibits the proliferation of T cells and arrests the cell cycle.[82] In the regulation of immune T cell responses, the immune checkpoint protein B7-H4 plays a significant part.[83] The binding of T cells from B7-H4 to $CD4^+$ and $CD8^+$ prevents their activation and proliferation.[83] B7-H4 is predominantly expressed in B cells, macrophages, mature DCs, and T cells.[84] However, the trans-binding partner in the T cell plasma membrane for B7-H4 has not been verified yet.[83] With 87% shared amino acids between the human and mice versions, this molecule comprises one IgV and one IgC domain.[14] B7-H4 is primarily expressed on non-lymphoid tissues rather than lymphoid tissues, for example, spleen and thymus.[9,85] Indeed, B7-H4 can be expressed at a low level in non-lymphoid tissues, for example, tubular cells and renal glomerular epithelial cells.[9] Previous studies have shown that an irregular B7-H4 expression is identified in people with inflammation, AID, and viral infections.[86] B7-H4 messenger RNA can be widely identified in normal human samples; however, the immunohistochemical study does not indicate positive staining of B7-H4 protein from healthy individuals in any samples.[28] Since this elevated soluble B7-H4 has been correlated with disease progression in RA subjects and lupus-prone autoimmune mice, the soluble B7-H4 will act as a decoy molecule to reduce the inhibitory role of the B7-H4-H4 cell surface.[8] In rheumatoid synovium, expression of B7-H4 was detected on endothelial cells $CD31^+$, $CD34^+$ $CD68^+$ macrophages, synovial cells, membranes, new blood vessels, $CD19^+$ B cells, and $CD14^+$ monocyte cytoplasm.[86]

As B7-H4 deficient mice have developed a more aggressive AID than wild ones, this molecule has been designated as an inhibitory molecule in T cell activation. In line with that, it has been described that the blockage of B7-H4 can exacerbate autoimmunity.[87] Overall, B7-H4 can control the initiation and severity of AID and has a remarkable role in peripheral tolerance.

4.7 | B7-H5

B7-H5, also referred to as V-domain-containing Ig suppressor of T cell activation (VISTA),[88] is a type I membrane protein homologous to PD-L1 which is an extracellular domain.[14] In mature CD11b high myeloid-derived APCs and, to a lesser extent, $CD4^+$, $CD8^+$, T reg, and tumor-infiltrating lymphocytes, VISTA is highly expressed.[89] VISTA-Ig study and genetic ablation have shown that VISTA is a detrimental activation of T cells as an immune checkpoint.[40] VISTA's genetic deletion culminates in autoimmunity mediated by T cells.[90] VISTA is expressed as a receptor on T cells and conveys the signals to control T cells activation.[89] Therefore, this axis can serve as a treatment intervention approach for AID-suffered patients.[40] In line with this, the KO of B7-H5 has contributed to strain-specific spontaneous autoimmunity.[66] Further, VISTA-deficient mice bred into transgenic 2D2 TCR mice specific for myelin oligodendrocyte glycoprotein have been susceptible to experimental autoimmune encephalomyelitis.[91] Antibody-mediated VISTA suppression has exacerbated the development of AID,[57,91] which indicates its unique and non-redundant function in regulating autoimmunity compared to other B7 family ligands, that is, PD-L1 and PD-L2.[57] Furthermore, blocking VISTA in mice models can enhance the progression of arthritis and lupus.[90]

Although B7-H5 has been found in healthy and affected human synovium tissues,[92] the role of B7-H5 in the normal human synovium tissues and the pathogenesis of RA remain unclear. There have been no substantial differences between SLE and discoid lupus

erythematosus in terms of B7-H5 expression.[66] Researchers are currently using immune-inhibitory receptors in autoimmune disorders such as ligand -Fc or receptor -Fc fusion proteins such as CTLA-4 receptor -Fc fusion protein, which is FDA-approved for RA. Moreover, patients with SLE frequently display higher expression levels of the VISTA gene in the circulating immune cells.[66] Although B7-H5 can reduce autoimmunity in MRL/IPR mice, the involved cells and immunosuppressive mechanisms are not well known.[66]

4.8 | B7-H6

B7-H6, also known as NK Cell Cytotoxicity Receptor 3 Ligand 1 (NCR3LG1), is a ligand of NKp30. B7-H6 consists of 2 Ig domains and its sequence is homologous to the other members of the B7 family.[14] B7-H6/NKp30 interaction results in NK cell activation and cytotoxicity. Inflammatory stress can induce the expression of B7-H6 in healthy cells.[93,94] There is no substantial about the B7-H6 gene and AID.

4.9 | B7-H7

B7-H7, also known as Human Endogenous Retrovirus-H Long Terminal Repeat-Associating 2 (HHLA2), is a new B7 family member which could have both inhibitory and stimulatory effects on activation and proliferation of T cells and cytokine production, depending on its receptor interaction.[95,96] The CD28 family member transmembrane and Ig domain containing 2 (TMIGD2) mediates HHLA2's co-stimulatory function on T and NK cells. KIR3DL3 (killer cell immunoglobulin-like receptor with 3 immunoglobulin domains and a long cytoplasmic tail) acts as an HHLA2 co-inhibitory receptor, confirming TMIGD2's co-stimulatory function.[97] There is no study on the relationship between this gene and autoimmune diseases and it can be evaluated as a therapeutic target in AID.

4.10 | B7DC

Two recognized ligands are present in PD-1: PD-L1 (B7H1; CD274) and PD-L2 (B7DC; CD273).[98,99] T cell proliferation, cytokine production, and cell adhesion are inhibited by both PD-L1 and PD-L2.[99] However, in DCs, PD-L2, but not PD-L1, activates reverse signaling leading to IL-12 development and T cells' activation.[99] Expression of PD-L1 and PD-L2 relies on separate stimuli, and their patterns of expression suggest both overlapping and differential functions in immune regulation.[99] After activation of APC, PD-L1 precedes PD-L2 expression.[54] PD-L2/PD-1 interactions suppress strong B7-CD28 signals at low antigen concentrations. In comparison, PD-L2/PD-1 interactions decrease cytokine secretion at high antigen concentrations but do not inhibit the proliferation of T cells.[100] In both lymphoid and non-lymphoid tissues, the expression of PD-L1 and PD-L2 indicates that the PD-L / PDCD1 pathway may be involved in modulating immune responses both in lymphoid organs and at peripheral locations.[54,101] DNA sequence variation in a single nucleotide of PD-1, PD-L1, and PD-L2 have a significant correlation with AIDs such as SLE, RA, T1DM, and AS.[102]

4.11 | BTNL2

The role of butyrophilin (Btn) family members in immune control is largely unknown, despite the extensive homology among butyrophilin proteins and B7 family members.[103] A member of the superfamily of Ig genes, the BTNL2 gene is connected with the co-stimulatory receptors CD86 and CD80.[104] Several recent studies have linked butyrophilin-like 2 (BTNL2; also referred to as BTL-II), to an MHC class II butyrophilin-like gene-linked molecule human AID.[103,105] It has been shown in previous studies that BTNL2 binds to a putative receptor on activated T cells and acts to prevent T cell proliferation.[103,105,106] Exome sequencing was applied to 19 cases of RA in one study to scan for gene-coding variants correlated with RA. They established single nucleotide polymorphisms (SNPs) that are possibly RA-susceptible gene variants within the butyrophilin-like protein 2 gene (BTNL2) in the MHC region.[107] In gastrointestinal tissue, BTNL2 has high expression in epithelial cells and DCs as well as Peyer's patches of the small intestine. Change in the expression pattern of this molecule can be associated with IBD[108,109] and also the mutation of this gene can be associated with RA,[107,110] vitiligo,[111] sarcoidosis,[112] thyroid disease,[113] and psoriasis.[114]

5 | CLINICAL APPLICATION

The control of the immune system for treating diseases dates back to the 18th century when smallpox inoculation was used in India, China, and Africa until it was introduced in Europe.[92] T cell activation, proliferation, and differentiation are regulated by the B7-1 and B7-2 pathways. Arthritis has been successfully treated with CTLA-4Ig selective inhibition of the CD28 co-stimulatory pathway.[66,115] There have been studies of the possible effects of PD-1 signaling in RA development.[115] Two immunoregulatory agents that belong to the B7 superfamily, B7-H1 (PD-L1) and B7-DC (PD-L2), were known as PD-1.[115] B7-H3 has also recently been designated to be expressed on RA synovium fibroblast-like synoviocytes (FLS).[115] Decreased B7-H3 expression on FLS by RNA interference (RNAi) resulted in increased TNF-alpha, IFN, and IL-2 production from co-cultivated resting T cells, indicating that the B7-H3 signal may help to reduce joint inflammation.[115] Immune checkpoint receptors have a vital role in maintaining peripheral immunity in both humans and mice. Using the immune checkpoints has shown promising outcomes for the affected patients with SLE, RA, MS, and T1DM.[76] In preclinical models, therapy with anti-CTLA-4 is known to improve the onset and occurrence of various experimental AID caused by T cells, including murine

encephalomyelitis models, myasthenia gravis, and T1DM.[92] Many immune checkpoint related products have already been approved for clinical care by the US FDA.[82] We present some clinical trials that have examined immune checkpoints for autoimmunity therapy. Promising results of studies on CTAL-4 and CD28 have led to FDA approval of CTLA-4Ig (abatacept) for RA.[116] This recombinant fusion protein can modulate T cell activation by binding to B7-1 and B7-2. Furthermore, some clinical trials have examined abatacept for treating SLE (NCT02429934) and primary biliary cirrhosis.[117] For BMS-931699 (lulizumab pegol), a human anti-CD28 receptor,[118] step II clinical trials for SLE therapy have been reviewed (NCT02265744). FR104 is a humanized anti-CD28 Fab antibody fragment. The safety and efficacy of this drug have been examined in phase I clinical trials in RA patients (NCT02800811). AMG 557/MEDI5872 is a fully human anti-ICOS-L antibody that has been assessed in phase II clinical trials in primary Sjögren's syndrome patients (NCT02334306).

6 | AID CAUSED BY CANCER IMMUNOTHERAPY

The immune response is regulated by a large number of different, specific cells, when infected, autoimmunized, or become cancerous. Interactions between dendritic cells and T cells are the primary method of creating immunity or resistance. Immunotherapy was initially thought to be a comparatively less harmful route to cancer care than other available drugs, and it undoubtedly is, as compared to most, a relatively less toxic way to cancer care.[119] If the use of immunotherapy becomes more common, though, immunotoxicity and autoimmunity emerge as the immunotherapy Achilles heel, especially as first and second-line therapies.[119] In individual patients, a new generation of cancer medications is causing AID. These drugs, known as checkpoint blockers, fire up the immune system to combat cancer, with often amazing effects.[120] Immune checkpoint inhibitors are medications that interact with inhibitory signaling to T cells, potentially activating an anti-tumor response and growing it.[121] Their use is linked to unique immune-related adverse effects (irAEs), including AID such as inflammatory arthritis, myositis, vasculitis, and sicca syndrome, considering the apparent benefits.[120,122] As such, the pathogenesis of irAEs is not well known and there are various immunological theories to describe their development.[123] These include: (a) diseases that occur through generalized immune activation and development of inflammatory cytokines; (b) off-target effects of control point inhibitors on host tissues that express ligands; and (c) exacerbation of pre-existing asymptomatic autoimmunity.[123] As cases increase, researchers around specialties are intensifying attempts to find out why those cancer patients on checkpoint inhibitors are at greater risk and to learn if such autoimmune attacks erupt from this rare side effect.[120] Both well-defined, co-inhibitory receptors or their ligands have been the immune control points that have been successfully targeted in cancer.[124] Recently, different types of cancer immune control point inhibitors have been approved: monoclonal antibodies (mAbs) to CTLA-4 (ipilimumab); mAbs to anti-PD-1 (pembrolizumab and nivolumab); and mAbs to anti-PD-L1 (atezolizumab, avelumab, and durvalumab).[125,126] Overall, with anti-CTLA-4 therapy, the prevalence, and incidence of irAEs are higher than with anti-PD-1/ PD-L1 treatments; however, their use in conjunction enhances the occurrence of irAEs.[127] Thyroid disease (including painless thyroiditis, hypothyroidism, thyrotoxicosis, or thyroid storm) is most commonly associated with anti-PD-1 antibodies, whereas hypophysitis is the most common anti-CTLA-4-related irAE. A 30% risk of irAEs is correlated with the combination of anti-CTLA-4 and anti-PD-1 antibodies.[126,127] For example, positive anti-tumor responses have been reported, but the treatment of these mAbs has been recorded to lead to systemic or organ-specific autoimmune events.[128] Therapeutic mAbs block immune checkpoints. Mitigating toxicity or adverse immune responses occurring from systemic exposure is one possible benefit of circulating or producing a protein or antibody locally.[129] The serum levels of such antibodies indicative of autoimmunity were computed to support this hypothesis. In clinical trials, blocking of CTLA-4 has been reported to enhance the levels of both antinuclear antibodies and anti-single-stranded DNA and anti-double-stranded DNA in preclinical investigations.[129] Data indicate that local administration of GM-CSF-secreting anti-CTLA-4 immunotherapy results in good anti-tumor responses in comparison to systemic treatment of anti-CTLA-4, resulting in lower levels of systemic autoimmunity-indicating autoantibodies.[129,130]

7 | CONCLUSION AND FUTURE PERSPECTIVE

The role of new checkpoint molecules, new ways of stimulating the innate immune response, and even the study of genetic determinants of the response, all provide information on the underlying immune mechanism, as well as effective immunity against pathogens. With the rising prevalence of AID, discovering new and successful approaches to manage them is crucial. Immunotherapy with co-stimulatory immune checkpoint suppression tends to be the appropriate cure for these diseases, but much is unclear about it. The B7-1/B7-2-CD28/CTLA-4 pathway is crucial in regulating T cell activation and tolerance.[131] New B7 and CD28 molecules have recently been discovered and their new pathways play a crucial role in regulating the responses of activated T cells. There is tremendous scope for the B7 family in autoimmunity prevention (Figure 2). The clinical success of B7-based clinical interventions for AID motivates further research of these molecules' function in immunological tolerance. A deeper knowledge of the B7 checkpoint's function is needed for developing an effective strategy for autoimmune therapy and therapies for other immune-mediated diseases. Given the considerable therapeutic effects of immune checkpoints in autoimmune conditions in preclinical models, these controversial molecules have moved forward into the clinic, and

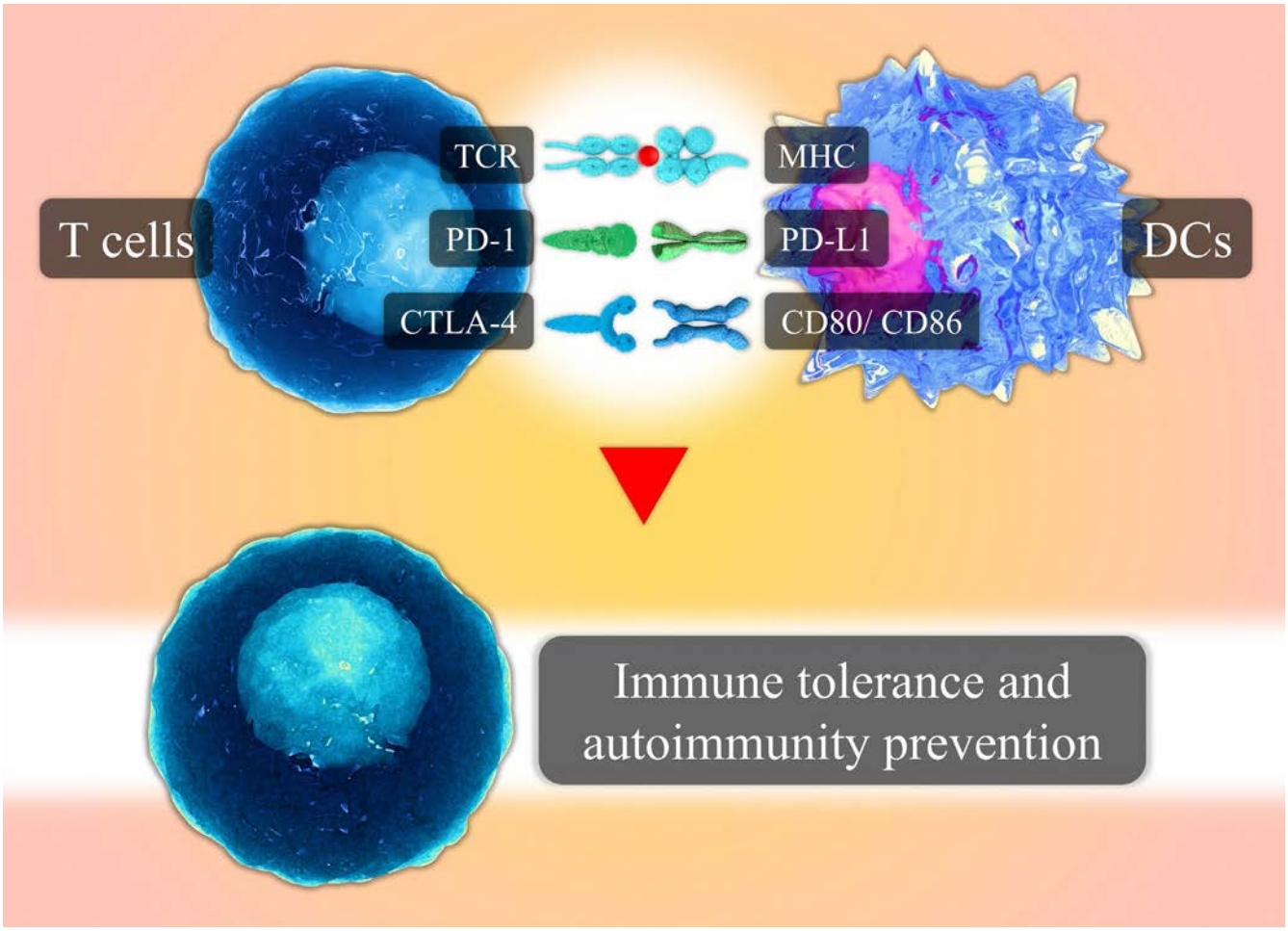

FIGURE 2 To date, many different emerging methods such as immunotherapy, which were based on B7 immune checkpoint family members, have transformed the landscape of treatment for autoimmune diseases. In these studies, the interaction of the B7 family of immune-regulatory ligands with the corresponding receptors resulted in the induction and inhibition of T cell responses by sending co-stimulatory and co-inhibitory signals, respectively. Manipulation of the signals provided by these checkpoint family members has significant potential in immune tolerance and autoimmunity prevention. CTLA-4, cytotoxic T lymphocyte antigen-4; DCs, dendritic cells; MHC, major histocompatibility complex; DP-L1, programmed death-ligand 1; TCR, T cell receptor

more appropriate treatment options can be offered by further research On their role in AID.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

KD and BB devised the main conceptual ideas. KD, NA, and HMS wrote the initial draft of the manuscript. AB prepared the figure. MAS, KH, LAM, NH, and NKA reviewed the manuscript and edited it critically for important intellectual content. BB supervised the study. All authors of this paper have read and approved the final submitted version.

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ORIGINAL ARTICLE

Diagnostic codes for low back pain, nomenclature or noise? A descriptive study of disease classification system coding of low back pain

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Abstract

Aim: To compare and contrast the diagnostic codes for spinal causes of low back pain (LBP) in 3 disease classification systems (International Classification of Diseases [ICD]-10, International Classification of Primary Care [ICPC]-2 PLUS and Systematized Nomenclature of Medicine Clinical Terms - Australia [SNOMED CT-AU]) and consider how well they are aligned with the diagnostic approach recommended in contemporary clinical practice guidelines for LBP.

Method: This was a descriptive study which included 3 disease classification systems: ICD-10, ICPC-2 PLUS and SNOMED CT-AU. Two independent authors extracted relevant LBP codes from each system and mapped the codes to 3 guideline-endorsed categories of spine-related diagnoses for LBP (specific spinal pathology, radicular syndromes, and non-specific LBP) and the various clinical conditions (sub-categories) within each of the 3 categories.

Results: ICD-10, ICPC-2 PLUS, and SNOMED CT-AU had 126, 118 and 100 codes for LBP, respectively. All systems provided codes that would cover the 3 guideline-endorsed categories of spine-related diagnoses for LBP. On the basis of contemporary guidelines, the authors developed lists of discrete sub-categories of specific spinal pathology (56 sub-categories), radicular syndromes (7 sub-categories), and non-specific LBP (10 sub-categories). Each of the classification systems was then mapped against these sub-categories to tally redundancy and determine exhaustiveness. However, no system covered all 73 sub-categories of LBP, and within each system, there was substantial redundancy with up to 22 codes for the same clinical condition.

Conclusion: LBP diagnostic codes used in popular disease classification systems are out of touch with current approaches to diagnosis, as reflected in contemporary LBP guidelines. Our findings suggest these disease classification systems need revision, but precisely how they should be revised is unclear.

KEYWORDS
diagnostic codes, disease classification systems, guideline-endorsed categories, low back pain, low back pain guidelines, redundant

1 | INTRODUCTION

Disease classification systems, such as the International Classification of Diseases (ICD),[1] provide standards for defining and reporting diseases and health conditions. To be useful the systems need to be comprehensive, that is, cover all diseases and conditions, while at the same time avoiding confusion and ambiguity that would arise if there were multiple codes for the 1 condition. In survey response design these 2 considerations are often termed "mutually exclusive and collectively exhaustive categories".[2] Finally, the disease names need to reflect contemporary thinking in the specific health field.

The 3 disease classification systems we studied (ICD-10, International Classification of Primary Care [ICPC]-2 PLUS and Systematized Nomenclature of Medicine Clinical Terms - Australia [SNOMED CT-AU]) provide codes for defining and reporting diseases and health conditions. These systems are used in clinical care and research to define diseases and study disease patterns, as well as manage health care, monitor outcomes, and allocate resources. Given the closely aligned purposes, we would expect that the diagnostic codes from disease classification systems should match the clinical guidelines.

Low back pain (LBP) is a symptom that can accompany many different diseases[3] and its diagnosis is covered by disease classification systems. A 2018 overview[4] of LBP guidelines provided a detailed overview of national LBP guidelines from 15 countries: Africa (multinational),[5] Australia,[6] Belgium,[7] Brazil,[8] Canada,[9] Denmark,[10] Finland,[11] Germany,[12] Malaysia,[13] Mexico,[14] The Netherlands,[15] Philippines,[16] Spain,[17] UK,[18] USA.[19] The majority of guidelines (13 of 15 guidelines) included in that overview recommended a diagnostic triage approach[3] to classify patients who present with LBP into 1 of 4 categories. The first category includes those with non-spinal causes of LBP including hip pathology, referred visceral pain (eg prostatitis) and vascular causes (eg abdominal aortic aneurysm). After ruling out non-spinal causes, the diagnostic triage process classifies individuals with LBP into 3 categories of spine-related diagnoses: specific spinal pathology (eg vertebral fracture), radicular syndromes (eg spinal stenosis) and non-specific LBP. Non-specific LBP represents 90%—95% of LBP cases in primary care where it is not possible to identify a specific pathoanatomical cause of LBP.[20] Within the 3 categories of spine-related diagnoses suggested by guidelines, there are sub-categories of related clinical conditions: for example, fracture, dislocation, infection and malignancy fit within the "specific spinal pathology" category.

While disease classification systems include diagnostic codes for LBP, there is a lack of research evaluating their utility in LBP clinical practice and research. The only published description is an early US paper[21] that argued that a large number of ICD codes for LBP appear to be excessive and impractical for routine clinical use. At present, it is unknown how well the LBP diagnostic codes in these disease classification systems cover the diagnoses clinicians would use for cases of LBP of spinal origin either for the 3 guideline-endorsed categories or sub-categories of related conditions.

2 | AIM

This study aimed to compare and contrast the diagnostic codes for spinal causes of LBP in 3 disease classification systems (ICD-10, ICPC-2 PLUS and SNOMED CT-AU) and consider how well they are aligned with the diagnostic approach recommended in contemporary clinical practice guidelines for LBP. We also sought to ascertain the degree of mutual exclusivity and exhaustiveness of each classification system.

3 | METHOD

3.1 | Study design

This is a descriptive study.

3.2 | Current LBP diagnostic categories

We sourced LBP guideline-endorsed categories from the above-mentioned overview of the current LBP clinical practice guidelines of 15 countries.[4] Thirteen out of 15 of these guidelines recommend a diagnostic triage approach with 4 categories: (a) a problem beyond the spine; (b) specific spinal pathology; (c) radicular syndromes; and (d) non-specific LBP. We have used the 3 guideline-endorsed categories of spine-related diagnoses for LBP and omitted the first category for problems beyond the spine as this category includes health conditions such as renal and gastrointestinal diseases.

3.3 | Disease classification systems

We included 3 disease classification systems: ICD-10,[22] ICPC-2 PLUS,[23] and SNOMED CT-AU.[24]

3.3.1 | ICD-10

The ICD-10[25] is an internationally used medical classification system recommended by the World Health Organization (WHO) to classify and monitor causes of injury and death and maintains information for health analyses. It is designed to promote international compatibility in health data collecting and reporting. ICD-10, and translations thereof, are used in over 13 countries.[26]

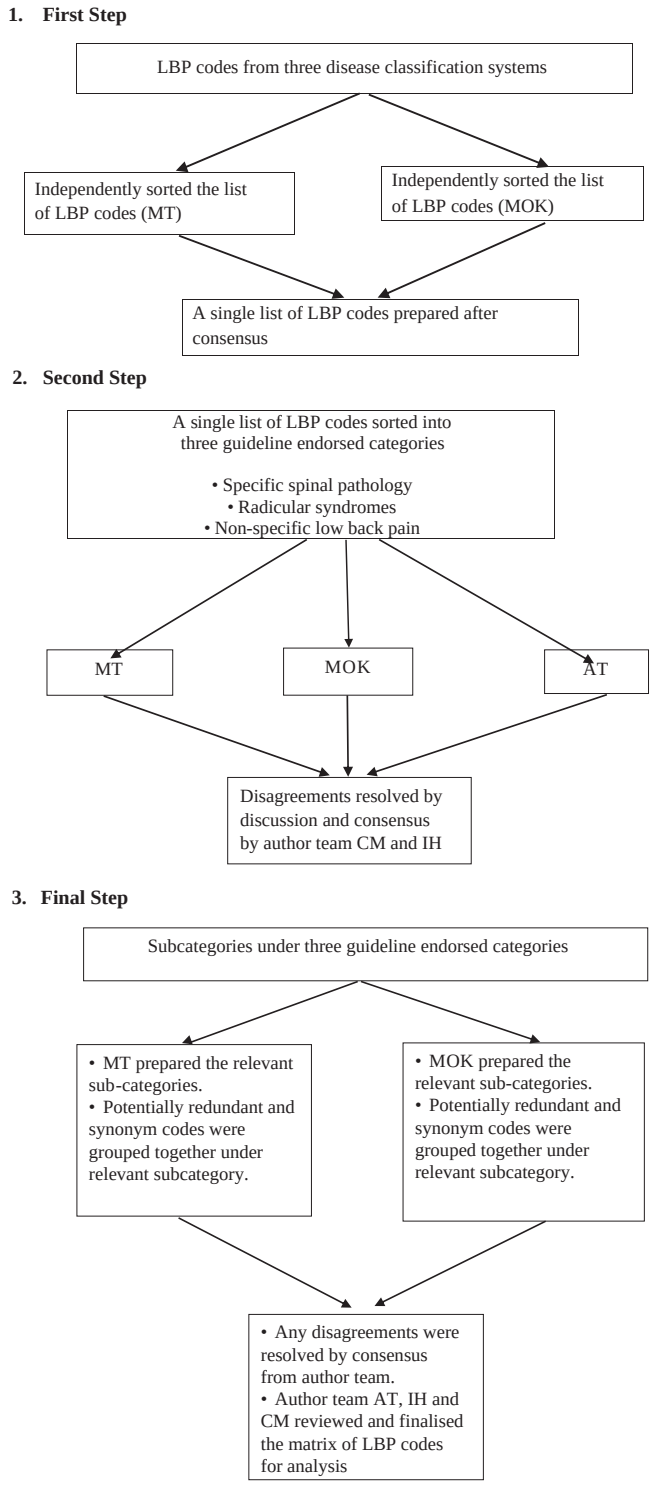

FIGURE 1 Method summary. LBP, low back pain

3.3.2 | ICPC-2 PLUS

The ICPC was developed by the World Organization of Family Doctors (WONCA). ICPC-2 PLUS is a clinical terminology and a user-friendly coding system which allows health professionals to record symptoms, diagnoses, past health problems and processes (such as procedures, counseling and referrals) at the point of care. It currently contains approximately 8000 terms that are commonly used in primary care.[27]

3.3.3 | SNOMED CT-AU

The SNOMED CT was developed for clinical documentation in electronic medical records. SNOMED CT is used in over 80 countries and can be mapped to other classification systems. SNOMED CT-AU is the Australian extension that includes words and ideas that are clinically and technically unique to Australia. It currently contains more than 400 000 concepts that are organized into 20 top-level hierarchies.[28,29]

We excluded the Read system as it was replaced by SNOMED CT in 2020 for both the primary and secondary care systems as per a decision by National Health Service England.[30] We excluded modified national versions of ICD-10.

3.4 | Screening and data extraction

In November 2020 we searched ICD-10, ICPC-2PLUS and SNOMED CT-AU for diagnostic codes relevant to LBP. The author team, which has extensive clinical and research experience in LBP and includes a senior orthopedic surgeon, developed a sorting system to identify alignment with guidelines and any redundancies in the systems. First, 2 independent authors (MT and MOK) conducted searches for codes that were relevant to LBP. Any disagreements on whether a code was relevant to LBP were resolved by consensus. At least 2 authors with expertise in LBP (MT, MOK, and AT) then allocated the LBP codes from the consensus lists to 1 of the 3 guideline-endorsed categories. For example, codes such as Osteoporosis of disuse with pathological fracture and Postmenopausal osteoporosis with pathological fracture were grouped into the "specific spinal pathology" category, codes such as Nerve root and plexus compressions in spondylosis and Nerve root and plexus compressions in neoplastic disease were grouped into the "radicular syndromes" category, and codes such as Coccygodynia and Kissing spine were grouped in the "non-specific LBP" category. These groupings were agreed on by the author team. Any disagreements during this step were resolved by discussion and consensus.

In the final step, 2 authors (MT and MOK) sorted the codes into 73 distinct clinical entities representing sub-categories under the 3 guideline-endorsed categories. The authors used a consensus model to define a list of discrete sub-categories within each of the specific spinal pathology, radicular and non-specific LBP categories. These lists aimed to be both mutually exclusive and exhaustive,[2] with the intention that they would be a criterion standard against which the different classification systems could be assessed. Within the 73 sub-categories, we grouped codes that were synonyms, for example "spondylosis" and "other spondylosis" and were potentially redundant. By counting the number of redundant codes, this allowed us to identify *mutual exclusivity*. By identifying and grouping all the

key clinical entities covered by the 3 systems, we could identify *exhaustiveness*, that is, whether the systems covered all the most important LBP-related conditions that would present for hospital or primary care. The author team reviewed and agreed on the final matrix, cross-tabulating LBP codes from the 3 systems against the 3 guideline-endorsed categories, each with their own sub-categories and potential synonyms marked. For example: within the sub-category "radicular pain", synonyms and potentially redundant codes like "sciatica", "lumbago with sciatica", and "neuropathic spondylopathy" were included.

3.5 | Analysis

For each disease classification system, we tallied the number of diagnostic codes under the 3 main guideline categories (specific spinal pathology, radicular syndromes and non-specific LBP) and the sub-categories (Figure 1 Method summary).

4 | RESULTS

We found that ICD-10 has 126 codes for LBP, ICPC-2 PLUS has 118 codes, and SNOMED CT-AU has 100 codes.

The number of diagnostic codes in the 3 disease classification systems relevant to each LBP guideline category is shown in Table 1. For specific spinal pathology, the number of codes ranged from 46 to 80; for radicular syndromes, it ranged from 9 to 19 and for non-specific LBP it ranged from 27 to 63.

We identified 56 discrete sub-categories for "specific spinal pathology", 7 for "radicular syndromes", and 10 for "non-specific LBP" These are listed in Tables 2, 3 and 4.

The number of diagnostic codes under different sub-categories of the specific spinal pathology category of the 3 disease classification systems is shown in Table 2. No disease classification system covered all 56 sub-categories of specific spinal pathology, yet there was still redundancy with each system, offering multiple codes for the same sub-category. For example, ICPC-2 PLUS's 46 codes mapped 28 of the 56 sub-categories of specific spinal pathology yet devoted 11 codes to the sub-category "inflammatory conditions".

The author team considered that there were 7 discrete sub-categories of radicular syndromes reflected in the 46 "radicular" codes from the 3 disease classification systems. The number of LBP diagnostic codes under the 7 sub-categories of radicular syndromes is shown in Table 3. ICD-10 covered all 7 sub-categories, whereas ICPC-2 PLUS and SNOMED CT-AU both only covered 3 of the 7 sub-categories. Within each of the 3 disease classification systems, there was redundancy with up to 12 separate codes for the same sub-category of radicular syndromes (SNOMED CT-AU: radicular pain).

The author team considered that there were 10 discrete sub-categories of non-specific LBP reflected in the 122 "non-specific" codes from the 3 disease classification systems. There was incomplete coverage of the 10 sub-categories with the 3 disease classification systems covering from 7 to 9 out of the 10 sub-categories of non-specific LBP. ICD-10 did not distinguish between acute and chronic LBP. This finding is important because the management recommendations for these 2 types of LBP are quite different. For example, management of chronic non-specific LBP comprises more expensive treatment and more prolonged treatment programs than is normally the case for acute non-specific LBP. Coding systems that ignore chronicity would mistakenly encourage the view that this represents unwarranted clinical variation, but if chronicity is recorded then the variation in management would make sense. There was also substantial redundancy with the disease classification systems offering up to 22 separate codes for the same sub-category of non-specific LBP (ICPC-2 PLUS: back pain unspecified duration). Full results are shown in Table 4.

5 | DISCUSSION

5.1 | Statement of principal findings

The 3 disease classification systems ICD-10, ICPC-2 PLUS and SNOMED CT-AU provide 126, 118 and 100 codes for LBP of spinal origin. All systems provided codes that would cover the 3 categories of spine-related diagnoses for LBP. However, no system covered all 73 of the identified sub-categories of LBP and within each system, there was substantial redundancy with up to 22 codes for the same clinical condition.

5.2 | Strengths and weaknesses of the study

The main strengths of our study are that we examined 3 widely used disease classification systems and took steps to ensure the

TABLE 1 Number of LBP codes in the 3 disease classification systems

LBP guideline-endorsed categories	ICD-10 (N = 126)	ICPC-2 PLUS (N = 118)	SNOMED CT-AU (N = 100)
Specific spinal pathology	80	46	50
Radicular syndromes	19	9	18
Non-specific LBP	27	63	32

Abbreviations: LBP, low back pain; ICD-10, International Classification of Diseases 10th edition; ICPC, International Classification of Primary Care; SNOMED CT-AU, Systematized Nomenclature of Medicine Clinical Terms – Australia.

TABLE 2 Mapping of disease classification codes to 56 sub-categories of specific spinal pathology

Sub-categories of specific spinal pathology	ICD-10 (N = 80)	ICPC-2 PLUS (N = 46)	SNOMED CT-AU (N = 50)
Fractures - general	1	1	2
Fractures - osteoporotic	5	2	4
Fracture coccyx	1	1	1
Fracture lumbar	1	1	1
Fracture lumbosacral	0	1	0
Fracture pelvis	0	1	1
Fracture sacrum	1	1	1
Fracture ilium	1	0	0
Fracture lumbar and/or pelvis	2	0	2
Fracture - pathological	0	1	1
Traumatic fractures	0	0	4
Fractures with spinal cord injury	0	0	5
Infection of disc	2	0	1
Infection of bone	2	4	4
Tuberculosis spine	1	0	0
Infective spondylopathies	2	0	0
Traumatic spondylopathy	1	0	0
Inflammatory conditions	13	11	1
Osteoporosis	0	1	0
Bone disease excluding infection	0	1	1
Ankylosing hyperostosis	1	0	0
Skeletal hyperostosis	0	1	0
Spinal instability	3	2	1
Subluxation	1	0	0
Dislocations	3	0	6
Open dislocation coccyx	0	0	1
Juvenile osteochondrosis of spine	1	0	0
Other osteochondrosis	2	1	0
Congenital scoliosis	1	1	1
Infantile idiopathic scoliosis	1	0	0
Juvenile idiopathic scoliosis	1	0	0
Post-radiation scoliosis	1	0	0
Neuromuscular scoliosis	1	0	0
Other scoliosis	4	1	2
Congenital kyphosis	0	1	0
Postsurgical kyphosis	1	0	0
Post-radiation kyphosis	1	0	0
Other kyphosis	3	1	0
Congenital kyphoscoliosis	0	1	0
Kyphoscoliosis	0	1	0
Congenital lordosis	0	1	0
Postsurgical lordosis	1	0	0
Other lordosis	2	1	0
Flatback syndrome	1	0	0
Spinal cord disorder	0	0	1

(Continues)

TABLE 2 (Continued)

Sub-categories of specific spinal pathology	ICD-10 (N = 80)	ICPC-2 PLUS (N = 46)	SNOMED CT-AU (N = 50)
Spinal enthesopathy	1	0	0
Spinal cord compression	1	2	1
Spinal cord injury	0	1	2
Disease of spinal cord, specified	1	0	0
Disease of spinal cord, unspecified	1	0	0
Fusion of spine	1	1	0
Disc pathology with myelopathy	2	0	3
Cauda equina syndrome	3	1	2
Mass of back	0	0	1
Neoplasms	4	3	0
Congenital malformations of spinal cord	4	0	0

Abbreviations: ICD-10, International Classification of Diseases 10th edition; ICPC, International Classification of Primary Care; SNOMED CT-AU, Systematized Nomenclature of Medicine Clinical Terms – Australia.

TABLE 3 Mapping of disease classification codes to 7 sub-categories of radicular syndromes

Sub-categories of codes	ICD-10 (N = 19)	ICPC-2 PLUS (N = 9)	SNOMED CT-AU (N = 18)
Radiculopathy	9	2	4
Radicular pain	3	5	12
Central canal stenosis: bone	2	2	2
Central canal stenosis: connective tissue	2	0	0
Lateral canal stenosis: bone	1	0	0
Lateral canal stenosis: connective tissue	1	0	0
Subluxation stenosis of neural canal	1	0	0

Abbreviations: ICD-10, International Classification of Diseases 10th edition; ICPC, International Classification of Primary Care; SNOMED CT-AU, Systematized Nomenclature of Medicine Clinical Terms – Australia.

accuracy of the data extraction and mapping. From the initial step of LBP codes selection by 2 authors (MT and MOK) until the identification of distinct sub-categories, a thorough cross-check by the author team was done. Any disagreements were resolved by consensus in each step before agreeing to a final matrix of LBP codes for analysis and results. In addition, our author team have extensive clinical experience in the management of LBP and LBP research. We studied 3 disease classification systems that are widely used around the world.[26,27,31] However, we are unable to comment on how well other systems might cover the various clinical entities that give rise to LBP.

5.3 | Strengths and weaknesses in relation to other studies, discussing important differences in results

The only previous studies to evaluate the adequacy of disease classification systems did not exclusively focus on LBP but found results that accord with ours. A study[32] of SNOMED CT coding of 7.4 million New South Wales emergency department presentations found substantial problems with redundancy. Out of 12 152 discrete codes used, 7000 codes were used less than 10 times across 3 years. While not a focus of the Dinh et al study,[32] their results pointed to redundancy in LBP codes with the top 50 most commonly used SNOMED CT codes including 2 codes for LBP: "Backache" and "Low back pain". A study of 1.7 million NSW emergency presentations[33] found a similarly high level of redundancy with the Emergency Department Presenting Problem Code Set (EDPPCS). Of the 64 849 unique codes, only 450 were used more than 100 times. A study of Read codes for allergic diseases[34] found, out of 352 Read codes for allergic diseases, only 10% were used in 95% of consultations and 21% were never used. Together, these findings suggested that a considerable number of existing codes are not used in clinical practice. This is in accordance with our study that also found a substantial number of redundant codes across all 3 systems.

TABLE 4 Mapping of disease classification codes to 10 sub-categories of non-specific low back pain

Sub-categories of codes	ICD-10 (N = 27)	ICPC-2 PLUS (N = 63)	SNOMED CT-AU (N = 32)
Back pain (unspecified duration)	8	22	10
Back pain (acute)	0	1	1
Back pain (chronic)	0	2	2
Degenerative conditions	8	13	3
Sprains and strains	3	8	7
Disc pathology	5	12	4
Sacrococcygeal disorders	1	1	0
Arthritis – unspecified type	1	4	1
Contusion	1	0	3
Back pain complicating pregnancy	0	0	1

Abbreviations: ICD-10, International Classification of Diseases 10th edition; ICPC, International Classification of Primary Care; SNOMED CT-AU, Systematized Nomenclature of Medicine Clinical Terms – Australia.

5.4 | Meaning of the study: possible explanations and implications for clinicians and policymakers

Our results suggest that none of the 3 systems is ideal for clinical practice or research. While each system provides codes for the 3 guideline-endorsed categories of LBP; there are probably too many if the interest is only in those 3 broad disease classifications. If the interest is in the various clinical entities or sub-categories of LBP all 3 systems will create problems. The absence of codes for recognized clinical entities means that these conditions will be invisible in clinical audit and research activities. If the hospital practice is to require a code for all presentations, miscoding will be necessary, and this will introduce error into the data.

The redundant codes provide numerous choices for coding a single clinical condition, for example SNOMED CT-AU provides 12 codes for radicular pain, which could be more time-consuming and unnecessary. Too much choice in code selection can be as much of a problem as not enough choice[2] and it could lead to inconsistent data recording, wasted time, and unusable data. Hence, some reconsideration of the codes used in these systems is vital for effective disease management and audits of the quality of patient care.[35,36] One potential solution to redundancy is to use a more constrained list of SNOMED codes as was recently suggested for an emergency department;[37] however, this will not address the problem of the absence of codes for accepted clinical conditions. To address this problem it has been suggested that self-made codes could be used.[35] These are codes formed when no unique code could be found in an existing coding system. However, self-made codes are problematic as they do not correspond to an existing coding system, are difficult to maintain, and, due to lack of standardization, may hamper communication. Revision of all 3 systems is necessary so that they align with contemporary thinking around the diagnosis of LBP.

5.5 | Unanswered questions and future research

Our study provides clear evidence that these disease classification systems need revision, but precisely how they should be revised is unclear. The challenge is in developing systems that provide mutually exclusive and collectively exhaustive categories for the range of clinical entities associated with LBP that are feasible to use. Further research should focus on exploring all other disease classification systems to identify issues such as redundant codes, missing codes for any important clinical condition, and coverage of LBP guideline-endorsed categories. This is necessary for clinicians and researchers to speak the same language in diagnostic coding across all systems.

6 | CONCLUSION

Our findings suggest LBP diagnostic codes used in these systems are out of touch with contemporary LBP guidelines. If the interest is simply recording which of the 3 guideline-endorsed categories of LBP of spinal origin a patient belongs to, it is unclear which one of the scores of codes should be used. If the interest is in coding sub-categories of LBP, none of the 3 systems offers codes that are exhaustive and mutually exclusive. Our findings suggest the need for revision of these systems to allow clear classification and consistent communication between clinicians and researchers.

CONFLICT OF INTEREST

The authors declare they have no competing interests.

AUTHOR CONTRIBUTIONS

CM and MOK conceived and designed the study. MT, MOK, AT, and CM contributed to the data collection. CM and IH contributed to the analysis of data. MT prepared the initial draft manuscript. CM, MOK, and AT reviewed the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The corresponding author (MT) is responsible if someone wants to request the study's data.

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ORIGINAL ARTICLE

Short-term pain trajectories in patients with knee osteoarthritis

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Abstract

Aim: It is unknown if pain in knee osteoarthritis (KOA) follows distinct patterns over the short term. Therefore, the aim of this study was to identify whether persons with a previous history of KOA pain fluctuations have distinct trajectories of pain over 90 days and to examine associations between baseline characteristics and pain trajectories.

Method: People with a previous history of KOA were selected from a web-based longitudinal study. Baseline variables were sex, age, being obese/overweight, years of KOA, knee injury, knee buckling, satisfactory Lubben Social Support Score, pain and stress scales, Intermittent Constant Osteoarthritis Pain Score (ICOAP), medication use, and physical activity. Participants completed a Knee Injury and Osteoarthritis Outcomes Score (KOOS) pain subscale (KOOS-p, rated 0 = extreme to 100 = no knee problems) at 10-day intervals for 90 days. Short-term KOOS-p trajectories were identified using latent growth mixture modeling and the baseline risk factors for these pain trajectories were examined.

Results: Participants (n = 313) had a mean age of 62.2 (SD ± 8.1) years and and a body mass index of 29.8 (SD ± 6.6) kg/m^2. The three-class latent growth mixture modeling quadratic model with best fit indices was chosen (based on lowest sample-size-adjusted Bayesian Information Criterion, high probability of belonging, interpretability). Three distinct pain trajectory clusters (over 90 days) were identified: low-moderate pain at baseline with large improvement (n = 11), minimal change in pain over 90 days (n = 248), and moderate-high pain with worsening (n = 46). Higher ICOAP (intermittent scale), perceived stress, negative affect score, and knee buckling at baseline were associated with a worse knee pain trajectory ($P < 0.05$).

Conclusions: Persons with KOA showed unique short-term pain trajectories over 90 days, with distinct characteristics at baseline associated with each trajectory.

KEYWORD
knee joint osteoarthritis pain, short-term pain, trajectory,

1 | INTRODUCTION

Pain is the dominant symptom in knee osteoarthritis (KOA) and is the main reason that people seek health care. The evolution of pain in KOA has been the subject of considerable interest because improved understanding of the pattern of longitudinal pain progression would better inform the pathogenesis of this disease, as KOA is essentially still without a cure. Previous studies of individuals with KOA, assessing pain at 12-18 month intervals, demonstrated that the stereotype portraying KOA as being slowly progressive is most likely inaccurate and that mild or improving symptom trajectories are present in a minority.[1] Further, it is unknown if fluctuations of knee pain over a short time period in individuals with symptomatic KOA follow distinct patterns, and which risk factor(s) are attributed to short-term pain fluctuation. As KOA pain fluctuations (KOAF) are disabling and negatively impact a person's life, limiting social participation and engagement, knowledge of short-term pain trajectories will provide valuable insights into the individual experience of pain in KOA.[2] It is envisaged that further knowledge on KOAF pain trajectories will provide valuable information for clinicians to counsel and educate patients and healthcare resource allocators to plan and organize healthcare services; and will give researchers more insight on the pathogenetic process that occurs in the initial phases in individuals who experience KOAF, who potentially have earlier stages of KOA.[3]

Large-scale studies on KOA pain trajectories have mainly explored long-term KOA pain trajectories.[4-7] Short-term changes in pain, for example periods of less than 3 months,[8] particularly in those with KOAF, are less well understood.[9] Exploration of short-term changes in pain provides the opportunity to identify modifiable risk factors early in the disease process, through characterization of early progressors, which may later inform management strategies. Therefore, it is pertinent to examine pain at shorter intervals in order to meaningfully ascertain the shorter-term pain patterns in KOA, especially in those reporting KOAF, to develop a full understanding of the disease. The aim of our study was to describe the trajectory of the Knee Injury and Osteoarthritis Outcomes Score pain (KOOS-p) scores in a group of individuals from the SPARK-Web Study at 10-day intervals over 90 days and examine the risk factors for these trajectories.[10]

2 | MATERIALS AND METHODS

Data were obtained from SPARK-web (web-based study of risk factors for pain exacerbation in KOA), an Australian longitudinal study, designed to examine associations between risk factors and pain exacerbation in KOA.[10] This study recruited individuals with a previous diagnosis of symptomatic KOA from existing databases or social media and followed the individuals longitudinally for 3 months collecting data including the KOOS at 10-day intervals (control points) and at points of flare. Data were collected via a specially constructed secure website designed to obtain self-reported information of risk factors.

The study inclusion criteria were as follows: persons aged more than 40 years,with an active email address with internet connectivity, who had experienced knee pain in at least one knee for most days in the preceding month with fluctuations in the level of knee pain.[10] In addition, it was necessary for those selected to have not had/have no plans for a knee joint replacement in the most painful knee. Those diagnosed with inflammatory joint disease or fibromyalgia were excluded.[10]

The participants' most recent knee radiographs were evaluated by the study physician as only persons with radiographic tibiofemoral osteoarthritis (at least Kellgren and Lawrence grade ≥2) or patellofemoral osteoarthritis on radiograph were recruited for the study as part of the eligibility criteria.

2.1 | Assessment of outcome

We used the KOOS score, a valid and reliable knee-specific instrument that was developed with the intent of assessing patient self-report on their KOA-related problems.[11,12] The KOOS examines 42 items, which are examined within five subscales. Each of these five subscales; Pain (KOOS-p), Symptoms, Function in daily living, Function in Sports and Recreation, and knee-related Quality of Life; are scored separately by a Likert scale with five possible options (0 = No problems to 4 = Extreme problems). Each subscale is calculated by the sum of the items that were included in it. These scores are then transformed on a 0–100 scale with 0 and 100 representing extreme knee problems and no knee problems, respectively.[11,12] This project examined the trajectory of KOOS-p subscales, which were assessed every 10 days for a period of 3 months.

2.2 | Assessment of risk factors

Participant characteristics evaluated at baseline were chosen a priori based on importance to understanding KOA and KOAF[10,13] and their potential to describe identified clusters. These included the following demographic variables: age (years), race (white Australian/Asian/other), weight (kg), and height (cm) (from which body mass index was calculated); and pain scores; background/usual and worst pain reported at baseline (on a 0–10 point numeric rating scale). In addition, information on whether an injury to the index knee occurred in the preceding 7 days or whether any buckling of the index knee happened during the preceding 2 days was assessed. The Intermittent and Constant Osteoarthritis Pain Score (ICOAP), which evaluates constant pain and intermittent pain (or “pain that comes and goes”) by two separate subscales (0-100).[2] The Positive/Negative Affect Scores (score from 10 to 50), which assesss psychological/mood-related factors; the Perceived Stress Score (score from 0 to 40), which measures an individual’s appraisal of their level of stress; and the Lubben Social Support Score (satisfactory score >12), a self-reported measure of social engagement[14-18] were assessed at baseline using previously validated questionanaires. The medication use

during the previous week was assessed and classified as daily, none, or intermittent. Similarly, self-reported physical activity during the previous week (using the previously validated Seven-Day Physical Activity Recall questionnaire) was assessed at baseline,[19] and the physical activity was classified as mild physical activity only or any moderate or any vigorous activity.[20]

Ethical approval was obtained from the University of Sydney Human Ethics Committee (Protocol No.: 14 435), University of Melbourne Human Research Ethics Committee (No. 0709220) and Radiation Safety Committee.

2.3 | Analysis

2.3.1 | Latent variable modeling

Latent variable longitudinal mixture modeling was used to explore the heterogeneity in KOOS-p scores over 90 days to classify individuals into unique groups ('classes' or 'clusters') based on their KOOS-p trajectory. A systematic approach to model selection was applied and followed the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) reporting guidelines[21] (Appendix 1). A three-class quadratic growth model based on latent growth mixture modeling (LGMM) was selected above others based on superior model fit indices (Akaike information criterion, sample-size-adjusted Bayesian Information Criterion, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test) and a range of pragmatic criteria (entropy, probability of membership, and interpretation). Missing data for KOOS-p scores were handled under missing at random and estimated using maximum likelihood. No imputation of KOOS-p scores was undertaken (Appendix 1).

2.3.2 | Multinomial logistic regression

After short-term pain trajectories were determined, univariate multinomial logistic regression analysis was used to investigate the association (odds ratio) of baseline characteristic for each trajectory cluster compared with a reference trajectory with poorest progression.[22]

3 | RESULTS

3.1 | Sample characteristics

A total of 313 individuals were included in the study. These persons had a mean age of 62.2 (SD ± 8.1) years with a mean body mass index of 29.8 (SD ± 6.6) kg/m^2. They reported having a mean duration of 10.2 (SD ± 10.6) years of KOA. The description of the entire study cohort and the description of characteristics in the individual clusters derived from the final trajectory model are given in Table 1. The medians (interquartile ranges) for the ICOAP constant subscale and the intermittent subscale are 35 (15-50) and 41.2 (29.2-54.2), respectively. The medians (interquartile ranges) for KOOS-p, KOOS-symptoms, KOOS-activities of daily living, KOOS-sport/recreation, and KOOS-quality of life were 55.6 (44.4-66.7), 42.8 (35.7-53.6), 63.2 (48.5-77.9), 15 (0-32.5), and 43.8 (31.2-56.3), respectively.

3.2 | Selection of a latent variable model

Model fit was tested for one to five trajectories using latent class growth analysis (LCGA) and LGMM, with both linear and quadratic growth curves tested (20 models in total), from which a single model was selected. All modeling used KOOS scores as the dependent variable. We used 100 random sets of starting values in the initial stage with 20 final-stage optimizations for each of the 20 separate models[23] (Table A1).

3.3 | Characteristics of cluster membership and between-cluster comparison

Table 1 describes the characteristics of individuals classified into each cluster in the three-trajectory model. Figure 1 shows both the averaged and individual trajectory patterns for each cluster in the final model (Figure A1 in the Appendix shows Averaged KOOS-p scores with 95% CI for each cluster). Figure 2(A, B) show the mean and individual KOOS trajectories for individuals assigned to each cluster in the final model with panel A depicting the KOOS scores reported by individuals and panel B showing the KOOS scores predicted by the growth model.

Cluster 1 (Low-moderate pain with large improvement over 90 days) comprised the smallest group of individuals (n = 11, average probability of belonging = 0.86) and was characterized by a baseline average KOOS score of 54.5 (SD ± 17.2), followed by large improvement over the study period (Day 90 KOOS score 78.3 (SD ± 16.0)).

Cluster 2 (Minimal change in pain over 90 days) comprised the largest group of individuals (n = 248, $P = 0.90$) and was characterized by a baseline average KOOS score of 62.5 (SD ± 8.1) followed by a small increase in average pain or relative stability over the study period (Day 90 KOOS score 63.7 [SD 14.5]).

Cluster 3 (Moderate-high pain with worsening over 90 days) comprised a group of individuals (n = 46, $P = 0.78$) who were characterized by a baseline average KOOS score of 38.2 (SD ± 12.7) followed by minimal worsening over the study period (Day 90 KOOS score 31.9 [SD ± 13.4]).

3.4 | Comparison of cluster membership characteristics

Table 2 reports the odds ratios (OR) for baseline characteristics for Clusters 1 and 2 compared with Cluster 3. No apparent associations were observed between sex, age over 65 years, social

TABLE 1 Baseline characteristics for the whole population and each cluster in the final three-cluster model

Variable	Pain improving Cluster 1 (n = 11)	Pain stable Cluster 2 (n = 248)	Pain worsening Cluster 3 (n = 46)	*P* value[b]
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Demographics				
Age, y	61.1 (6.5)	62.5 (8.1)	60.7 (8.1)	0.347
Years since KOA diagnosis	9.7 (11.5)	10.0 (10.2)	11.8 (12.5)	0.58
Body mass index, kg/m^2	26.9 (2.8)	29.3 (6.2)	33.6 (2.8)	<0.001
Pain levels				
Background level of pain[a]	4.8 (2.2)	3.9 (1.8)	6.3 (1.6)	<0.001
Worst level of pain	8.5 (1.1)	7.7 (1.7)	9 (1.0)	<0.001
Intermittent constant osteoarthritis pain score (ICOAP)				
ICOAP (constant subscale)	43.6 (23.2)	27.7 (21.4)	60.9 (22.9)	<0.001
ICOAP (intermittent subscale)	40.9 (24.6)	37.2 (18.7)	61.6 (20.6)	<0.001
ICOAP (total score)	42.1 (23.1)	32.9 (17.8)	61.3 (18.7)	<0.001
Positive-negative affect scores				
Positive affect score	36.4 (9.9)	34.6 (7.7)	31.4 (7.6)	0.025
Negative affect score	14.5 (0.7.8)	15.8 (5.7)	19.9 (8.0)	<0.001
KOOS subscales				
KOOS pain	54.5 (17.2)	58.9 (14.5)	38.2 (12.7)	<0.001
KOOS symptoms	43.8 (10.4)	45.6 (12.1)	37.6 (15.6)	<0.001
KOOS activities of daily living	62.0 (22.9)	66.9 (16.3)	40.6 (15.5)	<0.001
KOOS sport and recreation	18.2 (14.0)	25.0 (24.2)	6.5 (9.3)	<0.001
KOOS quality of life	32.4 (16.5.)	43.6 (16.5)	24.6 (15.7)	<0.001
Perceived stress scale	10.8 (8.4)	12.8 (6.7)	17.8 (7.8)	<0.001
Dichotomous variables	**N (%)**	**N (%)**	**N (%)**	
Female	5 (45.4)	153 (61.7)	31 (67.4)	0.396
Race				
White Australian	10 (90.9)	233 (94.7)	41 (89.1)	0.29
Asian	1 (9.1)	8 (3.2)	2 (4.4)	
Other	–	5 (2.0)	3 (6.5)	
Injury (yes)	2 (18.2)	9 (3.6)	4 (8.7)	0.029
Knee buckling (yes)	2 (18.2)	42 (16.9)	16 (34.8)	0.020
Obese/overweight (yes)	9 (81.8)	194 (78.2)	40 (87.0)	0.395
Satisfactory Lubben Score	7 (63.6)	175 (70.6)	33 (71.7)	0.868
Medication during past week				
None	8 (72.7)	149 (58.7)	14 (29.2)	<0.001
Intermittent	2 (18.2)	52 (20.5)	11 (22.9)	
Daily	1 (9.1)	53 (20.9)	23 (47.9)	
Physical activity category				
Mild physical activity only	5 (45.4)	4 (1.6)	2 (4.4)	0.684
Any moderate physical activity	6 (54.6)	112 (45.2)	21 (45.7)	
Any vigorous physical activity	–	132 (53.2)	23 (50.0)	

[a]The numeric rating scale 0-10 was used to assess background and worse levels of pain.

[b]Analysis of variance was used for continuous variables, chi-square test for dichotomous (or exact test if chi-square assumptions were not met).

support, and years of osteoarthritis with short-term pain trajectories. However, individuals with higher intermittent ICOAP pain subscales were less likely to be in Cluster 1 (OR 0.90, 95% CI 0.81-0.99) and Cluster 2 (OR 0.88 95% CI 0.83-0.94) than to be in Cluster 3. Interestingly, individuals in Cluster 2 were less likely to have high constant ICOAP subscales than Cluster 3 (OR 0.87, 95% CI 0.80-0.96) though a similar difference was not detected between Cluster 3 and Cluster 1.

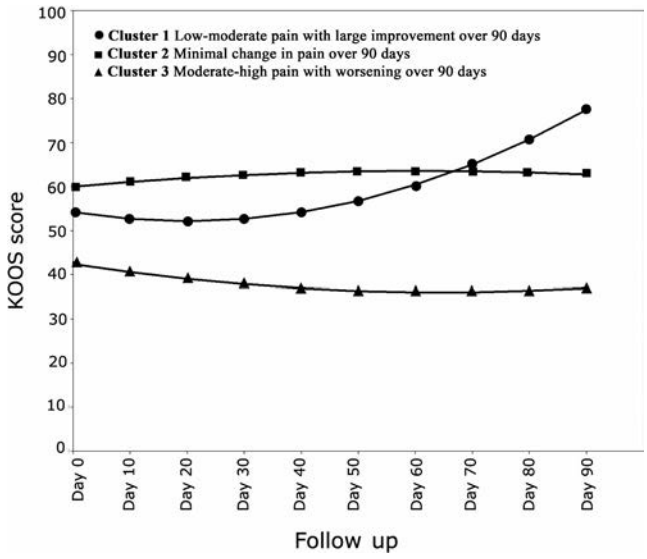

FIGURE 1 KOOS trajectory for individuals assigned to each cluster in the final model

Compared with Cluster 3, individuals in Cluster 1 and Cluster 2 were less likely to have higher negative affect scores (OR 0.46, 95% CI 0.31-0.70; OR 0.88, 95% CI 0.82-0.95, respectively), higher perceived stress (OR 0.79, 95% CI 0.64-0.98; OR 0.86, 95% CI 0.78-0.95), and higher pain scores (OR 0.57, 95% CI 0.33-0.98; OR 0.39, 95% CI 0.29-0.51).

Individuals in Cluster 2 were less likely to report a recent knee injury compared with individuals in Cluster 3 (OR 0.24, 95% CI 0.13-0.47), but there was no difference between Cluster 1 and Cluster 3 in terms of recent injury. On average, individuals in Cluster 1 and Cluster 2 were less likely to have knee buckling than those in Cluster 3 (OR 0.32, 95% CI 0.15-0.68; OR 0.26 95% CI 0.18-0.38, respectively). Similarly, individuals in Cluster 2 were less likely to be obese or overweight when compared with Cluster 3 (OR 0.38, 95% CI 0.22-0.68).

4 | DISCUSSION

This study identified three distinct short-term pain trajectories among individuals with symptomatic KOA over 90 days. Unlike

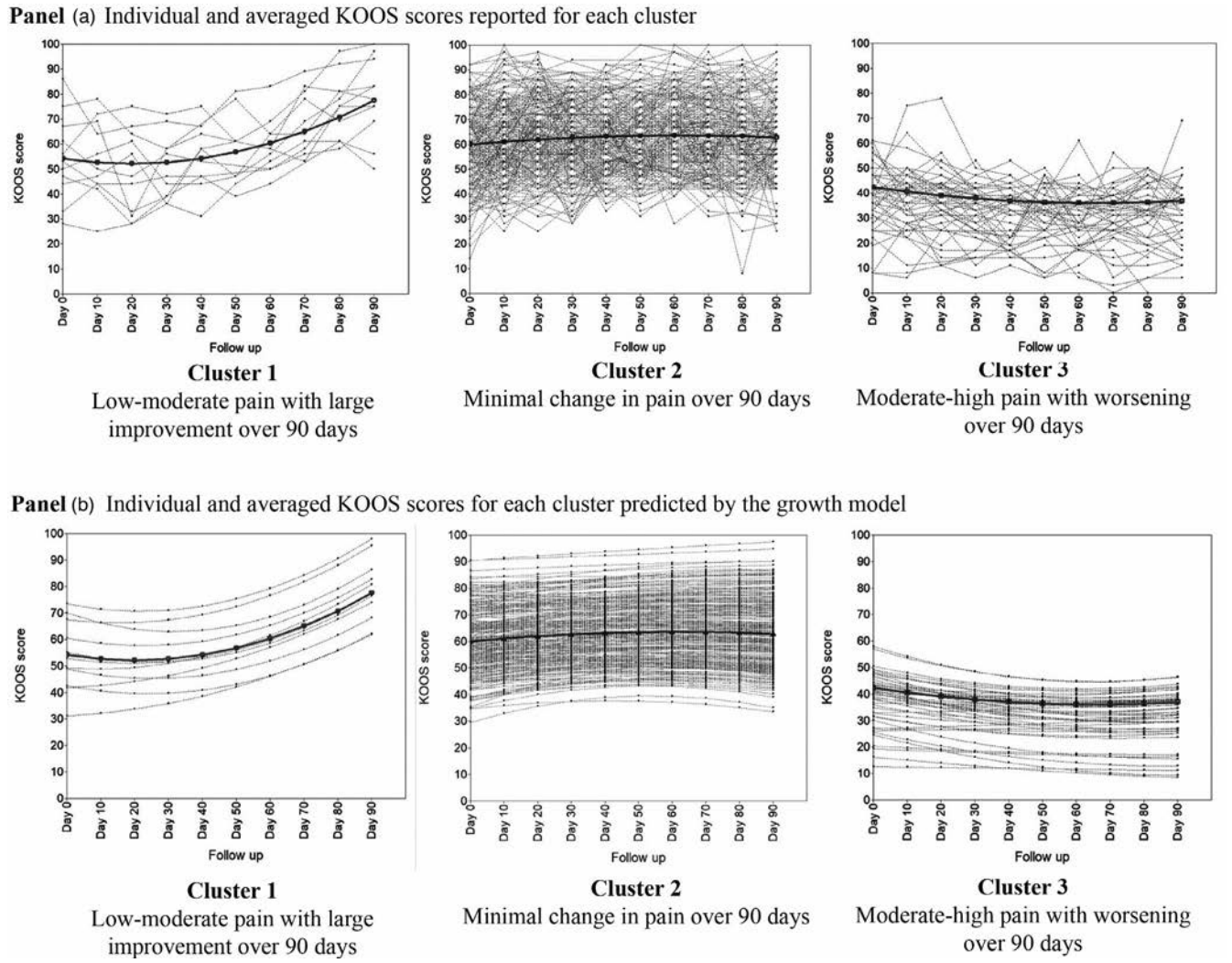

FIGURE 2 Mean and individual KOOS-pain trajectory for individuals assigned to each cluster in the final model

TABLE 2 Univariate multinomial logistic regression using three-step analysis (Cluster 3 as reference)

Baseline factor		Comparator	Odds ratio	95% CI	*P* value
Sex (female = 1)	n = 305*	Cluster 1 v 3	0.33	0.06-1.72	0.105
		Cluster 2 v 3	0.71	0.27-1.87	0.406
Age (≥65 y = 1)	n = 305*	Cluster 1 v 3	2.80	0.02-434.80	0.461
		Cluster 2 v 3	2.68	0.14-49.75	0.256
Years since diagnosis of KOA (continuous)	n = 303*	Cluster 1 v 3	0.98	0.90-1.06	0.615
		Cluster 2 v 3	0.98	0.95-1.02	0.287
Body mass index (obese/overweight = 1)	n = 313	Cluster 1 v 3	0.50	0.22-1.15	0.406
		Cluster 2 v 3	0.38	0.22-0.68	**0.037**
Background level of pain reported (continuous) (0-10 NRS)[a]	n = 303*	Cluster 1 v 3	0.57	0.33-0.98	**0.006**
		Cluster 2 v 3	0.39	0.29-0.51	**<0.001**
Worst level of pain reported (continuous) (0-10 NRS)[a]	n = 313	Cluster 1 v 3	0.28	0.15-0.54	**0.005**
		Cluster 2 v 3	0.15	0.15-0.54	**<0.001**
Perceived stress score-10 (continuous) (0-40)	n = 313	Cluster 1 v 3	0.79	0.64-0.98	**0.017**
		Cluster 2 v 3	0.86	0.78-0.95	**0.001**
ICOAP-intermittent (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.90	0.81-0.99	**0.033**
		Cluster 2 v 3	0.88	0.83-0.94	**<0.001**
ICOAP-constant (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.91	0.81-1.04	0.154
		Cluster 2 v 3	0.87	0.79-0.96	**0.002**
ICOAP-total (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.91	0.80-1.04	0.147
		Cluster 2 v 3	0.87	0.80-0.96	**0.003**
Positive affect Score (continuous) (10-50)	n = 313	Cluster 1 v 3	1.12	0.92-1.36	0.272
		Cluster 2 v 3	1.07	1.02-1.13	**0.014**
Negative affect Score (continuous) (10-50)	n = 305*	Cluster 1 v 3	0.46	0.31-0.70	**<0.001**
		Cluster 2 v 3	0.88	0.82-0.95	**<0.001**
KOOS pain (0-100)[b]	n = 313	Cluster 1 v 3	1.13	1.02-1.26	**0.031**
		Cluster 2 v 3	1.18	1.11-1.26	**<0.001**
KOOS symptoms (0-100)[b]	n = 313	Cluster 1 v 3	1.06	0.10-1.13	0.067
		Cluster 2 v 3	1.08	1.02-1.14	**0.008**
KOOS activities of daily living (0-100)[b]	n = 313	Cluster 1 v 3	1.11	1.01-1.20	**0.03**
		Cluster 2 v 3	1.14	1.10-1.18	**<0.001**
KOOS sports and recreation (0-100)[b]	n = 313	Cluster 1 v 3	1.09	1.02-1.17	**0.017**
		Cluster 2 v 3	1.11	1.04-1.19	**0.003**
KOOS quality of life (0-100)[b]	n = 313	Cluster 1 v 3	1.04	0.10-1.09	0.141
		Cluster 2 v 3	1.10	1.07-1.14	**<0.001**
Knee injury (yes=1)	n = 305*	Cluster 1 v 3	2.30	0.04-130.0	0.589
		Cluster 2 v 3	0.24	0.13-0.47	**0.001**
Knee buckling (yes =1)	n = 305*	Cluster 1 v 3	0.32	0.15-0.68	**0.039**
		Cluster 2 v 3	0.26	0.18-0.38	**<0.001**
Satisfactory Lubben Social Support Score (yes = 1)	n = 305*	Cluster 1 v 3	0.64	0.39-1.05	0.511
		Cluster 2 v 3	0.93	0.84-1.02	0.878
Any use of medication over the previous week	n = 313	Cluster 1 v 3	0.08	0.05-0.12	**<0.001**
		Cluster 2 v 3	0.16	0.11-0.23	**<0.001**
Any vigorous physical activity over the previous week	n = 313	Cluster 1 v 3	1.26	0.78-2.07	0.798
		Cluster 2 v 3	1.20	0.98-1.46	0.715

Note: Missing data for covariates was not imputed.

[a]NRS-Numeric Rating Scale (0-10).

[b]KOOS (0-100, with 0 = extreme and 100 = no knee problems).

Bold indicates statistical significant $P < 0.05$).

previous studies on the subject, the unique feature of this study was that it was able to both identify pain trajectories of individuals who had previous pain fluctuations and examine their change in pain over a short period of time.[1,4,5] We found that the majority of individuals (n = 248) reported minmal change in their pain on average, over the study period. The second largest cluster (n = 46) reported on average moderate-high pain that worsened, whereas the third and smallest cluster (n = 11) reported large improvement in pain over the study period. The characteristics of individuals allocated to each cluster were compared with characteristics of those in the cluster with the poorest outcome KOOS-p trajectory. This comparison identified that individuals in the cluster with the poorest outcome had a higher body mass index, poorer pain scores, higher negative affect, lower positive affect, higher perceived stress scores, and an increased propensity for buckling of knee or knee injury at baseline.

This study demonstrates that short-term pain trajectories in persons with previous KOAF are largely unaltered with a large cluster of individuals showing little improvement/deterioration in pain over 90 days. This contrasts with some of the previous studies on long-term pain trajectories in persons with KOA. Most assessed pain and physical function trajectories, but one study, with more than 3 years of follow up, identified four osteoarthritis phenotypes characterized by the following pain patterns: low-fluctuating pain, mild-increasing pain, and treatment sensitivity: moderate-treatment-sensitive and severe-treatment-insensitive pain.[24-26] In addition, another examined pain and physical function combined trajectories.[26] But, none of these studies examined short-term changes in pain, nor did they explore the pain trajectories in persons with previous KOAF. We selected individuals with a previous history of KOA pain fluctuations in the previous month; ie persons more prone to pain exacerbations; as our intent was to document pain trajectories in persons who have greater potential for pain progression. Pain fluctuation is a phenomenon that is possibly seen in earlier disease.[3] Therefore, the difference in our results when compared with the longer pain trajectories examined previously may be due to the different pathogenic mechanisms operational in KOAF compared with chronic KOA.[3,27]

Conceptually, knees with pain fluctuations (at least in the early stages) retain the capacity to resolve after a disruption/challenge to the baseline state[3] and it has been postulated that KOAF are of inflammatory origin and that these usually settle within a week.[28-31] As most cases of KOAF settle approximately within a week, it is felt that the 90-day pain trajectory was largely unaltered because pain resolves within the 10 days.[31] But it is noteworthy that in our study, these pain flucutations, in general, did not impact the short-term 90-day pain trajectory as a whole.

The differences we detected between the clusters are in keeping with existing knowledge on patient profiles observed in KOAF. Our study demonstrated that there was a difference in cluster membership based on pain trajectories in terms of knee injuries and buckling of knee, with individuals in the worsening pain cluster more likely to report recent injury or knee buckling than those in the small or large improvement clusters. This is in keeping with the current postulated mechanisms of KOAF, which are believed to be triggered by local perturbations in joint stress.[3,32] Similarly, individuals in the worsening pain cluster were more likely to be obese or overweight when compared with those in improving pain clusters. These findings further lend support to the micro-trauma KOAF relationship because heavier individuals are more likely to load the knee than others.[3,32,33]

The pain experience was different in the three clusters, with significant differences detected between clusters in terms of the ICOAP score. The ICOAP examines the constructs of 'constant' and 'intermittent' pain in KOA. It comprehensively evaluates the pain experience in KOA assessing pain (intensity, frequency) and the impact of pain on quality of life, mood, and sleep independently of physical function, and differentiates the pain experience between the intermittent and constant pain construct. As expected, the ICOAP intermittent subscale was significantly different between the three clusters, whereas the ICOAP constant subscale was only significantly different between Cluster 3 and Cluster 2. This finding adds strength to the different clusters identified by the trajectory analysis by demonstrating that these clusters are indeed different using previously validated robust measures used in osteoarthritis studies.

There were notable differences in negative affect between the clusters and we demonstrated that persons in Cluster 1 and Cluster 2 were less likely to have higher negative affect scores and higher pain scores compared with Cluster 3. It has been demonstrated that poorer mood and lower pain thresholds are associated with KOA pain.[34-36] Negative affect, in particular, has been demonstrated to be associated with clinically perceived pain in osteoarthritis as well as pain in other musculoskeletal diseases.[37-39] In addition, this study demonstrated a significantly higher positive affect between those with Cluster 2 compared with those with Cluster 3. Loss of positive affect makes a person more vulnerable to negative affect; whereas an increase in positive affect improves resilience and buffers a person from negative affect, which explains these findings in Cluster 3.[38,40] Further, a short-term increase in positive affect may dampen the effects of pain by minimizing and reducing the sensitization gating of central pain processing pathways.[40] There were significantly higher perceived stress scores in Cluster 3 compared with Clusters 1 and 2. This is in keeping with previous findings that perceived that stress scores play a role in pain perception.[37] All of these characteristics of our identified clusters are compatible with the study population and add further support to the findings of previous studies.[4]

Our study did not find a difference between the three clusters with regard to years of KOA, age over 65 years, female sex, and social support. This is in contrast to other longer-term pain trajectory studies, which assessed persons at yearly intervals and demonstrated that the participants in older age groups were more likely to have worse pain trajectories than those with minimal pain.[4,26] Another study that assessed participants annually found that younger age was associated with a poorer activity limitation trajectory. It is likely that the effect of age is more likely to be seen only in studies with longer assessment points than the short-term assessment in ours. There were no previous studies that assessed the association between years of osteoarthritis with cluster membership.

The key strengths of our study are that it was conducted in a targeted population with KOA, with distinct and narrow eligibility criteria, in a cohort who also had a history of previous KOAF. We believe that examining this targeted study population facilitates an important deeper understanding of the pain trajectory in persons with a tendency to have KOAF. In addition, this study has examined this population at smaller 10-day time intervals, thereby giving a better perspective of the pain trajectory in the short-term, which we feel is better suited to identify our study question. The 10-day assessment interval permitted better applicability of the KOOS-p instrument, which is designed to capture symptoms and disabilities in the preceding 7 days.[41] Robust methodology in accordance with the GRoLTS checklist was applied to explore heterogeneity in the study population and to identify distinct trajectories based on KOOS-p score (Appendix 1). Thereafter the characteristics of each cluster were described.[21] This approach uncovered unique patterns of pain progression in the short-term, which have not been documented previously in the literature. The majority of previous studies have focused on much longer pain windows of 3 months or more and there are no studies to date that have focused on a shorter window of pain evolution, ie time-points as short as 10 days.

This study has the following limitations. First, this study collected data from a pre-existing cohort in a relatively smaller group of participants compared with other studies. The reason for this sample size is in part due to one of the advantages of the study, in that it assessed data in real time and at shorter time intervals. It is not feasible to study individuals at this frequency of reporting using larger sample sizes because of participant burden and financial constraints. Assessing individuals at closer intervals in turn increases the validity and reduces recall bias while creating the potential to examine a smaller window of time than previous studies. In addition, this study was carried out in a predominantly White Australian population with ready access to the internet and may need replication in other more varied populations, ideally with a larger sample size.

Although the cluster with large pain improvement (n = 11) was small, the decision to adopt the model that included the smallest cluster was based both on model fit statistics and on clinical importance, especially given that this cluster showed a large improvement in pain over 90 days. Accordingly, further investigations are needed to verify the trajectory patterns observed in our study, especially that of the cluster with greater pain improvement over a short period. It is significant that pain improvement was detected at all within this relatively small window of 10 days of observation, even in this small sample size.

Cluster 3 had higher levels of pain at baseline and showed a trend towards worsening over the following 90 days. It is noteworthy that longer assessment points (ie 2 years) have identified greater KOOS-p Minimum Clinically Important Difference (MCID) thresholds—particularly in surgical interventions—than that identified in our Cluster 3.[42,43] But there are no currently established thresholds to identify (MCID) in KOOS-p at short-term assessments As the three clusters in this study were identified by best-fit modeling using a robust methodology, characterized by different clinical characteristics compatible with current evidence, it is likely that smaller MCID are relevant in the shorter term.

This study does not seek to provide prediction of recovery, but does offer new information towards profiling individuals who are more likely to follow one of the identified three trajectories. However, it is noteworthy that only the univariate relationships of the characteristics of the clusters were examined. Therefore, the collinearity of predictor variables could not be ascertained.

In addition, a web-based study design was used in data collection. KOA is a disease of older persons, but many older persons may not be internet savvy. Therefore, it is possible that these findings may not be generalizable to the entire population of persons with osteoarthritis. However, web-based study designs have been used in the multiple rheumatological diseases that are prevalent in older individuals.[13] Therefore, these findings are considered as valid. In addition, there is a potential for recall bias with self-reported information. But, the real-time data collection, with regular reminders, may have minimized delays in reporting information. In addition, pain scores were collected at regular intervals, during control periods, reducing the potential for recall bias.

Despite these limitations, we assert that this study has identified three clinically meaningful pain clusters based on pain trajectories in this KOA cohort. The three clusters identified broadly agree with previous osteoarthritis research and extend this knowledge to provide unique insights into pain trajectories in persons who have fluctuating pain. This is useful for both clinicians and policy-makers in that these findings indicate that individuals with episodes of pain fluctuations have different trajectories and may need different levels of care and support. Similarly, researchers need to enrol larger cohorts of individuals with pain fluctuations to further investigate mechanisms underlying the heterogeneity that our study uncovered. We also recommend that further imaging, genetic and molecular studies be carried out to better understand the unique characteristics in these different phenotypes.

5 | CONCLUSIONS

In conclusion, this study demonstrated that the short-term pain trajectories in knee osteoarthritis diverge during a period as short as 90 days. Each cluster identified in this cohort was also described by characteristics at baseline.

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CONFLICT OF INTEREST

The work reported in this manuscript has not received any financial support or other benefits from commercial sources. The authors

have no financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regards to the work.

AUTHOR CONTRIBUTIONS

All authors fulfil the International Committee of Medical Journal Editors criteria for authorship.

DISCLOSURES

DJH provides consulting services on the scientific advisory board for Pfizer, Lilly, Kolon TG, and TLCBio.

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APPENDIX 1

MISSING DATA MECHANISM AND LATENT VARIABLE MODELING APPROACHES

Exploration of missing data

Most longitudinal studies are affected by drop-outs of participants and missing data points.[1,2] As the mechanism by which the data are missing can impact or bias findings, we examined the missing data patterns. The missing data mechanism was explored using Little's MCAR (missing completely at random) test and its extension to test the covariate-dependent missingness using STATA v15.1 (StataCorp, College Station, TX, USA).

Complete data were available for the first two time points. To identify the pattern of missingness across all other time points, we used Little's MCAR test and its extension to test the covariate-dependent missingness (CDM) STATA v15.1. Without inclusion of covariates the missing data were not MCAR (n = 313, χ^2 distance = 817, df = 2420, P = 0.0016). When the following covariates were added individually: age (<65 or >65 years), years of osteoarthritis, ICOAP (intermittent, constant, and total scores), positive negative affect score, usual level of background pain, or worst level of background pain reported at baseline, being overweight/obese, a satisfactory Lubben Social Support Score, knee injury or knee buckling in the 7 days or 2 days before, respectively, the missing data satisfied MCAR (all tests, $P > 0.9$). Similarly, when important covariates were considered together—age (<65 or >65 years), years of osteoarthritis, ICOAP (intermittent, constant, and total scores), positive negative affect score, usual level of background pain—the missing data satisfied MCAR (n = 301, χ^2 distance = 650, df = 1540, P = 1.0).

Latent variable modeling

Latent variable longitudinal mixture modeling was used to model the heterogeneity in KOOS-p scores over 90 days in an attempt to classify individuals into unique groups (classes or clusters) based on their KOOS-p trajectory. A systematic approach to modeling latent variables was explored as recommended by the Guidelines for Reporting Latent Trajectory Studies (GRoLTS) reporting guidelines.[3] Latent class growth analysis (LCGA) was followed by latent growth mixture modeling (LGMM). LCGA is a special type of LGMM, where the within-class variance of latent intercept and slope are fixed to zero within class (individuals vary only between classes), which leads to a solution where classes differ mainly by intercept (initial KOOS score).[4-6] In contrast, LGMM permits within-group variability for the latent intercepts and slope for each class (individuals can vary within and between classes), which leads to a solution where classes differ by both intercept and shape.[7] GMM is more computationally intensive, which can result in model convergence issues.[8-10] Both modeling approaches were explored in this data set using linear and quadratic growth curves.

For each model, individuals with similar trajectories were classified into a single class based on posterior probability.[11] The optimal number of classes considered both data-driven (goodness-of-fit indices) and pragmatic (model parsimony, model interpretability) criteria. Goodness-of-fit indices included the sample-size-adjusted Bayesian Information Criterion (sBIC) and Akaike information criterion (AIC) where lower values represent a better fitting model.[11] In addition, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR LRT) and the Lo-Mendell-Rubin Adjusted Ratio Test (LMR-LRT) where the model with k classes is favored against the model with k-1 classes, were used.[11,12] Models were then tested until no further improvement in model fit occurred (LRT $P \geq 0.05$). Pragmatic model selection criteria considered acceptable entropy values and posterior probabilities per cluster (>0.7), potential clinical relevance, cluster membership size in each model tested without pre-specifying a minimum cluster size, and other practical concerns (eg model convergence).[13] Mplus version 8 (Muthén & Muthén, Los Angeles, CA) was used for all latent class modeling. In MPlus, missing data for KOOS-p scores are handled using MAR with estimating using maximum likelihood. No imputation of KOOS-p scores was undertaken.

When all models were considered, the three-class LGMM-quadratic model was chosen based on the best fit indices: (lowest sBIC = 21 402), ideal VLMR-LRT (three-class vs two-class LGMM, P = 0.058); high posterior probability (0.81-0.91), and acceptable entropy (0.73). The three-class LGMM-quadratic model identified the greatest number of improvers (n = 11) over the study period (Figure A1). Compared with LCGA models, LGMM models had superior goodness-of-fit indices for both AIC and sBIC. The three-class LGMM-quadratic model had the best fit indices with a combination of the lowest sBIC (21 402.21), ideal VLMR-LRT (P = 0.058) and LMR-LRT (P = 0.065).

Models had an acceptable average posterior probability of belonging to each class and acceptable entropy (>0.7). All LCGA models had higher posterior probability and entropy than the LGMM models (which was expected because of LCGA fixing within-class variance to zero). Minimum class size ranged from 11 to 137 for LCGA models, and from 1 to 33 for LGMM models. In addition, LGMM models identified one cluster of individuals that had a large improvement in KOOS scores over the study period with the three-class quadratic model capturing the greatest number of improvers (n = 11). The quadratic model had superior fit indices compared with the linear model, which suggests that individuals improved at a greater rate later in the study period (Table A1).

Overall, the three-class LGMM-quadratic model was chosen based on the best fit indices, acceptable posterior probability and entropy, parsimony, and potential clinical relevance. Table A1 details the goodness-of-fit indices and trajectory characteristics for each model (Figure A1).

A split validation of the data set (sequential 1:1 allocation) was conducted to explore: (a) ideal number of clusters in each "split" sample" and (b) stability of class membership for each individual (ie were the individuals in each split data set classified differently compared with full data set). This process confirmed that the three-class model remained ideal in each split solution, and that the classification of participants compared with the full model was high (Table A2).

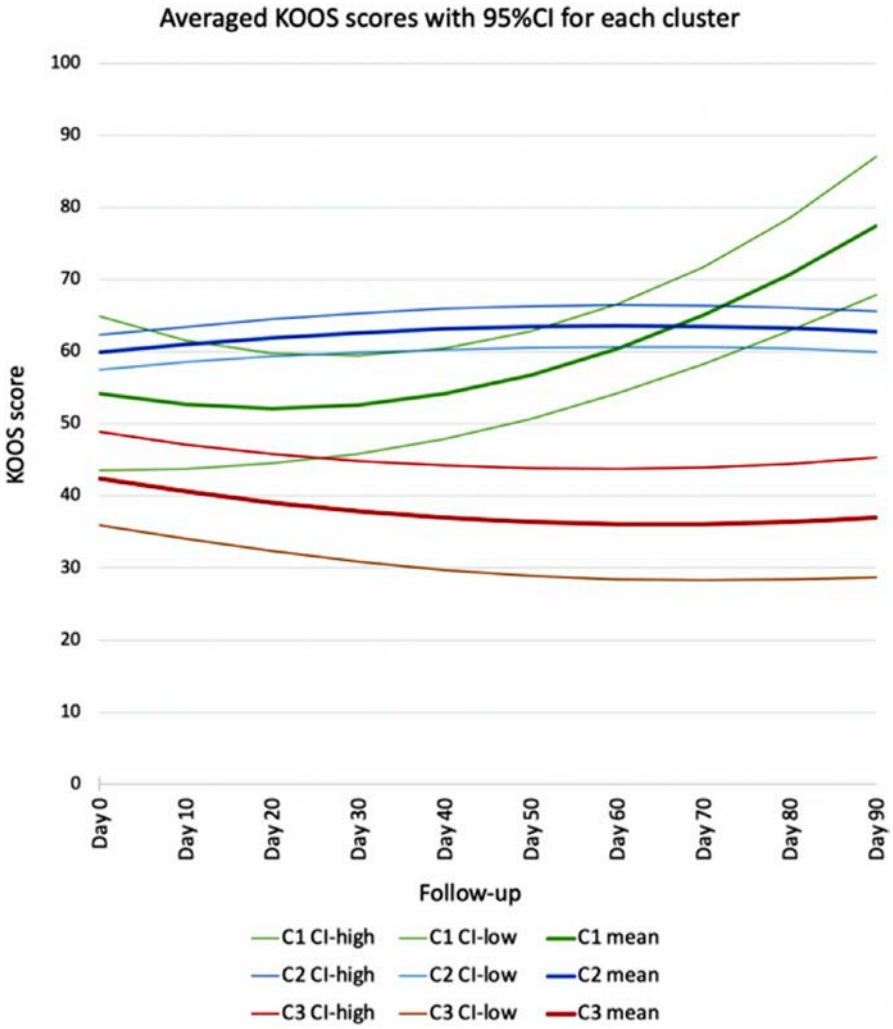

FIGURE A1 Averaged KOOS-p scores with 95% CI for each cluster

TABLE A1 Fit indices and model selection

Model	Fit indices	1-cluster model	2-cluster model	3-cluster model	4-cluster model	5-cluster model
LCGA-linear	Log likelihood	−12 420.42	−11 572.01	−11 166.22	−10 967.32	−10 856.52
	AIC	24 864.86	23 174.04	22 368.45	21 976.66	21 761.05
	sBIC	24 871.75	23 182.66	22 378.79	21 988.72	21 774.84
	VLMR LRT (*P* value)		0.008	0.165	0.085	0.078
	LMR LRT (*P* value)		0.010	0.175	0.091	0.085
	Entropy		0.92	0.94	0.92	0.92
	Posterior probabilities (range)	1.00	0.97-0.97	0.97-0.97	0.93-0.96	0.93-0.99
	Cluster membership (C1/C2/C3..)	313	176/137	59/143/111	107/69/97/40	91/49/98/64/11
LCGA-quadratic	Log likelihood	−12 420.27	−11 571.65	−11 164.45	−10 964.33	−10 854.62
	AIC	24 866.55	23 177.29	22 370.89	21 978.66	21 767.24
	sBIC	24 874.02	23 187.06	22 382.96	21 993.02	21 783.90
	VLMR LRT (*P* value)		0.008	0.183	0.185	0.178
	LMR LRT (*P* value)		0.009	0.190	0.193	0.185
	Entropy		0.92	0.94	0.93	0.93
	Posterior probabilities (range)		0.97-0.97	0.96-0.97	0.93-0.97	0.93-0.98
	Cluster membership (C1/C2/C3..)	313	137/176	143/59/111	107/40/69/97	11/98/92/48/64

Model	Fit indices	1-cluster model	2-cluster model	3-cluster model	4-cluster model	5-cluster model
LGMM-linear	Log likelihood	−10 693.88	−10 688.68	−10 683.85	−10 680.70	Model did not converge[a]
	AIC	21 417.75	21 413.37	21 409.69	21 409.39	
	sBIC	21 426.37	21 423.71	21 421.76	21 423.18	
	VLMR LRT (*P* value)		0.018	0.082	0.605	
	LMR LRT (*P* value)		0.022	0.092	0.623	
	Entropy		0.67	0.77	0.72	
	Posterior probabilities (range)		0.76-0.92	0.76-0.92	0.82-0.86	
	Cluster membership (C1/C2/C3..)	313	33/280	4/35/274	5/156/132/20	
LGMM-quadratic	Log likelihood	−10 683.61	−10 673.62	−10 667.35	−10 662.87	Model did not converge[a]
	AIC	21 405.22	21 393.24	21 388.70	21 387.74	
	sBIC	21 416.13	21 406.45	21 404.21	21 405.55	
	VLMR-LRT (*P* value)		0.017	0.058	0.185	
	LMR-LRT (*P* value)		0.019	0.065	0.193	
	Entropy		0.89	0.73	0.74	
	Posterior Probabilities (range)		0.98-0.85	0.81-0.91	0.78-0.99	
	Cluster membership (C1/C2/C3..)	313	301/12	11/254/48	251/1/12/49	

Abbreviations: AIC, Akaike information criterion; LMR-LRT, Lo-Mendell-Rubin Adjusted Ratio Test; sBIC, Bayesian Information Criterion; VLMR-LRT, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test.

[a]The latent variable covariance matrix (psi) was not positive definite (initial conditions: random start sets = 500, final stage optimizations = 100).

TABLE A2 Stability of cluster membership when split cohorts were compared

		Proportion assigned to original cluster after split		
		C1	C2	C3
Cluster membership full data set (n_{full} = 313)	C1 = 11	**0.82**	0.18	0.00
	C2 = 248	0.01	**0.97**	0.02
	C3 = 46	0.00	0.14	**0.86**

Note: C1 = Cluster 1: Low-moderate pain with large improvement over 90 days, C2 = Cluster 2: Minimal change in pain over 90 days, C3 = Cluster 3: Moderate-high pain with worsening over 90 days. Shaded boxes represent participants from each data set half ($n_a|n_b$) classified into the same cluster as full data set (n_{full}).

Mplus code for final model

```
(Auxiliary variable modeling [R3step] not shown)

Title:
GMM 3-class Quadratic model
Data: File = Koos Data set.dat;
Variable:
Names = ID pa1-pa10;
Usevariables = pa1-pa10;
Classes = c(3);
IDVariable = ID;
Missing = ALL(-99);
Analysis:
Type = Mixture;
PROCESSORS = 8;
Starts = 100 20;
Model:
%Overall%
i s q&#x007C; pa1@0 pa2@1 pa3@2 pa4@3 pa5@4 pa6@5
pa7@6 pa8@7 pa9@8 pa10@9;
! for 95%CI plot
%c#1%
[i s q] (p1 p2 p3);
%c#2%
[i s q] (p4 p5 p6);
%c#3%
[i s q] (p7 p8 p9);
Output:
TECH1 TECH8 CINTERVAL;
PLOT: SERIES = pa1-pa10 (s);
TYPE = PLOT3;
MODEL CONSTRAINT:
PLOT(class1 class2 class3);
LOOP(time,0,10,0.1);
class1 = p1+time*p2+time*time*p3;
class2 = p4+time*p5+time*time*p6;
class3 = p7+time*p8+time*time*p9;
```

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ORIGINAL ARTICLE

(Un)disclosed. Disease disclosure in people living with rheumatic diseases: An exploratory study

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Abstract

Objective: Little is known about disease-related disclosure (DD) in patients with rheumatic musculoskeletal diseases (RMDs). We aim to investigate DD behaviors and to explore which socio-demographic, clinical and psychological factors play a role in this self-disclosure process among patients with RMDs.

Methods: A cross-sectional Italian nationwide study captured DD in RMDs in different contexts (workplace, family, friends, partner, social networks). An ad hoc survey was developed and disseminated by the Patients' Association ALOMAR ODV (Lombard Association for Rheumatic Diseases) between June and July 2020. Patient demographics, clinical data, and questionnaires assessing anxiety, depression, anticipated stigma, patient health engagement, perceived social support, and perceived general health status were collected.

Results: There were 376 rheumatic patients who completed the survey. There were 73.9% of the participants who talk to others about their RMD "sometimes"; 18.7% disclose their RMD "always/very often", while 7.4% "never" talk about their RMD. A significant association was detected between DD and both perceived visibility ($P = .04$) and psychological support ($P = .01$). Moreover, participants who never/sometimes disclose their RMD reported significantly lower scores in the "Total" Social Support ($P < .01$) and in the "Friends" subscale ($P < .001$) compared to others. Psychological support and the "Friends" subscale were the only significant predictors of DD (both $P = .002$).

Conclusions: The majority of RMD patients disclosed their disease "sometimes". The DD behavior is not associated with any specific demographic or clinical variables. Further research on the subject might help to foster better DD decision-making processes for rheumatic patients in different contexts of daily life.

KEYWORDS
chronic disease, disease disclosure, health disclosure, invisible disability, rheumatic disease

1 | INTRODUCTION

Rheumatic musculoskeletal diseases (RMDs) are a group of more than 200 different medical conditions characterized by pain, inflammation, and associated with substantial morbidity and mortality.[1] Anxiety and depression symptoms are commonly associated with some RMDs.[2-4] In the last decades, thanks to research advances, the clinical management of RMD patients has significantly improved. Consequently, in most cases, the diseases are invisible; thus, it is up to the individual to determine whether, how, when, to whom to disclose their diagnosis.[5]

Self-disclosure can be defined as an interaction between at least 2 individuals where one intends to deliberately divulge personal information unlikely to be discovered in other ways[6] through an act of personal narrative.[7] Self-disclosure represents a multifaceted, dialectical, socially relevant act[8] which fosters the creation of intimate relationships[9] and seems to be related to well-being.[10] Self-disclosure decision-making processes imply the balancing of possible personal risks and benefits deriving to the individual by the act of self-disclosing.[11]

Disease disclosure (DD) refers to a subject who reveals personal information concerning his/her health.[11,12] A large number of chronic illnesses, such as RMDs, are concealable conditions: in these cases, DD can effectively be described as a coming-out process.[13] The choice to disclose a chronic illness is complex and might elicit dialectic dilemmas.[14] Indeed, DD is influenced by several factors, such as: type and severity of illness, stigma, access to support, fear of rejection, loss of social support and of employment.[11,15,16] Studies on the DD of human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS)[17,18] and chronic non-communicable diseases such as diabetes and cystic fibrosis have shown how stigma surrounding illness and fear of negative repercussions may contribute to the unwillingness to disclose one's disease.[19]

The PARE Youth Research Project[20,21] has shed a first light on DD behaviors among European young people living with a RMD, revealing that 85% of the respondents feel disadvantaged if others know about their disease.

Disclosure research across various chronic illnesses suggests that DD is associated with positive psychosocial outcomes, such as greater social support and social functioning,[12] fewer symptoms of depression,[16] better medication adherence;[11] however, any directional relationship between DD and such positive outcomes needs to be further investigated.

DD may have important clinical implications in RMD patients; however, scientific literature exploring DD in individuals with RMDs is limited and mainly focused on DD at work.[22-24] Further research is needed in order to explore this construct and its correlates in this specific population. We aim to supplement the existing literature by exploring DD in different life contexts (eg workplace, family, friends, partner, social networks) among individuals suffering from different RMDs, and to evaluate the associations between DD and socio-demographic, clinical and psychological factors in this specific population.

This study makes a novel contribution to the literature by assessing DD among a large sample of Italian individuals with RMDs.

2 | METHODS

2.1 | Participants and procedures

Participants were recruited from the no-profit rheumatic patients association (ALOMAR ODV) – Lombard Association for Rheumatic Diseases. A call for survey completion, outlining the nature and objectives of the study, was sent using the ALOMAR mailing list and the related website and social network (http://www.alomar.it/). The survey was conducted between June 18 and July 9 2020.

The study population is composed by rheumatic patients aged 18 or older, resident in Italy and fluent in the use of the Italian language who responded to the online survey by accepting the information and expressing consent to participate. The survey was anonymous and confidentiality of information was assured. The study was approved by the Board of Directors of ALOMAR ODV.

2.2 | Instruments

The survey was specifically developed for this study, exploring some of the main factors that literature associates with DD, such as perceived social support,[25,26] perception of stigma,[11,13,27,28] perceived visibility of the disease.[11,13] Some other constructs, such as patient engagement,[29] have been added on the basis of an exploratory perspective. The survey was divided into the following sections: (a) socio-demographic information (ie, gender, age, employment status); (b) clinical information (ie, RMD diagnosis, duration of illness, pharmacological therapy, therapeutic adherence); (c) DD: we assessed the general frequency of DD (ie, "how often do you usually talk to others about your RMD"), DD in different contexts (workplace, family, friends, partner, social networks) and potential barriers related to DD (ie, "I feel disadvantaged if others know").

Furthermore, the following psychological domains were investigated.

1. Mental health status was assessed using the Patient Health Questionnaire – 4 (PHQ-4),[30] a validated ultra-brief tool for detecting both anxiety and depressive symptoms. The PHQ-4 consists of the first 2 items of the Generalized Anxiety Disorder scale (GAD-7)[31] and the first 2 items of the longer Patient Health Questionnaire (PHQ-9).[32] Responses are provided on a Likert scale ranging from 0 (= "not at all") to 3 (= "nearly every day"). Cronbach's alpha for the current study was .893.
2. Anticipated stigma was detected through the Italian version of the Chronic Illness Anticipated Stigma Scale (CIASS)[33,34] a validated tool consisting of 12 items referring to possible experiences of stigma, contextualized in 3 social scenarios: friends and family (ie, "a friend or family member will think badly of you"), work colleagues (ie, "someone at work will discriminate against you"), health workers (ie, "a health worker will feel frustrated because of you"). Participants are asked to rate the likelihood of encountering

such situations on a Likert scale from 1 (= "very unlikely") to 5 (= "very likely"). Cronbach's alpha for the current study was .883.

3. Patient health engagement was measured through the Patient Health Engagement Scale (PHE-S)[29] a 5-item questionnaire, validated in the Italian population, which evaluates the degree of emotional elaboration reached by the patient concerning his/her own health. The PHE-S is made up of ordinal elements placed along an experiential continuum. The response options include responses corresponding to the 4 PHE positions (blackout, arousal, adhesion, eudaimonic project) as well as intermediate positions (ie, when thinking about my illness; "I feel lost", "I feel alarmed", "I am conscious", "I feel serene"). Cronbach's alpha for the current study was .896.
4. Perceived social support was measured through the Italian version of the Multidimensional Scale of Perceived Support (MSPSS),[35,36] a validated tool consisting of 12 items relating to perceived social support from family, (ie, "my family really tries to help me"), friends (ie, "I can count on my friends when things go wrong"), significant other (ie, "I have a particular person who is an authentic source of comfort for me"). Participants are asked to express their level of agreement or disagreement with the statements on a Likert scale from 1 (= "very much disagree") to 6 (= "very much agree"). Cronbach's alpha for the current study was .935.
5. Perceived general health status was measured using a single item from the 36-item Short-Form Health Survey (SF-36).[37,38] Response is provided on a Likert scale ranging from 1 ("excellent") to 5 ("poor").

2.3 | Statistical analysis

Descriptive statistics of the socio-demographic and clinical data and of the survey results of the total sample were carried out. In order to detect the existence of statistically significant differences between groups of patients for the variables of interest (ie, DD), the analysis of variance test was used for continuous variables and the non-parametric Chi-square test was used in the case of categorical variables. Multiple comparisons were corrected via Bonferroni's method. Furthermore, a multiple ordinal regression was performed by addressing the full range of the DD frequency scale (4 levels) as the criterion and all the above-mentioned socio-demographic and psychometric measures as predictors. SPSS 19.0 software for Windows was used for statistical analyses and P values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

In this cross-sectional survey, we retrieved a total of 391 questionnaires, of which 15 were excluded as incomplete. Therefore, a total of 376 RMD patients eligibly completed the survey: the majority of them reported suffering from rheumatoid arthritis (38%), fibromyalgia (32.4%) and psoriatic arthritis (13.3%) – both in primary or secondary form. The majority (91.2%) of the sample was composed of women; 66% of the participants were in a relationship, 52.1% had high school education, 55.1% were employed. The participants had a mean age of 47.22 years (±13.23). More details are reported in Table 1.

3.2 | DD characteristics

Most participants (47.9%) believed their RMD was not visible to others, 37% perceived their RMD as only "sometimes" visible and 15.2% perceived their RMD as visible to others. The majority of respondents (73.9%) disclosed their RMD "sometimes"; 18.7% of respondents disclosed their RMD "always/very often", while 7.4% "never" disclosed their condition to others (Figure 1).

The topic respondents mostly talk about when disclosing their disease in different social contexts are the RMD's symptoms: 76.3% talk about their symptoms with the family and 67% talk about their symptoms with their friends. The disclosure of symptoms is followed in the study population by the disclosure of information related to the pharmacological therapy: 44.9% mostly talk about their therapy with the family and 39.6% talk about their therapy with their friends.

In general, the respondents perceive that after disclosing their RMD their personal relationship with the DD's receivers has not changed: 68.9% of the participants referred that their relationship with family did not change after the DD. In the sample, only 1.1% of the participants referred that their relationship with friends got worse after the DD. The fear of being labeled as "sick" (47.7%) and the fear of being perceived as "a burden to others" (47.6%) after the DD are the perceived barriers to disclosing that convey the highest agreement among the respondents (Figure 2).

3.3 | Comparison in DD behaviors based on socio-demographic, clinical, psychological characteristics

A significant association was detected between DD and both perceived visibility and psychological support (see Table 2). A post-hoc decomposition of the association between DD and psychological support via standardized adjusted residuals yielded the following findings: (a) participants disclosing their disease "always/very often" reported a higher-than-expected rate of having received psychological support ($z = 3.1$), as well as a lower-than-expected rate of not having received it ($z = -0.31$); (b) participants who disclosed their disease "sometimes" reported a lower-than-expected rate of having received psychological support ($z = -0.22$), as well as a higher-than-expected rate of not having received it ($z = 2.2$). With respect to the association between DD and perceived visibility, the following results emerged: (a) participants disclosing their disease "always/very often" reported that their disease was visible more frequently than expected ("Visible" $z = 2.4$); consistently, they reported that their disease was not visible less than expected ($z = -2$); (b) participants

TABLE 1 Socio-demographic and clinical characteristics

	Mean, y	SD
Age	47.22	13.23
Disease duration	12.63	10.98
	%	n
Gender		
Female	91.2	343
Male	8.5	32
Relationship status		
Single	34.0	128
In a relationship	66.0	248
Education		
Primary/middle school	15.5	58
High school	52.1	196
University or higher	32.5	122
Employment status		
Employee	55.1	207
Self employed	11.4	43
Currently not working	33.5	126
Member of a patients' association		
Yes	63.0	237
No	37.0	139
Rheumatic comorbidity		
Yes	37.0	139
No	63.0	237
Other medical comorbidity		
Yes	62.2	234
No	37.8	142
Pharmacological therapy (monotherapy or combined)		
Disease-modifying antirheumatic drugs	32.7	123
Biotech/biosimilar	41.8	157
Non-steroidal anti-inflammatory	33.2	125
Pain relievers	37.0	139
Steroidal	33.5	126
Psychological support		
Yes	35.6	134
No	64.4	242
Is your disease visible to others?		
Yes	15.2	57
No	47.9	180
Sometimes	37.0	139

disclosing their disease "sometimes" reported less frequently than expected that their disease was visible ($z = -2$).

Table 3 describes differences for DD in relation to psychological questionnaires. No statistical differences were found for DD and mental health, stigma, perceived health and patient engagement. A statistically significant difference in DD was observed for the

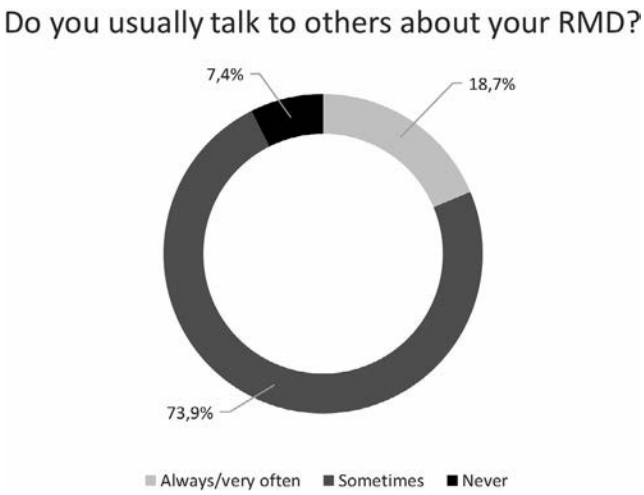

FIGURE 1 Prevalence of disease disclosure in the study population. RMD, rheumatic musculoskeletal disease

perceived social support: participants who never disclose their RMD reported significantly lower scores in the "Total" scale ($F = 4.952$; $P < .01$) and in the "Friends" subscale ($F = 13.309$; $P < .001$) compared to others.

Bonferroni-corrected post-hoc analyses revealed that participants who "always/very often" disclosed their RMD reported significantly higher ($P = .005$) MSPSS-total scores when compared to those who "never" disclosed it – remaining comparisons being non-significant. With respect to the "Friends" subscale, participants who "always/very often" disclosed their RMD reported significantly higher scores when compared to both those who "sometimes" disclosed it ($P = .038$) and those who never disclosed it ($P < .001$).

The multiple ordinal regression model yielded as significant predictors only having received psychological support ($\chi^2(1)=9.38$; $P = .002$) – with those not having received it reporting lower DD levels when compared to those having received it – and the MSPSS "Friends" subscale ($\chi^2(1)=9.67$; $P = .002$) – with higher MSPSS "Friends" scores predicting higher DD levels.

4 | DISCUSSION

To our knowledge, this is the first study exploring DD among Italian RMDs. We showed that the majority of the participants "sometimes" disclose their RMD, reflecting how people tend to only occasionally enact full disclosure or maintain full secrecy:[39] this is basically in line with the findings of the PARE Youth Research Project.[20,21]

When disclosing their rheumatological disease across different daily life contexts, the participants mostly discuss their RMD's symptomatology: this appears consistent with the fact that the symptoms of RMD may represent an obstacle for the subject; in the workplace for example, reporting one's symptoms might be necessary in order to motivate absences, or to request specific accommodations.[15] This topic is followed, by analogy, with disclosure about information related to one's pharmacological therapy. The majority of the sample,

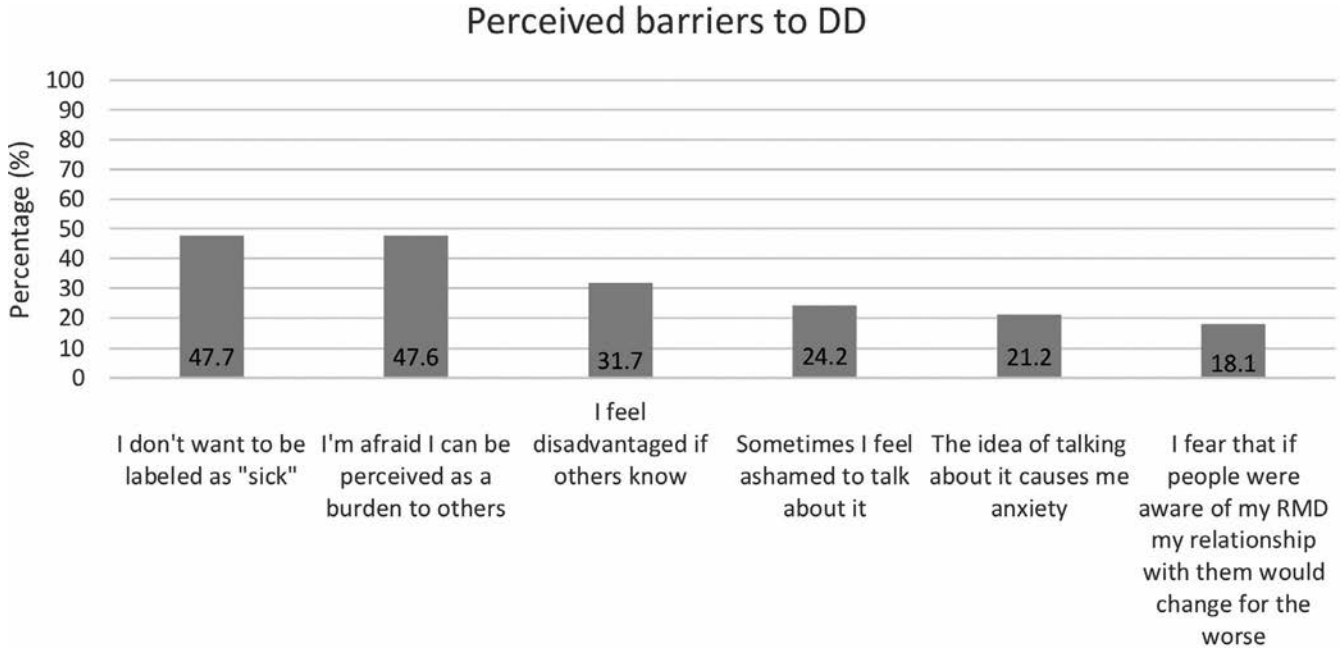

FIGURE 2 Prevalence of perceived barriers to disease disclosure in the study population. DD, disease disclosure; RMD, rheumatic musculoskeletal disease

TABLE 2 Demographic and clinical factors related to DD in patients with RMDs

	Frequency of DD				
	DD always/very often	DD sometimes	DD never		
	% (n)	% (n)	% (n)	χ^2	*P*
Psychological support					
Yes	26.9 (36)	67.2 (90)	6.0 (8)	9.51	.01*
No	14.0 (34)	77.7 (188)	8.3 (20)		
Perceived RMD visibility					
Visible	29.8 (17)	63.2 (36)	7.0 (4)	10.05	.04*
Not visible	14.4 (26)	75.6 (136)	10.0 (18)		
Sometimes visible	19.4 (27)	76.3 (106)	4.3 (6)		

DD, disease disclosure; RMDs, rheumatic musculoskeletal diseases.
*p values < .05 were considered statistically significant.

in most cases and across all contexts, tends to report that after the DD the relationship with the receivers has not changed. In the sample, the main barrier to DD is the perceived risk of undergoing a labeling process, in which the status of "sick" marks a "degraded identity":[40] this data relaunches the reflection about the weight of stigma when unveiling concealable stigmatized identities.[33,41]

The second aim of this study was to explore socio-demographic, clinical and psychological factors associated with DD in this specific population.

We found no association among DD and socio-demographic or clinical factors suggesting that DD could be less related to "objective" factors but more influenced by subjective and individual aspects. The lack of differences in DD with regard to gender is in line with the results of Dindia's (2014) meta-analysis referring to general behaviors of self-disclosure,[42] while deviating from the results of the PARE Youth Research Project[20,21] and from the studies by Munir (2004)[15] and Modi (2010)[16] which record a significant trend toward a higher frequency of DD in women.

We found that participants disclosing their disease "always/very often" reported that their disease was visible more frequently than expected: this evidence reiterates the need to think thoroughly about the (in)visibility, partial or intermittent visibility of many chronic conditions in relation to the behaviors of DD.

Furthermore, in this study we confirmed the key role of social support as reported in previous studies.[12,25,26] The detected significant difference in DD based on the perceived social support (both at a general level and specifically from friends) may reflect an aspect of circularity: the very enactment of DD can increase the social support

TABLE 3 Psychological factors related to disease disclosure (DD) in patients with rheumatic musculoskeletal diseases (RMDs)

	Frequency of DD					
	DD always/very often	DD sometimes	DD never			
	Mean (SD)	Mean (SD)	Mean (SD)	F	*P*	Post-hocs*
Patient Health Questionnaire - 4 Mental health status						
Total scale	3.84 (2.66)	4.44 (3.02)	3.92 (2.59)	1.439	.23	
Anxiety subscale	2.08 (1.48)	2.35 (1.56)	2.03 (1.45)	1.277	.28	
Depression subscale	1.75 (1.41)	2.08 (1.64)	1.89 (1.42)	1.315	.27	
Multidimensional Scale of Perceived Support Perceived social support						
Total scale	5.18 (1.34)[a]	4.86 (1.41)[b]	4.20 (1.44)[c]	4.952	.008*	a > c; a = b; b = c
Significant other subscale	5.42 (1.55)	5.19 (1.66)	4.64 (1.84)	2.235	.10	
Family subscale	5.14 (1.58)	4.95 (1.71)	4.84 (1.89)	0.446	.64	
Friends subscale	4.98 (1.58)[a]	4.44 (1.62)[b]	3.11 (1.66)[c]	13.309	>.001*	a > b>c
Chronic Illness Anticipated Stigma Scale Anticipated stigma						
Total scale	2.05 (0.77)	2.20 (0.94)	2.50 (0.83)	1.970	.14	
Friends and family subscale	1.87 (1.07)	2.00 (1.13)	1.93 (0.95)	0.433	.64	
Healthcare professionals subscale	2.02 (1.10)	1.99 (1.03)	2.27 (1.26)	0.842	.43	
Work colleagues subscale	2.55 (1.26)	2.66 (1.39)	3.14 (1.24)	1.571	.21	
Perceived health status	3.90 (0.98)	3.95 (0.82)	3.79 (0.87)	0.49	.62	
	% (n)	% (n)	% (n)	*F*	*P*	
Patient Health Engagement Scale Patient engagement						
Blackout	10.5 (6)	86 (49)	3.5 (2)	11.160	.08	
Arousal	14.7 (17)	75 (87)	10.3 (12)			
Adhesion	21.7 (38)	71.4 (125)	6.9 (12)			
Eudaimonic project	32.1 (9)	60.7 (17)	7.1 (2)			

Note: *Post-hoc analyses were corrected through Bonferroni's method.

[a]"DD always/very often".

[b]"DD sometimes".

[c]"DD never".

disclosers receive;[11] meanwhile, dialectically, those who feel more socially supported may tend to feel more effective in enacting DD,[10,43,44] thus engaging in more frequent DD behaviors.

Moreover, psychological support is positively associated with DD; this may be due to a more effective re-elaboration of the RMD diagnosis and, perhaps, also to a possible strengthening of one's perceived disclosure self-efficacy.[11] Indeed, psychological support itself can be considered an experience of self-disclosure.[7] It is interesting to read this data in relation to the significant differences observed in DD based on the social perceived support: psychological support could belong in the range of experiences of perceived support that the subject can benefit from in implementing DD behaviors.

This study has some limitations that need to be highlighted. First of all, the population under study might not be representative of the people living with RMDs in Italy since the participants were mainly recruited from the Lombard patients' association; however, the socio-demographic and clinical characteristics of our sample are in line with those provided by some other recent studies.[45]

Moreover, as an open web-based survey, the research incurs a specific selection bias, the volunteer effect.[46] Second, we used a cross-sectional approach, which is structurally unable to longitudinally grasp the temporal unraveling of DD behaviors. Third, the study observed frequency and breadth of DD but not its depth and level of intimacy;[47] qualitative research and new combinations of methods are necessary in order to deepen this issue.

In conclusion, this study, as a preliminary sketch, opens up a range of possible further studies to better understand predictors and characteristics of DD; including the relationship between DD and attachment styles,[39] DD and personality traits,[48] the role of the patient's level of self-management,[12,14] the impact of DD on the physiological and mental health of the individual.[49] A comparison between populations of different clinical areas (ie, rheumatology, diabetology, pneumology, neurology) could allow us to observe if and how DD "styles" might differ in patients suffering from different clinical conditions.

In the light of such reflections, the "best" DD would therefore not necessarily be the most frequent DD, but rather the most flexible, aware, integrated and dynamic,[11,50] capable of maintaining an adequate risk-benefit balance and of modulating silence and revelation according to the complex multiplicity of scenarios, contexts, relationships and phases characterizing one's personal chronic illness experience.

Further research on this construct will facilitate the orientation of training and services aimed at stimulating and fostering conscious DD decision-making processes in those who face a rheumatic condition.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Enhanced arthrocentesis of the effusive knee with pneumatic compression

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Abstract

Aim: Complete arthrocentesis of the effusive knee ameliorates patient pain, reduces intra-articular and intraosseous pressure, removes inflammatory cytokines, and has been shown to substantially improve the therapeutic outcomes of intra-articular injections. However, conventional arthrocentesis incompletely decompresses the knee, leaving considerable residual synovial fluid in the intra-articular space. The present study determined whether external pneumatic circumferential compression of the effusive knee permitted more successful arthrocentesis and complete joint decompression.

Methods: Using a paired sample design, 50 consecutive effusive knees underwent conventional arthrocentesis and then arthrocentesis with pneumatic compression. Pneumatic compression was applied to the superior knee using a conventional thigh blood pressure cuff inflated to 100 mm Hg which compressed the suprapatellar bursa and patellofemoral joint, forcing fluid from the superior knee to the anterolateral portal where the fluid could be accessed. Arthrocentesis success and fluid yield in mL before and after pneumatic compression were determined.

Results: Successful diagnostic arthrocentesis (≥3 mL) of the effusive knee was 82% (41/50) with conventional arthrocentesis and increased to 100% (50/50) with pneumatic compression ($P = .001$). Synovial fluid yields increased by 144% (19.8 ± 17.1 mL) with pneumatic compression (conventional arthrocentesis; 13.7 ± 16.4 mL, pneumatic compression: 33.4 ± 26.5 mL; 95% CI: $10.9 < 19.7 < 28.9$ mL, $P < .0001$).

Conclusions: Conventional arthrocentesis routinely does not fully decompress the effusive knee. External circumferential pneumatic compression markedly improves arthrocentesis success and fluid yield, and permits complete decompression of the effusive knee. Pneumatic compression of the effusive knee with a thigh blood pressure cuff is an inexpensive and widely available technique to improve arthrocentesis outcomes.

KEYWORDS
arthrocentesis, injections, intra-articular, knee, quality

1 | INTRODUCTION

Diagnostic arthrocentesis of the clinically effusive knee is usually straightforward for the experienced proceduralist with typically a 96%-100% success rate with proper positioning and an appropriate anatomic approach to the knee.[1-24] However, despite the success of diagnostic arthrocentesis, the effusive knee in the extended position with manual compression is often incompletely decompressed after conventional arthrocentesis with 30%-40% of resident synovial fluid typically remaining in the joint.[25-30] A residual effusion in the knee causes increased intra-articular and intraosseous pressures, compresses the resident circulation, painfully stretches the joint capsule with weight bearing, and has been associated with progressive articular, periarticular and supporting muscle degeneration.[31-33] Further, leaving synovial fluid in the joint prior to injection of corticosteroid or hyaluronan dilutes the injected medication, increases the failure rate, and decreases the therapeutic duration of the injected medication.[3,6,30,34,35] Thus, for a number of therapeutic reasons complete arthrocentesis is an important quality goal.[1-35]

External circumferential compression of the extended knee improves arthrocentesis success and completeness over manual compression by shifting fluid anatomically to the superolateral portal overlying the suprapatellar bursa where it can be more completely accessed.[26,27] Recently, arthrocentesis of the flexed knee with mechanical compression has also been shown to be equivalent to the customary conventional extended knee technique.[28,29] Although effective, a problem with existing compression-assisted arthrocentesis techniques is the requirement for an expensive specialty compression device that must be specially ordered and thus, decreases the convenience and increases the costs of arthrocentesis.[26-29]

We hypothesized that highly controlled pneumatic compression of the suprapatellar bursa and patellofemoral joint with a universally available and inexpensive conventional thigh blood pressure cuff would similarly improve arthrocentesis success and permit complete decompression of the effusive knee.[26-30]

2 | METHODS

This Arthrocentesis Quality Improvement Program and data analysis were formalized in the Division of Rheumatology, Department of Internal Medicine, University of New Mexico Health Science Center, and was approved by the Institutional Review Board (IRB) (approval Study ID: 20-662; approval end date: 10/26/2022) and by the Human Research Review Committee of the Office of Human Protections at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Patient confidentiality was protected according to the US Health Insurance Portability and Accountability Act (HIPAA) and all data have been de-identified. All patients provided written consent to all examinations and procedures. The study design was that typical of a quality improvement program with: (a) measurement of baseline quality factors in consecutive traditionally treated patients; (b) introduction of the quality intervention; and (c) re-measurement of quality factors in consecutive patients after the intervention. To improve statistical power, the study was designed as a paired study with first conventional arthrocentesis and then pneumatic compression-assisted arthrocentesis performed sequentially in the same patient to improve statistical power. This project assessed improvement of knee arthrocentesis outcomes before and after introduction of highly controlled pneumatic compression applied by a pneumatic blood pressure thigh cuff intended to remove the operator's hands from the operative field and thus from potential needle-stick, yet still providing robust compression of the flexed knee during arthrocentesis and injection procedures.[36]

Fifty total effusive osteoarthritic (OA) knees were included in this study. The presence of a knee effusion was determined clinically by palpation for suprapatellar bursa distention, ballottement of a floating patella, and fluid shift with asymmetric compression confirmed by physical examination. Inclusion criteria included: (a) a person 18 years old or older; (b) the presence of painful grade I-III OA of the knee; (c) the presence of a clinically palpable knee effusion; (d) indications for therapeutic-diagnostic arthrocentesis; and (e) formal signed consent of the patient to undergo the procedure. Exclusion criteria: (a) presence of confounding disease (inflammatory arthritides, aseptic necrosis, osteomyelitis, etc); (b) an asymptomatic knee; (c) the absence of a palpable effusion; (d) a person less than 18 years old; or (e) vulnerable individuals including children, pregnant women, prisoners, or persons unable to provide consent. Fifty consecutive clinically effusive knees underwent conventional arthrocentesis with the knee in the flexed position using the anterolateral approach without compression, and then pneumatic compression using a conventional thigh blood pressure cuff was applied and arthrocentesis resumed.

2.1 | Arthrocentesis technique

In the 50 flexed effusive knees, the patient was kept in the sitting position. The anterolateral portal was defined by palpation of the adjoining structures of anterolateral border of the patella, the lateral border of the patellar tendon, and the anterolateral tibial plateau with the entry point adjacent to the lateral patellar tendon, thus avoiding the lateral geniculate artery.[12-15] The anterolateral portal was thus determined and marked with the tip of a retractable ballpoint pen with the point retracted leaving a depression in the skin. A thigh blood pressure leg cuff (HCS 9029LF, Cuff and Bladder Latex-Free, Thigh Size, Sphygmomanometer, Dyad Medical Sourcing, LLC, Bannockburn, IL, USA) was placed around the superior flexed knee where it surrounded the upper leg and the suprapatellar bursa (Figure 1). The skin overlying the anterolateral portal was first cleaned with chlorhexidine 2% for antisepsis. The one-needle multiple-syringe technique was used where: (a) one needle is used

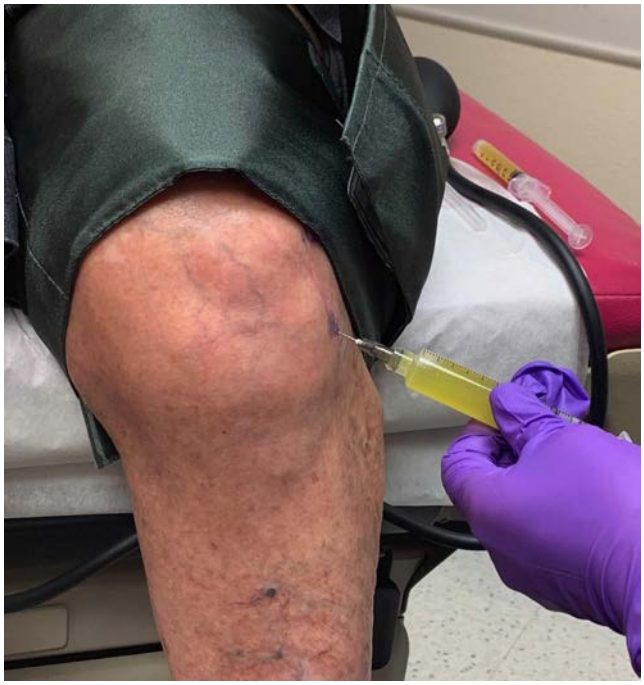

FIGURE 1 Flexed knee with pneumatic thigh cuff compression (front view). The thigh blood pressure cuff is wrapped around the superior knee in the flexed position and the cuff is fastened snuggly so it does not slide. After pneumatic compression at 100 mm Hg with the pneumatic compression cuff is applied to the suprapatellar bursa and patellofemoral joint, fluid is compelled by pressure to flow into the inferior knee where it can be accessed by the anterolateral portal

for anesthesia and arthrocentesis; and (b) a first syringe or syringes are used to anesthetize the synovial membrane and completely aspirate effusion employing subsequent syringe exchanges if the effusions were large. A 22 gage 2 inch needle (4 710 007 050 - 22 GX2 (0.7×50 mm), FINE-JECT, Henke Sass Wolf, Tuttlingen, Germany) was mounted on a 3 mL syringe (3 mL Luer Lok syringe, BD, Franklin Lakes, NJ, USA; website: http://www.bd.com) filled with 3 mL of 1% lidocaine (Xylocaine® 1%, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA). Lidocaine (3 mL) was used to first anesthetize the skin, subcutaneous tissues and synovial membrane as the 22 g needle was introduced through the skin through the anterolateral portal to the synovial membrane overlying the medial femoral condyle in the flexed knee. Arthrocentesis success, and fluid yield were then recorded.

The needle was left intra-articularly, and the pneumatic thigh blood pressure cuff was inflated to a standardized pressure of 100 mm Hg so that the suprapatellar bursa and patellofemoral joint were compressed, but not the inferior knee (Figures 1 and 2). Placed this way, without the use of human hands susceptible to needle-stick, the thigh cuff applies constant compression to the suprapatellar bursa, the synovial compartments of the superior medial and lateral knee, and patellofemoral joint, thus collapsing these synovial compartments and forcing fluid inferiorly to the synovial reflections of the femoral condyles and cruciate ligaments where the fluid could be accessed (Figures 2 and 3). After the pneumatic cuff was inflated to 100 mm Hg on the superior knee, 1-3 minutes were permitted to allow fluid to move from the superior knee to the inferior knee where it could be accessed (Figures 1-3). Arthrocentesis success, and fluid yield again were recorded. The needle was then extracted, and firm pressure and a sterile adhesive bandage strip applied to the puncture site.

2.2 | Outcome measures

Patient pain was measured with the standardized and validated 0-10 cm visual analog pain scale (VAS), where 0 cm = no pain and 10 cm = unbearable pain.[37] Pain by VAS was determined: (a) prior to the procedure (baseline pain); (b) during arthrocentesis (procedural pain); and (c) immediately post-procedure (post-procedural pain). Aspirated fluid volume was quantified in mL. Diagnostic fluid was defined as greater or equal to 3.0 mL (1 mL for culture, 1 mL for cell counts, 1 mL crystal examination). Fluid was evaluated for cell counts, crystals, and Gram stain, and sent for culture and sensitivity as appropriate. Patients were also observed for serious adverse events.

2.3 | Statistical analysis

Data were entered into Excel (Version 5, Microsoft, Seattle, WA, USA), and analyzed in Simple Interactive Statistical Analysis (SISA) (Consultancy for Research and Statistics, Hilversum, The Netherlands; http://www.quantitativeskills.com/sisa/). A power calculation was made using preliminary data at this level where $\alpha = .0001$, power = 0.9, and allocation ratio = 1.0 indicated that n = 20 in each group would provide statistical power at the $P < .05$ level, n = 30 in each group at the $P < .02$ level, and n = at the $P < .01$. Fisher's exact test with two by two table analysis was performed on categorical data calculating both P values with significance reported at the $P < .05$ level. Measurement data were analyzed using the Student t test calculating both P values and confidence intervals.

3 | RESULTS

The mean age of the subjects was 66.4 ± 11.7 years and the male to female ratio 6:44 (88% female), typical demographics for patients with OA of the knee.[38] Pre-procedural pain according to the 10 cm VAS was 7.6 ± 1.5 cm indicating a significant degree of pre-procedural knee pain. Procedural pain according to the 10 cm VAS was typically low at 4.4 ± 2.1 cm and post-procedural pain 1.5 ± 1.6 cm indicating significant pain relief with full decompression of the effusive knee. There were no serious adverse events encountered by the 50 patients in the cohort including but not limited to reaction to local anesthesia, septic joint, infection, dermal atrophy, needle-stick, deep venous thrombosis, pseudoseptic arthritis, significant bruising, hemarthrosis, hemorrhage or post-injection visits to emergency facilities.

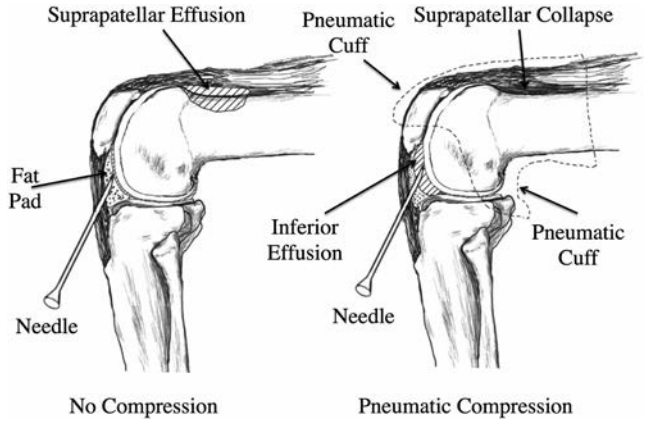

FIGURE 2 Flexed knee with and without pneumatic compression (side view). The figure on the left is the flexed effusive knee with a large synovial effusion accumulating in the lateral suprapatellar bursa (Suprapatellar Effusion) (diagonal hatch). The needle in the indicated position (Needle) cannot access the effusion because the fat pad (Fat Pad) (speckled area) presses on the femoral condyles thus fluid pools in the suprapatellar bursa (Suprapatellar Effusion) (diagonal hatch). The figure on the right is the effusive knee in the flexed position with the pneumatic cuff (Pneumatic Cuff) (broken line) compressing and collapsing the suprapatellar bursa (Suprapatellar Collapse) forcing the synovial fluid (Inferior Effusion) (diagonal hatch) to the lower knee cartilage of the femoral condyles and expands against the fat pad (speckled area). This inferior synovial effusion (Inferior Effusion) can then be accessed by the needle (Needle)

In the flexed knee cohort successful diagnostic arthrocentesis (≥3 mL) of the effusive flexed knee was 82% (41/50) without pneumatic compression and increased significantly to 100% (50/50) with pneumatic compression ($P = .001$). Synovial fluid yields were significantly greater with pneumatic compression (33.4 ± 26.5 mL, 144% more [19.8 ± 17.1 mL]) than without pneumatic compression (13.7 ± 16.4 mL; 95% CI: $10.9 < 19.7 < 28.9$, $P < .0001$) (Figure 4). Thus, pneumatic compression of the flexed knee significantly improves both synovial fluid yield and successful diagnostic arthrocentesis.

4 | DISCUSSION

In the current study we report significant improvement in arthrocentesis and fluid yield from pneumatic compression of the flexed knee (Figures 3 and 4). The use of a highly controllable pneumatic thigh blood pressure cuff to exert a constant circumferential pneumatic compression on the superior knee (suprapatellar bursa and patellofemoral joint) forced synovial fluid from the superior knee to the inferior knee (synovial reflections of the femoral condyles) where the fluid could be accessed by needle using the anterolateral portal (Figures 1-4). This study using pneumatic compression with a standard thigh blood pressure cuff demonstrates that external circumferential compression improves arthrocentesis success and extraction of synovial fluid (Figure 1).[26-30]

Obvious problems with specialty pneumatic and mechanical compression devices is the cost, the limited availability, and the decreased convenience of using these devices for routine arthrocentesis.[26-30] The pneumatic compression cuff and the mechanical compression cuff both for the extended knee positioning have a side portal, are relatively expensive, and are one-use devices because often they are contaminated with patient fluids during the procedure.[26,27] In contrast, the present study utilized a conventional thigh blood pressure cuff that is inexpensive, reusable, and is commonly available in outpatient clinics. However, a conventional blood pressure cuff cannot be used with the extended knee and still access the superolateral portal or suprapatellar bursa approach because the cuff covers these portals; thus, the reason for the use of the anterolateral portal is that it is not covered by the thigh blood pressure cuff. Further, because of the flexed knee positioning the anterolateral portal is physically below the compression device, thus any contaminated fluids from the puncture site flow downward and thus do not contaminate the brace (Figure 1).

For traditional arthrocentesis the patient is usually supine with the knee extended and the needle enters the skin 1-2 cm into the lateral portion of the suprapatellar bursa. The extended knee position is used to take advantage of the natural pooling in the lateral suprapatellar bursa.[8-10] If this positioning results in no fluid return the needle is manipulated into the patellofemoral joint and the intracondylar notch.[1-3,10-29] However, even with this standard extended knee approach, after conventional arthrocentesis typically there is considerable residual synovial fluid remaining in the joint (approximately 30%-40%), thus, full fluid extraction using conventional arthrocentesis even in the extended positioning is incomplete.[27]

Although the extended knee superolateral suprapatellar bursa approach is the traditional anatomic puncture point for arthrocentesis, there are a number of advantages to the anterolateral portal flexed knee approach for arthrocentesis and joint injection.[1-20] The anterolateral portal is defined by the adjoining structures of lateral border of the patella, the lateral border of the patellar tendon, and the lateral tibial plateau with the entry point adjacent to the lateral patellar tendon, and thus avoids the lateral geniculate artery.[2-15] The anterolateral approach uses the cartilage surface of the medial femoral condyle to determine the joint surface-synovial membrane interface and this is defined by a palpable "hard-stop" where the needle cannot go further.[12] Using a modified anterolateral portal approach, Hussein has demonstrated that the needle enters the intra-articular space with 97.1% accuracy.[13] Similarly, Chavez-Chiang et al and Choi et al demonstrated similar accuracy at 93% and 87.8% respectively even without synovial fluid return.[12,17] Further, Lee et al found the anterolateral portal was less painful than the superolateral approach yet had identical clinical results.[15] Chernchujit et al found that a modified anterolateral approach was more accurate that the standard superolateral approach.[16] Finally, Yaqub et al demonstrated that arthrocentesis in the flexed knee positioning using the anterolateral portal approach and mechanical compression markedly improved arthrocentesis outcomes and was equivalent to conventional superolateral arthrocentesis.[28]

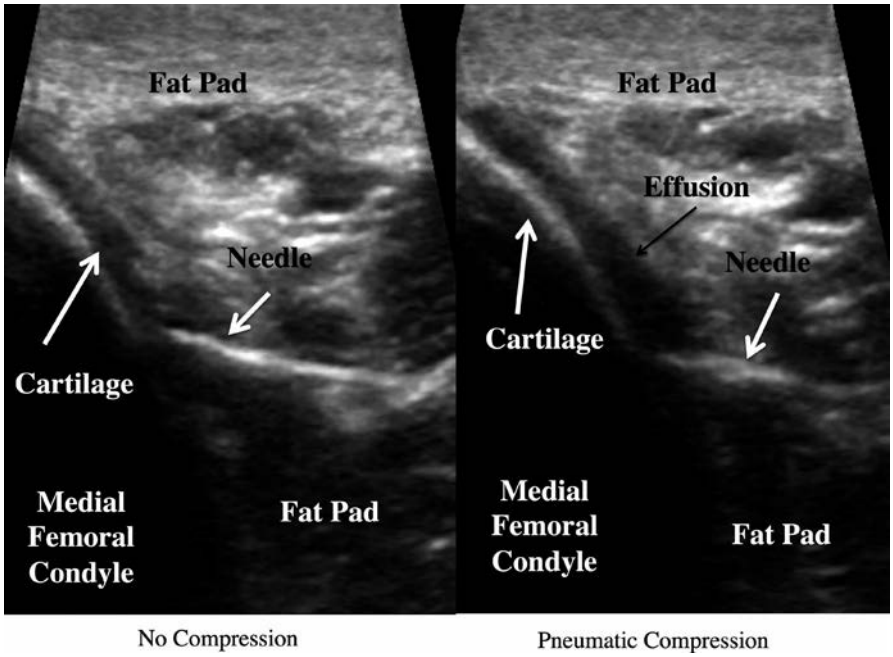

FIGURE 3 Ultrasound image of flexed knee with and without pneumatic compression. The figure on the left is the effusive flexed knee; however, the needle (Needle) does not access synovial fluid because the fat pad (Fat Pad) presses on and forces fluid from the surface of cartilage (Cartilage). The figure on the right is the effusive flexed knee with pneumatic compression of the suprapatellar bursa forcing the suprapatellar bursa (not seen in this image) to collapse forcing the synovial fluid inferiorly where the fluid layers in an effusion (Effusion) over the cartilage surface (Cartilage) of the femoral condyle (Medial Femoral Condyle) and expands against the fat pad (Fat Pad). This synovial effusion (Effusion) can then be accessed by the needle (Needle) through the anterolateral portal

More effective arthrocentesis removes synovial fluid, cytokines, inflammatory cells, and debris from the joint, and has been shown to more rapidly improve patient symptoms and outcomes in aspiration and injection procedures.[3,6,26,30-35] Significant amounts of synovial fluid remaining in the joint increase intra-articular and intraosseous pressures, compress the intrinsic circulation, induce ischemia, stretch the joint capsule causing pain, and are associated with progressive articular, periarticular and supporting muscle degeneration.[31-33] Further, leaving significant amounts of synovial fluid in the joint prior to injection of corticosteroid or hyaluronan dilutes the medication, decreases the response rate, and reduces the therapeutic duration of the injected medication.[3,6,30,34,35] Waddell et al demonstrated that non-aspirated synovial fluid markedly dilutes the concentration and presumably the effect of intra-articular therapeutics.[34] Weitoft et al demonstrated that complete arthrocentesis improved the therapeutic duration of injected corticosteroid and prevented premature relapses.[3] Bennett et al also demonstrated that complete arthrocentesis before injection prolonged the therapeutic effect and increased the interval to the next therapeutic injection.[30] Zhang et al demonstrated that complete arthrocentesis before injection of hyaluronan significantly improved pain and function scores.[35] Thus, for a number of therapeutic reasons complete arthrocentesis is an important goal and a quality measure.[1-35]

In 2019 Meehan demonstrated that a pneumatic compression device in the extended knee position provides improved synovial yield by shifting fluid to the superolateral portal where it can be accessed.[26] Similarly, a non-pneumatic mechanical compression system was described in 2017 by Bhavsar et al that improved arthrocentesis success and decreased the risk of needle-stick by removing the operator's hands from the procedural site.[27] Rather than use external compression to the medial and inferior knee in the extended position as described by these previous reports, the present arthrocentesis improvement technique utilized an inexpensive thigh blood pressure cuff that provided constant circumferential compression to the superior portion of the flexed knee and forced joint fluid from the superior knee to the inferior knee where the fluid could be readily accessed utilizing the anterolateral portal (Figures 1-4). Thus, this study demonstrates that arthrocentesis with pneumatic compression of the flexed effusive knee is a viable alternative technique to the standard superolateral extended knee arthrocentesis approach with or without compression (Figure 4).[26-30]

Certain subtleties to the pneumatic compression-assisted flexed knee technique were noted during the study and should be mentioned. An important aspect of the compression-assisted flexed knee technique is that a 5.1 cm (2-inch) needle is usually necessary so that the needle tip can predictably and effectively access the synovial space overlying the femoral condyle when utilizing the anterolateral portal.[12-17] Further, even though pneumatic compression forced fluid from the superior knee to the inferior knee where it could be accessed, the layering of the fluid over the femoral condyles was quite shallow dimensionally due to the presence of the overlying fat pad (Figures 2 and 3); thus positioning of the needle tip and bevel depth-wise was important for continued synovial fluid return.

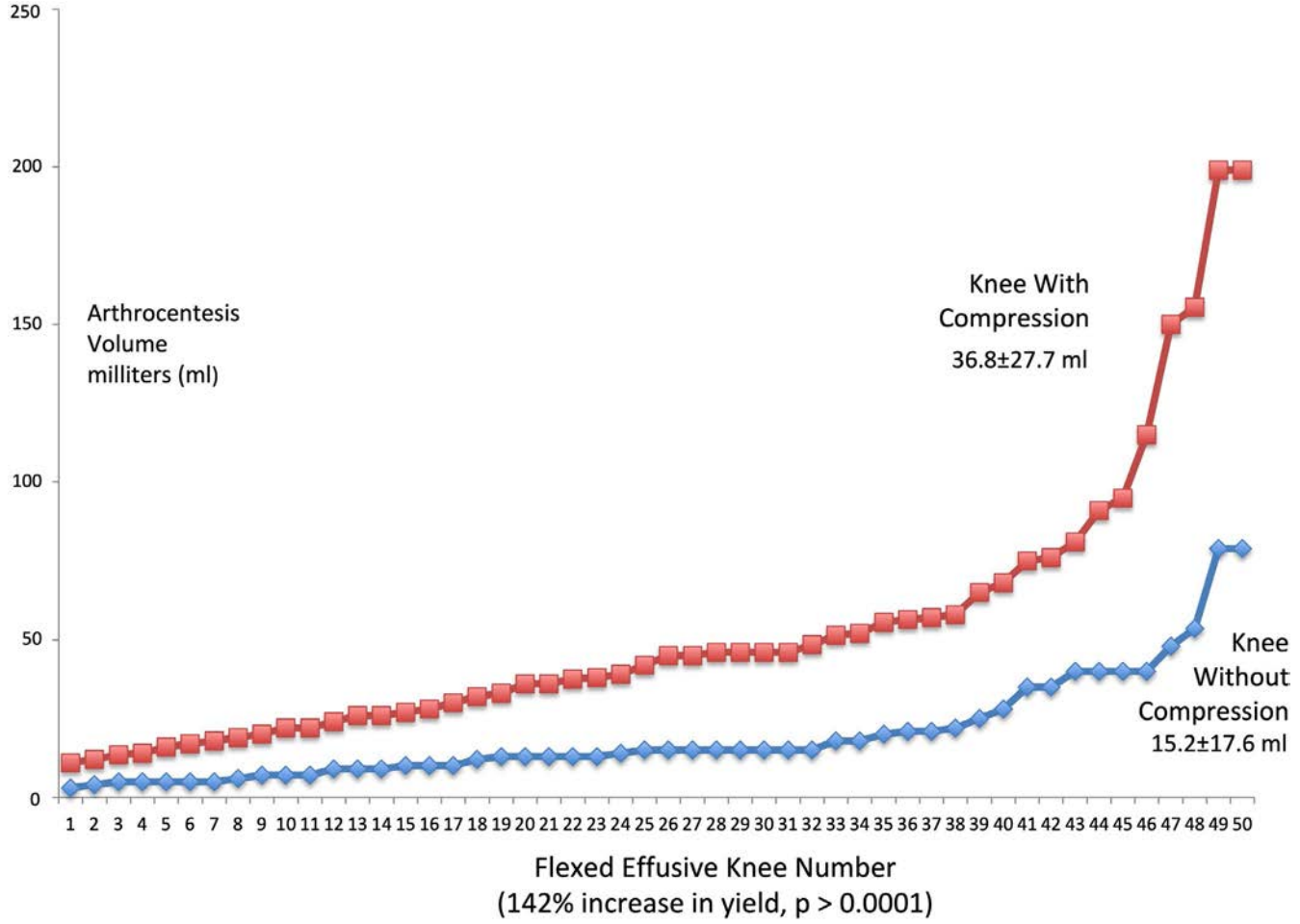

FIGURE 4 Arthrocentesis volume with pneumatic compression of the flexed knee. This graph demonstrates the synovial fluid yield with and without pneumatic compression. Pneumatic compression results in a significant increase in fluid yield

After the pneumatic thigh cuff inflated to 100 mm Hg, additional fluid return was not always immediate, but often required 1 to 3 minutes to permit synovial fluid to move from the superior knee to the inferior knee where it would accumulate. The high viscosity and semi-solid gel-like nature of synovial fluid, make it move slowly with pressure; thus, we recommend placing the pneumatic compression cuff on the flexed knee for several minutes at 100 mg Hg to allow full synovial fluid movement and accumulation before attempting arthrocentesis, and during the arthrocentesis procedure itself be patient to permit additional synovial fluid to flow to the access point.[39,40]

The routine use of a pneumatic thigh blood pressure cuff to compress the knee during arthrocentesis and injection procedures has a number of advantages. First, pneumatic thigh blood pressure cuffs are commonly available in most clinics and offices, and thus the technology is already present and does not require ordering and stocking a specialized expensive knee compression cuff.[26,27] Second, using the flexed knee sitting position and the anterolateral portal, any extravasated synovial fluid or blood tends to stream down the leg, not up, thus the cuff remains uncontaminated by patient fluids.[28,29,36] Similarly, there are already disposable commercial covers made for blood pressure cuffs that may be used between patients. Finally, the highly controlled pneumatic compression markedly improves diagnostic and therapeutic arthrocentesis yield (Figure 4).

There are limitations to this study. This study was a paired sequential rather than a randomized study and this study design potentially could present structural bias. However, a paired study design, where the baseline is determined, a quality intervention is introduced, and changes in outcome are determined in the post-intervention, is a typical structure for quality improvement studies and is a standard mechanism for change in all hospitals. Finally, only the anterolateral approach to flexed knee arthrocentesis was explored; it is possible that medial approaches such as the anteromedial portal might be just as successful with pneumatic compression.[17]

5 | CONCLUSIONS

Complete arthrocentesis and decompression of the effusive knee is important for patient comfort, removal of inflammatory cells and cytokines, mitigation of the pathologic effects of increased intra-articular pressure, and to optimize the clinical response to injected intra-articular therapies. Conventional arthrocentesis routinely does

not fully decompress the effusive knee. External circumferential compression using a pneumatic blood pressure cuff markedly improves arthrocentesis success, fluid yield, and permits more complete decompression of the effusive knee. External circumferential pneumatic compression with a thigh blood pressure cuff of the knee improves the quality and success of arthrocentesis procedures at minimal cost.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest concerning this study.

AUTHOR CONTRIBUTIONS

Sumir Brahmbhatt, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Ahsan Iqbal, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Fatemeh Jafari Farshami, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Fatemeh Jafari Farshami, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Jaren R. Trost, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. David R. Cisneros, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Adnan N. Kiani, MD: validation, analysis, investigation, resources, writing original draft, writing review and editing. Matthew K. McElwee, MD: writing review and editing. William A. Hayward, PhD: writing review and editing. Luke J. Haseler, PhD: writing review and editing. Philip A. Band, PhD: conceptulatization, writing review and editing. Wilmer L. Sibbitt, Jr, MDl: conceptulatization, methodology, validation, analysis, investigation, resources, data curation, writing original draft, writing review and editing, visualization, project administration.

ETHICAL STANDARDS

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to any procedures and prior to the inclusion in the study.

DATA AVAILABILITY STATEMENT

Raw data can be obtained from the authors on reasonable request but publication attribution is necessary.

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ORIGINAL ARTICLE

Early control of C-reactive protein levels with non-biologics is associated with slow radiographic progression in radiographic axial spondyloarthritis

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Abstract

Aim: Predicting radiographic progression is vital for assessing the prognosis of patients with radiographic axial spondyloarthritis, and C-reactive protein (CRP) may be a valuable biomarker for this purpose. This study aimed to investigate the relationship between changes in the CRP level and spinal radiographic progression in patients with radiographic axial spondyloarthritis who were initially treated with non-biologics.

Methods: Patients with radiographic axial spondyloarthritis who were followed up for 18 years at a single center and initially treated with nonsteroidal anti-inflammatory drugs and/or conventional disease-modifying antirheumatic drugs for 3 months were included. Patients with a CRP level of <0.8 mg/dL or 50% of the baseline CRP at 3 months were assigned to the controlled CRP group (n = 351), and the remaining patients were assigned to the uncontrolled CRP group (n = 452). A generalized estimating equation was used to analyze the differences in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) between the 2 groups.

Results: The increase in the mSASSS was slower in the controlled CRP group than in the uncontrolled CRP group (interaction term $\beta = -.499$, 95% confidence interval −0.699 to −0.300).

Conclusion: Controlled CRP achieved in response to initial treatment with non-biologic agents for 3 months was significantly associated with a slower rate of spinal radiographic change in patients with radiographic axial spondyloarthritis. The CRP level at 3 months after initial non-biologic treatment is a good predictor of radiographic progression.

KEYWORDS
ankylosing spondylitis, C-reactive protein, prognosis, radiography

Bon San Koo and Seunghun Lee contributed equally to this work.

1 | INTRODUCTION

Radiographic axial spondyloarthritis (r-axSpA) results in limited spinal function, leading to serious disabilities. Therefore, predicting radiographic progression is essential for assessing the prognosis of patients with r-axSpA. Various surrogate markers can predict disease activity and radiographic progression.[1-4] Among these markers, C-reactive protein (CRP) has been suggested as a useful predictor for monitoring the treatment response and predicting radiographic progression.[5-8] However, despite a high CRP level at diagnosis, a dramatic decrease in CRP can be observed in patients with r-axSpA who respond well to treatment with non-biologic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and/or conventional disease-modifying antirheumatic drugs (cDMARDs).

Considering the relationship between inflammation and radiographic progression, the patients with a maintained treatment response and controlled CRP levels after non-biologic treatment may exhibit slower radiographic progression than those with uncontrolled CRP levels after treatment. Therefore, the classification of patients in terms of radiographic progression according to the initial treatment response may help predict long-term structural changes in the spine more accurately than that according to the baseline information. Although few patients have slow radiographic progression because of sufficient improvement in the CRP level with non-biologic treatment, some of them may be classified into the rapid radiographic progression group because of their high baseline CRP level. Therefore, in this study, we focused on the CRP level at 3 months after non-biologic treatment instead of the baseline CRP level without treatment.

This study aimed to investigate the relationship between radiographic progression and the improvement in CRP level by initial treatment with non-biologics, such as NSAIDs and/or cDMARDs, for 3 months after diagnosis.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

Data of patients who were diagnosed with r-axSpA according to the modified New York criteria[9] at a single center between January 2001 and December 2018 were extracted from the electronic medical records (EMR).[10,11] The inclusion criteria were as follows: (1) patients diagnosed with r-axSpA and under follow-up; (2) those who had 2 or more radiographs taken; (3) those who were evaluated using the Ankylosing Spondylitis Disease Activity Score and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); (4) those who underwent blood tests; (and 5) those who had 2 or more visits at the rheumatology clinic. Based on these criteria, the data of 1280 anonymized patients were included in this study. Clinical characteristics, such as age, gender, disease duration from the first to the last follow-up visit, human leukocyte antigen (HLA)-B27 positivity, smoking history, eye involvement (uveitis), and peripheral joint involvement, were reviewed. Among biologic-naïve patients treated with non-biologics, such as NSAIDs and/or cDMARDs, for 3 months after diagnosis, those who underwent CRP measurement at diagnosis (baseline) and 3 months were included. Patients with a CRP level of <0.8 mg/dL were assigned to the controlled CRP group. In addition, patients with a CRP level of 50% of the baseline at 3 months were included in the controlled CRP group because they were likely those who would have responded slowly to non-biologic treatment. The remaining patients were assigned to the uncontrolled CRP group. Longitudinal modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) data were used to evaluate the difference in radiographic progression between the controlled and uncontrolled CRP groups. According to previous studies, the intraobserver and interobserver reliability values of the mSASSS are excellent (intraclass coefficient: 0.978, 95% confidence interval [CI] 0.976 to 0.979, and 0.946, 95% CI 0.941 to 0.950, respectively).[10,11]

This study was approved by the institutional review board (HYUH 2018-07-007). The need to obtain informed consent was waived as it was a retrospective study.

2.2 | Statistical analyses

All data are summarized as the mean (SD) or as numbers and percentages. A P value of ≤.05 was considered statistically significant. Regression analysis with generalized estimating equation analysis was used to analyze the longitudinal mSASSS data, and the correlations between variables are presented as beta coefficients and 95% CIs. In the initial step, to examine whether the rate of change in the mSASSS over time differed between the controlled and uncontrolled CRP groups, we used the following linear model: mSASSS ~baseline mSASSS + time since diagnosis (year) + group + time × group + error. During the analysis, the error was allowed to be correlated within each patient. In the next step, the association of each baseline variable with the mSASSS was evaluated by adjusting the baseline mSASSS, because the baseline mSASSS range was wide and highly associated with both CRP and the subsequent mSASSS. In the multivariable model, we built the linear model with the mSASSS as the response variable. The explanatory variables included group, time, interaction term (product of group × time), and baseline variables, excluding HLA-B27, which was not significant in the second step. Finally, the adjusted mean mSASSS change per year was calculated from the beta coefficients of the initial and multivariable models. All statistical analyses were performed using R statistical language version 3.6.1 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Clinical characteristics of patients

A total of 803 patients underwent CRP measurement at baseline and 3 months. Among them, 351 and 452 were assigned to the controlled and uncontrolled CRP groups, respectively (Table 1). The baseline

TABLE 1 Comparison between the uncontrolled and controlled CRP groups

Variables	Uncontrolled CRP group N = 452	Controlled CRP group N = 351	*P* value
Age at diagnosis, mean (SD), y	31.5 (9.2)	31.6 (9.2)	.868
Women, n (%)	33 (7.3)	54 (15.4)	<.001
Follow-up duration, mean (SD), y[a]	8.65 (2.85)	7.84 (2.39)	<.001
HLA-B27 positivity, n (%)	443 (98.7)	330 (94.3)	.001
Eye involvement, n (%)	167 (43.7)	69 (24.0)	<.001
Peripheral involvement, n (%)	156 (41.7)	90 (31.4)	.008
Smoking			
Non-smoker, n (%)	159 (37.1)	141 (42.7)	.132
Ex-smoker, n (%)	116 (27.1)	93 (28.2)	
Current smoker, n (%)	153 (35.7)	96 (29.1)	
CRP at baseline, mean (SD), mg/dL	2.2 (2.0)	1.8 (2.5)	.025
CRP during follow-up, mean (SD), mg/dL	1.59 (2.08)	1.16 (1.44)	<.001
mSASSS at baseline, mean (SD)	16.8 (17.0)	11.5 (13.7)	<.001
mSASSS during follow-up, mean (SD)	22.50 (20.25)	14.18 (16.09)	<.001
Interval between mSASSS, mean (SD), y	2.35 (0.94)	2.36 (0.89)	.676
Number of mSASSS per patient, mean (SD)	4.69 (1.25)	4.32 (1.07)	<.001
Treatment period of NSAIDs for the first 3 months, mean (SD), mo	2.14 (1.20)	2.12 (1.20)	.824

Abbreviations: CRP, C-reactive protein; HLA, human leukocyte antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Period from diagnosis to last radiograph.

CRP level and mSASSS were higher in the uncontrolled CRP group than in the controlled group. The longitudinal change in the mSASSS in each group is shown in Figure 1.

3.2 | Relationship between the mSASSS and variables

In the initial model, the mSASSS at baseline and year were significantly associated with an increased mSASSS (Table 2). The interaction between year and the controlled CRP group was significantly associated with a reduction in the rate of change in the mSASSS (β = −.484, 95% CI −0.661 to −0.306, $P < .001$).

Upon analyzing the association between each baseline variable and the mSASSS after adjustment for the baseline mSASSS (univariate), age at diagnosis, eye involvement, ex-smoking and current smoking versus nonsmoking, and CRP level at baseline were found to be significantly associated with an increase in the mSASSS change rate. In addition, female gender and peripheral involvement were significantly associated with a reduction in the rate of change in the mSASSS.

In the multivariable analysis, the mSASSS at baseline (β = 1.034, 95% CI 1.002 to 1.067, $P < .001$) and year (β = 1.036, 95% CI 1.002 to 1.067, $P < .001$) were significantly associated with an increase in the mSASSS rate of change. The interaction between the year and the controlled CRP group (β = −0.499, 95% CI −0.699 to −0.300, $P < .001$) was significantly associated with a reduction in the rate of change in the mSASSS. Among the baseline clinical variables,

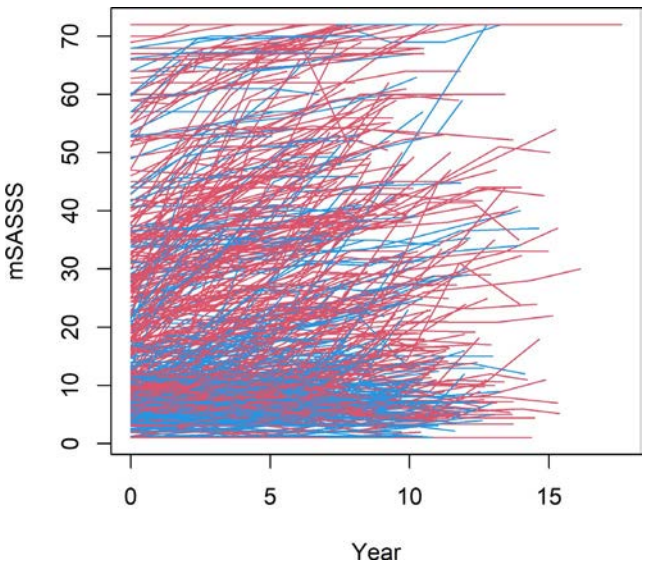

FIGURE 1 The longitudinal change in the mSASSS. The red line is the uncontrolled CRP group and the blue line is controlled CRP group. CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score

TABLE 2 Models for the relationship between the mSASSS and variables

	Initial model				Univariate[a]				Multivariable			
		95% CI				95% CI				95% CI		
	Beta	LB	UB	*P* value	Beta	LB	UB	*P* value	Beta	LB	UB	*P* value
(Intercept)	−1.071	−1.474	−0.667	<.001					−3.772	−5.245	−2.298	<.001
mSASSS at baseline	1.065	1.041	1.089	<.001					1.034	1.002	1.067	<.001
Y	1.003	0.877	1.129	<.001					1.036	0.897	1.175	<.001
CRP controlled group	0.293	−0.056	0.643	.100					0.382	−0.194	0.957	.193
Y × CRP controlled group	−0.484	−0.661	−0.306	<.001					−0.499	−0.699	−0.300	<.001
Age at diagnosis					0.053	0.014	0.093	.007	0.049	−0.003	0.101	.063
Women					−1.465	−2.439	−0.491	.003	−0.311	−1.456	0.833	.594
HLA-B27 positivity					0.016	−1.947	1.979	.987				
Eye involvement					1.877	0.815	2.939	.001	1.387	0.344	2.431	.009
Peripheral involvement					−1.429	−2.292	−0.566	.001	−2.372	−3.269	−1.475	<.001
Ex-smoker (ref: non-smoker)					2.568	1.477	3.658	<.001	2.183	0.968	3.399	<.001
Current smoker (ref: non-smoker)					1.498	0.634	2.362	.001	1.189	0.272	2.107	.011
CRP at baseline					0.371	0.118	0.625	.004	0.482	0.210	0.753	.001

Abbreviations: CRP, C-reactive protein; LB, lower bound; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; UB, upper bound.

[a]mSASSS at baseline with a wide range was adjusted.

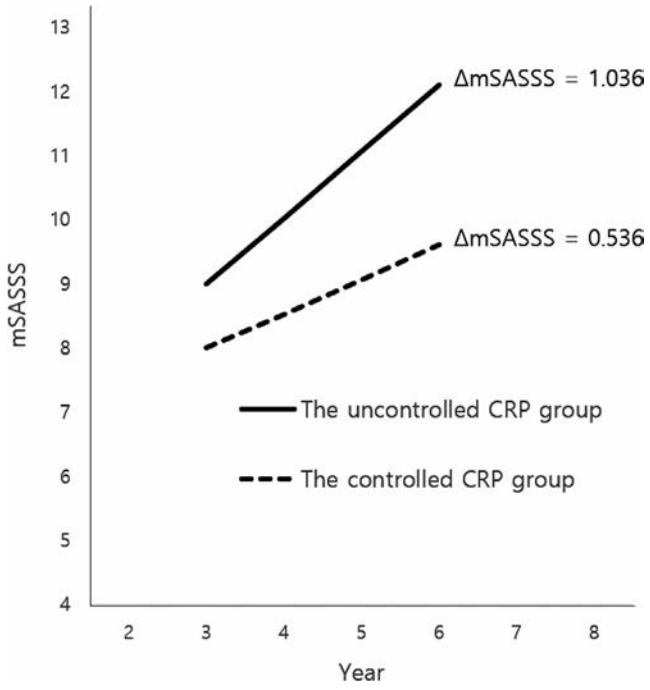

FIGURE 2 The adjusted mean mSASSS change per year in the multivariable model. CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score

eye involvement (β = 1.387, 95% CI 0.344 to 2.431, $P = .009$), ex-smoking and current smoking versus nonsmoking (β = 2.183, 95% CI 0.968 to 3.399, $P < .001$; β = 1.189, 95% CI: 0.272 to 2.107, $P = .011$, respectively), and CRP level at baseline (β = 0.482, 95% CI 0.210 to 0.753, $P = .001$) were significantly associated with an increase in the rate of change in the mSASSS. By contrast, peripheral involvement (β = −2.372, 95% CI −3.269 to −1.475, $P < .001$) was significantly associated with a reduction in the rate of change in the mSASSS.

3.3 | Adjusted mean mSASSS change per year

The adjusted mean mSASSS change per year was calculated from the beta coefficients of the intercept between the year and controlled CRP group. In the initial model, the adjusted mean mSASSS changes per year were 0.519 and 1.003 in the controlled and uncontrolled CRP groups, respectively. In the multivariable model, the adjusted mean mSASSS changes per year were 0.536 and 1.036 in the controlled and uncontrolled CRP groups, respectively (Figure 2).

4 | DISCUSSION

This study investigated the relationship between radiographic progression and the improvement in CRP level after initial treatment with NSAIDs and/or cDMARDs for 3 months after diagnosis. The results showed that a controlled CRP level at 3 months with initial non-biologic treatment after diagnosis was associated with a slower rate of spinal radiographic change. Thus, the CRP level after initial treatment may be predictive of radiographic progression.

In the treatment of r-axSpA, the initial administration of NSAIDs is recommended.[12,13] According to our longitudinal data, most patients were treated with NSAIDs and/or cDMARDs for >3 months because the health insurance system of South Korea approves coverage for biologics in patients with r-axSpA according to the disease activity 3 months after treatment. Based on the initial treatment response, the rheumatologist decides whether to start treatment with biologics, such as tumor necrosis factor inhibitors (TNFis), or to continue treatment with NSAIDs and/or cDMARDs.

Treatment with biologics or cDMARDs showed a small decrease in the mSASSS change rate (about 0.1 per year).[10,11] However, in this study, the controlled CRP level at 3 months showed a greater change in the mSASSS than treatment with biologics or cDMARDs (0.499 per year). Patients who initially do not respond to NSAIDs may be treated with biologics and maintain low disease activity and inflammation with biologic treatment. Therefore, the CRP level measured at 3 months is a more important predictor than the baseline CRP level and treatment outcome in distinguishing patients at a higher risk of radiographic progression and selecting new treatment strategies.

We identified several baseline characteristics related to radiographic progression. Eye and peripheral involvements were associated with an increase and decrease in radiographic progression, respectively. While these findings are supported by the literature,[10] the relationship between uveitis and radiographic progression requires further study. Smoking (ex- and current) was related to radiographic progression. Quitting smoking is emphasized because the total burden of smoking has been shown to be related to radiographic progression.[14]

This study has a few limitations. First, since we focused on the relationship between the initial CRP level and long-term radiographic progression, the effect of biologics and non-biologics on radiographic progression after 3 months was not considered. Second, in the EMR data, 477 of 1280 patients were excluded from the study due to insufficient data for the first visit and at 3 months. The EMR store real-world information and have a lot of missing data; thus, it was difficult to utilize some data. Sensitivity analysis with data from other hospitals or additional patients is required to consolidate the results of this study. Third, CRP levels may have been affected by other factors, such as infection.

Radiographic progression was slower in patients with a controlled CRP level at 3 months after treatment with non-biologics than in those with an uncontrolled CRP level. The CRP level at 3 months after treatment with non-biologics may be a good predictor of radiographic progression.

CONFLICT OF INTEREST

All authors have declared no competing interests.

AUTHOR CONTRIBUTIONS

Tae-Hwan Kim had full access to all data in the study and takes responsibility for the integrity of the data, study supervision, and accuracy of the data analysis. All authors participated in the interpretation of data and the drafting, revision, and approval of the manuscript. Bon San Koo, Seunghun Lee, and Tae-Hwan Kim contributed to the study conception and/or design. Bon San Koo, Ji Seon Oh, and Seo Young Park participated in the statistical analysis. Seunghun Lee, Ji Seon Oh, Ga Young Ahn Ji Hui Shin, Kyung Bin Joo, and Tae-Hwan Kim provided administrative, technical, or material support.

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ORIGINAL ARTICLE

Both ASDAS and ADC are associated with spinal mobility in active axial spondyloarthritis: A comparison between early and later disease

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Abstract

Objective: Using diffusion-weighted imaging (DWI)-derived apparent diffusion coefficient (ADC), we aimed to determine the relationship between intensity of spinal inflammation and mobility in patients with axial spondyloarthritis (SpA) in early and later stages of active disease. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was also used for a more comprehensive evaluation.

Methods: Participants with axial SpA and back pain were recruited from 10 rheumatology centers. Clinical, biochemical and radiological parameters were collected. Short tau inversion recovery (STIR) sequence magnetic resonance imaging (MRI) and DWI of the spine and sacroiliac (SI) joints were performed. ADC maps were generated. Participants were examined for Bath Ankylosing Spondylitis Metrology Index (BASMI). Linear regression models were used to determine associations between BASMI and various clinical, radiological, and MRI parameters in participants with active inflammation on spinal ADC maps.

Results: One-hundred and twenty-seven participants were included in the analyses. Multivariate linear regression showed that mean ADC spine (ß = .16; $P = .03$), ASDAS-C-reactive protein (CRP) (ß = .29, $P < .001$), and ASDAS-erythrocyte sedimentation rate (ESR) (ß = .25, $P < .01$) were associated with BASMI. In participants with duration of back pain ≤3 years, mean spine ADC (ß = .37; $P = .03$), ASDAS-CRP (ß = .44; $P = .01$), and ASDAS-ESR (ß = .42; $P = .01$) were associated with BASMI after adjustment for confounding factors. In participants with duration of back pain >3 years, only ASDAS-CRP (ß = .25; $P < .01$) and ASDAS-ESR (ß = .20; $P = .20$) were associated with BASMI.

Conclusion: Intensity of inflammation and clinical disease activity were independently associated with impairment of spinal mobility. The associations were stronger in early (≤3 years) than later disease.

Ho Yin Chung and Shirley Chiu Wai Chan contributed equally to this study.

KEYWORDS
ankylosing spondylitis disease activity index, apparent diffusion coefficient, Bath Ankylosing Spondylitis Metrology Index, diffusion-weighted imaging, inflammation, magnetic resonance imaging, spondyloarthritis

1 | INTRODUCTION

Axial spondyloarthritis (SpA) describes a spectrum of diseases characterized by spinal inflammation, peripheral arthritis and other extra-articular features. It could lead to decreased mobility and quality of life.[1] In addition to disease activity and functional assessment, the Assessment of SpondyloArthritis International Society (ASAS) also recommends the measurement of spinal mobility as one of the core domains.[2] It is one of the assessments that discriminate between responders and non-responders in clinical trials of anti-tumor necrosis factor (anti-TNF) agents.[3] Bath Ankylosing Spondylitis Metrology Index (BASMI) is the composite index recommended for spinal mobility assessment.[2,4] Measurements include lateral spinal flexion, modified Schober test, cervical rotation, tragus-to-wall distance, and maximum intermalleolar distance.[5]

Relationships between disease activity, structural changes, and spinal mobility in axial SpA have been studied. Spinal mobility was found to be more associated with clinical disease activity, extent of magnetic resonance imaging (MRI) inflammation, in early disease; and spinal structural damage in later stages.[6,7] Assessments of disease activity were based on the Ankylosing Spondylitis Disease Activity Score (ASDAS)[8] and MRI spinal inflammation score based on the short tau inversion recovery (STIR) sequence. Advancements in MRI techniques have led to the use of diffusion-weighted imaging (DWI) to assess intensity of spinal inflammation by generating an index of diffusivity, the apparent diffusion coefficient (ADC), which supplements information obtained from STIR imaging. DWI measures random Brownian motion of water molecules, which are hindered by cell membranes and macromolecules in vivo. Tissue discrimination of normal vs inflammation is attained by differential restriction of water molecules. DWI-derived ADC of the spine has been validated as a surrogate marker of intensity of spinal inflammation[9] in axial SpA. And ADC values can only be measured in active inflammatory disease.[10]

With reference to previous publications, we arbitrarily defined disease duration of less than or equal to 3 years as early disease.[6,11,12] The aim of this study was to determine the relationship between DWI-derived ADC values and spinal mobility in patients with axial SpA in early and later stages of active disease. ASDAS, a clinical disease activity score, was also included for a more comprehensive evaluation. Patients with disease duration less than or equal to, and more than 3 years were compared.

2 | METHODS

Cross-sectional data were obtained from an on-going, multicenter, observational cohort of participants with axial SpA which had been registered in the clinical trial registry of The University of Hong Kong (HKUCTR-2087) for evaluation of DWI in axial SpA. Participants with expert-diagnosed axial SpA were consecutively recruited from 10 public hospitals in Hong Kong (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital, Pamela Youde Nethersole Eastern Hospital, Caritas Medical Center, Tseung Kwan O Hospital, Kwong Wah Hospital, Prince of Wales Hospital, Prince Margaret Hospital, and Hong Kong Eye Hospital). Inclusion criteria included: (i) axial SpA diagnosed by a specialist in rheumatology; (ii) age >18 years; (iii) current back pain; (iv) biologics naïve; and (v) ability to give written consent. Exclusion criteria included: (i) inability to undergo MRI examination; (ii) pregnancy; and (iii) steroid therapy >10 mg prednisolone (or equivalent) daily. In this study, only participants with active spinal inflammation in ADC recruited from March 2014 to November 2020 were included in analyses.

All data collection and investigations including blood tests and imaging were done on the same day. Participants were interviewed to obtain demographic and clinic data including age, gender, duration of back pain, smoking status, alcohol use, family history of SpA, sulfasalazine and other conventional disease-modifying antirheumatic drug (cDMARD) therapy. Duration of back pain was defined as from onset to the date of interview. BASMI was independently measured by one investigator (LLN) using the linear definition ranging from 0 to 10 with higher scores representing greater impairment in spinal mobility. Self-assessment questionnaires including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and patient global assessment were completed, from which the latter was used to calculate ASDAS based on C-reactive protein (ASDAS-CRP) and erythrocyte sedimentation rate (ASDAS-ESR). Blood tests for human leucocyte antigen (HLA)-B27, CRP, and ESR were obtained.

2.1 | Radiographs and interpretations

Radiographs of the cervical spine (lateral view) and lumbo-sacral spine (antero-posterior and lateral view) were performed. Blinded to clinical and MRI data, an independent specialist in rheumatology (HHLT) with 7 years experience in radiographic interpretation in axial SpA, scored the lateral views to determine the modified

Stoke Ankylosing Spondylitis Spine Score (mSASSS),[13] and antero-posterior view of lumbo-sacral spine for radiographic sacroiliitis according to the modified New York criteria.[14] Radiographic axial SpA was defined as bilateral grade 2 or unilateral grade 3 sacroiliitis or above.

2.2 | MRI parameters, grading of STIR images, and acquisition of spinal ADC values

Whole spine (C2 to S1) and sacroiliac (SI) joint MRI were performed (3.0-T imaging unit, Achieva; Philips Healthcare) using a torso-coil with participants positioned supine. T1-weighted, STIR images, and DWI were performed consecutively in the same examination. The MRI parameters were as follows: imaging plane, sagittal; TR/TE (milliseconds) 800/8 for T1-weighted, 5000/80 for STIR, 3100/46 for DWI; section thickness (mm) 3.5 for T1-weighted and STIR, 4 for DWI; field of view (mm^2) 150 × 240 for T1-weighted and STIR, 300 × 241 for DWI; matrix 152 × 157 for T1 weighted and STIR, 124 × 100 for DWI. ADC maps were automatically generated by the MRI machine. Only STIR images and DWI were included in the analyses.

STIR images of whole spine and SI joint were read independently by 2 rheumatologists (HYC, with 9 years of experience in axial SpA MRI interpretation; SCWC, with 5 years of experience in axial SpA MRI interpretation). The readers were blinded to clinical and radiographic parameters to score the Spondyloarthritis Research Consortium of Canada (SPARCC) spine MRI index,[15] and the SPARCC SI MRI index.[16] Using the scored STIR images, a musculoskeletal radiologist (KHL, with 5 years of experience in axial SpA MRI interpretation) identified all spinal inflammatory lesions. ADC values measurement were performed by a rheumatologist (HYC). The rheumatologist drew regions of interest on the ADC maps based on the inflammatory lesions identified by the musculoskeletal radiologist. Adjacent normal tissue and intervertebral discs were excluded to calculate the mean (ADC spine mean) and maximum ADC (ADC spine max). In the analyses, ADC mean was defined as the mean ADC values of all inflammatory lesions while ADC max was defined as the highest ADC values of all inflammatory lesions. Active inflammation on ADC maps was defined as presence of hyperintensity in the vertebral bodies. All ADC values were measured twice and averaged. Since meaningful ADC values could only be acquired in participants with active lesions on STIR images,[9,10] those without active lesions were excluded from analyses. MRI interpretations were performed using commercial software OsiriX MD v 12.0.0 (OsiriX Foundation). A spinal image from STIR and an ADC map are shown in Figure 1.

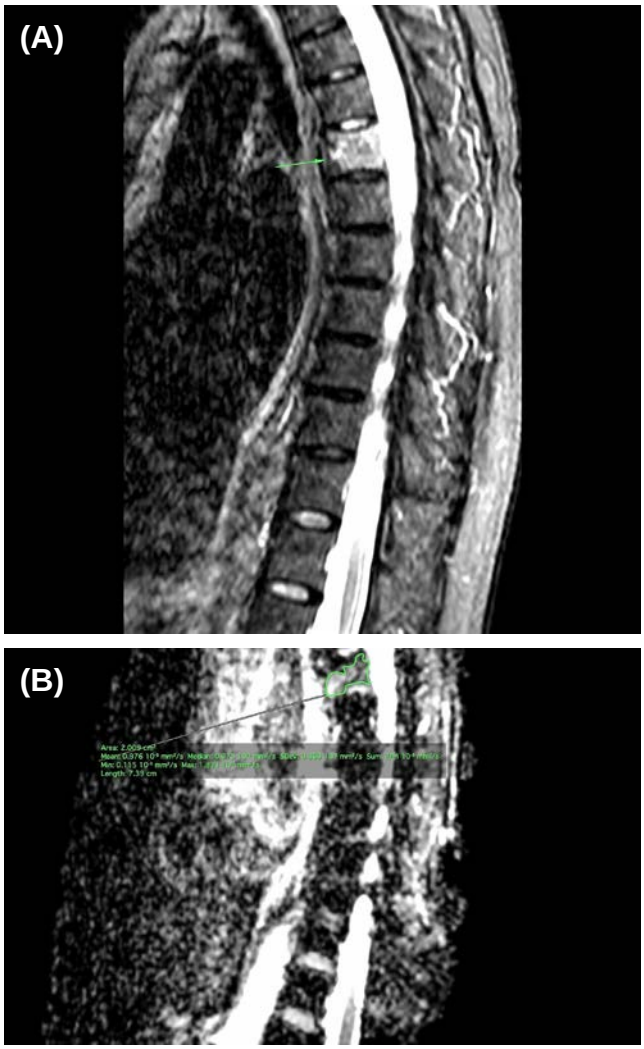


FIGURE 1 Short tau inversion recovery (STIR) sequence and acquisition of apparent diffusion coefficient (ADC) values of spine magnetic resonance imaging (MRI). (A) Spondylitis on STIR MRI of spine. (B) Acquisition of ADC values from ADC map

2.3 | Statistical analyses

Continuous baseline data were described using mean ± 95% confidence interval (CI), and medium. Categorial data were described in frequency. Independent *t* test and Chi-square test were used to compare continuous and categorial variables between axial SpA participants with disease duration ≤ and >3 years respectively. Intraclass correlation coefficient was used to determine the inter-reader agreements of the SPARCC spine and SI MRI indexes. The agreement was interpreted as slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-1.00).

Univariate linear regression analysis was used to test the associations of different independent variables with BASMI. The independent variables tested included: age, back pain duration, male gender, smoker and drinker, HLA-B27 positivity, family history of SpA, radiographic axial SpA, mSASSS, on sulfasalazine, on cDMARD other than sulfasalazine, ASDAS-CRP, ASDAS-ESR, ADC spine max, ADC spine mean, SPARCC SI joint MRI index, SPARCC spine MRI index. They were the factors known or expected to have associations with spinal mobility. Independent variables with a *P* value less than .1 in univariate analyses were re-tested in multivariate linear regression models

using BASMI as the dependent variable. A total of 4 multivariate regression models were built up using ADC spine max, ADC spine mean, ASDAS-CRP, and ASDAS-ESR independently in each model. The multivariate regressions were repeated in participants with disease duration ≤3 years and >3 years. Results were reported as standard coefficient (ß), and regression coefficient (B) ± 95% CI. Unless specified, a *P* value of less than .05 was considered to be statistically significant. List-wise deletion was performed for all missing values. All statistics were performed using the IBM Corporation Statistical Package for the Social Sciences (IBM SPSS) version 27.

3 | RESULTS

A total of 260 participants with axial SpA and current back pain were recruited. Only 127 (48.8%) had active inflammation on spinal ADC maps and were included in the analyses. Despite negative inflammatory lesions in MRI, 61.5% of participants still reported to have BASDAI >4. In the participants with active spinal inflammation, 55 (44.4%) had MRI sacroiliitis. Baseline characteristics and comparisons between participants with disease duration ≤3 years and >3 years are shown in Table 1. This study cohort was characterized by prolonged disease duration, male predominance, had moderate to high clinical disease activity, significant spinal MRI inflammation and radiographic changes, and impaired spinal mobility. Most were HLA-B27 positive and classified as radiographic axial SpA. Compared to longer duration of back pain, participants with ≤3 years of back pain had the same degree of impairment of spinal mobility despite less HLA-B27 positivity, less radiographic axial SpA, and less spinal radiographic damage. Clinical disease activity and spinal MRI inflammation were similar between the 2 groups (Table 1).

The intraclass correlation coefficient of SPARCC SI joint MRI score and SPARCC spine MRI score were 0.88 and 0.79 respectively, indicating the agreements between 2 readers were substantial to almost perfect.

3.1 | Independent factors associated with BASMI in all participants

Results of univariate and multivariate linear regressions using BASMI as dependent variable and ADC values as independent variables are shown in Table 2. Similarly, results of univariate and multivariate linear regressions using BASMI as dependent variable and ASDAS as independent variable are shown in Table 3. BASMI was independently associated with ADC spine mean, ASDAS-CRP, ASDAS-ESR; and ADC spine max lost the association. Male gender and mSASSS were also associated with BASMI in all multivariate linear regression

TABLE 1 Baseline characteristics and comparison between participants with back pain duration ≤3 years, and >3 years

	All patients with axial SpA (n = 127)	Back pain duration ≤3 years (n = 27)	Back pain duration >3 years (n = 99)	*P* value
Age, y	47.3 ± 13.3 (median = 48.0)	42.1 ± 13.8	48.6 ± 12.9	.02
Back pain duration, y	14.4 ± 12.0 (median = 10.0)	2.1 ± 0.9	17.8 ± 11.4	<.001
Male gender	89/127 (70.1%)	69/27 (69.7%)	19/27 (70.4%)	.95
Smoker	46/127 (36.2%)	9/27 (33.3%)	36/99 (36.4%)	.77
Drinker	15/124 (12.2%)	3/27 (11.1%)	12/95 (12.6%)	.83
HLA-B27 positivity	107/122 (87.7%)	20/27 (74.1%)	86/94 (91.5%)	.02
Family history of SpA	33/119 (27.7%)	5/27 (18.5%)	28/92 (30.4%)	.22
Radiographic axial SpA	86/127 (67.7%)	14/27 (51.9%)	72/99 (72.7%)	.04
mSASSS	16.4 ± 18.7 (median = 9.0)	9.8 ± 14.1	18.4 ± 19.6	.01
On sulfasalazine	34/126 (27.0%)	9/27 (33.3%)	25/98 (25.5%)	.42
On cDMARD other than sulfasalazine	11/126 (8.7%)	3/27 (11.1%)	8/98 (8.2%)	.63
ASDAS-CRP	2.1 ± 0.9 (median = 2.1)	1.9 ± 0.8	2.1 ± 0.9	.24
ASDAS-ESR	3.2 ± 1.0 (median = 3.2)	3.0 ± 1.0	3.3 ± 1.0	.19
ADC spine max	1487.7 ± 367.8 (median = 1415.0)	1483.1 ± 297.2	1487.8 ± 387.7	.95
ADC spine mean	777.0 ± 191.1 (median = 744.0)	767.0 ± 137.7	781.6 ± 203.7	.67
SPARCC SI joint MRI score	2.9 ± 5.5 (median = 0.0)	4.5 ± 7.7	2.4 ± 4.6	.17
SPARCC spine MRI score	13.5 ± 9.5 (median = 11.0)	12.7 ± 9.6	13.8 ± 9.6	.60
BASMI	4.0 ± 1.6 (median = 3.9)	3.6 ± 1.7	4.1 ± 1.6	.20

Abbreviations: ADC, apparent diffusion coefficient; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; cDMARD, conventional disease-modifying antirheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; MRI, magnetic resonance imaging; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SI, sacroiliac; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada.

TABLE 2 Univariate and multivariate linear regressions using BASMI as dependent variable and ADC values as independent variables

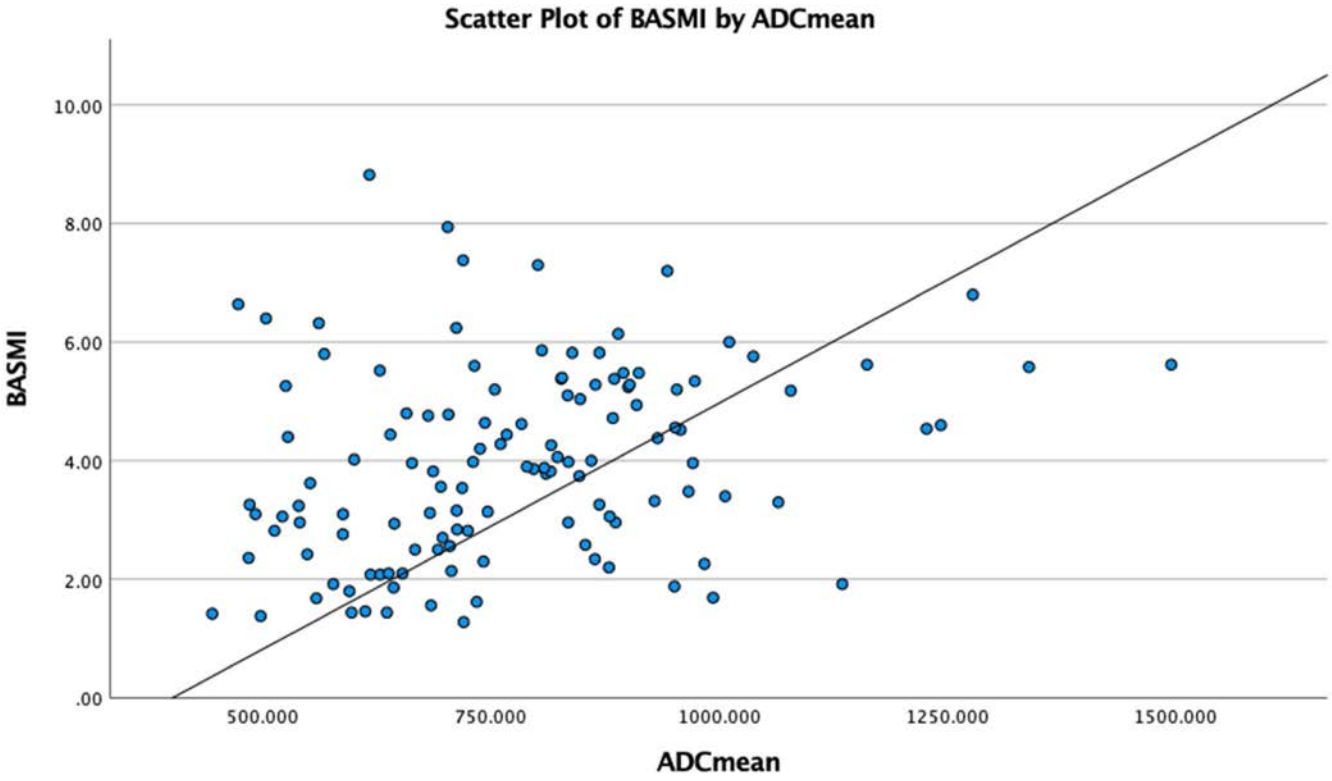
	Univariate regression		Multivariate regression using ADC max as independent variable (n = 119)		Multivariate regression using ADC mean as independent variable (n = 119)	
	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value
Age, n = 124	.34; 0.04 (0.02; 0.06)	<.001	.03; 0.004 (−0.02; 0.02)	.67	.05; 0.01 (−0.01; 0.02)	.55
Back pain duration, n = 123	.14; 0.02 (−0.01; 0.04)	.14				
Male gender, n = 124	.23; 0.79 (1.40; 0.19)	.01	.24; 0.84 (1.35; 0.33)	<.01	.21; 0.72 (1.24; 0.21)	.01
Smoker, n = 124	−.06; −0.19 (−0.79; 0.40)	.52				
Drinker, n = 120	−.08; −0.36 (−1.24; 0.51)	.41				
HLA-B27 positivity, n = 119	−.06; −0.29 (−1.17; 0.60)	.52				
Family history of SpA, n = 117	−.07; −0.26 (−0.93; 0.42)	.45				
Radiographic axial SpA, n = 124	.13; 0.48 (−0.15; 1.10)	.14				
mSASSS, n = 119	.57; 0.05 (0.04; 0.06)	<.001	.57; 0.05 (0.04; 0.06)	<.001	.54; 0.05 (0.03; 0.06)	<.001
On sulfasalazine, n = 126	.06; 0.22 (−0.43; 0.87)	.50				
On cDMARD other than sulfasalazine, n = 126	.05; 0.27 (−0.75; 1.28)	.60				
ADC spine max, n = 124	.17; 0.001 (0.00; 0.001)	.06	.10; 0.00 (0.00; 0.01)	.17	N/A	N/A
ADC spine mean, n = 124	.29; 0.002 (0.00; 0.004)	<.01	N/A	N/A	.16; 0.001 (0.00; 0.003)	.03
SPARCC SI joint MRI index, n = 121	−.11; −0.03 (−0.09; 0.02)	.21				
SPARCC spine MRI index, n = 124	.11; 0.02 (−0.01; 0.05)	.20				

Abbreviations: ADC, apparent diffusion coefficient; BASMI, Bath Ankylosing Spondylitis Metrology Index; cDMARD, conventional disease-modifying antirheumatic drug; CI, confidence interval; HLA, human leucocyte antigen; MRI, magnetic resonance imaging; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; N/A, not applicable; SI, sacroiliac; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada.

TABLE 3 Univariate and multivariate linear regressions using BASMI as dependent variable and ASDAS as independent variables

	Univariate regression		Multivariate regression using ASDAS-CRP as independent variable (n = 116)		Multivariate regression using ASDAS-ESR as independent variable (n = 116)	
	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value	Standardized coefficient (ß); regression coefficient (B) (95% CI)	*P* value
Age, n = 124	.34; 0.04 (0.02; 0.06)	<.001	.04; 0.004 (−0.02; 0.02)	.63	.03; 0.003 (0.02; 0.02)	.76
Back pain duration, n = 123	.14; 0.02 (−0.01; 0.04)	.14				
Male gender, n = 124	.23; 0.79 (1.40; 0.19)	.01	.21; 0.72 (1.21; 0.24)	<.01	.19; 0.65 (1.16; 0.15)	.01
Smoker, n = 124	−.06; −0.19 (−0.79; 0.40)	.52				
Drinker, n = 120	−.08; −0.36 (−1.24; 0.51)	.41				
HLA-B27 positivity, n = 119	−0.06; −0.29 (−1.17; 0.60)	.52				
Family history of SpA, n = 117	−.07; −0.26 (−0.93; 0.42)	.45				
Radiographic axial SpA, n = 124	.13; 0.48 (−0.15; 1.10)	.14				
mSASSS, n = 119	.57; 0.05 (0.04; 0.06)	<.001	.58; 0.05 (0.04; 0.06)	<.001	.56; 0.05 (0.04; 0.06)	<.001
On sulfasalazine, n = 126	.06; 0.22 (−0.43; 0.87)	.50				
On cDMARD other than sulfasalazine, n = 126	.05; 0.27 (−0.75; 1.28)	.60				
ASDAS-CRP, n = 120	.35; 0.65 (0.34; 0.96)	<.001	.29; 0.52 (0.27; 0.76)	<.001	N/A	N/A
ASDAS-ESR, n = 120	.38; 0.61 (0.34; 0.88)	<.001	N/A	N/A	.25; 0.39 (0.16; 0.61)	<.01
SPARCC SI joint MRI index, n = 121	−.11; −0.03 (−0.09; 0.02)	.21				
SPARCC spine MRI index, n = 124	.11; 0.02 (−0.01; 0.05)	.20				

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; N/A, not applicable; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada.



BASMI=Bath Ankylosing Spondylitis Metrology Index; ADC=apparent diffusion coefficient

FIGURE 2 The relationship between ADC mean and BASMI in scatter plot. ADC, apparent diffusion coefficient; BASMI, Bath Ankylosing Spondylitis Metrology Index

models. The relation between ADC spine mean and BASMI is represented in the scatter plot in Figure 2.

3.2 | Independent factors associated with BASMI in participants with back pain duration ≤3 years and >3 years

The independent multivariate linear regression models using ADC spine max, ADC spine mean, ASDAS-CRP, and ASDAS-ESR in participants with back pain duration ≤3 years and >3 years are shown in Figure 3. Upon adjustment for age, gender, and mSASSS, ADC spine mean, ASDAS-CRP, and ASDAS-ESR had stronger associations in participants with back pain duration ≤3 years. No association was found between ADC spine max and BASMI after confounding factors adjustment. The associations between mSASSS and BASMI after age, gender, and different disease activities are also shown in Figure 3. The associations appeared to be similar between the 2 groups.

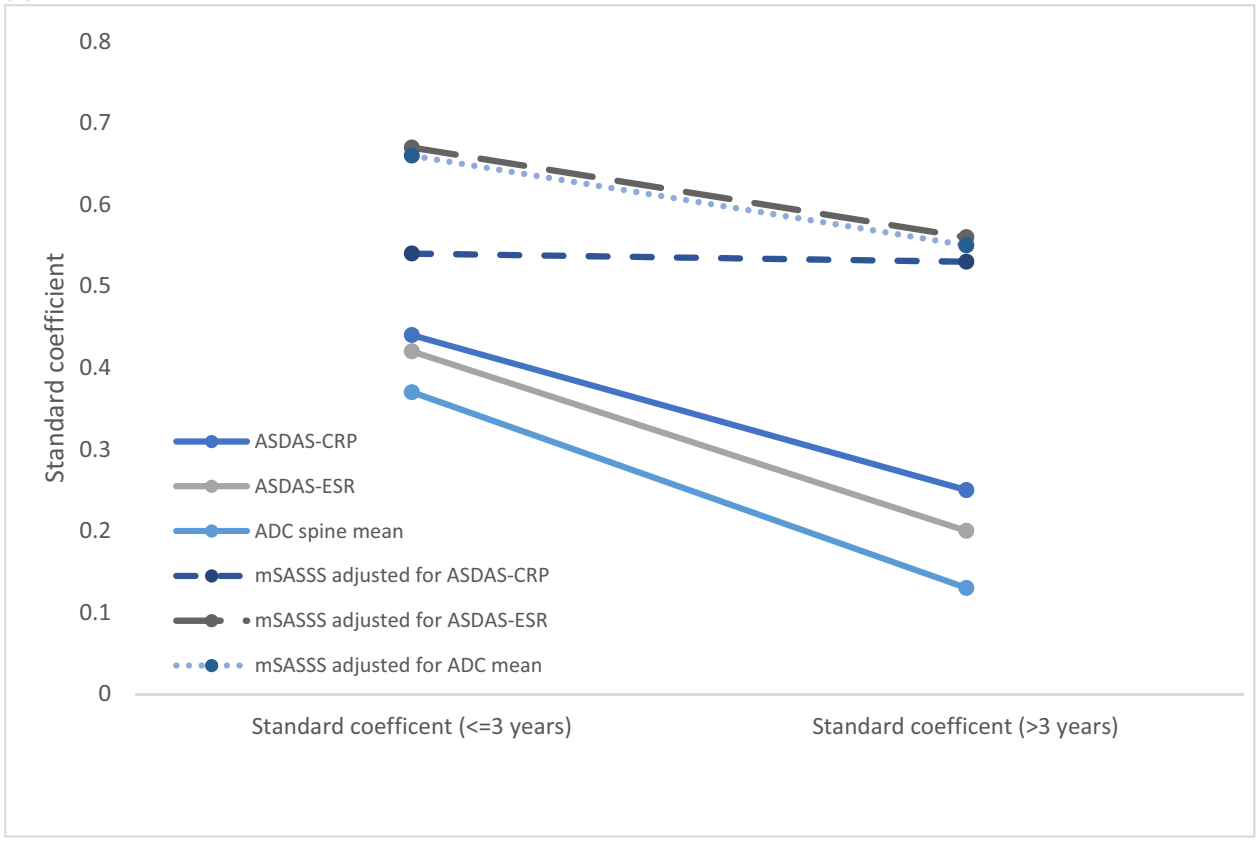
4 | DISCUSSION

Both ADC and ASDAS were associated with impairment of spinal mobility. Moreover, in participants with longer disease duration (>3 years), the effects of inflammation and disease activity on spinal mobility decreased. This was independent of the effect of radiographic damage.

Association between disease activity and impaired spinal mobility had been shown in previous studies. Both ASDAS[7,17] and inflammation on STIR MRI of the spine[6,7] were associated with higher BASMI scores. In this study, the association between mean ADC spine and BASMI showed the effect of the intensity of inflammation on spinal mobility. Compared to the max ADC spine, mean ADC spine appeared to give better description to disease activity. The ability of ADC in quantifying inflammation has been demonstrated in previous studies[18-20] and its usage has been validated in axial SpA.[9] In contrast, the currently recommended STIR imaging poorly visualizes intensity of inflammation. Suppression of spinal inflammation in order to improve mobility and function may be therapeutically beneficial even when complete remission has not been achieved.

The pathophysiology is complex. In addition to pain, inflammation disrupting the synovio-entheseal complex and articular surfaces could reduce spinal mobility.[21] Inflammation inhibits osteogenic differentiation and osteoblast activity. Therefore, osteitis of the vertebral bodies leads to net bone loss which may eventually affect skeletal stability and mobility.[22] Biochemically, inflammatory cytokines have also been linked with impaired spinal mobility,[23,24] which was further supported by therapeutic trials of anti-TNF drugs showing improved spinal mobility upon control of inflammation and disease activity.[25,26]

(A)



(B)

	Back pain duration<=3years (n=27)		Back pain duration >3 years (n=99)	
	SC; RC (95% CI)	P=value	SC; RC (95% CI)	P=value
ADC spine max**	0.13; 0.001 (-0.001; 0.003)	0.47	0.08; 0.00 (0.00; 0.001)	0.33
ADC spine mean**	0.37; 0.004 (0.00; 0.01)	0.03	0.13; 0.001 (0.00; 0.002)	0.15
ASDAS-CRP**	0.44; 0.86 (0.33; 1.39)	<0.01	0.25; 0.45 (0.16; 0.73)	<0.01
ASDAS-ESR**	0.42; 0.70 (0.22; 1.12)	0.01	0.20; 0.31 (0.05; 0.58)	0.02
mSASSS[1]	0.54; 0.06 (0.02; 0.10)	<0.01	0.53; 0.04 (0.03; 0.06)	<0.001
mSASSS[2]	0.67; 0.08 (0.05; 0.11)	<0.001	0.56; 0.05 (0.03; 0.06)	<0.001
mSASSS[3]	0.66; 0.08 (0.04; 0.11)	<0.001	0.55; 0.04 (0.03; 0.06)	<0.001

FIGURE 3 Standard coefficients between Bath Ankylosing Spondylitis Metrology Index and (i) disease activity scores (Ankylosing Spondylitis Disease Activity Score – C-reactive protein [ASDAS-CRP], ASDAS - erythrocyte sedimentation rate [ASDAS-ESR], apparent diffusion coefficient [ADC] spine mean); (ii) modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) adjusted for disease activity scores (ASDAS-CRP, ASDAS-ESR, ADC spine mean) for duration of back pain ≤3 years and >3 years. (A) Graph. (B) Table

The effect of disease activity on spinal mobility is multifactorial.[27] Spinal mobility has been found to be influenced by disease activity in earlier stages, and by structural damage in later stages.[6,7] This study has also found a greater effect of disease activity in the early (≤3 years) disease group; however, the lesser effect in the later stage (>3 years) was not accounted for by structural damage. Chronic structural changes quantified in mSASSS and BASMI appeared to be similar over time after adjustment for potential confounding factors, although some may have been unaddressed. That active inflammation in early disease was a predominant factor in impaired spinal mobility is a plausible explanation of improved clinical response of biologic therapies in early active axial SpA.[28,29]

Unsurprisingly, no association between BASMI and the SPARCC MRI SI joint index was found as BASMI measured spinal mobility on which sacroiliitis would have little effect. However, contrary to previous studies,[6,7] no association was also found with the SPARCC MRI spine index, which measured spinal inflammation. This inconsistency could be due to the selection of only participants with measurable spinal inflammation on STIR imaging on which ADC values from DWI can be determined, hence inadvertently excluding those with no active lesions on ADC. In spite of that, our study shows intensity of inflammation could have a more invaluable effect on spinal mobility than the extent of inflammation. This finding would imply that in axial SpA, quantitative assessment of inflammation using numerical ADC values could provide additional information above visualization of inflammation on STIR imaging. Similar to our findings, a recent study in active ankylosing spondylitis with planned golimumab therapy showed weak correlation between the SPARCC MRI score and impairment in spinal mobility,[30] suggesting a possible limitation of STIR imaging. A quantitative measure of spinal inflammation using ADC allows possible clinical applications in precise monitoring of treatment response for more personalized medicine.[31]

Unmodifiable factors such as age and gender affected spinal mobility. Similar to previous studies,[32,33] women were independently and consistently found with increased flexibility compared to male counterparts. Age has also been repeatedly shown to be associated with decreased spinal mobility;[32,34,35] however, in this study the association found in univariate analysis was lost in multivariate models. As expected, the use of sulfasalazine and other cDMARDs were not related to spinal mobility.

Our study had several limitations. DW-ADC analyses did not allow us to include participants without active spine MRI inflammation. Inclusion of only axial SpA participants with active spinal MRI lesions could create potential bias. ADC values may be affected by age, osteoporosis,[36] and skeletal maturity.[37] And active axial SpA is more prone to than inactive disease.[38] Systemic variability of ADC measured from different MRI machines have prompted a proposed use of normalized ADC (nADC) values for analysis.[39] However, nADC were not calculated since a single MRI machine was used in this study. Use of the SPARCC MRI index may have falsely excluded lesions with coexisting inflammation and degeneration.[40] Our study demonstrated the usefulness of spine DW-ADC in axial SpA research and potential in clinical practice. Future improvements in interpretation of DWI might allow recruitment of participants without active disease for a more comprehensive description of axial SpA.

5 | CONCLUSION

Intensity of inflammation and clinical disease activity were independently associated with impairment of spinal mobility. The associations were stronger in early (≤3 years) than later disease. Our findings highlight the potential therapeutic benefit of suppressing inflammation even when complete remission has not been achieved.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number UW 14-085) and local ethics committees. It was conducted in accordance with the Declaration of Helsinki and the guidance of Good Clinical Practice, November 30, 2006. All participants gave written informed consent before recruitment.

DATA AVAILABILITY STATEMENT

Data are available from Prof Chak Sing Lau upon reasonable request.

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ORIGINAL ARTICLE

Association of tumor necrosis factor-α inhibitors and liver cirrhosis in patients with rheumatoid arthritis: A nationwide population-based nested case-control study

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Abstract

Aim: Results from various studies are controversial regarding long-term hepatic effects of tumor necrosis factor (TNF)-α inhibitors. Here we aimed to investigate the development of liver cirrhosis with TNF-α inhibitors use in patients with rheumatoid arthritis (RA).

Method: This nested case-control study was based on the National Health Insurance Research Database (January 1, 2000 to December 31, 2008) of Taiwan. We identified 559 adult RA patients who developed liver cirrhosis, and 1055 matched control RA patients. TNF-α inhibitors of interest in the study period included adalimumab and etanercept. Multivariate logistic regression analysis for the development of liver cirrhosis with respect to use of TNF-α inhibitors was performed.

Results: The incidence rate of liver cirrhosis was 274 per 100 000 person-years in newly diagnosed RA patients. We found the use of TNF-α inhibitors was not associated with the development of liver cirrhosis in RA patients (odds ratio 1.02, 95% confidence interval 0.61, 1.70) after adjustment for potential confounders. In addition, the finding was robust to an unobserved confounder.

Conclusion: We found no association between the use of TNF-α inhibitors and development of liver cirrhosis in RA patients.

KEYWORDS
adalimumab, cirrhosis, etanercept, rheumatoid arthritis, tumor necrosis factor-α inhibitors

Der-Yuan Chen and Ching-Heng Lin contributed equally to the work.

1 | INTRODUCTION

Tumor necrosis factor (TNF)-α inhibitors have revolutionized the treatment strategy for patients with rheumatoid arthritis (RA).[1] Their efficacy in achieving disease control benefits those RA patients who do not respond to conventional therapy.[2] In addition to their therapeutic efficacy for RA, real-world data allow study of beneficial or harmful effects of such new drugs.[3] Some observational studies in RA patients receiving therapy with TNF-α inhibitors reported improved insulin resistance[4] and reduced cardiovascular risk.[5] The long-term hepatic effects of TNF-α inhibitors remain unclear.

Liver cirrhosis is ranked the 11th common cause of death, resulting in 1.16 million annual deaths worldwide.[6] Liver cirrhosis is initiated from hepatic insult, with inflammation that follows, eventually leading to fibrosis. RA patients are at risk of liver damage, due to potential hepatotoxicity of medications, nonalcoholic fatty liver disease (NAFLD) and concomitant autoimmune liver disease.[7,8] Notably, TNF-α plays a crucial role in the inflammatory response upon hepatic injury, including NAFLD.[9] Interventional trials supported the potential of TNF-α inhibitors in suppressing hepatic inflammation.[10-12] Nevertheless, TNF-α inhibitors in RA patients could cause reactivation of chronic hepatitis B, which is endemic in Taiwan.[13] A recent review on the safety of TNF-α inhibitors showed a potentially beneficial effect on NAFLD and a lack of evidence regarding their effect on liver cirrhosis.[14] A population-based cohort study in the UK reported a numerically reduced risk for liver cirrhosis in RA patients who used systemic therapy when compared with those patients who did not.[15] In contrast, another study in the US found an increased hazard for liver cirrhosis with the use of TNF-α inhibitors in patients with immune-related diseases.[16] Herein, we hypothesized that the use of TNF-α inhibitors does not alter the risk for developing liver cirrhosis in RA patients. A nested case-control study was therefore conducted based on a nationwide population-based cohort.

2 | MATERIALS AND METHODS

2.1 | Study population

We analyzed data obtained from the National Health Insurance Research Database (NHIRD), established and maintained by the Taiwan National Health Research Institute.[17,18] NHIRD contains healthcare data of >99% of the entire 24 million population of Taiwan. Diagnoses in the database were based on the International Classification of Diseases (ICD)-9-CM codes. The diagnosis of RA was made based on the Catastrophic Illness Patient Database (CIPD), a registry requiring certification by 2 experienced rheumatologists in line with the criteria of the 1987 American College of Rheumatology.[19] We first identified 25 214 patients diagnosed with RA in the period from January 1, 2000 to December 31, 2008 (Figure 1). We excluded those patients who had developed liver cirrhosis prior to the RA diagnosis. A total of 24 013 adult RA patients were finally analyzed. Among these patients, 559 later developed liver cirrhosis (ICD-9-CM code 571.5 for 3 outpatient visits or 1 inpatient visit). The index date was defined as the date of first diagnosis of liver cirrhosis. RA patients without liver cirrhosis were matched in a 2:1 ratio to those who developed liver cirrhosis, according to age, gender, index date, and time interval between RA diagnosis and the index date. Our study was conducted in accordance with the Declaration of Helsinki and the protocol approved

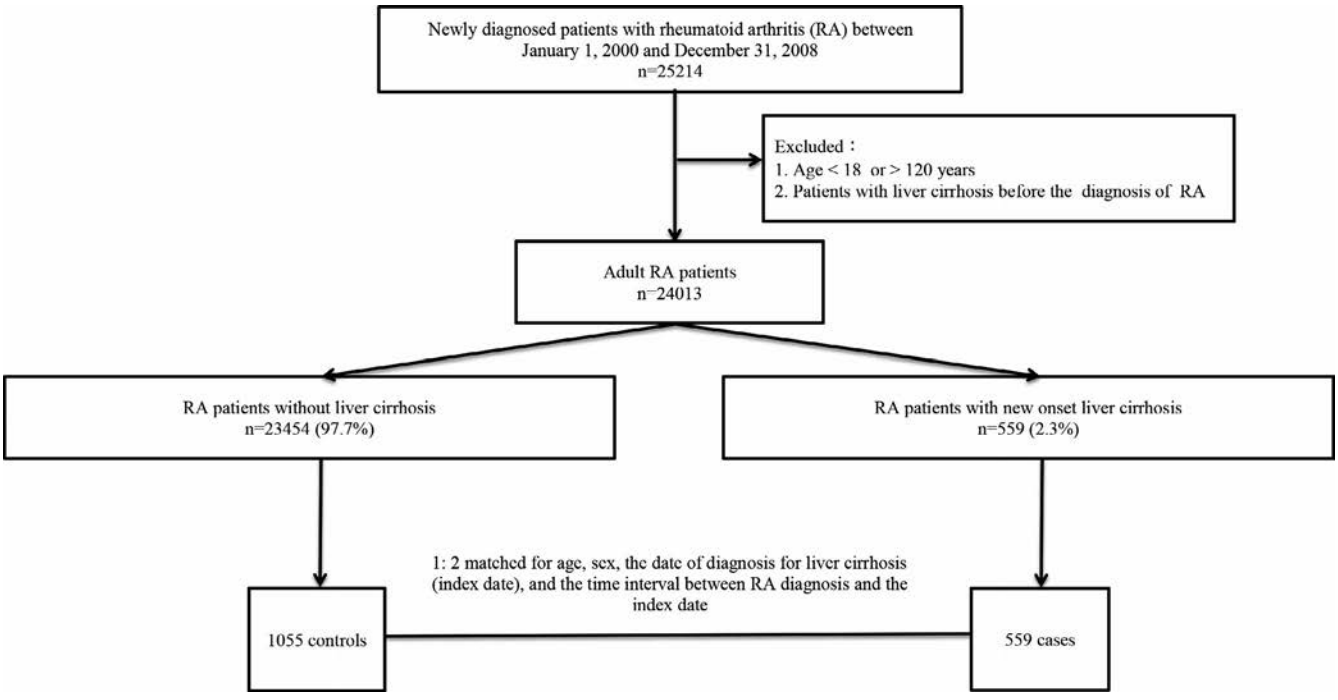

FIGURE 1 The study algorithm for identifying patients with rheumatoid arthritis

by the institutional review board of the Taichung Veterans General Hospital (Taichung, Taiwan; TCVGH CE13151B-7). Informed consent was waived due to the de-identified nature of the database.

2.2 | Clinical parameters

We identified for each subject, risk factors for liver cirrhosis, such as chronic hepatitis B (ICD-9-CM codes 070.2, 070.3, and/or V02.61), chronic hepatitis C (ICD-9-CM codes 070.54, 070.70, and/or V02.62), and diabetes mellitus (ICD-9-CM code 250 and/or A code A181), as well as comorbidities, such as dyslipidemia (ICD-9-CM code 272) and hypertension (ICD-9-CM codes 401-405 and/or A code A26).

2.3 | Medications

TNF-α inhibitors included adalimumab and etanercept. They were the only agents available in the Taiwan market during the study period. The disease activity of RA was represented by the dose of glucocorticoids averaged from the diagnosis of RA to the index date. Use of oral medications was defined based on their prescription for ≥84 days. Use of the other biologic in the market, rituximab, was defined when prescribed for at least once. Use of potentially hepatotoxic mediations like methotrexate, azathioprine, leflunomide, and/or sulfasalazine was documented for each subject.

2.4 | Social determinants

In Taiwan, the urbanization of townships is categorized into 7 levels based on variables such as population density, proportion of population completed college education, proportion of population aged >65 years, proportion of population working in agriculture, and the number of physicians per 100 000 people (Table S1).[20] We grouped the lower 4 levels of urbanization as one level 4 due to the fewer patients in these levels. Thus, level 1 represented the highest urbanization, and level 4, the lowest. The monthly income bracket of each patient was based on the National Health Insurance payroll upon which healthcare premiums were calculated.

2.5 | Statistics

Data on patient characteristics were represented as either mean and SD, or percentage. Multivariate logistic regression analyses for the development of liver cirrhosis were done with respect to the use of TNF-α inhibitors, adjusted for age, gender, family income, levels of urbanization, comorbidities including chronic hepatitis B, chronic hepatitis C, diabetes mellitus, dyslipidemia and hypertension, and use of medications including methotrexate, azathioprine, leflunomide, sulfasalazine, and/or rituximab. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc.).

2.6 | Sensitivity analyses

We examined odds ratios (ORs) for different time durations of TNF-α inhibitors use, with the cut-off at either 1.5 years, or 1 and 2 years. We also performed sensitivity analyses in subgroups of RA patients with either chronic hepatitis B or C. We also did ad hoc analyses for subgroups of RA patients living in less urbanized areas (urbanization level 3 or 4). Finally, we examined the sensitivity of our results to an unobserved binary confounder using Lin's approach.[21,22] This approach can be utilized to assess the sensitivity of the estimated exposure effect to the residual confounding effects of an unmeasured variable after adjusting for measured covariates in the multivariate regression.[22] An adjustment factor was derived based on the assumed prevalence of an unobserved confounder in the TNF-α inhibitors non-users, and ORs of an unobserved confounder with respect to the use of TNF-α inhibitors and the development of liver cirrhosis. The adjusted values of OR and 95% confidence interval (CI) were obtained by dividing with the adjustment factor, of the OR and upper and lower bounds of the CI.

3 | RESULTS

3.1 | Baseline characteristics of identified RA patients

After an average follow-up period of 8.5 years, 559 (2.3%) RA patients developed liver cirrhosis. The incidence rate of liver cirrhosis in these newly diagnosed RA patients was 274 per 100 000 person-years. Baseline characteristics of these eligible RA patients and matched controls are shown in Table 1. On the average, patients developed liver cirrhosis 4.4 years after their RA diagnosis. More than half of them (65%) were female, and lived in less urbanized areas.

3.2 | Characteristics of RA patients with and without new onset liver cirrhosis

A similar proportion of the use of TNF-α inhibitors was observed in RA patients with and without new onset liver cirrhosis (7% vs 8%). The majority of them (>85%) used etanercept. Durations of TNF-α inhibitor usage were similar between RA patients with and without new onset liver cirrhosis (1.7 vs 2.0 years). A higher proportion of RA patients who developed liver cirrhosis, compared with those who did not, lived in less urbanized areas. In addition, RA patients who developed liver cirrhosis had higher proportions of chronic hepatitis B, chronic hepatitis C, and diabetes mellitus,

TABLE 1 Baseline characteristics of RA patients with and without new onset liver cirrhosis

Variables	RA patients with new onset liver cirrhosis (N = 559)	RA patients without new onset liver cirrhosis (N = 1055)
Age, y[a]	60.2 ± 11.5	60.2 ± 11.1
Female	365 (65%)	724 (69%)
Use of TNF-α inhibitors	40 (7%)	87 (8%)
Etanercept	31 (6%)	65 (6%)
Adalimumab	13 (2%)	27 (3%)
Time period of TNF-α inhibitors use, y	1.7 ± 1.5	2.0 ± 1.7
Family income, NTD		
0-15 840	169 (30%)	321 (30%)
15 841-45 800	369 (66%)	680 (65%)
≧45 801	21 (4%)	54 (5%)
Levels of urbanization**		
1	108 (22%)	298 (30%)
2	144 (29%)	284 (29%)
3	81 (16%)	149 (15%)
4	166 (33%)	254 (26%)
The interval between diagnosis of RA and the index date, y	4.4 ± 3.1	4.5 ± 3.0
Comorbidity		
Chronic hepatitis B**	195 (35%)	61 (6%)
Chronic hepatitis C**	107 (19%)	28 (3%)
Diabetes mellitus**	118 (21%)	154 (15%)
Dyslipidemia	77 (14%)	165 (16%)
Hypertension	251 (45%)	422 (40%)
Medications		
Glucocorticoids (prednisone equivalent)		
Average daily dose 0-5 mg	148 (27%)	295 (28%)
Average daily dose 5-10 mg	293 (52%)	557 (53%)
Average daily dose ≥10 mg	118 (21%)	203 (19%)
Methotrexate*	229 (41%)	518 (49%)
Other hepatotoxic medications[b]	273 (49%)	545 (52%)
Rituximab	3 (1%)	7 (1%)

Note: *$P < .05$, **$P < .001$ between RA patients with and without new onset liver cirrhosis.

Abbreviations: NTD, National Taiwan Dollar (1 NTD = Euro€0.03 on 4 November 2021); RA, rheumatoid arthritis; TNF, tumor necrosis factor.

[a]At diagnosis of RA.

[b]Azathioprine, leflunomide, and/or sulfasalazine.

and a lower proportion of receiving methotrexate, compared with those who did not.

3.3 | The association between the use of TNF-α inhibitors and development of liver cirrhosis

With the multivariate logistic regression analysis, we found no significant association between the use of TNF-α inhibitors and development of liver cirrhosis (OR 1.02, 95% CI: 0.61, 1.70) (Figure 2). Chronic hepatitis B and hepatitis C were each significantly associated with the development of liver cirrhosis at high ORs: 9.92 (95% CI: 7.00, 14.06) and 9.72 (95% CI: 5.96, 15.87) respectively. Living in less urbanized areas was also associated with the development of liver cirrhosis.

3.4 | Sensitivity analyses

Results of sensitivity analyses are shown in Table 2. Different time lengths of receiving TNF-α inhibitors were accounted for in the

Variables	Adjusted OR (95% CI)
Use of TNF-α inhibitors	1.02 (0.61, 1.70)
Family income, NTD	
15,841-45,800 vs. 0-15,840	0.83 (0.63, 1.10)
≧45,801 vs. 0-15,840	0.50 (0.25, 1.00)
Levels of urbanization	
2 vs. 1	1.34 (0.96, 1.89)
3* vs. 1	1.52 (1.02, 2.27)
4* vs. 1	1.84 (1.30, 2.59)
Comorbidity	
Chronic hepatitis B**	9.92 (7.00, 14.06)
Chronic hepatitis C**	9.72 (5.96, 15.87)
Diabetes mellitus	1.30 (0.93, 1.83)
Dyslipidemia	0.75 (0.52, 1.08)
Hypertension	1.28 (0.98, 1.67)
Medications	
Glucocorticoids (prednisone equivalent)	
Average daily dose 5-10mg vs. 0-5mg	1.01 (0.75, 1.36)
Average daily dose >=10mg vs. 0-5mg	1.19 (0.83, 1.69)
Methotrexate	0.85 (0.64, 1.13)
Other hepatotoxic medications†	0.90 (0.68, 1.19)
Rituximab	0.54 (0.10, 2.90)

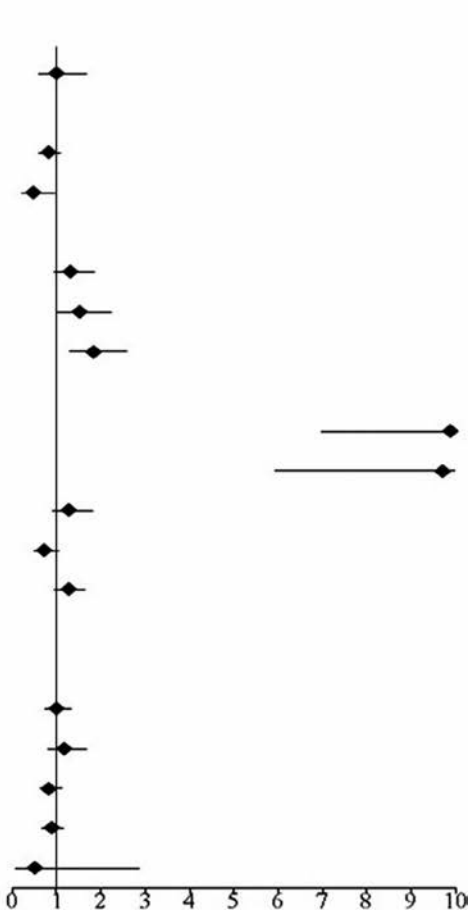

FIGURE 2 Results of multivariate analysis on developing liver cirrhosis in patients with rheumatoid arthritis. *$P < .05$; **$P < .001$. †Azathioprine, leflunomide, and/or sulfasalazine. CI, confidence interval; NTD, National Taiwan Dollar (1 NTD = Euro€0.03 on 14 November 2021); OR, odds ratio; TNF, tumor necrosis factor

logistic regression. To be noted, even use of TNF-α inhibitors for a longer period was not associated with the development of liver cirrhosis. In subgroups of RA patients with either chronic hepatitis B or C, regarding the association between TNF-α inhibitors use and the development of liver cirrhosis, the ORs were higher (OR: 1.72, 95% CI: 0.43, 6.82 in those patients with chronic hepatitis B and OR: 2.00, 95% CI: 0.32, 12.38 in those patients with chronic hepatitis C). Table S2 shows the results after adjustment for an unobserved binary confounder. Our results were not sensitive to an unobserved confounder that was associated with a 14-fold higher odds of developing liver cirrhosis and a 3-fold higher odds of receiving TNF-α inhibitors.

4 | DISCUSSION

TNF-α inhibitors are effective in treating immune-related diseases, including RA. However, long-term hepatic effect of TNF-α inhibitors remains unclear. We here have used a nationwide population-based case-control study and demonstrated no association between TNF-α inhibitors use and liver cirrhosis in RA patients. Furthermore, our results were robust to an unobserved confounder.

Hepatic inflammation could both initiate and maintain fibrogenesis, culminating in cirrhosis.[23] Previous studies have implied a potentially beneficial role of TNF-α inhibitors in the treatment of hepatic inflammation in alcoholic hepatitis[11,12] and chronic hepatitis C,[10] despite limited clinical utility.[24,25] Data are conflicting regarding the effect of TNF-α inhibitors upon NAFLD,[26] another important etiology of liver cirrhosis.[27] A case-control study on patients with inflammatory bowel disease (IBD) indicated that receiving TNF-α inhibitors was associated with a lower incidence of NAFLD.[28] Another retrospective cohort of IBD patients reported an increased hazard for NAFLD in users of TNF-α inhibitors.[29] Recent population-based studies provided direct evidence upon the association between TNF-α inhibitors and liver cirrhosis. A MarketScan study on patients with immune-related diseases including RA, reported an increased hazard for liver cirrhosis with the use of TNF-α inhibitors.[16] However, the conclusion was undermined by their median follow-up period of only 1.5 years. Another cohort study with a UK primary care database demonstrated, after a mean follow-up of 6 years, a lower risk in RA patients receiving systemic therapy, when compared with those

TABLE 2 Results of the sensitivity analyses[a]

	Adjusted OR for use of TNF-α inhibitors (95% CI)
Accounting for different time length of TNF-α inhibitors use	
Cut-off: 1.5 y	
Non-users	1.00
<1.5 y	1.08 (0.56, 2.07)
≥1.5 y	0.96 (0.46, 1.97)
Cut-off: 1 and 2 y	
Non-users	1.00
<1 y	1.34 (0.65, 2.75)
≥1 year and <2 y	0.66 (0.22, 2.05)
≥2 y	0.92 (0.42, 2.03)
Subgroup	
Level 3 urbanization	1.29 (0.40, 4.12)
Level 4 urbanization	0.62 (0.21, 1.84)
Chronic hepatitis B	1.72 (0.43, 6.82)
Chronic hepatitis C	2.00 (0.32, 12.38)

Abbreviations: CI, confidence interval; OR, odds ratio; TNF, tumor necrosis factor.

[a]Adjusted for age, gender, family income, levels of urbanization, comorbidities including chronic hepatitis B, chronic hepatitis C, diabetes mellitus, dyslipidemia and hypertension, and use of medications including methotrexate, azathioprine, leflunomide, sulfasalazine, and/or rituximab.

not receiving systemic therapy.[15] However, the use of biologics was rarely captured in the medical records kept by the general practitioners in the database. Our nationwide cohort had an average follow-up of approximately 4.5 years, and the use of TNF-α inhibitors was well recorded for each patient. We did not find any association between the use of TNF-α inhibitors and development of liver cirrhosis in RA patients, even for those receiving such inhibitors for a longer period.

The epidemiology of liver cirrhosis varies, among others, with age, gender, ethnicity, and etiology. In our RA patients, the incidence rate for liver cirrhosis was 274 per 100 000 person-years. The incidence appeared higher than that in the Global Burden of Disease statistics regarding the Taiwanese population (an incidence rate of as high as 122 per 100 000 person-years aged 30-69 years).[30] A prior population-based cohort study in the UK also reported a higher risk for liver cirrhosis in RA patients than in the general population.[15] Nevertheless, another NHIRD study reported no higher risk for liver cirrhosis in Taiwanese RA patients, although the diagnosis of liver cirrhosis was defined as the broader ICD-9-CM code 571 (chronic liver disease and cirrhosis).[7] Do RA patients have a higher risk for developing liver cirrhosis? More studies are required. In addition, we found that socioeconomic status had likely influenced the risk for liver cirrhosis in RA patients. Low family incomes and especially living in deprived areas, were associated with the increased odds for developing liver cirrhosis. Our findings corroborated a number of prior studies demonstrating increased mortality from liver cirrhosis in patients with low socioeconomic status.[31-33] Low socioeconomic status apparently not only increased the risk for liver cirrhosis, but also worsened its prognosis. This issue needs more attention as it might affect resource allocation, and planned interventions for socially deprived RA patients in preventing and managing liver cirrhosis. For example, public health measures such as screening, behavioral counseling and even pharmacological intervention for alcohol abuse, viral hepatitis, and NAFLD could eliminate additional risk factors for liver cirrhosis in these at-risk RA patients.[34] The association between methotrexate use and development of liver cirrhosis has long been a topic of debate. Our previous work showed no increased hazard of liver cirrhosis in RA and psoriatic patients with chronic hepatitis B or hepatitis C.[18,35,36] In the present study, neither did we find an increased odds of methotrexate use in RA patients who developed liver cirrhosis.

Chronic hepatitis B and C are both associated with a remarkably increased risk for liver cirrhosis in RA patients. Previous studies suggested reactivation of chronic hepatitis B, but not hepatitis C, in patients receiving TNF-α inhibitors.[13,37,38] A beneficial effect on the virologic response after etanercept use in addition to standard antiviral therapy has been demonstrated in a trial of hepatitis C patients.[10] In the present study, we observed a trend toward an increased odds for the use of TNF-α inhibitors in RA patients with chronic viral hepatitis who developed liver cirrhosis. These preliminary results were based on a small subgroup of RA patients and were for hypothesis generation only. Further studies with a larger sample size are needed. We also examined the association between the use of TNF-α inhibitors and development of liver cirrhosis in susceptible RA patients who lived in less urbanized areas. We did not find any association.

Some limitations of our study are as follows. First, information regarding disease activity, body mass index (BMI), smoking, and alcohol status were not well recorded in our database. RA disease activity could be inferred by the average dose of glucocorticoids for the patient. The way we matched study cases and controls based on the interval between the diagnosis of RA and index date could further minimize the confounding effect of disease activity. Previous studies have demonstrated that obesity (BMI >30 kg/m^2), smoking (≥1 pack per day), and alcohol (≥7 drinks per day), were associated with a 10.7-, 3- and 1.2-fold increased risk for liver cirrhosis respectively.[39-41] However, our result was shown to be robust to an unobserved confounder with even a 14-fold increase in the odds of developing liver cirrhosis. Second, the follow-up period of 8.5 years in our patients was likely not long enough for the development of liver cirrhosis. Additionally, the duration of the use of TNF-α inhibitors (1.7 years in average) in our patients who developed liver cirrhosis may have been too short to influence the development of liver cirrhosis. However, from our sensitivity analysis, we found that even a prolonged use of anti-TNF-α agents was not associated with a higher odds for the development of liver cirrhosis. Lastly, although only 2 of the TNF-α inhibitors (adalimumab and etanercept) were available in the study period, these are the most commonly prescribed TNF-α inhibitors for RA.[16,42]

5 | CONCLUSIONS

In conclusion, the present case-control study found no association between the use of TNF-α inhibitors and development of liver cirrhosis in RA patients.

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CONFLICT OF INTEREST

All the authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

DYC, CHL, and KTT conceived and designed the study, and conducted data analysis. KTT drafted the manuscript. HHC and DYC revised the manuscript. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article are available upon reasonable request to the corresponding author.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Predictive factors for retention of golimumab over a median 4-year duration in Japanese patients with rheumatoid arthritis in a real-world setting: A retrospective study and literature review

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Abstract

Objectives: To investigate 6-year drug survival (median: 48.5 months) of golimumab and predictors for lack of efficacy leading to golimumab discontinuation in Japanese patients with rheumatoid arthritis (RA) in routine practice.

Methods: This retrospective single-center study included 60 patients with RA treated with golimumab from November 2011 to August 2020. Patients were divided into 2 groups (retention, n = 28; withdrawal due to lack of efficacy, n = 24). The retention rate was assessed using the Kaplan-Meier method, and variables associated with golimumab discontinuation were identified using the Cox proportional hazard model.

Results: The prevalence of concomitant methotrexate and no biologics use was significantly higher in the retention than in the withdrawal group. Overall drug survival of golimumab was 66.3%, 48.3%, and 24.5% at 12, 36, and 72 months, respectively. There were statistical differences in retention rates among groups stratified by initiation dose, methotrexate, and biologics use. Multivariate analysis revealed the factor associated with golimumab discontinuation as history of 1 (hazards ratio: 4.42, 95% CI: 1.35-19.93, $P = .012$) and ≥2 biologics use (7.49, 1.97-36.27, $P = .003$).

Conclusions: Prior exposure of increasing number of biologics was identified as the most important factor negatively affecting long-term golimumab retention in Japanese patients with RA.

KEYWORDS
biological disease-modifying antirheumatic drug, golimumab, retention, rheumatoid arthritis, TNF inhibitor

1 | INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammatory arthritis associated with joint tenderness and swelling, causing irreversible joint damage without effective intervention with disease-modifying antirheumatic drugs (DMARDs).[1] The advent of biological DMARDs (bDMARDs) or targeted synthetic DMARDs has dramatically improved radiographic and functional outcomes in patients with RA. Currently, combination treatment with these molecular target agents is recommended for the management of RA in which therapeutic goals are difficult to be achieved despite conventional synthetic DMARDs therapy based on a treat-to-target approach.[2]

Golimumab (GLM) is one of 5 tumor necrosis factor (TNF) inhibitors approved for treatment of RA worldwide among biologics; structurally, it is a human monoclonal antibody targeting soluble and cell membrane-bound TNF. Thus far, growing evidence from several pivotal randomized controlled trials (RCTs) have confirmed the efficacy and safety of subcutaneous GLM therapy in patients with RA having clinically and ethnically diverse backgrounds.[3-7]

However, the results of RCTs are difficult to generalize directly into routine care because of the controlled study design, limited follow-up duration, and stringent criteria for inclusion and exclusion, which restricts to a minority of patients in real-world practice.[8-10] Thus, observational cohort studies are crucial for evaluating the long-term outcomes of antirheumatic therapy for diverse patient populations. Although various registries, primarily in many European countries, exploring factors associated with drug survival of GLM, which is considered an important composite indicator of effectiveness, safety, and patient preference,[11,12] have been reported,[13-18] clear evidence attributable to retention or discontinuation of GLM highlighting its effectiveness in patients with RA have not yet been established. In particular, there are few reports on long-term drug survival of GLM in routine care of Japanese patients,[19] and clinical predictors for sustained effectiveness of GLM remain unclear.

In this study, we aimed to investigate 6-year drug survival of GLM in patients with RA, and to precisely identify predictive factors associated with the lack of efficacy leading to discontinuation of GLM in daily practice. Moreover, we reviewed previously published literature focusing on factors for persistence of GLM to integrate recently increasing evidence regarding GLM therapy in a real-world setting.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective observational cohort study was conducted at Osaki Citizen Hospital. The study enrolled patients with RA classified according to the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria,[20] and treated with GLM from November 2011 to August 2020. These patients were bDMARDs naïve or refractory to bDMARDs prior to administration of GLM, observed for at least 6 months or more, and followed up until July 2021. The treatment decision was recommended by rheumatologists based on treat-to-target strategy to optimize the treatment outcomes. We collected and analyzed the following clinical information of patients at GLM initiation from electronic health records: age, gender, disease duration, rate of anti-citrullinated protein antibody (ACPA) or rheumatoid factor (RF), frequency and dose of concomitant methotrexate (MTX) or oral prednisolone (PSL), history of biologic administration, level of C-reactive protein (CRP), tender joint count, swollen joint count, dose and duration of GLM, and reasons for GLM discontinuation. The probability of retention of GLM therapy after its initiation was evaluated. The retention duration was defined as the period from the first GLM administration until GLM withdrawal. Reasons for GLM discontinuation included primary or secondary inappropriate responses to GLM, adverse events, patient preference, or other. Furthermore, the potential factors associated with GLM discontinuation due to insufficient responses were determined. Patients who discontinued GLM for reasons other than lack of efficacy were excluded as the analysis was focused on exploration of relevant risk factors to assess the correlation between retention and effectiveness of GLM. The remaining patients were classified into 2 groups based on drug survival as follows: (a) retention and (b) withdrawal due to inappropriate response to GLM (Figure 1). This study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Osaki Citizen Hospital.

2.2 | Clinical evaluation

Inappropriate response to treatment was based on clinical judgment by the attending rheumatologists and defined as worsening of arthritis derived from RA, requiring commencement, re-initiation, or dose escalation of DMARDs and/or

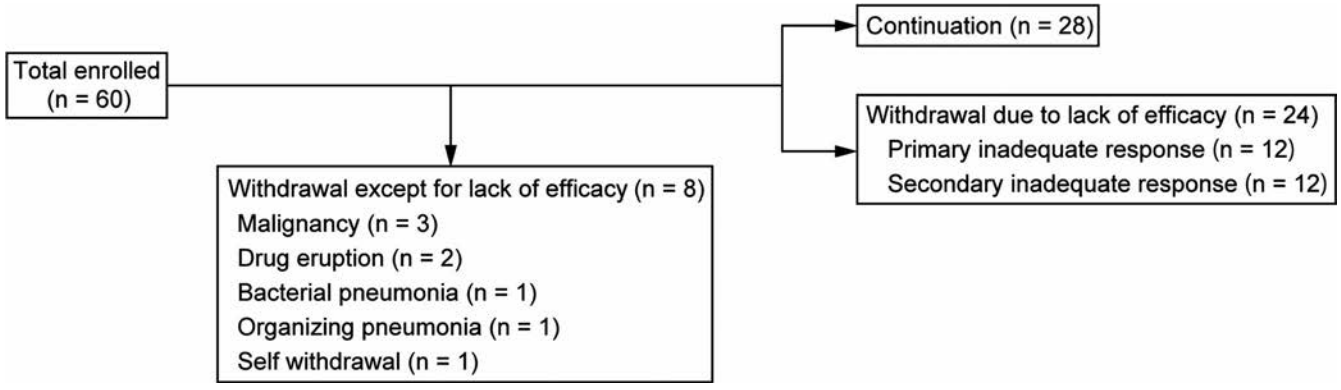

FIGURE 1 Study flowchart of 60 patients with rheumatoid arthritis treated with GLM. Lack of efficacy includes the primary or the secondary inadequate response to GLM. GLM, golimumab

glucocorticoids, as described in a previous study.[21] Specifically, the primary inadequate response was defined as no or insignificant response represented by no achievement of Disease Activity Score of 28 joints-CRP (DAS28-CRP) ≤3.2 or clinical disease activity index (CDAI) ≤10 within 3 to 6 months after commencement of GLM, whereas the secondary inadequate response was the lack of efficacy with DAS28-CRP >3.2 or CDAI >10 in patients treated with GLM who have once achieved clinical remission represented by DAS28-CRP ≤2.8 or CDAI ≤2.6.

2.3 | Search strategy

We searched PubMed databases using the following terms: "rheumatoid arthritis," and "golimumab" up to July 2021. We included cohort studies, published in English, that revealed factors attributable to long-term (≥2 years) persistence of GLM in patients with RA in a real-world setting.

2.4 | Statistical analysis

The Mann-Whitney *U* test was used to compare continuous variables expressed as median (interquartile range), and Chi-square or Fisher's exact test was used for binary variables expressed as number (percentage). The Cox proportional hazard model was adopted to identify independent risk factors attributable to lack of efficacy causing discontinuation of GLM by using variables with a *P* value of <.05, which was determined by univariate analysis, and hazard ratio (HR) with 95% confidence interval (CI) was analyzed. The retention rate was determined using the Kaplan-Meier method and evaluated by the log-rank test. All statistical analyses were performed using the GraphPad Prism 7.03 (GraphPad Software) or JMP version 10.2 Software (SAS Institute Inc.). Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Study flowchart

Figure 1 shows the study flowchart of patient enrolment. A total of 60 patients with RA receiving GLM therapy between November 2011 and August 2020 were enrolled in this study. The median follow-up period was 48.5 (24.0-63.0) months. Among them, 28 (46.7%) patients continued GLM, whereas 24 (40.0%) discontinued GLM because of lack of efficacy attributed to 12 (20.0%) primary inadequate responses and 12 (20.0%) secondary inadequate responses. The remaining 8 (13.3%) patients withdrew GLM during the study follow-up period for the following reasons: malignancy (in total 3 patients) including 1 gastric cancer, 1 pancreatic cancer, and 1 bladder cancer; drug eruptions (2); bacterial pneumonia (1); organizing pneumonia (1); and self-withdrawal (1).

3.2 | Patients' clinical features

Table 1 summarizes the baseline clinical characteristics of patients administered GLM. The median age at GLM initiation was 66.5 years (60.0-75.0). Females dominated the included patient population (76.7%), and median disease duration was 5.3 (1.0-11.3) years. There were 75.0% and 76.7% of ACPA- and RF-positive patients, respectively. MTX was simultaneously prescribed in 58.3% of the patients, and the median dose was 8.0 (6.0-10.0) mg/wk. The frequency and median dose of PSL were 63.3% and 4.0 (2.5-5.0) mg/d, respectively. GLM was administered as the first-line bDMARD in 41.7% of the patients. The median level of CRP was 1.0 (0.2-2.9) mg/dL. The median tender joint and swollen joint counts were 2.0 (1.3-4.0) and 2.0 (1.0-4.0), respectively. There were no statistical differences in the baseline clinical features between all patients included in this study and 8 patients who discontinued GLM other than for lack of efficacy (Table S1).

3.3 | Comparison between patients who continued and who discontinued GLM due to lack of efficacy

We next assessed the differences in clinical features between patients who continued GLM and who discontinued GLM because of inadequate response to GLM (Table 1). Significantly higher number of patients in the retention group received concomitant administration of MTX than in the withdrawal group (75.0% vs 41.7%, $P = .023$). Significantly lower number of patients in the retention group had a history of bDMARDs than in the withdrawal group (35.7% vs 87.5%, $P < .001$). Although the frequency of patients who initiated GLM at 50 mg tended to be slightly higher in the retention group than in withdrawal group (78.6% vs 54.2%), no significant difference was observed ($P = .080$). Intergroup differences with respect to other features were not statistically significant. In addition, we divided 52 patients into 2 groups based on the initial dose of GLM to compare clinical features (50 mg, n = 35; 100 mg, n = 17). The history of biologic exposure and prevalence of concurrent PSL use (≥ 7.5 mg) was significantly lower in patients who initiated GLM treatment at a dose of 50 mg than in those receiving 100 mg GLM (45.7% vs 88.2%, $P = .006$; 0.0% vs 57.1%, $P < .001$) (Table S2).

3.4 | Retention rate of GLM in overall population and subgroups stratified by different factors

The drug survival of GLM in all 60 patients was 66.3%, 48.3%, and 24.5% at 12, 36, and 72 months, respectively (Figure 2A). In addition, the retention rate after excluding patients who discontinued treatment because of the lack of efficacy (n = 52) was almost similar (67.0%, 50.0%, and 44.2% at 12, 36, and 72 months, respectively) (Figure 2A). Next, we evaluated the retention rate based on different

TABLE 1 Baseline clinical characteristics of patients with rheumatoid arthritis treated with GLM

	Total (n = 60)	Retention (n = 28)	Withdrawal due to lack of efficacy (n = 24)	*P* value
Age at GLM initiation, y	66.5 (60.0-75.0)	66.5 (56.3-75.8)	67.0 (60.0-74.8)	.82
Female, n (%)	46 (76.7%)	21 (75.0%)	19 (79.2%)	.75
Disease duration, y	5.3 (1.0-11.3)	5.1 (1.3-12.7)	8.4 (1.0-13.9)	.61
ACPA, n (%)	45 (75.0%)	21 (75.0%)	17 (70.8%)	.76
RF, n (%)	46 (76.7%)	22 (78.6%)	17 (70.8%)	.54
Initiation of GLM 50 mg, n (%)	42 (70.0%)	22 (78.6%)	13 (54.2%)	.080
MTX, n (%)	35 (58.3%)	21 (75.0%)	10 (41.7%)	.023
MTX dose, mg/wk	8.0 (6.0-10.0)	8.0 (6.0-10.0)	8.0 (6.0-10.5)	>.99
PSL, n (%)	38 (63.3%)	17 (60.7%)	15 (62.5%)	>.99
PSL dose, mg/d	4.0 (2.5-5.0)	3.5 (2.3-5.0)	4.0 (3.0-5.0)	.29
PSL ≥7.5 mg, n (%)	5 (8.3%)	1 (3.6%)	3 (12.5%)	.32
History of bDMARDs administration, n (%)				
Naïve	25 (41.7%)	18 (64.3%)	3 (12.5%)	<.001
Switch	35 (58.3%)	10 (35.7%)	21 (87.5%)	
CRP, mg/dL	1.0 (0.2-2.9)	0.83 (0.2-2.3)	1.1 (0.1-6.9)	.26
Tender joint count	2.0 (1.3-4.0)	2.0 (0.3-3.8)	2.5 (2.0-4.0)	.16
Swollen joint count	2.0 (1.0-4.0)	2.0 (1.0-3.8)	2.5 (1.0-4.0)	.41

Note: Data are expressed as the median (interquartile range) or number (%).

Abbreviations: ACPA, anti-citrullinated protein antibody; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C-reactive protein; GLM, golimumab; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor.

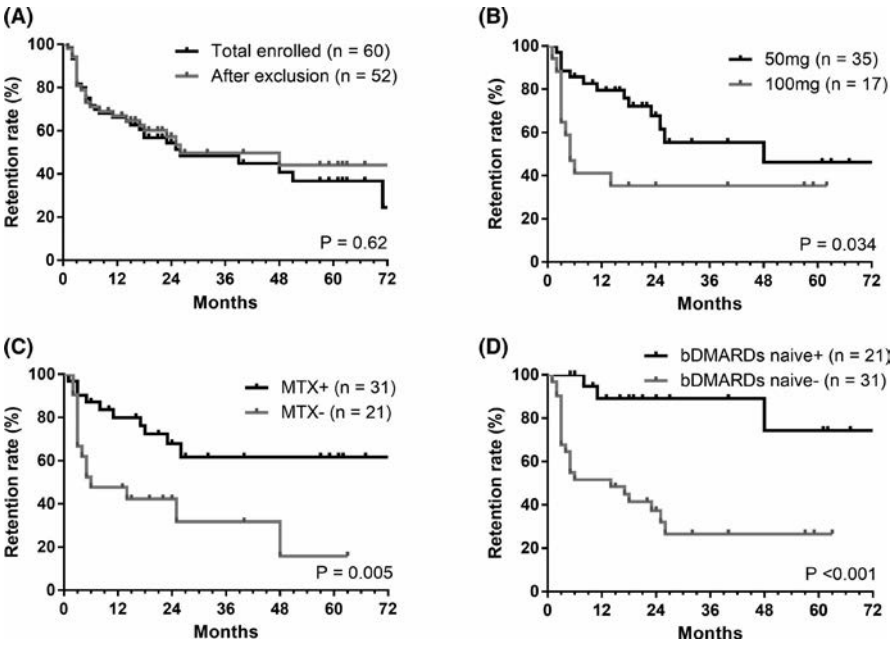

FIGURE 2 Kaplan-Meier curves of retention rate of GLM stratified by (A) all patients included in this study or those excluded who discontinued GLM except for lack of efficacy, (B) initial dose of GLM, (C) MTX co-therapy, and (D) history of biological therapy prior to GLM treatment. Log-rank test was performed to calculate *P* values. GLM, golimumab; MTX, methotrexate

clinical parameters (Figure 2B-D). Among them, the factors, including initiating GLM at a dose of 50 mg, combination MTX therapy, and no history of biologic therapy prior to GLM, were related to better drug survival. The retention rates at 12, 36, and 60 months between the 2 groups initiating either 50 mg (n = 35) or 100 mg (n = 17) were 79.5% vs 41.2%, 55.4% v. 35.3%, and 46.2% vs 35.3%, respectively (*P* =.034) (Figure 2B). Patients receiving concurrent MTX therapy showed significantly higher retention rates at 12, 36, and 60 months (80.0%, 61.7%, and 61.7%, respectively) than who did not (47.6%, 31.7%, and 15.9%, respectively; *P* =.005) (Figure 2C). The retention rates of bDMARDs naïve (n = 21) and bDMARDs-experienced groups (n = 31) were 89.2% and 51.6% at 12 months, 89.2% and 26.7% at 36 months, and 74.3% and 26.7% at 72 months, respectively, with statistically significant differences between the 2 groups (*P* <.001) (Figure 2D).

3.5 | Multivariate analysis for detecting factors associated with GLM discontinuation due to lack of efficacy

We explored independent factors determining lack of efficacy leading to discontinuation of GLM using the Cox proportional hazard model. As shown in Table 2, univariate analysis identified initiation at a dose of 50 mg GLM, MTX co-treatment, history of 1 or ≥2 bDMARDs therapy prior to GLM as significant variables. Furthermore, multivariate analysis revealed that factors associated with GLM discontinuation included a history of 1 or ≥2 biologics use. HR of treatment with one bDMARD tended to be higher than that with ≥2 bDMARDs (HR: 4.42 vs 7.49; 95% CI: 1.35-19.93 vs 1.97-36.27; *P* value: .012 vs .003), suggesting that an increasing number of previously prescribed biologics negatively impacted on effectiveness of GLM, potentially leading to reduction of retention rate.

4 | DISCUSSION

This study was conducted to evaluate 6-year drug survival of GLM (median: 48.5 months) and to determine prognostic factors for discontinuation of GLM resulting from lack of efficacy in Japanese patients with RA in a real-world setting. We first identified biological therapies prior to GLM administration as predictors for long-term retention associated with the effectiveness of GLM in Japan, along with illustrative evidence on factors related to GLM retention. The retention rate throughout the long-term period was significantly higher in patients with no prior bDMARDs use than in those administered GLM as the second-line therapy or additional therapy. Furthermore, increasing the number of previously administered biologics decreased persistence of GLM.

Retention rate is a valuable composite measure comprising drug efficacy, adverse events, tolerability, and patient preference in a real-world setting.[12] In particular, continuation of biologics for a prolonged duration is a critical issue, which is needed to produce beneficial effect against chronic inflammation resulting from an aberrant immune response in RA. Previous reports on real-world populations have indicated drug survival rates of 47.3%-69.0% at 2 years,[11,13-15,22,23] approximately 30%-60% at 3 years,[14,15,18,23] approximately 30%-40% at 4 years,[15,16,18] and 29.7% at 5 years.[18] In Japan, a multicenter registry, the ANSWER cohort, indicated the drug survival rate of GLM at 36 months as 45.4%.[24] Retention rate over 5 years in the overall population from our study was similar to these findings.

Six long-term (≥2 years) cohort studies, identified in the PubMed database, have evaluated predictive factors attributable to retention of GLM, as summarized in Table 3. In patients with RA, a good EULAR response at 3 months,[13] lower patients' visual analog scale (VAS),[14,16] seropositivity,[14] bDMARDs naïve,[17,18] which corresponded with our results, second-line GLM treatment,[18] concurrent MTX use,[17,18] female gender,[18] and overweight or obese[18] were related to better retention rates, whereas high DAS28-erythrocyte sedimentation rate,[15] glucocorticoid therapy,[15,18] and high CRP level[16] negatively affected drug persistence. Detection of these diverse factors could be greatly influenced by various differences

TABLE 2 Cox proportional hazard model for detecting factors associated with lack of efficacy leading to discontinuation of GLM

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at GLM initiation	1.00 (0.97-1.03)	.84		
Female	0.94 (0.31-2.34)	.90		
Disease duration	1.01 (0.97-1.05)	.69		
ACPA	0.91 (0.39-2.37)	.84		
RF	0.79 (0.34-2.04)	.60		
Initiation of GLM 50 mg	0.44 (0.19-0.99)	.049	0.74 (0.32-1.72)	.47
MTX use	0.34 (0.15-0.77)	.009	0.47 (0.19-1.09)	.079
MTX dose	1.04 (0.81-1.33)	.74		
PSL use	1.14 (0.51-2.72)	.75		
PSL dose	1.11 (0.94-1.25)	.20		
PSL, ≥7.5 mg	2.03 (0.32-7.08)	.39		
1 bDMARDs use	2.27 (1.02-5.28)	.046	4.42 (1.35-19.93)	.012
≥2 bDMARDs use	2.78 (1.06-6.59)	.039	7.49 (1.97-36.27)	.003
CRP	1.10 (0.99-1.20)	.057		
Tender joint count	1.16 (0.97-1.37)	.11		
Swollen joint count	1.11 (0.95-1.27)	.19		

Note: Lack of efficacy includes the primary or the secondary inadequate response to GLM.

Abbreviations: ACPA, anti-citrullinated protein antibody; bDMARDs, biological disease-modifying antirheumatic drugs; CI, confidence interval; CRP, C-reactive protein; GLM, golimumab; HR, hazard ratio; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor.

among studies, including study design, era in which investigation was conducted, clinical background, and accessibility to medical resources, thus complicating the interpretation of direct comparisons of these results.

In Japan, GLM at 100 mg has been approved for the treatment of RA when MTX is not concomitantly used. In Japanese patients with active RA despite combination treatment with MTX, GLM significantly inhibited the progression of joint damage compared to placebo, with no differences between 50 mg and 100 mg doses.[4] In another RCT, GLM monotherapy at both 50 mg and 100 mg showed almost similar improvement in clinical efficacy in Japanese patients with active RA despite treatment with DMARDs.[7] On the other hand, the dose escalation from 50 to 100 mg of GLM showed significant improvement of signs and symptoms in Japanese patients with RA,[25] suggesting GLM 100 mg was more likely to be effective than 50 mg. Nevertheless, in the current study, the retention rate associated with effectiveness of GLM in the 100 mg group was significantly lower than that in the 50 mg group (Figure 2B). As shown in Table S2, the 100 mg group comprised significantly greater number of patients with previous biologic failure or treatment with ≥7.5 mg of PSL than the 50 mg group, along with a relatively lower prevalence of concurrent use of MTX. Considering this situation advantageous to patients initiating 50 mg GLM, use of 100 mg GLM mostly in difficult-to-treat RA cases,[26] could disturb its beneficial effect, putatively resulting in insufficient response and poor retention in our study.

Previous RCTs revealed that the addition of MTX to GLM reduced the disease activity of RA, suppressed joint damage, and improved physical function compared to GLM monotherapy.[3,5] Recent cohort studies from Italy[17] and Spain[18] demonstrated concomitant MTX therapy as an independent factor for reducing the frequency of GLM discontinuation. In our study, although concomitant use of MTX has not been identified as a factor associated with lack of efficacy leading to discontinuation of GLM by multivariate analysis, 6-year retention rate was higher in patients receiving MTX than in those who did not (Figure 2C). These observations were compatible with the results from large-scale (more than 5000) post-marketing surveillance (PMS) evaluating the effectiveness and safety of GLM in Japanese patients with RA.[27] Collectively, based on the negative regulation of MTX against development of anti-drug antibodies[28] and tolerability in Japanese patients,[29] concomitant use of MTX needs to be considered with GLM unless contraindicated.

Currently, many biologics with different mechanisms of action have been approved for RA treatment. Therefore, studies focusing on the retention rate of drugs associated with its efficacy in patients with or without biologic exposure are essential in real-world clinical practice. Preceding research conducted within a few years in European countries exhibited that the previous use of bDMARDs reduced drug survival and clinical effectiveness of GLM in patients with rheumatic disorders.[17,18,23] In addition, these findings were re-confirmed by a recent systematic review based on real-world evidence that included articles published up to 2016;[30] however, few studies have addressed the long-term retention rate of GLM in Japanese patients with RA having previous biologic exposure in routine practice. In a single-center retrospective analysis, Kondo et al showed that the retention rate of GLM was 61.5% at 6 years in biologic-naïve patients and approximately 40% at 5 years in biologic-experienced patients,[19] which indicated a similar tendency as that observed in the present study (Figure 2D). Notably, our study revealed the history of biologic use as a unique factor related to GLM discontinuation due to lack of efficacy as identified by multivariate analysis (Table 2).

The effect of the number of previously used biologics influencing clinical response is another factor in routine care. According to our analysis, the higher the number of previously used biologics became, the higher the HR associated with GLM discontinuation due to lack of increased efficacy (Table 2). PMS results, as mentioned above, have shown that achievement of remission or low disease activity at 24 weeks was lower in patients receiving more than 2 biological therapies (27.87%) than in those receiving either no (56.24%) or 1 biological therapy (44.03%).[27] Additionally, further data from PMS in recent years have demonstrated that switching to GLM was effective despite the number of previously used biologics, but clinical response declined with an increasing number of prior biological therapies.[31] However, there has been limited evidence on long-term retention rates stratified by the number of prior biological therapies in routine practice. Two cohort studies demonstrated no significant difference in persistence of GLM between biologics-naïve and biologics-experienced patients at 2[11] and 5[15] years, respectively, whereas, 3 registries from European countries have reported an increase in retention rates at 2,[17] 5,[23] and 7[18] years, when GLM was used as the first-line biological therapy. Although our results are consistent with the findings of PMS[27,31] and several registries except for Japan,[17,18,23] further studies are necessary to validate these findings, particularly by including greater number of Japanese patients with longer observational periods.

This study has several limitations that need to be addressed. First, the sample size was small, and the nature of the study design was retrospective. Second, judgment of discontinuation due to inappropriate response to GLM and selection of the initial dose of GLM and patients administered with GLM were at the discretion of the attending rheumatologists based on treat-to-target approach.[2] Third, optimization of treatment strategy for each individual, such as dose escalation from 50 mg to 100 mg or shortening/adjusting intervals of administration of GLM, might have influenced the retention rate. Fourth, we used drug survival of GLM as a surrogate parameter for clinical effectiveness, in line with a previously conducted study in our institution;[21] however, in the current study, we excluded patients who discontinued GLM for reasons that were extraneous to insufficient response to GLM to minimize the involvement of confounding factors such as adverse events, tolerability, and patient preference, with an intention to reflect direct correlation between retention rate and drug effectiveness. Therefore, despite some limitations, this study precisely demonstrated clinical situations associated with long-term and sustainable effectiveness of GLM particularly in Japanese patients with

TABLE 3 Comparison between long-term cohort (≥2 years) studies evaluating factors attributable to GLM retention in patients with rheumatoid arthritis and our study

Cohort study	Nation	Duration of data collection	Reported period of drug survival, y	Sample size, n	Age, y	Disease duration, y	Combination with MTX, %	bDMARDs naïve, %	Factors related to GLM retention
Iannone F, 2017[13]	Italy	2013-2015	2	88	56[b]	8.1[b]	NA	46.6	Good EULAR response at 3 mo
Thomas K, 2018[14]	Greece	2010-2014	3	166	58.3[b]	9.9[b] (6.9[c])	67.5	45.2	Lower patient's VAS and seropositivity
Rotar, Ž, 2019[15]	Slovenia	2010-2018	5	125	58.9[c]	6.4[c]	NA	79	Lower DAS28-ESR and no GC therapy
Michelsen B, 2020[16]	Norway	2010-2017	4	163	51.2[b]	11.3[b]	69.9	39.1	Lower patient's VAS and CRP
Iannone F, 2021[17]	Italy	Since 2015	2	370	56[b]	9.3[b]	67.8	45.4	bDMARDs naïve and MTX co-therapy
Pombo-Suarez M, 2021[18]	Spain	Up to 2019	6[a]	195	57.1[b]	8.1[c]	59.1	39.2	Female, overweight or obese, MTX co-therapy, no GC therapy, and first/second-line GLM therapy
Our study	Japan	2012-2021	6	60	66.5[c]	5.1[c]	58.3	41.7	First line GLM therapy

Abbreviations: bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C-reactive protein; DAS28-ESR, Disease Activity Score of 28 joints-erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GC, glucocorticoid; GLM, golimumab; MTX, methotrexate; NA, not available; RA, rheumatoid arthritis; VAS, visual analog scale.

[a]Six-year data but not 7-year data are available for patients with RA.

[b]Mean.

[c]Median.

RA and provided useful information for guiding decisions on treatment strategies in clinical practice.

In conclusion, we investigated the long-term retention of GLM over 6 years in routine practice among a Japanese population. Furthermore, using data within an observational period (median: 48.5 months), we demonstrated that the absence of biological therapies prior to GLM decreased discontinuation due to lack of efficacy of GLM in Japanese patients with RA, leading to higher effectiveness; moreover, this is the first study to show that increasing the number of previously administered biologics decreased long-term persistence of GLM along with disclosing evidence established so far. The current study provides additional evidence on the choice of GLM as the first-line biological therapy for the management of patients with RA. These findings need to be validated in larger-scale trials in the future.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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SUPPORTING INFORMATION

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Transition readiness assessment in adolescents and young adults with rheumatic diseases: The Singapore experience

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Not applicable.

Abstract

Background: Transition from pediatric to adult care is a challenging time for adolescents and young adults (AYA) with rheumatic diseases. Validated tools have been developed to assess transition readiness.

Aim: To evaluate transition readiness among AYA with rheumatic diseases and to identify factors associated with transition readiness.

Methods: Patients ≥15 years old were enrolled into our transition program and administered a Transition Readiness Assessment Tool (TRAT) from July 2017. The TRAT consists of 3 components: (a) patient's perception on importance of transition and confidence toward transition on a Likert scale 0-10; (b) assessment of knowledge on medical and healthcare usage using a set of 23 questions; (c) transition readiness using the Transition Readiness Assessment Questionnaire (TRAQ). Differences between groups were compared to identify factors associated with transition readiness.

Results: Transition readiness assessment was performed in 152 patients. The median score for perception on transition importance was 7.0 (5.0-8.8) and the median score for confidence in transition was 7.0 (5.0-9.0). Majority of the patients (>50%) lack knowledge in health insurance, carrying health information, healthcare privacy changes and making own healthcare decision. Patients <20 years old were also deficient in knowledge in navigating healthcare systems. TRAQ scores were lowest in areas pertaining to healthcare insurance and obtaining financial help.

Conclusion: Healthcare insurance literacy and self-management skills were lacking in the assessment of transition readiness in AYA with rheumatic diseases. Targeted intervention in these areas will improve transition readiness and promote successful transition processes.

KEYWORDS
adolescents, healthcare transition, rheumatology, transition readiness assessment, young adults

1 | INTRODUCTION

The outcomes of childhood-onset rheumatic diseases have improved tremendously in the past decade with increasing use of biological and targeted therapies.[1,2] The majority of the patients with childhood-onset rheumatic diseases now live well into adulthood. However, there is still a high risk of active disease and flares. More than half of the patients with juvenile idiopathic arthritis (JIA) experience active disease in adulthood and require ongoing management of immunosuppressants,[3-5] while most patients with childhood-onset systemic lupus erythematosus (SLE) do not achieve drug-free remission.[6] It is therefore important to transit pediatric rheumatology patients to adult healthcare system to continue their care.

The transition from pediatric to adult care is often a challenging time for adolescents and young adults (AYA) with rheumatic diseases. A lack of proper transition care and support is associated with poor patient outcomes. Hersh et al described a cohort of 31 patients with chronic rheumatic diseases and showed that one-third of patients had disease flare requiring hospitalization in the year before transfer to adult care, and another one-third experienced worsening disease activity in the post-transfer year.[7] In an effort to improve the transition process and outcomes in AYA with childhood-onset rheumatic diseases, various taskforces have been set up to develop transition care guidelines. The Pediatric Rheumatology European Society (PRES)/European League Against Rheumatism (EULAR) published a set of recommendations and standards via international Delphi analysis and systemic literature review for transition care in AYA with rheumatic diseases,[8] while the American College of Rheumatology (ACR) Transition Work Group developed a subspecialty-specific toolkit tailored to pediatric and adult rheumatologists.[9]

In a survey administered to 138 physicians and allied health professionals attending the PRES Congress, 60% of the respondents cited transition readiness as an important initiating factor for transfer to adult care.[10] In 2002, the American Academy of Pediatrics, American Association of Family Physicians and American College of Physicians-American Society of Internal Medicine (ACP) jointly recommended that providers regularly assess transition readiness skills using an objective measure.[11] In line with these recommendations, various transition readiness measures have been developed, with the Transition Readiness Assessment Questionnaire (TRAQ) being one of the most robustly validated transition readiness tools.[12] Other examples include the TR(x)ANSITION Scale and AM I ON TRAC (Taking Responsibility for Adolescent/Adult Care).[13-15] While studies have been published to analyze factors influencing transition readiness in AYA with rheumatic diseases, structured transition care is still underdeveloped in Asia and data on transition readiness in this region is lacking. Therefore, it is imperative to determine factors affecting transition readiness in AYA with chronic rheumatic diseases among Asian countries.

As such, the objective of this paper is to evaluate transition readiness among AYA with rheumatic diseases in Singapore, a Southeast Asian country with multiple ethnic groups, and to identify socio-demographic, medical, patient, and parental factors associated with transition readiness.

2 | METHODS

2.1 | Patient selection and procedure

Patients who were enrolled into the Pediatric Rheumatology Transition Program (PRTP) between March 2016 to April 2020 were included in this study. PRTP is a multidisciplinary program established in KK Women's and Children's Hospital, Singapore, in March 2016. The program follows the model developed by Got Transition, a federally funded national resource center on healthcare transition in the United States. The model consists of 6 core elements: transition policy, transition planning, readiness assessment, transfer of care, tracking and monitoring of transited patients, and transfer completion.[16]

Patients on follow-up with our rheumatology clinic with chronic rheumatic diseases are enrolled into the program when they reach 15 years old and underwent education on their medical condition, medications as well as preparation for transition. Transition readiness assessment is performed at the age of 17 and older using a Transition Readiness Assessment Tool (TRAT). Patients who were already above the age of 15 when the transition program was first established were given similar transition preparation, and transition assessment was administered when the physicians deemed appropriate. This study was approved by SingHealth Institutional Review Board (CIRB2019/2274 (2009/919/E)), and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Outcome measures

The TRAT was adapted from the ACR transition toolkit and modified to our local culture and healthcare system.[16] It consists of 3 main components: (a) patient's perception on importance of transition preparation and confidence toward transition (Likert scale 0-10); (b) assessment of knowledge on medical and healthcare usage (MKHU), using a set of 23 questions; (c) transition readiness assessment, using the TRAQ. TRAQ is a validated, patient-centered questionnaire which assesses 5 domains: medicine management, appointment management, health issue tracking, communications with providers and daily activity management.[17] The questionnaire items are answered using a 5-point Likert-type scale based on the Stages of Change Model, ranging from “No, I do not need to do this” to “Yes, I always do this when I need to”.

Transition to adult healthcare system (AHCS) was initiated once patients were in clinical inactive disease state and achieved scores of ≥8 for all 3 components in TRAT. Successful transition was defined as compliance with every adult rheumatologist appointment during the first year of transition.

2.3 | Statistical analysis

All analyses were performed using SPSS, version 23.0 (IBM Corp., Armonk, NY, USA) with statistical significance set at $P < .05$. Data are described as means with SDs, or medians with interquartile range (IQR) and percentages as appropriate. Chi-square/Fisher's exact, Mann-Whitney *U*, and Kruskal-Wallis tests were applied to compare differences between groups where appropriate. Comparison was made between age groups using 20 years of age as a cutoff, and between confidence scores using score of 8 as a cutoff. These cutoffs were selected after considering the median age of transition assessment and transfer to the AHCS, as well as median confidence scores. Univariate logistic regression models were used to test the effect of potential predictors on transition readiness. Odds ratios and 95% confidence intervals were estimated from these univariate logistic regression models.

3 | RESULTS

3.1 | Demographics

A total of 184 patients (56% female, 75% Chinese) were recruited in our transition program (Table 1). Transition readiness assessment was performed in 152 patients (82.6%). The median age at first transition readiness assessment was 18.5 years (IQR 17.6-20.2) and the median age at transition was 21.6 years (IQR 19.7-22.8). JIA (47.4%) and SLE (39.5%) make up the majority of the rheumatic diseases. Of the patients who were transited to AHCS, 97.4% were successful.

TABLE 1 Characteristics of patients who received transition assessment

	n = 152
Male	68 (44.7%)
Age at onset, y[a]	12.8 (10.4 - 14.6)
Age at diagnosis, y[a]	13.4 (10.9 - 15.2)
Age at transfer to adult healthcare system	21.6 (19.7 - 22.2)
Diagnosis	
Juvenile idiopathic arthritis	72 (47.4%)
Systemic lupus erythematosus	60 (39.5%)
Connective tissue disease	5 (3.3%)
Juvenile dermatomyositis	4 (2.6%)
Others[b]	11 (7.2%)
In process of transition	113 (74.3%)
Completed transition	39 (25.7%)
Successful	38 (97.4%)

[a]Median (interquartile range), [b]mean (SD), otherwise n (%).

[b]Other conditions include: amplified pain syndrome (1), Behçet's disease (1), central nervous system vasculitis (1), Evan's syndrome (1), Henoch-Schönlein purpura with nephritis (2), linear scleroderma (1), psoriasis (1), Takayasu arteritis (1), Sjögren's syndrome (2).

3.2 | Attitude and perception

The median score for perception on transition importance was 7.0 (5.0-8.8) and the median score for confidence in transition was 7.0 (5.0-9.0). The median transition score in male patients is significantly higher than female patients ($P = .009$). Age at transition readiness assessment was not a predictor of higher perception on importance score ≥8 (OR 0.94, 95% CI 0.76-1.16) nor higher confidence score ≥8 (OR 0.84, 95% CI 0.69-1.04).

3.3 | Medical and healthcare usage knowledge

Figure 1 shows the responses for medical and healthcare usage knowledge, using a 23-item questionnaire. Of these items, the majority of the patients answered "No" to knowing how to get or keep health insurance (60.4%), carrying important health information (56.3%), understanding healthcare privacy change as an adult (50.7%) and ability to making own healthcare decisions (50.0%). There is a higher proportion of patients <20 years old who answered "No" to these 4 items compared to older patients (Table 2). In addition, patients <20 years old also lack knowledge in making own appointments (68.5% vs 90.2%, $P = .006$), places to seek medical care when clinics are closed (50.5% vs 75.6%, $P = .006$), channels to obtain referrals to other providers (51.% vs 75.6%, $P = .009$), completion of medical forms (79.3% vs 97.6%, $P = .005$) and having a record of one's own care plan (45.0% vs 65.9%, $P = .028$). In patients who scored ≥8 in confidence score, there is still a majority of patients who lack knowledge in having a plan to keep health insurance (51.4%) and carrying important health information (50.7%, Table S1).

3.4 | TRAQ scores

Figure 2 shows the responses for TRAQ. The items with the lowest proportion of patients who answered "Yes" were related to knowing health insurance coverage (29.7%), application for new health insurance (35.4%) and knowing how to get financial help with the medical social worker (49.0%). Patients <20 years old showed less readiness in knowing what to do for adverse drug reactions (63.6% vs 82.9%, $P = .023$), refilling medication before supply runs out (76.6% vs 97.6%, $P = .002$), calling for appointment (61.3% vs 85.4%, $P = .005$), following up laboratory test results or referrals (74.8% vs 92.7% $P = .013$), arranging for ride to appointment (81.1% vs 97.6%, $P = .009$), calling rheumatology nurse about unusual change in health (68.5% vs 87.8%, $P = .016$), managing money and budget expenses (50.5% vs 73.2%, $P = .012$) and getting financial help from a medical social worker (41.1% vs 70.0%, $P = .003$, Table 3). Patients who scored <8 in confidence score do not make a list of questions before doctor's visit compared to those with higher confidence score (42.3% vs 67.1%, $P = .003$), although a majority of them are still able to talk about their feelings (88.5%) and answer questions (97.4%, Table S2).

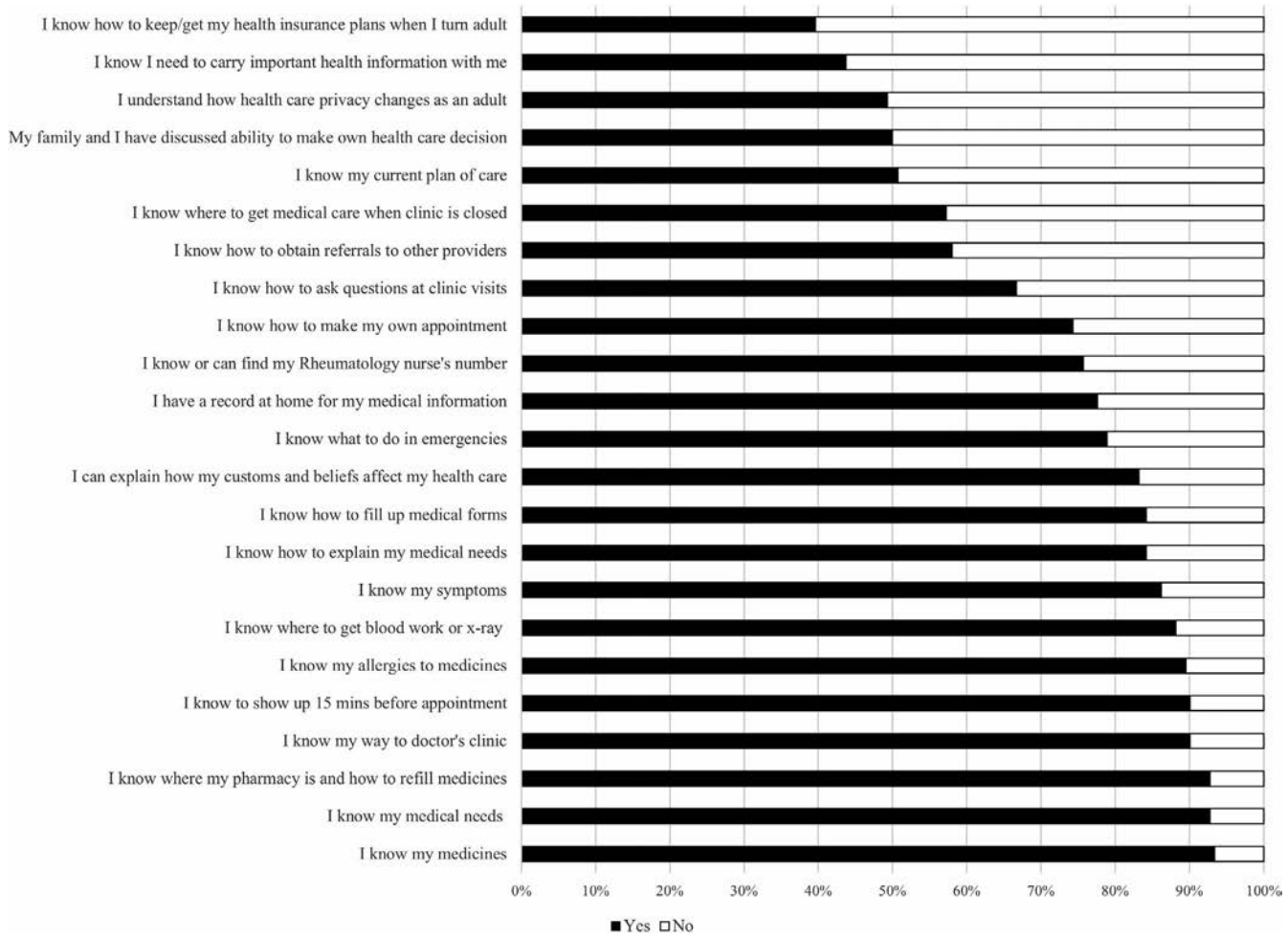

FIGURE 1 Individual health and using healthcare knowledge responses (n = 152)

4 | DISCUSSION

There has been an increasing recognition in the importance of proper transition care and this has led to implementation of structured transition programs as well as transition readiness measures in different centers.[18] Given that transition care is often influenced by local culture and healthcare systems, our study provides additional insight into factors affecting transition readiness in AYA with chronic rheumatic diseases in an Asian country.

Our study showed that most patients perceived transition preparation as important and were confident about their ability for transition to AHCS at first transition readiness assessment. Male patients exhibited more confidence in transition than female patients. Van Staa et al also reported similar finding in 954 adolescents with somatic chronic conditions (of which 10.2% were diseases of musculoskeletal system and connective tissue diseases). They also showed that self-perceived transition readiness was positively associated with older age.[19] However, this association was not found in our study. Self-perceived confidence and perception of importance were not significantly different between age groups, suggesting that transition preparation can be initiated at an earlier age even in Asian countries, in line with international guidelines that the transition process should start as early as 14 years old.[8]

Although the majority of the patients expressed self-perceived confidence for transition, there were few areas in which they lacked knowledge. Of note, most patients did not report a lack of health-related knowledge such as managing their medication, explaining their medical needs or seeking emergency treatment, as these are areas that physicians tend to focus on during routine clinic visits. However, more than half of the patients were deficient in knowledge on health insurance, carrying health information, healthcare privacy changes and making one's own healthcare decisions. In addition, younger patients were also deficient in knowledge on navigating healthcare systems (including obtaining referrals, making appointments, seeking alternative medical care when clinics are closed). Local education systems do not usually focus on health insurance and healthcare system literacy. Even though the healthcare and funding systems in Asian countries are vastly different from the West, the lack of knowledge in these areas is not unique to Asia and these are frequently cited barriers to successful transition.[20-22]

The lack of knowledge in these areas translates to decreased transition readiness. In our study, the lowest TRAQ scores for individual questionnaire items were all pertaining to healthcare insurance and

TABLE 2 Percentage of patients who answered "Yes" on individual health and using healthcare knowledge responses based on age group

Questions		<20 y (n = 111)	≥20 y (n = 41)	*P* value
Q1.	I know my medical needs	92.8	92.7	1
Q2.	I know how to explain my medical needs	82.9	87.8	.618
Q3.	I know my symptoms	84.7	90.2	.440
Q4.	I know what to do in emergencies	77.5	82.9	.511
Q5.	I know my medicines	93.7	92.7	.823
Q6.	I know my allergies to medicines	88.3	92.7	.560
Q7.	I know I need to carry important health information with me	43.6	43.9	.977
Q8.	I understand how healthcare privacy changes as an adult	44.1	63.4	.044
Q9.	I can explain how my customs and beliefs affect my health care	81.7	87.5	.467
Q10.	I know or can find my rheumatology nurse's number	73.0	82.9	.287
Q11.	I know how to make my own appointment	68.5	90.2	.006
Q12.	I know how to ask questions at clinic visits	63.6	75.0	.241
Q13.	I know my way to doctor's clinic	90.1	90.2	.977
Q14.	I know to show up 15 min before appointment	89.2	92.7	.760
Q15.	I know where to get medical care when clinic is closed	50.5	75.6	.006
Q16.	I have a record at home for my medical information	74.8	85.4	.193
Q17.	I know my current plan of care	45.0	65.9	.028
Q18.	I know how to fill up medical forms	79.3	97.6	.005
Q19.	I know how to obtain referrals to other providers	51.4	75.6	.009
Q20.	I know where my pharmacy is and how to refill medicines	91.0	97.6	.290
Q21.	I know where to get blood work or X-ray	85.6	95.1	.157
Q22.	I know how to keep/get my health insurance plans when I turn adult	33.9	55.0	.024
Q23.	My family and I have discussed ability to make own healthcare decisions	40.5	75.6	<.001

obtaining financial help. Lawson et al conducted a cross-sectional survey examining self-management skills in 52 adolescent patients with chronic rheumatic diseases.[23] The survey showed that only less than half of the patients had independent completion of tasks related to health insurance and information management. In that survey, younger patients also displayed less readiness in other self-management skills involving medication management and medical appointments. A similar finding was shown in our study with a greater proportion of patients younger than 20 years who do not manage their medications and appointments. Lazaroff et al observed that older age and high patient activation (defined as patients taking an active role in managing one's own health and health care) significantly predicted higher TRAQ scores among patients with JIA.[24] McColl et al administered a 14-item Transition-Q to 70 participants with JIA and childhood-onset SLE.[25] The Transition-Q focuses solely on self-management skills as compared to TRAQ, and their study also revealed that Transition-Q scores increased with age. In contrast, Jensen et al reported that self-management score was not associated with age.[26] The discrepancy in results may be reflective of differences seen in other chronic disease groups, as the study included patients with chronic endocrine and gastrointestinal conditions as well.

Previous literature looking at healthcare transition readiness in emerging adults with type 1 diabetes mellitus (T1DM) in South Korea has shown higher transition readiness scores on disease knowledge and medication management as compared to communication with doctors and engagement during appointments.[27] Even though Asian parents are less likely to foster independence in AYA because they perceived AYA with chronic diseases as more vulnerable,[28] our study did not show a lack in communication skills among AYA with chronic rheumatic diseases. The majority of the patients had no self-reported problems on communication with providers, even in younger patients and patients with lower confidence scores.

A recent systematic review investigating the potential association between transition readiness and both nonmodifiable (eg, demographic/ecological and disease) and modifiable (eg, psychosocial

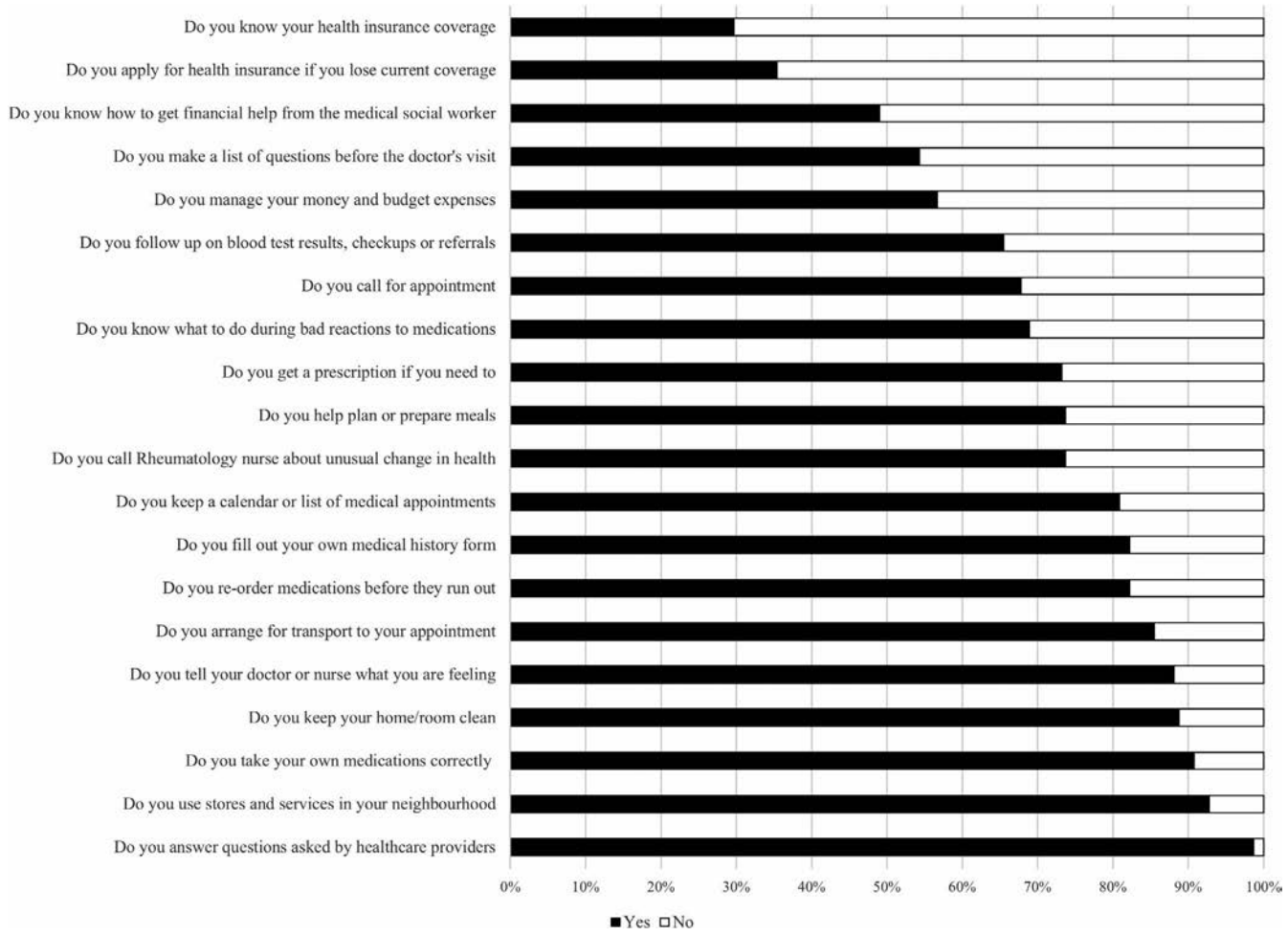

FIGURE 2 Individual TRAQ Response (n = 152)

and self-management/transition education) factors in 33 studies of youth with various chronic diseases identified older age and female gender as consistent factors associated with greater transition readiness.[29] While our study did not evaluate overall TRAQ scores and the association with age, we identified the specific domains and items in which younger patients were lacking in readiness, and this information is valuable when individualizing transition programs and targeted education. Apart from age and gender, in 2 studies that examine transition readiness in rheumatology patients, only greater health literacy consistently correlated with higher transition readiness.[24,30] A longer disease duration and having comorbid non-rheumatic conditions were other factors identified in 76 pediatric rheumatology patients that were associated with increased self-perceived autonomy (not specifically transition readiness).[30] Disease activity has not been shown to be a consistent predictive factor of transition readiness in rheumatology patients.[29,31] It will be beneficial to determine the effect of these factors on individual transition readiness domains for a more focused transition policy for certain subgroups of patients.

While TRAQ has been robustly validated even in Asian countries,[32] the other aspects of our TRAT including the 23-item MKHU assessment have not been validated. However, most studies on transition readiness do not include assessment of self-reported confidence scores as well as knowledge assessment on medical and healthcare usage. In our study, we were able to correlate deficiency in knowledge and transition readiness skillsets. To improve transition readiness, it is essential to provide targeted education and improve knowledge in deficient areas. In contrast, our study also demonstrated that younger patients and patients with lower confidence scores do not manage their own medications, despite having the knowledge to do so. This suggests that education alone may not be sufficient to equip these patients with skills to manage their medication, but patients must be encouraged to practice the refilling of prescriptions and checking of medication supplies to be familiar with these necessary skills.

4.1 | Strengths and limitations

While findings from TRAQ have been described in the literature, to our knowledge this is the first study that includes 2 other components: patient's perception on importance of transition preparation and confidence toward transition as well as assessment of knowledge on medical and healthcare usage. This allows correlation

TABLE 3 Percentage of patients who answered "Yes" on individual health Transition Readiness Assessment Questionnaire responses based on age group

Questions		<20 y (n = 111)	≥20 y (n = 41)	*P* value
Q1.	Do you get a prescription if you need to	69.7	82.5	.119
Q2.	Do you know what to do during bad reactions to medications	63.6	82.9	.023
Q3.	Do you take your own medications correctly	89.2	95.1	.354
Q4.	Do you re-order medications before they run out	76.6	97.6	.002
Q5.	Do you call for appointment	61.3	82.5	.005
Q6.	Do you follow-up on blood test results, checkups or referrals	74.8	82.9	.013
Q7.	Do you arrange for transport to your appointment	81.1	95.1	.009
Q8.	Do you call rheumatology nurse about unusual change in health	68.5	97.6	.016
Q9.	Do you apply for health insurance if you lose current coverage	31.8	82.5	.136
Q10.	Do you know your health insurance coverage	29.4	82.9	.869
Q11.	Do you manage your money and budget expenses	50.5	95.1	.012
Q12.	Do you fill out your own medical history form	81.1	85.4	.638
Q13.	Do you keep a calendar or list of medical appointments	77.5	90.2	.103
Q14.	Do you make a list of questions before the doctor's visit	50.0	65.9	.099
Q15.	Do you know how to get financial help from the medical social worker	41.1	70.0	.003
Q16.	Do you tell your doctor or nurse what you are feeling	89.2	85.0	.570
Q17.	Do you answer questions asked by healthcare providers	98.2	100.0	1.000
Q18.	Do you help plan or prepare meals	72.1	78.0	.537
Q19.	Do you keep your home/room clean	86.5	95.1	.159
Q20.	Do you use stores and services in your neighborhood	94.6	87.8	.168

of TRAQ findings to baseline knowledge and confidence level. Although our study sample size is small, it represents the majority of local pediatric patients with rheumatic diseases in Singapore since it was conducted in the largest pediatric tertiary care center and only stand-alone children's hospital in the country. Selection and referral bias was minimized as health care was accessible regardless of socioeconomic status with good support from the local government.

In our study, TRAT is only administered to patients, but current literature also acknowledged the role and impact of parents and parental readiness on health transition by incorporating parent-reported readiness.[10,33,34] The limitation of our TRAT includes the self-reported nature while there is a lack of assessment of actual mastery of skills. A study of AYA with liver transplants found that young adults (>18 years) had significantly greater self-reported healthcare self-management compared with younger adolescents, but less than half of the young adults consistently managed their healthcare independently, made their own appointments or understood health insurance issues.[35]

5 | CONCLUSION

Transition to adult care is a challenging time for AYA with lifelong chronic illnesses. Our results highlight specific domains which require more preparation prior to transition of AYA with chronic rheumatic diseases to adult care. Specifically, healthcare insurance literacy and self-management skills need to be addressed in all patients. An objective transition readiness assessment is a vital part of any structured transition program, as it allows identification of areas and skills in which individuals are lacking. Targeted and individualized intervention will improve transition readiness and ultimately lead to more successful transition care and improved health outcomes.

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CONFLICT OF INTERESTS

All authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Data collection and interpretation were performed by KLT, SFH, SWBC, XG, YXB and TA. Data analysis was done by KLT, SFH, YXB and TA. The first draft of the manuscript was written by KLT and SFH; and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CODE AVAILABILITY

Not applicable.

ETHICS APPROVAL

The SingHealth Centralised Institutional Review Board (CIRB) approved this study and waived the need for informed consent for this database study (CIRB 2019/2274).

DATA AVAILABILITY STATEMENT

Not applicable.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: A single-center study

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Abstract

Objective: Considering the concerns regarding the coronavirus disease-2019 (COVID-19) vaccine safety among pediatric patients with inflammatory rheumatic diseases (IRD) due to a lack of data, an urgent need for studies evaluating safety profiles of vaccines emerged.

Methods: Among participants vaccinated by CoronaVac inactive SARS-CoV-2 or BNT162b2 messenger RNA (mRNA) COVID-19 (Pfizer-BioNTech) vaccine, healthy children under 18 and patients under 21 with an at least 1-year follow-up period in our department for a childhood-onset rheumatic disease were included into this cross-sectional study.

Results: Overall, 246 subjects (141 [57.3%] females) (biologic group: 43, non-biologic group: 180, healthy control group: 23) were eligible for the study. The median age was 15.34 (12.02-20.92) years. The most common adverse events were fatigue (n = 68, 27.6%), headache (n = 44, 17.9%), myalgia (n = 38, 15.4%), arthralgia (n = 38, 15.4%), and fever (n = 35, 14.2%). Only 3 subjects (2 patients with familial Mediterranean fever, and one healthy child) were considered to experienced serious adverse events, since they required hospitalization. Local reactions were seen in 20 (8.13%), and 27 patients (12.1%) had disease flares within 1 month after the vaccines. Although it was significantly higher in those who received the BNT162b2 mRNA vaccine ($P < .001$), there was no significant relationship between adverse event frequency and age, gender, the existing diseases, ongoing treatment regimens and pre-vaccination COVID-19 histories.

Conclusion: Although immunogenicity studies for efficacy of the vaccines and long-term follow-up studies for adverse events monitoring are required, our study indicates an acceptable safety profile of COVID-19 vaccines and encourages children with IRD to be vaccinated.

KEYWORDS
COVID-19, pediatrics, rheumatology, SARS-CoV-2, vaccines

1 | INTRODUCTION

For almost 2 years, our planet has been suffering from coronavirus disease-2019 (COVID-19) caused by a novel coronavirus named severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2). Although scientists worldwide are mainly focused on the pandemic, there is still no available therapeutic option that may provide sufficient cure, and COVID-19 remains a significant global health concern. Thus, preventive strategies such as face masks, social distancing, personal hygiene, and vaccination come into prominence. Recently, several studies have shown newly developed vaccines to be effective and safe tools for the fight against COVID-19.[1,2]

In the early days of the pandemic, children were considered to have an asymptomatic or a mild COVID-19 disease course in contrast to adults.[3] However, a growing number of pediatric cases with multi-system inflammatory syndrome in children (MIS-C) caused by SARS-CoV-2 have been described with devastating consequences such as intensive care unit admission or even death.[4,5] Therefore, vaccination strategies are needed to be well-established for children, as well as for adults.

There is a vulnerable group such as immunocompromised patients among the pediatric population that merits to be prioritized for the vaccination. Patients with inflammatory rheumatic diseases (IRD) are considered to be in this group, due to their immune-disturbed conditions caused by their medications and chronic inflammatory states. However, it is still debated whether IRD increases the risk of severe COVID-19 due to conflicting findings of current studies.[6-11]

Although patients with IRD and those under immunosuppressive treatment were mainly excluded from the clinical trials of recent vaccines, they were widely vaccinated.[12] Since they may be at increased risk of worse outcomes from vaccine-preventable diseases, and due to limited source of vaccines in most of the developing countries, they were considered to be a prioritized group by authorities.[13,14] Yet there is no sufficient safety data, particularly for the vaccination of children with IRD.

There are 2 different kinds of COVID-19 vaccines, CoronaVac inactive SARS-CoV-2 and BNT162b2 messenger RNA (mRNA) COVID-19 (Pfizer-BioNTech), which are currently available in our country. Considering the concerns regarding COVID-19 vaccine safety among pediatric patients with IRD due to a lack of data, an urgent need for studies evaluating safety profiles of vaccines emerged. We designed this cross-sectional study to examine the vaccine-related adverse events among this group of patients.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

In our country, in January 2021, healthcare professionals, and in February 2021, patients with chronic health conditions, those older than 18, were started to be vaccinated by 2 doses of CoronaVac inactive SARS-CoV-2 with a 1-month interval. Afterward, the third dose was allowed for both groups in July 2021. Citizens were able to choose their vaccine type, as CoronaVac inactive SARS-CoV-2 or BNT162b2 mRNA COVID-19 (Pfizer-BioNTech). Finally, the fourth dose was approved for both groups in August 2021. Again, individuals were free to prefer their vaccine type.

In mid-August 2021, CoronaVac inactive SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccines started being administered to children older than 12 with chronic medical conditions and healthy children older than 15 in our country. Then, at the beginning of September 2021, vaccine administration against the novel coronavirus was launched for all children under 12, regardless of their underlying disease.

We conducted a web-based survey in mid-September 2021. Questionnaires regarding the data of the rheumatic diseases, COVID-19 vaccination status, disease flares within 1 month after the vaccines, and experienced adverse events (due to vaccines) of the participants were prepared in Google Forms and circulated through several social media platforms.

Healthy children under 18 and patients under 21 with an at least 1-year follow-up period in our department for a childhood-onset rheumatic disease were included in the study. While data of the rheumatic patients were verified by their medical records, data of COVID-19 vaccination status and experienced adverse events of the participants were verified by phone calls and national registries. Subjects whose data could not be verified by phone calls, registries or medical records were excluded from the study due to a lack of data.

Redness, warmth, regional pain, and tenderness at the injection site due to COVID-19 vaccines were considered as local reactions. While permanent disabilities, hospitalization or an extended hospital stay (if vaccinated while in the hospital), life-threatening illness, birth defects (congenital anomalies), and death were considered severe adverse events, the rest of the adverse events were considered non-severe adverse events, based on the recommendations of Vaccine Adverse Event Reporting System (VAERS) which is co-managed by the Centers for Disease Control and Prevention and the US Food and Drug Administration.[15]

Subjects were categorized into 3 different groups. Children with no underlying disease were considered the healthy control group. While rheumatic patients who were receiving at least one of the biologic agents such as etanercept, infliximab, adalimumab, anakinra, canakinumab, tocilizumab, and rituximab during their vaccination periods were considered the biologic group, the rest of the rheumatic patients were considered the non-biologic group.

The institutional ethics committee of our center approved the study protocol (03/09/21-29430533-903.99-175245). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. At least one of the family members of all the participants provided informed consent.

2.2 | Statistical analysis

The statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc). Categorical variables were expressed as numbers (percentages). Ages of the patients were given as median

(minimum-maximum), based on their distribution which was measured by using the Kolmogorov-Smirnov test. Categorical variables were compared by using Chi-square test or Fisher's exact test, when available. Ages of the patients were compared using the Mann-Whitney *U* or Kruskal-Wallis test, when appropriate. Statistical significance was defined as $P < .05$. Prism software (Prism 8, GraphPad Software) was used to analyze and graph data.

3 | RESULTS

3.1 | Study population

Following the link of our web-based survey that was shared on our clinic's online social media platforms, 466 participants fulfilled the questions. Those who stated that they were not vaccinated (n = 181) were not included in the study. Among those who stated they were vaccinated, those who could not be reached by phone (n = 19), whose follow-up period was <1 year (n = 8) and whose data could not be verified via the national registries, medical records of our department or phone calls (n = 12) were excluded.

Finally, 246 subjects (141 females) were eligible for the study. The median age was 15.34 (12.02-20.92) years. Twenty-three participants whose parents stated in the survey that they did not have any chronic diseases, and whose medical records were checked and confirmed by phone calls that they did not have any underlying disease or long-term medication were considered the healthy control (HC) group.

In the study group there were 126 patients with autoinflammatory diseases (AID) (familial Mediterranean fever [FMF], 123; cryopyrin-associated periodic syndrome [CAPS], 2; Blau syndrome [BS]), 54 patients with juvenile idiopathic arthritis (JIA) (oligoarticular JIA [oJIA], 43; juvenile spondylarthritis [jSPA], 8; polyarticular JIA [pJIA]), 30 patients with connective tissue disease (CTD) (systemic lupus erythematosus [SLE], 16; dermatomyositis [DM], 10; scleroderma, 3; Sjögren's syndrome, 1), 9 patients with vasculitis (Behçet's disease [BD], 2; deficiency of adenosine deaminase 2 [DADA2], 2; Takayasu arteritis [TA], 2; granulomatous polyangiitis [GPA], 1; Henoch-Schönlein purpura [HSP], 2; Kawasaki disease [KD]) and 4 patients with acute rheumatic fever (ARF) (Table 1).

During their vaccination periods, 128 patients were receiving colchicine (FMF, 123; CAPS, 2; BD, 2; DADA2, 1); 49 conventional disease-modifying antirheumatic drugs (cDMARDs) (methotrexate [MTX], 22 [JIA, 12; DM, 7; scleroderma, 2; SLE, 1]; hydroxychloroquine [HCQ], 21 [SLE, 16; DM, 3; Sjögren, 1; scleroderma, 1]; leflunomide, 10 [JIA; 9; SLE, 1]; mycophenolate mofetil [MMF]; 6 [SLE, 3; scleroderma, 2; DM, 1]; cyclosporine; 3 [DM; 3]; cyclophosphamide, 1 [SLE; 1]), 43 biologic disease-modifying antirheumatic drugs (bDMARDs) (etanercept, 16 [JIA, 12; DM, 2; DADA2, 2]; adalimumab, 10 [JIA, 10]; canakinumab, 8 [FMF, 7; CAPS, 1]; tocilizumab, 6 [JIA; 2; TA, 2; scleroderma, 2]; anakinra, 2 [FMF, 1; CAPS, 1]; rituximab, 1 [SLE, 1]); 21 systemic steroids (JIA, 10; SLE, 6; DM, 2; DADA2, 1; BD, 1; scleroderma, 1); and 6 patients were receiving acetyl-salicylic acid (SLE, 5; DADA2, 1) (Table 1). Four patients with ARF were under penicillin prophylaxis. Twenty-two patients with IRD excluding the ARF were in remission, and they were not receiving any treatment except non-steroidal anti-inflammatory drugs.

Before their vaccinations, 44 subjects recovered from COVID-19 (FMF, 18; JIA, 9; HC, 7; SLE, 5; ARF, 3; DM, 1; GPA, 1) (Table 1). While 4 of the recovered ones (HC, 2; JIA, 1; SLE, 1) had asymptomatic infection, the rest had mild COVID-19 symptoms. None of them had a severe clinical course.

While 214 subjects received BNT162b2 mRNA vaccine (FMF, 106; JIA, 49; HC, 19; SLE, 14; DM, 10; ARF, 4; CAPS, 2; scleroderma, 2; KD, 1; HSP, 1; BD, 1; DADA2, 1; Sjögren, 1; TA, 1; GPA, 1; BS, 1), 28 received inactivated SARS-CoV-2 vaccine (FMF, 16; JIA, 5; HC, 3; SLE, 2; DADA2, 1; scleroderma, 1), and 4 received both (FMF, 1; BD, 1; TA, 1; HC, 1) (Table 1).

Out of 246 subjects, 145 received a single dose of BNT162b2 mRNA vaccine, 19 received a single dose of inactivated SARS-CoV-2 vaccine, 69 received double doses of BNT162b2 mRNA vaccine, 8 received double doses of inactivated SARS-CoV-2 vaccine, 3 received double doses of inactivated SARS-CoV-2 vaccine plus a single dose of BNT162b2 mRNA vaccine, 1 received double doses of inactivated SARS-CoV-2 vaccine plus double doses of BNT162b2 mRNA vaccine, and 1 received 3 doses of inactivated SARS-CoV-2 vaccine.

3.2 | Adverse events

COVID-19 vaccine-related adverse events reported by the participants and their families were as follows: fatigue (n = 68, 27.6%), headache (n = 44, 17.9%), myalgia (n = 38, 15.4%), arthralgia (n = 38, 15.4%), fever (n = 35, 14.2%), nausea-vomiting (n = 19, 7.7%), diarrhea (n = 16, 6.5%), anorexia (n = 16, 6.5%), chest pain (n = 14, 5.7%), abdominal pain (n = 11, 4.5%), rhinorrhea (n = 8, 3.3%), arthritis (n = 8, 3.3%), cough (n = 8, 3.3%), dyspnea (n = 6, 2.4%), throat ache (n = 5, 2%), rash (n = 3, 1.2%), anosmia (n = 2, 0.8%), hypertension (n = 1, 0.4%), and hypotension (n = 1, 0.4%) (Figure 1).

Three subjects were considered to have severe adverse events, since they required hospitalization and additional treatment: 20.2 years-aged female patient with FMF who developed hypertension (2 weeks remained) after the second dose of BNT162b2 mRNA vaccine; 12.1 years-aged female with no underlying disease who experienced severe rash after the first dose of BNT162b2 mRNA vaccine; and 13.7 years-aged male patient with FMF who developed pre-syncope due to hypotension after the first dose of BNT162b2 mRNA vaccine.

All the adverse events but hypertension recovered in THE first 4 days. There was no adverse event after the administration of the second dose of CoronaVac inactive SARS-CoV-2 vaccine. Adverse event frequencies according to days and vaccine doses are given in Figure 2. Local reactions after the vaccines were seen in 20 subjects (JIA, 8; FMF, 7; HC, 3; DM, 1; BS, 1). Local reaction frequencies according to vaccine doses are also given in Figure 2.

Twenty-seven patients experienced disease flare within 1 month after the vaccination (after the first dose of BNT162b2 mRNA

TABLE 1 Baseline characteristics of the study population

	Healthy controls (n = 23)	Patients with AID (n = 126)	Patients with JIA (n = 54)	Patients with CTD (n = 30)	Patients with vasculitis (n = 9)	Patients with ARF (n = 4)
Age, y (median, min-max)	15.67 (12.04-19.94)	15.09 (12.06-20.72)	15.41 (12.06-20.64)	16.89 (12.49-20.64)	15.58 (12.02-20.92)	15.42 (13.71-18.1)
Gender						
Female, n (%)	10 (43.5%)	68 (54%)	35 (64.8%)	19 (63.3%)	6 (66.7%)	3 (75%)
Male, n (%)	13 (56.5%)	58 (46%)	19 (35.2%)	11 (36.7%)	3 (33.3%)	1 (25%)
Diagnoses (n)	-	FMF (123) CAPS (2) BS (1)	oJIA (43) jSPA (8) pJIA (3)	SLE (16) DM (10) Scleroderma (3) Sjögren (1)	BD (2) DADA2 (2) TA (2) GPA (1) HSP (1) KD (1)	-
Ongoing treatments						
Colchicine, n (%)	-	125 (99.2%)	-	-	3 (33.3%)	-
Steroid, n (%)	-	-	10 (18.5%)	9 (30%)	2 (22.2%)	-
ASA, n (%)	-	-	-	5 (16.7%)	1 (11.1%)	-
bDMARDs						
Anakinra, n (%)	-	2 (1.6%)	-	-	-	-
Canakinumab (n, %)	-	8 (6.3%)	-	-	-	-
Tocilizumab, n (%)	-	-	2 (3.7%)	2 (6.7%)	2 (22.2%)	-
Etanercept, n (%)	-	-	12 (22.2%)	2 (6.7%)	2 (22.2%)	-
Adalimumab, n (%)	-	-	10 (18.5%)	-	-	-
Rituximab, n (%)	-	-	-	1 (3.3%)	-	-
cDMARDs						
MTX, n (%)	-	-	12 (22.2%)	10 (33.3%)	-	-
Leflunomide, n (%)	-	-	9 (16.7%)	1 (3.3%)	-	-
Cyclosporine, n (%)	-	-	-	3 (10%)	-	-
Cyclophosphamide, n (%)	-	-	-	1 (3.3%)	-	-
HCQ, n (%)	-	-	-	21 (70%)	-	-
MMF, n (%)	-	-	-	6 (20%)	-	-
COVID-19 history before vaccination, n (%)	7 (30.4%)	18 (14.1%)	9 (17.3%)	6 (20%)	1 (11.1%)	3 (75%)
Vaccination info						
Vaccination type						
mRNA, n (%)	19 (82.6%)	109 (86.5%)	49 (90.7%)	27 (90%)	6 (66.7%)	4 (100%)

TABLE 1 (Continued)

	Healthy controls (n = 23)	Patients with AID (n = 126)	Patients with JIA (n = 54)	Patients with CTD (n = 30)	Patients with vasculitis (n = 9)	Patients with ARF (n = 4)
Inactive, n (%)	3 (13%)	16 (12.7%)	5 (9.3%)	3 (10%)	1 (11.1%)	-
Mix, n (%)	1 (4.3%)	1 (0.8%)	-	-	2 (22.2%)	-
Adverse events						
None, n (%)	12 (52.2%)	68 (54%)	33 (61.1%)	21 (70%)	3 (33.3%)	2 (50%)
Non-severe, n (%)	10 (435%)	56 (44.4%)	21 (38.9%)	9 (30%)	6 (66.7%)	2 (50%)
Severe, n (%)	1 (4.3%)	2 (1.6%)	-	-	-	-
Local reactions, n (%)	3 (13%)	8 (6.3%)	8 (14.8%)	1 (3.3%)	-	-
Disease flare within 1 month						
Yes, n (%)	-	15 (11.9%)	10 (18.5%)	2 (6.7%)	-	-
No, n (%)	-	111 (88.1%)	44 (81.5%)	28 (93.3%)	9 (100%)	4 (100%)

Abbreviations: AID, autoinflammatory diseases; ARF, acute rheumatic fever; ASA, acetylsalicylic acid; BD, Behçet disease; bDMARDs, biologic disease-modifying antirheumatic drugs; BS, Blau syndrome; CAPS, cryopyrin-associated periodic syndromes; cDMARDs, conventional disease-modifying antirheumatic drugs; CTD, connective tissue disease; DADA2, deficiency of adenosine deaminase 2; DM, dermatomyositis; FMF, familial Mediterranean fever; GPA, granulomatous polyangiitis; HCQ, hydroxychloroquine; HSP, Henoch-Schönlein purpura; JIA, juvenile idiopathic arthritis; jSPA, juvenile spondylarthritis; KD, Kawasaki disease; MMF, mycophenolate mofetil; MTX, methotrexate; oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TA, Takayasu arteritis.

vaccine, 17; after the second dose of BNT162b2 mRNA vaccine, 7; after the first dose of CoronaVac inactive SARS-CoV-2 vaccine, 3) (FMF, 15; JIA, 10; SLE, 2). Among those who experienced disease flare, all patients with FMF presented with typical attacks (fever, abdominal pain, chest pain, and/or arthralgia), and all JIA patients developed new-onset arthritis. In addition to increased inflammatory markers, 1 of 2 patients with SLE had cutaneous involvement, and bicytopenia was seen in the other.

3.3 | Comparison of the participant groups

There were no significant differences between the HC group, biological group and non-biological group in terms of age, gender, vaccine types, and frequencies of pre-vaccination COVID-19 histories, local reactions and adverse events. Moreover, the frequency of disease flares within 1 month after vaccines was not different between the biological group and the non-biological group. Detailed data Are given in Table 2.

3.4 | Assessment of the risk factors for vaccine-related adverse events

There was no significant relationship between adverse event frequency and age, gender, the existing diseases, ongoing treatments (except acetylsalicylic acid [ASA]) and pre-vaccination COVID-19 histories. While the adverse event frequency was significantly lower in those who were receiving ASA during their vaccination period ($P = .037$), it was significantly higher in those who received the BNT162b2 mRNA vaccine ($P < .001$). Detailed data were given in Table 3.

4 | DISCUSSION

Out of 246 participants, 107 (43.5%) experienced COVID-19 vaccine-related adverse events in this study. Adverse events were seen after vaccine administration in 100 of 218 mRNA vaccines and 7 of 32 inactive vaccines. Since they required hospitalization, 2 patients with FMF under colchicine treatment and a healthy child were considered to have severe adverse events, and the remaining 104 were non-severe. All 3 occurred due to mRNA vaccines, and none of those with severe adverse events were under bDMARDs or cDMARDs treatment.

There was no significant differences between HC, non-biologic, and biologic groups with regard to the frequencies of vaccine-related adverse events and local reactions. However, the non-biologic group in the study was highly heterogeneous because it included patients in remission and patients receiving therapies that potentially alter the vaccine responses due to their B cell depletion effects, such as CYC or MMF.[16-18] Thus, sub-analyses were not possible in this study due to low number of patients.

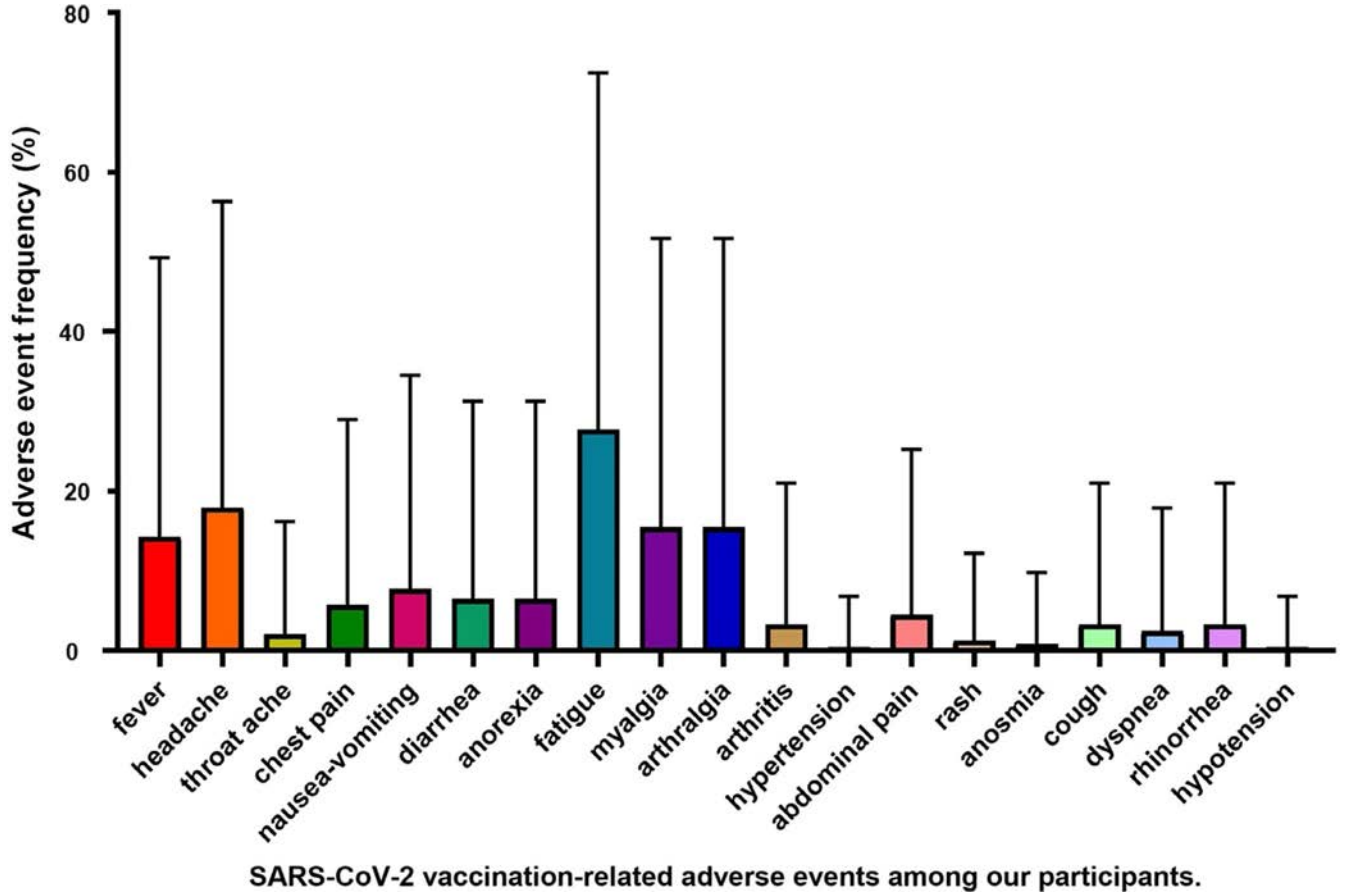

FIGURE 1 SARS-CoV-2 vaccination-related adverse events among our participants

While adverse events were significantly more common among the subjects who received the mRNA vaccine than those who received the inactive vaccine, there was no significant impact of age, gender, the existing diseases, ongoing treatments including DMARDs, and pre-vaccination COVID-19 histories on the adverse event frequency. The most common adverse events were fatigue, headache, myalgia, arthralgia, and fever, respectively. Local reactions were seen in 20 (8.13%) participants. Consistent with our findings, fatigue, headache, and muscle or joint pain were the most common vaccine-related systemic symptoms in the studies that enrolled adult patients with IRD.[19,20] Similarly, to the original phase 3 trial of the BNT162b2 COVID-19 mRNA vaccine, local pain in the injection site, fatigue and headache were the most common adverse events in a study that involved healthy adults and adult patients with SLE and rheumatoid arthritis. While reactogenicity was more frequent in the patient group, adverse events were not more severe than in the control group.[21]

Out of 27 (11%) patients who had disease flare within a 1-month period after the vaccines, those with JIA and MCTD required treatment modification, unlike 15 patients with FMF. Moreover, disease flare frequency was not different between biologic and non-biologic groups. Among the studies conducted in adult patients with IRD, while disease flare rate was 13.4% in the COVID-19 Global Alliance of Rheumatology Vaccine Study, it was reported as 5% in a study supported by the European League Against Rheumatism COVID-19 Vaccine Registry.[19,22] For accurate data regarding the disease flares, studies involving disease activity scores in all age groups are required.

Frequencies of local and systemic reactions caused by BNT162b2 COVID-19 mRNA vaccines were noted as 74% and 19%, respectively, in a recent study that involved 21 adolescents with JIA aged 16-21 years under anti-tumor necrosis factor (anti-TNF) treatment. Disease flares or serious adverse events were seen in none of the subjects. Although this study had a limited count of patients, it provided the first data on the vaccination of adolescent with IRD.[23] In our cohort, adverse events were seen in 10 of 26 patients under anti-TNF treatment and 21 of 54 patients with JIA, and similarly, none of them were serious.

In a phase 4 trial that evaluated immunogenicity and safety of the CoronaVac inactivated vaccine in adult patients with IRD, the most common systemic reactions were somnolence, headache, fatigue, and arthralgia, and none of them were moderate or severe. Systemic reaction frequencies after the first and second dose of the vaccine were 43.3%, and 33.4%, respectively.[24] Apart from local reactions, adverse events such as diarrhea, myalgia, arthritis, anosmia, anorexia, abdominal pain, rash, chest pain, and headache were seen in 7 of 32 CoronaVac inactivated vaccine administrations in our study. None of them remained for more than 2 days, and none of them were seen after the second dose. Consistent with the

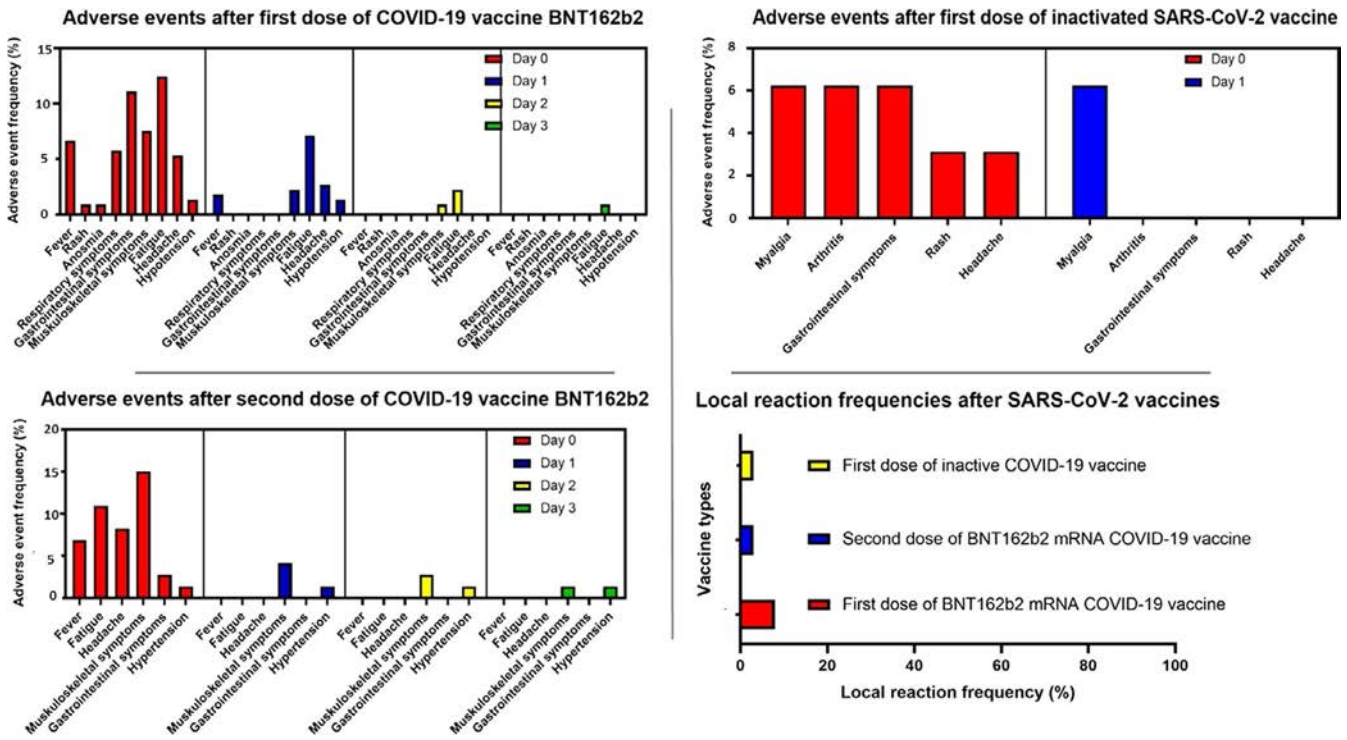

FIGURE 2 Adverse event frequencies according to days and vaccine types

TABLE 2 Comparison between the characteristics of healthy children, biologic group, and non-biologic group

	Healthy control group (n = 23)	Non-biologic group (n = 180)	Biologic group (n = 43)	*P*
Age, y (median, min-max)	15.67 (12.04-19.94)	15.14 (12.02-20.72)	16.09 (12.19-20.92)	.124
Gender				
Female, n (%)	10 (43.5%)	106 (58.9%)	25 (58.1%)	.369
Male, n (%)	13 (56.5%)	74 (41.1%)	18 (41.9%)	
Pre-vaccination COVID-19 history				
Yes, n (%)	7 (30.4%)	28 (15.6%)	9 (20.9%)	.182
No, n (%)	16 (69.6%)	152 (84.4%)	34 (79.1%)	
Vaccination type				
mRNA, n (%)	19 (82.6%)	160 (88.9%)	35 (81.4%)	.301
Inactive, n (%)	3 (13.0%)	18 (10.0%)	7 (16.3%)	
Mix, n (%)	1 (4.3%)	2 (1.1%)	1 (2.3%)	
Local reaction				
Yes, n (%)	3 (13.0%)	14 (7.8%)	3 (7.0%)	.581
No, n (%)	20 (87.0%)	166 (92.2%)	40 (93.0%)	
Disease flare within 1 month[a]				
Yes, n (%)	-	21 (11.7%)	6 (14.0%)	.680
No, n (%)	-	159 (88.3%)	37 (86.0%)	
Adverse events				
None, n (%)	12 (52.2%)	101 (56.1%)	26 (60.5%)	.579
Non-severe, n (%)	10 (43.5%)	77 (42.8%)	17 (39.5%)	
Severe, n (%)	1 (4.3%)	2 (1.1%)	0 (0.0%)	

[a]Healthy control group was not included into this analysis.

TABLE 3 Comparison of the patients with and without COVID-19 vaccine-related adverse events according to the baseline characteristics

	Adverse events		
	Yes (n = 107)	No (n = 139)	*P*
Age, y (median, min-max)	15.55 (12.02-20.92)	15.11 (12.18-20.72)	.376
Gender			
Female, n (%)	65 (60.7%)	76 (54.7%)	.340
Male, n (%)	42 (39.3%)	63 (45.3%)	
Disease			
Healthy control, n (%)	11 (10.3%)	12 (8.6%)	.323
Patients with AID, n (%)	58 (54.2%)	68 (48.9%)	
FMF, n	57	66	
CAPS, n	1	1	
BS, n	-	1	
Patients with JIA, n (%)	21 (19.6%)	33 (23.7%)	
oJIA, n	15	28	
jSPA, n	4	4	
pJIA, n	2	1	
Patients with CTD, n (%)	9 (8.4%)	21 (15.1%)	
SLE, n	4	12	
DM, n	4	6	
Scleroderma, n	1	2	
Sjögren, n	-	1	
Patients with vasculitis, n (%)	6 (5.6%)	3 (2.2%)	
BD, n	2	-	
DADA2, n	1	1	
TA, n	1	1	
GPA, n	1	-	
HSP, n	-	1	
KD, n	1	-	
Patients with ARF, n (%)	2 (1.9%)	2 (1.4%)	
Presence of a rheumatic disease, n (%)	96 (89.7%)	127 (%91.4)	.827
Ongoing treatments			
Colchicine, n (%)	60 (56.1%)	68 (48.9%)	.266
Steroid, n (%)	10 (9.3%)	11 (7.9%)	.819
ASA, n (%)	0 (0.0%)	6 (4.3%)	**.037**
bDMARDs, n (%)	17 (15.9%)	26 (18.7%)	.684
Anakinra, n	-	2	
Canakinumab, n	4	4	
Tocilizumab, n	3	3	
Etanercept, n	5	11	
Adalimumab, n	5	5	
Rituximab, n	-	1	
cDMARDs, n (%)[a]	18	31	
MTX, n	11	11	
Leflunomide, n	3	7	

TABLE 3 (Continued)

	Adverse events		
	Yes (n = 107)	No (n = 139)	*P*
Cyclosporine, n	3	-	
Cyclophosphamide, n	1	-	
HCQ, n	5	16	
MMF, n	3	3	
COVID-19 history before vaccination, n (%)			
Yes, n (%)	19 (17.8%)	25 (%18)	1
No, n (%)	88 (82.2%)	114 (%82)	
Vaccination type[b]			
mRNA, n	100	118	<.001
Inactive, n	7	25	

Abbreviations: AIDs, autoinflammatory diseases; ARF, acute rheumatic fever; ASA, acetylsalicylic acid; BD, Behçet disease; bDMARDs, biologic disease-modifying antirheumatic drugs; BS, Blau syndrome; CAPS, cryopyrin-associated periodic syndromes; cDMARDs, conventional disease-modifying antirheumatic drugs; CTD, connective tissue disease; DADA2, Deficiency of Adenosine Deaminase 2; DM, dermatomyositis; FMF, familial Mediterranean fever; GPA, granulomatous polyangiitis; HCQ, hydroxychloroquine; HSP, Henoch-Schönlein purpura; JIA, juvenile idiopathic arthritis; jSPA, juvenile spondylarthritis; KD, Kawasaki disease; MMF, mycophenolate mofetil; MTX, methotrexate; oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TA, Takayasu arteritis.

[a]Total of cDMARDs rows are not equal to cDMARDs columns due to several patients being under poly-cDMARDs treatment.

[b]Four patients received both vaccination types; 3 experienced adverse events after mRNA vaccination, and 1 did not experience any adverse events.

previously mentioned phase 4 trial, none of them were considered serious. Although inactive vaccines are generally safe, there are concerns regarding the sufficient immunogenicity in patients with IRD, based on current findings.[25]

In order to achieve sufficient immunogenicity, although not contraindicated, the American College of Rheumatology (ACR) currently recommended withholding MTX, MMF and cyclophosphamide for 1-2 weeks following each COVID-19 dose in patients with well-controlled disease. This approach is mainly based on data from previous studies conducted with other vaccines, such as influenza and pneumococci.[14] However, findings of a recent study do not support temporarily cessation of MTX during vaccination in terms of seropositivity.[26] Due to the lack of data in the first days of the mass vaccination schedules and the concerns of the families regarding the disease activities, none of our patients discontinued their medication during the vaccination process. Adverse events per vaccine administration rates of the patients under treatment with MTX, MMF and cyclophosphamide were 11/22, 3/6, and 1/1, respectively. Although there was no safety issue in these patients because none of the adverse events were severe, further studies evaluating acceptable immunogenicity by measuring antibody levels are required.

Due to its B cell depletion effect, rituximab is another medical option that was recommended to be stopped during vaccination in the current ACR guidelines. It was proposed that, if the disease activities allow, the next rituximab cycle for patients must be delayed to 2-4 weeks after the final vaccine dose, to achieve acceptable antibody levels.[14] A recent study verified these suggestions by showing significantly impaired immunogenicity in patients receiving rituximab.[26] However, since both T cells and B cells have a pivotal role in the fight against SARS-CoV-2, it remains unclear whether vaccines may protect patients with an impaired humoral response.[27,28] Moreover, rituximab was shown to be significantly associated with severe COVID-19 disease course.[29]

In our cohort, there was only one patient under rituximab treatment during the vaccination period. He was a 16-year-old partially controlled SLE patient. In addition to rituximab, he was receiving MMF and HCQ. He had a COVID-19 infection history with mild to moderate symptoms before the vaccination. Therefore, he and his family had enormous concerns regarding re-infection with severe symptoms. He was vaccinated by double dose of CoronaVac inactivated vaccine based on his choice, and neither disease flares nor any adverse events were seen. Although he received his regular rituximab schedule with 1-month delay in line with current recommendations, we planned to examine him in terms of immunogenicity.

Vaccine hesitancy rapidly raised due to growing number of cases who developed vaccine-related severe or permanent adverse events such as myocarditis, hypertension, acute respiratory failure, septic shock, sudden hearing loss, and thromboembolic events.[30-33] Therefore, studies like ours that present a well-documented safety profile even in patients with IRD as a vulnerable group may ameliorate the concerns.

There are notable limitations in our study. First, dosages of immunosuppressive treatments of our patients are not available. Second, we did not assess the exact duration of the patients' medications and their disease activities. Third, given that the survey method was used as the first step for gathering data, selection bias may have occurred due to the possible willingness of the individuals who experienced adverse events for filling the questionnaire. Fourth, considering the

difficulty of sub-analyses due to a low number of patients, although CYC and MMF are known to potentially alter vaccine response, they were included in the non-biologic group. Although we did not assess the intervals between vaccination times and COVID-19 infection histories of the subjects, we know that our Ministry of Health regulations do not allow infected individuals to be vaccinated within the first 6 months. The main strength of the study is that this is the first one which evaluates adolescents and young adults with a broad spectrum of IRD in terms of vaccine-related adverse events.

In conclusion, our study indicates an acceptable safety profile of COVID-19 vaccines available in our country and encourages children with IRD to be vaccinated. Thus, prospective immunogenicity studies evaluating the efficacy of the vaccines and long-term follow-up studies for adverse events monitoring are required.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article.

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NOVEL HYPOTHESIS

Eosinophilic fasciitis induced by a game of drumming probably via type 2 innate immunity

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Abstract

We report a case of eosinophilic fasciitis triggered by strenuous physical activity, which did not relapse during the follow-up period. We ascertained that interleukin-33 (IL-33) was released from the vascular endothelial cells after intense exercise, inducing type 2 innate lymphocytes (ILC2) and causing fasciitis. A healthy woman experienced itching on both limbs a few hours after a game of drumming. Her hand, knee joints, and legs gradually swelled up with groove signs along the superficial veins. White blood cell and eosinophil counts were significantly elevated. Magnetic resonance imaging revealed a high signal at the fascia on both lower limbs. Histopathological findings of the left lower limb tissue specimen showed edematous fascia with eosinophils. No relapse of eosinophilic fasciitis was observed after finishing treatment with prednisolone. Immunological staining for IL-4, IL-5, IL-33, tumor necrosis factor-α, and interferon-γ was performed on the fascial tissue. Both IL-4 and IL-5 were stained on the lymphocytes at the muscle and fascia levels; however, CD3 and CD4 were unstained in these cells, suggesting that those cells were ILC2. Tumor necrosis factor-α and interferon-γ were unstained. Vascular endothelial cells in the fascia strongly expressed IL-33. Eosinophilic fasciitis may be associated with type 2 immunity triggered by IL-33 in the current case.

KEYWORDS
drumming, eosinophilic fasciitis, interleukin-4, interleukin-5, interleukin-33, type 2 innate immunity

1 | CAUSES AND DIAGNOSIS OF EOSINOPHILIC FASCIITIS

A healthy 23-year-old woman experienced itching on both lower limbs a few hours after a game of drumming, *Taiko no Tatsujin* (the game is played by actually grasping a stick and rhythmically beating the drum according to the music played from the speakers and the instructions on the screen). Her hand, knee joints, and legs gradually swelled up with groove signs along the superficial veins (Figure 1A). She was referred to our hospital, because her symptoms were unchanged despite administration of an antihistamine. White blood cell and eosinophil counts were elevated (19 320/μL and 17 120/μL, respectively). Creatine phosphokinase, C-reactive protein, erythrocyte sedimentation rate, and γ-globulin were normal, but aldolase was slightly elevated (19 U/L). Magnetic resonance imaging revealed a high signal at the fascia on both lower limbs (Figure 1B), without

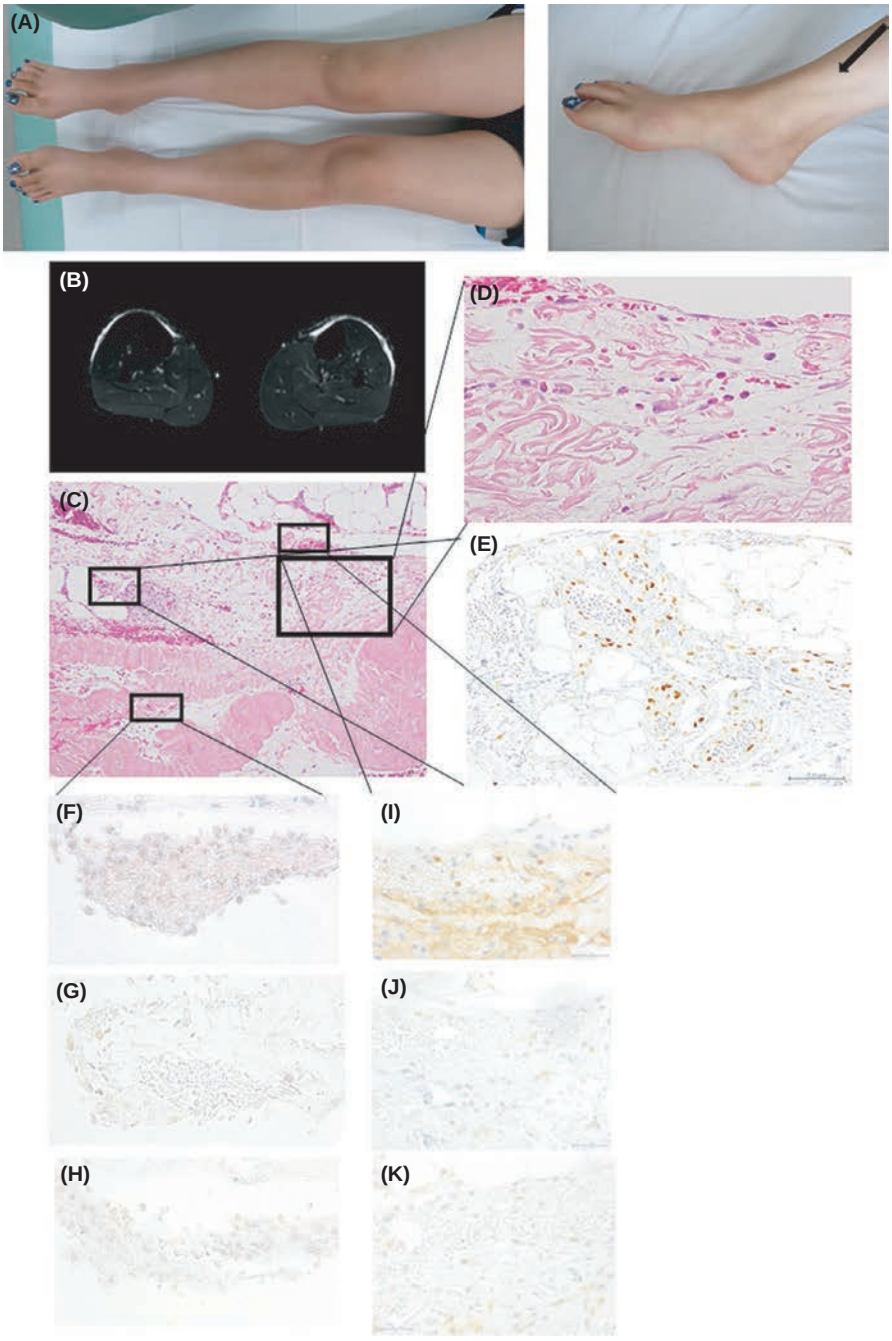

FIGURE 1 (A) Both legs were swollen, and the black arrowhead shows groove sign. (B) The inflammatory lesion in fascia on magnetic resonance imaging in T2 image scan was enhanced. (C) Histology tissue samples taken from the patient's leg showed the entire image around fascia and muscle stained by hematoxylin & eosin (×100). (D) Hematoxylin & eosin staining showed the presence of eosinophils within the swollen and convoluted fascia fibers (×400). (E) Interleukin-33 (IL-33) is strongly stained in endothelial cells around the fascia (×400). (F–H) Scattered lymphocytes in the fascia were stained with IL-4 (F), but negative for CD3 (G) and CD4 (H) (×400). (I–K) The lymphocytes in the fascia were positive for IL-5 (I), but negative for CD3 (J) and CD4 (K) (×400)

any abnormal signal in the muscles. Histopathological findings of the left lower limb tissue specimen showed edematous fascia with eosinophils, a few plasma cells, and lymphocytes from the deep reticular dermis to fascia (Figure 1C).

2 | THERAPY

The woman was diagnosed with eosinophilic fasciitis, so prednisolone 25 mg daily was started. The swelling of the extremities improved, and eosinophil count and aldolase stabilized at 23 days after the start of treatment. Creatine phosphokinase levels remained normal during the treatment course. Oral prednisolone was gradually reduced and completed after 16 months. No relapse of eosinophilic fasciitis was observed.

3 | CYTOKINE INVESTIGATION

Immunological staining for interleukin-4 (IL-4), IL-5, IL-33, tumor necrosis factor-α (TNF-α), and interferon-γ was performed on the fascial tissue. Both IL-4 and IL-5 were stained on the lymphocytes at the muscle and fascia levels (Figure 1F,I); however, CD3 and CD4 were unstained in these cells (Figure 1G,H,J,K), suggesting that those cells were type 2 innate lymphocytes (ILC2). Interferon-γ and TNF-α were unstained. Vascular endothelial cells in the fascia strongly expressed

IL-33 (Figure 1E). Eosinophilic fasciitis may be associated with type 2 immunity triggered by IL-33 in the current case.

4 | ILC2-MEDIATED EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis causes swelling and skin hardening after strenuous physical activity, infection, or chemical exposure. Between 30% and 46% of patients with eosinophilic fasciitis have a history of muscle injury due to strenuous exercise or trauma.[1] Histopathological report showed inflammatory cell infiltration including eosinophils around the fascia, causing thickening and fibrosis of the fascia. Eosinophil infiltration is characteristic, but not observed in one-third of cases. Around 60% of patients do not relapse without continuous steroid therapy.[2,3] Our question was why there was no recurrence of eosinophilic fasciitis. The patient's laboratory data showed elevated circulating eosinophils and eosinophils were present in the fascia, but neutrophil count and C-reactive protein level were within the normal range. Therefore, temporary mechanical stress inducing the production of IL-33 and ILC2 might have caused the eosinophilic fasciitis. The ILC2 respond to epithelial cytokines such as IL-33 and IL-25, and produce IL-5, IL-9, and IL-13. Interleukin-5 induces eosinophil activation and survival. Additional immunological examination revealed strong IL-33 staining in the vascular endothelial cells around fascia. Interleukin-33 is present in the nucleus of cells and is released by cell necrosis or cytotoxicity.[4,5] It acts as an alarmin to stimulate ILC2 to produce type 2 cytokines[6] and directly enhances adhesion of eosinophils.[7] The IL-5 produced by ILC2 can be recruited to the fascia, because IL-5-producing T cells congregate at the site of induced inflammation and induce eosinophil activity and maturation locally.[8] Anti-TNF-α therapy was reported to be effective in cases where steroids and immunosuppressive drugs were ineffective,[3] suggesting the involvement of type 1 cytokines. Eosinophilic fasciitis has two inflammation patterns, comprising type 1 or type 2 cytokines, which may affect the presence or absence of relapse after steroid termination.

5 | CONCLUSIONS

Herein, we report a case of eosinophilic fasciitis triggered by strenuous physical activity, which did not worsen during the follow-up period. We ascertained that IL-33 was released from the vascular endothelial cells after intense exercise, inducing ILC2 and causing fasciitis.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

SW, MK and YM wrote this article. MI, AH and YH contributed to pathological staining. KH and KY proofread the article.

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APLAR GRAND ROUND CASE

Disseminated drug-resistant tuberculosis and multiple autoimmune syndrome in a child with selective IgA deficiency—An uncustomary combination

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Abstract

Polyautoimmunity or multiple autoimmune syndrome (MAIS) is increasingly being recognized in pediatric clinical practice, often in conjunction with systemic lupus erythematosus (SLE). Besides multi-organ autoimmunity, children with SLE are often at a higher risk of developing infections including tuberculosis. The tendency to develop infections and multiple autoimmune diseases in childhood SLE often occurs in the absence of monogenic primary immunodeficiency disease. Conversely, children with inborn errors of immunity, of which selective IgA deficiency (sIgAD) is the most common, may develop recurrent infections and autoimmune disorders including SLE. Herein, we report a child with MAIS (including SLE) and sIgAD who developed drug-resistant tuberculosis, which was managed successfully with second-line antitubercular drug therapy. To the best of our knowledge, this combination of rare findings has not been reported previously in the pediatric literature. Although a majority of patients with sIgAD are either asymptomatic or have mild infections/autoimmunity, the index child had a myriad of infectious illnesses and multi-organ autoimmunity. Our case highlights the prudence of thoroughly evaluating children with SLE for other autoimmune diseases and vice versa. Given the higher probability of inherited disorders, including early complement deficiencies and monogenic interferonopathies, in childhood SLE compared with adult SLE, it may be prudent to perform a basic immunological workup (for example, immunoglobulin levels, 50% hemolytic complement) in such patients. A more extensive immunological and genetic evaluation (including next-generation sequencing) may also be required in the presence of unusual clinical or laboratory features, a positive family history, or a complicated clinical course.

KEYWORDS
antiphospholipid syndrome, autoimmune thyroiditis, primary immunodeficiency diseases, systemic lupus erythematosus, tuberculosis

1 | INTRODUCTION

Childhood-onset (<18 years of age) systemic lupus erythematosus (cSLE), a chronic multisystem autoimmune disorder, has been reported to have an incidence and prevalence of up to 2.5 per 100 000 and 25.7 per 100 000, respectively.[1] The disorder is increasingly being identified in conjunction with other autoimmune diseases including autoimmune thyroiditis (autoimmune thyroid disease [AITD]), anti-phospholipid syndrome (APS), vitiligo, type 1 diabetes mellitus, and autoimmune hepatitis. Consequently, polyautoimmunity (PA) has been defined as the coexistence of two or more autoimmune diseases in a patient, whereas the coexistence of three or more autoimmune diseases is termed multiple autoimmune syndrome (MAIS).[2,3]

Children with SLE are often at a higher risk of developing infections including tuberculosis (TB) because of the underlying immune dysregulation and chronic immunosuppressive therapy. Such predisposition in cSLE may occur in the absence of overt primary immunodeficiency diseases (also called inborn errors of immunity). Conversely, children with inborn errors of immunity may develop SLE of which selective IgA deficiency (sIgAD) is the most common. However, most patients with sIgAD are either asymptomatic or have mild infections. Patients with sIgAD have also been reported to develop autoimmune manifestations including SLE and occasionally life-threatening infections.[4]

Herein, we report a child with MAIS (SLE, APS, and AITD) and sIgAD who developed drug-resistant TB (DR-TB) that was managed successfully with second-line anti-tubercular drug (ATD) therapy. To the best of our knowledge, this combination of rare findings has not been reported previously in the pediatric literature.

2 | CASE DESCRIPTION

A girl aged 7 years presented to us with a 10 month history of intermittent fever, fatigue, excessive hair fall, anorexia, and arthralgia. Six months into her illness, she also started developing a photosensitive facial rash and change in color of fingers/toes on exposure to cold. She had been diagnosed elsewhere with autoimmune thyroiditis 9 months before presenting to us and was initiated on L-thyroxine therapy (37.5 μg/d). Her thyroid-stimulating hormone levels and anti-thyroid peroxidase antibodies were significantly elevated at diagnosis of AITD (thyroid-stimulating hormone: 182.6 and 184 mIU/L on two occasions [normal 0.5-4.5 mIU/L]; anti-thyroid peroxidase: 91.62 IU/mL [normal <34 IU/mL]). She had not been evaluated for SLE at the time of diagnosis of AITD.

On examination, we noted her to have alopecia, malar rash, painless oral ulcers, and erythematous violaceous papules over her extremities reminiscent of lupus vasculitis (Figure 1A-C). Laboratory investigations (Table 1) showed anemia, hypocomplementemia, antinuclear antibody positivity (Figure 1D), elevated anti-double-stranded DNA antibodies (1732 IU/mL [normal <40 IU/mL) and undetectable IgA levels (<6.7 mg/dL, repeated on multiple occasions subsequently). Lupus anticoagulant and anti-β_2-glycoprotein antibodies were positive (repeated at 12 weeks) and skin biopsy showed features of small-vessel vasculitis (Figure 1E). Diagnosis of sIgAD and MAIS was proffered and she was initiated on high-dose oral prednisolone (2 mg/kg/d), hydroxychloroquine (5 mg/kg/d), aspirin (4 mg/kg/d), and azathioprine (2 mg/kg/d).

Over subsequent months of follow up, her clinical course was complicated with episodes of arthritis (bilateral knee, ankle joints; which were managed with naproxen and temporarily increasing the dose of oral steroid), herpes zoster (managed with antiviral agents), paronychia, and methicillin-sensitive *Staphylococcus aureus* cellulitis (right shin) and *Klebsiella pneumoniae* urinary tract infection (managed with the appropriate antimicrobials). She also developed gangrenous changes in the left second toe for which low-molecular-weight heparin was initiated. Considering the possibility of an inborn error of immunity (resulting in infections and autoimmunity), whole-exome sequencing was performed that revealed no pathogenic or likely pathogenic variants (her peripheral blood lymphocyte immunophenotyping and dihydrorhodamine-123 assay were normal).

At 1 year of follow up, she presented with a 3-week history of fever, cough, and loss of appetite. On examination, she was noted to have warm shock, requiring fluid and ionotropic support. She also had bilateral axillary lymphadenopathy and splenomegaly. She was found to have a positive (15 × 14 mm) tuberculin skin test (which had been negative at here initial presentation to us). Contrast-enhanced computed tomography of chest and abdomen showed multiple large necrotic lymph nodes in the preaortic, para-aortic, precarinal, retrocaval, perigastric, periportal, and peripancreatic locations, the largest measuring 16 mm, with multiple hypodense lesions in the spleen. Gastric lavage showed positivity for *Mycobacterium tuberculosis* complex on a cartridge-based nucleic acid amplification test, resistant to rifampicin. She was initiated on second-line ATD therapy with delamanid, levofloxacin, linezolid, clofazimine, and cycloserine. She completed her 18-month ATD therapy (delamanid was given for 6 months) and is currently doing well. Her L-thyroxine, hydroxychloroquine, aspirin, azathioprine, and low-molecular-weight heparin therapy were continued while on ATDs without any adverse events.

3 | DISCUSSION

We report a young girl (who had non-consanguineous parents) with MAIS and sIgAD who developed a myriad of infections including DR-TB. Approximately one-fourth of all adult patients with an autoimmune disease are prone to develop additional autoimmune diseases.[2] In adults with SLE, the incidences of PA and MAIS have been reported to be 33%-45% and 8%-12%, respectively. Common autoimmune diseases in these patients (seen in 10%-20%) are AITD, APS, and Sjögren syndrome (SS).[4] Hypothyroidism often precedes SLE, whereas SS and APS frequently present within the first year of diagnosis of SLE.[5] A review of adult patients with MAIS showed that most presented with SLE, AITD, or SS as the first autoimmune disease.[6] Reported risk factors for

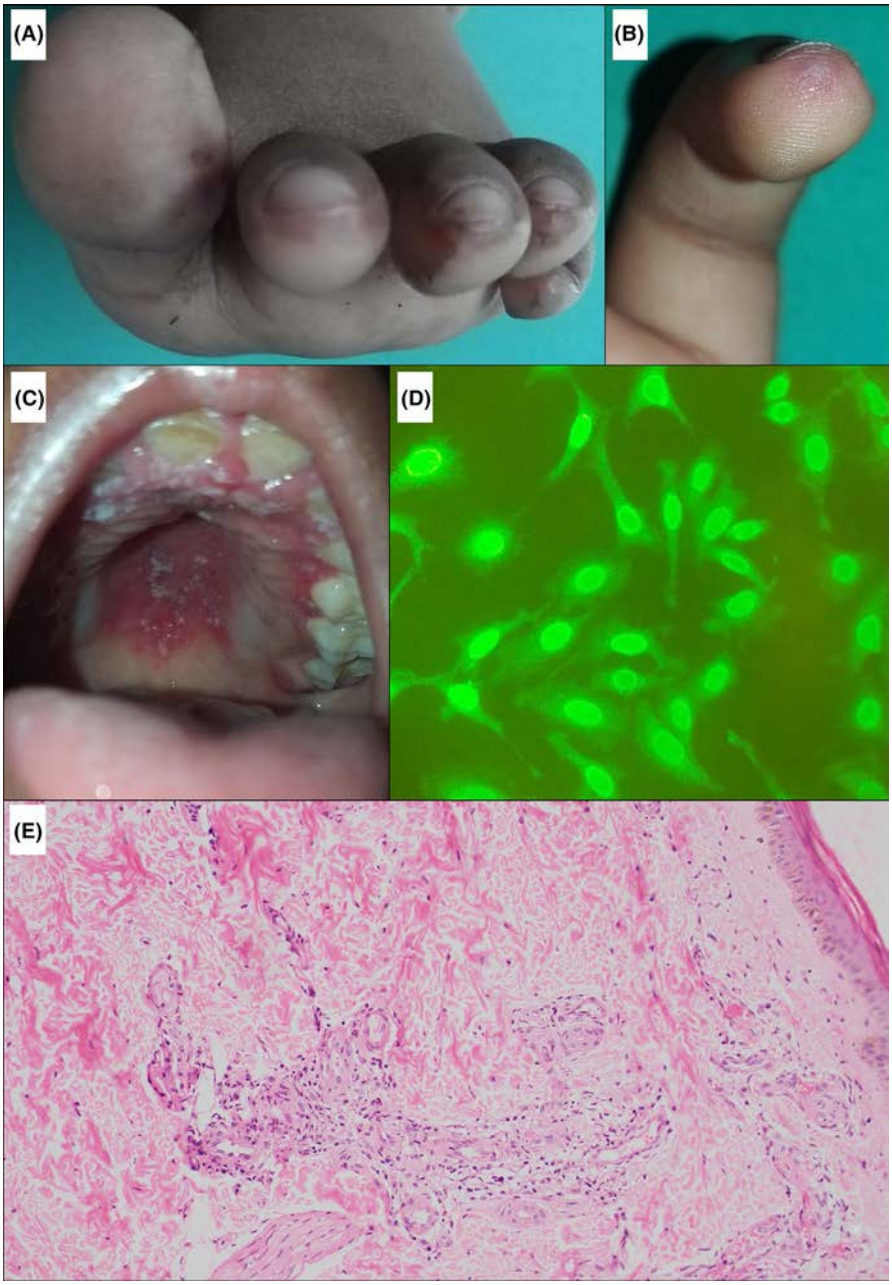

FIGURE 1 Profile of autoimmune manifestations in the index child at diagnosis of systemic lupus erythematosus. (A, B) Erythematous violaceous papules over tips of toes and left ring finger (suggestive of vasculitis); (C) painless oral ulcers over the palate; (D) 4+ nuclear homogeneous with rim enhancement and 2+ cytoplasmic pattern of antinuclear antibodies on indirect immunofluorescence on HEp-2 cell line; (E) skin biopsy showing features of small-vessel vasculitis including endothelial swelling, red blood cell extravasation, fibrinoid necrosis of vessel wall, and lymphomononuclear infiltrate in periadnexal and perivascular location

the development of PA in lupus include familial autoimmunity, articular involvement, and anti-Ro antibody positivity. The disease course in patients with SLE-related PA/MAIS may be milder, especially when associated with SS.[3]

Except for a few large studies, data on childhood-onset SLE with PA or MAIS (cSLE-PA or cSLE-MAIS, respectively) are largely limited to case reports. In a large pediatric study from Brazil, symptomatic PA was seen in approximately 10% of patients at the time of diagnosis of SLE. AITD and APS were the most frequent accompaniments, each seen in approximately 30% of patients with PA. Renal involvement was significantly less common in the subgroup with PA compared with lupus alone. MAIS was seen in 0.7% of the patients with cSLE with type 1 diabetes mellitus and autoimmune hepatitis being seen in about two-thirds of this subset.[7] In another multicenter study from Columbia, AITD and APS were the most frequent accompaniments in the setting of cSLE-PA, seen in 60% and 15%, respectively. In this study, MAIS was seen in 13.4% of patients with cSLE-PA.[8] Our patient had a similar profile of AITD and APS with cSLE; however, features of type 1 diabetes mellitus, autoimmune hepatitis, and SS have not been noted in her to date. Unlike adults, risk factors for the development of PA in cSLE are largely unknown.

Patients with SLE are prone to developing infections due to defects in regulatory T cells, complement deficiencies, mannose-binding lectin deficiency, and chronic inflammation, and organ damage that is further compounded by the use of potent long-term immunosuppressants.[9] As seen from adult studies, patients with SLE have a high risk of developing TB with its prevalence ranging from 5% to 30%.[10] These patients have more frequent extrapulmonary disease and more extensive pulmonary involvement.[10] The diagnosis

TABLE 1 Laboratory investigations in the index child at presentation to us

Parameter (unit)	Value (reference range)
Hemoglobin (g/L)[a]	**76** (115-155)
Hematocrit (%)	**18.8** (35-45)
Total RBC count ($\times 10^{12}$/L)	**2.33** (4.0-5.2)
Mean corpuscular volume (fL)	80.7 (77-95)
Mean corpuscular hemoglobin (pg)	32.6 (25-33)
Mean corpuscular hemoglobin concentration (%)	**40.4** (31-37)
RBC distribution width – coefficient of variation (%)	**16.8** (11.0-14.5)
Reticulocyte count (%)	**0.5** (1.0-2.7)
Direct Coombs (antiglobulin) test	**2+ for IgG**, negative for C3d
Peripheral blood smear	Anisopoikilocytosis, predominantly normocytic normochromic RBCs, occasional microcytes
Total leukocyte count ($\times 10^9$/L)	7.80 (5.0-14.5)
Differential leukocyte count	$N_{39}L_{49}M_{10}E_1B_1$
Total platelet count ($\times 10^9$/L)	**63** (150-400)
Urea (mg/dL)	23 (10-50)
Creatinine (mg/dL)	0.51 (0.5-1.2)
Total bilirubin (mg/dL)	**1.1** (<1.0)
Conjugated bilirubin (mg/dL)	0.1 (<0.2)
Alanine aminotransferase (U/L)	42.1 (5-45)
Aspartate aminotransferase (U/L)	**81.5** (15-50)
Alkaline phosphatase (U/L)	145 (145-420)
Creatine phosphokinase (U/L)	39 (25-308)
Lactate dehydrogenase (U/L)	**452** (135-225)
Total serum protein (mg/dL)	7.3 (6.4-8.3)
Total serum albumin (mg/dL)	**3.1** (3.5-5.6)
Albumin to globulin ratio	**0.74** (1.0-1.5)
C-reactive protein (mg/L)	2.81 (0-3.5)
Erythrocyte sedimentation rate (mm/h)	**53** (0-20)
Procalcitonin (ng/mL)	0.38 (0-0.5)
Immunoglobulin G (g/L)	**19.80** (5.9-14.6)
Immunoglobulin A (g/L)	**<0.067** (0.44-2.44)
Immunoglobulin M (g/L)	1.53 (0.45-2.78)
Urine routine microscopy (on three occasions)	RBCs, WBCs, albumin, casts – all negative
24-h urine protein (mg/m^2/h)	**4.26** (<4)
Prothrombin time (s)	10.6 (10.0-14.6)
International normalized ratio	0.94
Activated partial thromboplastin time (s)	**48** (26.9-38.7)
Fibrinogen (g/L)	2.88 (1.89-4.75)
Hepatitis B surface antigen	Negative
Anti-hepatitis C virus IgM antibody	Negative
Human immunodeficiency virus serology	Negative
Mantoux tuberculin skin test	0 mm/negative
ANA Immunoblot (antibodies against extractable nuclear antigens)	**dsDNA – 4+, U1-RNP – 4+** **Nucleosome – 2+, Ribo-P – 3+** **Sm – Faintly positive** Negative for histone, AMA-M2, SSA/60KDa, SSA/52KDa, SSB/La, PM-Scl, Jo-1, CBNP, PCNA
Anti-neutrophil cytoplasmic antibody (ELISA)	Anti-PR3/MPO – negative
Anti-double-stranded DNA antibody titers (IU/mL)	**1732** (<40)
Lupus anticoagulant [Dilute Russel Viper Venom Time] Lupus anticoagulant [Silica Clotting Time] (NR)	**1.54** (<1.2) **1.18** (<1.16)
IgG Anticardiolipin antibody assay (U/mL) IgM Anticardiolipin antibody assay (U/mL) IgG Anti β_2 glycoprotein 1 antibody assay (U/mL) IgM Anti β_2 glycoprotein 1 antibody assay (U/mL)	7.1 (<20) 18.7 (<20) **20.2** (<20) **22.6** (<20)
Complement C3 (mg/dL)	**<27** (78.9-178.9)
Complement C4 (mg/dL)	**<3** (14.5-61.6)
CH_{50} activity (%)	**18** (69-129)
Skin biopsy	Epidermis: thinned out, focal basket-weave hyperkeratosis; upper dermis: endothelial swelling, RBC extravasation, fibrinoid necrosis of vessel wall and nuclear debris is seen; deeper dermis: lymphomononuclear infiltrate in periadnexal and perivascular location
Skin biopsy (immunofluorescence)	IgG: 2+ band, IgA: 3+ band and 2+ in blood vessels, IgM: 3+ band and 3+ in blood vessels

Note: Abnormal values highlighted in bold, values refer to parameters measured in blood/plasma/serum (unless specified otherwise).

Abbreviations: ANA, anti-nuclear antibody; CH_{50}, 50% hemolytic complement; NR, normalized ratio; RBC, red blood cell; WBC, white blood cell.

[a]Laboratory parameters suggested the presence of both anemia of chronic disease and autoimmune hemolytic anemia in the index child.

of TB in these patients is often delayed and complicated by the close mimicking of symptoms with those of SLE flares. Despite several studies performed in adult patients with TB and SLE describing the epidemiological features, clinical manifestations, and outcomes, there have been only a handful of reports of TB in cSLE. Pulmonary, pleural, osteoarticular, or disseminated TB has been reported in these patients.[11,12] To the best of our knowledge, cSLE and DR-TB have been reported in very few children (fewer than five cases) whereas the combination of cSLE-MAIS and DR-TB has not been reported so far. The index child had disseminated DR-TB in association with cSLE-MAIS, which was managed successfully with second-line ATD therapy.

Although the occurrence of sIgAD and cSLE is not uncommon,[3,13] sIgAD in association with cSLE-MAIS has been described very rarely. In a Columbian study, sIgAD was reported in approximately 5% of patients with cSLE.[13] Gain-of-function mutation (p.R779H) in *IFIH1* (encoding for interferon-induced helicase C domain-containing protein 1, also known as MDA-5 [melanoma differentiation-associated protein]) gene has been reported in an adolescent female with lower-limb spasticity, cSLE, sIgAD, and elevated antiphospholipid and anti-thyroid antibodies.[14] Besides, 18p monosomy (resulting from whole-arm t(18;21)) has been reported in a child with dysmorphic features who developed cSLE, AITD, and sIgAD.[15] The index child did not have any dysmorphic features, lower-limb spasticity (or other features of a monogenic interferonopathy), and whole-exome sequencing did not reveal any pathogenic/likely pathogenic variants.

Selective IgAD in association with cSLE is usually asymptomatic and intravenous immunoglobulin replacement therapy is not required. However, development of common variable immune deficiency meriting immunoglobulin replacement therapy has been reported in a child previously diagnosed as having SLE with IgA and IgG2 deficiency.[16] The index child has had several infections requiring multiple courses of antimicrobials. Currently, she only has sIgAD and IVIg therapy has not yet been initiated. Although, patients with sIgAD are predisposed to develop autoimmune manifestations and infections,[3] a combination DR-TB and MAIS, as was seen in the index case, is rare.

4 | CONCLUSIONS

It is prudent to thoroughly evaluate children with SLE for other autoimmune diseases because children with SLE can develop other autoimmune diseases or vice versa. Given the higher probability of inherited disorders in cSLE compared with adult SLE, it may be prudent to perform a basic immunological work-up (for example, immunoglobulin levels, 50% hemolytic complement) in such patients. A high index of suspicion is required for early diagnosis of TB in cSLE, especially in endemic settings.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

HN and VV: writing of initial draft of manuscript, patient evaluation and management, data collection, review of literature, and final approval. AZB: inception of idea, patient evaluation and management, data collection, writing of initial draft of manuscript, editing and revision of manuscript, review of literature, and final approval. AKJ, RT and MKS: editing and revision of manuscript, patient evaluation and management, review of literature, and final approval. AB and DS: patient management and follow up, revision and editing of the manuscript, and final approval.

ETHICAL APPROVAL AND INFORMED CONSENT

As this manuscript pertains only to a case report, specific ethics approval is not mandated. Informed consent was obtained from the parents of the child before inclusion into the manuscript.

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CORRESPONDENCE

Pyoderma gangrenosum of the breast associated with rheumatoid arthritis: A challenging diagnosis

1 | INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis. It is associated with underlying diseases in up to 75% of cases, most frequently with inflammatory bowel disease, inflammatory arthritis, and hematological disorders.[1] It typically affects the lower limbs, while the breast is an unusual localization. Approximately 80% of known cases occur after surgeries, such as mastectomy.[2] Herein, we report a case of a patient without a history of preceding surgery or trauma diagnosed with bilateral breast PG associated with rheumatoid arthritis (RA).

A 68-year-old woman, with a history of type 2 diabetes, and seropositive RA presented with painful, bilateral lesions of the breast evolving for 1 month. She denied diarrhea, abdominal pain, fever, or night sweats. Physical examination revealed a 4 × 4 cm ulceration with necrotic debris and raised, violaceous borders on her right breast (Figure 1A,B). Multiple cribriform scars and nodules were present bilaterally (Figure 1A,C). A skin biopsy specimen showed a neutrophilic inflammation in the dermis with dense diffuse neutrophilic infiltrate. Complete laboratory investigations and mammography revealed normal findings. We retained the diagnosis of PG based on the rapid onset, the nipple-areolar complex sparing (NAC), the bilateral involvement, and the histopathological findings. Treatment was initiated with topical steroid and colchicine with progressive healing.

2 | DISCUSSION

PG is an uncommon ulcerative cutaneous condition. It can have different clinical presentations with varying degrees of severity. Clinically, it can present as ulcerative subtype, bullous, pustular, vegetative, drug-induced, post-surgical, or peristomal types.[3] Our patient had clinical manifestations compatible with ulcerative PG with 2 distinct phases. The ulcerative phase consisted of an initial pustule which rapidly progressed to a necrotic center with erythematous, irregular edges, and the healing stage with projections of epithelium extending into the center of the ulcer termed Gulliver's sign.

PG is frequently preceded by inflammatory arthritis, most commonly RA,[4] the association of which portends a poor prognosis.[5] In fact, the ulcers seem more refractory to treatment. The arthritis associated with PG can be seropositive or seronegative. The details regarding the clinical pattern of joint inflammation are variable, but the most common presentation is large-joint seronegative monoarticular arthritis.[5] The type of inflammatory arthritis associated with PG may not be a helpful treatment guide as it was not significantly associated with treatment outcomes or healing time.

The breast is an uncommon site for PG. Surgical intervention is the main inducer of the lesions.[2] Regarding our patient, there was no previous history of surgery or injury and the etiology of PG remains unclear. Unnoticed minor trauma may partially explain it.

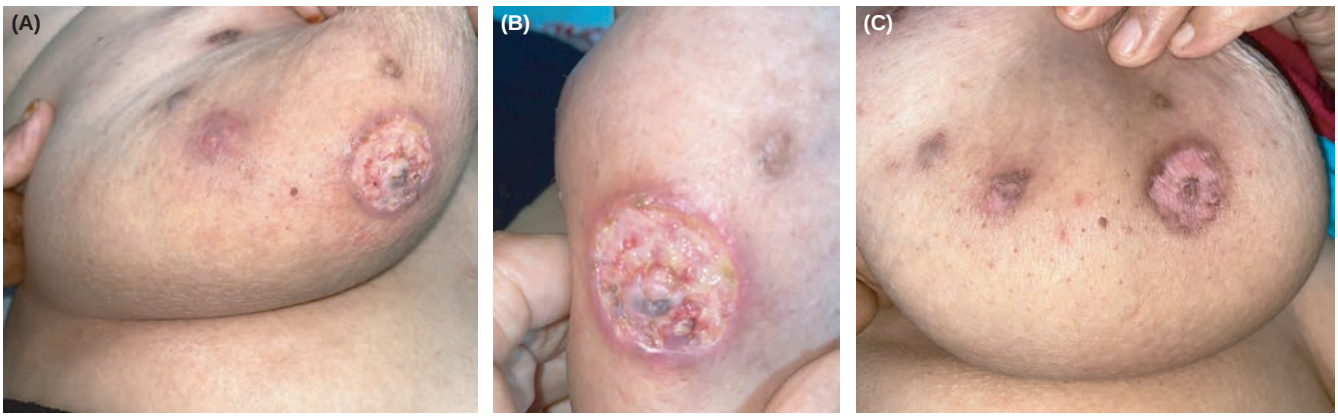

FIGURE 1 (A, B) A 4 × 4 cm ulceration with necrotic debris and raised, violaceous borders on the patient's right breast. (C) Multiple cribriform scars and nodules

Misdiagnosis of PG is common, and differential diagnosis in the breast often includes inflammatory breast cancer, chronic granulomatous mastitis and acute bacterial infections.[2] This common mistake often leads to antibiotic therapy and unnecessary debridement which may even be harmful and perpetuate the pathergic response. Hence, correlation of clinical features which include a rapid onset of ulceration with undermined edges and cribriform scars, NAC sparing, and bilateral involvement, negative microbiological cultures and histopathological findings that shows a neutrophilic inflammation in the dermis without granulomas unlike chronic granulomatous mastitis is important, to rule out these serious diagnoses.

Su et al propose diagnostic criteria for PG and require 2 major and 2 out of 4 minor criteria to establish the diagnosis.[6] Major criteria include rapid progression of painful, necrolytic, cutaneous ulcer with an irregular violaceous border and exclusion of other causes of cutaneous ulceration.[6] Minor criteria include history suggestive of pathergy or clinical findings of cribriform scarring, systemic diseases associated with PG, compatible histopathological findings, and response to treatment.[6] Our patient met both of the 2 major criteria and all 4 of the minor criteria.

Therefore, although an unusual site, our case illustrates the importance of considering the diagnosis of PG in patients with RA in the differential diagnosis of rapidly progressing ulcerative lesions on the breast. Prompt recognition of PG and timely initiation of treatment are critical to avoid disease spread, unesthetic scarring, hospitalization, physical morbidity, and psychological consequences.

KEYWORDS

breast, pyoderma gangrenosum, rheumatoid arthritis

CONFLICT OF INTEREST

None.

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CORRESPONDENCE

Multisystem inflammatory syndrome in children associated with erythema multiforme-like eruption following COVID-19

1 | INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory syndrome associated with SARS-CoV-2 infection. It is characterized by a multi-organ involvement similar to Kawasaki disease (KD).[1] We report a case of erythema multiforme (EM)-like eruption as a manifestation of MIS-C in a10-month-old infant.

2 | CASE REPORT

A 10-month-old female infant was admitted to the pediatric department with a 7-day history of fever, skin eruption, vomiting, and diarrhea. Her mother had been diagnosed with SARS-CoV-2 infection 3 weeks earlier. There was no history of recent medication or vaccination. Clinical examination revealed an EM-like eruption consisting of targetoid lesions, localized mainly on the extremities and trunk (Figure 1A). These lesions rapidly became ulcerated with a necrotic center (Figure 1B). Desquamation of the extremities was also noted. There was no mucosal involvement. There were no respiratory or cardiovascular symptoms. Laboratory tests showed hyperleukocytosis (19.370/mm^3), thrombocytosis (612.400/mm^3), and elevated inflammatory biomarkers including C-reactive protein of 39.3 mg/L and erythrocyte sedimentation rate of 63 mm/h. Increased D-dimers of 1316 ng/mL (normal [N] <500 ng/mL) associated with high ferritin (413 ng/mL; N = 20-250 ng/mL) and fibrinogen (5.7 g/L; N = 2-4 g/L) levels were also noted. Brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and troponin levels were normal. Mycoplasma pneumonia and herpes simplex virus (HSV) serology were negative. SARS-CoV-2 serology revealed positive immunoglobulin G (IgG) (4.2; positive if >1) and IgM (2.38) (positive if >1). Histopathology of skin lesions showed epidermal hyperplasia with focal ulceration and keratinocyte necrosis, associated with lymphocytic inflammatory infiltrate of the dermis compatible with the diagnosis of EM (Figure 2). These clinical and biological findings were consistent with the diagnosis of MIS-C associated with COVID-19. Three days after the initial presentation, the patient presented with hypotension and tachycardia. Laboratory investigations, showed normal troponin, pro-BNP levels and mild elevation in inflammatory biomarkers. Echocardiography did not reveal cardiac dysfunction or coronary arteries abnormalities. These symptoms responded rapidly to fluid resuscitation and skin lesions improved within a few days

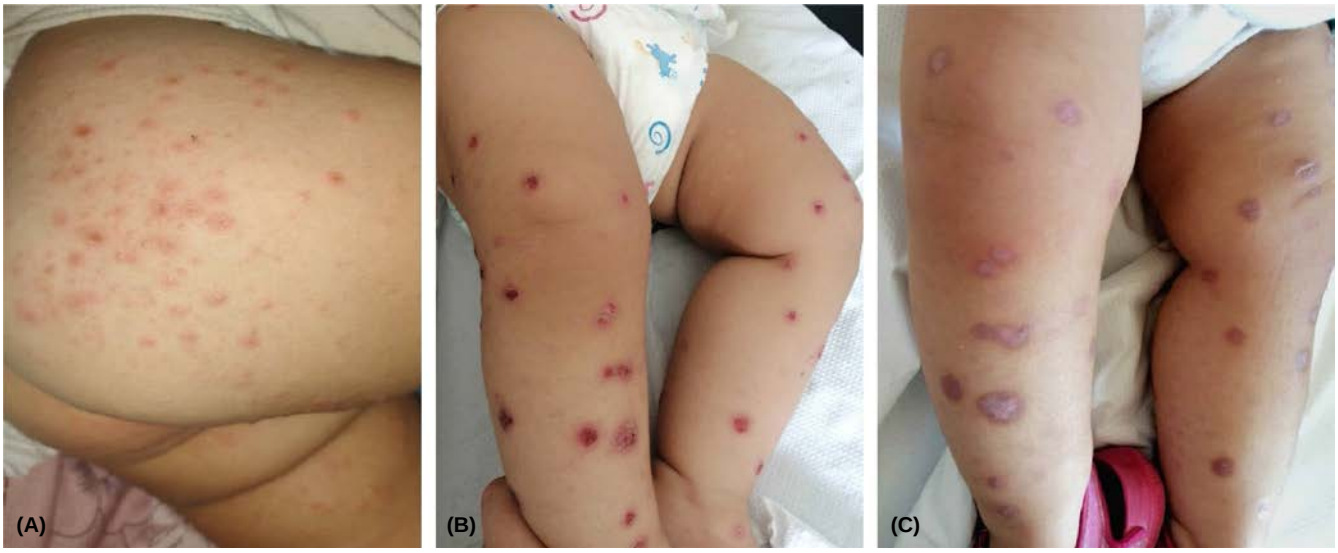

FIGURE 1 (A) Targetoid lesions on the buttocks and lower limbs. (B) Targetoid lesions with ulcerated center on the lower limbs. (C) Improvement of lesions after treatment with topical steroids

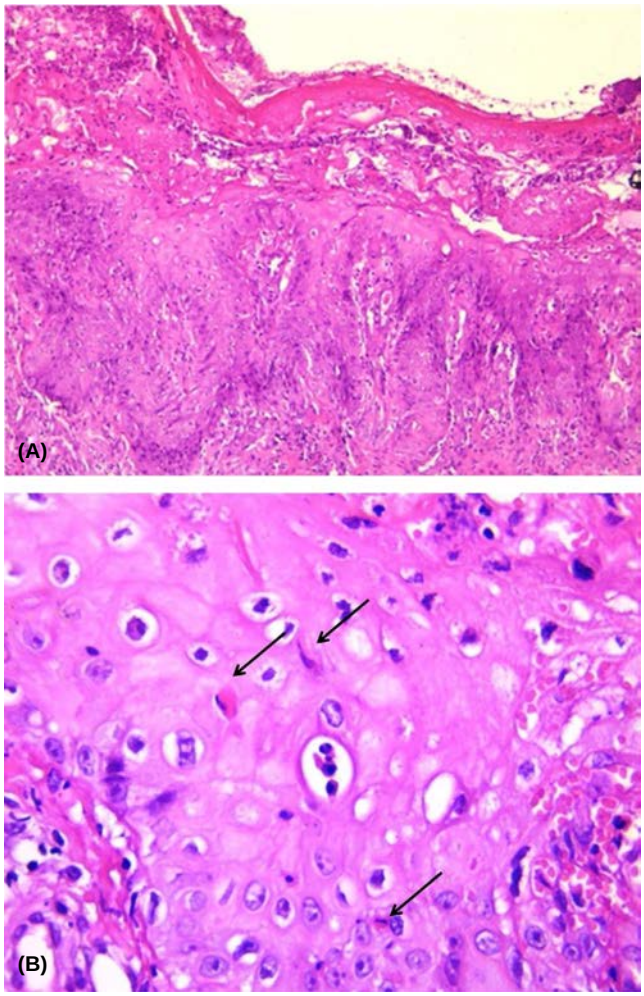

FIGURE 2 The epidermis is ulcerated and shows regenerative changes of the basal layers (A hematoxylin and eosin [HE] ×100) and numerous necrotic keratinocytes (arrows) (B HE ×400)

after treatment with topical corticosteroids (Figure 1C). At follow up, 3 months later, the infant was in good health and there was no recurrence of skin lesions or other symptoms.

3 | DISCUSSION

We described a case of MIS-C following COVID-19 infection with EM-like lesions as a dermatological manifestation. The positive SARS-CoV-2 serological test with a multi-organ involvement and the laboratory alterations supported this diagnosis. Our patient fulfilled the Centers for Disease Control, Biomed Central and World Health Organization criteria for MIS-C.[1]

Many patients with MIS-C fulfill the criteria for complete or incomplete KD.[2] However, in MIS-C, gastrointestinal manifestations and cardiovascular abnormalities including myocarditis, ventricular dysfunction and coronary artery aneurysms are more common. On the other hand, mucosal involvement is less frequently reported.[2]

Skin lesions are common and nonspecific.[2] Patients with MIS-C show a range of clinical features, including polymorphous skin eruption, conjunctivitis, mucositis, and extremity lesions, similar to KD. Maculopapular, morbilliform rash and diffuse erythroderma are the most common cutaneous manifestations. Urticarial, reticular and purpuric skin lesions were also described in single case reports.[2] Palm and sole involvement including edema, erythema and desquamation of the extremities and/or digits, like in our case, were also reported.

To our knowledge, EM-like lesions, similar to our case were previously described in only 3 patients, aged 57 days, 6 and, 13 years old.[3-5] Targetoid lesions appeared 10 days to weeks after COVID-19 infection and were localized on the face, extremities and trunk respectively.

Our case is particular by the necrotic and ulcerated aspect of the lesions. We excluded EM in association with HSV or mycoplasma pneumoniae infection based on negative serological tests.

The majority of MIS-C cases were diagnosed 3-4 weeks after SARS-CoV-2 infection,[6] as in our case. This finding shows that this phenomenon develops during the post-infectious phase. In MIS-C, hyperinflammation is caused by an imbalance between T-helper cells and regulatory T cells. It is thought that SARS-CoV-2 can trigger macrophage activation followed by T-helper cell activation, leading to cytokine release and multisystem damage.[7] Most of the affected children were treated with intravenous Ig therapy or oral corticosteroids with favorable responses in the majority of cases. Our patient did not require systemic therapy since there was no major organ dysfunction.[6]

KEYWORDS

COVID-19, erythema multiforme, Kawasaki disease, MIS-C, targetoid lesions

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None.

CONFLICT OF INTEREST

None.

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UPCOMING EVENTS