Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guidelines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

Volume 78 No. 7 July 2026

Arthritis Care & Research

An Official Journal of the American College of Rheumatology
www.arthritiscareres.org and wileyonlinelibrary.com

Cover design: Sandra Pulmano

♾ This journal is printed on acid-free paper.

Arthritis Care & Research

An Official Journal of the American College of Rheumatology
www.arthritiscareres.org and wileyonlinelibrary.com

VOLUME 78 • JULY 2026 • NO. 7

Cover image: The image on the cover (from Billups et al; pages 883–892) shows the distribution of Colorado zip codes for patients receiving internal or external eConsults to Rheumatology.

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 815–839
DOI 10.1002/acr.25690

American College of Rheumatology
Empowering Rheumatology Professionals

2025 American College of Rheumatology (ACR) Guideline for the Treatment of Systemic Lupus Erythematosus

Lisa R. Sammaritano, MD,[1] Anca Askanase, MD, MPH,[2] Bonnie L. Bermas, MD,[3] Maria Dall'Era, MD,[4] Alí Duarte-García, MD, MSc,[5] Linda T. Hiraki, MD, MSc, ScD,[6] Mary Beth F. Son, MD,[7] Victoria P. Werth, MD,[8] Cynthia Aranow, MD,[9] April Barnado, MD, MSCI,[10] Anna Broder, MD, MSc,[11] Hermine I. Brunner, MD, MSc, MBA,[12] Benjamin F. Chong, MD, MSCS,[3] Vaidehi R. Chowdhary, MBBS, MD, DM,[13] Aimee O. Hersh, MD,[14] Peter M. Izmirly, MD,[15] Marimee Jules,[16] Kenneth Kalunian, MD,[17] Diane Kamen, MD, MSCR,[18] Tamar B. Rubinstein, MS,[19] Benjamin J. Smith, DMSc, PA-C,[20] Natalie M. Smith,[21] Asha Thomas, MD,[22] Homa Timlin, MD, MSc,[23] Daniel J. Wallace, MD,[24] Muayad Azzam, MD,[25] Christie M. Bartels, MD, MS,[26] Joanne S. Cunha, MD,[27] Kimberly DeQuattro, MD, MM,[28] Andrea Fava, MD,[23] Gabriel Figueroa-Parra, MD, MSc,[29] Shivani Garg, MD, MS,[26] Lais Lopes Almeida Gomes, MD,[8] Maria C. Cuéllar-Gutiérrez, MD,[30] Priyanka Iyer, MD, MPH,[31] Andrew S. Johannemann, MD,[32] April Jorge, MD,[33] Shanthini Kasturi, MD, MS,[34] Hassan Kawtharany, MD,[25] Jana Khawandi, MD,[25] Alexandra Legge, MD, MSc,[35] Kimberly P. Liang, MD, MS,[25] Megan M. Lockwood, MD,[36] Alain Sanchez-Rodriguez, MD,[37] Marat Turgunbaev, MD,[38] Jessica N. Williams, MD, MPH,[39] Amy S. Turner,[38] and Reem A. Mustafa, MD, PhD, MPH[25]

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the clinician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, and drug formularies or other third-party analyses that cite ACR guidelines should state this. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To provide evidence-based and expert guidance for the treatment and management of non-renal systemic lupus erythematosus (SLE); treatment and management of lupus nephritis are addressed in a separate guideline.

Published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.
[1]Hospital for Special Surgery Weill Cornell Medicine, New York, New York; [2]Columbia University, New York, New York; [3]University of Texas Southwestern Medical Center, Dallas; [4]University of California, San Francisco; [5]Mayo Clinic, Rochester, Minnesota; [6]The Hospital for Sick Children, Toronto, Ontario, Canada; [7]Boston Children's Hospital, Boston, Massachusetts; [8]University of Pennsylvania and Corporal Michael J. Crescenz VAMC, Philadelphia; [9]Feinstein Institutes for Medical Research, Manhasset, New York; [10]Vanderbilt University Medical Center, Nashville, Tennessee; [11]Hackensack University Medical Center, Hackensack, New Jersey; [12]Cincinnati Children's Hospital, University of Cincinnati, College of Medicine, Department of Pediatrics, Cincinnati, Ohio; [13]Yale University School of Medicine, New Haven, Connecticut; [14]The University of Utah, Salt Lake City; [15]NYU Grossman School of Medicine, New York, New York; [16]Salt Lake City, Utah; [17]University of California, San Diego; [18]Medical University of South Carolina, Charleston; [19]Albert Einstein College of Medicine, Bronx, New York; [20]Florida State University, Tallahassee; [21]Hanover, Pennsylvania; [22]The Central Texas Veterans Health Care System (CTVHCS), Temple; [23]Johns Hopkins University, Baltimore, Maryland; [24]Cedars-Sinai, Los Angeles, California; [25]University of Kansas, Kansas City; [26]University of Wisconsin, Madison, Madison; [27]Warren Alpert Medical School of Brown University, East Providence, Rhode Island; [28]University of Pennsylvania, Philadelphia; [29]Mayo Clinic, Rochester, Minnesota, and University Hospital Dr. José Eleuterio González, Universidad Autónoma de Nuevo León,

Methods. Clinical questions for treatment and management of SLE were developed in the PICO format (population, intervention, comparator, and outcome). Systematic literature reviews were developed for each PICO question, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to assess evidence quality and formulate recommendations. The Voting Panel achieved a consensus of ≥70% agreement on the direction (for or against) and strength (strong or conditional) of each recommendation.

Results. We present recommendations and ungraded, consensus-based good practice statements for the treatment and management of SLE that are applicable to pediatric and adult patients. Recommendations emphasize uniform treatment with hydroxychloroquine, limiting duration of glucocorticoid use, and early introduction of conventional and/or biologic immunosuppressive therapies to achieve and maintain control of SLE inflammation (remission or a low level of disease activity), reduce SLE-related morbidity and mortality, and minimize medication-related toxicities.

Conclusion. This guideline presents direction regarding treatment and management of SLE and provides a foundation for well-informed, shared clinician–patient decision-making. These recommendations should not be used to limit or deny access to therapies, as treatment decisions may vary due to the unique clinical situation and personal preferences of each person with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a clinically heterogeneous, multisystem autoimmune disease with a prevalence of 72.8/100,000 persons in the United States[1] and a predilection for reproductive-aged females; prognosis is worse for those of Black, Hispanic, American Indian/Alaskan Native, and Asian ancestry.[1–7] Genetic, epigenetic, hormonal, infectious, and environmental factors contribute to its pathogenesis. Guidelines for management of SLE in adults were last published by the American College of Rheumatology in 1999.[8] Since then, treatment regimens incorporating mycophenolate mofetil/mycophenolic acid or lower-dose cyclophosphamide (CYC) have proven effective compared to the older, higher-dose CYC regimen. Belimumab, voclosporin, and anifrolumab are US Food and Drug Administration (FDA)-approved for SLE and/or lupus nephritis (LN) treatment, and clinical trials are ongoing to identify additional new therapies. This guideline addresses overall treatment strategies as well as management of specific organ system manifestations, except for LN which is covered in a separate guideline.[9]

These recommendations follow general guiding principles (Table 1) and are based on systematic literature review, patient values and preferences, and clinical expertise of a heterogenous guideline panel, including 31 adult rheumatologists, 5 pediatric rheumatologists, 2 dermatologists, 1 pediatric dermatologist, 1 rheumatology physician assistant, and 2 people with SLE.

Recommendations are intended to promote optimal outcomes for common SLE scenarios using therapies available in the United States as of 2024 and are applicable to the pediatric population with specific considerations, as noted. In practice, therapeutic decisions will vary based on clinical presentation, patient preferences, and limitations in access to specialists, procedures, and medications.

METHODS

This guideline follows the American College of Rheumatology (ACR) guideline development process using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[10,11] and ACR policy that guides the management of conflicts of interest and disclosures.[12] Supplementary Materials 1 includes a detailed description of the methods. The Core Leadership Team (LRS, RAM, AA, BLB, MD, AD, LTH, MBS, VPW) drafted clinical population, intervention, comparator, and outcomes (PICO) questions (see Supplementary Materials 2). The Literature Review Team performed systematic literature reviews for the PICO questions, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Materials 3). Moderated by three rheumatologists (SG, LTH, MBS), a Patient Panel of 13 individuals with SLE and varied organ system manifestations provided their perspectives on therapy and management; a separate manuscript detailing the Patient Panel process, discussion, and results is in progress. Tw-

Monterrey, Nuevo León, México; [30]Mayo Clinic, Rochester, Minnesota, and Hospital del Salvador, Santiago, Chile; [31]University of California Irvine Medical Center, Orange; [32]Carolina Arthritis Center, Greenville, North Carolina; [33]Massachusetts General Hospital, Boston; [34]Tufts Medical Center, Boston, Massachusetts; [35]Dalhousie University, Halifax, Nova Scotia, Canada; [36]Georgetown University Hospital, Washington, DC; [37]Mayo Clinic, Rochester, Minnesota, and Department of Internal Medicine, The American British Cowdray Medical Center, I.A.P., Mexico City, Mexico; [38]American College of Rheumatology, Atlanta, Georgia; [39]Washington University, St. Louis, Missouri.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25690).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25690.

Address correspondence via email to Lisa R. Sammaritano, MD, at sammaritanol@hss.edu

Submitted for publication May 27, 2025; accepted in revised form October 2, 2025.

SIGNIFICANCE

- Hydroxychloroquine should be standard therapy for all people with SLE unless contraindicated.
- Glucocorticoids should be used primarily for initial control of immune-mediated inflammation and during flares as needed, with tapering as soon as possible.
- Early introduction of immunosuppressive therapies (conventional and/or biologic) for ongoing SLE activity is encouraged to achieve control of SLE inflammation (remission or a low level of disease activity), reduction in SLE-related morbidity and mortality, and minimization of glucocorticoid-related toxicities.

o Patient Panel members served as Voting Panel members and shared the Patient Panel's concerns and preferences. The Voting Panel reviewed evidence and voted on recommendations derived from the initial PICO questions; certain recommendations were rewritten and revoted upon based on Voting Panel discussion. Per ACR policy, consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation. A recommendation is categorized as strong if the panel was very confident that the benefits of the intervention clearly outweighed its harms, or vice versa. A conditional recommendation denotes uncertainty regarding the balance of benefits and harm due to low-quality evidence, or that the decision is particularly sensitive to individual patient preferences or cost constraints. Good practice statements (GPS) were also generated; these are actionable statements where the desirable effects clearly outweigh the undesirable effects of an intervention.[13] Rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Materials 4. Search strategies and study selection details are provided in Supplementary Materials 5 and 6. This guideline will be reviewed and updated periodically.

Table 1. Guiding Principles*

The goals of SLE treatment are to achieve and maintain SLE remission or low lupus disease activity, reduce SLE-related morbidity and mortality, and minimize treatment related toxicities.
Collaborative care between rheumatologists and appropriate specialists should be provided whenever possible.
Shared decision-making is essential to respect patient values and preferences and leads to better treatment adherence and outcomes.
Healthcare disparities, including racialized and socioeconomic disparities, are crucial factors impacting outcomes of those living with SLE; treatment recommendations are aimed to alleviate health disparities.
Pediatric-specific guidance is provided when possible.
Some therapies are presented without hierarchy when evidence-based data, clinical expertise, and patient-reported experiences do not clearly support the use of one medication over another; treatment decisions should be individualized to the patient's clinical status and preference.
Potential limitations to implementing care recommendations may arise due to limitations in access to testing, specialists, procedures, and medications; if recommended therapies are unavailable, are not tolerated, or are not preferred by patients, we encourage discussion of reasonable alternative therapies.
Assumptions • All treatment recommendations assume other appropriate workups have been done to rule out non-SLE etiologies. • Organ-specific treatment recommendations assume all patients are taking hydroxychloroquine unless there is a contraindication to therapy.

* SLE, systemic lupus erythematosus.

Scope

Treatment for all people with SLE regardless of age, ancestry, or other individual patient variables is presented here. General and organ-specific treatment recommendations and monitoring are offered, except for LN, which is addressed in a separate guideline.[9] Some SLE-related clinical issues were beyond the scope of this project. We do not offer guidance on diagnosis of SLE and do not include recommendations for treatment of certain broader and/or less well understood SLE-related issues including "type 2" SLE symptoms, mental health issues, and antiphospholipid syndrome (APS).

"Type 2" SLE symptoms, including fatigue, generalized pain, and brain fog, impact quality of life for individuals with SLE[14]. The pathophysiology and optimal treatment of "type 2" symptoms are incompletely understood and are acknowledged as a high research priority; treatment recommendations here address SLE manifestations that are more clearly mediated through inflammation ("type 1"). Similarly, depression and anxiety – common in adults, adolescents, and children with SLE – often impact general well-being for people with SLE.[15,16] No specific recommendations are offered, but we suggest that routine mood screening and attention to mental health should ideally be incorporated into general SLE care, with appropriate referrals to specialists when indicated. Presence of antiphospholipid antibodies (aPL) impacts therapy considerations for patients with SLE. This guideline does not include specific recommendations for APS; while often overlapping with SLE, therapy and management of APS are beyond the scope of this SLE treatment guideline.

Comprehensive management recommendations for common SLE-associated comorbidities are also considered beyond the scope of this project, but important adjunct considerations referencing other guidelines and sources are briefly summarized as a resource to complement the SLE-directed treatment recommendations. Recommendations regarding SLE treatment options during pregnancy are not included; they are addressed in the ACR's guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.[17]

RESULTS/RECOMMENDATIONS

Terminology, definitions, and abbreviations are summarized in Table 2; recommendations and GPS are listed in Table 3. Limitations in available evidence and heterogeneity in clinical practice patterns

Table 2. Terminology, definitions and abbreviations*

Terminology	ACR SLE Treatment Guideline Definition
SLE Disease Activity Level	
Severe	Very active disease that may be organ- and/or life-threatening or cause permanent damage or severe symptoms due to active inflammation
Moderate	Active, uncontrolled disease that is not immediately life-threatening and/or causes moderate symptoms due to active inflammation
Mild	Active disease that is not immediately organ- or life-threatening and/or causes no more than mild symptoms due to active inflammation
SLE Disease Activity State	
Remission	Symptoms and signs of disease activity are significantly reduced or absent for an extended time. Specific definitions vary. Example: DORIS remission: SLEDAI-2K = 0, Prednisone ≤5 mg/day, PGA <0.5, stable antimalarials, immunosuppressives, biologics (no requirement for normal serology)[34]
Low level disease activity	A period with a low level of disease activity with no major organ involvement. Specific definitions vary. Example: Lupus Low Disease Activity State (LLDAS): SLEDAI-2K score ≤4 (with no activity in major organ systems or new/worsening symptoms), prednisone ≤7.5 mg/d, PGA ≤1, stable antimalarials, immunosuppressives, biologics[28]
Medication Abbreviations	
Anti-CD20-therapy	Rituximab, obinutuzumab
AZA	Azathioprine
Biologic Immunosuppressive therapy	IL-1 inhibitor, anti-CD 20 therapy, anifrolumab, belimumab
CCB	Calcium-channel blocker
CNI	Calcineurin inhibitor
CYC	Cyclophosphamide [monthly IV CYC, 0.5-1.0 g/m2]
Conventional Immunosuppressive therapy	Azathioprine, calcineurin inhibitors, intravenous cyclophosphamide, mycophenolic acid analogs, methotrexate
GC	Glucocorticoid
GPS	Good practice statement
HCQ	Hydroxychloroquine
Immunosuppressive therapy	Conventional and biologic therapies
IVIG	Intravenous immunoglobulin G
MPAA	Mycophenolic acid analogs (including mycophenolate mofetil [MMF] and mycophenolic acid [MPA])
MTX	Methotrexate
PLEX	Plasma exchange

* Terminology, definitions, and abbreviations vary across specialties, guidelines, and clinical trials. Those listed here reflect the consensus of the Voting Panel as being both reasonable and relevant; however, no systematic analyses were performed, and others may prefer alternative definitions. ACR, American College of Rheumatology; IL, interleukin; PGA, Physician Global Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

among Voting Panel members presented important challenges in reaching consensus on many recommendations. Explanatory text throughout the "Results" section addresses this, as well as the rationale and suggested implementation of the recommendations.

Monitoring SLE

In people with SLE, we conditionally recommend assessing disease activity regularly, including when there is a change in clinical status or SLE-directed medications

Evidence was indirect and extrapolated from data showing that having a low level of disease activity is associated with better long-term outcomes.[18,19] The frequency of disease activity assessment was discussed extensively; no agreement was reached regarding any one specific time interval leading to the decision to suggest that assessment be done regularly. The Voting Panel felt that while this will most often mean assessment at each follow-up visit, this acknowledges that timing will vary according to the type, severity, and rate of progression of SLE clinical manifestations. The Voting Panel prefers using a version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[20] to measure disease activity, conceding the challenge of administration in daily practice e.g., limitations in electronic medical record (EMR) infrastructure, provider burden, and time constraints. A physician's global assessment is also acceptable. The Voting Panel acknowledges the importance of information provided through patient-reported outcome tools as suggested by the ACR.[21]

In people with SLE, we conditionally recommend assessing disease damage at least annually

Damage accrual is associated with increased mortality.[22,23] Damage assessment involves tools such as the Systemic Lupus International Collaborating Clinics ACR Damage Index (SLICC/ACR-DI)[22] that evaluate long-term effects of both disease and

Table 3. Recommendations and Good Practice Statements*. Color table can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25690/abstract

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
Note: We suggest referring to the explanatory text throughout the "Results" section for each statement below, for details regarding rationale, development, and implementation of the recommendations and good practice statements.			
Monitoring			
In people with SLE, we conditionally recommend:			
Assessing disease activity regularly, including when there is a change in clinical status or SLE-directed medications.	Conditional	Very Low	P26a
Assessing disease damage at least annually.	Conditional	Very Low	P26b
Comorbidities and Risk Management			
GPS: *All people with SLE should receive screening, monitoring, and management for comorbid conditions associated with SLE and its therapies (including infection, cardiovascular disease, bone and joint damage, malignancy, reproductive health complications, and presence of antiphospholipid antibodies. (*Table 4*).*			
Medication Guidance and Treatment Goals			
GPS: *The goal of SLE treatment should be optimal control of disease (e.g., remission or a low level of disease activity) to improve long-term clinical outcomes.*			
GPS: *Prescribe glucocorticoids promptly to obtain rapid control of acute inflammation using the lowest dose and shortest duration necessary and initiate immunosuppressive therapy early to minimize glucocorticoid-related toxicity.*			
Glucocorticoid therapy:			
In people with SLE:			
With organ- or life-threatening SLE flares:			
…We conditionally recommend pulse methylprednisolone treatment (250–1,000 mg for 1–3 days) followed by oral glucocorticoid taper over high-dose oral glucocorticoid taper without pulse treatment.	Conditional	Very low	P29.1
With stable controlled SLE on prednisone >5 mg/day:			
…We strongly recommend tapering the prednisone to a dose of ≤5 mg daily (and ideally to zero) within 6 months.	Strong	Low	P28.1
With sustained remission on prednisone ≤5 mg/day:			
…We conditionally recommend a slow taper toward zero.	Conditional	Very low	P32.1
Who are unable to taper prednisone to ≤5 mg/day:			
…We conditionally recommend initiating or escalating immunosuppressive therapy.	Conditional	Very low	P30.1, P31.1
Hydroxychloroquine therapy:			
In people with SLE, we strongly recommend routine treatment with HCQ unless contraindicated.	Strong	Very low to Moderate	P35.1
In people with SLE, we conditionally recommend continuing HCQ therapy indefinitely, even in the setting of sustained remission.	Conditional	Low	P36.3, P36.4
In people with SLE receiving HCQ therapy:			
…We conditionally recommend a long-term average daily HCQ dose goal of ≤5 mg/kg over a dose goal of >5 mg/kg to minimize retinal toxicity; use of short courses of higher dose (between 5 and 6.5 mg/kg/d) therapy may be necessary at initiation of treatment or to maintain disease control.	Conditional	Very low to Low	P33.1
Immunosuppressive therapy:			
In people with SLE with sustained clinical remission or low disease activity:			
…We conditionally recommend tapering immunosuppressive therapy after 3-5 years with the goal of discontinuation.	Conditional	Low	P36.1, P36.2
General treatment strategies			
GPS: *People with active SLE symptoms should be diagnosed and treated promptly, with severity of lupus activity guiding intensity and choice of therapy.*			
GPS: *When multiple organ systems are involved at onset or during a flare of SLE, therapy should be directed toward all manifestations but should prioritize areas at greatest risk for irreversible damage.*			
GPS: *Organ- or life-threatening SLE should be treated urgently/emergently with aggressive therapy (e.g., pulse/high-dose glucocorticoid and immunosuppressive therapy), including consideration of combination therapies, as time may not permit sequential therapy; the clinical situation and patient's preference should guide the specific combination therapy.*			
GPS: *When medications, procedures, and surgeries beyond the scope of rheumatology practice are considered, the decision to proceed with such therapies requires multidisciplinary discussion between the rheumatologist and the relevant specialists/proceduralists/surgeons.*			
GPS: *When clinical or serologic findings suggest an additional diagnosis or overlap with SLE (e.g., aquaporin-4 antibodies in setting of known SLE and new onset transverse myelitis or optic neuritis), therapy should be adjusted if necessary, depending upon which process is predominant and in consultation with the relevant specialist(s).*			
Organ-specific manifestations*			
For ongoing SLE disease activity in any organ system(s) refractory to initial therapy,			

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
...We strongly recommend escalation of therapy.	Strong	Very low to Moderate	P37.1-P65.1
Hematologic			
Leukopenia: For asymptomatic neutropenia and/or lymphopenia (absolute counts <1,000/mcL for either) attributed to SLE ...We conditionally recommend *against* initiating immunosuppressive treatment (glucocorticoids, conventional or biologic immunosuppressants) in the absence of other lupus disease activity.	Conditional Against	Very Low	P37.1-3
Thrombocytopenia: For chronic asymptomatic thrombocytopenia (<30,000/mcL) attributed to SLE ...We conditionally recommend initiation of glucocorticoid with an additional therapy (MPAA, AZA, CNI, anti-CD 20 agents, belimumab and/or IVIG) over observation or glucocorticoid monotherapy.	Conditional	Very Low	P38.1-5
Thrombocytopenia: For symptomatic thrombocytopenia (i.e., active significant bleeding) attributed to SLE: ...We conditionally recommend initial glucocorticoid therapy with addition of IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents.	Conditional	Very Low	P39.1-8
***Hemolytic Anemia*:** For symptomatic autoimmune hemolytic anemia (i.e., ischemic manifestations and/or hemodynamic instability) attributed to SLE: ...We conditionally recommend initial glucocorticoid therapy with addition of IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents.	Conditional	Very Low	P40.1-8
Neuropsychiatric			
Severe neuropsychiatric syndromes: For Active lupus optic neuritis -OR- Lupus acute confusional state -OR- Active lupus mononeuritis multiplex: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper plus immunosuppressive therapy with IV CYC, MPAA, or anti-CD20 therapy over pulse/high-dose glucocorticoid monotherapy alone.	Conditional	Very Low	P42.1-4 P44.1-4 P46.1-3
For active lupus myelitis: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid and IV CYC over pulse/high-dose glucocorticoid combined with other (non-CYC) immunosuppressive agents.	Conditional	Very Low	P41.1-4
For active lupus psychosis: ...We conditionally recommend anti-psychotic therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-psychotic therapy alone.	Conditional	Very Low	P45.1
***Seizure**:* For seizures attributed to active SLE: ...We conditionally recommend anti-seizure medication plus glucocorticoid, CYC, MPAA, AZA, and/or anti-CD20 over anti-seizure medication alone.	Conditional	Very Low	P43.1, P43.2
***Cognitive dysfunction**:* For isolated cognitive dysfunction attributed to SLE and documented by neuropsychological testing: ...We conditionally recommend *against* adding immunosuppressive therapy (including glucocorticoid) to cognitive therapy over using cognitive therapy alone.	Conditional Against	Very Low	P48.1, P48.2
Cutaneous/mucocutaneous			
GPS: *People with SLE should be educated on the use of sunscreen and other sun-protection measures to reduce risk of rash and potential disease flare.*			
GPS: *Initial therapy for cutaneous lupus rash—in addition to HCQ—should be topical, including glucocorticoid and/or calcineurin inhibitors (*Table 6*); initial therapy may also include a course of intralesional glucocorticoid with dermatology and/or a brief, limited course of oral glucocorticoid.*			
Acute, subacute and chronic cutaneous lupus: For mild, ongoing skin-predominant lupus despite treatment with HCQ and/or topical therapies: ...We conditionally recommend modifying antimalarial therapy (adding quinacrine or switching to chloroquine) over adding an immunosuppressive agent.	Conditional	Very low	P50.1, P50.2 P51.1, P51.2

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
For ongoing moderate-severe cutaneous lupus refractory to topical and antimalarial therapies, and/or oral glucocorticoid necessitating escalation of therapy ...We conditionally recommend the addition of MTX, MPAA, anifrolumab, and/or belimumab.	Conditional	Very low to Moderate	P50.3 P51.5, P51.7
For ongoing moderate-severe cutaneous lupus refractory to topical therapies, antimalarials, and conventional and/or biologic immunosuppressive agents necessitating escalation of therapy: ...We conditionally recommend adding or substituting lenalidomide.	Conditional	Very low	P51.6
Bullous lupus erythematosus:			
For mild ongoing bullous lupus despite treatment with topical therapies and antimalarial therapies: ...We conditionally recommend the initial addition of dapsone over initiation of glucocorticoid.	Conditional	Very low	P52.1
For moderate-severe bullous lupus refractory to topical therapies, antimalarials, and/or oral glucocorticoid necessitating escalation of therapy: ...We conditionally recommend adding a conventional immunosuppressive agent (MPAA, MTX, AZA) and/or anti-CD-20 therapy.	Conditional	Very low	P52.2, P52.3
Chilblain lupus:			
For chilblain lupus despite symptomatic, topical, and antimalarial therapies (including quinacrine): ...We conditionally recommend the addition of pentoxifylline, PDE5 inhibitors (e.g., sildenafil, tadalafil) and/or calcium channel blockers (e.g., nifedipine) over initiation of immunosuppressive therapies.	Conditional	Very low	P53.1-P53.5
Leukocytoclastic vasculitis:			
For ongoing mild cutaneous vasculitis despite topical and antimalarial therapies: ...We conditionally recommend addition of dapsone or colchicine over immunosuppressive therapies including oral glucocorticoid.	Conditional	Very low	P54.4, P54.5
Serositis			
Pleuropericarditis:			
For lupus pleuropericarditis: ...We conditionally recommend initial treatment with NSAID, colchicine, or their combination, with a low threshold for escalation to glucocorticoid therapy over initiating glucocorticoid therapy alone.	Conditional	Very low	P57.1, P58.2
For ongoing/recurrent episodes of lupus pleuropericarditis despite treatment with HCQ, NSAIDs, colchicine, and/or glucocorticoids necessitating escalation of therapy: ...We **conditionally** recommend conventional (MPAA, AZA) or biologic immunosuppressive therapies.	Conditional	Very low	P58.3 P58.4
Musculoskeletal			
GPS: *Initial therapy for acute or recurrent episodes of inflammatory arthritis in people with SLE may include a course of NSAID or a limited course of oral glucocorticoid while waiting for recommended long-term therapies to take effect.*			
Arthritis:			
For persistent or recurrent active SLE arthritis on HCQ, regardless of prior/current NSAIDs or short-term glucocorticoid therapy: ...We conditionally recommend initial therapy with MTX, MPAA, or AZA, with a low threshold to add or substitute with belimumab or anifrolumab for inadequate response over initial biologic therapy.	Conditional	Very low to Low	P60.1-5 P61.1-5
Systemic Vasculitis			
For vasculitis attributed to active SLE: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper and conventional (IV CYC, MPAA, AZA) or biologic (anti-CD 20 therapy, belimumab, anifrolumab) immunosuppressive therapy over glucocorticoid monotherapy alone.	Conditional	Very low to Low	P63.1-3
For severe vasculitis attributed to SLE: ...We conditionally recommend IV CYC or anti-CD20 therapy as initial therapy over other immunosuppressive therapies.	Conditional	Very low	P63.2, P63.3

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
For life-threatening vasculitis attributed to active SLE (e.g., diffuse alveolar hemorrhage or mesenteric vasculitis): ...We conditionally recommend the addition of PLEX and/or IVIG to pulse/high-dose glucocorticoid taper and immunosuppressive therapy over glucocorticoid and immunosuppressive therapy alone.	Conditional	Very low	P63.4
Cardiopulmonary			
Myocarditis: For lupus myocarditis that is acute and/or worsening: ...We conditionally recommend treatment with glucocorticoid and IV CYC, MPAA, anti-CD20 therapy, and/or IVIG over glucocorticoid monotherapy.	Conditional	Very low	P64.1
Non-bacterial (Libman-Sacks) endocarditis: For non-bacterial (Libman-Sacks) endocarditis: ...We conditionally recommend immunosuppressive therapy and/or anticoagulation.	Conditional	Very low	P65.1

* Treatment and management of lupus nephritis is addressed in the 2024 American College of Rheumatology Guideline for the Screening, Treatment, and Management of Lupus Nephritis.[9] AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GPS, good practice statement; HCQ, hydroxychloroquine; IVIG, intravenous Ig; MTX, methotrexate; MPAA, mycophenolic acid analogs; NSAID, non-steroidal anti-inflammatory drugs; PDE5, phosphodiesterase type 5; PICO, population, intervention, comparator, and outcome; PLEX, plasma exchange; SLE, systemic lupus erythematosus.

medication toxicities. The process of formally assessing damage criteria can serve to identify individual vulnerabilities and prompt changes in therapy or management; it can also guide discussion of prognosis. Yearly evaluation is favored, especially for pediatric/adolescent patients who are undergoing rapid physical development.[24]

Comorbidities and Risk Management

GPS: All people with SLE should receive appropriate screening, monitoring, and management for comorbid conditions associated with SLE and its therapies

SLE and its therapies are associated with infection, cardiovascular disease, bone and joint damage (e.g., osteoporosis, avascular necrosis), malignancy, and reproductive health complications. aPL may increase risk for certain disease manifestations and disease damage;[25] accordingly, aPL assessment should be included in comorbidity screening. Promoting a healthy diet, sleep hygiene, and physical activity for people with SLE is important. Reduced comorbidity risk and improved management are ideally achieved by collaboration with primary care providers and relevant subspecialists. We do not provide formal recommendations addressing comorbidities due to scope limitations but do include a summary of general suggestions with relevant references in Table 4. We emphasize that these suggestions are based on outside sources: they are not formal recommendations. Table 4 is included to provide convenient access to relevant information for the clinician, and as a reminder to incorporate comorbidity management into general SLE care.

Medication Guidance and Treatment Goals

Glucocorticoids, antimalarials, and conventional and biologic immunosuppressive therapies are the cornerstones of treatment for people with SLE, aimed at reducing disease activity while limiting treatment toxicity (Figure 1). Adherence to antimalarial therapy should be assessed when any change in medication use is anticipated. Table 5 reviews monitoring and dosing for commonly used SLE medications. Table 5 presents supporting information that is relevant to but not part of our formal recommendations with the goal of providing convenient access to these published suggestions from outside sources. Prescribing and monitoring should be tailored to individual clinical situations.

GPS: Treatment for SLE should be directed toward optimal control of disease (remission or low level of disease activity) in order to improve long-term clinical outcomes

Prolonged medication-free remission is rare in SLE;[26] however, remission or low disease activity on stable antimalarial and immunosuppressive therapies with low-dose (or no) glucocorticoid are often attainable. Routine implementation of a treat-to-target (T2T) strategy is an important future goal for SLE management.[27–32] T2T involves a formal process of ongoing treatment adjustments to attain a well-defined, clinically meaningful goal, and has been recommended by the ACR for

Table 4. Suggestions for adjunctive therapies and management of comorbidities*

Suggested Comorbidity Guidance and Management	
General	
Lifestyle[a,b]	Physical activity, sleep hygiene, and therapeutic exercise Photoprotection Smoking cessation Psychosocial interventions
a. EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis. Parodis I, et al. Ann Rheum Dis 2024;83:720.	
b. Recommendations for physical activity and exercise in persons living with Systemic Lupus Erythematosus (SLE): consensus by an international task force. Blaess J, et al. RMD Open 2024;10:e004171.	
Cardiovascular Health	
ASCVD risk:	SLE is a "risk-enhancing factor": Assess using risk calculator and manage traditional risk factors[c,d];
c. ***2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines****. Arnett DK, et al. J Am College Cardiol. 2019;74:1376.*	
d. ***The use of risk-enhancing factors to personalize ASCVD risk assessment: evidence and recommendations from the 2018 AHA/ACC multi-society cholesterol guidelines****. Agarwala A, et al. Curr Cardio Risk Rep 2019;13:1.*	
Infection Screening	
HBV	General: All adults at least once in lifetime[e] All people with SLE before immunosuppressive therapy (including glucocorticoid according to dose/duration)[f]
HCV	General: All adults at least once in lifetime (except where HCV prevalence is <0.1%)[e] Consider for all people with SLE before immunosuppressive therapy (including glucocorticoid according to dose/duration)[f]
Tuberculosis	Adults: Before biologic (and targeted synthetic) immunosuppressives[g]; Consider before conventional immunosuppressives, other immunosuppressives and/or glucocorticoids (according to dose/duration)[f] Children and adolescents: Before biologic immunosuppressives[h]
HIV	Adults: Before biologic immunosuppressives[f] Consider before conventional (and targeted synthetic) immunosuppressives, other immunosuppressives and/or glucocorticoids (according to dose/duration)[f]
e. ***Centers for Disease Control and Prevention***	
f. ***2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases.*** *Fragoulis GE, et al. Ann Rheum Dis 2023;82:742–753.*	
g. ***United States Preventive Services Taskforce***	
h. ***American Academy of Pediatrics***	
Vaccinations	
High-dose influenza, Pneumococcal, Recombinant VZV	>18 years of age on immunosuppressive therapy[i]
COVID-19	All ages ≥6 months if moderately/severely immunocompromised (initial and boosters)[e]
RSV	Adults 60–74 years if increased risk; includes immunocompromised individuals[e]
HBV	Adults 19–59 years[e] Adults ≥60 years with risk factors Children/adolescents <19 years
HPV	Adults >26 years and <45 years on immunosuppressive therapy (if not previously vaccinated)[i] All children/adolescents/young adults (9–26 years)[e]
e. ***Centers for Disease Control and Prevention***	
i. ***2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases.*** *Bass AR, et al. Arthritis Care Res (Hoboken) 2023;75:449–464.*	
Infection Prophylaxis	
PJP	Consider for all people on high-dose glucocorticoid (daily dose >15–30mg of prednisolone or equivalent for >2–4 weeks[f]) Note: Prophylaxis considered controversial outside of organ transplant[j]; rates in people with SLE are very low (0.4%)[k] Higher risk: • Glucocorticoid in combination with immunosuppressives[f] • Underlying interstitial lung disease[f] • Lymphopenia <500[f]
HBV[l]	Determine by both hepatitis B serologic profile and immunosuppressive regimen[9] *Serologic profiles*:

(Continued)

Table 4. (*Cont'd*)

Suggested Comorbidity Guidance and Management	
	• Higher risk: HBsAg positive and anti-HBc positive. • Lower risk: HBsAg negative and anti-HBc positive *Immunosuppressive regimens:* Prophylaxis for high reactivation risk therapy (>10%) including treatment with: • B-cell depleting therapy • Moderate- to high-dose glucocorticoid (>20 mg daily for > 4 weeks) Consider prophylaxis for moderate reactivation risk therapy (1–10%) including treatment with: • TNF-inhibitors • Other cytokine inhibitors Monitor only for low reactivation risk therapy (<1%) including treatment with: • Conventional immunosuppressives
f. ***2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases.*** *Fragoulis GE, et al. Ann Rheum Dis 2023;82:742–753.*	
j. ***Risk factors and prevention of Pneumocystis jirovecii pneumonia in patients with autoimmune and inflammatory diseases****. Ghembaza A, et al. Chest 2020;158:2323–2332.*	
k. ***Rates of Pneumocystis jirovecii pneumonia and prophylaxis prescribing patterns in a large electronic health record cohort of patients with systemic lupus erythematosus****. Boone B, et al. Sem Arthritis Rheum 2022;57:152106.*	
l. ***American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy****. Perrillo RP, et al. Gastroenterology 2015;148:221–244.e3.*	
Bone health	
No chronic GC[g]	Screen all women 65 years and older Screen postmenopausal women <65 years at risk No recommendations for men
GC ≥2.5 mg pred > 3 mo[m]	
Screening	≥40 years: FRAX and BMD with vertebral fracture assessment or spinal x-rays <40 years: BMD with vertebral fracture assessment or spinal x-rays
Therapy	Assess fracture risk as per ACR guideline Offer oral bisphosphonates (or alternative) to all with medium or higher fracture risk. For very high risk, consider denosumab or parathyroid hormone/ parathyroid hormone-related protein over bisphosphonates.
g. **United States Preventive Services Taskforce**	
m. ***2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis****. Humphrey MB, et al. Arthritis Rheumatol 2023;75:2088–2102.*	
Cancer screening	
General[n,o]	All general population screening measures should be observed Consider urine cytology screening if prior CYC therapy
Cervical cancer[p,q]	Enhanced screening protocol: All women with SLE, regardless of immunosuppressive use, should follow screening guidelines for HIV-infected women[p]
n. ***European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies.*** *Mosca M, et al. Ann Rheum Dis 2010;69:1269–1274.*	
o. ***Managing cancer risk in patients with systemic lupus erythematous****. Ladouceur A, et al. Expert Rev Clin Immunol 2018;14:793–802.*	
p. ***Guidelines for cervical cancer screening in immunosuppressed women without HIV infection****. Moscicki AB, et al. J Low Genit Tract Dis 2019;23:87–101.*	
q. ***New WHO recommendations on screening and treatment to prevent cervical cancer among women living with HIV: policy brief****. World Health Organization; 2021.*	
Reproductive health	
Contraception[r]	IUD or subdermal progestin implant preferred No estrogen-containing methods if active disease or aPL-positive IUD or 2 methods if taking MPAA
Fertility[r]	Defer assisted reproductive therapy if active SLE Low molecular weight heparin for ovarian stimulation in aPL+ patients Fertility preservation with monthly IV CYC: • Females: Gonadotropin-releasing hormone agonist co-therapy • Males: consider pre-treatment sperm cryopreservation
Pregnancy[r]	Defer pregnancy if active SLE Avoid pregnancy if significant organ damage Attempt conception after stable/low disease activity on pregnancy compatible-medications for 4–6 months Low-dose aspirin for preeclampsia prophylaxis Hydroxychloroquine (if not contraindicated) Assess, monitor, and treat for aPL and anti-Ro/La antibodies

(Continued)

Table 4. (*Cont'd*)

Suggested Comorbidity Guidance and Management	
Menopause[r]	Avoid hormone replacement therapy if active SLE or aPL-positive
r. ***2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.*** *Sammaritano LR, et al. Arthritis Rheumatol 2020;72:529–556.*	
Medication toxicity	
Glucocorticoid	Assess for glucocorticoid withdrawal syndrome and adrenal insufficiency with taper which may mimic nonspecific SLE symptoms[s]
s. ***European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency.*** *Beuschlein F, et al. Eur J Endocrinol 2024;190:G25–G51.*	

* This table is a synthesis of published sources, some with limited data and/or differing recommendations, and was constructed with input from SLE Guideline Team members. We present suggestions (with reference to outside sources) to guide screening and management of common comorbidities. These are suggestions only; they are not formal recommendations. Care for individuals with SLE will vary based on their clinical situation and personal preferences. References and guidelines cited here are the most current sources available at the time of guideline preparation and will be updated when this guideline is revised; however, be aware that revisions of these sources may be published in the interim.
The vaccine summary here includes recommendations for immunizations deemed relevant to SLE and is not comprehensive. Children and adolescents with cSLE are more likely to have delays in their vaccine schedule due to immunosuppressive medications; consult the CDC website for recommendations: https://www.cdc.gov/vaccines/?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-changes.html#guidance.
ACC, American College of Cardiology; ACR, American College of Rheumatology; AHA, American Heart Association; aPL, antiphospholipid antibodies; ASCVD, atherosclerotic cardiovascular disease; BMD, bone mineral density; cSLE, childhood-onset SLE; CYC, cyclophosphamide; FRAX, fracture risk assessment tool; GC, glucocorticoid; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; IV, intravenous; IUD, intrauterine device; MPAA, mycophenolic acid analogs; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; VZV, varicella zoster virus.

treatment of rheumatoid arthritis.[33] DORIS remission and the Lupus Low Disease Activity State (LLDAS)[28,34] definitions (Table 2) are the most widely accepted validated clinical goals for SLE, however, evidence from randomized trials of T2T for SLE are not yet available. SLE disease modification, i.e., slowing or preventing organ damage, remains an emerging concept.[30,31,35]

Glucocorticoid Therapy

GPS: Prescribe glucocorticoids promptly to obtain rapid control of inflammation using the lowest dose for the shortest duration and initiate immunosuppressive therapy early to minimize glucocorticoid-related toxicity

In people with organ- or life-threatening SLE flares, we conditionally recommend pulse methylprednisolone treatment (250 – 1,000 mg for 1-3 days) followed by oral glucocorticoid taper over high-dose oral glucocorticoid taper without pulse treatment

Glucocorticoids provide rapid suppression of SLE disease activity, but side effects may lead to significant toxicity.[36,37] Intravenous (IV) glucocorticoids have a more rapid onset of action than oral preparations and are preferred for life- or organ-threatening manifestations of SLE, such as transverse myelitis or severe thrombocytopenia; however, Voting Panel members acknowledged that challenges with access to infusion centers may limit their outpatient use.

In people with stable controlled SLE taking prednisone >5 mg/day we strongly recommend tapering the prednisone to a dose of ≤5 mg/day (and ideally discontinue prednisone) within 6 months

In people with sustained remission taking prednisone ≤5 mg/day, we conditionally recommend a slow taper toward prednisone discontinuation

In people unable to taper prednisone to ≤5 mg/day, we conditionally recommend initiating or escalating immunosuppressive therapy

Risks of glucocorticoid toxicity led to a strong recommendation to taper glucocorticoids quickly to avoid long-term exposure.[36,37] Tapering off glucocorticoids completely (with addition of immunosuppressive therapy when unable to do so) is recommended because even low-dose long term glucocorticoid confers risk.[38] The recommendation to taper off completely is conditional because the balance of benefit and harm will vary depending on individual risks as well as personal preferences.[39] For individuals with stable controlled disease we strongly discourage a chronic daily dose of >5 mg due to the well-recognized harms of chronic therapy. Even for those in clinical remission, (i.e., DORIS remission, which permits 5 mg/d prednisone), we encourage an effort to reduce or stop prednisone. A slow taper in 1 mg increments from a low prednisone dose such as 5 mg/day, with continued hydroxychloroquine (HCQ) or other therapies, may permit discontinuation.[40–42] Glucocorticoid withdrawal syndrome and adrenal insufficiency may be confused with nonspecific SLE symptoms and may impact the ability to taper off glucocorticoid therapy.[43]

Hydroxychloroquine therapy

In people with SLE, we strongly recommend routine treatment with HCQ unless contraindicated

In people with SLE, we conditionally recommend continuing HCQ therapy indefinitely, even in the setting of sustained remission

In people with SLE receiving HCQ therapy, we conditionally recommend a long-term average daily HCQ dose goal of ≤5 mg/kg over a dose goal of >5 mg/kg to minimize retinal toxicity; use of short courses of higher dose (between 5 and 6.5 mg/kg/d) therapy may be necessary at initiation of treatment or to maintain disease control

Hydroxychloroquine is preferred over other antimalarials due to its better safety profile,[44] although use of other antimalarials may be considered. Due to its multiple benefits, continuing HCQ with appropriate monitoring (Table 5) is strongly recommended, even during remission. Level of certainty for evidence varied from very low to moderate for differing outcomes; it was moderate for complete and partial response (Supplementary Materials 3). A maintenance goal of ≤5 mg/kg/day is endorsed to minimize long-term toxicity. Higher doses (between 5 and 6.5 mg/kg/day) may be justified for shorter term use, i.e., when initiating therapy, addressing periods of incomplete disease control, or during pregnancy.[45–48] Routine screening for HCQ retinopathy is important for all long-term HCQ users to mitigate the risk of vision loss, as it can identify asymptomatic, early-stage retinopathy.[47,49] The recommendation for indefinite use of HCQ is conditional; further research is needed to determine benefits versus harms. Given challenges in testing methodologies and interpretation, no consensus was reached on the optimal use of HCQ blood levels for guiding therapy. The primary utility of HCQ blood level monitoring presently lies in assessing adherence. As HCQ testing becomes more standardized and available, blood levels may inform medication dosing in the future.

Immunosuppressive Therapy

In people with SLE with sustained clinical remission or with low disease activity, we conditionally recommend tapering immunosuppressive therapy after 3-5 years, with the goal of discontinuation

The decision for discontinuation of immunosuppressive therapy should be based on individual risk for recurrence of active disease, severity of organ system involvement, and patient preference. Withdrawal of mycophenolate mofetil in individuals with quiescent SLE did not result in a higher rate of clinically significant disease reactivation in a randomized controlled trial.[50]

Pediatric considerations regarding medication guidance and treatment goals

This guideline is broadly applicable to childhood-onset SLE with specific considerations. A pediatric rheumatologist should be consulted, when possible, especially in highly complex or acutely ill patients. The combination of severe disease onset in youth necessitating high glucocorticoid exposure and its associated comorbidities can diminish peak bone mass, reduce adult height, and alter pubertal development.[51,52] Glucocorticoids impact physical appearance, influencing self-identity and mood.[53] Applying pediatric specific glucocorticoid dosing is important to minimize glucocorticoid adverse effects.[54] School attendance and performance should be assessed regularly for potential support with pharmacologic and non-pharmacologic intervention, as they can influence long-term vocational outcomes.[55] We recommend a planned transition to adult care to decrease risks of unscheduled health care utilization, care gaps, and disease flares.[51,52,56–59]

Organ-Specific Manifestations

Good practice statements and recommendations address both overall disease activity and specific organ system manifestations. For each organ system, GPS are listed first followed by recommendations.

GPS: People with active SLE symptoms should be treated promptly, with degree and type of lupus activity guiding intensity and choice of therapy

GPS: When multiple organ systems are involved at onset or during a flare of SLE, therapy should prioritize life-threatening systems or areas at greatest risk for irreversible damage

While it is important to identify optimal therapy for any given lupus manifestation, it is most common for multiple organ systems to be affected during a flare. For this reason, many of the good practice statements and recommendations in this guideline are general in scope and address broad tenets of multisystem therapy. Recommendations are provided to address organ specific manifestations where possible; these will be most useful when one organ system predominates. We suggest prioritizing life-threatening involvement and/or risk for irreversible damage when reconciling treatment recommendations that may have variable effectiveness for different organ systems in the setting of multi-organ involvement. We acknowledge, however, that this is a major challenge in management of SLE, and include this as a future research priority (Supplementary Materials 7).

GPS: Organ-or life-threatening SLE should be treated urgently/emergently with aggressive therapy (e.g., pulse/high-dose glucocorticoid and immunosuppressive therapy), including consideration of combination therapies, as time may not permit sequential therapy; the clinical situation and patient's preference should guide the specific combination therapy

GPS: When medications, procedures, and surgeries beyond the scope of rheumatology practice are considered, the decision to proceed requires multidisciplinary discussion between the rheumatologist and the relevant specialists/ proceduralists/surgeons

GPS: Adjust therapy when clinical or serologic findings suggest an additional diagnosis or overlap with SLE (e.g., aquaporin-4 antibodies in setting of known SLE and new onset transverse myelitis or optic neuritis), depending upon which process is predominant and in consultation with the relevant specialist(s)

For ongoing SLE disease activity in any organ system(s) refractory to initial therapy, we strongly recommend escalation of therapy over continuing the current therapy

The Voting Panel strongly recommends escalating treatment for ongoing, nonresponsive disease activity in any organ system. All members agreed upon the dual priorities of rapid and effective control of immune-mediated manifestations while minimizing glucocorticoid use. Organ-specific recommendations for specific therapies, however, are conditional for several reasons. Available evidence for organ-specific manifestations has lower certainty, with data stemming from observational studies or post-hoc analyses of randomized controlled trials. Studies often group manifestations differently: e.g., "severe neuropsychiatric lupus" includes myelitis, optic neuritis, and acute confusional state. Voting Panel participants' experience and clinical practice patterns varied. In the setting of limited evidence and an absence of data that directly compared treatment options for specific organ systems, Voting Panel members' clinical practice patterns and the preferences outlined by the Patient Panel guided recommendations. The initial PICO-generated recommendations were extensively discussed; when necessary, they were rewritten and revoted upon until consensus was reached. The final recommendations represent compromises among Voting Panel discussants who, while reviewing the same evidence, sometimes had varying clinical perspectives on optimal therapy.

In many clinical situations, the Voting Panel members did not recommend that one medication – or even one class of medication – take priority over another; however, in some clinical scenarios, a specific medication may be suggested when evidence and clinical experience is supportive. Recommendations may change in subsequent guideline revisions as more direct evidence becomes available.

HEMATOLOGIC MANIFESTATIONS

In situations with life-threatening hematologic manifestations, including marked cytopenias suggestive of macrophage activation syndrome or thrombotic microangiopathy[60], co-management with hematologists is suggested.

Leukopenia

For asymptomatic neutropenia and/or lymphopenia (absolute counts <1,000/mcL for either) attributed to SLE, we conditionally recommend *against* initiating immunosuppressive treatment (glucocorticoids, conventional or biologic immunosuppressants) in the absence of other lupus disease activity

Neutropenia attributed to SLE is treated with recombinant human granulocyte colony-stimulating factor (G-CSF) only if it is severe and associated with infection;[61] G-CSF should be used with caution as lupus flares have been reported after treatment.[62] Lymphopenia, which is more common than neutropenia, is usually associated with overall lupus disease activity and generally does not require specific treatment.[61]

Thrombocytopenia

For chronic asymptomatic thrombocytopenia (<30,000/mcL) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with addition of mycophenolic acid analogs (MPAA), azathioprine (AZA), calcineurin inhibitor (CNI), anti-CD 20 agents, belimumab and/or IVIG over observation or glucocorticoid monotherapy alone

For symptomatic thrombocytopenia (i.e., active, significant bleeding) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents

Most data are indirect and extrapolated from hematology guidance; the American Society of Hematology guideline suggests treatment rather than observation for platelet counts <30,000/mcL in cases of idiopathic thrombocytopenic purpura.[63,64] Initial aggressive treatment is generally followed by maintenance immunosuppressive therapy. The use of thrombopoietin mimetics is effective in SLE but

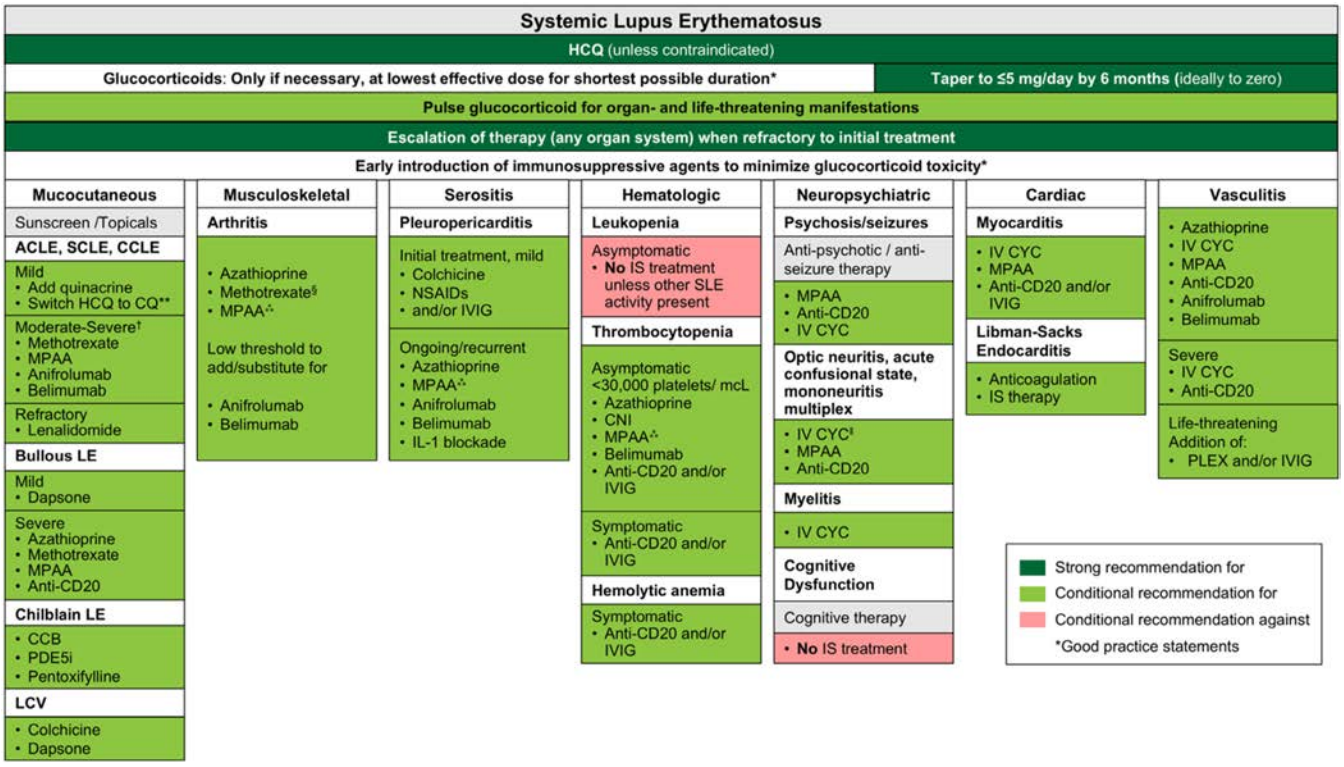

Figure 1. Overview of the recommended management for systemic lupus erythematosus (SLE). This schematic illustrates the approach to SLE treatment, with organ-specific therapies presented in separate boxes and stratified by disease severity. **The order of the medications in each box does not indicate preference unless noted otherwise.** Lupus nephritis treatment is addressed in the 2024 American College of Rheumatology Guideline for the Screening, Treatment, and Management of Lupus Nephritis.[9] **In CLE, switch HCQ to CQ with the intention of changing back to HCQ once the rash is under control. †Azathioprine may be used when pregnancy is planned. Based on the Voting Panel members' clinical experience, anifrolumab has a more rapid onset of benefit and a greater likelihood of response than belimumab. ⁂MPAA may be preferable over azathioprine. §Alternative agents such as leflunomide are occasionally used for those with arthritis. ‖Evidence for severe neurologic syndromes was largely limited to IV CYC.
ACLE, acute cutaneous lupus erythematosus; CCB, calcium channel blockers; CCLE, chronic cutaneous lupus erythematosus; CNI, calcineurin inhibitor (cyclosporin or tacrolimus); CQ, chloroquine; HCQ, hydroxychloroquine; IL-1, interleukin-1; IS, immunosuppressive therapy; IV CYC, intravenous cyclophosphamide; IVIG, intravenous Ig; LCV, leukocytoclastic vasculitis; LE, lupus erythematosus; MPAA, mycophenolic acid analogs; NSAIDs, non-steroidal anti-inflammatory drugs; PDE5i, phosphodiesterase type 5 inhibitors; PLEX, plasma exchange; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

should involve consultation with a hematologist.[65] Splenectomy is a therapy of last resort. For asymptomatic thrombocytopenia with platelet count 30-100,000/mcl, treatment is generally not indicated.[64]

Hemolytic Anemia

For <u>symptomatic</u> autoimmune hemolytic anemia (i.e., ischemic manifestations and/or hemodynamic instability) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents

For mild, well-compensated hemolytic anemia, alternate therapies such as short-term glucocorticoids and conventional/biologic immunosuppressive agents may be considered.

NEUROPSYCHIATRIC MANIFESTATIONS

Neuropsychiatric SLE (NPSLE) consists of a broad range of neurologic and psychiatric manifestations that can involve any aspect of the central, peripheral, or autonomic nervous system.[66] Once ascribing signs or symptoms to SLE, an assessment of active disease (inflammatory or aPL immune-mediated) versus chronic damage should occur. In general, treatment of stroke in the setting of SLE is best directed by neurologists[67] with addition of immunosuppressive therapy when SLE-mediated inflammation is identified. We suggest a multi-disciplinary approach, including co-management with neurologists and/or psychiatrists/psychologists.

No recommendations were made for small fiber neuropathy; while found in SLE, no consensus was reached regarding immunomodulatory therapy. All agreed that this is an important research agenda item.

Table 5. Medications to treat SLE: suggested dosing and monitoring[a]

MEDICATION[a,b,c]	MONITORING	DOSING
Anakinra (Kineret®)	**CBC with differential** monthly for 3 months, then every 3 months for 3 months, then every 6 months	• Adult dosing: 100 mg SC or IV daily • Pediatric dosing: 2 mg/kg/day SC or IV daily (max 100 mg/dose). Maximum dosing of 8 mg/kg/day • Dosing for macrophage activation syndrome: 100 mg SC or IV daily, can be increased to 100 mg q 6 hours
Anifrolumab (Saphnelo®)	For adults ≥ 18 years of age, suggest at least one dose of **recombinant varicella-zoster vaccine** prior to initiation[c]	• Adult dosing: 300 mg IV q 4 weeks • Preliminary pediatric dosing: ≥ 10 years and ≥40 kg: 300 mg IV q 4 weeks. If ≥ 12 years, 300 mg IV q 4 weeks
Azathioprine (Imuran®)	**CBC with differential, AST, ALT** every 2 weeks for 8 weeks, then every 2 months **TPMT** genotyping, and **NUDT15**[d] if available, prior to initiation. Caution with allopurinol as co-administration increases azathioprine levels.	• Adult dosing: 2–3 mg/kg/day PO daily or in 2 divided doses • Pediatric dosing: 2–3 mg/kg/day PO daily or in 2 divided doses

Belimumab (Benlysta®)	**Mood changes**: Monitor for new or worsening depression or suicidal thoughts.	Adult dosing:
		• IV dosing: 10 mg/kg/dose q 2 weeks x 3 doses then q 4 weeks
		• SC dosing: 200 mg weekly
		Pediatric dosing ≥ 5 years old:
		• IV dosing: 10 mg/kg/dose q 2 weeks x 3 doses then q 4 weeks
		• SC dosing:
		  ○ 15 kg to < 40 kg: 200 mg q 2 weeks
		  ○ ≥ 40 kg: 200 mg weekly

Chloroquine (Aralen®)	**CBC with differential, AST, ALT and creatinine** at baseline and periodically **Eye Screening:** at baseline and then every 4–6 months from onset of use. **ECG:** at baseline and subsequently if at risk for QTc prolongation due to concomitant medications or cardiac risk factors for arrythmia, including Congenital Long QT Syndrome.[e]	• Adult dosing: 2.3 mg/kg/day is the maximum dosing. • Pediatric dosing: none established
Colchicine (Colcrys®)	Concomitant use of colchicine with inhibitors of CYP3A4 or P-glycoprotein efflux transporters can lead to significant increases in colchicine plasma levels. Check drug interactions prior to use.	• Adult Dosing: 0.6–1.2 mg PO daily or in 2 divided doses. Maximum dose of 3 mg daily • Pediatric Dosing: 0.6–1.2 mg PO daily or in 2 divided doses. Maximum dose of 2 mg daily
Cyclophosphamide (Cytoxan®)	**CBC with differential and creatinine** weekly for 4 weeks, then monthly **Urine pregnancy testing** for women of reproductive age prior to each infusion **Urinalysis** with infusions per local protocols and then every 6 months following completion of course **Mesna** is not routinely recommended for standard dose intravenous cyclophosphamide[f] **Urine cytology** to screen for bladder cancer if cumulative dose > 36 grams **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 750–1,000 mg/m^2/dose IV monthly x 6 months; maximum 1200 mg/dose • Pediatric dosing: 500–750 mg/m^2/dose IV monthly x 6 months; maximum 1200 mg/dose
Cyclosporine (Gengraf®, Neoral®, Sandimmune®)	**Creatinine, potassium, magnesium** every 2 weeks for 12 weeks, then monthly **CBC with differential**, **AST, ALT** monthly for 3 months, then every 3 months **Lipid screen** every 6 months **Blood pressure** monitoring at initiation and periodically, including when adding, modifying or discontinuing other medications	• Adult dosing: 3–5 mg/kg/day PO in 2 divided doses[h] • Pediatric dosing: same as adult dosing[h]
Dapsone	**CBC with differential, AST, ALT** weekly for 4 weeks, then every 4 weeks for 3 months, then every 3 months thereafter Check for **G6PD deficiency** before starting treatment	• Adult dosing: 50 mg PO once daily; Maximum dosing of 150 mg/day divided BID

(Continued)

Table 5. (*Cont'd*)

MEDICATION[a,b,c]	MONITORING	DOSING
		• Pediatric dosing: 1–2 mg/kg/day PO once daily. Maximum dosing of 100 mg/day
Hydroxychloroquine (Plaquenil®)	**CBC with differential, AST, ALT, creatinine** at baseline and periodically **Eye Screening:** at baseline and then annually no later than 5 years after starting treatment[l] **ECG:** at baseline and subsequently if at risk for QTc prolongation due to concomitant medications or cardiac risk factors for arrythmia, including Congenital Long QT Syndrome.[e]	• Adult dosing: 5 mg/kg/day, usually 200–400 mg daily or divided BID. Maximum dosing of 400 mg/day • Pediatric dosing: same as adult dosing
Intravenous Immunoglobulin (IVIG)	**CBC with differential** prior to first administration, then monthly if high dose to follow for hemolysis **AST, ALT, chemistry panel** prior to administration	• Adult dosing: 2 g/kg given over 2–5 consecutive days monthly • Pediatric dosing: 1 to 2 g/kg q 2–4 weeks
Leflunomide (Arava®)	**CBC with differential, AST, ALT, creatinine** monthly for 3 months, then every 3 months **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 10–20 mg PO daily in one dose • Pediatric dosing: • >20 kg: 10 mg PO QOD • 20-40 kg: 10 mg PO daily • >40 kg: 20 mg PO daily
Lenalidomide (Revlimid®)	**CBC with differential, AST, ALT, creatinine** at baseline, at one month and then q 2-3 months **TSH** at baseline and every 3–6 months during treatment **Urine pregnancy testing** 10–14 days and again 24 hours prior to initiating therapy, weekly during first 4 weeks of treatment, then every 2–4 weeks through 4 weeks after therapy is discontinued Please see the REMS website: https://www.lenalidomiderems.com/	• Adult dosing: 5 mg PO daily • Pediatric dosing: none established
Methotrexate (Trexall®, Rheumatrex®)	**CBC with differential, AST, ALT, creatinine** monthly for 3 months, then every 3 months **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 20–25 mg SC or PO once a week. Maximum dosing of 25 mg weekly • Pediatric dosing: • 15 mg/m^2 SC or PO once a week. Maximum dosing of 25 mg weekly; OR • 1 mg/kg SC or PO once a week. Maximum dosing of 25 mg weekly
Mycophenolate mofetil (Cellcept®)	**CBC with differential** with initiation and approximately 2 weeks after each dose change; regularly once on stable dosing **Urine pregnancy screen** at baseline, 8–10 days after baseline and at subsequent visits for females of reproductive potential. **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g] Please see the REMS website: https://www.mycophenolaterems.com/#Main	• Adult dosing: 2–3 grams PO daily in 2 divided doses. Maximum dosing of 3 grams daily • Pediatric dosing: 300–600 mg/m^2/dose PO twice daily. Maximum dosing of 3 grams daily
Non-steroidal anti-inflammatory Drugs (NSAIDs)	**CBC with differential, creatinine, potassium** every 6 months **Blood pressure** every 12 months	Varies according to NSAID
Obinutuzumab (Gazyva®)	**CBC with differential** at 3 months, then every 6 months **IgG levels** assessed every 6 months	• Adult dosing: 1,000 mg IV on Day 1 and at weeks 2, 24, 26 and 52 • Pediatric dosing: none established
Quinacrine	**CBC with differential, complete metabolic panel** 2 weeks after starting and then 4 weeks later	• Adult dosing: 100 mg PO daily • Pediatric dosing: none available Requires compounding in the US; availability varies in other countries
Rituximab (Rituxan®) and biosimilars	**CBC with differential** at 3 months, then every 6 months **IgG levels** assessed every 6 months	Adult dosing: • 1 gram IV on Days 1 and 15

(Continued)

Table 5. (*Cont'd*)

MEDICATION[a,b,c]	MONITORING	DOSING
		Pediatric dosing: • 375 mg/m^2/dose IV weekly x 4 doses. Maximum dosing of 1 gram/dose OR • 750 mg/m^2/dose IV every 2 weeks x 2 doses. Maximum dosing of 1 gram/dose
Tacrolimus (Prograf®)	**CBC with differential, AST, ALT** monthly for 3 months, then every 3 months **Creatinine, potassium, magnesium** every 2 weeks for 12 weeks, then monthly **Lipid screen** every 6 months **Blood pressure** monitoring at initiation and periodically, including when adding, modifying or discontinuing other medications	• Adult dosing: 0.05–0.1 mg/kg/day PO in 2 divided doses[h] • Pediatric dosing: 0.2–0.3 mg/kg/day PO in 2 divided doses[h]

ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, bis in die (twice a day); CBC, complete blood counts; ECG, electrocardiogram; FDA, US Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; NUDT15, nudix hydrolase 15; PO, orally; QOD, every other day; QT, measurement from start of Q wave to end of T wave on electrocardiogram (ventricular repolarization time); QTc, corrected QT interval; REMS, Risk Evaluation and Mitigation Strategy; SC, subcutaneous; SLE, systemic lupus erythematosus; TSH, thyroid stimulating hormone; TPMT, thiopurine methyltransferase.

[a] Dosing and monitoring listed here are suggestions and not recommendations by the Voting Panel. They are based on a compilation of data from online medication formularies, FDA package inserts for those medications with approved indications, published trial data, other relevant guidelines, and the clinical expertise of the Core and Voting Panels. As such, these suggestions may differ from other sources. Prescribing and monitoring should be tailored to individual patients, including adjustments for chronic kidney disease if indicated, and aided by the assistance of local pharmacists as needed.

[b] Please consult Table 4 for pre-treatment screening that is complementary to this guidance.

[c] We recommend routine vaccinations for all patients prior to starting immunosuppressive therapy, if possible. Please consult Table 4 and the following guideline for vaccination in patients with rheumatic and musculoskeletal disease: Bass AR, Chakravarty E, Akl EA, et al. 2022 American College of Rheumatology Guideline for vaccinations in patients with rheumatic and musculoskeletal diseases. *Arthritis Care Res (Hoboken)* 2023;75 (3):449–464.

[d] Pratt VM, Cavallari LH, Fulmer ML, et al. TPMT and NUDT15 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn* 2022 Oct;24 (10):1051–1063.

[e] Desmarais J, Rosenbaum JT, Costenbader KH, et al. American College of Rheumatology White Paper on Antimalarial Cardiac Toxicity. *Arthritis Rheumatol* 2021;73 (12):2151–2160.

[f] Hensley ML, Schuchter LM, Lindley C, et al. American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol* 1999;17:3333–3355.

[g] Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol* 2020;72 (4):529–556.

[h] Therapeutic levels are based on literature in transplant patients. There are minimal data in SLE patients. Trough levels can be used for adherence and toxicity assessments.

[i] Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. Arthritis Rheumatol 2021;73:908-911.

Severe Neuropsychiatric Syndromes

For active lupus optic neuritis -OR- lupus acute confusional state -OR- active mononeuritis multiplex, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper plus IV CYC, MPAA, or anti-CD20 therapy over pulse/high-dose glucocorticoid monotherapy alone

For active lupus myelitis, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid plus IV CYC over pulse/high dose glucocorticoid with other non-CYC immunosuppressive agents

For active lupus psychosis, we conditionally recommend anti-psychotic therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-psychotic therapy alone

Evidence for severe neurologic syndromes was largely limited to IV CYC, and level of certainty was very low. Voting Panel members opted to include MPAA and anti-CD20 therapy as options based on their clinical experience, the wide spectrum of severity in these syndromes, and the desire to avoid or limit use of IV CYC especially in young women of reproductive age. Glucocorticoid-induced psychosis may confound the assessment of clinical response to immunosuppressive therapy. When using IV CYC, we consider treatment with 3 monthly infusions followed by an alternative immunosuppressant, usually MPAA, to minimize the risk of potential toxicities, including impaired fertility. An ischemic etiology that might require anticoagulation, or the presence of an alternative diagnosis such as neuromyelitis optica spectrum disorder or myelin oligodendrocyte glycoprotein antibody disease, should be ruled out as these may impact therapy. Plasma exchange (PLEX) and/or IVIG are reasonable additional therapies for severe or refractory disease.[68,69]

Seizures

For seizures attributed to active SLE, we conditionally recommend anti-seizure therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-seizure therapy alone

It is important to rule out fixed neurologic damage (i.e., scarring) rather than active inflammation as the etiology for seizures. Decision for a particular therapy may vary depending on concomitant SLE manifestations, as well as clinician and patient preferences.

Cognitive Dysfunction

For isolated cognitive dysfunction attributed to SLE and documented by neuropsychological testing, we conditionally recommend *against* adding immunosuppressive therapy (including glucocorticoid) to cognitive therapy over using cognitive therapy alone

Neuropsychological testing should be performed to document cognitive dysfunction (or decline) that is potentially attributable to SLE and to rule out other identifiable or treatable etiologies. The efficacy of immunosuppressive therapy (including glucocorticoid) for isolated cognitive dysfunction in the absence of inflammatory signs (e.g. abnormal CSF or imaging studies) has not been demonstrated and so is not recommended; alternative pharmacological and non-pharmacological therapies are under study,[70,71] however some clinicians may choose to add immunosuppressive therapy if active lupus inflammation is strongly suspected. Cognitive dysfunction associated with other recognized NPSLE syndromes (e.g., acute confusional state, psychosis) that are characterized by an immunologic or inflammatory etiology should be treated with immunosuppressive therapy, as detailed in preceding recommendations.

MUCOCUTANEOUS MANIFESTATIONS

Most reports of therapy for cutaneous lupus combine acute with subacute/chronic rash in the treatment group; as a result, these are grouped together here for most recommendations. Diagnosis and classification are reviewed elsewhere.[72] Treatment for alopecia, acknowledged by the Patient and Voting Panels as a common and distressing SLE manifestation, is not addressed with a specific recommendation due to its multifactorial nature.[73] Dermatology evaluation should be considered.

GPS*: *People with SLE should be educated on the use of sunscreen and other sun-protection measures to reduce risk of rash and potential disease flare

GPS*: *Initial therapy for cutaneous lupus rash—in addition to HCQ—should be topical, including glucocorticoid and/or calcineurin inhibitors (Table [6]). Initial therapy may also include a course of intralesional glucocorticoids and/or a brief course of oral glucocorticoids

Sunscreens should block both UVB and UVA light: Sun Protection Factors of ≥70[74] for chemical and ≥50 for physical blocker-based sunscreens are recommended. Physical blocker sunscreens may be preferable in allergy-prone people.[75] Clinicians should provide counseling on proper sunscreen use,

Table 6. Suggested topical therapies for cutaneous lupus

Glucocorticoid topical therapies	Agent	Body Location	Comments
Super-potent Very high	Augmented betamethasone dipropionate (solution) Clobetasol propionate Halobetasol propionate	Scalp Body	For body: BID for refractory lesions then switch to BID moderate potency agent
High	Betamethasone dipropionate Fluocinonide Halcinonide Mometasone furoate		
Moderate	Betamethasone valerate Fluocinolone acetonide (0.025%) Triamcinolone acetonide Hydrocortisone valerate (0.2%)	Body	Use for longer term treatment on body after initial high or very high potency
Low	Desonide (0.05%) Fluocinolone acetonide (0.01%) Hydrocortisone {0.5-2.5%)	Face	Short term only
Non-glucocorticoid topical therapies			
Calcineurin Inhibitors	Pimecromus cream Tacrolimus ointment	Face	No limit to duration of use
JAK Inhibitors (off label)	Ruxolitinib Tofacitinib		

There is no significant difference in which topical options should be used for different cutaneous lupus subtypes, except for lupus panniculitis (topical glucocorticoids will not reach the fat, the area of inflammation in panniculitis). Body location guides the choice of topical agents. Generally, avoid use of fluorinated glucocorticoids on the face except for a few days if severe flare. Topical therapies are generally used BID. More potent topicals are generally used for up to 2 weeks duration (not on the face however) and then switched to less potent topical agents. Solutions are favored for scalp; creams or ointments for elsewhere (patient preference). BID, twice a day.

including reapplication, sun avoidance techniques, and alternative sun-protection methods (e.g., sun-protective clothing). Dermatology evaluation in people with significant skin disease is encouraged; lesional skin biopsy is suggested when needed to guide therapy or to rule out other diagnoses and should ideally be interpreted by a dermatopathologist.

Prevention of skin scarring was a high priority for the Patient Panel, especially in visible areas such as the face. Low-potency glucocorticoids can be used for active disease for a limited time on the face, but higher-potency glucocorticoids should be used only for a few days due to risk of skin atrophy. Involvement of non-facial or non-intertriginous areas of the body can be treated with moderate or higher potency topical glucocorticoids. Topical calcineurin inhibitors can be used without restriction. Suggestions for topical therapy of cutaneous manifestations are summarized in Table 6; these are not formal recommendations. Table 6 is a summary of general information provided as a convenience for the clinician utilizing the formal treatment recommendations, in order to help guide choice of specific topical therapy.

Acute, Subacute, and Chronic Cutaneous Lupus

For mild, ongoing, and skin-predominant lupus despite treatment with HCQ and/or topical therapies, we conditionally recommend adding quinacrine or switching to chloroquine over adding an immunosuppressive agent

Change in antimalarial therapy is a common dermatology practice, as it may improve mild rash without the need for more aggressive therapy. Quinacrine is not associated with increased retinopathy risk and is available through compounding pharmacies at variable cost; addition of quinacrine is preferred over a switch to chloroquine, given that chloroquine has a higher risk for retinal toxicity than HCQ.[76,77] For chloroquine, we suggest every 4–6-month retinal monitoring (Table 5); this differs from the American Academy of Ophthalmology's yearly recommendation[78] and is based on an increasing appreciation of chloroquine risk from both clinical experience and published evidence.[76,77] Chloroquine is an option in patients without major risk factors for retinopathy (Table 5), with the intention to change back to HCQ when rash is better controlled.

For ongoing moderate-severe cutaneous lupus refractory to topical and antimalarial therapies and/or oral glucocorticoid necessitating escalation of therapy, we conditionally recommend the addition of methotrexate (MTX), MPAA, anifrolumab, and/or belimumab

The Patient Panel placed a very high priority on scar prevention. The choice of specific therapy should be based on severity of lesions, risk for scarring, comorbidities, and patient preference. The Voting Panel voted against prioritizing specific conventional or biologic immunosuppressive agents due to limited data and a difference of opinion among panel members. MTX and MPAA are the preferred conventional agents, but AZA may be used when pregnancy is planned. There are no comparative effectiveness studies of the FDA-approved biologics anifrolumab and belimumab for cutaneous SLE. Both may be beneficial;[79–82] however, panel

members emphasized their clinical experience with anifrolumab's rapid onset of benefit and greater likelihood of response.[80]

For ongoing moderate-severe cutaneous lupus refractory to topical therapies, antimalarials, and conventional and/or biologic immunosuppressive agents necessitating escalation of therapy, we conditionally recommend adding or substituting lenalidomide

Lenalidomide is suggested as a potential therapy of "last resort" despite the potential teratogenicity and thrombosis risk;[83–85] prescribers must participate in the Risk Evaluation and Mitigation Strategy (REMS) program.

Bullous Lupus Erythematosus

For mild ongoing bullous lupus despite treatment with topical therapies and antimalarial therapies, we conditionally recommend the initial addition of dapsone over initiation of glucocorticoid

Metabolites of dapsone may lead to hemolytic anemia, methemoglobinemia, or other hematologic issues; G6PD should be assessed prior to start of therapy, with appropriate monitoring during use[86,87] (Table 5).

For moderate-severe bullous lupus refractory to topical therapies, antimalarials, and/or oral glucocorticoid necessitating escalation of therapy, we conditionally recommend adding a conventional immunosuppressive (MPAA, MTX, AZA) and/or anti-CD-20 therapy

The Voting Panel relied on indirect evidence from pemphigus due to its similar disease process. Trials in pemphigus support either glucocorticoids with conventional immunosuppressive or anti-CD20 therapy for bullous diseases.[88,89]

Chilblain Lupus

For chilblain lupus, despite symptomatic, topical, and antimalarial therapies, we conditionally recommend the addition of pentoxifylline, phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil, tadalafil), and/or calcium channel blockers (e.g., nifedipine) over initiation of immunosuppressive therapies

Topical therapies for chilblain lupus may include glucocorticoid, calcineurin inhibitors, and topical nitrates. Most evidence reviewed was low-level and indirect, from primary chilblains. The role of immunosuppressive therapy is unclear.[90,91]

Leukocytoclastic Vasculitis

For mild ongoing cutaneous vasculitis despite topical and antimalarial therapies, we conditionally recommend the addition of dapsone or colchicine over immunosuppressive therapies, including oral glucocorticoid

The Voting Panel emphasized avoiding overtreatment of minor cutaneous vasculitis. Extensive or severe cutaneous vasculitis, however, generally requires glucocorticoid or immunosuppressive treatment.

SEROSITIS

Pleuropericarditis

For pleuropericarditis, we conditionally recommend initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or their combination, with a low threshold for escalation to glucocorticoid therapy, over initiating glucocorticoid therapy alone

For ongoing/recurrent episodes of lupus pleuropericarditis despite treatment with HCQ, NSAIDs, colchicine, and/or glucocorticoids necessitating escalation of therapy, we conditionally recommend conventional (MPAA, AZA) or biologic immunosuppressive therapies over initiating/increasing glucocorticoid monotherapy

Recommendations for pericarditis and pleuritis are combined, given similarities in management. NSAIDs and colchicine may be used together as initial therapy, and oral glucocorticoid added as needed. Evidence was of low certainty and inadequate to direct clinicians regarding use of conventional versus biologic therapies; however, severe or worsening disease necessitates rapid escalation of immunosuppressive treatment. Escalation to immunosuppressive therapy for ongoing/recurrent symptoms reflects the desire to avoid complications from pleuropericarditis and prolonged glucocorticoid use.

The Voting Panel's preferred biologic therapy for predominant pleuropericarditis is interleukin-1 (IL-1) blockade, for which there is primarily indirect evidence for SLE;[92–98] a decision to use IL-1 blockade may depend in part on presence or absence of other SLE manifestations as well as cost and

accessibility issues. Limited data support potential roles for other biologic agents.[79,81]

MUSCULOSKELETAL

Arthritis

GPS: Therapy for acute or recurrent episodes of inflammatory arthritis in people with SLE may include a course of NSAID or a limited course of oral glucocorticoid while waiting for long-term therapies to take effect

Joint involvement occurs in up to 95% of those with SLE,[99,100] resulting in permanent joint damage in 11.7%.[101] It is associated with lower quality of life and work disability.[102,103] Lupus-related joint involvement ranges from arthralgia to deforming arthropathy and erosive arthritis. While NSAID and glucocorticoids are useful in providing rapid symptom relief, the goal of therapy is management with longer-term disease-modifying agents.

For persistent or recurrent active SLE arthritis in people taking HCQ, regardless of prior/current NSAIDs or short-term glucocorticoid therapy, we conditionally recommend initial therapy with MTX, MPAA, or AZA, with a low threshold to add or substitute with belimumab or anifrolumab for inadequate response, over initial biologic therapy

The recommendation for the treatment of lupus arthritis is conditional due to the widely varying clinical practice patterns and preferences among panelists. There will be individuals for whom initial biologic therapy[79,104,105] with belimumab or anifrolumab is considered preferable, or for whom combination (conventional plus biologic) therapy is required. For people with predominant arthritis without a history of significant other organ involvement, MTX may be considered first; for those with history of or current other organ involvement, MPAA might be preferable. A randomized controlled trial in patients with moderate-to-severe active (extra-renal) lupus disease activity compared overall disease activity response in patients randomized to MPAA versus AZA. While the study was not powered for specific organ response, those treated with MPAA had significantly higher rates of remission, shorter times to achieving remission, and fewer side effects than did those receiving AZA, suggesting MPAA may be preferred over AZA as initial therapy when conventional immunosuppressives are planned.[106] AZA is preferred for those planning pregnancy.

Alternative agents such as leflunomide or other therapies approved for rheumatoid arthritis treatment are occasionally used when arthritis is the predominant feature. The Voting Panel emphasizes early escalation/change in therapy for inadequate response. Shared decision-making is vital; Patient Panel members placed a high value on consideration of specific side effects and tolerability for any given therapy.

Jaccoud Arthropathy

Jaccoud arthropathy was discussed but no consensus was reached on surgical or medical therapy, given the paucity of data[107] and clinical /patient experience. Voting Panel members suggest referral to occupational/physical therapy, splinting, or bracing; all agree this is an area for future research.

SYSTEMIC VASCULITIS

For vasculitis attributed to active SLE, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper and conventional (IV CYC, MPAA, AZA) or biologic (anti-CD 20 therapy, belimumab, anifrolumab) immunosuppressive therapy

For severe vasculitis attributed to active SLE, we conditionally recommend IV CYC or anti-CD20 therapy as initial therapy over other immunosuppressive therapies

For life-threatening vasculitis attributed to active SLE (e.g., diffuse alveolar hemorrhage or mesenteric vasculitis), we conditionally recommend the addition of PLEX and/or IVIG to pulse/high-dose glucocorticoid taper and immunosuppressive therapy, over no additional therapy

Pulse/high-dose glucocorticoid and immunosuppressive therapies are recommended for vasculitis due to the high risk of organ- and life-threatening outcomes. The evidence was of very-low certainty and primarily addressed treatment for mesenteric vasculitis, diffuse alveolar hemorrhage, and retinal vasculitis. PLEX and IVIG are suggested as adjunctive therapies to high-dose glucocorticoid and immunosuppressive agents for life-threatening vasculitis.[108,109] Shared decision-making is emphasized.

CARDIAC MANIFESTATIONS

Myocarditis

For acute or worsening lupus myocarditis, we conditionally recommend treatment with glucocorticoid and IV CYC, MPAA, or anti-CD20, and/or IVIG over glucocorticoid monotherapy

The treatment of lupus myocarditis relies on a combination of glucocorticoids and immunosuppressants in addition to heart failure

therapy. Cyclophosphamide and MPAA have the most evidence to support their use; however, positive reports from case-series also substantiate treatment with anti-CD-20 and IVIG. No randomized controlled trials are available to guide decision-making.[110–112]

Non-Bacterial (Libman-Sacks) Endocarditis

For non-bacterial (Libman-Sacks) endocarditis,[113] we conditionally recommend anticoagulation and/or immunosuppressive therapy (including glucocorticoid) over no medical therapy

The decision for medical therapy should be based on discussion with cardiologists and reflect the risk for embolization. A decision regarding potential use of immunosuppressive therapy may be informed, in part, by evidence for SLE activity in other organ systems. Non-bacterial (Libman-Sacks) endocarditis is closely associated with the presence of aPL (valvular heart disease constitutes a clinical domain in the 2023 ACR/EULAR antiphospholipid classification criteria[114]) and anticoagulation is generally suggested. A small case series (n=17) noted significant improvement in valvular function and reduction in vegetation size with combined conventional anti-inflammatory and antithrombotic therapy.[115] However, it should be noted that in this series only 9 of 17 patients were treated with immunosuppression; 5 patients died, 2 of infection (it is not clear whether they were on immunosuppressive therapy). Surgical valve replacement is usually required for severe disease.

DISCUSSION

In this guideline, we recommend HCQ, limiting glucocorticoid exposure, and early introduction of conventional and/or biologic immunosuppressive therapies to achieve remission or low disease activity while minimizing medication toxicity for all people with SLE. Many recommendations are conditional and do not specify one particular immunosuppressive agent, or even one class of agent. This is a direct result of the limited evidence available, variations in treatment approach among the Voting Panel members, and the high value Patient Panelists placed on the impact of side effects and tolerability for any given therapy. Thus, we strongly emphasize the role of shared decision-making between patients and clinicians because multiple factors impact therapy choice. Shared decision-making allows people with SLE to choose optimal medications in terms of efficacy, tolerability, and availability. This yields the added benefit of enhancing medication adherence, an important goal since this ultimately is a critical determinant of any therapy's effectiveness. Likewise, routine assessment of medication adherence is suggested. Self-report, electronic health record-based automated adherence monitoring, or measuring blood levels merit future research.

Shared decision-making was also a major theme throughout the Patient Panel discussion, reflecting the importance of fostering trust and respect for patient values and priorities. These priorities, influenced by a person's life stage and disease state, change over the course of the disease and should be regularly explored. Other highlighted themes included judicious glucocorticoid use to minimize adverse effects and a strong desire for patient involvement and partnership in research, from planning to execution, to ensure trials include representative cohorts and address patient needs.

Both provider and patient panel members cited difficulties in accessing care and medications due to a range of barriers. We acknowledge that diverse healthcare settings with varied access to medications and care providers is a critical issue contributing to racialized and socioeconomic disparities. With these recommendations, we aimed to reduce health care disparities by providing an evidence-based standard for patient-centered care.

Current gaps in the SLE literature helped identify important areas of future research (Supplementary Materials 7). Comparative effectiveness trials within specific organ systems, in addition to well-designed observational and cohort studies, will inform future guideline treatment recommendations.

Clinical rheumatologists and rheumatology teams are vital in the care of people with SLE. This guideline provides direction for therapeutic decisions after clinician-patient discussion; it also encourages close working relationships between rheumatologists (or expert rheumatology teams) and the other medical specialists integral to providing comprehensive and collaborative lupus care.

ACKNOWLEDGMENTS

We thank the patients who (along with authors Marimee Jules and Natalie M. Smith) participated in the Patient Panel meeting: Hiya Bhavsar, LaKeisha Coach, Seneka Epasinghe, Christele Felix, Monique C. Gore-Massy, Natacha Guerrero, Rashelle Howell, Jolanda Jackson, Ksisha Johnson, Wambui Machua, Michael Okechuku, Nahirannette Pulido, Brandi Rollins, Bené Williams, and one patient who requested anonymity. We thank the Lupus Foundation of America and its Research Accelerated by You (RAY) patient and caregiver registry for assistance with recruitment for the Patient Panel. We thank Ashira D. Blazer, MD, MSC, Titilola Falasinnu, PhD, Kyriakos Kirou, MD, and Julie Bolvig for their assistance with the literature review. We thank Liza Li, PharmD, and Alanna Wong, PharmD, for their review of the medication table. We thank ACR staff, including Regina Parker for assistance in coordinating the administrative aspects of the project and Cindy Force for assistance with manuscript preparation. We thank Kathryn Vela for her assistance in developing the literature search strategy and performing initial and updated literature searches. We thank Leila Khalili, NP, for her assistance to the Core Team. We also thank Larry J. Prokop, MLIS, for his peer review of the literature search strategy.

REFERENCES

1. Izmirly PM, Parton H, Wang L, et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention national lupus registries. Arthritis Rheumatol 2021;73:991–996.
2. Dall'Era M, Cisternas MG, Snipes K, et al. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California: The California Lupus Surveillance Project. Arthritis Rheumatol 2017;69:1996–2005.

3. Drenkard C, Lim SS. Update on lupus epidemiology: advancing health disparities research through the study of minority populations. Curr Opin Rheumatol 2019;31:689–696.
4. Duarte-García A, Hocaoglu M, Valenzuela-Almada M, et al. Rising incidence and prevalence of systemic lupus erythematosus: a population-based study over four decades. Ann Rheum Dis 2022; 81:1260–1266.
5. Ferucci ED, Johnston JM, Gaddy JR, et al. Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people, 2007-2009. Arthritis Rheumatol 2014;66:2494–2502.
6. Izmirly PM, Wan I, Sahl S, et al. the incidence and prevalence of systemic lupus erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program. Arthritis Rheumatol 2017;69:2006–2017.
7. Lim SS, Bayakly AR, Helmick CG, et al. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357–368.
8. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 1999;42:1785–1796.
9. Sammaritano LR, Askanase A, Bermas BL, et al. 2024 American College of Rheumatology (ACR) guideline for the screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2025;77(9):1045–1065.
10. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66: 726–735.
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
12. American College of Rheumatology Clinical Practice Guidelines. Accessed 10/28/2023. https://rheumatology.org/clinical-practice-guidelines.
13. Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 2016;80:3–7.
14. Pisetsky DS, Clowse MEB, Criscione-Schreiber LG, et al. A novel system to categorize the symptoms of systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2019;71:735–741.
15. Quilter MC, Hiraki LT, Korczak DJ. Depressive and anxiety symptom prevalence in childhood-onset systemic lupus erythematosus: A systematic review. Lupus 2019;28:878–887.
16. Zhang L, Fu T, Yin R, et al. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC Psychiatry 2017;17:70.
17. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2020;72:529–556.
18. Alarcón GS, Ugarte-Gil MF, Pons-Estel G, et al. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. Results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. Lupus 2019;28: 423–426.
19. Gerosa M, Beretta L, Ramirez GA, et al. Long-term clinical outcome in systemic lupus erythematosus patients followed for more than 20 years: The Milan Systemic Lupus Erythematosus Consortium (SMiLE) Cohort. J Clin Med 2022;11:3587.
20. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630–640.
21. Katz PP, Barber CEH, Duarte-García A, et al. Development of the American College of Rheumatology Patient-Reported Outcome Quality Measures for systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2024;76:777–787.
22. Gladman DD, Goldsmith CH, Urowitz MB, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000;27:373–376.
23. Murimi-Worstell IB, Lin DH, Nab H, et al. Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis. BMJ Open 2020;10:e031850.
24. Hiraki LT, Hamilton J, Silverman ED. Measuring permanent damage in pediatric systemic lupus erythematosus. Lupus 2007;16: 657–662.
25. Taraborelli M, Leuenberger L, Lazzaroni MG, et al. The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. Lupus 2016;25:1365–1368.
26. Steiman AJ, Urowitz MB, Ibañez D, et al. Prolonged clinical remission in patients with systemic lupus erythematosus. J Rheumatol 2014; 41:1808–1816.
27. Cody EM, Wilson BE, Ogbu EA, et al. Usefulness of the lupus low disease activity state as a treatment target in childhood-onset SLE. Lupus Sci Med 2023;10:e000884.
28. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2016;75:1615–1621.
29. Parra Sánchez AR, Voskuyl AE, van Vollenhoven RF. Treat-to-target in systemic lupus erythematosus: advancing towards its implementation. Nat Rev Rheumatol 2022;18:146–157.
30. Smith EMD, Aggarwal A, Ainsworth J, et al. PReS-endorsed international childhood lupus T2T task force definition of childhood lupus low disease activity state (cLLDAS). Clin Immunol 2023;250:109296.
31. van Vollenhoven R, Askanase AD, Bomback AS, et al. Conceptual framework for defining disease modification in systemic lupus erythematosus: a call for formal criteria. Lupus Sci Med 2022;9: e000634.
32. Wahadat MJ, van den Berg L, Timmermans D, et al. LLDAS is an attainable treat-to-target goal in childhood-onset SLE. Lupus Sci Med 2021;8:e000571.
33. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2021;73:924–939.
34. van Vollenhoven RF, Bertsias G, Doria A, et al. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. Lupus Sci Med 2021;8:e000538.
35. Bergkamp SC, Kanagasabapathy T, Gruppen MP, et al. First validation of the childhood lupus low disease activity state (cLLDAS) definition in a real-life longitudinal cSLE cohort. Clin Immunol 2024;262: 110172.
36. Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76:543–546.
37. Stone JH, McDowell PJ, Jayne DRW, et al. The glucocorticoid toxicity index: Measuring change in glucocorticoid toxicity over time. Semin Arthritis Rheum 2022;55:152010.
38. Rice JB, White AG, Scarpati LM, et al. Long-term systemic corticosteroid exposure: A systematic literature review. Clin Ther 2017;39: 2216–2229.
39. Floris A, Chessa E, Sebastiani GD, et al. Glucocorticoid tapering and associated outcome in patients with newly diagnosed systemic

lupus erythematosus: the real-world GULP prospective observational study. RMD Open 2022;8:e002701.

40. Boers M, Hartman L, Opris-Belinski D, et al. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. Ann Rheum Dis 2022;81:925–936.
41. Ji L, Gao D, Hao Y, et al. Low-dose glucocorticoids withdrawn in systemic lupus erythematosus: a desirable and attainable goal. Rheumatology (Oxford) 2022;62:181–189.
42. Ji L, Xie W, Zhang Z. Low-dose glucocorticoids should be withdrawn or continued in systemic lupus erythematosus? A systematic review and meta-analysis on risk of flare and damage accrual. Rheumatology (Oxford) 2021;60:5517–5526.
43. Beuschlein F, Else T, Bancos I, et al. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency. Eur J Endocrinol 2024;190:G25–G51.
44. Cramarossa G, Liu HY, Turk MA, et al. Guidelines on prescribing and monitoring antimalarials in rheumatic diseases: a systematic review. Clin Exp Rheumatol 2021;39:407–412.
45. Dabit JY, Hocaoglu M, Moder KG, et al. Risk of hydroxychloroquine retinopathy in the community. Rheumatology (Oxford) 2022;61: 3172–3179.
46. Jorge AM, Mancini C, Zhou B, et al. Hydroxychloroquine dose per ophthalmology guidelines and the risk of systemic lupus erythematosus flares. JAMA 2022;328:1458–1460.
47. Melles RB, Jorge AM, Marmor MF, et al. Hydroxychloroquine dose and risk for incident retinopathy: A cohort study. Ann Intern Med 2023;176:166–173.
48. Nestor J, Choi H, Mancini C, et al. Hydroxychloroquine dose and hospitalizations for active lupus. Arthritis Rheumatol 2024;76:1512–1517.
49. Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. Arthritis Rheumatol 2021;73:908–911.
50. Chakravarty EF, Utset T, Kamen DL, et al. Mycophenolate mofetil withdrawal in patients with systemic lupus erythematosus: a multicentre, open-label, randomised controlled trial. Lancet Rheumatol 2024;6:e168–e177.
51. Rygg M, Pistorio A, Ravelli A, et al. A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Ann Rheum Dis 2012;71:511–517.
52. Sontichai W, Liao F, Dominguez D, et al. Timing of childhood-onset systemic lupus erythematosus diagnosis relative to menarche and the impact on final adult height. Arthritis Care Res (Hoboken) 2022; 74:199–207.
53. Rubinstein TB, Dionizovik-Dimanovski M, Davis AM, et al. Multicenter study of utility and acceptability of depression and anxiety screening in adolescents and young adults with childhood-onset systemic lupus. Arthritis Care Res (Hoboken) 2023;75:724–733.
54. Chalhoub NE, Wenderfer SE, Levy DM, et al. International consensus for the dosing of corticosteroids in childhood-onset systemic lupus erythematosus with proliferative lupus nephritis. Arthritis Rheumatol 2022;74:263–273.
55. Groot N, Kardolus A, Bijl M, et al. Effects of childhood-onset systemic lupus erythematosus on academic achievements and employment in adult life. J Rheumatol 2021;48:915–923.
56. Bitencourt N, Bermas BL, Makris UE, et al. Time to first completed visit and health care utilization among young adults transferring from pediatric to adult rheumatologic care in a safety-net hospital. Arthritis Care Res (Hoboken) 2021;73:1730–1738.
57. Chang JC, Knight AM, Lawson EF. Patterns of healthcare use and medication adherence among youth with systemic lupus erythematosus during transfer from pediatric to adult care. J Rheumatol 2021;48:105–113.
58. Haro SL, Lawson EF, Hersh AO. Disease activity and health-care utilization among young adults with childhood-onset lupus transitioning to adult care: data from the Pediatric Lupus Outcomes Study. Lupus 2020;29:1206–1215.
59. Son MB, Sergeyenko Y, Guan H, et al. Disease activity and transition outcomes in a childhood-onset systemic lupus erythematosus cohort. Lupus 2016;25:1431–1439.
60. Shakoory B, Geerlinks A, Wilejto M, et al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Ann Rheum Dis 2023;82:1271–1285.
61. Santacruz JC, Mantilla MJ, Rueda I, et al. A practical perspective of the hematologic manifestations of systemic lupus erythematosus. Cureus 2022;14:e22938.
62. Vasiliu IM, Petri MA, Baer AN. Therapy with granulocyte colony-stimulating factor in systemic lupus erythematosus may be associated with severe flares. J Rheumatol 2006;33:1878–1880.
63. Gafter-Gvili A. Current approaches for the diagnosis and management of immune thrombocytopenia. Eur J Intern Med 2023;108: 18–24.
64. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829–3866.
65. Lusa A, Carlson A. Safety and efficacy of thrombopoeitin mimetics for refractory immune thrombocytopenia purpura in patients with systemic lupus erythematosus or antiphospholipid syndrome: a case series. Lupus 2018;27:1723–1728.
66. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42:599–608.
67. Bushnell C, Kernan WN, Sharrief AZ, et al. 2024 Guideline for the Primary prevention of stroke: A guideline from the American Heart Association/American Stroke Association. Stroke 2024;55:e344–e424.
68. Ahn SM, Hong S, Lim DH, et al. Clinical features and prognoses of acute transverse myelitis in patients with systemic lupus erythematosus. Korean J Intern Med 2019;34:442–451.
69. Kovacs B, Lafferty TL, Brent LH, et al. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann Rheum Dis 2000;59:120–124.
70. Kello N, Anderson E, Diamond B. Cognitive dysfunction in systemic lupus erythematosus: A case for initiating trials. Arthritis Rheumatol 2019;71:1413–1425.
71. Legge AC, Hanly JG. Recent advances in the diagnosis and management of neuropsychiatric lupus. Nat Rev Rheumatol 2024;20: 712–728.
72. Stull C, Sprow G, Werth VP. Cutaneous involvement in systemic lupus erythematosus: A review for the rheumatologist. J Rheumatol 2023;50:27–35.
73. Concha JSS, Werth VP. Alopecias in lupus erythematosus. Lupus Sci Med 2018;5:e000291.
74. Ou-Yang H, Stanfield J, Cole C, et al. High-SPF sunscreens (SPF ≥ 70) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts. J Am Acad Dermatol 2012;67:1220–1227.
75. Keyes E, Werth VP, Brod B. Potential allergenicity of commonly sold high SPF broad spectrum sunscreens in the United States; from the

perspective of patients with autoimmune skin disease. Int J Womens Dermatol 2019;5:227–232.
76. Mittal L, Zhang L, Feng R, et al. Antimalarial drug toxicities in patients with cutaneous lupus and dermatomyositis: A retrospective cohort study. J Am Acad Dermatol 2018;78:100–106.e101.
77. Wallace DJ. The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. Semin Arthritis Rheum 1989;18:282–296.
78. Marmor MF, Kellner U, Lai TY, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology 2016;123:1386–1394.
79. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis 2012;71:1833–1838.
80. Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 2020;382:211–221.
81. Morand EF, Furie RA, Bruce IN, et al. Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials. Lancet Rheumatol 2022;4:e282–e292.
82. Vashisht P, Borghoff K, O'Dell JR, et al. Belimumab for the treatment of recalcitrant cutaneous lupus. Lupus 2017;26:857–864.
83. Fairley JL, Oon S, Saracino AM, et al. Management of cutaneous manifestations of lupus erythematosus: A systematic review. Semin Arthritis Rheum 2020;50:95–127.
84. Cortés-Hernández J, Ávila G, Vilardell-Tarrés M, et al. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. Arthritis Res Ther 2012;14:R265.
85. Yuki EFN, Silva CA, Aikawa NE, et al. Thalidomide and lenalidomide for refractory systemic/cutaneous lupus erythematosus treatment: A narrative review of literature for clinical practice. J Clin Rheumatol 2021;27:248–259.
86. Lovell KK, Momin RI, Sangha HS, et al. Dapsone use in dermatology. Am J Clin Dermatol 2024;25:811–822.
87. Bhat RM, Madhumita M, Monteiro RC. Dapsone - reinventing the wheel or rekindling possibilities? Clin Derm Rev 2024; 8: 171–177.
88. Murrell DF, Peña S, Joly P, et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol 2020;82:575–585.e1.
89. Sprow G, Afarideh M, Dan J, et al. Bullous systemic lupus erythematosus in females. Int J Womens Dermatol 2022;8:e034.
90. Dubey S, Joshi N, Stevenson O, et al. Chilblains in immune-mediated inflammatory diseases: a review. Rheumatology (Oxford) 2022;61:4631–4642.
91. Pratt M, Mahmood F, Kirchhof MG. Pharmacologic treatment of idiopathic chilblains (Pernio): A Systematic review. J Cutan Med Surg 2021;25:530–542.
92. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: The AIRTRIP randomized clinical trial. JAMA 2016;316:1906–1912.
93. Correia ETO, Dos Santos Barbetta LM, de Almeida J, et al. Anakinra in recurrent pericarditis: current evidence on clinical use, effectiveness, and safety. J Cardiovasc Pharmacol 2020;76:42–49.
94. Cremer PC, Klein AL, Imazio M. Diagnosis, risk stratification, and treatment of pericarditis: A review. JAMA 2024;332:1090–1100.
95. Fava A, Cammarata M, Adamo L. Rilonacept use in lupus pericarditis. Clin Exp Rheumatol 2024;42:1115–1117.
96. Klein AL, Imazio M, Cremer P, et al. Phase 3 Trial of Interleukin-1 trap rilonacept in recurrent pericarditis. N Engl J Med 2021;384:31–41.
97. Kumar S, Khubber S, Reyaldeen R, et al. Advances in imaging and targeted therapies for recurrent pericarditis: A review. JAMA Cardiol 2022;7:975–985.
98. Wan Y, He S, Wang S, et al. Efficacy and safety of interleukin-1 inhibitors in the management of patients with recurrent pericarditis: A systematic review and meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs 2024;24:537–545.
99. Fessel WJ. Systemic lupus erythematosus in the community. Incidence, prevalence, outcome, and first symptoms; the high prevalence in Black women. Arch Intern Med 1974;134:1027–1035.
100. Zoma A. Musculoskeletal involvement in systemic lupus erythematosus. Lupus 2004;13:851–853.
101. Conti F, Ceccarelli F, Perricone C, et al. The chronic damage in systemic lupus erythematosus is driven by flares, glucocorticoids and antiphospholipid antibodies: results from a monocentric cohort. Lupus 2016;25:719–726.
102. Baker K, Pope J. Employment and work disability in systemic lupus erythematosus: a systematic review. Rheumatology (Oxford) 2009; 48:281–284.
103. Drenkard C, Bao G, Dennis G, et al. Burden of systemic lupus erythematosus on employment and work productivity: data from a large cohort in the southeastern United States. Arthritis Care Res (Hoboken) 2014;66:878–887.
104. Merrill JT, Furie R, Werth VP, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus Sci Med 2018;5:e000284.
105. Zen M, Gatto M, Depascale R, et al. Early and late response and glucocorticoid-sparing effect of belimumab in patients with systemic lupus erythematosus with joint and skin manifestations: Results from the Belimumab in Real Life Setting Study-Joint and Skin (BeRLiSS-JS). J Pers Med 2023;13:691.
106. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. Ann Rheum Dis 2017;76:1575–1582.
107. Santos WD, Baleeiro C, Santiago MB. Surgery for Jaccoud Arthropathy: A Systematic review. J Clin Rheumatol 2016;22:35–38.
108. Papadaki TG, Zacharopoulos IP, Papaliodis G, et al. Plasmapheresis for lupus retinal vasculitis. Arch Ophthalmol 2006;124:1654–1656.
109. Wang CR, Liu MF, Weng CT, et al. Systemic lupus erythematosus-associated diffuse alveolar haemorrhage: a single-centre experience in Han Chinese patients. Scand J Rheumatol 2018;47:392–399.
110. Ammirati E, Moslehi JJ. Diagnosis and treatment of acute myocarditis: A review. JAMA 2023;329:1098–1113.
111. Appenzeller S, Pineau CA, Clarke AE. Acute lupus myocarditis: Clinical features and outcome. Lupus 2011;20:981–988.
112. Zagelbaum Ward NK, Linares-Koloffon C, Posligua A, et al. Cardiac manifestations of systemic lupus erythematous: An overview of the incidence, risk factors, diagnostic criteria, pathophysiology and treatment options. Cardiol Rev 2022;30:38–43.
113. Gartshteyn Y, Tamargo M, Fleischer S, et al. Endomyocardial biopsies in the diagnosis of myocardial involvement in systemic lupus erythematosus. Lupus 2020;29:199–204.
114. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687–1702.
115. Roldan CA, Sibbitt WL, Jr., Greene ER, et al. Libman-Sacks endocarditis and associated cerebrovascular disease: The role of medical therapy. PLoS One 2021;16:e0247052.

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 840–842
DOI 10.1002/acr.25699

EDITORIAL

Two Birds, One Stone: Lung Cancer Screening in Patients With Rheumatoid Arthritis Identifies Malignancy and Rheumatoid Arthritis–Associated Lung Disease

Amir A. Razmjou[1,2] and Bryant R. England[3,4]

Rheumatoid arthritis (RA)–associated lung disease can affect nearly any compartment of the respiratory system, resulting in interstitial lung disease (ILD), bronchiectasis, nodulosis, and many other pulmonary diseases.[1] There is much discussion around both the utility of and patient selection for RA-ILD screening. These discussions center around balancing the risks of overdiagnosing mild/nonprogressive RA-ILD, radiation exposure,[2] and the scarcity of high-quality evidence in treating RA-ILD, with the benefits of early identification of those with early ILD who are at high risk of progression and may benefit from early ILD-targeted treatments.[3]

In 2023, the American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) provided screening guidelines for RA-ILD, emphasizing the importance of selecting high-risk patients for incident and progressive ILD.[4] The guidelines recommend considering screening in high-risk patients with RA and, if screening is pursued, using a combination of high-resolution computed tomography (HRCT) of the chest and pulmonary function tests.[4] However, the current real-world practice patterns of rheumatologists screening for RA-ILD are not known.

One intriguing route to explore for RA-ILD screening is the utility of the well-established lung cancer screening guidelines by the US Preventive Services Task Force (USPSTF).[5] The initial 2013 USPSTF guidelines for lung cancer screening recommended screening those between the ages of 55 and 80 years who have a ≥30 pack-year smoking history, are current smokers, or have quit in ≤15 years with a low-dose computed tomography (LDCT) scan of the chest.[6] These guidelines were updated in 2021 to broaden the inclusion of those screened to the ages of 50 to 80 years and a ≥20 pack-year smoking history.[5]

Although the proportion of patients with RA who are eligible for USPSTF lung cancer screening is not known, there are likely significant numbers of patients given cigarette smoking is the strongest environmental risk factor for RA.[1,7] Depending on the RA cohort analyzed, ever smoking in patients with RA can range between 50% and 80%,[8,9] and RA itself has been linked to an increased risk of lung cancer when controlling for smoking status compared to non-RA comparisons.[10]

Could applying the USPSTF lung cancer screening guidelines to patients with RA provide early ILD detection in addition to early detection of lung cancer? And because both cigarette smoking and RA itself may lead to pulmonary nodules and other fibrotic/airway abnormalities, how often are abnormal LDCT findings in patients with RA leading to the diagnosis of malignancy or other lung diseases?

Study by McDermott et al

In the article titled "Detection of Lung Abnormalities in Patients With Rheumatoid Arthritis Who Smoke and Who Were Screened for Lung Cancer With Low-Dose Chest Computed Tomography Imaging in Routine Clinical Care: Results From a Large Multihospital System" in this issue of *Arthritis Care & Research*, McDermott and colleagues[11] performed a cross-sectional study comparing the findings from routinely performed LDCT scans for lung cancer screening in the Mass General Brigham health system (Boston, Massachusetts) from patients with RA and non-RA comparators between 2015 and 2023. Patients who were eligible for lung cancer screening and underwent LDCT scans were included. Patients were identified as having RA by diagnostic codes, followed by manual chart review and confirmation that the cases met the 2010 ACR/EULAR RA classification criteria.[12] LDCT scans were interpreted by thoracic radiologists as part of routine clinical practice, and the investigators evaluated for the following findings: lung nodules, fibrotic lung changes, bronchiectasis, a composite "positive screen" (lung nodule

[1]David Geffen School of Medicine, University of California, Los Angeles; [2]Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California; [3]University of Nebraska Medical Center, Omaha; [4]Veterans Affairs Nebraska-Western Iowa Healthcare System, Omaha.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25699.

Address correspondence via email to Amir A. Razmjou, MD, MSc, at ARazmjou@mednet.ucla.edu.

Submitted for publication October 22, 2025; accepted October 27, 2025.

requiring follow-up or biopsy), and a composite "any actionable abnormality" ("positive screen," fibrotic lung changes, or bronchiectasis). Finally, whether patients were ultimately diagnosed with lung cancer after screening was recorded.

There were 228 patients with RA and 14,805 non-RA comparators. Although the demographics were overall similar between patients with RA and comparators, there were significantly more women in the RA cohort, as expected. About half of the patients were current smokers, and the other half were former smokers. The average age at RA diagnosis was 55 years, with a mean RA disease duration of 9.6 years and seropositivity (rheumatoid factor or cyclic citrullinated peptide) in 71%. Lung nodules were detected in approximately 86% of both groups, "positive screens" were detected in 22% to 27%, and lung cancer was ultimately diagnosed in approximately 4%. The rates of lung nodules, "positive screens," and lung cancer diagnosis did not significantly differ between patients with RA and non-RA comparators.

As expected, there were higher rates of fibrotic lung changes (7.9% vs 5.1%; $P = 0.06$) and bronchiectasis (15.4% vs 11.0%; $P = 0.04$) detected in patients with RA versus non-RA comparators. In multivariable logistic regression models with RA (ref non-RA) as a predictor that were adjusted for age, sex, year of screen, and smoking status/pack-year history, RA was found to be independently associated with the risk of a "positive screen" (odds ratio [OR] 1.4 [95% confidence interval (CI) 1.0–1.9]), fibrotic changes (1.8 [95% CI 1.1–2.9]), bronchiectasis (1.6 [95% CI 1.1–2.4]), and "any actionable finding" (1.4 [95% CI 1.1–1.9]). When this analysis was stratified by serostatus, the increased risks of fibrotic changes and bronchiectasis were found to be driven by the seropositive patients with RA rather than seronegative patients.

Lung cancer screening and the role of the rheumatologist

Several studies have demonstrated the increased risk of lung cancer in patients with RA.[10,13] Though, in the study by McDermott et al,[11] there was no difference in lung cancer diagnoses between patients with RA and those without RA undergoing LDCT. Given the substantial number of patients with RA who have a cigarette smoking history that would make them eligible for lung cancer screening,[8,9] rheumatologists may benefit from awareness of lung cancer screening indications. Although lung cancer screening is likely largely occurring through primary care practices for patients with RA, there may be room for incorporating screening protocols in certain rheumatology practices, as allowed by resources and practice setting. This is of particular importance for patients with RA who receive the majority of their health care through their rheumatologists and who have little or no regular follow-up with a primary care provider.

Regardless of whether or not an individual rheumatology practice is able to refer patients themselves for lung cancer screening, rheumatologists can play a pivotal role in discussing the importance of screening and refer patients to their primary care physicians for further discussion and imaging. The study by McDermott et al[11] provides us with helpful data for discussion around lung cancer screening in patients with RA. Although up to 86% of patients with RA may have a lung nodule detected, a nodule requiring further imaging or biopsy was only present in about 25% of patients, and only 5% of scans were found to have a malignancy. Additionally, about 37% of patients with RA undergoing LDCT will have a nodule requiring follow-up/biopsy, fibrotic lung changes, or bronchiectasis.

How effective is LDCT in screening for ILD?

It is well known that HRCT scans of the chest are the gold standard imaging modality for screening, diagnosing, staging, and monitoring RA-ILD. Although LDCT can diagnose ILD in certain circumstances, such as more advanced disease, it is optimized for nodule detection and population-level screening by using a lower radiation dose and thicker slices, which lead to a lower sensitivity for detecting early and/or mild findings of ILD, such as ground-glass opacities or fine reticulations.[14] A consensus statement by the American Thoracic Society and meta-analysis of 13 studies evaluating the use of HRCT for screening patients with RA for ILD found a pooled prevalence of 23% (95% CI 17%–29%) of ILD or interstitial lung abnormalities in scanned asymptomatic patients with RA.[15] In the study by McDermott et al,[11] fibrotic changes were seen in only 7.9% of patients with RA, which may reflect the lower sensitivity for ILD detection using LDCT compared to HRCT.

Although sensitivity for early ILD features is lower on LDCT, there may still be clinical utility in its ability to detect ILD features such as fibrosis or ILD more likely to progress.[15,16] A study evaluating LDCT in patients without RA undergoing lung cancer screening with LDCT found that the presence of honeycombing was significantly associated with increased risk of fibrosis progression on subsequent scans.[16] Additionally, if LDCT detects more clinically significant ILD than HRCT in patients with RA, perhaps this trade-off in sensitivity may decrease the "overdiagnosis" of clinically insignificant ILD. These factors were considered in the 2023 ACR/CHEST guidelines, with the authors concluding "Nearly all cases of significant ILD can be detected on high-quality low-dose chest CT or even on standard chest CT imaging, all without contrast."[4] Future studies evaluating ILD detection and progression between LDCT and HRCT modalities may help shed light on this situation.

Conclusions

Lung cancer screening in patients with RA is an important clinical consideration in rheumatology practices given the increased risk of lung cancer and relatively high rates of cigarette

smoking history in patients with RA. Although LDCT scans of the chest provide high-value lung cancer screening in patients with RA, McDermott and colleagues[11] have shown in this study that they may also help screen for the presence of RA-associated lung disease. LDCT for lung cancer screening just may enable us to kill two birds with one stone.

AUTHOR CONTRIBUTIONS

Both authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Razmjou confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Wang D, Zhang J, Lau J, et al. Mechanisms of lung disease development in rheumatoid arthritis. Nat Rev Rheumatol 2019;15(10):581–596. doi:https://doi.org/10.1038/s41584-019-0275-x
2. Smith-Bindman R, Chu PW, Azman Firdaus H, et al. Projected lifetime cancer risks from current computed tomography imaging. JAMA Intern Med 2025;185(6):710–719. doi:https://doi.org/10.1001/jamainternmed.2025.0505
3. Nettleton E, Carlson K, Putman M. The emerging risk of overdiagnosis in rheumatoid arthritis and polymyalgia rheumatica. Lancet Rheumatol 2025;7(2):e141–e143. doi:https://doi.org/10.1016/S2665-9913(24)00227-3
4. Johnson SR, Bernstein EJ, Bolster MB, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic diseases. Arthritis Rheumatol 2024;76(8):1201–1213. doi:https://doi.org/10.1002/art.42860
5. Krist AH, Davidson KW, Mangione CM, et al; US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325(10):962–970. doi:https://doi.org/10.1001/jama.2021.1117
6. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160(5):330–338. doi:https://doi.org/10.7326/M13-2771
7. Källberg H, Ding B, Padyukov L, et al; EIRA Study Group. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70(3):508–511. doi:https://doi.org/10.1136/ard.2009.120899
8. Wheeler AM, Baker JF, Riley T, et al. Development and internal validation of a clinical and genetic risk score for rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2025;64(1):268–275. doi:https://doi.org/10.1093/rheumatology/keae001
9. Sparks JA, He X, Huang J, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. Arthritis Rheumatol 2019;71(9):1472–1482. doi:https://doi.org/10.1002/art.40904
10. Cho MH, Cho JH, Eun Y, et al. Rheumatoid arthritis and risk of lung cancer: a nationwide cohort study. J Thorac Oncol 2024;19(2):216–226. doi:https://doi.org/10.1016/j.jtho.2023.10.006
11. McDermott GC, Hammer M, Wang X, et al. Detection of lung abnormalities in patients with rheumatoid arthritis who smoke and who were screened for lung cancer with low-dose chest computed tomography imaging in routine clinical care: results from a large multihospital system. Arthritis Care Res (Hoboken) 2026;78(7):843–849. doi:https://doi.org/10.1002/acr.25680
12. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford) 2012;51(suppl 6):vi5–vi9. doi:10.1093/rheumatology/kes279
13. Wu X, Peng H, Wen Y, et al. Rheumatoid arthritis and risk of lung cancer: meta-analysis and Mendelian randomization study. Semin Arthritis Rheum 2021;51(3):565–575. doi:https://doi.org/10.1016/j.semarthrit.2021.03.015
14. Christe A, Charimo-Torrente J, Roychoudhury K, et al. Accuracy of low-dose computed tomography (CT) for detecting and characterizing the most common CT-patterns of pulmonary disease. Eur J Radiol 2013;82(3):e142–e150. doi:https://doi.org/10.1016/j.ejrad.2012.09.025
15. Podolanczuk AJ, Hunninghake GM, Wilson KC, et al. Approach to the evaluation and management of interstitial lung abnormalities: an official American Thoracic Society clinical statement. Am J Respir Crit Care Med 2025;211(7):1132–1155. doi:https://doi.org/10.1164/rccm.202505-1054ST
16. Salvatore M, Henschke CI, Yip R, et al. JOURNAL CLUB: evidence of interstitial lung disease on low-dose chest CT images: prevalence, patterns, and progression. AJR Am J Roentgenol 2016;206(3):487–494. doi:https://doi.org/10.2214/AJR.15.15537

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 843–849
DOI 10.1002/acr.25680

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Detection of Lung Abnormalities in Patients With Rheumatoid Arthritis Who Smoke and Who Were Screened for Lung Cancer With Low-Dose Chest Computed Tomography Imaging in Routine Clinical Care: Results From a Large Multihospital System

Gregory C. McDermott,[1,2] Mark Hammer,[1,2] Xiaosong Wang,[1] Misti L. Paudel,[1,2] Sung Hae Chang,[1,3,4] Pierre-Antoine Juge,[5,6] Qianru Zhang,[1,7] Jessica Lorusso,[8] Amie Samuylov,[8] Kathleen M. M. Vanni,[1] Alene Saavedra,[1] Emily N. Kowalski,[1] Grace Qian,[1] Katarina J. Bade,[1] Kevin T. Mueller,[1] Jeffrey A. Sparks,[1,2] and Suzanne Byrne[1,2]

Objective. Rheumatoid arthritis (RA) is associated with interstitial lung disease, bronchiectasis, rheumatoid lung nodules, and lung cancer. Recent guidelines proposed criteria for lung disease screening in RA, but the prevalence of abnormal lung findings in patients with RA is unknown.

Methods. Among all patients screened for lung cancer with low-dose chest computed tomography (CT) in the Mass General Brigham health care system between 2015 and 2023, we identified patients with and without RA. We compared the prevalence of lung nodules, "positive screen" (nodules requiring further imaging or biopsy), fibrotic lung changes, bronchiectasis, and lung cancer between patients with RA and comparators without RA using multivariable logistic regression.

Results. Among consecutive patients screened for lung cancer with clinically indicated low-dose chest CT, we identified 228 patients with RA and 14,805 comparators without RA. "Positive screens" were noted in 26.8% of patients with RA and 22.2% of patients without RA (P = 0.10). Lung cancer was found in 4.8% of patients with RA and 3.6% of patients without RA (P = 0.33). In multivariable models, RA was associated with positive screen (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.02–1.87), fibrotic lung changes (OR 1.77, 95% CI 1.08–2.91), and bronchiectasis (OR 1.64, 95% CI 1.12–2.39).

Conclusion. Patients with RA had higher prevalence of positive screening, fibrotic changes, and bronchiectasis detected by low-dose chest CT performed for lung cancer screening. Approximately one in four patients with RA who met US Preventive Services Task Force lung cancer screening criteria had a positive screen, whereas 1 in 20 had lung cancer. These results emphasize the importance of lung cancer screening among eligible patients with RA and may inform screening strategies for other lung abnormalities.

Dr McDermott's work was supported by the Rheumatology Research Foundation Scientist Development Award. the Arthritis Foundation; the R. Bruce and Joan M. Mickey Research Scholar Fund; and the Llura Gund Award funded by the Gordon and Llura Gund Foundation.

[1]Mass General Brigham/Brigham and Women's Hospital, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts; [3]Soonchunhyang University, Cheonan, Republic of South Korea; [4]Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of South Korea; [5]Université de Paris Cité, INSERM UMR 1152, F-75018, Paris, France; [6]Hôpital Bichat-Claude Bernard, AP-HP, F-75018, Paris, France; [7]Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China; [8]Mass General Brigham, Boston, Massachusetts.

Drs McDermott and Hammer are co-first authors and contributed equally to this work. Drs Sparks and Byrne are co-last authors and contributed equally to this work.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25680).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25680.

Address correspondence via email to Jeffrey A. Sparks, MD, MMSc, at jsparks@bwh.harvard.edu.

Submitted for publication May 27, 2025; accepted in revised form September 30, 2025.

SIGNIFICANCE & INNOVATIONS

- Rheumatoid arthritis (RA) is associated with increased risk of interstitial lung disease (ILD), bronchiectasis, and lung cancer. Some patients with RA and smoking history meet criteria for lung cancer screening, and this may inform RA-ILD screening strategies.
- We analyzed a large cohort of patients screened for lung cancer and identified those with and without RA. We compared the prevalence of lung cancer, fibrotic lung changes, and bronchiectasis between the two groups.
- RA was associated with increased positive screens, findings of fibrotic lung changes, and bronchiectasis, including after multivariable adjustment for age, sex, year of scan, and smoking. Lung cancer was detected in 4.8% of patients with RA versus 3.6% of patients without RA.
- These findings emphasize the importance of lung cancer screening in eligible patients with RA and highlight the increased prevalence of ILD and bronchiectasis in these patients that may have additional clinical relevance.

INTRODUCTION

Cigarette smoking is a risk factor for both lung cancer[1] and rheumatoid arthritis (RA).[2] Furthermore, RA is associated with lung abnormalities including interstitial lung disease (ILD), bronchiectasis, and rheumatoid lung nodules[3] and has also been associated with an increased risk of lung cancer.[4] Despite recognition of these associations, there is uncertainty about the use of chest computed tomography (CT) imaging in patients with RA for screening purposes due to concerns about radiation exposure and incidental findings. We used a large cohort of consecutive patients screened for lung cancer with low-dose CT chest imaging to investigate associations between RA and abnormal imaging findings detected on CT chest screening as part of usual clinical care.

Prior research has demonstrated associations between RA and several different pulmonary abnormalities, which are primarily diagnosed by CT chest imaging.[3] Despite the recognition of increased prevalence of lung disease in patients with RA, there has been limited guidance on screening for lung disease in patients with RA. The recent 2023 American College of Rheumatology (ACR)/American College of Chest Physicians guideline on the screening and monitoring of patients with systemic autoimmune disease–associated ILD conditionally recommended consideration of lung screening in patients with RA who have one or more risk factors for RA-ILD, including older age at diagnosis, male sex, higher body mass index, active articular disease, and high titer RA-related autoantibodies.[5]

In 2013, the US Preventive Services Task Force (USPSTF) recommended lung cancer screening with low-dose chest CT for asymptomatic adults aged 55 to 80 years who are current or former smokers (quit within 15 years) with ≥30 pack-years of smoking history.[6] In 2021, the guidelines were revised to reduce smoking history to ≥20 pack-years.[7] Because also at increased risk for RA-related lung diseases including ILD and bronchiectasis, the experience of performing lung cancer screening in this population may inform for future lung screening initiatives among patients with RA.

We investigated the prevalence of abnormal findings including lung nodules, fibrotic changes, bronchiectasis, and lung cancer in patients with RA and comparators without RA who underwent lung cancer screening with low-dose CT chest imaging. All patients received lung cancer screening as part of usual clinical care and met criteria for lung cancer screening as outlined by the USPSTF. We hypothesized that RA would be associated with increased abnormal findings on low-dose chest CT imaging, including pulmonary nodules, fibrotic lung changes, bronchiectasis, and lung cancer.

METHODS

Study sample and design. We performed a cross-sectional study using data from the Mass General Brigham (MGB) health care system. The MGB health care system is a collection of academic and community hospitals as well as outpatient clinics in the greater Boston, Massachusetts, area. All patients who had low-dose chest CT imaging performed for lung cancer screening in the MGB health care system between 2015 and 2023 were included in the cohort, which has been described separately.[8] Notably, the presence or absence of respiratory symptoms was not a specific inclusion or exclusion criteria for screening. Details of current or past smoking history as well as pack-years were collected at the time of ordering low-dose chest CT imaging to document eligibility. Demographic data including birth date, sex, and self-reported race were extracted from the electronic health records. Visit diagnosis and billing codes were extracted from the electronic health records to facilitate identification of patients with RA and comparators without RA, as detailed below. This study was approved by the MGB Institutional Review Board (2008P002302 and 2021P001913).

From the cohort of all consecutive patients screened for lung cancer with low-dose chest CT imaging, we identified all patients with at least one International Classification of Diseases (ICD) code for RA (ICD-9 714 or ICD-10 M05 or M06). We then performed medical record review of each patient to identify those who met 2010 ACR/EULAR classification criteria for RA.[9] Patients who had at least one RA ICD code but did not meet classification criteria for RA were excluded. Patients who were diagnosed with RA after the low-dose chest CT imaging were also excluded because our study focused on screening prevalent RA and this would introduce immortal time bias for comparators who later developed RA. For all patients meeting criteria, we determined

the date of RA diagnosis for all patients by manual review of electronic health records. We extracted laboratory testing from the electronic health records for rheumatoid factor and anti-cyclic citrullinated peptide antibodies to determine seropositive and seronegative RA. For patients missing results of these autoantibodies, we performed manual medical record review to determine serostatus.

Identification of comparators without RA. We defined comparators without RA as all patients in the low-dose chest CT screening cohort with no RA ICD codes in their electronic medical records.

Interpretation of low-dose chest CT imaging. All low-dose chest CT imaging was reviewed through routine clinical care by thoracic radiologists to assess for the presence of lung cancer, lung nodules, or other abnormal parenchymal lung findings using a standardized form. Lung cancer screening studies were interpreted according to the American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) categorization system.[10] A "positive screen" was defined as Lung-RADS category 3 or 4, which denotes the presence of lung nodules requiring further imaging follow-up or biopsy. Fibrotic lung changes were defined as thoracic radiologist documentation of "interstitial lung changes," "interstitial fibrosis," "pulmonary fibrosis," "reticular changes," "reticulation," "honeycombing," or "bronchiolectasis" on the clinical radiology report. Presence of bronchiectasis was determined by thoracic radiologist documentation of "bronchiectasis." We combined "positive screen," fibrotic lung changes, and bronchiectasis into a category called "any actionable abnormality." All outcomes were determined based on the presence of abnormal findings on any low-dose CT scan performed while the patient was enrolled in the lung screening program during the study period. For each patient, the index date was defined as the first date of low-dose chest CT imaging.

Lung cancer diagnoses. We reviewed the electronic health records of all patients to identify those who were ultimately diagnosed with lung cancer between their initial low-dose CT chest screening and the end of the study period in July 2023. We assessed all patients with ICD codes for lung cancer diagnosis and defined a confirmed lung cancer diagnosis as positive biopsy findings or definitive radiologic findings treated as lung cancer in the absence of a biopsy.

Statistical analysis. We used descriptive statistics including mean ± SD as well as median and interquartile range to compare continuous variables between patients with RA and comparators without RA. We also compared the frequencies of lung nodules, positive screen, fibrotic lung changes, bronchiectasis, and lung cancer between patients with RA and comparators without RA using chi-squared tests. We then constructed multivariable logistic regression models that examined the association between RA versus non-RA status and lung nodules, positive screen, fibrotic lung changes, bronchiectasis, and lung cancer. The models were adjusted for age at screening, sex, calendar year of screening, smoking status (current or former), and continuous pack-years of smoking history. We then stratified the patients with RA by serostatus and examined the associations between seropositive RA versus non-RA and positive screen, lung cancer, fibrotic changes, and bronchiectasis adjusting for age at screening, calendar year of screening, sex, smoking status, and pack-years of smoking history. We repeated this for seronegative RA versus non-RA. We also performed a sensitivity analysis stratified by sex and another analysis additionally adjusted for race. There were no missing data. Two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SAS version 9.4.

RESULTS

Study sample. Among all consecutive patients who met guideline criteria and underwent low-dose chest CT imaging for lung cancer screening, we identified 228 patients with RA and 14,805 comparators without RA (Supplementary Figure S1). Characteristics of patients with and comparators without RA are detailed in Table 1. Among the patients with RA, the mean age was 64.7 years, 71.9% were female, 51.8% were former smokers, 71.0% were seropositive, and the mean RA duration was 9.6 years. The comparators without RA had mean age of 63.6 years, 46.2% were female, and 46.3% were former smokers.

Lung abnormalities. Details of the prevalence of lung nodules, "positive screen" (Lung-RADS category 3 or 4—requiring further imaging follow-up or biopsy), fibrotic lung changes, bronchiectasis, and lung cancer comparing in patients with RA to comparators without RA is described in Table 2. The prevalence of lung nodules detected on low-dose chest CT imaging was 86.4% for patients with RA and 86.0% for comparators without RA ($P = 0.86$). The prevalence of a "positive screen" on the low-dose chest CT imaging was 26.8% in patients with RA and 22.2% in comparators without RA ($P = 0.10$). The prevalence of confirmed lung cancer was 4.8% in patients with RA compared to 3.6% in comparators without RA ($P = 0.33$). A total of 7.9% of patients with RA had fibrotic lung changes compared to 5.1% of comparators without RA ($P = 0.06$). Bronchiectasis was more common among patients with RA (15.4%) compared to comparators without RA (11.0%; $P = 0.04$). A total of 36.8% of patients with RA compared to 31.4% of comparators without RA ($P = 0.08$) had "any actionable abnormality" on screening, including

Table 1. Characteristics of patients with RA and comparators without RA screened for lung cancer using low-dose chest CT imaging*

Characteristic	Patients with RA (n = 228)	Comparators without RA (n = 14,805)	*P* value
Age at scan, mean (±SD), y	64.7 (±6.5)	63.6 (±6.7)	0.02
Female, n (%)	164 (71.9)	6,838 (46.2)	<0.0001
Race, n (%)			0.28
American Indian or Alaska Native	2 (0.9)	36 (0.2)	–
Asian	3 (1.3)	304 (2.1)	–
Black	13 (5.7)	686 (4.6)	–
Hispanic	5 (2.2)	219 (1.5)	–
Unknown/other	9 (4.0)	791 (5.3)	–
White	196 (86.0)	12,769 (86.3)	–
Smoking status, n (%)			0.10
Current	110 (48.3)	7,950 (53.7)	–
Past	118 (51.8)	6,855 (46.3)	–
Smoking history, mean (±SD), pack-years	40.7 (±22.6)	43.8 (±32.4)	0.16
Time since quit smoking, mean (±SD), y	3.8 (±4.8)	3.4 (±5.3)	0.34
Calendar year of screening (median, IQR)	2021 (2019, 2022)	2020 (2018, 2022)	0.052
Age at RA diagnosis, mean (±SD), y	55.1 (±9.8)	–	–
RA duration, mean (±SD), y	9.6 (±8.0)	–	–
Seropositive RA, n (%)	152/214 (71.0)	–	–
RF positive	139/206 (67.5)	–	–
Anti-CCP positive	120/193 (62.2)	–	–

* CCP, cyclic citrullinated peptide; CT, computed tomography; IQR, interquartile range; RA, rheumatoid arthritis; RF, rheumatoid factor.

nodules requiring further follow-up, fibrotic lung changes, or bronchiectasis.

Multivariable associations of patients with RA versus comparators without RA. Results from multivariable logistic regression models examining associations of RA with low-dose CT chest findings adjusted for age, sex, calendar year of screening, smoking status, and pack-years of smoking are detailed in Figure 1. RA was statistically associated with a positive screen requiring further imaging follow-up or biopsy (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.02–1.87), fibrotic lung changes (OR 1.77, 95% CI 1.08–2.91), bronchiectasis (OR 1.64, 95% CI 1.12–2.39), and the composite of "any actionable abnormality" (OR 1.40, 95% CI 1.05–1.86). RA was not statistically associated with lung cancer (OR 1.35, 95% CI 0.72–2.52). In analyses that compared patients with seropositive or seronegative RA to comparators without RA, seropositive RA was associated with fibrotic lung changes (OR 2.43, 95% CI 1.43–4.14) and bronchiectasis (OR 1.72, 95% CI 1.10–2.70). There were no associations for any of the lung abnormalities for seronegative RA versus comparators without RA. In analyses stratified by sex (Supplementary Table S1), RA was significantly associated with positive screen (OR 1.55, 95% CI 1.09–2.20), fibrotic lung changes (OR 2.21, 95% CI 1.25–3.92), and bronchiectasis (OR 1.48, 95% CI 1.16–2.83) in those with female sex. After additionally adjusting for race in our multivariable models (Supplementary Table S2) we saw similar results compared to our primary analysis.

DISCUSSION

In usual clinical care, smokers with RA had a high prevalence of pulmonary abnormalities detected by low-dose chest CT imaging performed for lung cancer screening. A total of 27% of

Table 2. Prevalence of abnormal findings on low-dose chest computed tomography performed for lung cancer screening among patients with RA and comparators without RA*

Finding	Patients with RA (n = 228), n (%)	Comparators without RA (n = 14,805), n (%)	*P* value
Lung nodules	197 (86.4)	12,732 (86.0)	0.86
Positive screen[a]	61 (26.8)	3,283 (22.2)	0.10
Fibrotic changes	18 (7.9)	757 (5.1)	0.06
Bronchiectasis	35 (15.4)	1,629 (11.0)	0.04
Lung cancer	11 (4.8)	535 (3.6)	0.33
Any actionable finding[b]	84 (36.8)	4,645 (31.4)	0.08

* RA, rheumatoid arthritis.
[a] Lung nodule required additional follow-up or biopsy (includes lung cancer).
[b] Findings include positive screen, fibrotic changes, or bronchiectasis.

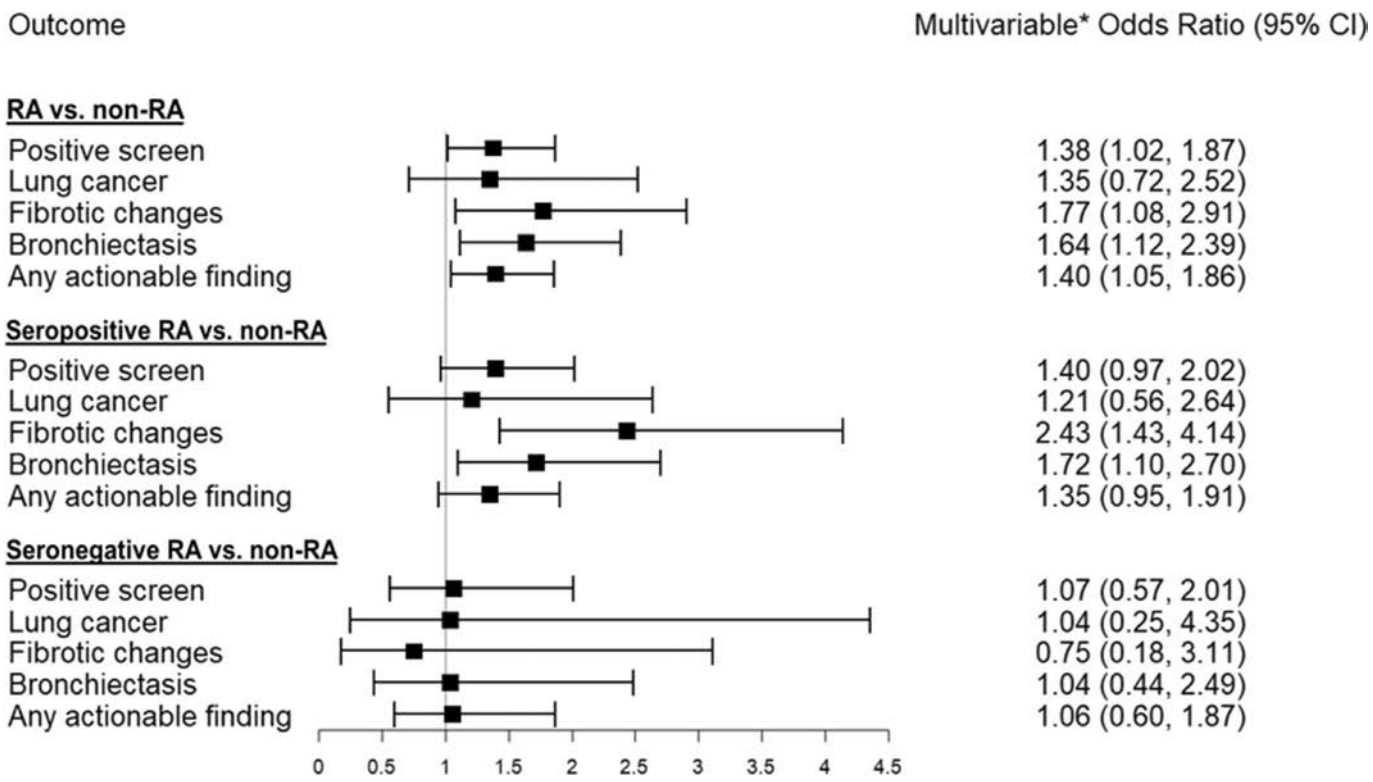

Figure 1. Associations of patients with rheumatoid arthritis (RA) versus comparators without RA with abnormal findings on low-dose chest computed tomography imaging performed for lung cancer screening. The asterisk (*) indicates adjustment for age at screening, sex, calendar year of screening, smoking status (current or former), and continuous pack-years of smoking history. CI, confidence interval.

patients with RA who underwent screening had a "positive screen" with nodules that required closer imaging follow-up or further management, and patients with RA were more likely to have positive lung cancer screening and had more fibrotic changes and bronchiectasis compared to patients without RA in multivariable models. Approximately 5% of patients with RA were ultimately diagnosed with lung cancer after screening, though this was not statistically different from the comparators without RA. These findings demonstrate the high prevalence of lung nodules and subclinical lung disease in patients with RA with a smoking history, emphasize the importance of lung cancer screening among eligible patients with RA, and provide data on the prevalence of abnormal findings that may assist patient–clinician discussions. These results also may inform future screening strategies for RA-related lung diseases targeting groups with high risk such as patients who smoke.

Our study adds to the prior literature investigating the prevalence of pulmonary abnormalities in RA. Our findings of associations between RA and fibrotic lung changes and bronchiectasis among smokers are consistent with previous literature. Prior studies have demonstrated associations between RA and interstitial lung abnormalities when comparing patients with RA to the general population[11] and in studies specifically investigating smokers.[12] Similarly, a large population study using a nationwide Korean registry demonstrated associations between RA diagnosis and bronchiectasis.[13] However, ours is the first controlled study to focus on screening for lung diseases performed through routine clinical care. Previous studies have used clinically indicated scans on people with symptoms or were performed prospectively in research settings among people who agreed to obtain scans and may not be generalizable to all patients with RA. We found that over a quarter of patients with RA screened for lung cancer in routine clinical care had a "positive screen" requiring further follow-up and 36.8% had "actionable findings" of either parenchymal lung disease or a "positive screen." These findings can help inform discussions of risks and benefits of performing CT chest screening in this population. In addition, our study examines incidental findings, whereas most prior studies were focused on specific outcomes such as ILD, bronchiectasis, and lung cancer.

Our findings also provide further insight into lung cancer risk for patients with RA. One recent study published using cohort data from Korea found an increased prevalence of lung cancer in patients with RA.[4] However, the absolute risks of lung cancer were low in this general population study.[14] The risk for lung cancer seems highest in patients with seropositive RA.[4,15] In our study, we saw increased prevalence of lung cancer among patients with RA, though this did not meet statistical significance. Notably, the risk difference we observed between patients with RA and comparators without RA was similar to prior literature,[4]

and the sample size may not have been large enough to detect statistical associations. Additionally, because low-dose chest CT imaging for lung cancer screening is recommended for patients who were asymptomatic, we could not account for patients with symptomatic lung cancer who were included in the previously published population studies.[4] Regardless, our results support the recommendations to screen patients with RA who smoke for lung cancer that meet the USPSTF recommendations as in the general population.

Our study has several strengths to consider. First, we performed our investigation and report the prevalence of abnormal findings using a large cohort of all consecutive patients screened by low-dose chest CT imaging for lung cancer in our health care system as part of routine clinical care. Because low-dose screening chest CT chest is not used for indications other than lung cancer screening, we expect nearly all patients to not have other indications that led to CT chest imaging. Furthermore, detailed information about smoking status and pack-years of smoking exposure was systematically collected for all patients. Finally, we confirmed that all patients with RA met classification criteria through manual medical record review and had data on RA serostatus and duration.

Our study also has limitations to consider. First, there is a possibility of selection bias among patients who are offered and chose to undergo screening for lung cancer. This may impact the generalizability of the findings in a broader population of patients who smoke. Second, low-dose chest CT imaging may be less sensitive for the detection of lung abnormalities than high resolution CT chest imaging due to differences in scan technique or radiologist reporting of mild disease. Therefore, we may have underestimated the true prevalence of ILD-related changes in this population. However, we would expect that this limitation does not preferentially affect patients with RA, and those detected may have been more likely to have clinical relevance. Third, we used report mentions of fibrotic changes and bronchiectasis to identify these abnormalities, and this approach has not been compared to formal screening techniques or other imaging approaches. Fourth, lung cancer screening guidelines apply to patients irrespective of symptoms, and it is possible that some patients were experiencing respiratory symptoms at the time of imaging. Due to the retrospective nature of the cohort, we were not able to assess for that possibility in a systematic manner. Fifth, given the small number of lung cancer outcomes in the patients with RA, we were not able to assess the individual impact of specific immunosuppressive treatments on lung cancer risk. Future studies are needed to clarify lung cancer risks with specific disease-modifying antirheumatic drugs. Finally, although we used data from a large health care system for our study and included 228 patients with RA compared to 14,805 comparators without RA, many of our outcomes were uncommon and some of our effect estimates were imprecise. However, this is the largest controlled study investigating incidental lung abnormalities found through a screening program in a real-world setting.

In conclusion, we found that patients with RA with current or past smoking history had a high prevalence of lung abnormalities on lung cancer screening performed for routine clinical care. A total of 27% of patients with RA had lung nodules requiring further follow-up or biopsy, and patients with RA were more likely to have positive screening, fibrotic changes, and bronchiectasis. These findings highlight the high prevalence of abnormal findings on CT chest imaging performed in patients with RA with a smoking history, emphasize the importance of lung cancer screening among eligible patients with RA, and provide prevalence data to inform risk-benefit considerations for lung screening among patients with RA who are current or former smokers, a group that may be selected for screening for RA-related lung diseases.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Sparks confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Hecht SS. Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. Lancet Oncol 2002;3(8):461–469.
2. Karlson EW, Chang S-C, Cui J, et al. Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. Ann Rheum Dis 2010;69(1):54–60.
3. Esposito AJ, Chu SG, Madan R, et al. Thoracic manifestations of rheumatoid arthritis. Clin Chest Med 2019;40(3):545–560.
4. Cho MH, Cho JH, Eun Y, et al. Rheumatoid arthritis and risk of lung cancer: a nationwide cohort study. J Thorac Oncol 2024;19(2):216–226.
5. Johnson SR, Bernstein EJ, Bolster MB, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic diseases. Arthritis Rheumatol 2024;76(8):1201–1213.
6. Moyer VA; US Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160(5):330–338.
7. Krist AH, Davidson KW, Mangione CM, et al; US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325(10):962–970.
8. El Alam R, Byrne SC, Hammer MM. Rate of benign nodule resection in a lung cancer screening program. Clin Imaging 2023;104:109984.
9. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European

League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569–2581.

10. Christensen J, Prosper AE, Wu CC, et al. ACR Lung-RADS v2022: assessment categories and management recommendations. J Am Coll Radiol 2024;21(3):473–488.
11. Johnson C, Giles JT, Bathon J, et al. Smoking and subclinical ILD in RA versus the multi-ethnic study of atherosclerosis. PLoS One 2016; 11(4):e0153024.
12. McDermott GC, Hayashi K, Yoshida K, et al. Prevalence and mortality associations of interstitial lung abnormalities in rheumatoid arthritis within a multicentre prospective cohort of smokers. Rheumatology (Oxford) 2023;62(SI3):SI286–SI295.
13. Choi H, Han K, Jung JH, et al. Impact of rheumatoid arthritis and seropositivity on the risk of non-cystic fibrosis bronchiectasis. Chest 2024; 165(6):1330–1340.
14. Bermas BL, Gerber DE. The joint problem of rheumatoid arthritis and lung cancer. J Thorac Oncol 2024;19(2):196–198.
15. Chatzidionysiou K, di Giuseppe D, Soderling J, et al. Risk of lung cancer in rheumatoid arthritis and in relation to autoantibody positivity and smoking. RMD Open 2022;8(2):e002465.

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 850–859
DOI 10.1002/acr.70009

American College of Rheumatology
Empowering Rheumatology Professionals

Temporal Trends and Short- and Long-Term Mortality of People With Acute Myocardial Infarction and Rheumatoid Arthritis: A Nationwide Cohort Study

Megan Butler, MBChB,[1] Nicholas Weight, MBChB,[1] Muhammad Rashid, PhD,[1,2,3] Rodrigo Bagur, PhD,[4] Purvi Parwani, MD,[5] Samantha Hider, PhD,[1,6] Edward Roddy, PhD,[1,6] Robert Butler, MD,[7] and Mamas A. Mamas, DPhil[1,8]

Objective. We investigated whether a diagnosis of rheumatoid arthritis (RA) affects the quality of inpatient acute myocardial infarction (AMI) care and long-term mortality post-AMI.

Methods. We analyzed data from 784,091 adults, 6,047 with a diagnosis of RA, from England and Wales hospitalized with AMI between 2005 and 2019 from the Myocardial Ischaemia National Audit Project registry, linked with Office for National Statistics mortality data and hospital episode statistics. Cox regression models were used to compare risk of all-cause mortality at different time points according to the presence of RA.

Results. There was no difference in adjusted 30-day mortality between groups (adjusted hazard ratio [aHR] 1.09, 95% confidence interval [CI] 0.99–1.19; $P = 0.075$). Beyond this, at 1 year (aHR 1.14, 95% CI 1.07–1.21), 5 years, (aHR 1.28, 95% CI 1.23–1.33), and to the end of the study period (aHR 1.31, 95% CI 1.26–1.36), the risk of all-cause mortality was significantly higher in patients with RA (all $P < 0.001$). Risk of cardiovascular mortality was not significantly different at 30 days or 1 year (aHR 1.08, 95% CI 1.00–1.17; $P = 0.058$), but it was at 5 years (aHR 1.15, 95% CI 1.08–1.23; $P < 0.001$) and to the study endpoint post-AMI (aHR 1.18, 95% CI 1.11–1.24; $P < 0.001$).

Conclusion. We found no meaningful disparities in inpatient care according to the presence of RA; however, those with RA have elevated long-term all-cause mortality post-AMI. Our findings suggest that the mortality burden of RA post-AMI is not driven by the quality of AMI care during admission and is likely driven by the progressive nature of the comorbidities and the complications of treatments associated with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is part of a heterogeneous group of autoimmune rheumatic diseases, affecting approximately 1% of the world's population, and is associated with progressive disability and premature death.[1] Importantly, cardiovascular disease (CVD), including acute myocardial infarction (AMI) is the most common cause of mortality in patients with RA.[2]

People with RA are at elevated risk of AMI,[3] with the systemic proinflammatory state of RA driving accelerated atherogenesis,[4,5] and at increased risk of long-term mortality following AMI, consistently shown across different health care settings.[6,7] The impact of RA on in-hospital outcomes and care quality is more complex. US data have suggested lower in-hospital mortality and comparable quality of care after AMI,[8] whereas similar studies from Australia have shown poorer in-hospital care and outcomes for those with RA.[9] RA disease severity is correlated with poorer long-term mortality, especially higher glucocorticoid doses,[7] with higher coronary plaque burden shown in people with poorer RA control.[10] However, there are encouraging data suggesting a

Supported by the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Dr Rashid's work was supported by the NIHR Development and Skills Enhancement Award (NIHR304156) and Academy of Medical Sciences (grant SGL025/1064).

[1]Keele University, Keele, United Kingdom; [2]University of Leicester, Leicester, United Kingdom; [3]National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, United Kingdom; [4]Western University, London, Ontario, Canada; [5]Loma Linda University Health, Loma Linda, California; [6]Midlands Partnership Foundation Trust, Stoke-on-Trent, United Kingdom; [7]Royal Stoke University Hospital, University Hospitals North Midlands, Stoke-On-Trent, United Kingdom; [8]National Institute for Health and Care Research Birmingham Biomedical Research Centre, Birmingham, United Kingdom.

Dr Butler and Dr Weight contributed equally to this work.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70009).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70009.

Address correspondence via email to Mamas A. Mamas, DPhil, at mamasmamas1@yahoo.co.uk.

Submitted for publication June 2, 2025; accepted in revised form November 12, 2025.

SIGNIFICANCE & INNOVATIONS

- In a nationwide cohort study of 784,091 patients with acute myocardial infarction (AMI) between 2005 and 2019, patients with rheumatoid arthritis (RA) received the same standard of care as patients without RA.
- Patients with RA had elevated long-term all-cause mortality, but 30-day mortality post-AMI was not significantly higher than that of patients without RA.
- There is a long-term elevated risk of cardiovascular-specific mortality, which manifests at 5 years and beyond.

potential reduction in major adverse CV events (MACEs) and reduced vascular inflammation among individuals with RA treated successfully with immunomodulatory therapy.[11,12]

We used data from the Myocardial Ischaemia National Audit Project (MINAP) registry, linked to Office for National Statistics (ONS) mortality data and hospital episode statistics (HES), to investigate the in-hospital quality of care that patients receive according to RA status and to assess whether this influences their long-term all-cause and CV mortality over an extended period of follow-up for a median duration of >6 years and whether mortality risk has changed over our study period.

METHODS

Study design. This study was a retrospective cohort study of routinely collected data from MINAP linked to the ONS and HES. MINAP is a prospective national registry of patients with acute coronary syndrome admitted to 230 hospitals in the United Kingdom. MINAP includes data on patient demographics, clinical characteristics, comorbidities, pharmacotherapy, management, and in-hospital outcomes on approximately 90,000 patients admitted with acute coronary syndrome per year. The ONS is the independent provider of mortality statistics in the United Kingdom, collecting data on all deaths registered in England and Wales, using *International Classification of Diseases, Tenth Revision (ICD-10)* codes, and cause of death from the Medical Certificate of Cause of Death. Mortality follow-up was available for all included patients up to July 31, 2021.

Secondary use of anonymized MINAP data set for research purposes is authorized under NHS research governance arrangements and further supported under section 251 of NHS act 2006 (NIGB: ECC1-06(d)/ 2011), which allows researchers to use patient information collected within the data set for medical research without patient consent. Therefore, a formal ethical approval was not sought for this study. The study underwent formal ethical approval for the data linkages of the MINAP and ONS registries. Ethical approval was provided by the Health Research Authority, Health and Care Research Wales, and the Confidentiality Advisory Group, which is an independent body that provides expert advice on the use of confidential patient information.

Study population. All index admissions between January 2005 and March 2019 with a primary diagnosis of AMI (comprising both ST-elevation myocardial infarction [STEMI] and non-STEMI but not including unstable angina) were extracted from MINAP and stratified according to the presence of RA at the time of presentation. This was conducted using *ICD-10* codes M05 and M06, which were contained in the linked HES record, reflecting comorbidities at time of admission with index AMI. Linked HES records with *ICD-10* codes M05 and M06 have been used in previous studies of the UK population to ascertain diagnosis of RA,[13] with a consistent prevalence between studies of approximately 1%. Usage of *ICD-10* code M05 for the diagnosis of seropositive RA has been shown to have a positive predictive value of 77% to 94% in administrative data sets, and usage of more detailed *ICD-10* definitions, as we demonstrate in Supplementary Table 1, have been shown to increase this further.[14–16]

AMI diagnosis was made by clinicians according to the presenting history, clinical examination and investigations, and results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology.[17] Patients were excluded if there were missing data for variables such as in-hospital mortality, MACE, cause of death, or missing unique identifier, which is the patient NHS number. The first admission with AMI over our study period for each patient was included, with duplicate records or readmissions over the study period identified and removed using the date of admission and NHS number.

Outcomes. The primary outcomes were all-cause mortality, assessed at 30 days, 1 year, 5 years, and over the entire study period, which ended in July 2021, which we referred to as "overall mortality." Secondary outcomes of interest were quality of care measures, including the Opportunity-Based Quality Indicators, which consists of prescription of aspirin, P2Y12 inhibitors, beta-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, and whether referral to cardiac rehabilitation was made while an inpatient. Additionally, we assessed CV mortality only, with a full list of *ICD-10* codes used for assessing CV death displayed in the Supplementary Materials. One-year mortality according to RA status was calculated for each study year to display temporal trends over the study period.

Statistical analysis. Continuous variables such as age at admission and body mass index were summarized using mean and SD if normally distributed and median and interquartile ranges if the data were not normally distributed. Normality of distribution was assessed using the Shapiro-Wilk test. These data were

compared using Student's *t*-test if normally distributed and Wilcoxon rank sum test if not normally distributed. Categorical variables were compared using the Pearson chi-square test and summarized as percentages. Multiple imputation with 10 imputed data sets was used to account for the missing data across our data set after first undertaking a complete case analysis. The imputation model closely resembled the analytical model and included survival times and outcomes to avoid bias toward the null. Results of the complete case analysis undertaken before multiple imputation are shown in the Supplementary Materials. Multiple imputation with chained equations (MICE) is the best practice when dealing with missing data and can provide unbiased estimates even with high levels of missingness and some protection when data are missing not at random.[18] Imputed data were used for our adjusted models as detailed below, whereas descriptive tables are reflective of registry data before imputation, where denominators reflect all patients for which data was available for that variable, hence the varying denominators throughout.

Multivariate Cox models were applied to 10 imputed data sets to generate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for mortality over our study period, with estimates combined using Rubin's rules.[19] Our model was adjusted for the following characteristics: age, sex, ethnicity, year of admission, hospital region, heart rate, blood pressure, comorbid conditions (hypertension; diabetes mellitus; history of asthma or chronic obstructive pulmonary disease [COPD]; history of cerebrovascular accident or peripheral vascular disease; hypercholesterolemia; family history of coronary artery disease; smoking history; chronic renal failure; previous AMI; angina; previous percutaneous coronary intervention [PCI] and previous coronary artery bypass graft [CABG]; and medical therapy, including warfarin, invasive coronary angiogram, and inpatient revascularization by PCI or CABG) cardiac arrest, left ventricular systolic function, ischemic electrocardiogram change, and Killip classification. Variables included were collected at baseline, with time-varying variables not included in this study. The HRs shown are from a comparison of patients with RA at the time of admission with AMI with those without RA. Separate Cox models were used to create HRs for 30-day, 1-year, 5-year, and overall mortality (referring to until the study endpoint of July 31, 2021). Kaplan-Meier curves were plotted to demonstrate unadjusted survival, and the 'stcurve' function was used in Stata 18.0 to illustrate adjusted survival, using the previously specified Cox model on a single extracted data set from our imputed model. Cox models were judged to be appropriate after assessment of Kaplan-Meier survival curves and confirmed by the assessment of the Schoenfeld residuals, demonstrating proportional hazard over our study period.

A secondary analysis was undertaken to assess the risk of CV mortality over the study period, adjusting for the same variable list as the previous Cox model, with CV mortality as the failure and remaining non-CV mortality censored at the time of occurrence. For the display of temporal trends of 1-year mortality and 5-year mortality, years were arranged into 3-year periods to ensure adequate numbers of deaths in people with RA (2005–2007, 2008–2010, 2011–2013, 2014–2016, and 2017–2019; not included in 5-year mortality), and the risk of mortality was calculated using our Cox regression model for each period, correcting for the same variables, aside from year of study, which was removed as a covariate.

Supplementary analyses assessed CV mortality with non-CV mortality as a competing risk with a Fine and Gray competing risk regression model. Given our substantial population size, we used one-to-one nearest neighbor propensity score matching, with matching undertaken for all previously defined Cox model covariates using the 'psmatch2' function on Stata 18.0. A Fine and Gray competing risk regression model was then applied, with non-CV mortality as a competing risk. Further supplementary analyses identified patients with *ICD-10* code Z922 (personal history of drug therapy, including monoclonal drugs, regular glucocorticoids, and immune checkpoint inhibitors) and used this to form "mild" and "severe" RA groups. All statistical analyses were performed using Stata (version 18.0). The authors do not have authorization to share the data, but the data can be accessed through contacting the National Institute for CV Outcomes Research on approval.

RESULTS

Study population and baseline characteristics. A total of 784,091 patients with AMI remained after applying the exclusion criteria (Supplementary Figure 1): 6,047 with a diagnosis of RA at the time of admission (1%) and 778,044 without. People with RA were older in median years (74 vs 70), more likely to be female (56% vs 34%) and more likely to be of White race (94% vs 91%) (all $P < 0.001$) (Table 1).

People with RA were less likely to be current smokers (21% vs 28%), less likely to have hypercholesterolemia (26% vs 32%), and less likely to present with STEMI (33% vs 39%) (all $P < 0.001$). People with RA were more likely to have a diagnosis of asthma or COPD (22% vs 15%, $P < 0.001$) and were more likely to present with diabetes mellitus (21% vs 19%, $P = 0.005$). Supplementary Figure 2 shows the increasing proportion of patients with AMI with a diagnosis of RA in the MINAP registry over the study period, from 0.4% in 2005 to 1.7% in 2019. Supplementary Figure 3 illustrates the different proportions of cause of death between patients with RA and those without RA. People with RA were less likely to die of a CV cause (37% vs 41%) but were more likely to die because of chronic respiratory disease (11% vs 7%).

Quality of AMI care. People with RA were less likely to receive low molecular weight heparin (LMWH) (49% vs 55%) but more likely to receive fondaparinux (42% vs 30%) (both $P < 0.001$). Rates of prescription of aspirin (96% vs 96%,

Table 1. Baseline demographics of people with AMI according to presence of RA*

Variables	RA (N = 6,047)	AMI with no RA (N = 778,044)	*P* value
Age, median (IQR), y	74 (65–81)	70 (59–80)	<0.001
Female, n/N (%)	3,364/6,047 (56)	261,753/778,044 (34)	<0.001
BMI, median (IQR), kg/m^2	26.4 (23.0–30.4)	26.9 (24.0–30.5)	<0.001
Ethnicity: White, n/N (%)	4,104/4,371 (94)	353,299/389,833 (91)	<0.001
Ethnicity: Asian, n/N (%)	169/4,371 (4)	24,046/389,833 (6)	
Ethnicity: Black, n/N (%)	40/4,371 (1)	3,918/389,833 (1)	
Ethnicity: Mixed, n/N (%)	58/4,371 (1)	8,570/389,833 (2)	
Basal crepitations, n/N (%)	698/4,080 (17)	44,132/345,458 (13)	<0.001
Pulmonary edema, n/N (%)	217/4,080 (5)	17,311/345,458 (5)	
Cardiogenic shock, n/N (%)	70/4,080 (2)	5,698/345,458 (2)	
EKG ST changes, n/N (%)	4,816/5,923 (81)	653,385/752,328 (87)	<0.001
Previous smoker, n/N (%)	2,096/5,601 (37)	239,615/720,020 (33)	<0.001
Current smoker, n/N (%)	1,173/5,601 (21)	202,349/720,020 (28)	<0.001
CCF, n/N (%)	314/5,431 (6)	37,337/704,929 (5)	0.112
Hypercholesterolemia, n/N (%)	1,388/5,396 (26)	223,191/702,101 (32)	<0.001
Cerebrovascular disease, n/N (%)	431/5,429 (8)	58,423/705,183 (8)	0.357
History of angina, n/N (%)	1,084/5,445 (20)	160,857/711,075 (23)	<0.001
Peripheral vascular disease, n/N (%)	241/5,393 (4)	30,311/699,205 (4)	0.631
Chronic renal failure, n/N (%)	378/5,423 (7)	39,463/703,966 (6)	<0.001
Diabetes mellitus, n/N (%)	1,138/5,880 (19)	156,539/751,208 (21)	0.005
Hypertension, n/N (%)	2,851/5,476 (52)	357,274/718,109 (50)	0.001
Asthma/COPD, n/N (%)	1,204/5,437 (22)	107,087/701,425 (15)	<0.001
Family history of CAD, n/N (%)	1,082/4,590 (24)	178,783/581,791 (31)	<0.001
Previous AMI, n/N (%)	809/5,463 (15)	123,930/718,248 (17)	<0.001
Previous PCI, n/N (%)	389/5,383 (7)	50,168/706,756 (7)	0.715
Previous CABG, n/N (%)	235/5,392 (4)	39,781/708,137 (6)	<0.001
STEMI, n/N (%)	2,016/6,047 (33)	303,966/778,044 (39)	<0.001
Heart rate, median (IQR), bpm	80 (69–94)	78 (66–92)	<0.001
Systolic blood pressure, median (IQR), mm Hg	137 (119–156)	138 (120–157)	0.090
Good LV function, n/N (%)	1,733/4,591 (38)	192,704/539,767 (36)	<0.001
Moderate LVSD, n/N (%)	1,052/4,591 (23)	118,860/539,767 (22)	
Severe LVSD, n/N (%)	351/4,591 (8)	39,406/539,767 (7)	
Cardiac arrest, n/N (%)	296/5,910 (5)	48,125/753,488 (6)	<0.001

* AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; EKG, electrocardiogram; IQR, interquartile range; LV, left ventricular; LVSD, LV systolic dysfunction; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis; STEMI, ST-elevation myocardial infarction.

P = 0.006) and P2Y12 inhibitors (86% vs 86%, *P* = 0.130) were similar (Table 2). People with RA were less likely to receive ACE inhibitors (71% vs 75%) or statins (80% vs 83%) post-AMI (both *P* < 0.001). Rates of invasive coronary angiography (68% vs 68%, *P* = 0.478), PCI (43% vs 44%, *P* = 0.642), and CABG (2% vs 3%, *P* = 0.005) were similar between groups.

Post-AMI outcomes. Inpatient (7% vs 6%), 30-day (9% vs 7%), and 1-year (20% vs 16%) all-cause mortality were higher in the RA cohort (all *P* < 0.001). The Kaplan-Meier estimate of 5-year all-cause mortality was significantly higher in the RA cohort (45% vs 33%). Figure 1A illustrates the long-term unadjusted survival of people with RA compared with people with >10 years of follow-up where available. Figure 1B illustrates long-term unadjusted survival from CV causes of death only over the same study period. Supplementary Figure 4 demonstrates a log plot of our survival model, and Supplementary Figure 5 shows variables included in our multiple imputation model. Supplementary Figure 6 shows adjusted survival over our entire study period.

There was no significant difference in 30-day mortality between people with RA and those without after the models were adjusted for all available confounders (aHR 1.0, 95% CI 0.99–1.19; *P* = 0.075) (Table 3). However, at 1 year (aHR 1.14, 95% CI 1.07–1.21; *P* < 0.001), 5 years (aHR 1.28, 95% CI 1.23–1.33; *P* < 0.001), and to the end of the study period (July 31, 2021) (aHR 1.31, 95% CI 1.26–1.36; *P* < 0.001), the risk of all-cause mortality was significantly higher in the RA cohort. Thirty-day (aHR 1.08, 95% CI 0.97–1.19; *P* = 0.172) and 1-year (aHR 1.08, 95% CI 1.00–1.17; *P* = 0.058) CV-specific mortality was not significantly higher in those with RA, but 5-year (aHR 1.15, 95% CI 1.08–1.23; *P* < 0.001) and total study period CV mortality (aHR 1.18, 95% CI 1.11–1.24; *P* < 0.001) were higher in those with RA (Table 4). Figure 2A and B illustrates the temporal trends of adjusted 1-year and 5-year mortality for the five 3-year periods across our study period, illustrating that the disparity in 1-year and 5-year mortality across study years according to the presence of RA has not improved in the years between 2005 and 2019.

Table 2. Management strategy and clinical outcome comparison between people with AMI according to presence of RA*

Variables	RA (N = 6,047)	AMI with no RA (N = 778,044)	*P* value
Low molecular-weight heparin, n/N (%)	2,347/4,785 (49)	356,160/645,362 (55)	<0.001
Fondaparinux, n/N (%)	1,870/4,504 (42)	165,686/544,626 (30)	<0.001
Warfarin, n/N (%)	255/4,776 (5)	33,600/634,894 (5)	0.885
Glycoprotein 2b/3a inhibitor, n/N (%)	294/4,821 (6)	56,028/647,310 (9)	<0.001
IV nitrate, n/N (%)	776/4,778 (16)	112,371/635,401 (18)	0.009
MRA, n/N (%)	326/4,181 (8)	33,964/454,171 (7)	0.435
Aspirin, n/N (%)	5,751/6,010 (96)	743,675/771,812 (96)	0.006
P2Y12 inhibitor, n/N (%)	5,100/5,916 (86)	637,060/745,000 (86)	0.130
Statins, n/N (%)	4,794/5,994 (80)	634,549/767,133 (83)	<0.001
ACE inhibitors/ARB, n/N (%)	4,268/5,973 (71)	571,091/764,507 (75)	<0.001
Beta-blockers, n/N (%)	4,827/5,999 (80)	603,214/766,230 (79)	0.001
Inpatient invasive coronary angiogram, n/N (%)	3,946/5,800 (68)	505,413/738,159 (68)	0.478
Inpatient PCI, n/N (%)	2,578/5,962 (43)	332,127/762,804 (44)	0.642
CABG surgery, n/N (%)	102/4,378 (2)	16,787/597,557 (3)	0.055
Revascularization (CABG surgery/PCI), n/N (%)	2,662/5,921 (45)	348,182/762,988 (46)	0.299
Inpatient mortality, n/N (%)	437/6,047 (7)	45,696/778,044 (6)	<0.001
Thirty-day mortality, n/N (%)	520/6,047 (9)	55,638/778,044 (7)	<0.001
One-year mortality, n/N (%)	1,183/6,047 (20)	123,658/778,044 (16)	<0.001
Five-year mortality (Kaplan-Meier estimate), %	45	33	
Reinfarction, n/N (%)	65/5,461 (1)	10,167/700,668 (1)	0.108
Major bleeding, n/N (%)	49/5,835 (1)	6,522/747,931 (1)	0.792
MACE, n/N (%)	484/6,047 (8)	53,760/778,044 (7)	0.001

* MACE is defined as the composite endpoint of in-hospital death and reinfarction. ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; IV, intravenous; MACE, major adverse cardiovascular event; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis.

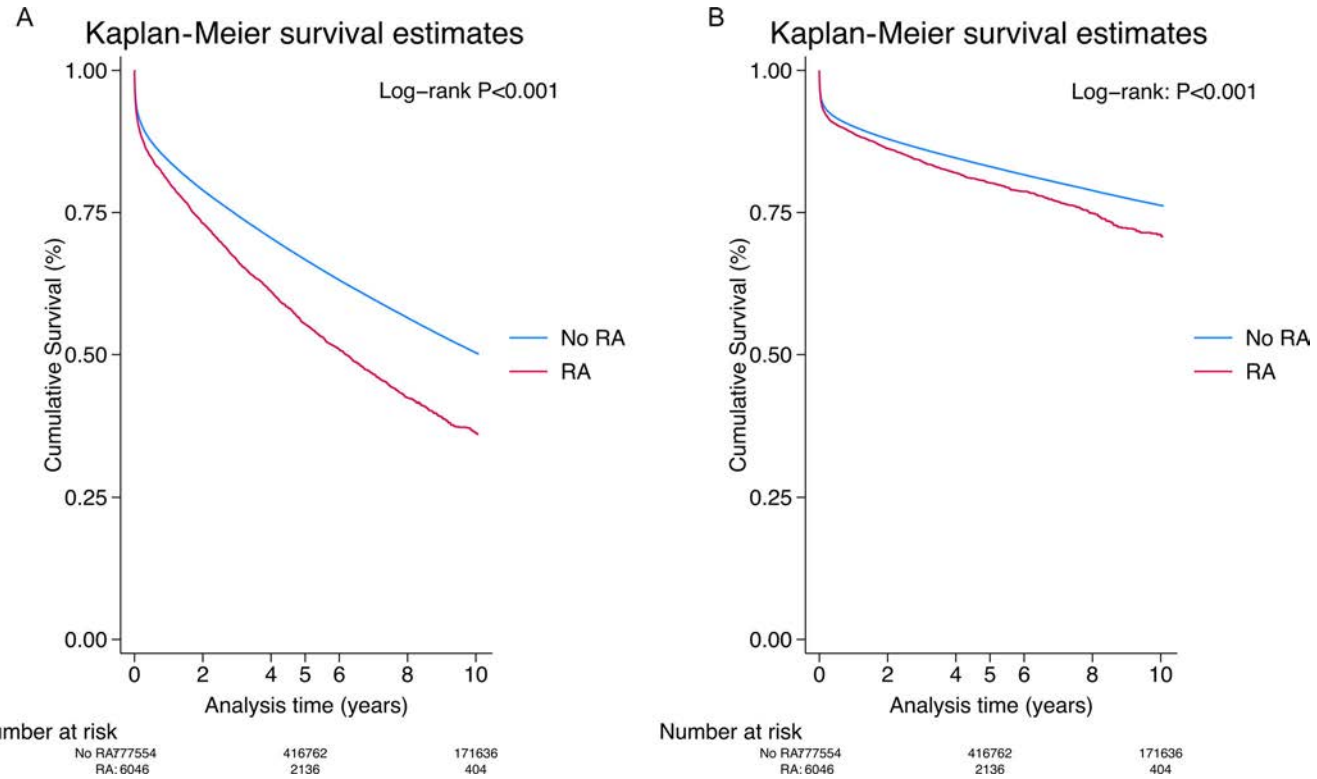

Figure 1. Kaplan-Meier survival analysis for patients with acute myocardial infarction and RA compared with those without (A) all-cause mortality or (B) cardiovascular mortality. RA, rheumatoid arthritis.

Table 3. All-cause mortality survival analysis for people with acute myocardial infarction with or without RA at time of presentation*

Outcome variables	aHR (95% CI)[a]	*P* value
Primary outcomes		
Thirty-day mortality	1.09 (0.99–1.19)	0.075
One-year mortality	1.14 (1.07–1.21)	<0.001
Five-year mortality	1.28 (1.23–1.33)	<0.001
Overall mortality	1.31 (1.26–1.36)	<0.001

* The aHRs are presented with 95% CIs, adjusted for age at admission, sex, ethnicity, year of admission, heart rate, blood pressure, comorbid conditions (hypertension; diabetes mellitus; history of asthma or chronic obstructive pulmonary disease; history of cerebrovascular accident or peripheral vascular disease; hypercholesterolemia; family history of coronary artery disease; smoking history; chronic renal failure; previous acute myocardial infarction; angina; previous percutaneous coronary intervention and previous coronary artery bypass graft; and medical therapy, including warfarin, invasive coronary angiogram, and inpatient revascularization by percutaneous coronary intervention or coronary artery bypass graft), cardiac arrest, left ventricular systolic function, Killip classification, and admission hospital region. aHR, adjusted hazard ratio; CI, confidence interval; RA, rheumatoid arthritis.
[a] Values show comparison between patients with RA and those without.

Supplementary analyses. Supplementary Table 1 shows the *ICD-10* diagnostic codes used to identify patients with RA. When evaluating specific quality indicators for patients without STEMI, the proportion of people undergoing their invasive coronary angiogram within 72 hours was not significantly different between people with or without RA (58% vs 57%, $P = 0.813$) (Supplementary Table 2). The proportion of people receiving dual antiplatelet therapy (DAPT) was the same between groups (83% vs 83%, $P = 0.605$). The proportion of people referred to cardiac rehabilitation on discharge was lower in the RA group (76% vs 78%, $P < 0.001$).

Table 4. Cardiovascular mortality survival analysis for people with acute myocardial infarction with or without RA at time of presentation*

Outcome variables	aHR (95% CI)[a]	*P* value
Primary outcomes		
Thirty-day mortality	1.06 (0.95–1.17)	0.322
One-year mortality	1.08 (1.00–1.17)	0.058
Five-year mortality	1.15 (1.08–1.23)	<0.001
Overall mortality	1.18 (1.11–1.24)	<0.001

* The aHRs are presented with 95% CIs, adjusted for age at admission, sex, ethnicity, year of admission, heart rate, blood pressure, comorbid conditions (hypertension; diabetes mellitus; history of asthma or chronic obstructive pulmonary disease; history of cerebrovascular accident or peripheral vascular disease; hypercholesterolemia; family history of coronary artery disease; smoking history; chronic renal failure; previous acute myocardial infarction; angina; previous percutaneous coronary intervention and previous coronary artery bypass graft; and medical therapy, including warfarin, invasive coronary angiogram, and inpatient revascularization by percutaneous coronary intervention or coronary artery bypass graft), cardiac arrest, left ventricular systolic function, Killip classification, and admission hospital region. Noncardiovascular mortality was censored at the time of occurrence. aHR, adjusted hazard ratio; CI, confidence interval; RA, rheumatoid arthritis.
[a] Values show comparison between patients with RA and those without.

For STEMI, people with RA had a lower proportion of patients receiving a call to balloon time of <120 minutes (51% vs 60%, $P < 0.001$), although there was no significant difference in the proportion of people achieving a door to balloon time of

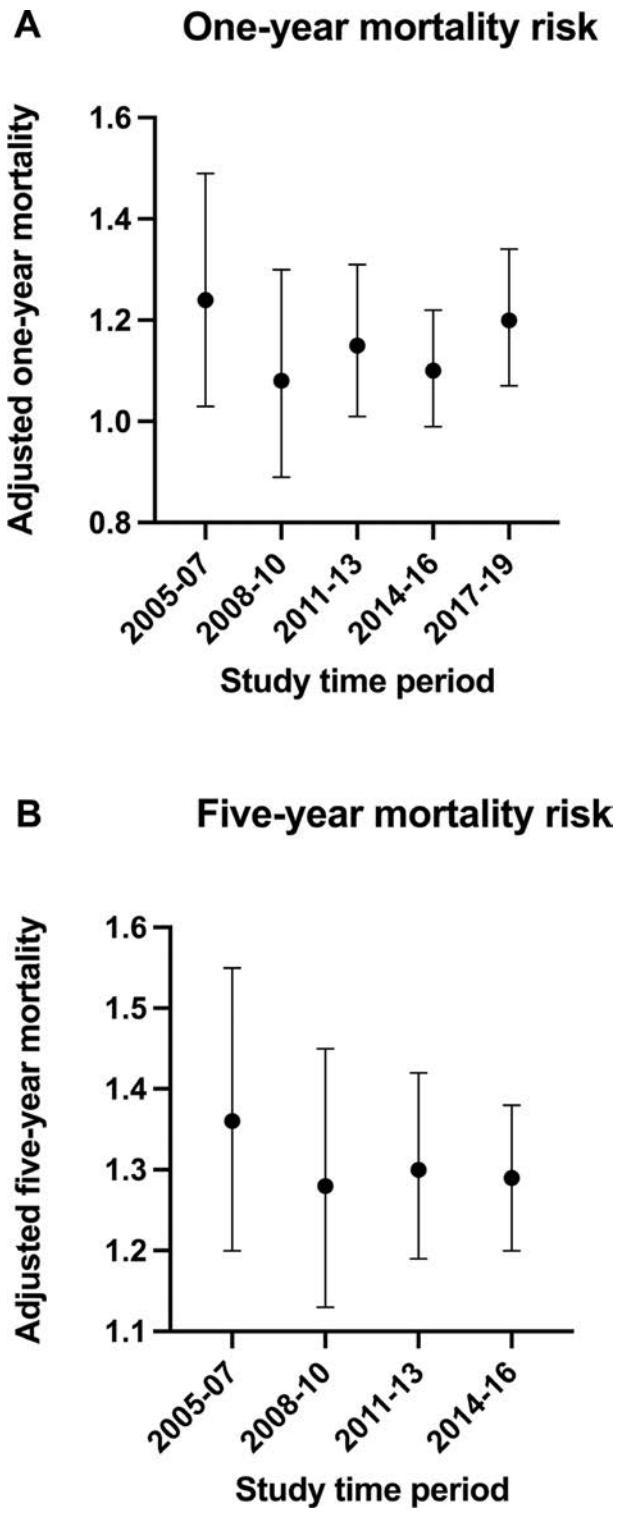

Figure 2. Temporal trends of all-cause mortality over the study period according to the presence of rheumatoid arthritis. (A) One-year mortality. (B) Five-year mortality.

<60 minutes (71% vs 73%, $P = 0.149$) or 90 minutes (85% vs 86%, $P = 0.108$) (Supplementary Table 3). People with RA were more likely to have their left ventricular function assessed while an inpatient (76% vs 71%, $P < 0.001$). There was no significant difference in mean Opportunity-Based Quality Indicators score between people with and without RA (86.9 vs 87.0, $P = 0.086$). The results of our complete case analysis, on all study participants with full data available are shown in Supplementary Tables 4–6.

The results for our supplementary analysis, categorizing patients' severity of RA (mild or severe) according to whether patients are taking disease-modifying antirheumatic drugs or biologic therapies are shown in Supplementary Table 7 (all-cause mortality) and Supplementary Table 8 (CV mortality). When including non-CV mortality as a competing risk, the results for CV mortality were very similar, with no significant increase in risk at 1 year (aHR 1.04, 95% CI 0.93–1.17; $P = 0.478$) but elevated risk in people with RA at 5 years (aHR 1.11, 95% CI 1.01–1.22; $P = 0.029$) and for the total study period (aHR 1.10, 95% CI 1.01–1.21; $P = 0.025$) (Supplementary Table 9).

DISCUSSION

Our comprehensive analysis of >780,000 individuals admitted with AMI, with a median follow-up of >6 years, shows important differences in the long-term outcomes of people with RA and AMI. First, the number of people in our registry with RA presenting with AMI increased progressively over our study period, likely reflecting that this is a growing population, worthy of future study and additionally reflecting improved comorbidity coding over the study. Second, there was no significant difference in the quality of care received between people with or without RA after AMI, with people with RA receiving high-quality AMI care throughout the course of the study, with regard to guideline-directed medical therapy, invasive coronary angiography, and revascularization by either PCI or CABG.

Despite this, people with RA had significantly higher adjusted all-cause mortality at 1 year, 5 years, and up to the end of the study period, with a median follow-up of 6 years for included persons. Importantly, this elevated mortality risk was not significant at 30 days. People with RA had significantly higher CV mortality at 1 year and beyond, emphasizing the importance of CVD in the RA cohort. Despite contemporary improvements in therapies for RA, the increased risk of 1-year mortality for patients with RA remains persistent from the early to latter years of our study.

Previous studies in this area have important limitations, meaning that our study adds an important perspective in the contemporary management of AMI in people with RA in a large, universal health care system. Studies have frequently been limited by either a small population of people with RA, who are limited to either in-hospital or short-term mortality follow-up, or have mostly enrolled patients in the early 2000s, when access to newer biologic therapies was more restricted.[6,17]

Given that people with RA have a systemic inflammatory response, leading to significantly higher concentrations of circulating pro-inflammatory cytokines, it is no surprise that there is accelerated formation of coronary artery plaque[4] alongside a challenging combination of endothelial dysfunction, insulin resistance, and dyslipidemia, which all contribute to the excess CV mortality seen in those with RA.[4,5] The long-term all-cause mortality risk in those with RA after AMI is replicated in studies worldwide, in the United States, Finland, Sweden, and Taiwan,[6,7,20,21] for example showing a consistent association with premature mortality across different health care systems and populations. Our study adds to the literature that in individuals with AMI those with RA have a higher risk of long-term all-cause mortality, but we additionally demonstrate the importance of CV-specific mortality.

Although the picture of elevated long-term all-cause mortality is now clear, there has been uncertainty in the interpretation of literature regarding in-hospital quality of care and early mortality according to the presence of RA. Previous studies have shown a range of findings in this domain. Van Doornum et al demonstrated poorer rates of guideline-directed medical therapy, reperfusion, and in-hospital mortality in those with RA,[9] and Lai et al noted increased in-hospital and overall mortality in patients with RA in their nationwide Taiwanese study.[21] Conversely, Francis et al and Elbadawi et al show that RA was associated with lower inpatient mortality in their US nationwide studies.[8,22] With no significant difference in in-hospital quality of care or all-cause mortality at 30 days in our study, we add further evidence to the suggestion that in a contemporary, universal health care setting, there is no significant disparity in access to high-quality AMI care for people with RA and that their early mortality post-AMI does not seem to be any different to that of the non-AMI population.

Although we are considering the impact of AMI, it must be considered that people with RA already have significantly elevated longer-term all-cause mortality than the general population, with higher rates of not just MI but additionally heart failure and stroke.[23] This is not surprising, given the elevated risk of important modifiable risk factors such as obesity, physical inactivity, hypertension, hyperlipidemia, and diabetes mellitus in people with RA, which are significant contributors to the elevated long-term all-cause mortality seen in this cohort.[24–26] Furthermore, there is increased risk associated with medications used to treat RA, such as glucocorticoids and JAK inhibitors, with regard to CVD and all-cause mortality.[27,28] Historically, it has been the excess burden of CV mortality that is a major driver of this higher all-cause mortality, but there has been recent evidence suggesting that CV mortality in patients with RA is declining, likely through a combination of improvements in RA therapy and reductions in modifiable risk factors such as smoking, whereas respiratory and neoplastic causes of death are either static or increasing.[29] There are also growing data in the more contemporary era to suggest that in well-treated inflammatory arthritis, 5-year survival is becoming comparable

with that of the baseline population.[30] It was therefore disappointing that despite advances in RA therapy over our study period, this has not translated to narrowing the disparity in survival post-AMI, and that CV-specific mortality remains a significant contributor to this. Our cause of death analysis on our RA population shows higher rates of neoplastic, chronic respiratory and infective deaths than the general AMI population, which is in keeping with previous analyses of cause of death in people with RA.[31]

One area of potential improvement in the quality of care of all patients post-AMI could be increased rates of referral to cardiac rehabilitation at the point of discharge, an intervention with well-established evidence to reduce long-term mortality and improve quality of life.[32] We acknowledge that there could be patient-level reasons why referral, attendance, or completion of cardiac rehabilitation is lower than ideal in all patients and lower still in patients with RA. Furthermore, our study shows that over time, the proportion of people with an RA diagnosis at the time of AMI is increasing. This is in keeping with predictive modeling using data from the Global Burden of Diseases, Injuries, and Risk Factors Study suggesting that the RA population will continue to grow over the coming years, partly attributable to improvement of diagnosis and reduction of excess mortality in early RA.[33,34] We suspect that improvement in the comorbidity coding for AMI admissions in the MINAP registry also contributes. Despite this, we suggest that the rates of people with RA presenting with AMI are increasing, just not to the extent suggested by our temporal trends analysis.

In summary, our findings indicate that RA remains associated with significantly increased long-term mortality following AMI, even in the context of equitable inpatient care, and that this disparity has not narrowed over a 15-year study period despite advances in modern RA therapies. We suggest that further studies should focus on identifying and addressing the disparities in the management of RA and its effects on patients' long-term health and to determine if more aggressive RA therapies are warranted.

There are several major strengths to this study. The MINAP registry collects robust data, with many variables recorded from all those presenting to the hospital with AMI in the United Kingdom. Our results are more likely to be representative of other publicly funded health care models globally, owing to the balancing out of regional differences. Our postdischarge mortality data from the ONS enables us to assess cause-specific mortality at least 2 years for all included persons. Furthermore, our paper studies people within a universal health care system, in which health care is free at the point of use; therefore, there should not be significant regional or socioeconomic disparities in access to aspects of high-quality AMI care that one may expect to see in insurance-based health care systems.[35]

There are several important limitations to consider in this study. First, there is no external validation of data inputs in the MINAP database. RA status is determined by HES coding, which may lack clinical verification (eg, seropositive vs seronegative RA). We can see increased and improved comorbidity coding over the study period; therefore, we suspect that the proportion of people with RA in the early years of the study is underestimated. Second, although the MINAP database collects many variables, it does not collect data on frailty, an exhaustive list of comorbidities, disease severity, or the intensity or timescale of RA treatments; these important covariates are not then able to be included within our adjusted models, leaving a risk of residual confounding. Therefore, our ability to subclassify patients is limited and we may miss disparities in management. We additionally lack detailed data on baseline CV risk status of patients, with no access to whether there is baseline coronary calcification from prior imaging, for example, and we do not have access to biomarker data such as high-sensitivity C-reactive protein levels. Furthermore, long-term mortality outcomes may be influenced by adherence to therapy, ongoing RA care, or postdischarge cardiac follow-up, none of which are captured, and therefore cannot be included within our adjusted models.

Given that we are assessing long-term mortality, a further limitation is our usage of baseline variable collection at time of admission, and we are unable to adjust for time-varying confounders over the course of the study. The most important limitation of our study is the lack of ability with which to accurately stratify the severity of RA given the limited capture of important additional metrics that could stratify severity, such as the usage of disease-modifying antirheumatic drugs, usage of long-term glucocorticoids, or active usage of biologic therapy. Additionally, the inclusion of a second measure of RA status would improve the reliability of capturing RA status from administrative data sets, and we acknowledge a risk of misclassification of patients because of the lack of a second measure.[36] Overall, our method of identification of patients with RA carries a risk of overestimating patient numbers by including patients that either do not have RA or have very mild disease; therefore, we may be underestimating mortality risk post-AMI in the RA cohort by including low-risk patients, reflecting bias toward the null, and it is important that our results are interpreted in this context.

There was a possible selection bias in our quality-of-care groups, because to receive a referral for cardiac rehabilitation people need to be fit enough to attend, have sufficient renal function to tolerate ACE inhibitors, and have a prognosis good enough to start on statins. Finally, it must be considered that MINAP is an AMI-specific registry, and we are unable to compare outcomes with people without AMI.

Our nationwide analysis of the long-term outcomes of >780,000 people in England and Wales with AMI, 6,047 of whom had RA, shows that there is a growing proportion of patients admitted with AMI who have a diagnosis of RA, but those with RA do not experience significant disparities in inpatient AMI care. Although there is no significant difference in 30-day mortality,

those with RA have an elevated risk of long-term all-cause and CV-specific mortality. Finally, we report that the degree of elevated mortality risk in those with RA has not decreased over our study period despite advances in RA therapies.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Professor Mamas confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res 2018;6(1):15. doi:10.1038/s41413-018-0016-9
2. Puttevils D, De Vusser P, Geusens P, et al. Increased cardiovascular risk in patients with rheumatoid arthritis: an overview. Acta Cardiol 2014;69(2):111–118. doi:10.1080/AC.69.2.3017291
3. Chung WS, Lin CL, Peng CL, et al. Rheumatoid arthritis and risk of acute myocardial infarction--a nationwide retrospective cohort study. Int J Cardiol 2013;168(5):4750–4754. doi:10.1016/j.ijcard.2013.07.233
4. Sattar N, McCarey DW, Capell H, et al. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108(24):2957–2963. doi:10.1161/01.CIR.0000099844.31524.05
5. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105(9):1135–1143. doi:10.1161/hc0902.104353
6. McCoy SS, Crowson CS, Maradit-Kremers H, et al. Longterm outcomes and treatment after myocardial infarction in patients with rheumatoid arthritis. J Rheumatol 2013;40(5):605–610. doi:10.3899/jrheum.120941
7. Palomäki A, Kerola AM, Malmberg M, et al. Patients with rheumatoid arthritis have impaired long-term outcomes after myocardial infarction: a nationwide case-control registry study. Rheumatology (Oxford) 2021;60(11):5205–5215. doi:10.1093/rheumatology/keab204
8. Elbadawi A, Ahmed HMA, Elgendy IY, et al. Outcomes of acute myocardial infarction in patients with rheumatoid arthritis. Am J Med 2020;133(10):1168–1179.e4. doi:10.1016/j.amjmed.2020.02.039
9. Van Doornum S, Brand C, Sundararajan V, et al. Rheumatoid arthritis patients receive less frequent acute reperfusion and secondary prevention therapy after myocardial infarction compared with the general population. Arthritis Res Ther 2010;12(5):R183. doi:10.1186/ar3151
10. Karpouzas GA, Ormseth SR, Hernandez E, et al. Impact of cumulative inflammation, cardiac risk factors, and medication exposure on coronary atherosclerosis progression in rheumatoid arthritis. Arthritis Rheumatol 2020;72(3):400–408. doi:10.1002/art.41122
11. Solomon DH, Giles JT, Liao KP, et al; TARGET Trial Consortium. Reducing cardiovascular risk with immunomodulators: a randomised active comparator trial among patients with rheumatoid arthritis. Ann Rheum Dis 2023;82(3):324–330. doi:10.1136/ard-2022-223302
12. Karpouzas GA, Ormseth SR, van Riel PLCM, et al. Biological use influences the impact of inflammation on risk of major adverse cardiovascular events in rheumatoid arthritis. RMD Open 2024;10(3):10. doi:10.1136/rmdopen-2024-004546
13. Clynes MA, Jameson K, Prieto-Alhambra D, et al. Impact of rheumatoid arthritis and its management on falls, fracture and bone mineral density in UK Biobank. Front Endocrinol (Lausanne) 2019;10:817. doi:10.3389/fendo.2019.00817
14. Lee H, Sparks JA, Lee SB, et al. Validation of serostatus of rheumatoid arthritis using ICD-10 codes in administrative claims data. Pharmacoepidemiol Drug Saf 2023;32(5):586–591. doi:10.1002/pds.5597
15. Curtis JR, Xie F, Zhou H, et al. Use of ICD-10 diagnosis codes to identify seropositive and seronegative rheumatoid arthritis when lab results are not available. Arthritis Res Ther 2020;22(1):242. doi:10.1186/s13075-020-02310-z
16. Callhoff J, Albrecht K, Marschall U, et al. Identification of rheumatoid arthritis in German claims data using different algorithms: validation by cross-sectional patient-reported survey data. Pharmacoepidemiol Drug Saf 2023;32(5):517–525. doi:10.1002/pds.5562
17. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36(3):959–969. doi:10.1016/S0735-1097(00)00804-4
18. Kontopantelis E, White IR, Sperrin M, et al. Outcome-sensitive multiple imputation: a simulation study. BMC Med Res Methodol 2017;17(1):2. doi:10.1186/s12874-016-0281-5
19. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc 1996;91(434):473–489. doi:10.1080/01621459.1996.10476908
20. Mantel Ä, Holmqvist M, Jernberg T, et al. Long-term outcomes and secondary prevention after acute coronary events in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76(12):2017–2024. doi:10.1136/annrheumdis-2017-211608
21. Lai CH, Hsieh CY, Barnado A, et al. Outcomes of acute cardiovascular events in rheumatoid arthritis and systemic lupus erythematosus: a population-based study. Rheumatology (Oxford) 2020;59(6):1355–1363. doi:10.1093/rheumatology/kez456
22. Francis ML, Varghese JJ, Mathew JM, et al. Outcomes in patients with rheumatoid arthritis and myocardial infarction. Am J Med 2010;123(10):922–928. doi:10.1016/j.amjmed.2010.05.017
23. Løgstrup BB, Ellingsen T, Pedersen AB, et al. Cardiovascular risk and mortality in rheumatoid arthritis compared with diabetes mellitus and the general population. Rheumatology (Oxford) 2021;60(3):1400–1409. doi:10.1093/rheumatology/keaa374
24. Panoulas VF, Metsios GS, Pace AV, et al. Hypertension in rheumatoid arthritis. Rheumatology (Oxford) 2008;47(9):1286–1298. doi:10.1093/rheumatology/ken159
25. Jagpal A, Navarro-Millán I. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. BMC Rheumatol 2018;2(1):10. doi:10.1186/s41927-018-0014-y
26. Nadkarni A, You M, Resuehr H. The risk for cardiovascular events associated with hyperlipdemia among patients with and without rheumatoid arthritis. J Arthritis 2015;4(4):178. doi:10.4172/2167-7921.1000178
27. So H, Lam TO, Meng H, et al. Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based study. Ann Rheum Dis 2023;82(11):1387–1393. doi:10.1136/ard-2023-224185
28. Wei Q, Wang H, Zhao J, et al. Cardiovascular safety of Janus kinase inhibitors in patients with rheumatoid arthritis: systematic review and network meta-analysis. Front Pharmacol 2023;14:1237234. doi:10.3389/fphar.2023.1237234

29. Abhishek A, Nakafero G, Kuo CF, et al. Rheumatoid arthritis and excess mortality: down but not out. A primary care cohort study using data from Clinical Practice Research Datalink. Rheumatology (Oxford) 2018;57(6):977–981. doi:10.1093/rheumatology/key013
30. Bournia VK, Fragoulis GE, Mitrou P, et al. All-cause mortality in systemic rheumatic diseases under treatment compared with the general population, 2015-2019. RMD Open 2021;7(3):e001694. doi:10.1136/rmdopen-2021-001694
31. Avouac J, Amrouche F, Meune C, et al. Mortality profile of patients with rheumatoid arthritis in France and its change in 10 years. Semin Arthritis Rheum 2017;46(5):537–543. doi:10.1016/j.semarthrit.2016.10.007
32. Pouche M, Ruidavets JB, Ferrières J, et al. Cardiac rehabilitation and 5-year mortality after acute coronary syndromes: the 2005 French FAST-MI study. Arch Cardiovasc Dis 2016;109(3):178–187. doi:10.1016/j.acvd.2015.09.009
33. Cai Y, Zhang J, Liang J, et al. The burden of rheumatoid arthritis: findings from the 2019 Global Burden of Diseases study and forecasts for 2030 by Bayesian age-period-cohort analysis. J Clin Med 2023;12(4):1291. doi:10.3390/jcm12041291
34. van Nies JA, de Jong Z, van der Helm-van Mil AH, et al. Improved treatment strategies reduce the increased mortality risk in early RA patients. Rheumatology (Oxford) 2010;49(11):2210–2216. doi:10.1093/rheumatology/keq250
35. Danchin N, Neumann A, Tuppin P, et al. Impact of free universal medical coverage on medical care and outcomes in low-income patients hospitalized for acute myocardial infarction: an analysis from the French National Health Insurance system. Circ Cardiovasc Qual Outcomes 2011;4(6):619–625. doi:10.1161/CIRCOUTCOMES.111.961193
36. Chung CP, Rohan P, Krishnaswami S, et al. A systematic review of validated methods for identifying patients with rheumatoid arthritis using administrative or claims data. Vaccine 2013;31 Suppl 10:K41–K61. doi:10.1016/j.vaccine.2013.03.075

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 860–874
DOI 10.1002/acr.70004

American College of Rheumatology
Empowering Rheumatology Professionals

Clinical Practice Guideline for Evaluation and Management of Peripheral Nervous System Manifestations in Sjögren's Disease

Anahita Deboo, MD,[1] Robert Fox, MD, PhD,[2] Katherine M. Hammitt, MA,[3] Julie Frantsve-Hawley, PhD,[3,4] Matthew C. Baker, MD, MS,[5] Stamatina Danielides, MD,[6,7] Eduardo De Sousa, MD,[8] Brent P. Goodman, MD,[9] Jennifer K. King, MD, PhD,[10] Steven Mandel, MD,[11] Ghaith Noaiseh, MD,[12] Pantelis P. Pavlakis, MD, PhD,[13] George Sarka, MD, DrPH,[14,15,16] R. Hal Scofield, MD,[17,18,19] Arun Varadhachary, MD, PhD,[20] Daniel J. Wallace, MD,[10,14] Matt Makara, MPH,[3] Nancy Carteron, MD,[21,22] and Steven Carsons, MD,[23] in collaboration with the Consensus Expert Panel (CEP) members

Objective. Sjögren's disease is an autoimmune disorder that can impact multiple organ systems, including the peripheral nervous system (PNS). PNS manifestations, which can exist concurrently, include mononeuropathies, polyneuropathies, and autonomic nervous system neuropathies. To help patients and providers in the decision-making process, we developed an evidence-based clinical practice guideline for the evaluation and management of PNS manifestations in patients with Sjögren's disease.

Methods. A Topic Review Group, comprising experts in rheumatology, neurology, and guideline methodology, developed Patient, Intervention, Comparison, and Outcome questions and conducted a systematic review to identify the current best evidence on management of PNS manifestations of Sjögren's disease. PubMed and Embase were searched for evidence published up to July 22, 2025. Literature screening, data extraction, and critical appraisal were performed in duplicate. Six case series, one retrospective cohort, and two prospective cohort studies lacking a comparison group met the inclusion criteria.

Results. We developed an aligned nomenclature of PNS terms that can be used across disciplines, 31 good practices for evaluation of suspected PNS manifestations, and 20 evidence-based treatment recommendations, the latter of which were rated as conditional or strong based on the Grading of Recommendations Assessment, Development, and Evaluation methodology. Because of the scarcity of high-level evidence, this guideline predominantly derives from expert opinion.

Conclusion. This clinical practice guideline on PNS manifestations of Sjögren's disease provides clinicians a rigorous, evidence-based resource, developed through an expert consensus-based process, for the assessment, diagnosis, and treatment of peripheral neuropathy in patients with Sjögren's disease. Recommendations were rated as strong when the benefits significantly outweighed potential harms, creating a scenario in which most patients would prefer the advised action.

[1]Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; [2]Scripps Memorial Hospital and Research Foundation, La Jolla, California; [3]Sjögren's Foundation, Reston, Virginia; [4]Temple University Kornberg School of Dentistry, Philadelphia, Pennsylvania; [5]Stanford University, Palo Alto, California; [6]Inova Health Systems, Ashburn, Virginia; [7]University of Virginia, Charlottesville, Virginia; [8]Mercy Hospital, Moore, Oklahoma; [9]Honor Health, Scottsdale, Arizona; [10]David Geffen School of Medicine Center at University of California, Los Angeles; [11]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York Medical College, New York; [12]University of Kansas, Kansas City; [13]Athens Medical Center, Athens, Greece; [14]Cedars-Sinai Medical Center, Los Angeles, California; [15]California State University, Northridge; [16]Memorial Care, Saddleback Medical Center, Laguna Hills, California; [17]Medical Research Foundation, Oklahoma City, Oklahoma; [18]University of Oklahoma Health Sciences Center, Oklahoma City; [19]Oklahoma City Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma; [20]Washington University School of Medicine, Saint Louis, Missouri; [21]University of California, San Francisco; [22]Herbert Wertheim School of Optometry and Vision Science, University of California, Berkeley; [23]NYU Grossman Long Island School of Medicine, Mineola, New York.

Drs. Carteron and Carsons are co-last authors and contributed equally to this work.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70004).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70004.

Address correspondence via email to Katherine M. Hammitt, MA, at khammitt@sjogrens.org

Submitted for publication April 18, 2025; accepted in revised form November 6, 2025.

SIGNIFICANCE & INNOVATIONS

- An evidence-based clinical practice guideline was developed to assist in the evaluation and management of peripheral nervous system (PNS) manifestations in Sjögren's disease, including mononeuropathies, polyneuropathies, and autonomic nervous system (ANS) neuropathies.
- A multidisciplinary team of rheumatologists, neurologists, and guideline methodologists conducted a systematic review and developed standardized nomenclature, 31 good practices for evaluation, and 20 treatment recommendations for PNS and ANS manifestations in Sjögren's disease.
- The guideline also uses a unified terminology and framework to facilitate multidisciplinary collaboration and improve patient outcomes in the management of Sjögren's disease–related PNS manifestations.
- The available evidence, primarily from case series and cohort studies without comparison groups, necessitated reliance on expert consensus for many recommendations, although strong recommendations were made when potential benefits clearly outweighed risks.

INTRODUCTION

Sjögren's disease (SjD), a complex autoimmune disorder, impacts multiple organ systems including the peripheral nervous system (PNS). Reports on the prevalence of PNS manifestations in SjD range from 8% to 60%.[1–11] Evidence suggests the prevalence of PNS manifestations in SjD is significantly underestimated.[12] Contributing to underreporting are neuropathies that are asymptomatic in early stages and/or underrecognized as a feature of SjD.[9] The mean age of diagnosis of PNS manifestations is 59 years, often preceding the SjD diagnosis in up to 90% of patients.[2,6,11,13] The consequences of PNS manifestations in SjD significantly diminish patients' quality of life (QOL) while presenting diagnostic and management challenges for health care providers.[9,14–17]

PNS manifestations encompass a spectrum of neurologic abnormalities, including cranial neuropathies (trigeminal neuropathy and facial neuropathy), polyneuropathies (large fiber neuropathy, small fiber neuropathy, and demyelinating polyradiculoneuropathy), and autonomic nervous system (ANS) neuropathies (postural tachycardia, orthostatic hypotension, and autonomic dysfunction).[2,11,18–20] Additionally, some patients with SjD may develop vasculitic neuropathy or ganglionopathy, which can be rapidly debilitating.[21,22] Autonomic disorders contribute to reduced QOL and function, which can be overlooked or misdiagnosed as anxiety or functional disorders. Patients with SjD may experience various multiple peripheral neuropathies concurrently. Understanding the specific subtype of peripheral neuropathy and the underlying pathophysiologic mechanisms is essential to effectively diagnosing and treating comorbid conditions. Therefore, a collaborative, multidisciplinary approach to patient evaluation involving neurologists, rheumatologists, and other specialists proves invaluable.

In response to the growing recognition of PNS involvement and management uncertainties, the Sjögren's Foundation convened a Topic Review Group (TRG) of neurologists and rheumatologists to develop an evidence-based guideline on PNS manifestations in patients with SjD. The guideline incorporates aligned nomenclature of PNS terms that can be used across disciplines, which was used in developing good practices for the evaluation of suspected PNS manifestations and evidence-based treatment recommendations. This guideline provides rheumatologists, neurologists, primary care providers, and other members of the health care team with an evidence-based and consensus-based resource for collaborative assessment, diagnosis, and treatment of PNS manifestations in SjD.

METHODS

We developed this evidence-based guideline based on the methodology of the American College of Rheumatology (ACR),[23] which was previously used for other Sjögren's Foundation guidelines.[24,25] We used principles of the American Society of Clinical Oncology, the US Preventive Services Taskforce, and the American Dental Association to formulate the methodology.[26–29] During the process of developing the recommendations, we transitioned to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for rating the strength of each recommendation.[29–32]

We assembled the PNS TRG, consisting of six neurologists (AD, EDS, BPG, SM, PPP, and AV), six rheumatologists (RF, MCB, SD, JKK, GN, and DJW), one member dual-specialized in neurology and rheumatology (GS), and one patient representative (KMH). We invited neurologists with specific experience in SjD and who collaborate with rheumatologists in managing their patients with SjD. Leadership for the PNS TRG included coleaders (a rheumatologist [RF] and a neurologist [AD]), guideline oversight committee members (SC, NC, and RHS), and a guideline expert (JF-H).

The Sjögren's Foundation guideline policy is that TRG members with a direct financial conflict of interest (COI), defined as receiving funds directly from industry related to a treatment or procedure addressed in the guideline, must be recused from engaging in that part of the project, and no more than 49% of the TRG members can have a direct COI. All TRG members signed a COI and disclosed any potential financial conflicts at the project's onset, which was periodically updated. The guideline leadership (SC, NC, RHS, RF, and AD) managed conflicts accordingly. Panelists were aware of disclosures. No direct COIs were identified, and only 40% had indirect COI disclosures

(defined as engagements with industry not directly related to a treatment or procedure addressed in this guideline).

Our systematic review protocol is registered with International Platform of Registered Systematic Review and Meta-analysis Protocols (protocol 2025110020). The TRG defined systematic review parameters, inclusion/exclusion criteria, endpoints (Supplementary Material 1), and the Patient, Intervention, Comparison, and Outcome (PICO) questions. The overarching therapy PICO question for the treatment recommendations was as follows: in patients with SjD and PNS manifestations (mononeuropathies, polyneuropathies, and vasculitis) and ANS manifestations, which therapies are most effective in improving neurologic symptoms or function? The overarching evaluation and monitoring PICO question for the good practice statements was as follows: in patients with SjD and suspected PNS or ANS manifestations, which diagnostic and monitoring strategies are clinically useful for diagnosis and tracking disease progression or treatment response? The full set of PICO questions is available in Supplementary Material 2. We searched PubMed for articles published in English between January 1, 1990, and May 1, 2023 (Supplementary Material 3), and updated the search through July 22, 2025. An Embase literature search was conducted through July 22, 2025. At least two TRG members screened titles and abstracts, and subsequently full-text articles, in duplicate, with discrepancies resolved by mutual discussion. Two TRG members conducted data extraction and quality assessment in duplicate, with discrepancies resolved via discussion. The quality assessment involved rating the overall quality of each study according to criteria related to study design and the risk of bias used in recommendation development.

The TRG engaged in collaborative efforts to unify terminology and define the nomenclature used to describe PNS manifestations. The unified nomenclature provided the structure and categories for the subsequent good practices and treatment recommendations.[33]

The TRG intended to develop evidence-based recommendations for the evaluation of PNS manifestations in patients with SjD. However, the identified studies provided information on which tests were used but did not address sensitivity, specificity, positive predictive values, negative predictive values, and likelihood ratios in an SjD population. Thus, we used a good practices approach for the evaluation portion of the project. For this, we categorized the most common diagnostic tests reported and used expert opinion to develop good practice statements for evaluating patients with SjD who present with PNS symptoms.

The TRG drafted recommendations on therapies for patients with SjD with PNS manifestations. Each recommendation was rated based on two factors: (1) the level of the available evidence and (2) the strength of the recommendation based on confidence that the recommendation offers the best current guidance for practice (Supplementary Material 4). For each recommendation, the TRG evaluated the balance between desirable and undesirable effects, the quality of evidence, patients' values and preferences, and feasibility, including costs.[34] Based on GRADE methodology, a recommendation was considered strong, even if the quality of evidence is low or very low, when the potential benefit significantly outweighed the potential harm, aligning with the majority of patients' preferences, and when the potential harms of inaction were unacceptable to patients. A conditional recommendation was given when the potential benefit slightly outweighed the potential harm, leading to a more varied preference among patients. We followed an anonymous Delphi-type process to ascertain the level of agreement from the Consensus Expert Panel (CEP)—composed of 69 members, including 39 rheumatologists, 20 neurologists who actively work with patients with SjD, and 10 additional members, all of whom were patients with SjD or family of patients (Appendix A; Supplementary Material 5). At least 75% agreement was required for inclusion in the manuscript, with repeated rounds of revision by the TRG and voting until the consensus threshold was met. The formal consensus process was deemed critical in view of the lack of high-quality evidence.

The guideline process adhered to the Appraisal of Guidelines for Research and Evaluation II instrument (Supplementary Material 6). For the systematic review component, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Supplementary Material 7). This work did not require institutional review board approval.

RESULTS

Systematic review

The TRG developed 102 clinical questions on SjD-related PNS manifestations (Supplementary Material 2). These questions spanned mononeuropathy, polyneuropathy, and autonomic neuropathy and addressed diagnostic/evaluation procedures or therapeutic interventions.

The literature search yielded 13,848 articles. After duplicates were removed, 11,174 articles remained. Of these, 10,918 articles were excluded based on title/abstract review, and 247 were excluded based on full-text review (Figure 1). A list of studies excluded at the full-text review stage, with the reason for exclusion, is provided in Supplementary Material 8.

Nine studies that addressed therapeutic interventions met the inclusion criteria and were used to develop evidence-based recommendations. Six were case series, one was a retrospective cohort study, and two were prospective cohort studies lacking a comparison group. Data extraction and quality assessment are provided in Supplementary Material 9. Because of the lack of high-quality evidence, most of the treatment recommendations are based on expert opinion, informed by balancing benefits, harms, and patient values.

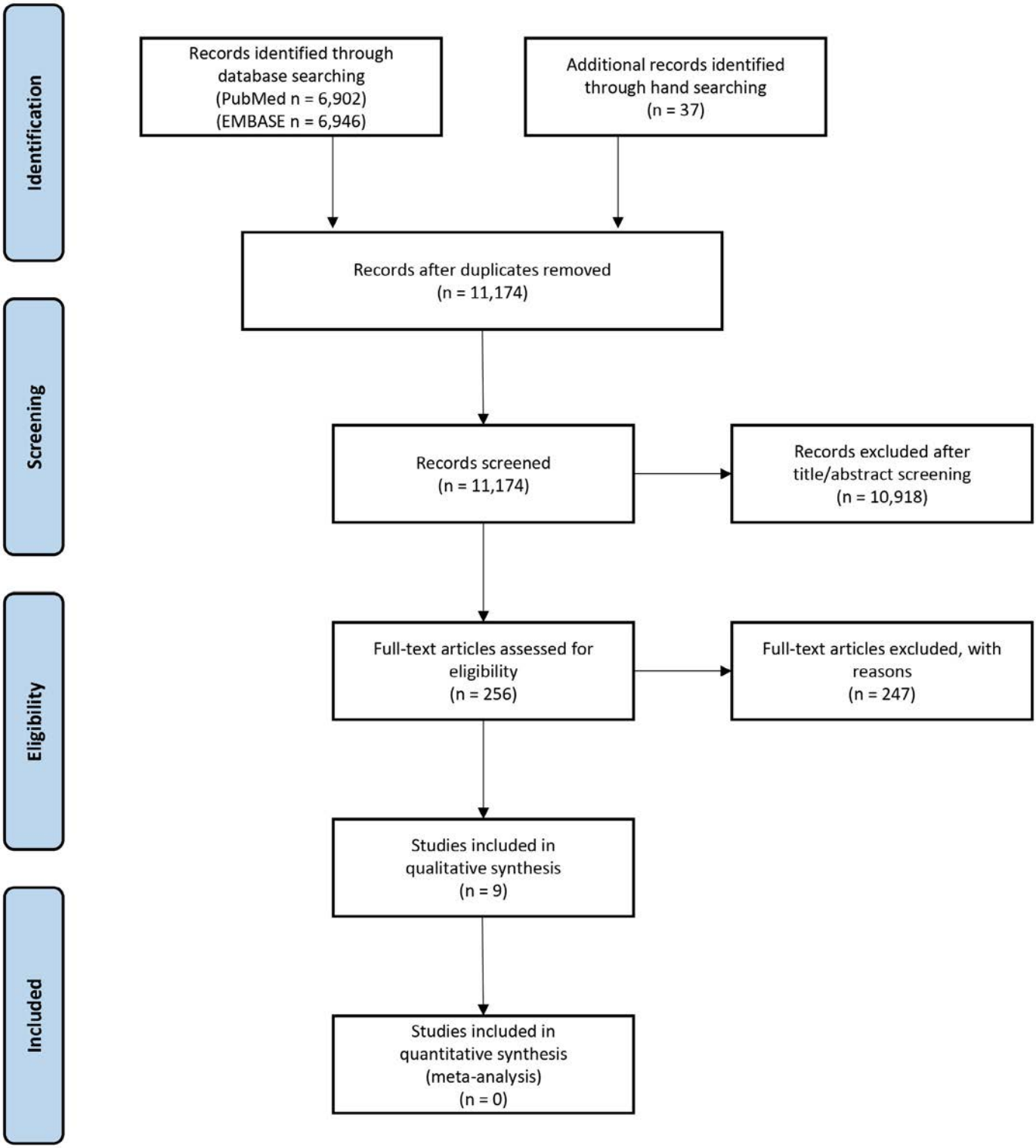

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

PNS nomenclature and definitions

The guideline development process highlighted a critical communication gap between rheumatology and neurology clinicians because of differing terminologies used by the two specialties that posed challenges to collaboration in clinical management and guideline formulation.[5,6,35] We aimed to bridge this gap by establishing consensus on the nomenclature among neurologists and rheumatologists for PNS involvement in SjD. A unified nomenclature that formed the

basis of the guideline is available in Supplementary Material 10.[33]

Good practices and recommendations

The most common tests reported for evaluation of PNS manifestations in patients with SjD were used to inform good practice statements (Supplementary Material 11). Evidence from the systematic review informed the recommendations (Supplementary Material 9). Four rounds of anonymous consensus Delphi voting occurred, with modifications to statements made based on comments received from the survey as well as journal reviewers. There was 74.3% to 95.7% participation in each round (Supplementary Material 12).

Good practices and recommendations for each PNS category are provided below, and a decision tree is provided in Supplementary Material 13. The rationales for each good practice as well as the rationale, balance of desirable and undesirable effects, quality of evidence, values and preferences, and feasibility for each recommendation are provided in Supplementary Material 14. Additionally, Table 1 provides a list of questions for the clinician to ask when the diagnosis of SjD is being considered.

Mononeuropathy. Various mononeuropathies are seen in individuals with SjD, with a prevalence of 12% to 50%.[11] These include trigeminal neuralgia, trigeminal neuropathy, facial neuropathy, and upper-extremity neuropathies. Trigeminal neuralgia, characterized by severe facial pain, and trigeminal neuropathy, presenting with numbness or tingling, are common manifestations. Facial neuropathy results in weakness of the muscles of the upper and lower face. Upper-extremity neuropathies include median neuropathy at the wrist (carpal tunnel syndrome) and ulnar neuropathy.

When considering SjD as the etiology of a mononeuropathy, it is important to exclude alternative causes, such as demyelinating lesions, neoplastic involvement, or infectious processes. Prompt evaluation and treatment can mitigate symptoms and may prevent long-term complications. Management includes symptomatic medications for pain relief and treatments aimed at the underlying pathology and preserving nerve function. The specific treatment will be dictated by the type and severity of the mononeuropathy to optimize outcomes and enhance QOL. Good practices and recommendations for the evaluation and management of specific mononeuropathies in patients with SjD are listed in Table 2, Supplementary Material 13A, and Supplementary Material 14.

Polyneuropathy. Polyneuropathies encompass a spectrum of neurologic disorders affecting peripheral nerves with a published prevalence of 10% to 20% in patients with SjD.[11,35–38] These polyneuropathies include large fiber neuropathies, small fiber neuropathies, demyelinating polyradiculoneuropathies, ganglionopathies, and vasculitic neuropathies. The first step in

Table 1. Screening questions for potential Sjögren's disease in patients with peripheral nervous system symptoms*

Systemic symptoms	Oral symptoms	Ocular symptoms
• Do you experience extreme fatigue? • Do your joints or muscles ache when you are not sick (arthralgias, myalgias)? • Do you have gland swelling in your face or along the jawline (swollen parotid and/or submandibular glands)? • Do you often experience heartburn, a sour or bitter taste in your mouth, especially when lying down or bending over? • Do you experience irritable bowel, frequent diarrhea, constipation, bloating, pain, or nausea (gastrointestinal dysmotility)? • Do you notice your fingers turning pale or blue in the cold (Raynaud disease)? • Do you have issues with memory, difficulty concentrating on tasks, or experiencing mental fatigue? • Do you have shortness of breath, a persistent cough, chest discomfort, or recurrent respiratory infections? • Do you have dryness of the vagina and/or is intercourse painful? (women) • Do you have chronic prostatitis? (men) • Do you have dry, itchy, or flaking skin?	• Does your mouth feel dry? • Do you need liquids to swallow dry foods? • Do you frequently sip/drink water? • Do you have a burning sensation in your mouth (burning mouth syndrome)? • Do you have painful sores or red patches at the corners of the mouth (angular cheilitis)? • Do you get frequent dental cavities and/or cavities at the gumline? • Do your teeth tend to chip, crack, and/or erode on the surfaces? • Do you experience gum inflammation or receding gums (gingivitis?) • Do foods high in acid or heat (spicy) feel irritating or painful?	• Do your eyes frequently feel dry, irritated, itchy, or painful? • Do you have a sensation that there might be a foreign body in your eye? • Are your eyes light-sensitive? • Do you frequently use eye drops for irritation or dryness? • Is your vision frequently blurry, or do you have unexplained vision changes? • Are you prone to getting eye infections? • Do your eyes feel "gummy" and eyelids stick together, especially upon waking?

* Symptoms should prompt further serologic evaluation and/or rheumatology consultation. An estimated 30% to 40% of patients with Sjögren's disease are negative for the anti-SSA autoantibody, so a patient can still have Sjögren's disease without a positive test for this antibody.
Source: Reprinted with permission from the Sjögren's Foundation.

Table 2. Good practices and recommendations for mononeuropathies in patients with Sjögren's disease

Screening good practices for mononeuropathies			
Good practice 1	Sjögren's patients with persistent facial pain or numbness should be assessed for dysfunction of cranial nerve V which can manifest as either trigeminal neuralgia or trigeminal neuropathy. • Physical examination: assess for numbness or pain of the face in the distribution of one or more branches of the trigeminal nerve, unilateral or bilateral, by testing for loss of light touch and either pin prick or cold sensation. • If the distribution of symptoms or findings on physical examination is consistent with trigeminal neuralgia or trigeminal neuropathy, a contrast-enhanced brain MRI with attention to brainstem/skull base and exiting cranial nerves should be performed to exclude structural or other etiologies of trigeminal dysfunction. • Consider electrophysiological testing, including blink reflex.		
Good practice 2	Sjögren's patients with unilateral facial weakness should be assessed for facial (cranial nerve VII) neuropathy. • Symptoms and physical examination findings: weakness of the upper and ipsilateral lower face. Upper facial weakness manifests as an inability to raise the eyebrows, inability to wrinkle the forehead, weakness of eye closure, or a widened palpebral fissure. Involvement of the lower facial muscles manifests as lip closure weakness, and facial droop. Some patients experience a loss of taste on the anterior two-thirds of the tongue and/or hyperacusis (hearing sensitivity) on the affected side. • Physical examination findings that may suggest an alternative etiology include coexisting cranial mononeuropathies, ear canal vesicles, neck stiffness, headaches, and fevers. These findings should prompt an evaluation for Lyme disease, herpes zoster, sarcoidosis, or variants of Guillain-Barré Syndrome (GBS), which may include lumbar puncture. • Perform a contrast-enhanced brain MRI with attention to the brainstem/skull base and exiting cranial nerves to exclude structural or other etiologies of facial neuropathy. • Consider electrophysiological testing with nerve conduction study, including blink reflex, and electromyography (EMG). • Facial neuropathy rarely presents bilaterally. If the manifestations are bilateral or recurrent, a thorough evaluation for more generalized systemic disease should be pursued.		
Good practice 3	Sjögren's patients who present with cranial mononeuropathies of other cranial nerves should be evaluated for alternative etiologies. Work-up should include referral to the appropriate specialist, such as a neurologist, otolaryngologist, ophthalmologist, speech pathologist, or gastroenterologist for evaluation.		
Good practice 4	Sjögren's patients with numbness, pain, or weakness of the hand should be evaluated for median or ulnar neuropathy. • Physical examination: Median neuropathy presents with sensory loss of the lateral (radial) three and ½ digits, atrophy of the thenar eminence, and weakness of thumb abduction. Ulnar neuropathy presents with sensory loss of the medial one and ½ digits, atrophy of intrinsic hand muscles, a "claw-hand" appearance, and weakness of the fingers. • If a median or ulnar neuropathy is suspected, consider electrodiagnostic studies and/or nerve ultrasound. • Referral to a hand surgeon or other specialist who evaluates and treats carpal tunnel syndrome or ulnar neuropathy should be considered. • If carpal tunnel surgical release is performed, a tenosynovial biopsy may be obtained to exclude amyloidosis.		
Therapy recommendations for mononeuropathies		**Evidence rating**	**Strength of recommendation**
Recommendation 1	For patients with Sjögren's-related trigeminal neuropathy, we recommend a short course of oral glucocorticoids for suspected acute inflammatory etiology.	Very Low	Conditional
Recommendation 2	For patients with Sjögren's-related trigeminal neuralgia (neuropathic pain), we recommend: • First-line treatment with carbamazepine or oxcarbazepine. • Second-line treatments, either as alternatives or adjuncts, may include gabapentin, pregabalin, baclofen, lamotrigine, lacosamide, or phenytoin.	Very Low	Conditional
Recommendation 3	For patients with Sjögren's who develop an acute facial neuropathy, we recommend: • A short course of glucocorticoid treatment for at least 10 days. • Consider the addition of valacyclovir.	Very Low	Conditional

patients with suspected polyneuropathy is to characterize the particular type, as further evaluation varies based on this classification (Supplementary Material 10).[33] Neurology expertise can assist in the accurate classification of polyneuropathies. The type and severity of polyneuropathy will determine treatment strategies. Again, early recognition and management can improve outcomes and QOL. Clinicians should be aware that polyneuropathies can be the initial manifestation of SjD, and identifying the etiology or the pathophysiologic cause of the neuropathy may be challenging. Good practices and recommendations for the evaluation and management of polyneuropathies in patients with SjD are listed in Table 3, Supplementary Material 13B, and Supplementary Material 14.

Autonomic neuropathy. ANS impairment can occur in up to 50% of patients with SjD[2,11] with the potential to affect various autonomic systems and ranging from mild to severe autonomic failure. Symptoms of ANS impairment in SjD typically result from autonomic neuropathy or ganglionopathy and may include orthostatic intolerance, vasomotor dysfunction, secretomotor

Table 3. Good practices and recommendations for polyneuropathies in patients with Sjögren's disease

Screening good practices for polyneuropathies			
Good practice 5	Recognize that neuropathies can have many causes, including Sjögren's disease. Potential alternative etiologies should be identified, such as diabetes, hypothyroidism, B-12 deficiency, monoclonal gammopathies, infectious etiologies, toxins, and medications. Labs related to these etiologies should be ordered.		
Good practice 6	Recognize that Sjögren's patients can present with a wide range of symptoms, including diverse presentations of peripheral neuropathies. For abnormal sensations suspected of being neuropathic, ask the following questions to characterize the neuropathy: 1. Do you have numbness, tingling, pins and needles or buzzing sensation, burning pain, other abnormal sensations, and/or weakness? 2. Are the symptoms symmetric or asymmetric? 3. Where is it worse—hands, feet, or all over? 4. Where did you notice it first? (distal onset?) 5. How long have symptoms been present? 6. Do you have any gait disturbances/abnormalities? Additional questions that may be useful in screening are: 7. Was the onset of neuropathy gradual or abrupt? 8. How have symptoms changed? (worse? persistent? intermittent? more proximal?) 9. Do symptoms awaken you from sleep? 10. Under what circumstances did symptoms begin (i.e. Did they start before or after new medication or infection?) 11. Have there been any exposures to medications, supplements, complementary and alternative medicine, or occupational exposures that could be neurotoxic?		
Good practice 7	Sjögren's patients who have symptoms suggesting a peripheral neuropathy should have a comprehensive neurological examination.		
Good practice 8	For Sjögren's patients who have history and physical examination findings suggesting a peripheral neuropathy, consider referral to a neurologist.		
Good practice 9	For Sjögren's patients with persistent neuropathic symptoms, electrodiagnostic studies (nerve conduction studies [NCS] and electromyography [EMG]), should be performed by an experienced electromyographer. The study is best timed at 1-4 weeks from the onset of symptoms, depending on the type, progression, and severity of the neuropathy.		
Good practice 10	For Sjögren's patients with suspected small fiber neuropathy, consider evaluation of epidermal nerve fiber density with punch skin biopsy to support this diagnosis.		
Good practice 11	For Sjögren's patients with suspected peripheral neuropathy and electrodiagnostic studies (NCS/EMG) warranting additional evaluation or when there is no response to treatment, the following should be considered: • Fat pad and/or minor salivary gland biopsy if amyloid is suspected. • Nerve and muscle biopsy if vasculitis, amyloid, or other infiltrative processes are suspected. • Lumbar puncture should be reserved for assessing suspected cases of inflammatory demyelinating polyradiculoneuropathy (including acute inflammatory demyelinating polyradiculoneuropathy [AIDP] and chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]), ganglionopathy, neoplastic diseases, or infection.		
Good practice 12	For Sjögren's patients with gait disturbance due to weakness, sensory loss, ataxia, or imbalance, consider assessments for gait and balance training and for assistive devices by physical therapy, physical medicine rehabilitation (PMR), and/or other related healthcare professionals.		
Good practice 13	For Sjögren's patients with polyneuropathy with neuropathic pain who have not benefited from initial treatments for neuropathic pain, referral to a neurologist and/or a pain specialist may be warranted.		
Good practice 14	For Sjögren's patients with confirmed polyneuropathy, treatment choice depends on the type and location of neuropathy, disease severity, and degree of systemic involvement (e.g., vasculitis).		
Good practice 15	Vasculitic neuropathy should be considered in Sjögren's patients with polyneuropathy and the following clinical scenarios: Acute, painful, rapid onset, or stepwise progression of neurological deficit, clinical and electromyographic evidence of multiple mononeuropathies, evidence of single-organ or systemic vasculitis, or immunologically active disease as defined by cryoglobulinemia, hypocomplementemia, monoclonal gammopathy, positive rheumatoid factor (RF), and elevated inflammatory markers.		
Good practice 16	We recognize the technical difficulties in correctly identifying serum cryoglobulins. Therefore, other surrogate markers associated with the presence of cryoglobulinemia (i.e., positive RF and C4 hypocomplementemia), in the appropriate clinical context, may also be suggestive in those negative for serum cryoglobulins.		
Good practice 17	For Sjögren's patients with a suspicion of vasculitic neuropathy, EMG and NCS should be performed. The timing of this study is based on the severity and tempo of presentation, typically 1-4 weeks after the onset of symptoms.		
Good practice 18	For Sjögren's patients with clinical and electrodiagnostic findings suggestive of a vasculitic etiology, a nerve and muscle biopsy is warranted.		
Good practice 19	For Sjögren's patients with vasculitic neuropathy with cryoglobulinemia, repeat testing for serum cryoglobulin as a biomarker for therapeutic response, along with complement C4 and RF as markers of biological response.		
Therapy recommendations for polyneuropathies		**Evidence rating**	**Strength of recommendation**
Recommendation 4	For Sjögren's patients with neuropathic pain in the setting of a peripheral neuropathy, we recommend first-line symptomatic treatment that includes gabapentin, pregabalin, or serotonin-	Very Low	Strong[a]

(Continued)

Table 3. (*Cont'd*)

	norepinephrine re-uptake inhibitors (SNRIs), depending on individual patient tolerance, comorbidities, and side effect risk.		
Recommendation 5	For Sjögren's patients with neuropathic pain in the setting of a peripheral neuropathy who are not helped by first-line treatments, we recommend sodium channel blocking agents (carbamazepine, oxcarbazepine, lamotrigine) or tricyclic antidepressants (nortriptyline and desipramine may be better tolerated). For patients who are refractory to, or intolerant of, first- and second-line neuropathic pain medications, referral to a neurologist and/or pain management specialist may be warranted.	Very Low	Conditional
Recommendation 6	For patients with Sjögren's-related polyneuropathy with a progressive or aggressive presentation, we recommend an empiric glucocorticoid treatment trial. The specific dose and length of treatment with glucocorticoids will depend on the individual circumstances. Factors such as the response to treatment, and the potential side effects of the medication should be considered when determining the appropriate duration of treatment.	Very Low	Conditional
Recommendation 7	For Sjögren's-related immune-mediated non-vasculitic large fiber polyneuropathy, we recommend considering intravenous immunoglobulin (IVIG).	Very Low	Conditional
Recommendation 8	For Sjögren's-related immune-mediated small fiber neuropathies that do not respond to symptomatic treatment and have recent onset, severe, or progressive disease, we recommend considering treatment with IVIG for a duration of at least 3 months. Treatment with subcutaneous immunoglobulin (SCIG) is an alternative.	Very Low	Conditional
Recommendation 9	For Sjögren's patients with acquired chronic demyelinating polyradiculoneuropathy, we recommend offering standard treatments for CIDP.	Very Low	Strong[b]
Recommendation 10	For Sjögren's patients with sensory ganglionopathy who manifest significant symptoms, we recommend instituting aggressive and immediate treatment with moderate to high dose glucocorticoids and immunomodulatory/immunosuppressive therapy.	Very Low	Strong[c]
Recommendation 11	For Sjögren's patients with high suspicion of vasculitic neuropathy, we recommend immediate initiation of high-dose systemic glucocorticoids with rituximab as the first line of therapy.	Very Low	Strong[d]
Recommendation 12	For Sjögren's patients with vasculitic neuropathy unresponsive to first-line therapy with glucocorticoids and rituximab, we recommend glucocorticoids and cyclophosphamide as a second line of therapy.	Very Low	Conditional
Recommendation 13	For Sjögren's patients with vasculitic neuropathy with cryoglobulinemia, we recommend maintenance with immunomodulatory therapy.	Very Low	Conditional
Recommendation 14	For Sjögren's patients with vasculitic neuropathy and persistent neuropathic pain, we recommend symptomatic management as discussed in Therapy Recommendations 4 and 5: Polyneuropathies.	Very Low	Strong[a]
Recommendation 15	We do not recommend IVIG as a first line of therapy for Sjögren's patients with vasculitic neuropathy.	Very Low	Conditional

[a] This recommendation is rated strong based on a balance of benefits vs harms because most patients would choose the intervention to reduce pain and improve quality of life. Additionally, pain management is the standard of care.
[b] This recommendation is rated strong because most patients and clinicians would use standard treatments for CIDP based on strong literature for CIDP in general, because the benefits likely outweigh the risks.
[c] This recommendation is rated strong because the profound ataxia of ganglionopathy can be severe, rapidly progressing, and disabling if not treated. Thus, the benefits outweigh the risks of not treating this condition.
[d] This recommendation is rated strong because, given the risk of irreversible axonal loss and chronic disability, most physicians and patients would opt for initial immune therapy. Because rituximab has a generally lower risk of adverse events than cyclophosphamide, it is recommended as a first-line treatment for vasculitic neuropathy.

dysfunction, gastrointestinal disturbances, bladder dysfunction, and pupillomotor dysfunction. Recognizing autonomic signs and symptoms in SjD can be challenging because of their nonspecific nature, overlapping symptoms with other aspects of the disease, or patients' adaptation to longstanding symptoms. Referral to specialists such as neurologists, gastroenterologists, cardiologists, urologists, or ANS testing centers may be necessary for comprehensive evaluation and management. Differential diagnostic considerations for autonomic neuropathy in SjD include vitamin deficiencies, autoimmune dysautonomia, and other systemic diseases. A skin biopsy for sweat gland nerve fiber density may aid in diagnosing autonomic small fiber neuropathy. Management strategies for autonomic dysfunction include lifestyle modifications, pharmacotherapy, and, in severe cases, immunomodulatory therapy. Multidisciplinary collaboration is crucial for optimal management and improved QOL for patients with SjD with autonomic neuropathies. Good practices and recommendations for evaluation and management of ANS neuropathies in SjD are listed in Table 4, Supplementary Material 13C, and Supplementary Material 14.

DISCUSSION

The PNS manifestations of SjD include mononeuropathies, polyneuropathies, and ANS neuropathies. The Sjögren's Foundation convened a panel of experts (the PNS TRG) to develop this guideline based on the best available evidence to improve the evaluation and management of these manifestations. Thirty-one good practice evaluation statements were made. Of the 20 recommendations, 14 are rated as conditional and 6 are rated as strong. Clinicians should approach each recommendation with a balanced view, in discussion with the patient, weighing the potential benefits against possible harm as part of shared decision-making.

This guideline is generally consistent with the PNS domain of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) addressed in the 2020 EULAR recommendations for the management of SjD, similarly drawing on glucocorticoids, immunomodulatory agents, and biologic therapies, while providing distinct additional guidance.[39] Distinctions include the following: (1) classification of neuropathies aligned between rheumatology and neurology (Supplementary Material 10)[33]; (2) localization-specific guidance and addresses autonomic neuropathy, an important but underrecognized dysfunction in SjD; (3) prioritization of specific immunosuppressive agents based on an integration of available evidence and expert neurorheumatology opinion; (4) guidance on ANS dysfunction, small fiber neuropathy, mononeuropathies, and neuropathic pain; and (5) guidance on the use of B cell–targeted therapy, rituximab, for patients with severe or refractory disease, including vasculitic neuropathy and severe, progressive, and treatment-resistant immune-mediated autonomic neuropathy. In alignment with this, two late-phase clinical trials have recently demonstrated positive results for B cell–targeted therapies in SjD, with ianalumab (anti–B cell activating factor receptor antibody) showing efficacy in Phase 3 and telitacicept (a B lymphocyte stimulator/a proliferation-inducing ligand dual inhibitor approved for systemic lupus erythematosus in China) also meeting its primary endpoints.[40]

We used consensus expert opinion, informed by commonly employed evaluation tests, to develop good practices for evaluating patients with SjD presenting with PNS manifestations. According to the GRADE working group, good practice statements address topics that panels consider essential but are not suitable for formal evidence-quality ratings because they are supported by a substantial body of indirect evidence, the formal appraisal of which would represent an inefficient use of the panel's resources.[41,42] These good practices emphasize the need for a comprehensive diagnostic evaluation to characterize PNS disorders and exclude other potential etiologies. Early detection and the correct diagnosis are essential to provide the best chance to halt progression and improve QOL.[9]

The treatment recommendations are partially informed by six case series studies and three observational studies, underscoring the scarcity of high-level evidence in this area. Because of the lack of evidence, most of the treatment recommendations are based on expert opinion, informed by balancing benefits, harms, and patient values. As stated in two articles by Djulbegovic and Guyatt (2017 and 2019),[43,44] all clinical guidelines should be evidence-based, even when the evidence is of very low quality—as in the case of this guideline. They emphasize that evidence-based medicine involves using the best available evidence—whether from randomized trials, observational studies, case series, or the experience of individual clinicians—to guide clinical decision-making and practice guidelines. Distinguishing between "evidence-based" and "consensus-based" guidelines is misleading because interpreting any evidence requires consensus among experts. Therefore, consensus is integral to interpreting and applying evidence in clinical practice, and all guidelines inherently require both evidence evaluation and consensus regardless of the available evidence. Our guideline aligns with these principles, systematically reviewing and assessing evidence, and balancing benefits, harms, and patient values, to provide practical recommendations for managing SjD.

The TRG faced situations in which the available evidence was of low or very low quality. Despite this, strong recommendations reflect the expert consensus on what is most beneficial for patients (even with limited evidence), while noting any uncertainties about the evidence quality, after careful consideration of potential benefits and harms, patient values, and the potential risks of inaction. Patients affected by PNS and ANS manifestations frequently report pain and dysfunction that substantially impair their QOL. Available treatment options are consistent with what patients prioritize: relief of suffering, preservation of function, and prevention of worsening disease. Thus, for many of the interventions considered, even low-certainty evidence suggested

Table 4. Good practices and recommendations for autonomic nervous system neuropathies in patients with Sjögren's disease

Screening good practices for autonomic nervous system neuropathies	
Good practice 20	The following screening process is recommended for the initial assessment of potential autonomic nervous system (ANS) involvement in Sjögren's: For primary screening, ask the following questions: 1. Do you experience postural lightheadedness, syncope (fainting), near-syncope, or a racing heart when upright? 2. Do you experience problems with sweating too little, or too much? 3. Do you have chronic GI symptoms or problems, such as: ◦ Difficulty swallowing ◦ Nausea ◦ Abdominal pain ◦ Feel like you fill up more quickly than you ought to when eating a meal (early satiety) ◦ Diarrhea or constipation. If yes, does diarrhea occur at night? ◦ Significant abdominal bloating 4. Do you have genitourinary problems, such as: ◦ Sexual dysfunction ◦ Difficulty emptying your bladder completely or incontinence ◦ Frequent urination, particularly frequent nocturnal enuresis ◦ Urogenital problems and/or pelvic pain
Good practice 21	For Sjögren's patients with suspected ANS involvement, conduct further assessments with the Composite Autonomic Symptom Scale (COMPASS-31) questionnaire and orthostatic blood pressure and pulse measurements (postural vital signs).
Good practice 22	For Sjögren's patients with suspected ANS involvement and abnormal COMPASS-31 or abnormal postural vital sign results, refer to a neurologist, neurogastroenterologist, cardiologist, urologist, or ANS testing center for further evaluation.
Good practice 23	For Sjögren's patients with symptoms of orthostatic intolerance, including postural lightheadedness, syncope, and near-syncope, conduct formal autonomic testing at centers or facilities where this testing is available. Autonomic testing should include tilt table, the Quantitative Sudomotor Axon Reflex Test (QSART), measures of heart rate variability, and assessments of blood pressure changes, including the Valsalva maneuver, to characterize the nature of the ANS involvement.
Good practice 24	If formal autonomic testing is performed, a Composite Autonomic Severity Scale (CASS) score could be calculated to quantify the severity of autonomic nervous system impairment in Sjögren's.
Good practice 25	For Sjögren's patients with significant autonomic neuropathy, the following should be considered to exclude other causes: B-12 and B-6 measurement, hemoglobin A1C, serum immunofixation, serum-free light chains, and an autoimmune dysautonomia panel (screen of antibodies associated with autonomic neuropathy other than Sjögren's, such as acetylcholine receptor ganglionic antibody, ANNA-1, CASPR-2IgG CBA, CRMP-5, DPPX, LGI1-IgG CBA, PCA-2, AP3B2 IFA). Testing for supine and standing catecholamines (norepinephrine) may be considered.
Good practice 26	For Sjögren's patients where there is concern for autonomic neuropathy or symptoms of abnormal sweating, a skin biopsy could be considered to assess sweat gland nerve fiber density.
Good practice 27	Provided the initial study was abnormal, quantitative autonomic testing (such as tilt table, the QSART, measures of heart rate variability, and assessments of blood pressure changes, including the Valsalva maneuver) could be repeated in 6-12 months after institution of immunomodulatory therapy to assess peripheral nervous system remodeling in Sjögren's patients.
Good practice 28	Autonomic failure in conjunction with sensory neuropathy and sensory ataxia may indicate an autonomic ganglionopathy. Providers should recognize that this may require an urgent referral to a neurologist and aggressive treatment.
Good practice 29	For Sjögren's patients with complex gastrointestinal symptoms, refer to a gastroenterologist or neurogastroenterologist for evaluation and treatment. Motility testing to look for esophageal, gastric, or intestinal dysmotility should be considered.
Good practice 30	For Sjögren's patients with genitourinary symptoms, refer to a urologist, urogynecologist, or neurologist for evaluation and treatment.
Good practice 31	Symptoms related to problematic sweating may result from autonomic neuropathy in Sjögren's. Nocturnal sweating, hyperhidrosis, hypohidrosis, and heat intolerance may be reported by patients. A careful history and examination, supplemented by autonomic tests of sweating function (such as QSART) can be helpful in identifying severity and pattern of impairment.

ANNA-1 = anti-neuronal nuclear antibody, type 1
CASPR2-IgG CBA, S = contacting-associated response protein 2
CRMP-5 IgG Western Blot, S = collapsing response-mediator protein – 5
DPPX = dipeptidyl-peptidase-like protein-6 (regulatory subunit neuronal Kv4.2 potassium channel)
LGI1-IgG CBA, S = leucine-rich glioma inactivated 1 protein antibody
PCAB-2 = Purkinje cell cytoplasmic antibody, type 2
AP3B2 IFA Titer, S = adaptor protein 3 beta 2 antibody by IFA (immunofluorescence)

(Continued)

Table 4. (*Cont'd*)

Therapy recommendations for autonomic nervous system neuropathies		Evidence rating	Strength of recommendation
Recommendation 16	For Sjögren's patients with autonomic neuropathy, we recommend patient education about autonomic dysfunction and non-pharmacologic tools such as lifestyle measures and therapies that target symptoms caused by their disease.	Low	Strong[a]
Recommendation 17	For Sjögren's patients with orthostatic tachycardia, we recommend providing patient education to facilitate lifestyle management and initiating non-pharmacologic approaches such as increased fluid intake, abdominal and lower limb compression garments, increased salt intake, and gentle graded exercise in a seated or supine position. Assess if current medications predisposing to hypotension or tachycardia can be tapered/discontinued (stimulants, diuretics, vasodilators). For patients with severe symptoms of orthostatic intolerance or those who do not respond to lifestyle measures, consider the following: • For heart rate control, use non-selective beta blockers or ivabradine, which is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker, especially for those patients with prominent heart rate variability. • For individuals with orthostatic tachycardia with low blood pressure thought to potentially contribute to tachycardia, consider vasopressors (midodrine, droxidopa) or fluid expansion (fludrocortisone, IV saline). • Pyridostigmine may be useful in stabilizing heart rate and blood pressure in individuals with orthostatic tachycardia.	Low	Conditional
Recommendation 18	For Sjögren's patients with orthostatic hypotension, we recommend a multidisciplinary team (could include a rheumatologist, cardiologist, and neurologist) for assessment (tilt table, QSART, etc.) and management, depending on services available regionally.	Very Low	Conditional
Recommendation 19	For Sjögren's-related immune-mediated autonomic dysfunction that is severe, progressive, and not responsive to lifestyle and pharmacologic measures, we recommend considering intravenous immunoglobulin (IVIG), with frequency and dosage that manages symptoms.	Very Low	Conditional
Recommendation 20	For Sjögren's-related immune-mediated autonomic dysfunction that is severe and not responsive to IVIG, we recommend rituximab.	Very Low	Conditional

[a] This recommendation is rated strong because patients will likely prioritize non-pharmacologic approaches and educational measures that offer control and understanding of their condition without the risks associated with medication.

meaningful improvements in outcomes such as pain reduction, functional ability, and activities of daily living. Importantly, withholding treatment would risk deterioration in patient well-being. In reaching these conclusions, the TRG benefited from a strong suite of rheumatologists and neurologists who conduct research and treat patients with SjD. Taken together, these factors justify the panel's decision to issue strong recommendations despite very low certainty of evidence. This approach reflects the principle that guideline development must consider not only the level of evidence but also the consensus of experts, patient needs and values, and the ethical responsibility to minimize harm. The TRG is confident that the resulting recommendations are consistent with current therapeutic practices and concordant with patient values and preferences, reflecting prevailing clinical consensus.

We used the term "consider" in conjunction with certain recommendations to acknowledge the variability in patient-specific factors, preferences, and clinical scenarios that may influence the appropriateness of a given intervention in the shared decision-making process. Importantly, the term "consider" should not be construed by insurance providers as a justification for denying coverage but rather as recognition of the need to tailor interventions to the unique circumstances of each individual patient.

The CEP review reached a high level of agreement, with 18 of 20 recommendations and 30 of 31 good practices achieving 90% or higher consensus. Notably, the lowest level of agreement was 79% in the vote for the "strong" rating for the strength of recommendation 7. This recommendation addresses intravenous Ig (IVIG) for patients with nonvasculitic large fiber polyneuropathy. Comments pertaining to this vote included the cost of IVIG, side effects, and strength of the evidence.

In developing this guideline, the TRG acknowledges that management of these manifestations necessitates a multidisciplinary approach to care. To the extent possible, neurologists should play a role in teams managing PNS manifestations in collaboration with primary care physicians and rheumatologists.

Other specialists, such as those in ear, nose, and throat; ophthalmology; speech pathology; cardiology; gastroenterology; neurogastroenterology; physical therapy; urology; and neurology may also be part of the treatment team. Additionally, it is important to note that patients can have more than one co-occurring PNS manifestation. Thus, providers may need to implement more than one treatment modality concurrently and may need to coordinate among multiple specialties. Finally, SjD should be considered in patients presenting with multiple PNS and central nervous system presentations, especially when a singular pattern of localization is lacking.

An important consideration in the management of SjD-related immune-mediated neuropathies is the differing perspectives between neurologists and rheumatologists regarding the use of IVIG therapy. Neurologists often encounter a high volume of idiopathic neuropathies and may be more skeptical about considering IVIG in cases that are not clearly immune-mediated. In contrast, rheumatologists frequently manage patients whose existing neuropathies were not recognized as immune-mediated, delaying appropriate diagnosis and treatment and negatively impacting outcomes. This divergence highlights the need for neurologists to collaborate across disciplines and consider immune-mediated etiologies, such as SjD, in their differential diagnoses when assessing patients with neuropathy. Likewise, rheumatologists should note the potential of immune-mediated neuropathy and SjD.

Acknowledging the significant evidence gap in our understanding of effective therapies for PNS manifestations in SjD is important. A major limitation is the absence of study designs with comparison groups, which increases the risk of bias and limits generalizability. However, for understudied diseases such as SjD, case series can provide crucial initial insights, guiding future research. Another weakness is the lack of current literature supporting a direct link with specific conditions, such as hearing loss, vertigo, and dysfunction of cranial nerves (CNs) IX and X. Thus, we did not make a recommendation regarding these potential manifestations.

Current clinical trials are exploring biologic and small-molecule therapies for systemic features of SjD, including PNS manifestations.[45–50] These trials may result in multiple potential therapies for more effective management. With this in mind, this guideline will be reviewed and updated in 3 to 5 years or sooner if substantial new evidence becomes available that may impact the recommendations. Corneal neuropathy will be included in the forthcoming update to the Sjögren's Foundation ocular clinical practice guidelines.

There is a dire need to improve the evidence base for patients who have SjD with PNS manifestations. This would include observational studies with comparison groups and, ideally, randomized controlled trials. Because of the difficulties in performing such studies, big data analyses of electronic health care records may provide additional evidence to support causal inferences. Additionally, studies are needed to address the following gaps in clinical knowledge:

Prevalence

1. What is the incidence and prevalence of PNS and ANS manifestations in SjD?
2. What is the prevalence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in patients with SjD? Does SjD play a role in the pathophysiology of CIDP?
3. Does COVID-19 exacerbate neurologic morbidities in patients with SjD?
4. What is the true incidence and pathophysiology of other cranial neuropathies, such as CN VIII, CN IX, and CN X, which have been reported to occur in SjD?

Prevention

5. What are the risk factors for PNS and ANS manifestations in SjD?
6. What interventions can prevent PNS and ANS manifestations in SjD?
7. What are the genetics, epigenetics, and pathophysiology of PNS and ANS manifestations in SjD? How can understanding these factors lead to therapies to prevent and treat these disorders?

Diagnosis and Evaluation

8. Is the scale used for interpreting skin punch biopsies when diagnosing small fiber neuropathies in diabetes applicable to SjD, or is a new or modified scale needed?
9. How can we develop improved scales to measure dynamic disabilities associated with ANS neuropathies that effectively capture the temporal variability of symptoms?
10. How can we standardize diagnostically accurate and minimally invasive testing methods, including imaging, biomarkers, and electrodiagnostic techniques, for ANS and PNS manifestations in SjD?
11. What is the sensitivity and specificity of lip biopsy in seronegative sicca-free patients with PNS and/or ANS dysfunction and personal and/or family history of autoimmune disease?
12. How can we develop diagnostic tools or scales to differentiate between progressive PNS/ANS manifestations and irreversible nerve damage?
13. What are the positive and negative predictive values for rheumatoid factor, complement component 4, and complement component 3 for the diagnosis of vasculitis?

Management of PNS and ANS Manifestations

14. What are the optimal first-line, second-line, and maintenance strategies (ie, IVIG or other immunotherapies and pain management treatments) for PNS and ANS manifestations with varying degrees

of symptom severity in SjD, and should treatment decisions be affected by autoantibody (anti-SSA, anti-SSB, rheumatoid factor, and antinuclear antibodies) positivity?
15. What are the effects of pharmacologic interventions versus behavioral interventions in managing neuropathic SjD symptoms?
16. What are the differences in the comparative effectiveness of treatment options for ANS and PNS manifestations between SjD and non-SjD populations?
17. What is the possible role of microbial imprint/dysbiosis in patients with SjD with PNS and ANS manifestations? Does correcting the dysbiosis by lifestyle interventions prevent or ameliorate PNS or ANS symptoms?
18. What are the mechanisms of neuronal injury and disease course of PNS and ANS manifestations in SjD as shown by autopsy studies?

Outcomes

19. How can we establish standardized and defined patient-centered outcomes for measuring PNS and ANS manifestations in SjD, considering their preferences in managing the benefits versus harms of treatment modalities?
20. What strategies can be developed to monitor response to therapy in SjD, including the potential utility of serial electrodiagnostic testing and patient-centered evaluations?
21. How can the ESSDAI and other outcome measures be enhanced to increase sensitivity to identify the spectrum of neurologic and other systemic manifestations?
22. How can standardized outcome measures be used to evaluate treatment effectiveness for PNS and ANS manifestations in SjD?

Guideline Implementation

23. How can implementation science be used to understand the barriers and facilitators in implementing guidelines for SjD in clinical practice, and what strategies can be developed and evaluated to enhance this implementation?
24. What is the impact of educating the health care community about the diverse presentations of PNS and ANS manifestations in SjD?
25. How does engaging interdisciplinary teams affect the diagnosis and management of PNS and ANS manifestations in SjD?

This guideline offers an evidence-based approach to evaluate and manage PNS manifestations of SjD. The recommendations emphasize the need for multidisciplinary care, including primary care physicians, rheumatologists, neurologists, and other specialists in some cases, and patient-centered decision-making. Given the limited evidence on PNS manifestations in SjD, the guideline also highlights research priorities to propel the field forward and improve our understanding and management of this challenging aspect of SjD.

ACKNOWLEDGMENTS

The authors extend special thanks for review and input by cardiologist John K. Lee, MD, University of Missouri Kansas City School of Medicine, and Saint Luke's Mid America Heart Institute, Kansas City, MO; for execution of literature searches by Rebecca Landau, MLS, Librarian and formerly, Health Sciences Library, Penn Presbyterian Medical Center; for contributions by former TRG participants Elaine L. Alexander, MD, PhD, Rheumatology and Neurology, deceased; Donald Bloch, MD, Rheumatology, Harvard Medical School and Massachusetts General Hospital, Boston, MA; Richard Brasington, MD, Rheumatology, Washington University, St. Louis, MO, deceased; Dale J. Lange, MD, Neurology, Hospital for Special Surgery and Weill Medical College of Cornell University, New York, New York; and Jeffrey W. Wilson, MD, Rheumatology, formerly private practice at Central Virginia Rheumatology, Lynchburg, VA. The authors gratefully acknowledge Kristie Cox for her contributions to copyediting the manuscript and developing the graphical abstract. This project was supported by the Sjögren's Foundation. We used OpenAI's ChatGPT-1 for copy editing purposes. The AI tool was employed to refine the language, improve clarity, and enhance the overall readability of the manuscript. All final edits and content decisions were made by the authors to ensure accuracy and coherence.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Ms. Hammitt confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Delalande S, de Seze J, Fauchais AL, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004;83(5):280–291.
2. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain 2005; 128(Pt 11):2518–2534.
3. Massara A, Bonazza S, Castellino G, et al. Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable--clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 2010;49(8): 1540–1549.
4. Moutsopoulos HM, Sarmas JH, Talal N. Is central nervous system involvement a systemic manifestation of primary Sjögren's syndrome? Rheum Dis Clin North Am 1993;19(4):909–912.
5. Margaretten M. Neurologic manifestations of primary Sjögren syndrome. Rheum Dis Clin North Am 2017;43(4):519–529.

6. Liampas A, Parperis K, Erotocritou MF, et al. Primary Sjögren syndrome-related peripheral neuropathy: a systematic review and meta-analysis. Eur J Neurol 2023;30(1):255–265.
7. Gwathmey KG, Satkowiak K. Peripheral nervous system manifestations of rheumatological diseases. J Neurol Sci 2021;424:117421.
8. De Souza JM, Trevisan TJ, Sepresse SR, et al. Peripheral neuropathy in systemic autoimmune rheumatic diseases-diagnosis and treatment. Pharmaceuticals (Basel) 2023;16(4):587.
9. S B, Naidu G, Sharma A, et al. Peripheral nervous system involvement in Sjogren's syndrome and its impact on quality of life. Clin Exp Med 2023;23(2):539–545.
10. Konak HE, Gök K, Armağan B, et al. Neurological involvement in patients with primary Sjögren's syndrome: a retrospective cross-sectional study. Ann Indian Acad Neurol 2023;26(4):424–430.
11. Barsottini OGP, Moraes MPM, Fraiman PHA, et al. Sjogren's syndrome: a neurological perspective. Arq Neuropsiquiatr 2023;81(12):1077–1083.
12. Seeliger T, Kramer E, Konen FF, et al. Sjögren's syndrome with and without neurological involvement. J Neurol 2023;270(6):2987–2996.
13. Hoshina Y, Wong KH, Galli J, et al. Neurologic involvement in seronegative primary Sjögren's syndrome with positive minor salivary gland biopsy: a single-center experience. Front Neurol 2023;14:1174116.
14. Vivino FB. Sjogren's syndrome: clinical aspects. Clin Immunol 2017;182:48–54.
15. Lackner A, Ficjan A, Stradner MH, et al. It's more than dryness and fatigue: the patient perspective on health-related quality of life in Primary Sjögren's Syndrome - a qualitative study. PLoS One 2017;12(2):e0172056.
16. Argyropoulou OD, Valentini E, Ferro F, et al. One year in review 2018: Sjogren's syndrome. Clin Exp Rheumatol 2018;36 Suppl 112(3):14–26.
17. McCoy SS, Bartels CM, Saldanha IJ, et al. National Sjögren's Foundation survey: burden of oral and systemic involvement on quality of life. J Rheumatol 2021;48(7):1029–1036.
18. Birnbaum J. Peripheral nervous system manifestations of Sjögren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. Neurologist 2010;16(5):287–297.
19. Newton JL, Frith J, Powell D, et al; UK primary Sjögren's syndrome registry. Autonomic symptoms are common and are associated with overall symptom burden and disease activity in primary Sjogren's syndrome. Ann Rheum Dis 2012;71(12):1973–1979.
20. Koh JH, Kwok SK, Lee J, et al. Autonomic dysfunction in primary Sjogren's syndrome: a prospective cohort analysis of 154 Korean patients. Korean J Intern Med (Korean Assoc Intern Med) 2017;32(1):165–173.
21. Blaes F. Diagnosis and therapeutic options for peripheral vasculitic neuropathy. Ther Adv Musculoskelet Dis 2015;7(2):45–55.
22. Pereira PR, Viala K, Maisonobe T, et al. Sjögren sensory neuronopathy (Sjögren ganglionopathy): long-term outcome and treatment response in a series of 13 cases. Medicine (Baltimore) 2016;95(19):e3632.
23. American College of Rheumatology. Policy and procedure manual for clinical practice guidelines. Published February 2023. Accessed June 2, 2023. https://rheumatology.org/api/asset/bltae11ca9142708dfa
24. Carsons SE, Vivino FB, Parke A, et al. Treatment guidelines for rheumatologic manifestations of Sjögren's syndrome: use of biologic agents, management of fatigue, and inflammatory musculoskeletal pain. Arthritis Care Res (Hoboken) 2017;69(4):517–527.
25. Sjogren's Foundation. Clinical practice guidelines. Accessed January 15, 2024. https://www.sjogrens.org/researchersproviders/clinical-practice-guidelines
26. GRADE. Grading of Recommendations Assessment, Development and Evaluation (GRADE). Accessed June 2, 2023. https://www.gradeworkinggroup.org/
27. Somerfield MR, Bohlke K, Browman GP, et al. Innovations in American Society of Clinical Oncology practice guideline development. J Clin Oncol 2016;34(26):3213–3220.
28. US Preventive Services Task Force. Methods and processes. Accessed June 2, 2023. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes
29. Lockhart PB, Tampi MP, Abt E, et al. Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: a report from the American Dental Association. J Am Dent Assoc 2019;150(11):906–921.e12.
30. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66(7):719–725.
31. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66(7):726–735.
32. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336(7651):995–998.
33. Noaiseh G, Deboo A, King JK, et al. Recommendations for aligned nomenclature of peripheral nervous system disorders across rheumatology and neurology. Arthritis Rheumatol 2025;77(4):383–389.
34. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. BMJ 2008;336(7652):1049–1051.
35. McCoy SS, Baer AN. Neurological complications of Sjögren's syndrome: diagnosis and management. Curr Treatm Opt Rheumatol 2017;3(4):275–288.
36. Perzyńska-Mazan J, Maślińska M, Gasik R. Neurological manifestations of primary Sjögren's syndrome. Reumatologia 2018;56(2):99–105.
37. Brito-Zerón P, Akasbi M, Bosch X, et al. Classification and characterisation of peripheral neuropathies in 102 patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2013;31(1):103–110.
38. Ramos-Casals M, Muñoz S, Zerón PB. Hepatitis C virus and Sjögren's syndrome: trigger or mimic? Rheum Dis Clin North Am 2008;34(4):869–884, vii.
39. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al; EULAR-Sjögren Syndrome Task Force Group. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis 2020;79(1):3–18.
40. Meglio M. Ianalumab meets primary end points in phase 3 NEPTUNUS trials of Sjögren's disease. Neurology Live. Published August 12, 2025. Accessed August 28, 2025. https://www.neurologylive.com/view/ianalumab-meets-primary-end-points-phase-3-neptunus-trials-sjogren-disease?utm_source=chatgpt.com
41. Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 2016;80:3–7.
42. Dewidar O, Lotfi T, Langendam MW, et al; eCOVID-19 recommendations map collaborators. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. BMJ Evid Based Med 2023;28(3):189–196.
43. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. Lancet 2017;390(10092):415–423.
44. Djulbegovic B, Guyatt G. Evidence vs consensus in clinical practice guidelines. JAMA 2019;322(8):725–726.

45. Three-arm study to assess efficacy and safety of ianalumab (VAY736) in patients with active Sjogren's syndrome (NEPTUNUS-2). ClinicalTrials.gov identifier: NCT05349214. Updated December 22, 2025. Accessed May 31, 2024. https://www.clinicaltrials.gov/study/NCT05349214?cond=Sjogren%27s&term=Neptunus&rank=3
46. Two-arm study to assess efficacy and safety of ianalumab (VAY736) in patients with active Sjogren's syndrome (NEPTUNUS-1). ClinicalTrials.gov identifier NCT05350072. Accessed May 31, 2024. https://www.clinicaltrials.gov/study/NCT05350072?cond=Sjogren%27s&term=Neptunus&rank=2
47. A study to evaluate the efficacy and safety of deucravacitinib in adults with active Sjögren's syndrome (POETYK SjS-1). ClinicalTrials.gov identifier NCT05946941. Accessed May 31, 2024. https://www.clinicaltrials.gov/study/NCT05946941?cond=Sjogren%27s&term=POETYK&rank=1
48. A safety and efficacy study of dazodalibep in participants with Sjögren's syndrome (SS) with moderate-to-severe symptom state. ClinicalTrials.gov identifier NCT06245408. Accessed May 31, 2024. https://www.clinicaltrials.gov/study/NCT06245408?cond=Sjogren%27s&term=Dazodalibep&rank=2
49. A study to evaluate the efficacy and safety of dazodalibep in participants with Sjögren's syndrome (SS) with moderate-to-severe systemic disease activity. ClinicalTrials.gov identifier NCT06104124. Accessed May 31, 2024. https://www.clinicaltrials.gov/study/NCT06104124?cond=Sjogren%27s&term=Dazodalibep&rank=1
50. argenx SE. argenx Advances clinical development of efgartigimod in primary Sjogren's disease. Yahoo Finance. Published March 27, 2024. Accessed May 31, 2024. https://finance.yahoo.com/news/argenx-advances-clinical-development-efgartigimod-060000906.html?guccounter=1

APPENDIX A: CONSENSUS EXPERT PANEL (CEP) MEMBERS

Members of the CEP are as follows: G. Alden Adkins, MD (Rheumatology Fellow, University of Virginia); Brittany Adler, MD (Assistant Professor of Medicine, The Johns Hopkins University School of Medicine); Hossein Ansari, MD (Director of Headache and Facial Pain Clinic, Associate Professor of Neuroscience, Kaizen Brain Center, La Jolla, CA, and University of California, San Diego); Senada Arabelovic, DO (Assistant Professor of Medicine, Brigham and Women's Hospital, Boston, MA); Alan Baer, MD (Director, Jerome Greene Sjögren's Syndrome Clinic, Professor of Medicine, The Johns Hopkins University School of Medicine); Denis Balaban, MD (Instructor in Neurology, Massachusetts General Hospital and Harvard Medical School); Shamik Bhattacharyya, MD (Program Leader, Autoimmune Neurology, Brigham and Women's Hospital and Harvard Medical School); Evelyn Bromet, PhD (Distinguished Professor Emerita, Stony Brook University); Krishna Chaganti, MD, MS (Associate Professor of Medicine, University of California San Francisco); Kamal Chemali, MD (Professor of Neurology, Case Western Reserve University and University Hospitals of Cleveland); Melissa Cortez, DO (Associate Professor, Department of Neurology, Founding Director, Autonomic Physiology Laboratory, University of Utah); Schartess Culpepper, MD (Staff Physician, University of Miami); Paul Dellaripa, MD (Associate Professor, Harvard Medical School, Brigham and Women's Hospital, Boston, MA); Dana Direnzo, MD, MHS (Assistant Professor of Clinical Medicine (Rheumatology), University of Pennsylvania); Daniel El Bogdadi, MD (Assistant Clinical Professor of Medicine, Arthritis & Rheumatism Associates and Georgetown University); Robert Fearon; Mehrnez Fischbach, MD (Chief, Division of Rheumatology, Associate Professor of Medicine, National Jewish Health); Judi Furlong, MD (Retired Family Medicine); Christopher Gibbons, MD, MMSc (Professor of Neurology, Harvard Medical School); Rachael Gordon, MD, PhD (Rheumatology Fellow, University of Pittsburgh Medical College); Thomas Grader Beck, MD (Assistant Professor of Medicine, The Johns Hopkins University School of Medicine); Syed Haider, MD (Attending Cardiologist, Director of Pericardial Disease Program, MedStar Washington Hospital Center and Georgetown University Hospital); Larry Hollenbeck, MD (Neurologist, Meritas Health Neurology, Kansas City, MO); Chadwick R. Johr, MD (Associate Professor of Clinical Medicine, University of Pennsylvania); Stuart S. Kassan, MD (Distinguished Clinical Professor of Medicine, National Jewish Health and University of Colorado School of Medicine); Brian King, MD (Rheumatology Resident, University of Virginia); Octavia Kincaid, MD (Assistant Professor, Rush University Medical Center); Eugene Kissin, MD (Director, Rheumatology Fellowship Program, Clinical Professor of Medicine, Boston Medical Center); Vasileios Kyttaris, MD (Assistant Professor of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School); Lindsay Lally, MD (Hospital for Special Surgery, New York, NY); Brandon M. Law, MD (Massachusetts General Hospital, Boston, MA); Janet Lewis, MD (Associate Professor of Medicine, University of Virginia); Scott M. Lieberman, MD, PhD (Associate Professor of Pediatrics, Division of Rheumatology, Allergy and Immunology, University of Iowa Carver College of Medicine); Amanda Lusa, MD (Assistant Professor of Rheumatology, University of Virginia); Joseph Lutt, MD (Rheumatologist, Colorado Center for Arthritis & Osteoporosis); Rashmi Maganti, MD (Interim Section Chief, Department of Medicine, Immunology, Allergy & Rheumatology, Rheumatology, Medical Subspecialty Clinic Director, Baylor College of Medicine); Arthur M. Mandelin II, MD, PhD (Associate Professor of Medicine, Northwestern University Feinberg School of Medicine); Sara McCoy, MD, PhD (Assistant Professor, University of Wisconsin School of Medicine and Public Health); Kerry Neall, MD, MPH (Emergency Medicine, Orlando Health, Orlando, FL); Timothy Niewold, MD, FACR (Vice Chair for Research, Department of Medicine, Hospital of Special Surgery, New York, NY); Anne Louise Oaklander, MD, PhD (Associate Professor of Neurology, Assistant in Pathology (Neuropathology), Massachusetts General Hospital and Harvard Medical School); Ruben A. Peredo-Wende, MD (Site Director, Veteran Affairs Medical Center, Albany, NY); Lynn Petruzzi, RN, MSN (Retired Registered Nurse); Mark A. Porter, MD (Retired Neurologist); Guada Respicio Duque, MD, MSc (Rheumatologist, Arthritis and Rheumatism Associates); Tania Reyna, MD (Associate Professor, University of Texas Health San Antonio); Nathaniel M. Robbins, MD (Director, MGB Program in Small Fiber and Autonomic Neurology, Harvard Medical School, Massachusetts General Hospital, and Brigham and Women's Hospital); Elliot D. Rosenstein, MD (Rheumatologist, Overlook Medical Center/Atlantic Health System); Laura Rosow, MD (Associate Professor of Neurology, University of California, San Francisco); Breanna Ruthrauff, MD (Retired Neurologist); Amit Sachdev, MD (Director, Neuromuscular Medicine, Assistant Professor, Michigan State University); Nora Sandorfi, MD (Professor of Clinical Medicine, University of Pennsylvania); Sarah Schafer, MD (Medical Educator, Retired Physician); Elena Schiopu, MD (Professor of Medicine, Rheumatology Division, Medical College of Georgia); Chokkalingam Siva, MD (Professor of Clinical Medicine, University of Missouri School of Medicine); Daniel Small, MD (Rheumatologist, Mayo Clinic Healthcare System SW Wisconsin); Sara M. Stern, MD (Assistant Professor, University of Utah School of Medicine and Primary Children's Medical Center); Lauren Stiles, JD (President, Dysautonomia International, Research Assistant Professor, Neurology, Stony Brook University); Susan Stoddard, RN (Research Coordinator in Cardiology); Jinny Tavee, MD (Professor of Medicine, National Jewish Health); Donald Thomas, MD (Rheumatologist, Arthritis and Pain Associates for Prince George's County); Edward L. Treadwell, MD (Professor of Medicine/Rheumatology/Immunology, East Carolina University School of Medicine); Nagagopal Venna, MD (Chief, Division of Neuroimmunology and Neuro-Infectious Diseases, Massachusetts General Hospital, Boston, MA); Steven Vernino, MD (Professor of Neurology, University of Texas Southwestern); Frederick B. Vivino, MD, MS (Director Emeritus, Penn Sjögren's Center, University of Pennsylvania); Brittany Weber, MD, PhD (Director of the Cardio-Rheumatology Clinic, Associate Physician in Prevention Cardiology and Cardiovascular Imaging, Assistant Professor, Brigham and Women's Hospital and Harvard Medical School); Sepideh Yadollahi, MD (Resident Physician, University New Mexico, Kaizen Brain Center); Huiying Yu, MD (Director of Neurodiagnostic Lab, Neuromuscular Section, NYU Langone Hospital Long Island); Scott Zashin, MD (Texas Health, Dallas, Texas).

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 875–882
DOI 10.1002/acr.70005

American College of Rheumatology
Empowering Rheumatology Professionals

Diagnostic Use of Testing for Novel Murine Autoantibodies for Sjögren Disease in the Rheumatology Outpatient Setting

Chadwick R. Johr, MD,[1,2] Michael D. George, MD, MSCE,[2] Vatinee Y. Bunya, MD, MSCE,[3] Nora Sandorfi, MD,[2] Mina Massaro-Giordano, MD,[4] and Frederick B. Vivino, MD, MS, MACR[1,5]

Objective. The goal was to assess the diagnostic performance of three novel autoantibodies (NA) for Sjögren disease (SjD) by comparing NA prevalence in patients with SjD, other autoimmune rheumatic diseases (ARDs), nonspecific chronic sialadenitis (CS), and controls.

Methods. We identified rheumatology outpatients with confirmed SjD, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), CS, and healthy controls. Participants underwent serum testing for antibodies to salivary gland protein 1 (SP-1), parotid secretory protein, and carbonic anhydrase-6 (CA-6). Participants with SjD, CS, and controls also underwent testing of saliva. Receiver operating characteristic (ROC) curve C-statistics along with sensitivity, specificity, positive, and negative likelihood ratios were calculated for each serum autoantibody for SjD vs CS or controls.

Results. Among the 468 patients screened, 444 were analyzed, including cohorts with SjD (n = 149), SLE (n = 70), SSc (n = 56), RA (n = 73), CS (n = 31), and control patients (n = 65). There was no statistical difference (P = 0.80) in the presence of one or more NA in the serum of patients with SjD compared with participants with other ARDs, CS, or control patients. ROC curves demonstrated poor discriminative ability for SjD versus CS or control patients for any positive NA (0.47) or any individual NA (range 0.44–0.53). The positive likelihood ratio for having any positive novel autoantibody was 1.04 and 0.83 for SjD vs CS or control patients, respectively.

Conclusion. Testing serum for NA demonstrated a poor ability to distinguish patients with SjD from control patients or those with CS or other ARDs. This serum autoantibody panel is not likely to be useful as a diagnostic test for SjD.

INTRODUCTION

Sjögren disease (SjD) can be extremely difficult to diagnose in its early stages because of the heterogeneity of clinical presentations, need for extensive testing, and input required from multiple specialists as part of the evaluation.[1]

Recent classification criteria for SjD[2–4] were designed to define homogeneous populations of patients for clinical trials and other studies but were not intended to facilitate diagnosis. Nevertheless, classification criteria are frequently used by clinicians to diagnose SjD by default because of the lack of universally accepted diagnostic criteria. Patients with seronegative SjD (negative anti-SSA) comprise approximately one-third of the overall group and are at the highest risk of misclassification because minor salivary gland biopsies are often not offered to or are refused by patients. This diagnostic challenge underscores the need to identify novel biomarkers that may be present when established biomarkers are not. As with other autoimmune rheumatic diseases (ARDs), therapeutic measures for SjD are most likely to be successful when initiated in the early stages before permanent irreversible damage occurs to the exocrine glands and other organs.

Previous work has convincingly demonstrated that the novel murine autoantibodies antiparotid secretory protein (PSP), antisalivary protein 1 (SP-1), and anticarbonic anhydrase 6 (CA-6) are markers of early disease in the interleukin-14α transgenic mouse model for SjD because these autoantibodies appear in the blood earlier in the disease course than anti-SSA/SSB.[5] These novel

[1]Penn Sjögren's Center, Philadelphia, Pennsylvania; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia; [3]Penn Dry Eye & Ocular Surface Center, Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [4]Department of Ophthalmology, New York University Grossman School of Medicine, New York; [5]Penn-Presbyterian Medical Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70005).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70005.

Address correspondence via email to Chadwick R. Johr, MD, at Chadwick.johr@pennmedicine.upenn.edu.

Submitted for publication March 14, 2025; accepted in revised form November 5, 2025.

SIGNIFICANCE & INNOVATIONS

- This is the first study in the adult rheumatology literature to report the diagnostic performance of novel autoantibodies (NA) to salivary gland protein 1, parotid secretory protein, and carbonic anhydrase-6 in a well-characterized cohort of patients with Sjögren disease (SjD) fulfilling accepted classification criteria.
- This is one of the first studies to test for the presence of NA in the sera of several well-defined cohorts of non-SjD autoimmune rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis.
- This is the first study to compare the prevalence of the NA in the saliva of patients with SjD vs healthy control patients and those with chronic sialadenitis.
- This study is particularly relevant for everyday clinical practice because it includes two separate well-defined control groups, including one with sicca symptoms and nonspecific inflammation on minor salivary gland biopsy.

autoantibodies (NA) have also been detected in the nonobese diabetic mouse model for SjD and in humans with established SjD.[5,6] It was also observed that among 20 patients with SjD who had positive biopsies but lacked anti SSA or SSB, the NA anti–SP-1 and anti-CA6 were present in 45% and 5% of cases, respectively,[5] which suggests a possible role for diagnosis in seronegative cases.

Despite limited evidence, a diagnostic panel to test serum for the NA or "Early Sjögren's Profile," also known as "Sjö," became commercially available in 2013 (Immco Diagnostics, Inc., Buffalo, NY) and has been used by some specialists in clinical practice to diagnose "early SjD." Several studies and case reports in the eye literature provided evidence that the "Early Sjögren's Profile" can be used to screen patients with dry eye for SjD, and, when positive, may provide a rationale for early referral to other specialists for further diagnostic evaluation.[7–13]

The purpose of the present study was to investigate the prevalence of NA in patients with known SjD, related autoimmune diseases, SjD mimics (eg, chronic nonspecific sialadenitis), and nonautoimmune controls to determine the sensitivity, specificity, likelihood ratios, and discriminative ability of the "Early Sjögren's Profile" as a diagnostic test.

METHODS

Patient selection and inclusion/exclusion criteria

The electronic medical record was used to screen for *International Statistical Classification of Diseases, Tenth Revision* (ICD-10) codes among established patients at two large rheumatology outpatient practices within the same university health system. Participants with ICD-10 codes from rheumatology visits corresponding to SjD, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc) and dry mouth/nonspecific chronic sialadenitis (CS) were identified. All records were reviewed by rheumatologists to confirm diagnoses, and patients were observed for at least one year. Control participants included established patients with osteoarthritis, fibromyalgia, osteoporosis, other non-ARDs, or healthy volunteers. Patients with incomplete or unconfirmed diagnoses and control participants with a history of dry eyes and/or dry mouth, other autoimmune diseases, family history of autoimmune diseases, or previous referral for antinuclear antibody positivity were excluded from the study. Control participants and those with CS with positive anti-SSA antibodies on study assays were excluded from analysis.

Sjögren evaluation

Patients with suspected SjD routinely underwent a complete history and physical examination, serological testing, measurement of unstimulated whole-mouth salivary flow, salivary scintigraphy,[14,15] an unanesthetized Schirmer test, and vital dye staining of the ocular surface. Patients who tested negative for anti-SSA were asked to undergo a labial minor salivary gland biopsy. All patients with a diagnosis of SjD met one or more classification criteria for SjD,[2–4] demonstrated objective evidence of dry eyes and dry mouth and either anti-SSA positivity and/or a positive labial minor salivary gland biopsy (focal lymphocytic sialadenitis with a focus score ≥1/4 mm^2). Information on which SjD criteria were met was not available, but to assess impact of isolated anti-SSB antibodies, a sensitivity analysis was performed, excluding five patients with positive anti-SSB but negative anti-SSA antibodies. Patients diagnosed with nonspecific CS[16] demonstrated objective evidence of dry eyes and/or dry mouth and had abnormal biopsies but failed to meet histologic and classification criteria for SjD.

Study design and specimen collection

After signing informed consent and Health Insurance Portability and Accountability Act (HIPPA) authorization, all participants completed a medical questionnaire and specimen collection during one study visit. Recorded information included history of dry eyes and dry mouth, medical diagnoses, demographics, medications, associated autoimmune diseases, and family history of autoimmune or connective tissue disease. Additional information was collected on patients with known SjD regarding the duration of xerostomia, dry eye, and extraglandular or internal organ manifestations. Serum samples were obtained from all participants, and saliva samples were obtained from patients with SjD, CS, and control participants.

Specimen processing

Blood specimens for all eligible participants were collected in one serum separator red top tube and centrifuged for storage at –80°C until shipment. Additionally, for some participants, random whole-mouth salivary flow rates (sialometry) were measured (15-minute collection) after swallowing once at the time of blood specimen collection. Saliva specimen collection tubes were weighed on an analytical balance pre- and post-collection to determine the volume of saliva produced (1 g saliva = 1 mL). A protease inhibitor cocktail was added in proportion to the saliva sample volume (10 μL of 100 × protease inhibitor cocktail per 1 mL saliva). Specimen collection tubes were then vortexed for 5 to 10 seconds to homogenize the samples for storage at –80°C until shipment.

Novel autoantibody assay

The tests were performed as a solid phase immunoassay by Immco Diagnostics Reference Laboratory (Trinity Biotech, Inc.) in Buffalo, New York. All specimens were anonymously coded and laboratory personnel were blinded to patient diagnoses. Briefly, microtiter plates were coated with recombinant antigen (CA-6, PSP, or salivary gland protein 1 [SP1]) proteins expressed and purified from *Escherichia coli*, followed by blocking the unreacted sites to reduce nonspecific binding. Control participant and patient serum samples were incubated in the antigen coated wells that allow specific antibodies present in the serum to bind to the antigen. Unbound antibody and other serum proteins were removed by washing the microtiter plate. Bound antibodies were detected by adding horseradish peroxidase labeled anti-human IgA, IgG, or IgM conjugate to the plates. Unbound conjugate is removed by washing. A specific enzyme substrate 3,3′,5,5′-tetramethylbenzidine (TMB) was then added to the wells, and the presence of antibodies was detected by a color change produced by the conversion of the TMB substrate to a colored reaction product. The reaction was stopped and the intensity of the color change, which is proportional to the concentration of antibody, was read by a spectrophotometer at 450 nm. Results were expressed in enzyme-linked immunosorbent assay (ELISA) units per milliliter (EU/mL) and reported as positive or negative, with positive defined as ≥20 EU/mL. Salivary autoantibodies were evaluated using the same methods and expressed as EU/mL without a specific cut-off defined for positivity.

Statistical analysis

Characteristics of patients with SjD, SLE, SSc, RA, CS, and control patients were compared descriptively. Differences in the frequency of novel serum autoantibody positivity across these diagnoses was assessed by Fisher exact testing (given small cell frequencies). Bonferroni correction was applied for multiple comparisons, with an adjusted *P* value of 0.0056 (0.05 divided by 9) considered statistically significant across all analyses given the nine antibodies studied. Receiver operating characteristic (ROC) curve C-statistics were used to evaluate the ability of each serum autoantibody (dichotomized as positive or negative) to discriminate patients with SjD versus either CS or control participants, first with these two groups combined to maximize power, and then versus each individually. Comparison versus CS was thought to mimic how testing might be used in clinical practice, whereas comparisons versus control participants included a population with less likelihood of misclassification (ie, patients with CS who may actually have or develop SjD). Sensitivity, specificity, and positive and negative likelihood ratios (LR) were calculated for each serum autoantibody for SjD versus control participants or SjD versus CS. C-statistics were then recalculated using each autoantibody as a continuous measure to assess whether a different cut-off might lead to different performance. In a sensitivity analysis, novel serum autoantibody positivity was also assessed for each group of patients among those who were SSA negative to assess the utility of these autoantibodies for SjD diagnosis among patients who were SSA negative (a specific group for whom NA may be particularly useful). An additional sensitivity analysis excluded those with CS and control participants with rheumatoid factor (RF) ≥20 or antinuclear antibody (ANA) ≥1:80 to address any potential misclassification.

For novel salivary autoantibodies, dot plots were used to visualize the optical density for patients with SjD, CS, or control participants given the lack of an established cut-off for positivity. Medians were compared using Kruskal-Wallis testing given the skewed nature of the data (SjD vs CS or control participants given lower sample size). Again, ROC C-statistics were used to assess the ability of salivary autoantibody values to distinguish SjD vs CS/control participants, with continuous values used for autoantibodies. In this analysis, the largest differences between groups were found for PSP salivary antibodies. As an exploratory analysis, a binary cut-off for each of PSP IgG, IgM, and IgA was chosen as the 95th percentile value for each antibody among control participants, not including patients with CS (in whom autoantibody levels tended to be slightly higher). We calculated C-statistics, sensitivity, specificity, and positive and negative LR for distinguishing SjD versus CS or control participants using these binary definitions of salivary PSP antibodies. These analyses were repeated among patients with a negative SSA antibody.

All analyses were performed using Stata version 15.1 (College Station, TX: StataCorp LLC). The study was approved by the University of Pennsylvania Institutional Review Board.

RESULTS

A total of 468 patients with diagnoses of interest were recruited. After excluding patients who did not meet the classification criteria, including 3 patients with possible SjD, 1 patient with

Table 1. Cohort characteristics*

Characteristic	Primary SjD	Lupus	SSc	RA	CS	Control
N	149	70	56	73	31	65
Female, n (%)	143 (96.0)	66 (94.3)	53 (94.6)	57 (78.1)	29 (93.5)	52 (80.0)
Age, mean (SD), y	60.8 (13.7)	48.7 (15.3)	58.7 (12.5)	59.2 (12.8)	60.8 (16.6)	41.8 (20.5)
Dry eye, n (%)	143 (96.0)	42 (60.0)	37 (66.1)	27 (37.0)	26 (83.9)	0 (0.0)
Dry mouth, n (%)	144 (96.6)	38 (54.3)	37 (66.1)	29 (39.7)	26 (83.9)	0 (0.0)
ANA ≥ 1:40, n (%)	104 (69.8)	64 (91.4)	53 (94.6)	55 (75.3)	13 (41.9)	23 (35.4)
ANA ≥ 1:80, n (%)	96 (64.4)	64 (91.4)	52 (92.9)	47 (64.4)	11 (35.5)	15 (23.1)
RF IgM ≥ 10, n (%)	66 (44.3)	30 (42.9)	27 (48.2)	60 (82.2)	9 (29.0)	21 (32.3)
RF IgM ≥ 20, n (%)	45 (30.2)	19 (27.1)	15 (26.8)	51 (69.9)	6 (19.4)	8 (12.3)
Anti-SSA, n (%)	92 (61.7)	25 (35.7)	18 (32.1)	7 (9.6)	0 (0.0)	0 (0.0)
Anti-SSB, n (%)	48 (32.2)	9 (12.9)	4 (7.1)	6 (8.2)	2 (6.5)	2 (3.1)

* ANA, antinuclear antibody; CS, chronic sialadenitis; RA, rheumatoid arthritis; RF, rheumatoid factor; SjD, Sjögren disease; SSc, systemic sclerosis.

biopsy-proven CS who also met Sjögren classification criteria, 3 control participants or patients with CS with anti-SSA antibodies, and 17 patients who did not complete antibody testing, there were 444 patients for analysis, including 149 with SjD, 70 with SLE, 56 with SSc, 73 with RA, 31 with CS, and 65 control participants (non-ARD or healthy volunteers). All groups were primarily female, and patients with SLE and control participants were younger than the other patient groups (Table 1). SSA antibody positivity was most common among those with SjD (61.7%).

Novel serum autoantibodies

The frequency of each novel serum autoantibody by disease is shown in Table 2. At least one serum autoantibody was positive in 43.6% of those with SjD, 44.3% with SLE, 51.8% with SSc, 45.2% with RA, 41.9% with CS, and 52.3% of control participants, with no significant difference across diseases ($P = 0.80$). Among individual serum autoantibodies, significant differences in CA-6 IgG were seen ($P < 0.001$, statistically significant after Bonferroni correction), but this was driven by higher rates among those with SLE, SSc, and RA. There were no significant differences between SjD and CS or between SjD and control participants across any of the antibodies (all $P > 0.05$). Results were similar in a sensitivity analysis limited to patients with SjD with a negative anti-SSA (Supplemental Table 1), as well in analyses excluding five patients with SjD with anti-SSB but negative anti-SSA, and in analyses excluding CS and control participants with RF ≥20 or ANA ≥1:80 (not shown). Among those with SLE, SSc, or RA, frequencies of NA were also similar in those with and without dry eye ($P = 0.83$) and those with and without dry mouth ($P = 0.34$). No significant differences in the prevalence of NA were observed among patients with SjD classified by salivary flow rate (ie, <0.2 cc/min or >0.2 cc/min).

Table 2. Novel serum autoantibody positivity by disease*

Variable	Primary Sjögren disease	Lupus	SSc	RA	CS	Control	Primary SjD vs CS or control participants ROC (95% CI)
N	149	70	56	73	31	65	
CA-6 IgG, n (%)[a]	11 (7.4)	16 (22.9)	19 (33.9)	18 (24.7)	5 (16.1)	7 (10.8)	0.47 (0.44–0.51)
CA-6 IgM, n (%)	21 (14.1)	7 (10.0)	6 (10.7)	4 (5.5)	3 (9.7)	13 (20.0)	0.49 (0.44–0.53)
CA-6 IgA, n (%)	5 (3.4)	3 (4.3)	2 (3.6)	2 (2.7)	3 (9.7)	4 (6.2)	0.48 (0.45–051)
CA-6 any, n (%)	33 (22.1)	22 (31.4)	23 (41.1)	22 (30.1)	10 (32.3)	22 (33.8)	0.44 (0.39–0.50)
PSP IgG, n (%)	5 (3.4)	5 (7.1)	4 (7.1)	3 (4.1)	3 (9.7)	(0.0)	0.50 (0.48–0.52)
PSP IgM, n (%)	10 (6.7)	1 (1.4)	1 (1.8)	(0.0)	1 (3.2)	8 (12.3)	0.49 (0.45–0.52)
PSP IgA, n (%)	16 (10.7)	4 (5.7)	4 (7.1)	5 (6.8)	2 (6.5)	2 (3.1)	0.53 (0.50–0.56)
PSP any, n (%)	29 (19.5)	9 (12.9)	7 (12.5)	8 (11.0)	5 (16.1)	10 (15.4)	0.52 (0.47–0.57)
SP-1 IgG, n (%)	6 (4.0)	4 (5.7)	1 (1.8)	4 (5.5)	4 (12.9)	3 (4.6)	0.48 (0.45–0.51)
SP-1 IgM, n (%)	16 (10.7)	9 (12.9)	10 (17.9)	6 (8.2)	(0.0)	14 (21.5)	0.48 (0.44–0.52)
SP-1 IgA, n (%)	11 (7.4)	1 (1.4)	2 (3.6)	2 (2.7)	(0.0)	3 (4.6)	0.52 (0.49–0.55)
SP-1 any, n (%)	31 (20.8)	13 (18.6)	12 (21.4)	12 (16.4)	4 (12.9)	19 (29.2)	0.48 (0.43–0.54)
Any of the above, n (%)	65 (43.6)	31 (44.3)	29 (51.8)	33 (45.2)	13 (41.9)	34 (52.3)	0.47 (0.41–0.54)

* Positive serum autoantibody defined as ≥20. ROC is the receiver operating characteristic curve C-statistic for distinguishing patients with primary SjD from patients with CS or control participants. All $P > 0.05$ for pairwise comparison between SjD and CS and between SjD and controls. CA-6, anticarbonic anhydrase 6; CI, confidence interval; CS, chronic sialadenitis; PSP, antiparotid secretory protein; RA, rheumatoid arthritis; SjD, Sjögren disease; SP-1, antisalivary protein 1; SSc, systemic sclerosis.

[a] Fisher's exact $P < 0.001$ for CA-6 IgG, $P = 0.006$ for PSP IgM, and $P = 0.021$ for SP-1 IgM when examining differences across all diagnosis groups, with only CA-6 IgG meeting statistical significance after Bonferroni correction ($P < 0.0056$).

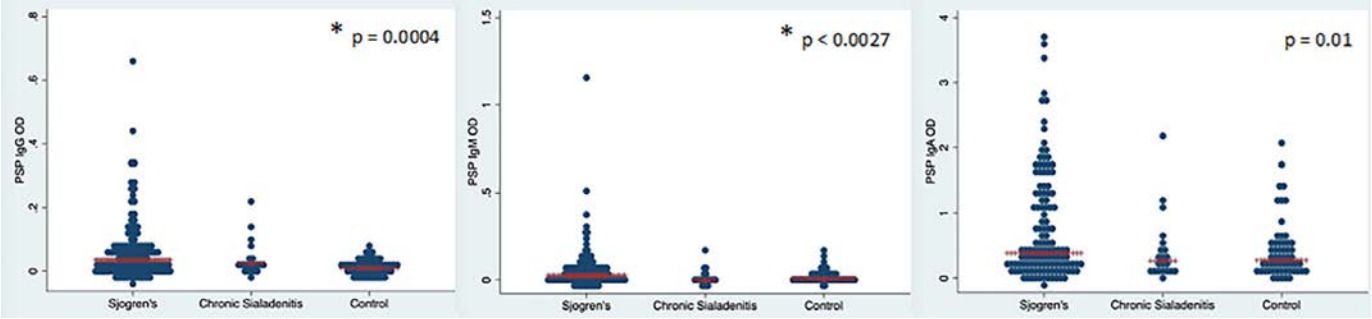

Figure 1. Levels of PSP saliva autoantibodies in patients with SjD, CS, or control participants. Dotplots show optical densities of novel saliva autoantibodies with red hashes representing medians for each group. *Kruskal-Wallis testing comparing values in patients with SjD with those with CS or control participants showed higher levels in patients with SjD for PSP IgG and PSP IgM (both P <0.0056, statistically significant after Bonferroni correction). PSP IgA P = 0.01 not statistically significant after Bonferronni correction. CS, chronic sialadenitis; PSP, parotid secretory protein; SjD, Sjögren disease.

ROC curve C-statistics for the ability of having any novel serum antibody to discriminate patients with SjD from those with CS or control participants was 0.47 (95% confidence interval [CI] 0.41–0.54) (worse than chance, with a greater frequency of the antibody in CS/control participants) and for individual autoantibodies ranged from 0.44 to 0.53, demonstrating minimal discriminative ability (Table 2). Results were similar when comparing SjD versus CS (Supplemental Table 2) or SjD versus control participants (Supplemental Table 3), with poor discrimination indicated by C-statistics. For detection of any positive NA, the positive LR was 1.04 (95% CI 0.66–1.64) and 0.83 (95% CI 0.62–1.12) for SjD versus CS or control participants, respectively, and negative LR was 0.97 (95% CI 0.70–1.35) and 1.18 (0.88–1.58). For individual autoantibodies, all negative LR were >0.5, and all positive LR were <2 except for rare cases in which autoantibody frequency was low and sensitivity poor (Supplemental Tables 2 and 3).

Novel salivary autoantibodies

Salivary autoantibodies were available in 127 patients with SjD, 21 with CS, and 57 control participants. Dot plots showing levels of these autoantibodies in each group are in Figure 1. Median level autoantibody levels were higher in SjD versus CS and control participants for PSP IgG (P = 0.0004) and PSP IgM (P = 0.0027), whereas differences in PSP IgA did not meet statistical significance after Bonferroni correction (P = 0.01). There were no significant differences for CA6 or SP1 antibodies in SjD vs CS and control participants. ROC curve C-statistics were also highest for PSP salivary antibodies and were 0.65 (95% CI 0.57–0.72), 0.63 (95% CI 0.55–0.70), and 0.60 (95% CI 0.53–0.68) for PSP IgG, IgM, and IgA salivary autoantibodies, respectively (Supplemental Table 4). Using the 95th percentile in controls (not including patients with CS) as a cut-point for positive/negative, PSP salivary autoantibodies were more common in SjD than in CS or control participants (Table 3); sensitivity for SjD was 39.4%, 16.5%, and 18.9% with positive LR of 5.12, 4.30, and 4.91 for IgG, IgM, and IgA autoantibodies, respectively. Positivity of any PSP salivary autoantibody had sensitivity of 44.9% and positive LR of 3.50. Results were similar among patients with SjD with a negative anti-SSA (Supplemental Table 5).

DISCUSSION

Novel biomarkers for SjD that appear early in the disease course or that can be detected in patients who lack anti-SSA are sorely needed. In this study we evaluated the diagnostic utility of three NA for SjD: anti–SP-1, anti–CA-6, and anti-PSP. We found that the NA have no significant diagnostic value to distinguish SjD from healthy control participants or those with CS in the rheumatology practice setting, with LRs near 1 and a receiver operating characteristic curve C-statistic very close to 0.5. In addition, the NA were not useful in distinguishing between SjD and other systemic ARDs, including RA, SLE, and SSc. The prevalence of NA in patients with other ARDs was not significantly different in patients with and without sicca symptoms. Thus, this panel would be unlikely to accurately predict the presence of secondary or associated SjD among these latter individuals.

The literature regarding the utility of the NA up to this point has been inconsistent. Some studies suggest evidence of potential diagnostic utility with only SP-1,[6,8,17] other studies with only CA-6,[18] and yet others with only PSP.[19] One Chinese study suggests potential diagnostic utility with all three NA.[20] The only study outside of ours that reports on the diagnostic performance of the NA was performed on children and demonstrates that the NA were not helpful in distinguishing between patients with SjD and control participants.[21] The potential reasons for the inconsistent results in the literature are myriad. First of all, early studies included both mice and humans and were initially measured by Western blot.[5,6,17] As the testing for NA became commercialized and more widespread, the assay was switched from Western blot

Table 3. Performance of PSP saliva autoantibodies using a cut-point at levels above the 95th percentile in control participants*

Parameter	Primary SjD, N = 127	CS, N = 21	Control, N = 57	Test characteristic for SjD vs CS or control participants				
				Sens (95% CI)	Spec (95% CI)	LR+ (95% CI)	LR− (95% CI)	ROC (95% CI)
PSP IgG saliva >0.0537, n (%)[a]	50 (39.4)	4 (19.0)	2 (3.5)	39.4% (30.8–48.4)	92.3% (84.0–97.1)	5.12 (2.30–11.40)	0.66 (0.56–0.77)	0.66 (0.61–0.71)
PSP IgM saliva > 0.0994, n (%)	21 (16.5)	1 (4.8)	2 (3.5)	16.5% (10.5–24.2)	96.2% (89.2–99.2)	4.30 (1.33–13.90)	0.87 (0.79–0.95)	0.56 (0.52–0.60)
PSP IgA saliva > 1.4819, n (%)	24 (18.9)	1 (4.8)	2 (3.5)	18.9% (12.5–26.8)	96.2% (89.2–99.2)	4.91 (1.54–15.80)	0.84 (0.77–0.93)	0.58 (0.54–0.62)
Any PSP saliva >95th percentile, n (%)[a]	57 (44.9)	5 (23.8)	5 (8.8)	44.9% (36.1–54.0)	87.2% (77.7–93.7)	3.50 (1.90–6.44)	0.63 (0.53–0.76)	0.66 (0.60–0.72)

* The ROC C-statistic is based on a binary cut-off for defining a positive test. CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PSP, antiparotid specific protein; ROC, receiver operating characteristic curve C-statistic; Sens, sensitivity; SjD, Sjögren disease; Spec, specificity.

[a] Fisher's exact comparing across all three groups $P < 0.001$ for PSP IgG, $P = 0.02$ for PSP IgM, $P = 0.007$ for PSP IgA, and <0.001 for any PSP saliva antibody >95th percentile in healthy control participants. Differences for PSP, IgG, and any PSP antibody meet statistical significance after Bonferroni correction ($P < 0.0056$, still accounting for nine comparisons given that nine total salivary antibodies were measured).

to ELISA, and it is conceivable that this change in assays resulted in a loss of specificity. Next, most NA publications involve only a small number of participants. Many do not specify whether those with SjD met any classification criteria. Control groups, if present, were often not well-defined. It is notable that we found similar rates of NA positivity in patients with SjD compared to previous studies, but importantly, we also found high rates of NA positivity in control participants.[5] Last, differences in geography may also help explain some of the inconsistencies that have been reported.

The NA are also marketed as early markers of SjD. It seems this is based largely on evidence from mouse models. Previous authors have noted that to evaluate this suggestion more thoroughly, longitudinal studies are needed. However, the presence of autoantibodies is typically maintained in systemic autoimmune diseases. For example, in one longitudinal registry study from Sweden, serum autoantibodies were detected in SjD up to 18 years before diagnosis, and the prevalence of RF, ANA and anti-SSA/SSB actually increased over time.[22] Because of this, we would expect to find significantly higher levels of NA in those with "late" or established SjD compared with controls, but this was not the case in our study. Additionally, we found no differences in NA prevalence among patients with SjD classified as "early" or "advanced" SjD based on salivary flow rates.

It has also been suggested that the NA may be diagnostically helpful for cases in which established seromarkers (ie, anti-SSA/SSB) for SjD are negative and labial salivary biopsy declined. With this in mind, a sensitivity analysis was performed for the confirmed participants with SjD who had a negative SSA but a positive labial salivary biopsy (n = 58). The results were essentially unchanged.

Because autoantibody formation in SjD occurs locally in exocrine glands,[23] we also tested saliva for the NA. We observed statistically higher levels of PSP in saliva samples from patients with SjD compared with those with CS or control participants. However, the relative insensitivity of this finding renders this observation less useful as the basis for a future diagnostic test. Furthermore, the specimen processing for saliva required at the present time is more labor intensive than a simple blood test and further diminishes its potential diagnostic value.

Our study has multiple strengths. First, this is one of the largest NA studies to date with well-defined cohorts. All participants with SjD met modern classification criteria, and patients with other connective tissue disorders were diagnosed by rheumatologists at an academic center. The "normal" control group bore little relation to SjD. By definition, they had no sicca symptoms and no personal nor family history of autoimmune disease. These were largely patients with osteoarthritis, osteoporosis, chronic pain syndrome (with negative previous evaluations) or healthy volunteers. The CS control group included patients who presented with sicca symptoms, underwent a thorough evaluation for SjD, and exhibited evidence of nonspecific inflammation on labial salivary biopsy but who were SSA negative and did not meet classification criteria for SjD. This "practical" control group represented patients for whom the NA test would be typically applied. In addition, we tested for the prevalence of NA in autoimmune diseases related to SjD to see if the NA could help distinguish between SjD and other closely related connective tissue disorders. Similarly, it could not. Last, all participants were observed for at least a year to ensure that they remained as initially classified.

Our study has limitations. This was not a longitudinal study and does not conclusively prove that levels of NA do not diminish in SjD over time. Additionally, this is a single center study, and evaluations with more than one center have demonstrated positive results. It was a single-specialty study involving only rheumatology outpatients. As such, it may not be applicable in other contexts. We used one or more among three different sets of classification criteria (2016 American College of Rheumatology [ACR]/EULAR, 2012 ACR, and 2002 American-European Consensus Group) to classify the participants as SjD and were unable stratify results by which criteria was met.[2–4] However, many individuals fulfilled more than one set of classification criteria, and all participants with SjD were either anti-SSA positive or had a positive labial minor salivary gland biopsy with objective evidence of dry eyes and dry mouth. Previous studies have documented only small differences in sensitivity and specificity when different criteria sets are applied to the same population with SjD.[24] We also found similar results after excluding five patients who were anti-SSB positive but anti-SSA negative. These observations, therefore, make it unlikely that exclusive use of the 2016 ACR/EULAR classification criteria[4] would have significantly altered our results. It is possible that some patients with CS could have had SjD with negative biopsy, but we also included a separate control group and conducted sensitivity analyses excluding those with CS or controls with low titer ANA and RF with similar results. Future studies should be longitudinal, re-evaluating patients years later to see if there has been any change in the NA levels or the underlying diagnoses. Investigators could look at whether NA are associated with a particular subset of patients with SjD such as those with interstitial lung disease or renal tubular acidosis. Measuring NA in saliva has potential diagnostic utility and could be further explored with additional testing in more cohorts with SjD, healthy normal controls, and other groups.

In summary, based on the analysis of NA data in this large, well-defined cohort, we conclude that testing for the NA with the present commercial assay is not useful in distinguishing between SjD and non-SjD in the outpatient rheumatology setting. The NA are not likely to be helpful for diagnosing SjD in practice nor useful for inclusion in further classification criteria of SjD for clinical research.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding

author, Dr Johr confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Vivino FB. Diagnosis and evaluation of Sjögren's syndrome. In: Vivino FB, ed. Sjögren's Syndrome: A Clinical Handbook. Elsevier; 2019:21–35.
2. Vitali C, Bombardieri S, Jonsson R, et al; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61(6):554–558. doi:https://doi.org/10.1136/ard.61.6.554
3. Shiboski SC, Shiboski CH, Criswell L, et al; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012;64(4):475–487. doi:https://doi.org/10.1002/acr.21591
4. Shiboski CH, Shiboski SC, Seror R, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol 2017;69(1):35–45. doi:https://doi.org/10.1002/art.39859
5. Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjogren's syndrome. Clin Immunol 2012;145(3):251–255. doi:https://doi.org/10.1016/j.clim.2012.09.013
6. Shen L, Kapsogeorgou EK, Yu M, et al. Evaluation of salivary gland protein 1 antibodies in patients with primary and secondary Sjogren's syndrome. Clin Immunol 2014;155(1):42–46. doi:https://doi.org/10.1016/j.clim.2014.08.009
7. Bunya VY, Massaro-Giordano M, Vivino FB, et al. Prevalence of novel candidate Sjögren syndrome autoantibodies in the Penn Sjögren's International Collaborative Clinical Alliance Cohort. Cornea 2019;38(12):1500–1505. doi:https://doi.org/10.1097/ICO.0000000000002147
8. Bunya VY, Ying GS, Maguire MG, et al; DREAM Study Research Group. Prevalence of novel candidate Sjogren syndrome autoantibodies in the Dry Eye Assessment and Management (DREAM) study. Cornea 2018;37(11):1425–1430. doi:https://doi.org/10.1097/ICO.0000000000001714
9. Matossian C, Micucci J. Characterization of the serological biomarkers associated with Sjögren's syndrome in patients with recalcitrant dry eye disease. Clin Ophthalmol 2016;10:1329–1334. doi:https://doi.org/10.2147/OPTH.S106973
10. Beckman KA. Detection of early markers for Sjögren syndrome in dry eye patients. Cornea 2014;33(12):1262–1264. doi:https://doi.org/10.1097/ICO.0000000000000278
11. Vishwanath S, Everett S, Shen L, et al. Xerophthalmia of Sjogren's syndrome diagnosed with anti-salivary gland protein 1 antibodies. Case Rep Ophthalmol 2014;5(2):186–189. doi:https://doi.org/10.1159/000364941
12. Vishwanath S, Shen L, Suresh L, et al. Anti-salivary gland protein 1 antibodies in two patients with Sjogren's syndrome: two case reports. J Med Case Rep 2014;8(1):145. doi:https://doi.org/10.1186/1752-1947-8-145
13. Everett S, Vishwanath S, Cavero V, et al. Analysis of novel Sjogren's syndrome autoantibodies in patients with dry eyes. BMC Ophthalmol 2017;17(1):20. doi:https://doi.org/10.1186/s12886-017-0412-8
14. Hermann GA, Vivino FB, Shnier D, et al. Diagnostic accuracy of salivary scintigraphic indices in xerostomic populations. Clin Nucl Med 1999;24(3):167–172. doi:https://doi.org/10.1097/00003072-199903000-00006
15. Hermann GA, Vivino FB, Goin JE. Scintigraphic features of chronic sialadenitis and Sjögren's syndrome: a comparison. Nucl Med Commun 1999;20(12):1123–1132. doi:https://doi.org/10.1097/00006231-199912000-00004
16. Kassimos DG, Shirlaw PJ, Choy EH, et al. Chronic sialadenitis in patients with nodal osteoarthritis. Br J Rheumatol 1997;36(12):1312–1317. doi:https://doi.org/10.1093/rheumatology/36.12.1312
17. Xuan J, Wang Y, Xiong Y, et al. Investigation of autoantibodies to SP-1 in Chinese patients with primary Sjögren's syndrome. Clin Immunol 2018;188:58–63. doi:https://doi.org/10.1016/j.clim.2017.12.008
18. Karakus S, Baer AN, Agrawal D, et al. Utility of novel autoantibodies in the diagnosis of Sjögren's syndrome among patients with dry eye. Cornea 2018;37(4):405–411. doi:https://doi.org/10.1097/ICO.0000000000001471
19. Karakus S, Baer AN, Akpek EK. Clinical correlations of novel autoantibodies in patients with dry eye. J Immunol Res 2019;2019:7935451. doi:https://doi.org/10.1155/2019/7935451
20. Jin Y, Li J, Chen J, et al. Tissue-specific autoantibodies improve diagnosis of primary Sjögren's syndrome in the early stage and indicate localized salivary injury. J Immunol Res 2019;2019:3642937. doi:https://doi.org/10.1155/2019/3642937
21. Thatayatikom A, Jun I, Bhattacharyya I, et al. The diagnostic performance of early Sjögren's syndrome autoantibodies in juvenile Sjögren's syndrome: The University of Florida Pediatric Cohort Study. Front Immunol 2021;12:704193. doi:https://doi.org/10.3389/fimmu.2021.704193
22. Theander E, Jonsson R, Sjöström B, et al. Prediction of Sjögren's syndrome years before diagnosis and identification of patients with early onset and severe disease course by autoantibody profiling. Arthritis Rheumatol 2015;67(9):2427–2436. doi:https://doi.org/10.1002/art.39214
23. Du W, Han M, Zhu X, et al. The multiple roles of B cells in the pathogenesis of Sjögren's syndrome. Front Immunol 2021;12:684999. doi:https://doi.org/10.3389/fimmu.2021.684999
24. Le Goff M, Cornec D, Jousse-Joulin S, et al. Comparison of 2002 AECG and 2016 ACR/EULAR classification criteria and added value of salivary gland ultrasonography in a patient cohort with suspected primary Sjögren's syndrome. Arthritis Res Ther 2017;19(1):269. doi:https://doi.org/10.1186/s13075-017-1475-x

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 883–892
DOI 10.1002/acr.70003

American College of Rheumatology
Empowering Rheumatology Professionals

Improving Access to Rheumatology Care: Evaluation of a Rheumatology Electronic Consultation Program

Sarah J. Billups,[1] Brittney R. Fraumeni,[2] Lisa M. Schilling,[2] Alison G. Abraham,[3] Gregory Matesi,[2] Hannah D. Bauguess,[2] and Jason Kolfenbach[2]

Objective. Specialty care access remains a significant challenge, particularly for patients in rural and underserved areas. This study evaluates the implementation and impact of an electronic consultation (eConsult) program aimed at improving access to rheumatology care within the University of Colorado Hospital network.

Methods. This mixed methods evaluation of a rheumatology eConsult program used electronic health record and Medicaid claims data to describe patient, provider, and referral characteristics; care process and utilization outcomes; and interviews to gain provider insights about the program.

Results. The analysis included 10,433 traditional referrals and 670 internal and external eConsults placed between April 2018 and June 2022. Most internal eConsults (445 of 595, 75%) were completed electronically without the need to convert to an in-person consultation, and 73% (325 of 445) were completed within three days. The eConsults that were converted to traditional face-to-face referrals had a higher 180-day completion rate (36%) compared to traditional referrals (19%, $P < 0.001$). Overall, eConsults and traditional referrals had comparable rates of pharmacotherapy initiation for referrals related to suspected rheumatoid arthritis (57.1% vs 31.4%, $P = 0.082$). Most eConsults came from primary care providers internal to the network (596 of 670, 89%). Interviews with team members highlighted successes such as improved efficiency and reduced patient travel burdens, while also identifying challenges, notably the need for increased provider familiarity and usage of the eConsult platform.

Conclusion. Overall, the eConsult program represents a promising strategy to enhance specialty care delivery, particularly for underserved and distant populations, though ongoing education and system integration efforts are crucial for maximizing its impact.

INTRODUCTION

Specialty visits constitute more than half of all outpatient visits in the US.[1] Referral rates to specialty providers doubled between 1999 and 2009, and an estimated 10% of primary care visits during that time frame resulted in consultation or referral to another provider.[2] This increase in demand for specialty services has occurred at a time when the number of specialty providers in many fields has declined across the US, creating significant workforce shortages.[3] Limited access to specialty care, especially for uninsured patients and those on public insurance, such as Medicaid, has become a significant contributor to health inequality in the US. Health care interruption due to limited access to specialty care can result in deterioration of patient outcomes including hospitalization, delays in diagnosis, and delays in therapeutic initiation.[4,5]

For patients in rural and micropolitan (population centers of 10,000–50,000) areas of the country, the shortage of local specialists is especially significant. Studies estimate an average of 30 specialty physicians per 100,000 people in such areas, compared to 263 per 100,000 in urban areas.[6] The field of rheumatology is a nonproceduralist specialty with an uneven distribution of available specialists across geographic regions of the country.[7] This creates disparities in access by necessitating some patients travel between three and seven hours for management of their rheumatologic condition.[4]

Health care insurance barriers also impact specialty care access. Medicaid enrollees in Colorado report waiting 1.4 times

Supported by supplemental funding provided through the Centers for Medicare & Medicaid Services.

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora; [2]University of Colorado School of Medicine, University of Colorado Anschutz Medical Campus, Aurora; [3]Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70003.

Address correspondence via email to Sarah J. Billups, PharmD, at sarah.billups@cuanschutz.edu.

Submitted for publication April 29, 2025; accepted in revised form November 7, 2025.

SIGNIFICANCE & INNOVATIONS

- Most electronic consultations (eConsults) were completed without the need for an in-person follow-up, suggesting that some rheumatology care is appropriate for primary care environments when under the consult of a specialist.
- Rheumatologic care eConsults, particularly with health care providers outside of the academic medical setting, have the potential to reach more underserved and rural populations.

longer than privately insured patients to receive specialty care and are 3 times more likely to not see a specialist due to challenges in identifying providers who accept new Medicaid patients.[8] Additional studies have shown that Medicaid enrollees travel significantly more miles to obtain care compared to individuals with other forms of insurance, with distance to rheumatology care averaging nearly 20 more miles.[9]

The rising demand for rheumatology care has outpaced the supply of rheumatologists,[10] creating a need to develop new ways of extending specialty expertise to local primary care networks. In a traditional model, a primary care provider (PCP) in need of additional guidance on the evaluation or management of a patient has several options. First, if the PCP feels the problem is within the scope of their practice, they may elect to consult the literature or other resources. Second, PCPs can informally discuss the clinical scenario with specialty colleagues, commonly referred to as a "curbside consult." Third, the PCP may choose to place a traditional referral to a specialist. PCPs in rural and micropolitan areas may not have proximity to or relationships with specialty providers that afford informal communications, limiting their specialist access to only traditional consultations. In addition, studies have shown that evaluation and management plans based on curbside consultation are often inferior compared to a formal consult, largely due to inaccurate or incomplete information associated with the curbside consultation.[11] In a traditional in-person evaluation, the specialist may provide treatment and management recommendations back to the PCP or assume responsibility for the management of the patient for the referred condition.[12]

Electronic consultation (eConsult) programs represent a novel way to supplement traditional approaches to health care delivery and may improve access for those in nonurban settings or the underinsured.[1] An eConsult is an asynchronous electronic consult between the PCP and a specialist within a shared electronic platform.[13] This process allows the specialist to quickly provide advice to the PCP regarding evaluation and management. Implementation of eConsult programs have been proposed as an effective way to provide patients with timely access to specialty care, decrease unnecessary transitions between primary and specialty care providers, and prioritize patients with urgent needs.[8,13] Such programs have demonstrated their ability to reduce wait times for rheumatology care.[14,15] eConsult programs may be an effective mechanism to deliver specialty care to medically underserved patients through primary care channels.[16]

To improve access to specialty care, the Peer Mentored Care Collaborative at the University of Colorado School of Medicine (SOM) leveraged the eConsult platform developed with the Association of American Medical Colleges (AAMC) to bring a formal eConsult program to University of Colorado Hospital (UCH) network, using the Epic Electronic Health Record (EHR) system. Later, this program was expanded to allow for eConsults from PCP partners practicing within Federally Qualified Health Centers (FQHCs) in Colorado. The aim of this evaluation was to describe this project's impact on access to rheumatology care, quality, and health care use.

METHODS

Evaluation study design. This evaluation used EHR data and Medicaid claims data to describe patient and provider characteristics, referral characteristics, care process outcomes, and health care use for patients with a new referral for a traditional in-person evaluation or an eConsult to the SOM Rheumatology Clinic. Additionally, semistructured qualitative interviews were conducted with rheumatologists and the director of finance and administration for the Division of Rheumatology to gather insights and opinions regarding perceived facilitators, barriers, and successes of the program.

EHR data were used to identify new referrals to the SOM Rheumatology Clinic between April 1, 2018 and June 30, 2022. This included traditional referrals and eConsults. A new patient referral was defined as a referral with no prior rheumatology encounters or completed eConsults within the prior three years, in accordance with established coding practice.[17] Patients were categorized into two groups according to their initial referral type: traditional referrals or eConsults. The latter group was further separated into "internal referrals" (providers internal to the UCH network) and "external referrals" (providers from partner FQHCs in Colorado, who used a referral platform that was external to the Epic EHR system—AristaMD). Both eConsults and traditional referrals to UCH Rheumatology undergo screening by a rheumatologist. An eConsult could be declined if deemed inappropriate for rheumatology care (condition better addressed by another specialist) or if insufficient data were available to supply a satisfactory response (in which case, additional information was requested). Accepted eConsults were either completed by rheumatology faculty or converted to a traditional referral if the rheumatologist determined appropriate care required a patient visit. In the traditional referral pathway, rheumatology faculty performed triage and divided all referrals into three categories: (a) automatic scheduling for in-person evaluation, (b) needs additional information from referring office, and (c) no in-person

rheumatology evaluation or low suspicion for rheumatic disease. Clinical scenarios deemed medically urgent by the rheumatology faculty member from either pathway were prioritized and scheduled for prompt evaluation.[18]

Patient characteristics and encounter outcomes. EHR data and external referral data were used to describe the patient characteristics and referral characteristics, including diagnosis and referring physician characteristics, stratified by referral type (traditional, internal eConsult, external eConsult). Some patient characteristics (patient age and insurance information) were unavailable for patients referred by external providers. To assess sociodemographic status, patients' five-digit home zip codes from the EHR were linked to the Area Deprivation Index (ADI; version 3.2) published by the Center for Health Disparities Research.[19,20] The ADI is published at the five-digit zip +4 level, so the patient-specific ADI value was obtained by averaging across all five-digit zip +4 ADIs within the patient's five-digit zip code. We used the zipcodeR package available through the Comprehensive R Archive Network (CRAN)[21] to obtain a complete list of Colorado and neighboring state (Arizona, Kansas, Nebraska, New Mexico, Oklahoma, Utah, Wyoming) zip codes and then used the gmapdistance R package, available through Github,[22] to calculate driving distances from each of these zip codes to the SOM Rheumatology Clinic. The gmapdistance package queries Google Maps for driving distances. The exact point within the zip codes that Google uses as a starting point is unknown. We then matched a patient with their driving distance to the clinic using their recorded zip code. Patient zip codes were matched to a Colorado county using the zipcodeR package for classification into urban, rural, or frontier county types.

Referring providers were characterized as either primary care (family medicine, internal medicine, or geriatrics) or by other specialty or subspecialty and by frequency of unique new referrals placed during the observation period. The specialty eConsult process was primarily marketed for PCP use.

The "reason for referral" for both traditional referrals and internal eConsults was identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnostic codes recorded by the referring provider during the encounter in which the referral was placed. This information was not available for external eConsults. Diagnostic codes were grouped into categories based on ICD-10-CM code hierarchies and the condition descriptions associated with the codes at the time of the encounter. The following categories were defined: (1) osteoarthritis (also other arthritis, other cartilage disorders excluding spine), (2) systemic connective tissue disorders (systemic lupus erythematosus [SLE], scleroderma, dermatomyositis/polymyositis, other), (3) rheumatoid arthritis (RA), (4) spondyloarthritis (ankylosing spondylitis, other spinal disorders), (5) crystalline arthritis, (6) psoriatic and other reactive arthritis, (7) dermatologic conditions (urticaria, Stevens–Johnson Syndrome, erythema multiforme, purpura, cutaneous scleroderma), (8) Raynaud and vascular disorders, and (9) other conditions (autoimmune hepatitis, autoinflammatory syndromes, disorders of bone density and structure, disorders of synovium and tendon, dry eyes and mouth, and Ehlers-Danlos, Marfans and other heritable connective tissue disorders). If none of the above diagnoses were identified, the consult was categorized according to symptoms or signs that may be related to a rheumatologic disorder as follows: (1) positive antinuclear antibody (ANA) or erythrocyte sedimentation rate with arthralgia-myalgia, (2) myalgia, pain, and swelling, (3) malaise, fatigue, and weakness, and (4) chronic pain.

To assess the impact of the eConsult program on access to rheumatology care, referral completion rate and time between referral order and completion were compared between eConsults and traditional referrals. For traditional referrals and converted eConsults, completion date was the date the patient was seen by the SOM Rheumatology department, limited to visits occurring within 180 days of the referral order date. For eConsults, completion date was the date the SOM rheumatologist completed the eConsult. In both cases, time to completion represents the time elapsed before a SOM rheumatologist provided service or medical advice.

Prescription orders for initiation of a new disease-modifying antirheumatic drug (DMARD) were assessed among internal referral patients with a diagnosis of RA within 60 days of a completed SOM Rheumatology consultation, as defined in the previous paragraph. Patients' hospital and emergency department (ED) use for a rheumatology-related condition within 60 days of referral were measured for the subset of patients with Medicaid insurance due to the availability of claims data for this population.

Interviews with eConsult team members. To gather insight into the development and growth of the eConsult program, including notable successes and challenges, semistructured interviews were conducted with six eConsult team members (five rheumatologists and the director of finance and administration for the Division of Rheumatology). Interview questions focused on the health care delivery issues that eConsults address, perceived impact on the patient population served, impact on rheumatology access, and areas for program improvement. Interviews were held over Zoom, and audio recordings were generated from each interview.

Quantitative analysis methods. Descriptive analysis compared traditional referrals to eConsults across the factors described previously, including patient demographics, referring provider characteristics, time to referral completion, DMARD initiation in the subset of patients with a diagnosis of RA, and hospital and ED usage. Categorical variables were compared using a chi-square or Fisher's exact test, and continuous variables were

compared using an independent *t*-test or the Kruskal–Wallis test where appropriate. The unit of analysis was a unique new patient referral (either electronic or traditional) to SOM Rheumatology. Individual patients potentially contributed more than one encounter if referrals were separated by at least three years with no intervening rheumatology encounters. No adjustment was made for repeated patient measures as this occurrence was rare and repeat referrals likely represented new patient problems that were independent of the original referral with patient outcomes of interest unlikely to be highly correlated.

Qualitative analysis. Thematic analysis was used to summarize the semistructured interviews conducted with eConsult team members. Audio from the interviews was transcribed using the artificial intelligence software, Trint. The transcriptions were then analyzed together using rapid qualitative analysis, with quotes grouped into themes of project successes and challenges/areas for improvement.

Ethics. This evaluation was submitted to and approved by the Colorado Multiple Institutional Review Board as nonhuman subjects' review.

RESULTS

Characterization of referrals. Between April 1, 2018 and June 30, 2022, 10,433 traditional referrals and 670 eConsults were placed for rheumatology consultation. Of the 670 eConsults, 595 (88%) were from providers internal to the UCH network, and 150 of 595 (25%) were converted to traditional consultations by the rheumatologist. Eighteen patients contributed two referrals to the analysis. Patient characteristics differed between recipients of eConsult and recipients of traditional rheumatology referrals (Table 1). The racial distribution in the eConsult group was statistically different from patients in the traditional referrals group ($P < 0.001$), as was the distribution of the patients' primary language ($P < 0.001$). Patients in the eConsult group were more likely to live in urban counties and live closer to the SOM Rheumatology Clinic than traditional referrals (median 12.3 miles for all eConsults vs 34.1 miles for traditional referrals, $P < 0.001$) and had a lower ADI score compared to the group with traditional referrals (mean ADI = 5.2 vs 5.7, respectively, $P < 0.001$) (Table 1). Of potential importance, the 75 recipients of external eConsults, which made up 11% of the total eConsult group, lived a median of 42.0 miles from the rheumatology clinic and had a higher mean ADI score of 6.8. Figure 1 shows the geographic spread of internal and external eConsults,

Table 1. Characteristics of patients receiving traditional referrals and eConsults from April 1, 2018 to June 30, 2022*

	eConsults			Traditional referrals	*P* value[a]
	Internal n = 595	External n = 75	All n = 670	n = 10,433	
Age, mean (SD)	50.8 (17.7)	–	–	47.9 (16.3)	<0.001[b]
Male sex, n (%)	176 (29.6)	19 (25.3)	195 (29.1)	2,793 (26.8)	0.204[c]
Race, n (%)					<0.001[c]
White	426 (71.4)	25 (33.3)	451 (67.3)	7,136 (68.4)	
Black/African American	67 (11.3)	2 (2.7)	69 (10.3)	627 (6.0)	
Other/more than one race	101 (17.0)	20 (26.7)	121 (18.1)	1,851 (17.7)	
Missing	1 (0.2)	28 (37.3)	29 (4.3)	819 (7.9)	
Hispanic ethnicity, n (%)	78 (13.1)	23 (30.7)	101 (15.1)	1,469 (14.1)	0.474[c]
Primary language, n (%)					<0.001[c]
English	562 (94.5)	28 (37.3)	590 (88.1)	9,109 (87.3)	
Spanish	20 (3.4)	17 (22.7)	37 (5.5)	261 (2.5)	
Other	11 (1.8)	0 (0)	11 (1.6)	183 (1.8)	
Missing	2 (0.3)	30 (40.0)	32 (4.8)	880 (8.4)	
Medicaid insurance, n (%)	80 (13.4)	–	–	2,704 (25.9)	<0.001[c]
County designation, n (%)					<0.001[d]
Urban	586 (98.5)	28 (37.3)	614 (91.6)	8,417 (80.7)	
Rural	3 (0.5)	4 (5.3)	7 (1.0)	1,097 (10.5)	
Frontier	0 (0)	0 (0)	0 (0)	310 (3.0)	
Out of state or missing zip code	6 (1.0)	43 (57.3)	49 (7.3)	609 (5.8)	
Driving distance to clinic, median (IQR), miles	12.3 (6.8, 21.7)	42.0 (20.8, 71.7)	12.3 (6.8, 21.8)	34.1 (14.3, 84.7)	<0.001[e]
Outside of 8-state area or missing zip code, n (%)	4 (0.7)	43 (57.3)	47 (7.0)	223 (2.1)	
ADI, mean (SD)	5.1 (2.0)	6.8 (1.9)	5.2 (2.0)	5.7 (2.3)	<0.001[b]
Out of state or missing zip code or ADI value, n (%)	7 (1.2)	43 (57.3)	50 (7.5)	603 (5.8)	

* ADI, Area Deprivation Index; eConsult, electronic consultation; IQR, interquartile range.
[a] Comparison between all eConsults and traditional referrals unless otherwise noted.
[b] Comparison between internal eConsults and traditional referrals.
[c] Chi-square test.
[d] Fisher's exact test.
[e] Kruskal–Wallis rank sum test.

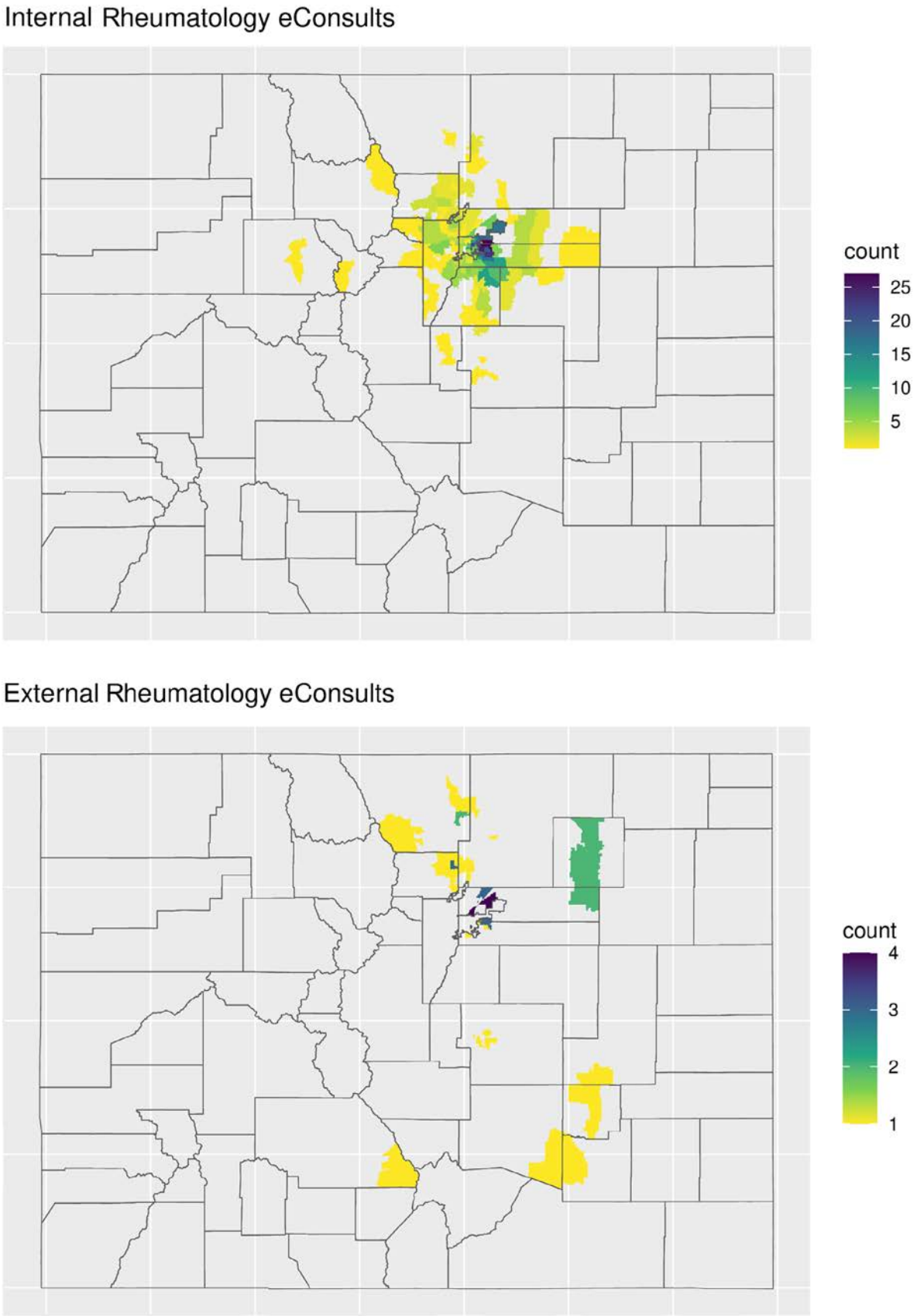

Figure 1. Geographic distribution of Colorado zip codes for patients receiving internal or external eConsults to rheumatology. eConsult, electronic consultation.

Table 2. Characteristics of internal electronic versus traditional referrals*

	Internal eConsults				
	Completed as eConsult (n = 445)	Converted to traditional (n = 150)	All eConsults (n = 595)	Traditional referrals (n = 10,433)	*P* value[a]
Osteoarthritis	153 (34.4)	64 (42.7)	217 (36.5)	2,910 (28.0)	<0.001[b]
Connective tissue disorders (eg, lupus)	27 (6.1)	5 (3.3)	32 (5.4)	1,393 (13.4)	<0.001[b]
Rheumatoid arthritis	11 (2.5)	7 (4.7)	18 (3.0)	1,360 (13.0)	<0.001[b]
Other conditions	49 (11.0)	17 (11.3)	66 (11.1)	–	
Spondylopathies	28 (6.3)	12 (8.0)	40 (6.7)	581 (5.6)	0.273[b]
Crystalline arthritis	42 (9.4)	9 (6.0)	51 (8.6)	365 (3.5)	<0.001[b]
Psoriatic arthritis	6 (1.4)	8 (5.3)	14 (2.4)	350 (3.4)	0.225[b]
Dermatologic conditions	17 (3.8)	2 (1.3)	19 (3.2)	244 (2.3)	0.184[b]
Raynaud	13 (2.9)	1 (0.6)	14 (2.3)	326 (3.1)	0.349[b]
None of the above diagnoses but possible rheumatologic-related signs or symptoms					
Positive ANA results	67 (15.1)	25 (16.7)	92 (15.5)	1,011 (9.7)	<0.001[b]
Myalgia, pain, swelling	35 (7.9)	9 (6.0)	44 (7.4)	821 (7.9)	0.676[b]
Malaise, fatigue, weakness	11 (2.5)	3 (2.0)	14 (2.4)	133 (1.3)	0.026[b]
Chronic pain	1 (0.2)	1 (0.7)	2 (0.3)	74 (0.7)	0.441[c]
None of the above diagnoses or symptoms	49 (11.0)	10 (6.7)	59 (9.9)	1,172 (11.2)	0.318[b]

* Values are the number (%) unless indicated otherwise. ANA, antinuclear antibody; eConsult, electronic consultation.
[a] Comparison between all eConsults and traditional referrals; diagnosis categories are not mutually exclusive.
[b] Chi-square test.
[c] Fisher's exact test.

demonstrating the extended reach outside the Denver metro area by the external eConsult group. Zip code data, and therefore associated county designation and ADI score information, were missing for 43 of 75 (57.3%) of these individuals in the external eConsult group, however, limiting full interpretation of results.

The most common reason for referral for both eConsults and traditional referrals was osteoarthritis, but the relative frequency was higher for eConsults (36.5%) than traditional referrals (28.0%, $P < 0.001$) (Table 2). The next most common reasons for eConsults were positive ANA results (15.1%) and crystalline arthritis (9.4%). SLE and RA were more common referral reasons for traditional referrals (13.4% and 13.0% respectively), compared to eConsults (5.4% and 3.0%, respectively, $P < 0.001$ for both categories).

Characterization of referring providers. A total of 4,176 unique providers placed a traditional referral, and 183 placed an internal eConsult during the observation period (Table 3). Most providers using traditional referrals placed only one (59.4%), whereas most providers placing eConsults placed more than one during the observation period, with 29.5% placing two to three and 33.3% placing four or more.

Access. All completed eConsults were returned to the referring PCP within 30 days, with 73% returned within 3 days

Table 3. Referring provider characteristics*

	Providers placing internal eConsult referrals (n = 183)	Providers placing traditional referrals (n = 4,176)	*P* value
Provider specialty, n (%)			<0.001[a]
Family medicine	91 (49.7)	1,154 (27.6)	
Medicine specialty	4 (2.2)	580 (13.9)	
Internal medicine/geriatrics	72 (39.3)	505 (12.1)	
Other specialty	16 (8.6)	866 (20.9)	
Unknown	2 (1.1)	1,071 (25.6)	
Number of referrals placed by individual providers during the observation period, n (%)			<0.001[a]
One	68 (37.2)	2,482 (59.4)	
Two or three	54 (29.5)	1,113 (26.7)	
Four or more	61 (33.3)	581 (13.9)	

* eConsult, electronic consultation.
[a] Chi-square test.

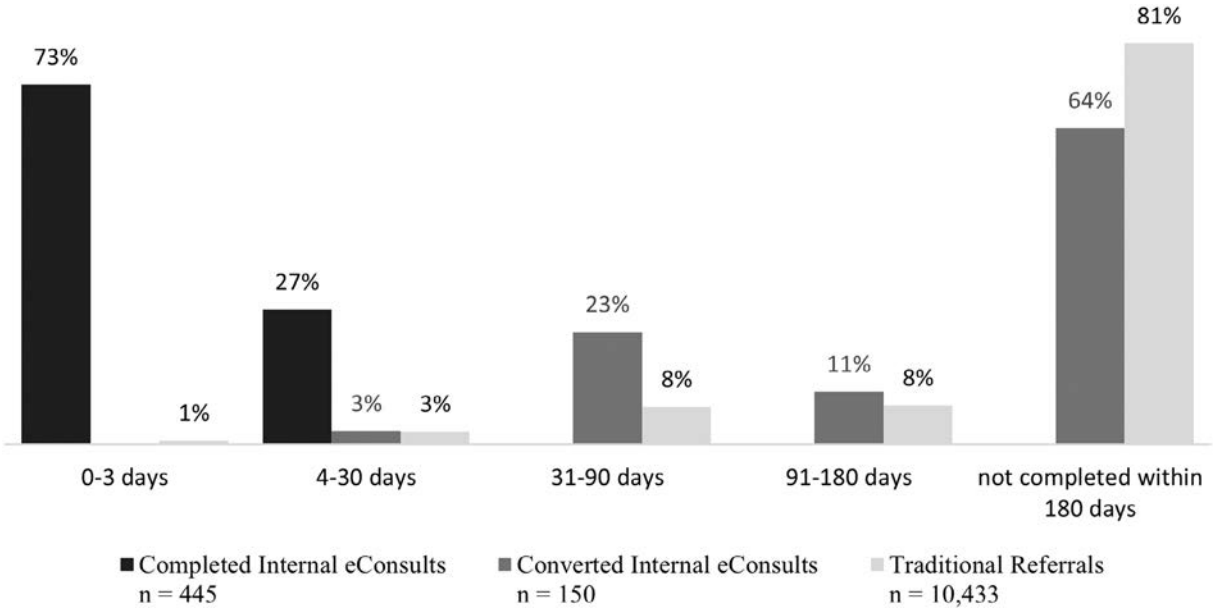

Figure 2. Number of days to completion for traditional referrals and internal eConsults. eConsult, electronic consultation.

(Figure 2). eConsults that were converted to a traditional referral were completed within 90 or 180 days at a higher rate (26% and 36%, respectively) compared to the traditional referral pathway (11% completed within 90 days and 20% within 180 days, $P < 0.001$ for both comparisons).

Quality. Of the 18 eConsults placed for patients with an associated diagnosis of RA, 7 were converted to a traditional consultation and 11 were retained as an eConsult (Table 2). Of these 11 completed eConsults, 8 (72.7%) resulted in a new order for DMARD therapy within 30 days of consultation completion. Of traditional referrals, 421 of those completed within 180 days of referral placement were associated with RA diagnosis, and 132 of these (31.4%) resulted in a new order for DMARD therapy.

Health care use. Emergency and hospital admissions for a rheumatology-related condition occurring within 60 days of the referral placement were examined among the Medicaid population, which included 80 individuals with internal eConsults and 2,704 with traditional referrals (Table 4). A total of 8 eConsult recipients (10%) and 455 traditional referral recipients (16.8%) used the ED within this time frame ($P = 0.143$), and 4 (5.0%) and 151 (5.6%), respectively, had at least one hospitalization ($P = 1.00$).

Perceived project successes and challenges. All project team members felt that the rheumatology eConsult program was a successful method for improving access to specialty care. The rheumatologists identified the following benefits: reduced time to care, costs savings for patients (transportation costs, missed time at work for clinic visit) and for the health care system (reduced third-payor expense for reimbursement of eConsult vs a traditional in-person encounter), and reduced travel burden for patients by redirecting care through the PCP when appropriate. In comparison to traditional referrals, visits for patients with converted eConsults were deemed more efficient due to advanced knowledge by the rheumatology team of the evaluation completed to date and a higher index of suspicion for rheumatic disease. Another commonly discussed benefit was perceived improvement in time to care. Rheumatologists shared that they

Table 4. Emergency visits or hospital admissions (for rheumatologic indications) within 60 days of referral (Medicaid-insured patients)*

	Internal eConsults (n = 80)	Traditional referrals (n = 2,704)	*P* value
At least one emergency department visit	8 (10.0)	455 (16.8)	0.143[a]
More than one emergency department visit	1 (1.3)	93 (3.4)	0.523[b]
At least one hospital admission	4 (5.0)	151 (5.6)	>0.999[b]
More than one hospital admission	1 (1.3)	33 (1.2)	>0.999[b]

* Values are the number (%) unless indicated otherwise. eConsult, electronic consultation.
[a] Chi-square test.
[b] Fisher's exact test.

had seen the wait time for in-person evaluation decrease since offering eConsults, with one provider sharing, "It frees up our ability to get people in the clinic faster."

Although all the rheumatology team members stated they felt eConsults were working well, one common suggestion for improvement was increasing usage of eConsults by PCPs. Rheumatologists felt that PCPs were not familiar enough with the eConsult system, hindering usage. They believed continued education and messaging around eConsults were necessary to increase eConsult usage by PCPs.

DISCUSSION

In this study, eConsults resulted in more timely provision of specialty care or advice to patients compared to traditional referrals. eConsults that were converted to a traditional face-to-face encounter were completed at a higher rate and in a shorter time frame compared to those initiated as a traditional referral. Although several factors may be associated with the difference in time to completion, perhaps most pertinent is the referral triage process for traditional referrals at SOM Rheumatology. Previous data from our group demonstrated that 30% of referrals were considered very low suspicion for an autoimmune or inflammatory condition and hence not offered an in-person visit.[18] We did not have access to screening data from the physician review team for this analysis. As such, results pertaining to the percentage of referrals scheduled within 90 and 180 days in the traditional pathway are taken from the entire cohort of referrals to rheumatology and not the subset deemed most appropriate for scheduling after physician review. Thus, the low completion rate in the traditional pathway (11% and 20% at 90 and 180 days, respectively) was likely impacted by the review process itself. Nonetheless, our findings regarding the timeliness of eConsults as well as subsequent conversions to in-person care are consistent with outcomes reported in other studies of eConsult programs.

The rheumatologists in our study attributed the timeliness of completed visits within the eConsult pathway in part to the ability to gain advanced knowledge of the patient's condition ahead of the visit, making the care process more efficient. Furthermore, eConsults that were not deemed to require an in-person evaluation were addressed far more rapidly than a traditional referral, with PCPs receiving actionable recommendations within three days of consultation placement in 75% of cases. eConsult programs also have the potential to improve access to specialty care in medically underserved communities far from urban areas, where physician specialty practices are typically located.[13] In our evaluation, the majority of eConsults were submitted by internal providers sharing the same EHR platform and a similar geographic location. External eConsult recipients, in contrast, lived significantly farther away from the rheumatology practice (median 42.0 miles) than either internal eConsult (12.3 miles) or traditional eConsult recipients (34.1 miles), had a higher ADI score, and comprised a higher proportion of Spanish-speaking individuals. Unfortunately, the number of external consultations in our study was low, limiting our investigations on the impact of the eConsult program in rural and underserved populations.

The eConsult program through SOM Rheumatology was initiated with the help of the AAMC Project Coordinating Optimal Referral Experiences (CORE).[23] This project began as a collaboration between specialists and PCPs within the University of Colorado system and later became available to select FQHC facilities. The rheumatologists involved in the eConsult program suggested that broader advertising and education regarding the program to FQHC facilities in rural and underserved areas may increase use of the tool, which in the future, should allow for a more thorough evaluation of the effect of eConsults on specialty access in rural settings. Statewide efforts to increase the use of eConsult services are underway as well. In February 2024, the Colorado Department of Health Care Policy and Financing launched a statewide Medicaid electronic consultation platform, which aims to improve health care equity, access, and outcomes for Medicaid patients.[24]

eConsults provide a unique opportunity to address the growing volume of specialty referrals to rheumatology. Thoughtfully designed eConsult programs can reduce the need for in-person specialty evaluation (hence preserving access for patients requiring a face-to-face encounter) by empowering PCPs with the tools to evaluate and manage patients. This study provides data regarding the feasibility and safety of a rheumatology eConsult program in a large academic medical center. The three most common diagnoses associated with the nearly 600 eConsults described in this study were for osteoarthritis, crystalline arthritis, and positive ANA results. These are conditions that many PCPs are familiar with and are often comfortable managing, especially if guidance is available through an eConsult. Each of these conditions were more common in eConsults compared to traditional referrals in our study. It is important to highlight, however, that these conditions represented over 40% of the more than 10,000 requests for in-person evaluation received by our institution during this study. This demand for rheumatologic expertise far exceeds the supply of rheumatologists in our practice and is reflective of national trends described by the American College of Rheumatology Workforce Study Group in 2015, in which the demand for rheumatologic services was expected to double by the year 2030.[10] As our study suggests, eConsults may represent a tool in which noninflammatory conditions can be efficiently addressed outside of the rheumatology clinic, enhancing access for patients with inflammatory disease.

In our study, referrals for autoimmune conditions, such as lupus and RA, were less in the eConsult pathway compared to traditional referrals, which may reflect primary care preference for management of these conditions directly by a rheumatologist. In cases in which eConsults on management of autoimmune conditions were placed, it commonly arose due to barriers to an in-

person visit. Nonetheless, among the 11 completed eConsults for a diagnosis of RA, 8 (72.7%) were started on a DMARD, indicating the impact of eConsults even in medically complex scenarios.

eConsult programs have increased since the COVID-19 pandemic. Prior analysis of our data (unpublished) suggests that eConsults require an average of 10 to 12 minutes for completion. In contrast, traditional face-to-face new-patient encounters are often significantly longer, often taking 40 to 60 minutes at SOM Rheumatology. This suggests that eConsults may provide a way to preserve access in our clinics by serving a larger number of patients in a shorter timeframe. Synchronous video visits avoid transportation time and costs on an *individual patient level* and, as such, may represent a tool to enhance access to vulnerable patient populations. At the same time, such visits are commonly allotted the same amount of time as traditional face-to-face encounters, meaning their ability to impact the overall demand for rheumatologic services from a *population perspective* may not be as significant as eConsults. Finally, our experience suggests that eConsult programs may also be financially viable for rheumatology practices under increasing scrutiny for efficiency and productivity. Although reimbursement for clinical services varies according to insurance payor, eConsults are often assigned 0.7 work relative value units (wRVUs), whereas a new-patient complex encounter yields 3.5 wRVUs. At SOM Rheumatology, completing five eConsults in one hour would roughly equate to the same wRVU production as seeing one new patient in clinic. Perhaps equally important is the improved access for in-patient visits created by this alternative form of care delivery. If 2 hours are spent weekly completing 12 eConsults and the alternative option was to see each of these 12 patients during a 1-hour new patient visit, 10 additional hours are "created" to provide access for patients with complex autoimmune conditions.

One limitation of this study was the missing data elements for recipients of external eConsult referrals (with less consistent access to information such as patient age, insurance status, ICD and area codes, and ADI score information, due to the lack of a shared EHR). This, alongside the nonrandomized design, confounded direct comparison between eConsult referral groups. Nonetheless, the unique characteristics identified for the external referral group suggest that this modality reached a population that may lack access to traditional referrals. In addition, the percentage of completed visits within the traditional pathway should be interpreted in the context of the referral triage system. Finally, this analysis was conducted within the context of quality improvement and program evaluation; thus, the results may not be generalizable outside of this setting.

The rheumatology eConsult program described in this study successfully delivered rheumatology specialty care to patients in urban and resource-limited settings, with PCPs receiving actionable recommendations within 72 hours in the vast majority of cases. Nonautoimmune conditions represented 60% of eConsults in our study, highlighting the potential utility of an eConsult program in addressing the growing volume of specialty referrals. Extension of eConsult platforms to rural and underserved communities has the potential to reach additional vulnerable populations, and focused education to primary care networks may improve use of this tool. Rheumatology team members expressed satisfaction with the program, but obtaining additional perspectives from patients and referring providers would be beneficial in future evaluations.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Billups confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Mehrotra A, Forrest CB, Lin CY. Dropping the baton: specialty referrals in the United States. Milbank Q 2011;89(1):39–68.
2. Barnett ML, Song Z, Landon BE. Trends in physician referrals in the United States, 1999-2009. Arch Intern Med 2012;172(2):163–170.
3. GlobalData Plc. The Complexities of Physician Supply and Demand: Projections From 2021 to 2036. Washington, DC: AAMC; 2024. Accessed February 2, 2026. https://www.aamc.org/media/75236/download
4. Miloslavsky EM, Bolster MB. Addressing the rheumatology workforce shortage: a multifaceted approach. Semin Arthritis Rheum 2020;50(4):791–796.
5. Liddy C, Afkham A, Drosinis P, et al. Impact of and satisfaction with a new eConsult service: a mixed methods study of primary care providers. J Am Board Fam Med 2015;28(3):394–403.
6. About Rural Health Care. National Rural Health Association. Accessed February 2, 2026. https://www.ruralhealth.us/about-us/about-rural-health-care
7. FitzGerald JD, Battistone M, Brown CR Jr, et al; American College of Rheumatology Committee on Rheumatology Training and Workforce Issues. Regional distribution of adult rheumatologists. Arthritis Rheum 2013;65(12):3017–3025.
8. Caldwell A. Colorado's Unmet Demand for Specialty Care. Colorado Health Institute. Updated June 5, 2023. Accessed January 3, 2024. https://www.coloradohealthinstitute.org/research/colorados-unmet-demand-specialty-care
9. Pryor KP, Barbhaiya M, Costenbader KH, et al. Disparities in lupus and lupus nephritis care and outcomes among US Medicaid beneficiaries. Rheum Dis Clin North Am 2021;47(1):41–53.
10. Battafarano DF, Ditmyer M, Bolster MB, et al. 2015 American College of Rheumatology Workforce Study: supply and demand projections of adult rheumatology workforce, 2015-2030. Arthritis Care Res (Hoboken) 2018;70(4):617–626.
11. Burden M, Sarcone E, Keniston A, et al. Prospective comparison of curbside versus formal consultations. J Hosp Med 2013;8(1):31–35.
12. Gandhi T. Improve the Referral Process, Improve Safety. Institute for Healthcare Improvement. Published December 19, 2017. Accessed

February 2, 2026. https://www.ihi.org/library/blog/improve-referral-process-improve-safety

13. Bergman J, Neuhausen K, Chamie K, et al. Building a medical neighborhood in the safety net: an innovative technology improves hematuria workups. Urology 2013;82(6):1277–1282.
14. Anderson D, Porto A, Angelocci T, et al. The impact of eConsults on access to specialty care for the uninsured in rural Texas. J Health Care Poor Underserved 2022;33(2):779–789.
15. 15. Patel V, Stewart D, Horstman MJ. E-consults: an effective way to decrease clinic wait times in rheumatology. BMC Rheumatol 2020;4(1):54.
16. Bifulco L, Guidotti O, Velez I, et al. Impact of eConsults on clinical care in primary care: a cross-sectional analysis of primary care provider behavior. J Prim Care Community Health 2023;14:21501319231202201.
17. AMA releases the CPT 2024 code set. American Medical Association. Published September 8, 2025. Accessed February 2, 2026. https://www.ama-assn.org/press-center/ama-press-releases/ama-releases-cpt-2024-code-set
18. West SG, Pearson DW, Striebich CC, et al. The effect of pre-appointment consultation triage on patient selection and revenue generation in a university rheumatology practice. Arthritis Care Res (Hoboken) 2019;71(5):689–693.
19. Kind AJH, Buckingham, WR. Making neighborhood-disadvantage metrics accessible — The Neighborhood Atlas. N Engl J Med. 2018; 378(26):2456–2458.
20. Neighborhood Atlas. Mapping. Accessed April 9, 2024. https://www.neighborhoodatlas.medicine.wisc.edu/mapping
21. Rozzi G. zipcodeR: Data & Functions for Working with US ZIP Codes. Comprehensive R Archive Network. Published online October 3, 2022. Accessed April 9, 2024. https://cran.r-project.org/web/packages/zipcodeR/index.html
22. Azuero R. rodazuero/gmapsdistance. Github. Published online October 24, 2023. Accessed April 9, 2024. https://github.com/rodazuero/gmapsdistance
23. Project CORE®: Coordinating Optimal Referral Experiences. AAMC. Accessed September 5, 2025. https://www.aamc.org/about-us/mission-areas/health-care/project-core
24. eConsult Platform. Colorado Department of Health Care Policy and Financing. Accessed January 21, 2025. https://hcpf.colorado.gov/eConsult-Platform

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 893–898
DOI 10.1002/acr.70002

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Experiential Learning for Developing Telehealth and Shared Decision-Making Skills during Rheumatology Fellowship

Alberto Sobrero,[1] Grace A. McMahon,[1] Amanda S. Alexander,[2] Caleb Bolden,[1] Marcy B. Bolster,[1] Lisa Criscione-Scheiber,[3] Faye N. Hant,[4] Rumey C. Ishizawar,[5] Jason Kolfenbach,[6] David Leverenz,[3] Amaad Rana,[7] Rachel M. Wolfe,[8] and Lisa Zickuhr[9]

Objective. Telehealth and shared decision-making (SDM) enhance the care of people with rheumatic diseases. Responding to calls for training on telehealth and SDM, we developed an educational intervention for rheumatology fellows-in-training (FITs).

Methods. FITs conducted two patient care telehealth encounters (pre- and post-intervention). Following the first encounter, FITs completed an online module highlighting the nuances of SDM during telehealth and a simulated patient encounter to practice telehealth skills, especially SDM. After each observation, FITs received feedback on their "webside" manner, SDM, and visit coordination skills via feedback forms (FF). Wilcoxon-signed rank tests compared quantitative FF measures, whereas qualitative methods analyzed written comments. FITs completed a survey and self-reported their confidence in SDM during telehealth visits.

Results. A total of 9 and 11 FITs completed pre- and post-intervention encounters, respectively; 47 FITs completed the simulation. Total points earned on the FF and points specific to the visit coordination subsection of the FF significantly increased from pre- to post-intervention ($P = 0.011$ and $P = 0.049$, respectively). "Webside" manner scores improved without reaching statistical significance ($P = 0.067$). SDM scores remained unchanged, whereas confidence conducting SDM during telehealth improved significantly ($P < 0.001$). Qualitative analysis highlighted the apt use of technology as a skill FITs could further develop for enhancing SDM during telehealth.

Conclusion. Education dedicated to telehealth skills with an emphasis on SDM improves FITs' confidence in practicing SDM during telehealth and advances general telehealth skills implemented during patient care. Our materials and approach to instruction prepare FITs for delivering telehealth care and enriching patient-centeredness as new entrants into the rheumatology workforce.

INTRODUCTION

Telehealth is an essential method of care delivery that remains prevalent following the COVID-19 pandemic.[1] Telehealth expands access to care for people with rheumatic diseases and supports shared decision-making (SDM), the process through which patients and providers create care plans aligned with patients' preferences to enhance outcomes.[2]

The Rheumatology Core Curriculum lists telehealth as a requisite of fellowship training, and educators have designed materials to teach telehealth skills to rheumatology fellows-in-training (FITs) in preparation for entering the workforce.[3,4] Nonetheless, FITs report low confidence in their telehealth competence.[4,5] Furthermore, successful SDM during telehealth requires applying multiple nuanced skills simultaneously. Patients and providers recommend dedicated training in this domain, yet no published curricular materials focus on SDM during

Supported by the Rheumatology Research Foundation Clinician Scholar Educator Award (18652465).

[1]Massachusetts General Hospital, Boston; [2]University of Alabama at Birmingham Marnix E. Heersink School of Medicine, Birmingham; [3]Duke University School of Medicine, Durham, North Carolina; [4]Medical University of South Carolina, Charleston; [5]University of North Carolina School of Medicine, Chapel Hill; [6]University of Colorado Anschutz School of Medicine, Aurora; [7]Yale School of Medicine, New Haven, Connecticut; [8]Wake Forrest University School of Medicine, Winston-Salem, North Carolina; [9]Washington University in St. Louis School of Medicine, St. Louis, Missouri.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70002).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70002.

Address correspondence via email to Lisa Zickuhr, MD, MHPE, at zickuhrl@wustl.edu.

Submitted for publication May 18, 2025; accepted in revised form November 5, 2025.

SIGNIFICANCE & INNOVATIONS

- Optimizing the components of telehealth visits and shared decision-making (SDM) during telehealth enhance the care and outcomes of people with rheumatic diseases.
- Rheumatology fellows-in-training (FITs) must develop skills related to telehealth and SDM during telehealth to uphold access to patient-centered care after entering the rheumatology workforce.
- We created an educational intervention comprised of a module, a simulated telehealth encounter featuring SDM, and a structured feedback form that increased FITs' confidence conducting SDM during telehealth and enhanced overall telehealth performance. When integrated into a series of observed patient care telehealth encounters, the educational intervention enhanced the telehealth skills FITs applied to patient care.
- These educational materials may be used by training programs to supplement their existing curricula and enhance trainee skills in the delivery of telehealth and SDM.

telehealth.[6] Combined, these factors identify the need for additional telehealth instruction with an emphasis on SDM.

In this study, we applied experiential learning theory to address these educational needs. Experiential learning theory states that skills are developed and refined through iterative cycles of learning, reflection, and experimentation.[7,8] We designed, implemented, and evaluated a series of educational interventions comprised of patient care experiences, independent learning with guided reflection, simulated encounters, and feedback for FITs. Our primary aim sought to improve FITs' confidence sharing decisions during telehealth, and our secondary aim focused on enhancing FITs' skills in delivering general telehealth care, including SDM, during patient encounters.

METHODS

FITs from rheumatology programs at Duke University, Massachusetts General Hospital, Medical University of South Carolina, University of Alabama at Birmingham, University of Colorado, University of North Carolina, Wake Forest University, and Washington University in St. Louis (WUSM) were invited to participate if they engaged in their program's annual rheumatology objective structured clinical examination (ROSCE) and/or delivered telehealth care to people with rheumatic diseases. Program directors (ASA, MBB, JK, DL, AR, LZ) recruited and consented FITs for participation, emphasizing that data would be deidentified and would not contribute to their standing in the training program. Patients granted permission for FITs to be observed during their telehealth encounters. Methods complied with the Declaration of Helsinki, as approved by the WUSM Institutional Review Board (#202310110).

Rheumatology faculty with clinical and scholarly expertise in rheumatology telehealth (ASA, JK, DL, AR, LZ) observed FITs conduct telehealth encounters, scoring their skills against the Rheumatology Telehealth Feedback Form (RTFF) and delivering feedback on this "pre-intervention encounter."[9] The RTFF is used to observe and provide formative feedback on telehealth skills. It includes numeric scores, areas for written comments, and "not applicable" options for skills integral to telehealth, including "webside" manner, history-taking, virtual physical examination, SDM, and care coordination, with overall performance reflecting FITs' general telehealth skill level. We selected the RTFF because its design optimized validity, incorporating content expertise, including instructions for response process validity, and demonstrating moderate-to-strong internal structure validity.[9]

Participants then completed an online module about techniques for successful SDM during telehealth, including explaining the general steps of SDM, identifying patient scenarios in which telehealth will benefit SDM, describing health systems that support SDM during telehealth, and demonstrating facile use of communication skills and tools within telehealth platforms that promote SDM (https://rheumatology.wustl.edu/fellowship-program/courses/). To meet these objectives, the module presented two lessons titled "Shared Decision-Making During Telehealth" and "How to Optimize Shared Decision-Making in the Virtual Setting." A third segment, "Putting Things Together," featured a recorded telehealth encounter followed by a guided reflection of areas of excellence and areas for improvement. A key provided answers. Researchers (AS, LZ) made modifications to enhance the clarity of wording after educators reviewed and provided feedback on the module.

FITs then completed a simulated telehealth encounter during their ROSCE in January or February 2024 that featured a person with ankylosing spondylitis who wished to stop treatment (Supplement 1). We selected ankylosing spondylitis for the station because published ROSCE materials focus on rheumatoid arthritis, and we sought to incorporate content underrepresented in previous educational initiatives.[4] The station prompted FITs to practice general and SDM telehealth skills while patient actors (AS, GAM, CB) and faculty (LCS, LZ) scored the encounter against a modified version of the RTFF (Supplement 2). To allow enough time for SDM discussions, FITs were provided physical examination findings in advance, and virtual physical examination skills were not assessed. Patient actors and faculty attended training sessions to standardize patient portrayal and the feedback delivered to FITs. After the ROSCE, FITs completed a survey, retrospectively reporting their confidence practicing SDM during telehealth before and after completing the online module and simulated encounter on a four-point Likert scale (1 = not confident; 4 = very confident), as well as sharing their opinions on the instructional materials. Wilcoxon-signed rank tests compared survey responses.

Following the ROSCE, researchers (ASA, JK, DL, AR, LZ) observed and scored FITs conducting a second, "post-intervention" telehealth encounter. Participants received feedback on their telehealth skills via the RTFF. Patient telehealth encounters were selected for pre- and post-observations based on ease of scheduling without screening for scenarios that emphasized SDM.

We calculated the percentage of points earned on the RTFF at the pre-intervention, ROSCE, and post-intervention stages. Percentages standardized the number of possible points because encounters variably included "not applicable" observations on the RTFF. When comparing pre- and post-intervention scores to ROSCE scores, we excluded physical examination points because the ROSCE did not assess virtual physical examination skills. Mann-Whitney U and Kruskal-Wallis tests analyzed changes in RTFF scores. Spaghetti plots depicted changes in scores across time points for FITs with at least two RTFF scores.

Researchers collected written comments on the RTFFs from all three time points and identified themes using qualitative content analysis and Dedoose software (SocioCultural Research Consultants, LLC, Los Angeles, CA).[10] Two researchers (AS and GAM) created a list of codes, each applying the codes to half of the data. Then, the researchers cross-checked the others' coding, convening to discuss areas of disagreement with a third reviewer (LZ). Once consensus was attained, the trio defined themes that reflected the data set and quantified how frequently codes and themes emerged as areas of exemplary performance and improvement.

RESULTS

A total of 9 fellows completed pre-intervention encounters (4 first-year, 4 second-year, 1 third+-year), and 11 (6 first-year, 4 second-year, and 1 third+-year) fellows completed post-intervention encounters. Forty-seven FITs completed the ROSCE, representing 21 (44.7%) first-year, 21 (44.7%) second-year, and 5 (10.6%) third+-year FITs. Thirty-eight (81%) ROSCE participants answered the post-ROSCE survey. Of the 38 survey participants, 36 (94.7%) completed the module.

Survey participants reported significant increases in their confidence conducting SDM during telehealth ($P < .001$) and the module's learning objectives (Table 1). Effect sizes ranged from 0.571 to 0.730, indicating the module and ROSCE's moderate-to-strong influence on FITs' confidence regarding their skills in implementing SDM during telehealth. Confidence related to "utilizing the features of telehealth platforms to facilitate SDM" grew the most ($P < 0.001$; $r = 0.730$).

FITs' general telehealth skills significantly improved across patient care telehealth observations, the online module, and the ROSCE (Table 2). This improvement occurred when including and excluding the assessment of virtual physical examination skills ($P = 0.001$ and $P = 0.046$, respectively). FITs developed their skills pertaining to visit coordination the most, with scores in this domain significantly increasing between the ROSCE and post-intervention observations ($P < 0.001$). Scores within "webside" manner and physical examination skills increased between pre- and post-intervention observations without reaching statistical significance. We observed no statistical change in SDM scores, although scores were lowest during the ROSCE encounter, which specifically targeted SDM during telehealth. Spaghetti plots demonstrate changes in scores for individual FITs who received feedback at two or three time points (Supplement 3).

Participants reflected positively on the online module and ROSCE. All survey participants (100%) agreed or strongly agreed that the module and ROSCE encounter were relevant to their practice, with 97% agreeing or strongly agreeing that they would apply what they had learned to their clinical practice. Furthermore, 96% of FITs agreed or strongly agreed that the module helped them transfer their SDM skills from in-person to telehealth. FITs also appreciated the ROSCE station, with 95% agreeing or strongly agreeing that the patient care scenario was realistic. Most FITs (97%) agreed or strongly agreed that they received meaningful feedback on their telehealth and SDM skills during the ROSCE.

Five themes emerged from comments written on RTFFs describing FITs' delivery of telehealth and practice of SDM during telehealth: building foundations for SDM during telehealth, practicing SDM, coordinating next steps, using technology, and establishing "webside" interactions (Supplement 4). Relationships among the themes demonstrate FITs applying their medical knowledge and assessing the patient's clinical status before introducing decisions (foundations for SDM during telehealth). Then, FITs incorporate this information with patient preferences and

Table 1. Change in self-reported confidence conducting SDM during TH after completing an online module and simulated encounter*

Telehealth skill	Mean score before online module and simulation (N = 38)[a]	Mean score after online module and simulation (N = 38)	Effect size (*r*)	*P* value
Implementing the four steps of SDM during TH	2.58	3.16	0.647	**<0.001**
Identifying scenarios when TH can benefit SDM	2.63	3.26	0.660	**<0.001**
Identifying scenarios when TH can hinder SDM	2.89	3.34	0.573	**<0.001**
Utilizing the features of TH platforms to facilitate SDM	2.16	3.13	0.730	**<0.001**
Describing health systems that benefit SDM during TH	2.50	2.97	0.571	**<0.001**

* Bolded *P* values indicate statistical significance. Measured on a four-point Likert Scale (1 = not at all confident, 4 = very confident). SDM, shared decision-making; TH, telehealth.
[a] Measured retrospectively.

Table 2. Comparison of FIT's total and subdomain scores during simulated and patient care telehealth encounters*

Rubric scores	Pre-intervention mean score, % ± SD (n = 9)	Simulation mean score, % ± SD (n = 47)	Post-intervention, mean score, % ± SD (n = 11)	Comparison across all time points, *P* value[a]	Pre-intervention vs simulation, *P* value[b]	Simulation vs post-intervention, *P* value[b]	Pre- vs Post-intervention, *P* value[b]
Total score with physical examination	83 ± 11	NA	92 ± 7	NA	NA	NA	**0.046**
Total score without physical examination	86 ± 11	79 ± 15	96 ± 5	**0.001**	0.346	**< 0.001**	**0.011**
"Webside" manner	90 ± 12	95 ± 8	98 ± 4	0.130	0.186	0.163	0.067
Shared decision-making	83 ± 27	78 ± 23	87 ± 16	0.543	0.513	0.330	0.756
Visit coordination	76 ± 35	59 ± 30	98 ± 5	**<0.001**	0.068	**<0.001**	**0.049**
Physical examination	70 ± 16	NA	81 ± 23	NA	NA	NA	0.085

* Bolded *P* values indicate statistical significance. Measured using the RTFF, which includes subsections for the domains of "webside" manner, physical examination and objective data, SDM, and visit coordination. SDM, shared decision-making; RTFF, Rheumatology Telehealth Feedback Form.
[a] Kruskal-Wallis Test.
[b] Mann-Whitney U Test.

their recommendations for management to reach an agreement (practicing SDM). SDM during telehealth concludes when FITs coordinate the necessary steps to implement the plan (coordinating next steps). Finally, SDM uniquely occurs during telehealth only when FITs adeptly leverage the technology available during telehealth encounters (using technology) and demonstrate successful "webside" manner (establishing "webside" interactions).

Quantitative reports of the frequency with which themes appeared in written comments describing areas of excellence or improvement highlight FITs' strengths and shortcomings (Table 3). FITs demonstrated strong skills in "webside" interactions and overall SDM, excellently eliciting and incorporating patient perspectives. However, FITs hesitated to provide their management recommendations and leverage technology within the telehealth platform to enhance patients' understanding. Last, FITs could better coordinate next steps in patient care after telehealth encounters.

DISCUSSION

Telehealth remains a prevalent mode of delivering care to people with rheumatic diseases, making it essential that FITs develop telehealth skills before entering the workforce. Although some telehealth educational resources have been created, FITs continue to report low confidence in their telehealth skills, and no resources yet focus on teaching the nuances of SDM during telehealth.[4] Herein, we produced a module, a simulated encounter featuring SDM during telehealth, and feedback that improves FITs' confidence practicing SDM during telehealth. When combined with observations of patient care telehealth encounters, the educational initiative advances FITs' general telehealth skills, especially in tasks related to coordinating after-visit care.

Experiential learning theory underpins the success of our intervention because it describes the progression of skills that occurs through iterative cycles of learning, reflection, and experimentation.[7,8] We intentionally designed the online module and ROSCE encounter to incorporate this cycle. FITs first learned about general telehealth skills and the nuanced characteristics of SDM during telehealth through the online module. They then had the opportunity to reflect on how to implement these skills before participating in a simulated telehealth encounter featuring SDM and receiving feedback. The pre-and post-intervention patient care telehealth observations provided additional opportunities for FITs to learn, reflect on feedback, incorporate recommendations for improvement, and implement adjusted methods. Interestingly, FITs' skills most strikingly improved in pre-to-post-intervention and ROSCE-to-post-intervention comparisons but not between pre-intervention and ROSCE observations. This finding likely reflects the importance of iterative practice cycles for skill development, as emphasized in experiential learning theory.

The qualitative analysis of written feedback informs future educational efforts. Thematic analysis collectively reflects established descriptions of successful SDM during telehealth, identifying areas of strength and future improvement that exist throughout the process of SDM.[6] Frequency analysis of themes and subcodes further describes FITs' telehealth skill development to celebrate FITs' achievement of establishing "webside" manner and eliciting patient preferences. Moving forward, rheumatology educators may focus future telehealth instruction on the skills most often marked for improvement, namely features of SDM that patients request of their providers,[6] including coordinating after-visit details, using features within the telehealth platform to enhance patient education, and sharing their management recommendations.

Table 3. Frequency of comments submitted as areas of excellence and improvement for each theme and code with illustrative quotes describing FITs SDM and TH skills*

Theme	Codes	"Area of excellence" code count	"Area of improvement" code count	Illustrative quotes
Building foundations for shared decision-making	Communication strategies to enhance patient understanding	34	14	(+) "Did an excellent job of explaining the graphic from the paper at each step and doing check-ins to make sure I wasn't lost. Was very prepared to explain and share limitations of the data as it related to me as well"
	Sharing information	79	28	
	Clinical assessment	7	5	
	Physical examination	20	56	(–) "Consider chunking and taking a pause after sharing a lot of info (especially when it pertains to a study) to make sure the patient is still with you and following you."
Practicing shared decision-making	Patient perspective	112	16	(+) "Of note, I think he struck an excellent balance between making sure my preferences were respected but also being very clear on what he felt was medically indicated based on the data."
	Provider recommendation	70	23	
	Adapting SDM to TH	36	30	(–) "The patient would have preferred a more direct recommendation when the patient asked for one, rather than re-hashing the data that was discussed earlier."
Coordinating next steps	After-visit tasks	12	6	(+) "After patient prompting, did a great job with laying out explicit instructions for further contact 'Stay on the call and I'll have my MA come in to directly schedule you.'"
	Coordination of next visit	49	48	(–) "Would be helpful to explicitly lay out expectations and details on further follow-up (timing, type of visit, who to communicate with—schedulers, MA/nurses—for different types of tasks)"
Using technology	Naming the limitations of TH	9	15	(+) "He started off with making sure both mine and his zoom were working and let me know what to do in case the call gets dropped."
	Technology	29	21	
	Technology problem solving	13	13	(–) "Could be helpful to more explicitly lay out the AV quality and visit encounter setting—making sure they could hear you, were comfortable with the technology and setting, etc."
Establishing "webside" interactions	"Webside" manner	61	14	(+) "Very conversational approach. Highly effective at using reflective listening and verifying understanding of my concerns multiple times."
	TH communication skills	31	23	(–) "At times speaks over patient, especially at the end of sentences, cutting short patient's input."

* AV, audio visual; FIT, fellow-in-training; MA, medical assistant; SDM, shared decision-making; TH, telehealth.

We employed rigorous evaluation metrics in our study's design. Medical education initiatives, including those focused on teaching SDM, often report low-level outcomes of learners' satisfaction and confidence scores.[11,12] Feasibility directs these evaluations because of the challenges associated with researching skills in unpredictable patient care environments. Our primary aim measured FITs' change in confidence conducting SDM during telehealth, and we expanded our secondary aim to detect changes in general telehealth and SDM skills to demonstrate our initiative's potential effect on patient care.

General telehealth skills improved during the study, although skills specific to SDM during telehealth remained unchanged, highlighting a shortcoming in our study design. Patient care telehealth encounters were selected for pre- and post-intervention observations based on ease of scheduling rather than their focus on SDM, recognizing that outcomes might underrepresent SDM during telehealth skills. Telehealth encounters incorporate SDM to varying degrees, resulting in differential opportunities for FITs to demonstrate and develop their skills. Reassuringly, FITs reported improved confidence conducting SDM during telehealth with intentions to apply what they learned to clinical encounters, demonstrating the benefit and achievement of the study's primary aim.

The RTFF's design also may have underdetected changes in skills pertinent for sharing decisions during telehealth. SDM uses multiple telehealth skills, including professionalism, communication and "webside" manner, obtaining physical examination and objective data, and coordinating post-visit details.[6] Therefore, the RTFF section dedicated to SDM during telehealth underrepresents the totality of the SDM skill set, decreasing sensitivity for

measuring change. Improvement in FITs' general telehealth skills after our educational intervention, including components of "webside" manner, physical examination, and visit coordination that contribute to SDM, may indicate that FITs are better equipped to share decisions during telehealth after completing our educational intervention despite the lack of statistical significance.

Other limitations of our study include the smaller number of FITs who completed pre- and post-intervention observations, which reduced the power of our statistical analysis and emphasized comments from the ROSCE over patient care telehealth encounters during our qualitative analysis. Observation during simulated and patient care encounters precludes blinding assessors to FITs' identities, which may introduce bias into assessment data. Last, FITs experienced technical difficulties completing the post-ROSCE survey, decreasing the response rate. We suspect this only marginally affected survey results, given our response rate of 81% exceeds survey standards.

Strengths of our study include the large number and diversity of participants who completed the module and simulated telehealth encounter. This substantial sample size from eight rheumatology fellowship training programs representing three+ years of fellowship training enhances the generalizability and trustworthiness of our conclusions. Additionally, our procedures, namely using the RTFF, which has strong validity evidence,[9] and training patient actors and faculty scorers, supported the standardization and reliability of ROSCE results.

People with rheumatic diseases continue to use telehealth, and FITs must develop skills to deliver telehealth care as new entrants into the rheumatology workforce. Additionally, patients and providers with expertise in telehealth recommend FITs undergo specific training in the nuances of SDM during telehealth to enhance patient-centered care delivered to people with rheumatic diseases.[6] Our study is the first to create an online module and simulated telehealth encounter that emphasizes the nuanced skills of SDM during telehealth and incorporates these materials into iterative cycles of learning, reflection, and experimentation while demonstrating their effect on FITs' skills implemented during patient care telehealth encounters. This approach to telehealth education promises to enhance FITs' development and prepare them to optimally deliver telehealth care and share decisions, expanding access to and delivery of patient-centered care among people with rheumatic diseases.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Zickuhr confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Centers for Medicare & Medicaid Services. *Medicare telehealth trends snapshot*. Published 2024. Accessed April 23, 2025. https://data.cms.gov/sites/default/files/2024-03/Medicare%20Telehealth%20Trends%20Snapshot%2020240307_508.pdf
2. Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns 2015;98(10):1172–1179.
3. Criscione-Schreiber L, Annapureddy N, Berlinberg A, et al. Core curriculum outline for rheumatology fellowship programs. Published 2023. Accessed April 23, 2025. https://assets.contentstack.io/v3/assets/bltee37abb6b278ab2c/blt5451c0437b4e2037/core-curriculum-outline.pdf
4. Bolster MB, Kolfenbach J, Poeschla A, et al. Incorporating telemedicine in rheumatology fellowship training programs: needs assessment, curricular intervention, and evaluation. Arthritis Care Res (Hoboken) 2023;75(12):2428–2434.
5. Zickuhr L, Albert DA, Herndon C, et al; American College of Rheumatology Committee on Training and Workforce. Addressing competency in rheumatology telehealth care delivery. Arthritis Care Res (Hoboken) 2023;75(6):1213–1219.
6. Zickuhr L, McCarthy C, Nolan-Thomas E, et al. Shared decision-making during virtual care regarding rheumatologic and chronic conditions: qualitative study of benefits, pitfalls, and optimization. ACR Open Rheumatol 2024;6(1):32–42.
7. Kolb DA, Boyatzis RE, Mainemelis C. Experiential learning theory: previous research and new directions. In: Sternberg RJ, Zhang LF, eds. Perspectives on Thinking, Learning, and Cognitive Styles. Routledge; 2014:227–247.
8. Kolb AY, Kolb DA. Experiential learning theory: a dynamic, holistic approach to management learning, education and development. In: Armstrong SJ, Fukami CV, eds. The SAGE Handbook of Management Learning, Education and Development. Sage; 2009:42–68.
9. Zickuhr L, Sobrero A, Albert D, et al; American College of Rheumatology Workforce Solutions Committee. Development, usability, and validity evidence of a rheumatology telehealth feedback form. Arthritis Care Res (Hoboken) 2025;77(10):1246–1253.
10. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15(9):1277–1288.
11. Singh Ospina N, Toloza FJK, Barrera F, et al. Educational programs to teach shared decision making to medical trainees: a systematic review. Patient Educ Couns 2020;103(6):1082–1094.
12. Müller E, Strukava A, Scholl I, et al. Strategies to evaluate healthcare provider trainings in shared decision-making (SDM): a systematic review of evaluation studies. BMJ Open 2019;9(6):e026488.

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 899–904
DOI 10.1002/acr.70006

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Disabilities and Generative Artificial Intelligence Education in Rheumatology Fellowship: Educational Module and Simulation Exercise

Sana G. Cheema, MD,[1] Matthew A. Sullivan, PhD,[1] Emily Balczewski, PhD,[2] Amanda S. Alexander, MD,[3] Anisha B. Dua, MD, MPH,[4] Lacey Feigl-Lenzen,[1] Brian Jaros, MD,[4] Jason Kolfenbach, MD,[5] Nicholas Kortan, MD,[5] and Lisa Zickuhr, MD, MHPE[1]

Objective. People with rheumatic and musculoskeletal diseases (RMDs) can acquire disabilities that affect their participation in work and school. Generative artificial intelligence (genAI) may reduce documentation time, providing a tool for providers to efficiently write letters for accommodation and maximally advocate for people with disabilities. Therefore, fellows-in-training (FITs) must develop skills in disability advocacy and genAI for clinical care. We created an online module and simulation activity in which FITs wrote letters for accommodation using genAI. We aimed to improve FITs' confidence implementing these skills and to identify areas needing further instruction.

Methods. FITs completed an online module and simulation activity engineering genAI prompts for letters for accommodation. Educators scored FITs' skills against a rubric. FITs measured their confidence conducting these skills in retrospective pre-post Likert scales that we compared with Wilcoxon signed rank tests.

Results. Twenty-three FITs participated; 18 FITs (78.6%) completed the Likert scales. On average, FITs scored 83.83% against the rubric. The strongest skill was engineering genAI prompts (95.45%), and the lowest was differentiating the scope of practice between rheumatology providers and disabilities professionals coordinating accommodations (74.55%). FITs' confidence significantly improved across all objectives, most notably in engineering genAI prompts and finalizing letters drafted with genAI ($P < 0.0001$).

Conclusion. Our educational materials teach FITs to incorporate genAI into writing letters for accommodation and addressing disparities from medical disabilities. Such skill development prepares FITs to enter the rheumatology workforce confident in their abilities to integrate genAI into clinical activities and deliver care to people with disabilities from RMDs.

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) can affect how people engage in daily activities.[1] Rheumatology providers advocate for individuals with disabilities and write letters for accommodation that remove barriers to access, create equal opportunity for engagement, and maximize patients' participation at work and school.[2] The Accreditation Council for Graduate Medical Education's (ACGME) systems-based practice milestones expect rheumatology fellows-in-training (FITs) to develop advocacy skills,[3] yet curricula, especially in graduate medical education (GME), routinely lack disabilities education.[4] In searching MedEdPORTAL, only two publications delivered disabilities education to GME trainees, teaching neurology residents adaptations to the physical examination and instructing pediatrics residents how to navigate special education for children.[5,6] No educational

Supported by the Rheumatology Research Foundation Clinician Scholar Educator Award (award 18652465).

[1]Washington University in St Louis School of Medicine, St Louis, Missouri; [2]University of Michigan Medical School, Ann Arbor; [3]University of Alabama at Birmingham Marnix E. Heersink School of Medicine; [4]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [5]University of Colorado Anschutz School of Medicine, Aurora.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70006).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70006.

Address correspondence via email to Lisa Zickuhr, MD, MHPE, at zickuhrl@wustl.edu.

Submitted for publication July 18, 2025; accepted in revised form November 14, 2025.

SIGNIFICANCE & INNOVATIONS

- Disabilities are common among people with rheumatic and musculoskeletal diseases (RMDs). Generative artificial intelligence (genAI) helps rheumatology providers overcome time constraints that limit their capacity to advocate for people with disabilities.
- It is essential that rheumatology fellows-in-training (FITs) develop skills in patient advocacy and using genAI to write letters for accommodation.
- We created an online module and simulated experience with a scoring rubric that successfully teaches FITs how to write letters for accommodation using genAI as well as identifies needs for future instruction.
- The online module and simulated experience begin to address gaps in disabilities and genAI education during rheumatology fellowship. Continued development of educational materials will further enhance FITs' skills, preparing them as future entrants into the workforce to optimally deliver care to people with disabilities from RMDs.

materials were designed for GME trainees in internal medicine or its subspecialties, including rheumatology. Without dedicated education, providers report being unprepared to treat people with disabilities.[4]

Additionally, providers are experiencing a heavy burden for documentation,[7] which could limit their time for advocacy. Safe and ethical use of generative artificial intelligence (genAI), the deep learning models that create products resembling human-developed content, may improve rheumatology providers' clinical efficiency and enhance their capacity to draft letters for accommodation.[7] The American Association of Medical Colleges forecasts the benefit of genAI and calls medical educators to integrate genAI throughout curricula.[8] When writing this article, only one MedEdPORTAL publication introduced the clinical applications of genAI to medical students, providing programs few options for integrating established instructional materials into their curricula.[9,10] Medical educators in rheumatology must address curricular shortcomings in genAI and disabilities advocacy and can incorporate both topics simultaneously through teaching FITs how to use genAI as a tool for addressing disparities from medical disabilities in the clinical setting.

We created an online, interactive module and simulated experience to teach FITs how to write letters for accommodation using genAI as a form of advocacy for people with disabilities from RMDs. Primarily, we aimed to expand FITs' curricula to incorporate underrepresented content while improving their confidence writing letters for accommodation using genAI. Secondarily, we sought to identify gaps in FITs' skills that will guide future interventions in disabilities and genAI education.

METHODS

Content selection. The Midwest Mountain Rheumatology Collective (MMRC), an educational alliance among adult rheumatology fellowship training programs at Northwestern University, University of Alabama at Birmingham, University of Colorado, and Washington University School of Medicine (WashU Medicine), hosts an annual virtual rheumatology objective structured clinical experience (vROSCE). Medical educators representing each MMRC program (ASA, BJ, NK, and LZ) discussed curricular gaps, identifying content areas that benefited all programs: advocating for people with disabilities from RMDs and integrating genAI into clinical work.

Design of educational materials. A team with expertise in disabilities, genAI, and medical education (MAS, EB, and LZ) created an online interactive module and simulated exercise grounded in experiential learning theory, whereby FITs learned through cycles of activity, reflection, and implementation.[11] They developed the module with ArticulateRise 360 (https://rheumatology.wustl.edu/fellowship-program/courses/). Learning objectives included describing the impact of RMDs on people's ability to participate in work and school, describing rheumatology providers' role in supporting disability accommodations, generating prompts for drafting medical letters using genAI, and revising AI-generated letters for accuracy. The module design incorporated experiential learning theory, delivering factual content alongside exercises prompting conceptualization into FITs' practice. For instance, the module began with a video that defines disabilities among people with RMDs and reviews the components of letters for accommodation. Then FITs critiqued example letters. In the second half, FITs learned about AI applications in rheumatology and how to engineer genAI prompts with the "Task, Impact, and Instruction" framework before practicing drafting a medical letter using Doximity GPT, finalizing it with the EVERY framework, and checking their work against an answer key.[12,13] The module incorporated Doximity GPT because it complies with the Health Insurance Portability and Accountability Act and is available with a free account.

The team (SGC, MAS, EB, and LZ) designed a simulation exercise featuring Ami, a 20-year-old woman with polyarticular juvenile idiopathic arthritis who encounters challenges in college because of disabilities from her diagnosis. A two-minute video of Ami describing her disabilities and requesting a letter for accommodation started the exercise (https://www.youtube.com/watch?v=RnJKKtYoQI0). FITs then followed prompts, describing their role in Ami's application for accommodations, engineering a genAI prompt to draft the letter, and producing and finalizing a letter with Doximity GPT (Supplement 1).

We created a rubric that scored fellows' achievement of the module's learning objectives in five components: (1) describing rheumatology providers' scope of practice in disability

accommodations, (2) engineering a prompt for genAI, (3) introducing the provider, (4) describing the disability, and (5) finalizing the letter (Supplement 1). The rubric used entrustment scales and defined behaviors for each component.[14] Experts in disabilities (MAS) and genAI (EB) verified the rubric's content. The rubric concluded with space for written comments describing what was done well and areas for improvement.

Implementation and data collection. The MMRC distributed the online module among FITs to complete independently one week before the vROSCE, and during the vROSCE, FITs submitted their responses to the simulated experience prompts through Qualtrics. Program directors (ASA, ABD, JK, and LZ) invited FITs attending the 2025 MMRC vROSCE to participate in the study. FITs provided verbal consent at the start of the vROSCE for their deidentified responses to be included in data analysis, voluntarily participating without incentive beyond educational benefit. Medical educators (ASA and LZ) scored FITs' responses against the rubric and wrote comments describing what FITs did well and how they could improve. These rubrics were returned to FITs, delivering formative feedback to advance their skills. A third team member (SGC) scored the FITs' responses a second time against the rubric's entrustment scales.

Following the vROSCE, FITs provided feedback on the module and simulation experience in an online survey (Qualtrics). On a five-point scale (1 = very unconfident, 5 = very confident), the survey asked FITs to retrospectively rate their confidence and previous experience advocating for patients with disabilities from RMDs via letters for accommodation and using genAI to draft medical letters before and after completing the module and simulated experience. The WashU Medicine Institutional Review Board verified the research proceedings complied with the Declaration of Helsinki (IRB no. 202501175).

Data analysis. Descriptive statistics summarized the demographic characteristics of participating FITs. We determined the intraclass correlation coefficient (ICC) for total rubric scores using a one-way random effects model. With the medical educators' scoring, we calculated the average total and percentage scores earned by FITs on the overall rubric and its five components, using percentage scores to normalize for one FIT who did not answer all the simulated experience prompts. We compared component percentages with chi-square analysis to determine if fellows performed significantly better or worse on any of the five rubric components. We determined if total score percentages varied between first- and second-year fellows and among the four MMRC fellowship training programs using the Mann–Whitney U test and Kruskal–Wallis test, respectively. The Wilcoxon signed rank test compared FITs' confidence levels before and after completing the module and simulated experience, and descriptive statistics were used to analyze FITs' feedback on the educational materials. We used SPSS for statistical analyses.

We conducted qualitative content analysis of the written comments submitted on rubrics to generate themes reflecting FITs' strengths and areas for improvement.[15] Team members (SGC and LZ) inductively analyzed each written comment together, labeling and defining codes, organizing themes, and discussing discrepancies at the time of review. We reviewed the comments twice, once to generate the codes and then to verify coding. We used Microsoft Excel to track our analysis and calculated the frequency each code described areas of excellence or improvement.

RESULTS

Twenty-three fellows, specifically 11 first-year (47.8%) and 12 second-year fellows (52.2%), from all four MMRC fellowship training programs participated in the simulated experience. The ICC between rubric scores was 0.849 ($P < 0.0001$), demonstrating strong interrater reliability.

Based on the medical educators' scoring, FITs on average earned 83.8% of the total rubric points. No significant differences in total score percentages emerged between first- and second-year fellows ($P = 0.162$) or among the fellowship training programs ($P = 0.868$). FITs scored highest on engineering genAI prompts (95.5%) and lowest on defining rheumatology providers' scope of practice advocating for accommodations (74.6%; Table 1), though performance across the five components was statistically similar ($P = 0.645$).

Qualitative analysis highlighted FITs' areas of excellence and improvement, contextualizing rubric scores. Defined themes depict the requisite steps to write an effective letter of accommodation using genAI (Figure 1). Supplement 2 presents illustrative quotes and the frequency with which each code designated an area of excellence or improvement. FITs most excelled in describing the rheumatic disease and disability. Alternatively, FITs can improve their understanding of providers' and universities' scopes of practice when addressing disabilities from RMDs as well as revising medical letters drafted with genAI.

Eighteen FITs (78.6%) completed the evaluation survey. FITs' confidence improved across all objectives, most notably for engineering genAI prompts and finalizing medical letters written with genAI (r = 0.827 and 0.833, respectively; Table 2). Twelve FITs (66.7%) encountered disabilities incurred from RMDs five or more

Table 1. Rheumatology fellows-in-training percentage total and component scores on the simulated experience rubric*

Metric of performance	n[a]	Mean percentage score ± SD
Total score	23	83.83 ± 12.79
Defining scope of practice	22	74.55 ± 27.73
Engineering AI prompt	22	95.45 ± 8.58
Introducing the provider	23	86.09 ± 14.06
Describing the disability	23	87.83 ± 18.82
Finalizing the letter	23	82.61 ± 15.41

* AI, artificial intelligence.
[a] Number of fellows-in-training who responded to the prompt.

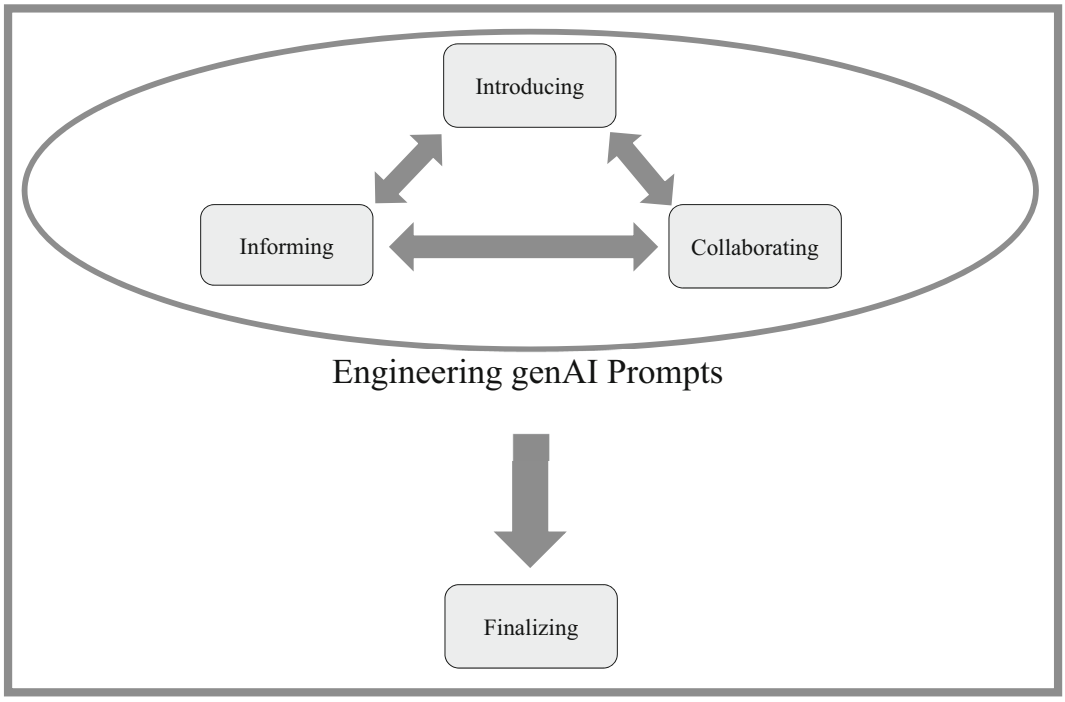

Figure 1. Thematic representation of the process writing letters for accommodation using genAI. When writing letters for accommodation using genAI, providers introduce themselves and their clinical relationship with the patient (introducing); clearly explain the patient's diagnosis, treatment, and how the condition impacts daily life (informing); and collaborate with disability professionals to align medical needs with appropriate accommodations (collaborating). These elements are conveyed through well-crafted genAI prompts to ensure the drafted letter of accommodation reflects appropriate tone, structure, and purpose (engineering). Finally, rheumatology providers must edit AI-generated drafts to ensure accuracy (finalizing). genAI, generative artificial intelligence.

times in clinical encounters during fellowship, but most FITs (16 of 18, 88.9%) learned about disabilities incurred from RMDs four or fewer times during fellowship. Only five FITs (27.8%) had previously used genAI as a tool for clinical work, and most FITs (16 of 23, 88.9%) never or seldom learned about genAI as a tool for clinical work. Seventeen FITs (94.4%) reported the module and simulated experience were "relevant" or "very relevant," and 14 FITs (77.8%) said they would "likely" or "very likely" incorporate teaching points into clinical practice. Most fellows indicated the module's instruction was clear and of an appropriate length (78% and 72%, respectively).

DISCUSSION

People with RMDs can face disabilities, and clinical applications of genAI intend to enhance efficiency and expand rheumatology providers' capacity for advocacy. In response, FITs will benefit from entering the workforce confident in their skills to support patients' needs, including using genAI to write letters for accommodation. This study presents the first published approach for teaching and assessing these skills while demonstrating the need for additional instruction regarding disabilities from RMDs and genAI for patient care.

Medical educators design rheumatology curricula that prepare FITs for delivering compassionate, up-to-date care. In our survey, a substantial number of FITs reported minimal-to-no previous instruction or experience delivering care to people with disabilities from RMDs or applying genAI clinically, underscoring shortcomings in curricula. Disabilities education expands FITs' awareness of the lived experiences of people with limitations from RMDs and of the nuances to patient care in, for example, medical

Table 2. Retrospective change in confidence writing letters for accommodation and using generative AI after completing an online module and simulated experience*

Objective	Before activity, mean ± SD	After activity, mean ± SD	Z statistic	*P* value	Effect size (r)
Defining provider's scope of practice	3.56 ± 0.89	4.44 ± 0.56	3.025	0.002	0.713
Describing impact of disabilities	3.61 ± 0.96	4.28 ± 0.50	2.652	0.008	0.625
Engineering AI prompts	3.06 ± 0.91	4.33 ± 0.58	3.508	<0.0001	0.827
Finalizing medical letters written with AI	3.22 ± 0.63	4.39 ± 0.59	3.535	<0.0001	0.833

* Confidence based on five-point Likert scale: 1 = very unconfident; 5 = very confident. AI, artificial intelligence.

documentation regarding disabilities, to best prepare them for independent practice. A lack of disabilities education may result in underdeveloped skills and lower success rates among FITs advocating for people with disabilities from RMDs.[4] Similarly, a failure to teach genAI's clinical applications could disadvantage FITs who enter the workforce unprepared to use the technology, possibly positioning them to apply genAI without safety and ethical guardrails. genAI is developing rapidly,[7] and the longer medical educators delay integrating genAI into curricula, the more challenging it can become for FITs to develop skills using genAI upon entering independent practice. The module and simulated experience address these concerns, introducing FITs to the advocacy of people with disabilities from RMDs and clinical applications of genAI.

Our educational materials innovate instruction in the ACGME competency of systems-based practice or skills for navigating health care and other intersecting systems while also advocating for people with RMDs. Traditionally, systems-based practice is challenging to instruct and assess, leaving medical educators looking to supplement content in rheumatology curricula.[16] The module and simulated exercise simultaneously incorporate system navigation for patient-centered care and rheumatology providers' role in health care systems. In publishing our work, we share didactic and formative feedback materials that meet educational needs.[4]

Rheumatology fellowship training programs beyond the MMRC can use our educational materials easily. Infused with the knowledge of experts in medical disabilities and genAI, the materials can be used without requiring local expertise. The online module and simulated exercise materials are free and feature resources that any FIT may access. We used an online survey platform to collect FITs' responses during the simulation exercise, and educators could modify these methods to match their resources.

The educational materials may provide benefit beyond their initial design. Although we created them for adult rheumatology FITs, they may enhance the training of pediatric rheumatology FITs because the simulated experience features a college-age young adult whose characteristics are within the scope of pediatric care. Furthermore, we initially sought to design a scoring rubric that delivered formative feedback to enhance FITs' skill development. The rubric's strong validity evidence indicates it may be useful for observations during patient care and/or summative assessment in overall evaluation of skills.

The data obtained from scoring rubrics and FITs' survey responses highlight areas of future focus in disabilities and genAI education. Disparities between clinical exposure and didactic instruction combined with variable training exposures among MMRC FITs may explain the wide standard deviations in FITs' rubric performance and further emphasize the need for integrating disabilities and genAI education consistently into rheumatology curricula overall. Qualitative analysis of written comments identified skills in need of further development, specifically defining scope of practice for providers and disabilities professionals designing accommodations and editing medical letters drafted with genAI. These findings can direct future educational initiatives toward the skills in greatest need of improvement.

Weaknesses of our study include a sample size of 23 FITs, which may limit the generalizability of our educational materials' success for future disabilities and genAI teaching. The sample size also may explain FITs' statistically similar skill level among the five scoring rubric components, with areas for improvement emerging more clearly in qualitative data. Additionally, the focus on disabilities and genAI education came from a regional needs assessment among the MMRC, which may not reflect FITs' needs elsewhere. Furthermore, our evaluation metrics measure simulated rather than patient care data to standardize and streamline data collection. Lastly, potential confirmation bias may have been introduced because a researcher both generated and analyzed qualitative comments; a second researcher participated in qualitative analysis to limit biasing the results.

We also identify the strengths of our study. We grounded the development of the online module and simulated experience in experiential learning theory to optimize FITs' skill development, included experts in disabilities and genAI to reinforce content validity, and applied best practices in assessment to create a reliable scoring rubric.[14,17,18] We measured FITs' skills during simulation, which is a more meaningful metric than satisfaction alone, and we incorporated qualitative analysis into our evaluation plan, further investigating suggestive trends in quantitative data. Lastly, multiple rheumatology fellowship training programs are represented in our data, enhancing generalizability of our findings in the setting of a sample size of 23 participants.

Rheumatology fellowship curricula underrepresent instruction in disabilities and using genAI for clinical tasks. These shortcomings can leave providers ill prepared to deliver care to people with disabilities from RMDs. When medical educators adapt their curricula and instructional methods to incorporate these topics, they prepare FITs to safely use genAI and to expand their capacity for addressing disparities from medical disabilities. In doing so, FITs will enter the rheumatology workforce confident to advocate for and optimize the care of people with RMDs.

ACKNOWLEDGMENT

We thank Cassandra Cole for serving as our honest broker.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Zickuhr confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration

by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Palazzo C, Ravaud JF, Papelard A, et al. The burden of musculoskeletal conditions. PLoS One 2014;9(3):e90633. doi:https://doi.org/10.1371/journal.pone.0090633
2. Story J, Ash E. Be careful what you write: employment, disability, and healthcare law considerations for doctor's notes. Mo Med 2021;118(4):318–321.
3. Liebowitz JE, Torralba KD, Kolfenbach J, et al. Rheumatology milestones 2.0: a roadmap for competency-based medical training of rheumatology fellows in the 21st century. Arthritis Care Res (Hoboken) 2022;74(4):675–685. doi:https://doi.org/10.1002/acr.24507
4. Sapp RW, Lee E, Bereknyei Merrell S, et al. Disability health in medical education: development, implementation, and evaluation of a pilot curriculum at Stanford School of Medicine. Front Med (Lausanne) 2024;11:1355473. doi:https://doi.org/10.3389/fmed.2024.1355473
5. Benjamin JC, Groner J, Walton J, et al. A blended curriculum to improve resident physical exam skills for patients with neuromuscular disability. MedEdPORTAL 2019;15:10792. doi:https://doi.org/10.15766/mep_2374-8265.10792
6. Ihyembe D, Stager K, Deavenport-Saman A, et al. Navigating school-based special education services: a self-paced virtual learning module. MedEdPORTAL 2021;17:11108. doi:https://doi.org/10.15766/mep_2374-8265.11108
7. Moulaei K, Yadegari A, Baharestani M, et al. Generative artificial intelligence in healthcare: a scoping review on benefits, challenges and applications. Int J Med Inform 2024;188:105474. doi:https://doi.org/10.1016/j.ijmedinf.2024.105474
8. Association of American Medical Colleges. Principles for responsible AI in medical school and residency selection. 2025. Accessed July 9, 2025. https://www.aamc.org/about-us/mission-areas/medical-education/principles-ai
9. Wong A, Sussman J, Price N, et al. The data-augmented, technology-assisted medical decision making (DATA-MD) curriculum: a machine learning and artificial intelligence curriculum for clinical trainees. Acad Med 2025;100(9):1035–1039. doi:https://doi.org/10.1097/ACM.0000000000006089
10. Agarwal G, Ramamoorthi L, Yuen T, et al. Exploring applications of artificial intelligence tools in clinical care and health professions education: an online module for students. MedEdPORTAL 2025;21:11524. doi:https://doi.org/10.15766/mep_2374-8265.11524
11. Kolb DA. Experiential Learning: Experience as the Source of Learning and Development. Prentice-Hall; 1984.
12. Lie M, Rodman A, Crowe B. Harnessing generative artificial intelligence for medical education. Acad Med 2025;100(1):116. doi:https://doi.org/10.1097/ACM.0000000000005760
13. Matthews L, Cubero V. How to use AI responsibly EVERY time. AI for Education. 2024 Accessed July 8, 2025. https://www.aiforeducation.io/ai-resources/how-to-use-ai-responsibly-every-time
14. Jarrett JB, Goliak KL, Haines ST, et al. Development of an entrustment-supervision assessment tool for pharmacy experiential education using stakeholder focus groups. Am J Pharm Educ 2022;86(1):8523. doi:https://doi.org/10.5688/ajpe8523
15. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77–101. doi:https://doi.org/10.1191/1478088706qp063oa
16. Martinez J, Phillips E, Harris C. Where do we go from here? Moving from systems-based practice process measures to true competency via developmental milestones. Med Educ Online 2014;19(1):24441. doi:https://doi.org/10.3402/meo.v19.24441
17. Warm EJ, Mathis BR, Held JD, et al. Entrustment and mapping of observable practice activities for resident assessment. J Gen Intern Med 2014;29(8):1177–1182. doi:https://doi.org/10.1007/s11606-014-2801-5
18. Kogan JR, Dine CJ, Conforti LN, et al. Can rater training improve the quality and accuracy of workplace-based assessment narrative comments and entrustment ratings? A randomized controlled trial. Acad Med 2023;98(2):237–247. doi:https://doi.org/10.1097/ACM.0000000000004819

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 905–913
DOI 10.1002/acr.25702

Validation of the Pediatric Arthritis Ultrasound Scoring System for the Elbow, Wrist, and Finger Joints in Children With Juvenile Idiopathic Arthritis

Patricia Vega-Fernandez, Pinar Ozge Avar-Aydin, Kelly Rogers, Daniel J. Lovell, Jennifer Huggins, Alexei Grom, Hermine I. Brunner, Grant S. Schulert, Sheila T. Angeles-Han, Mekibib Altaye, Amy Cassedy, Arthur B. Meyers, and Tracy V. Ting

Objective. We aimed to validate the Pediatric Arthritis Ultrasound Scoring System (PAUSS) for upper extremity joints in children with juvenile idiopathic arthritis (JIA).

Methods. Children with JIA were evaluated for elbow, wrist, or finger arthritis by clinical examination (CE) and musculoskeletal ultrasound (MSUS) with images scored according to the joint-specific PAUSS. A subset of children received contrast-enhanced magnetic resonance imaging (ceMRI) of the affected joint(s). The performance of the PAUSS as a measure of arthritis activity was compared to CE and ceMRI, using ceMRI as the reference standard.

Results. Seventy-five children contributed 44 elbows, 55 wrists, and 106 fingers for MSUS and 15 elbows, 16 wrists, and 40 fingers for ceMRI. B-mode PAUSS scores for the finger joints demonstrated moderate correlations with CE findings of arthritis, and the PAUSS-elbow noted a strong correlation. PAUSS scores for all joints showed a sensitivity of 75% to 94% in detecting synovitis when compared to ceMRI and good to excellent diagnostic accuracy for elbow and finger arthritis. The addition of MSUS to CE markedly improved the sensitivity of CE to 92% to 100%. The PAUSS and ceMRI scores for assessment of disease severity had strong correlation for each specific joint (r = 0.65–0.84, $P \leq 0.005$).

Conclusion. There is moderate to high sensitivity and diagnostic accuracy of the PAUSS in detecting synovitis in elbow, wrist, and finger joints, as well as a strong correlation of the PAUSS severity scores with the ceMRI severity scores, providing strong support that the PAUSS enhances the clinical assessment of disease activity in children with JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis of childhood, characterized by joint inflammation that may lead to permanent damage if not treated quickly and effectively.[1] In JIA, active inflamed joints are clinically appreciated by the presence of joint swelling, warmth, tenderness, and limited range of motion (LROM) as determined by expert providers. Clinical examination (CE) of arthritis and physician and patient global assessments of disease activity are key determining factors of JIA disease activity and treatment decisions.[2] However, the lack of standardization on the measurement of these factors results in low reliability among providers and patients, which over time may lead to an invalid assessment of JIA disease activity and burden.[3,4] Additionally, joint involvement patterns at diagnosis and during the disease course have been associated with prediction of disease trajectories and treatment decisions, making accurate detection of the joints with inflammation critical in tailoring treatments.[5]

Imaging, most specifically magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS), are recognized

Supported by the National Center for Advancing Translational Sciences, NCATS at the University of Cincinnati funded by the NIH Clinical and Translational Science Award program (grant 2UL1TR001425-05A1). Dr Vega-Fernandez's work was supported by the National Center for Advancing Translational Sciences, NIH (award 2KL2TR001426-05A1), the National Institutes of Health, NIH (awards P30AR076316 and K23AR081424A), and the Diversity and Health Disparity Award by the Cincinnati Children's Hospital Medical Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Cincinnati Children's Hospital Medical Center.

Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25702).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25702.

Address correspondence via email to Patricia Vega-Fernandez, MD, MSc, RhMSUS, at Patricia.VegaFernandez@cchmc.org.

Submitted for publication February 25, 2025; accepted in revised form October 31, 2025.

SIGNIFICANCE & INNOVATIONS

- The joint-specific Pediatric Arthritis Ultrasound Scoring System (PAUSS) demonstrated good to excellent sensitivity in detecting active synovitis in the elbow, wrist, and finger joints when using contrast-enhanced magnetic resonance imaging (ceMRI) as the reference standard.
- The PAUSS B-mode scores were highly correlated with the ceMRI scores for the assessment of elbow, wrist, and finger disease severity.
- The PAUSS showed excellent diagnostic accuracy for detection of wrist and finger tenosynovitis.
- This study demonstrates that the PAUSS improves the accuracy of clinical assessment for the detection of elbow, wrist, and finger arthritis in children with juvenile arthritis.

complementary tools to the clinical assessment in diagnosing and managing children with JIA.[6] Contrast-enhanced MRI (ceMRI) is acknowledged as the "reference standard" imaging modality in JIA, given its high sensitivity and specificity in the detailed evaluation of joint effusion, synovial hypertrophy, synovial hyperenhancement, bone marrow edema, osteitis, erosions, and inflammation in surrounding tissues.[7] Nevertheless, ceMRI has several shortcomings, primarily related to relatively high cost, limited availability, need for intravenous contrast and sedation, and low patient tolerance especially in younger children, which detract it from being the optimal choice for monitoring JIA.[8] MSUS objectively evaluates synovial hypertrophy, synovial effusion, tenosynovitis, and enthesitis with an ability to detect increased vascularity by power Doppler (PD) imaging.[9] Standardization of MSUS use in JIA has significantly progressed in recent years, including determination of normative references for age- and sex-related findings[10–13] and MSUS definitions of joint pathologies.[14–18] MSUS offers many advantages, including real-time dynamic examination of multiple joints at the bedside, noninvasiveness, and a child-friendly examination.[19]

Pediatric joint-specific MSUS image acquisition and scoring systems in JIA have recently been proposed.[20–22] Among these, the Pediatric Arthritis Ultrasound Scoring System (PAUSS) proposed by the Childhood Arthritis and Rheumatology Research Alliance MSUS workgroup demonstrated excellent reliability for the elbow, wrist, and finger joints among pediatric rheumatology providers with different levels of MSUS expertise.[23] Furthermore, the elbow, wrist, and finger joints have been included among the targeted joints in different abbreviated MSUS protocols that aim to assess disease activity by scanning a reduced number of joints.[20,24] However, the validation of the MSUS as a measure of disease activity in these joints is lacking in JIA.

The aim of this cross-sectional study was two-fold. The first was to examine the performance of the PAUSS for the detection of synovitis in the elbow, wrist, and finger joints compared to CE and ceMRI while using ceMRI as the reference standard. Second, we aimed to assess the relationship between the severity of the findings on the joint-specific PAUSS and ceMRI.

METHODS

Study design and participants. This observational cross-sectional study recruited children with a diagnosis of JIA as per the International League of Associations for Rheumatology criteria from the outpatient Rheumatology Clinics at Cincinnati Children's Hospital Medical Center (CCHMC) between June 2020 and June 2024.[25] The inclusion criteria were (1) current age between 2 and 18 years and (2) the presence of either physician-reported arthritis and/or patient-reported pain or stiffness in the elbow, wrist, or finger joints. The exclusion criteria were (1) intra-articular glucocorticoid injection of the affected joint within four weeks and (2) intolerance to MSUS. The study was approved by the Institutional Review Board of the CCHMC (approval number: 2018-7939). All participants and their legal guardians gave written informed consent before any study procedures. All study procedures were completed on the same day.

Clinical assessment. Participants received a standard CE of the target joint(s) by the treating pediatric rheumatologist before imaging was obtained. Demographic data, disease characteristics, clinical findings, physician global assessment of disease activity (range: 0: inactive to 10: very active disease), and current medications were recorded from electronic medical charts. Clinically active arthritis was defined as presence of joint swelling or the combination of joint tenderness and LROM in the target joint.

MSUS assessment. The affected elbow(s), wrist(s), and/or fingers were examined according to a previously published pediatric-specific MSUS scanning protocol[20] by pediatric sonographers with more than 10 years of experience (PVF, TVT) who were blinded to patient's symptoms and CE findings. General acquisition guidelines recommended by the MSUS scanning protocols, such as presence of a layer of gel overlying the image and dynamic examination, were considered when obtaining the images. Dynamic MSUS examination included the evaluation of the joint recess on its full extent (ie, medial to lateral aspect) and with movement was performed during all scans. Still images in B-mode and PD-mode were obtained at the area with maximum findings of abnormality of the joint recess and/or the tendon sheath. A General Electric (GE) US Logiq S8 XDclear or a GE LOGIC Fortis (GE HealthCare) equipped with multifrequency linear probes (6–24 MHz) was used for the MSUS examinations.

The elbow joint was evaluated by the longitudinal anterior scan of the humeroradial joint (HRJ), the longitudinal anterior scan of the humeroulnar joint (aHUJ), and the longitudinal posterior scan of the HUJ (pHUJ). MSUS examination of the wrist joint

was performed on the dorsal aspect including the longitudinal scan of radiocarpal (RCJ) and midcarpal joints (MCJ) as well as the transverse scan of the distal radioulnar joint (DRUJ) and wrist extensor tendons. For finger joints, dorsal and volar aspects of metacarpophalangeal (MCP) joint, volar aspect of proximal interphalangeal (PIP) joint, and extensor and flexor tendons of the second to fifth fingers were examined.[20] The first finger (thumb) was excluded due to its unique anatomy and given the specific technical requirements for MRI scanning.

MSUS images were deidentified and stored in a secured research platform managed by the Imaging Research Center (IRC) at CCHMC. Deidentified images were scored by pediatric rheumatologist experts in MSUS (PVF, TVT) according to the PAUSS, a semiquantitative scoring system (grade range 0–3) for B-mode and PD-mode for the elbow, wrist, and finger joint as indicated.[23] Interrater reliability for scoring synovitis according to the joint-specific PAUSS for these sonographers was found to be excellent in previous studies[20,23] and was reassessed in this study. For the current study, B-mode grade 0 (normal) and grade 1 (mild) findings were interpreted as physiologic, and they were assigned a score of 0, whereby grade 2 (moderate) and grade 3 (severe) B-mode findings received a score of 1 and 2, respectively. For the PD-mode images, grade 1 (mild), grade 2 (moderate), and grade 3 (severe) findings were interpreted as pathologic and assigned a score of 1, 2, and 3, respectively, only if B-mode findings were regarded as positive and PD signals were within the synovial hypertrophy area.[23] Subsequently, the severity of the sonographic findings was calculated with the sum scores assigned to the HRJ, aHUJ, and pHUJ for the PAUSS-elbow total score (range for B-mode: 0–6, PD-mode: 0–9); the RCJ and DRUJ for the PAUSS-wrist total score (range for B-mode: 0–4, PD-mode: 0–6); and the MCP dorsal and volar aspects for the PAUSS-MCP total score (range for B-mode: 0–4, PD-mode: 0–6). The volar aspect of the PIP joint corresponded to the PAUSS-PIP score (range for B-mode: 0–2, PD-mode: 0–3). Tenosynovitis was also graded on a binary scale (1: presence, 0: absence) according to the MSUS definitions of tenosynovitis proposed for JIA.[18]

MRI assessment. A nonsedated ceMRI of the affected joint was offered as an optional study procedure to study participants. A 3T Philips Ingenia scanner (Philips Healthcare) by an 8-channel dStream small upper extremity coil (Philips Healthcare) was used with the following protocol: axial T2 fat-suppressed (FS), coronal T2 FS, sagittal T2 FS, three-dimensional multi-echo fast field echo (sagittal plane for the elbow and finger and in coronal plane for the wrist), and T1 FS postcontrast sequences performed in axial plane for all joints with additional sagittal plane for the elbow and finger and coronal plane for the wrist. MRI images were deidentified and stored in the secured image system managed by the IRC at CCHMC. The Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system, a semiquantitative scoring system, was used for the evaluation of MRI images because it was previously used in children with JIA and identified as an acceptable tool in the evaluation of synovitis.[26–28] A RAMRIS score of 0 indicated normal findings, and scores of 1 to 3 (mild, moderate, severe) were represented by the thirds of presumed maximum volume of the enhancing tissue in the synovial compartment.[29,30] The synovitis was evaluated in the anterior and posterior recesses for the elbow joint; in the area from RCJ, MCJ, and DRUJ to the second to fifth carpometacarpal joints for the wrist joint; and in the MCP and PIP for the finger joints. To grade the severity of the ceMRI findings, the RAMRIS-elbow (range: 0–6) was calculated by the sum of the scores assigned to the anterior and posterior recesses of the elbow joint; the RAMRIS-wrist (range: 0–9) was calculated by the scores in RCJ, MCJ, and DRUJ; the RAMRIS-MCP score (range: 0–3) corresponded to the score in the MCP joint; and the RAMRIS-PIP score (range: 0–3) corresponded to the score in the PIP joint. Tenosynovitis in the wrist and the finger joints, defined by peritendinous effusion and/or postcontrast enhancement of the tendon sheath, was also evaluated using a binary scale (1: presence, 0: absence).[31] MRI images were analyzed by a pediatric musculoskeletal radiologist with more than 10 years of experience (ABM) who was blinded to the CE and MSUS data.

Statistical analysis. Descriptive characteristics were presented by frequency (percentage) for categorical data and by mean ± SD or median (interquartile range) for continuous data. Intraclass correlation coefficient (ICC) was used to analyze the agreement of PAUSS MSUS scores of the two pediatric rheumatologists; values greater than 0.80 indicated almost perfect agreement.[32] For the binary physical examination, PAUSS abnormal, and MRI abnormal variables, repeated measures logistic regression was conducted to assess the associations. Each model was fit separately using participant identifier as the clustering variable. Odds ratios, area under the curve, and corresponding 95% confidence intervals (CIs) are reported. To evaluate the association between physical examination findings and PAUSS severity scores as continuous variables, we computed Spearman's rank correlation coefficient using participant-level summaries. This approach preserves the rank-based nature of Spearman's correlation while addressing the repeated measures structure of the data with the correlations well as the corresponding 95% CI reported. Subclinical synovitis was defined as presence of moderate to severe findings of synovitis on MSUS but with normal CE findings. The strength of correlation was evaluated as follows: very weak (0.0–0.19), weak (0.2–0.39), moderate (0.4–0.59), strong (0.6–0.79), or very strong (0.8–1.0).[33] In addition, sensitivity and specificity values were reported. The diagnostic accuracy of CE and MSUS against ceMRI was calculated by an area under the receiver operating characteristic curve (AUC). An AUC below 0.5 defines no discrimination, 0.7 to 0.8 is defined as good, 0.8

to 0.9 is defined as excellent, and greater than 0.9 is defined as outstanding.[34] The specificity and AUC could not be calculated if one group had a sample size of 0. Discrepancies between MSUS and MRI findings were reviewed by the study team after initial data analysis was completed. The SAS 9.4 was used for statistical analyses and statistical significance was accepted when two-sided testing resulted in $P < 0.05$.

RESULTS

Patient characteristics. A total of 24, 29, and 22 children participated in the validation of the PAUSS-elbow, wrist, and finger study, respectively. Overall, rheumatoid factor–negative polyarthritis was the most common subtype of JIA, and all patients were receiving pharmacologic therapy for JIA. Patient characteristics in validation studies per joint are presented in Table 1.

MSUS and CE of arthritis. A total of 44 elbows, 55 wrists, and 106 fingers were included in the association analysis between MSUS and CE. The PAUSS scores for each joint had excellent interrater reliability (ICC ≥ 0.80). Due to the low frequency of PD positivity in our study sample, only B-mode data were included in the analysis.

The association between PAUSS and CE findings is shown in Table 2. Although 36% (n = 16), 38% (n = 21), 20% (n = 21), and 45% (n = 44) of the elbow, wrist, MCP, and PIP joints were found to be positive for active arthritis by CE, 55% (n = 24), 60% (n = 33), 25% (n = 26), and 40% (n = 39) of these joints were positive for synovitis on MSUS, respectively. Subclinical synovitis as defined by MSUS was found in 36% of the elbow joints, 47% of the wrist joints, 20% of the MCP joints, and 28% of the PIP joints scanned. The highest association for MSUS synovitis in the presence of clinically active arthritis was observed for the elbow joint (odds ratio = 11.5; $P = 0.021$). The PAUSS B-mode scores demonstrated moderate significant correlations with CE of arthritis for the MCP and PIP joints ($r = 0.43$; $P = 0.039$ and $r = 0.59$; $P = 0.004$, respectively), strong significant correlation ($r = 0.75$; $P < 0.001$) for the elbow joint, and no correlation for the wrist joint.

MSUS, CE, and ceMRI assessment of arthritis. A total of 15 ceMRI studies for the elbow, 16 for the wrist, and 10 for the hands (40 fingers, including 39 MCP and 40 PIP joints) along with their corresponding CE and MSUS data were included for these analyses. ceMRI was found to be positive for synovitis in 66.7% (n = 11) of the elbows, 100% (n = 16) of the wrists, 31% (n = 12) of the MCP joints, and 47.5% (n = 19) of the PIP joints included in the study.

Test characteristics of the PAUSS scores and CE when compared to ceMRI as the reference standard are presented in Table 3. Overall, the sensitivity and diagnostic accuracy of the

Table 1. Details on patient disease involvement characteristics per joint*

	Elbow (n = 24)	Wrist (n = 29)	Finger (n = 22)
Total number of joints in the study	44	55	106
Age, mean ± SD y	13.7 ± 4.3	13.0 ± 3.5	13.1 ± 4.1
Age at diagnosis, median (IQR), y	7.7 (4.2–12.4)	7 (4–12)	14.4 (9.2–15.4)
Disease duration, median (IQR), y	4.5 (0.7–7.6)	3.2 (1.8–5.2)	2.5 (0.7–8.4)
Sex, n (%)			
Female	17 (70.8)	24 (82.8)	16 (72.7)
Male	7 (29.2)	5 (17.2)	6 (27.3)
JIA subtype, n (%)			
Oligoarticular JIA, persistent	3 (12.5)	3 (10.3)	2 (9.1)
Oligoarticular JIA, extended	1 (4.2)	3 (10.3)	2 (9.1)
Polyarticular JIA, RF negative	12 (50.0)	12 (41.4)	11 (50.0)
Polyarticular JIA, RF positive	2 (8.3)	5 (17.2)	3 (13.6)
Psoriatic arthritis	3 (12.5)	3 (10.3)	1 (4.5)
Enthesitis related arthritis	1 (4.2)	0 (0)	0 (0)
Systemic JIA	1 (4.2)	2 (6.9)	0 (0)
Undifferentiated JIA	1 (4.2)	1 (3.5)	3 (13.6)
Physician global assessment of disease activity,[a] median (IQR)	2.0 (1.4–3.0)	1.5 (0–2)	1.5 (0.5–2.0)
Treatment, n (%)			
No	0 (0)	0 (0)	0 (0)
Yes[b]			
NSAIDs	16 (66.7)	21 (72.4)	16 (72.7)
Conventional DMARDs	16 (66.7)	18 (62.1)	14 (63.6)
Biologic DMARDs	15 (62.5)	26 (89.7)	10 (45.5)
Oral glucocorticoid	10 (41.7)	11 (37.9)	9 (40.9)
Intravenous glucocorticoid	1 (4.2)	0 (0)	0 (0)

* DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; JIA, juvenile idiopathic arthritis; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor.
[a] Physician global assessment of disease activity ranges from 0 (inactive disease) to 10 (very active disease).
[b] List is not mutually exclusive.

Table 2. Association between MSUS findings and CE of arthritis in elbow, wrist, and finger joints*

MSUS[a]	CE		Odds ratio[b] (95% CI); *P* value
	Negative for active arthritis, n (%)	Positive for active arthritis, n (%)	
Elbow, n (%)			
Negative for synovitis	18 (64.3)	2 (12.5)	11.5 (1.5–86.9); 0.021
Positive for synovitis	10 (35.7)	14 (87.5)	
Wrist, n (%)			
Negative for synovitis	18 (52.9)	4 (19.1)	4.52 (1.1–18.9); 0.040
Positive for synovitis	16 (47.1)	17 (80.9)	
MCP joint, n (%)			
Negative for synovitis	68 (80.0)	12 (57.1)	3.10 (0.76–12.6); 0.113
Positive for synovitis	17 (20.0)	9 (42.9)	
PIP joint, n (%)			
Negative for synovitis	39 (72.2)	20 (45.5)	1.61 (0.47–5.5); 0.443
Positive for synovitis	15 (27.8)	24 (54.5)	
PAUSS[c]			
PAUSS-elbow total B-mode score, median (IQR)	0 (0–1)	3 (3–3)	0.75 (0.51–0.88); <0.001
PAUSS-wrist total B-mode score, median (IQR)	0 (0–1)	1 (1–2)	0.25 (−0.11 to 0.56); 0.170
PAUSS-MCP B-mode score, median (IQR)	0 (0–0)	0 (0–3)	0.43 (0.02–0.72); 0.039
PAUSS-PIP B-mode score, median (IQR)	0 (0–0)	1 (0–2)	0.59 (0.21–0.81); 0.004

* CE, clinical examination; CI, confidence interval; MCP, metacarpophalangeal; MSUS, musculoskeletal ultrasound; IQR, interquartile range; PAUSS, Pediatric Arthritis Ultrasound Scoring System; PIP, proximal interphalangeal.
[a] Positive MSUS findings are defined by B-mode grades 2 or 3.
[b] For PAUSS scores, values are given as correlation (95% CI).
[c] Strength of the correlation calculated using Point-Biserial correlations as follows: very weak: 0.0–0.19, weak: 0.2–0.39, moderate 0.4–0.59, strong 0.6–0.79, very strong 0.8–1.0.

Table 3. Test characteristics of CE and MSUS assessments for findings of arthritis in elbow, wrist, and finger joints as determined by ceMRI*

	ceMRI		Sensitivity (95% CI), specificity (95% CI)	AUC (95% CI)
	Negative for synovitis, n (%)	Positive for synovitis, n (%)		
Elbow				
Negative for CE of arthritis	3 (75.0)	3 (30.0)	0.70 (0.35–0.93), 0.75 (0.19–0.99)	0.72 (0.44–1.00)
Positive for CE of arthritis	1 (25.0)	7 (70.0)		
Negative for MSUS synovitis	3 (75.0)	1 (9.0)	0.90 (0.56–1.00), 0.75 (0.19–0.99)	0.82 (0.56–1.00)
Positive for MSUS synovitis[a]	1 (25.0)	9 (90.0)		
Negative for CE of arthritis and/or MSUS synovitis	2 (50.0)	0 (0.0)	1.00 (1.00–1.00), 0.50 (0.07–0.93)	0.75 (0.47–1.00)
Positive for CE of arthritis and/or MSUS synovitis	2 (50.0)	10 (100)		
Wrist				
Negative for CE of arthritis	0 (0.0)	9 (56.3)	0.43 (0.20–0.70)	–
Positive for CE of arthritis	0 (0.0)	7 (43.7)	–	
Negative for MSUS synovitis	0 (0.0)	1 (6.3)	0.94 (0.70–1.00)	–
Positive for MSUS synovitis[a]	0 (0.0)	15 (93.7)	–	
Negative for CE of arthritis and/or MSUS synovitis	0 (0.0)	1 (6.3)	0.94 (0.70–1.00)	–
Positive for CE of arthritis and/or MSUS synovitis	0 (0.0)	15 (93.7)	–	
MCP				
Negative for CE of arthritis	22 (81.5)	6 (50.0)	0.50 (0.21–0.79), 0.81 (0.61–0.94)	0.66 (0.49–0.82)
Positive for CE of arthritis	5 (18.5)	6 (50.0)		
Negative for MSUS synovitis	22 (81.5)	3 (25.0)	0.75 (0.43–0.95), 0.81 (0.62–0.94)	0.72 (0.56–0.88)
Positive for MSUS synovitis[a]	5 (18.5)	9 (75.0)		
Negative for CE of arthritis and/or MSUS synovitis	19 (70.4)	1 (8.3)	0.92 (0.62–1.00), 0.70 (0.50–0.86)	0.75 (0.61–0.89)
Positive for CE of arthritis and/or MSUS synovitis	8 (29.6)	11 (91.7)		
PIP				
Negative for CE of arthritis	15 (71.4)	3 (15.8)	0.84 (0.60–0.97), 0.71 (0.47–0.88)	0.77 (0.64–0.91)
Positive for CE of arthritis	6 (28.6)	16 (84.2)		
Negative for MSUS synovitis	17 (81.0)	2 (10.5)	0.89 (0.67–0.99), 0.81 (0.58–0.94)	0.85 (0.74–0.96)
Positive for MSUS synovitis[a]	4 (19.0)	17 (89.5)		
Negative for CE of arthritis and/or MSUS synovitis	13 (61.9)	0 (0)	1.00 (0.82–1.00), 0.62 (0.38–0.82)	0.81 (0.71–0.86)
Positive for CE of arthritis and/or MSUS synovitis	8 (38.1)	19 (100)		

* AUC, area under receiver operating characteristic curve; CE, clinical examination; ceMRI, contrast-enhanced magnetic resonance imaging; CI, confidence interval; MCP, metacarpophalangeal; MSUS, musculoskeletal ultrasound; PIP, proximal interphalangeal.
[a] Positive MSUS findings defined as B-mode grade 2 or 3.

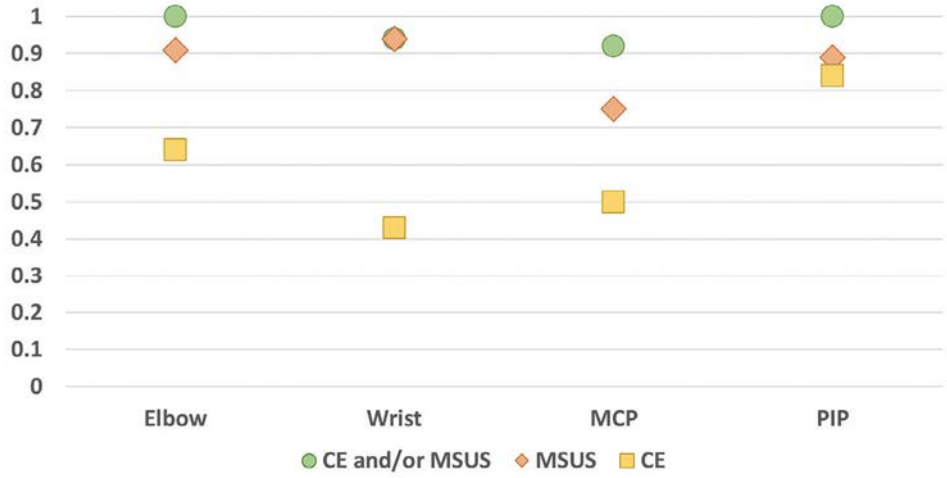

Figure 1. Sensitivity of CE, MSUS, and combination of CE and MSUS findings (CE and/or MSUS) for detection of arthritis in elbow, wrist, and finger joints when compared to contrast-enhanced magnetic resonance imaging. CE, clinical examination; MCP, metacarpophalangeal; MSUS, musculoskeletal ultrasound; PIP, proximal interphalangeal.

PAUSS scores were both higher than CE for all joints, whereas the specificity of the PAUSS scores was found to be similar to slightly higher than CE. The PAUSS scores for elbow, MCP, and PIP joints demonstrated good to excellent diagnostic accuracy for synovitis when using ceMRI as the reference standard. Furthermore, when PAUSS scores and CE were used in conjunction, the sensitivity to detect arthritis markedly improved to 92% to 100%, whereas the specificity decreased (Figure 1). All wrists imaged by ceMRI were positive for the presence of synovitis, which precluded the evaluation of the PAUSS-wrist specificity and diagnostic accuracy. The sensitivity and specificity of PAUSS scores in detecting synovitis at specific anatomic joint recesses for the elbow and wrist when compared to ceMRI, as the reference standard, are presented in Supplementary Table 1. The reasons for discrepancies between MSUS and ceMRI for the evaluation of synovitis are represented in Supplementary Tables 2–4.

The correlation between the PAUSS and RAMRIS scores of elbow, wrist, MCP, and PIP findings of synovitis is demonstrated in Table 4. The PAUSS and RAMRIS scores were found to be strongly correlated for each specific joint (r = 0.65–0.76; all P < 0.017). MSUS was found to have excellent diagnostic accuracy for detecting tenosynovitis in the extensor tendons of the wrist and extensor and flexor tendons of the fingers when using ceMRI as the reference standard (Supplementary Table 5).

DISCUSSION

This study compared the PAUSS of the elbow, wrist, and finger joints against CE and ceMRI assessments in children with JIA, providing key details on the validity of the PAUSS for these upper extremity joints. The joint-specific PAUSS demonstrated good to excellent diagnostic accuracy in detecting synovitis in these joints when using ceMRI as the reference standard. In regard to the detection of the severity of joint inflammation, the PAUSS scores highly correlated with the RAMRIS scores. When the PAUSS scores were added to the CE, the sensitivity and accuracy of CE for the detection of arthritis improved. In addition, the PAUSS also demonstrated excellent diagnostic accuracy for wrist and finger tenosynovitis.

The elbow, wrist, and finger joints are among the most common joints involved in JIA.[35] However, the determination of arthritis in these joints by CE is challenging. Disagreement on the clinical determination of arthritis in the joints, particularly in the assessment of joint swelling and LROM, has been related to the subjective nature of CE, mainly to clinicians' differences in judgment and examination technique, as well as to the severity

Table 4. Association of PAUSS B-mode and RAMRIS scores of each specific joint*

	RAMRIS score,[a] Spearman correlation (95% CI); P value[b]
PAUSS-elbow (n = 14), total B-mode score	0.74 (0.34–0.91); 0.002
PAUSS-wrist (n = 16), total B-mode score	0.65 (0.24–0.87); 0.005
PAUSS-finger (n = 11)	
MCP B-mode score	0.69 (0.15–0.91); 0.017
PIP B-mode score	0.76 (0.31–0.93); 0.004

* CI, confidence interval; MCP, metacarpophalangeal; PAUSS, Pediatric Arthritis Ultrasound Scoring System; PIP, proximal interphalangeal; RAMRIS, rheumatoid arthritis magnetic resonance imaging scoring.
[a] The RAMRIS scores correspond to each specific joint, ie, RAMRIS-elbow, RAMRIS-wrist, RAMRIS-MCP, and RAMRIS-PIP.
[b] The strength of the correlation calculated using Spearman rank order correlations as follows: very weak: 0.0–0.19, weak: 0.2–0.39, moderate: 0.4–0.59, strong: 0.6–0.79, very strong: 0.8–1.0.

of the disease.[3] Subclinical synovitis has been reported to be the highest in the MCP (44%) and PIP joints (38%) while also being common in the elbow (33%) and wrist (22%) joints.[36] Interestingly, in our study subclinical synovitis as defined by MSUS and ceMRI was most commonly observed in the wrist joint when either comparing CE findings to MSUS findings (47% of wrists with subclinical synovitis) or to ceMRI findings (56% of wrists with synovitis). Our study suggests that determination of elbow, wrist, and finger involvement by CE alone underestimates JIA disease burden and that the addition of MSUS, as an objective and standardized bedside tool, may support a more accurate determination of JIA disease activity which may result in more targeted treatment approaches and consequently in improved outcomes in these vulnerable patients.

Although MSUS is increasingly used in the clinical care of adults with inflammatory arthritis, knowledge of the validity of MSUS in pediatrics remains sparse. A recent meta-analysis in rheumatoid arthritis (RA) found the summary estimates of sensitivity, specificity, and accuracy of MSUS against MRI as the reference to be 73%, 78%, and 81% for the wrist joint; 64%, 93%, and 91% for the MCP joint; and 71%, 94%, and 91% for the PIP joints, respectively.[37] Similarly, Szkudlarek et al determined that the sensitivity, specificity, and accuracy in detecting signs of inflammation in finger joints were 70%, 78%, and 76% for MSUS and 40%, 85%, and 72% for CE in adults with RA, when using MRI as the reference method.[38] However, the validation of MSUS in elbow involvement has been incorporated into very few studies in RA mainly focusing on enthesitis,[39] and to our knowledge, there are no studies in JIA. Our results are consistent with adult data in that the PAUSS for elbow, wrist, MCP, and PIP joints had higher sensitivity in detecting synovitis without loss of specificity when compared to CE. In addition, to the best of our knowledge, this study provided initial results on the validity of the use of MSUS for the assessment of elbow synovitis. Notoriously, in our study tenosynovitis was not detected by CE but MSUS demonstrated excellent accuracy detecting tenosynovitis over the extensor tendons of the wrist and finger joints. The improved sensitivity for the detection of arthritis in elbow, wrist, MCP, and PIP joints, and wrist and finger tenosynovitis, as defined by ceMRI, when adding the MSUS information to CE, emphasizes the additive value of MSUS for the detection of inflammation in these joints to support JIA diagnosis and disease monitoring.

Owing to the high sensitivity of ceMRI in detecting soft tissue and joint inflammation as well as osteochondral changes and damage, ceMRI is considered the reference standard for the detection of synovitis.[7] Although pediatric-specific MRI scoring systems for elbow, wrist, MCP and/or PIP synovitis have not been validated, the OMERACT-RAMRIS system has been found to be a reliable tool for assessing disease activity in JIA.[40,41] To support the use of MSUS as an accurate instrument for the assessment of the severity of JIA disease activity, we investigated the correlation of the PAUSS scores with the OMERACT-RAMRIS scores. The strong correlations of the joint-specific PAUSS scores with the RAMRIS scores detected in the elbow, wrist, MCP, and PIP joints underpin the utility of the PAUSS as an outcome measure of disease severity. Future larger studies investigating the correlations of the joint-specific PAUSS with conventional measures of disease activity and determination of its sensitivity to change are necessary to support the use of MSUS as an outcome measure in JIA.

For ethical considerations, due to invasive nature of ceMRI, children enrolled in this study needed to have symptoms and/or clinical findings suggestive of arthritis in the elbow, wrist, or finger joints. This enrollment criterion may have introduced selection bias favoring the presence of pathology. Indeed, although more than 50% of wrist joints included in the ceMRI arm were classified as normal by CE, all of these wrist joints were positive for synovitis by ceMRI. This is an unforeseen limitation of our study and precludes determination of the specificity and accuracy analysis for the PAUSS-wrist. This limitation, however, highlights the value of MSUS and ceMRI as complementary tools to CE, as they have the availability to specifically examine the RCJ, MCJ and DRUJ, which is challenging to accurately assess clinically. Given variability in the severity of synovitis findings according to ceMRI for all of the examined joints, our study suggests that the PAUSS can serve as a bedside objective proxy instrument to determine the severity of disease activity. Discrepancy between MSUS and MRI findings of synovitis are reported in adult literature.[37] For our study, the explanations for discrepancies are discussed in Supplementary Tables 2–4. Borderline findings of synovitis as determined by MSUS and/or ceMRI, as well as different positioning of the joint during the scanning sessions, were the most common explanation for discrepancies between these two imaging modalities. To avoid overcalling for pathology, only grade 2 or 3 MSUS B-mode findings were classified as pathologic in our study. Although PD settings were carefully adjusted for all anatomic sites, we detected a low frequency of abnormal PD signals. However, the improved sensitivity of B-mode findings over the CE findings for the detection of synovitis when using ceMRI as reference standard suggests that PD findings are not essential for MSUS detection of synovitis in JIA. Of note, all participants had good tolerance to the MSUS examination, but the majority of the children who completed an elbow ceMRI complained of significant pain during the MRI scanning due to the positioning of the elbow joint.

The subjective nature of the clinical determination of joint inflammation makes it desirable to have access to a more objective, accurate, noninvasive, and readily available tool to support the medical decision-making process in JIA. This study provides data on the sensitivity, specificity, and accuracy of the PAUSS-elbow, -wrist, -MCP, and -PIP as an outcome measure for the detection and severity assessment of synovitis in the elbows, wrists, and fingers, and wrist and finger tenosynovitis in JIA. The improved accuracy of CE, when PAUSS scores were considered,

demonstrates that MSUS improves the determination of disease burden and, therefore, can optimize the management of JIA.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Vega-Fernandez confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Costello A, Rasooly I, Weiss P. Rheum for improvement? Delayed diagnosis of juvenile idiopathic arthritis: a narrative review. Arthritis Care Res (Hoboken) 2025;77(3):283–290.
2. Trincianti C, Van Dijkhuizen EHP, Alongi A, et al; Paediatric Rheumatology International Trials Organisation. Definition and validation of the American College of Rheumatology 2021 juvenile arthritis disease activity score cutoffs for disease activity states in juvenile idiopathic arthritis. Arthritis Rheumatol 2021;73(11):1966–1975.
3. Guzmán J, Burgos-Vargas R, Duarte-Salazar C, et al. Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. J Rheumatol 1995;22(12):2331–2336.
4. Backström M, Tarkiainen M, Gottlieb BS, et al. Paediatric rheumatologists do not score the physician's global assessment of juvenile idiopathic arthritis disease activity in the same way. Rheumatology (Oxford) 2023;62(10):3421–3426.
5. Eng SWM, Aeschlimann FA, van Veenendaal M, et al; ReACCh-Out Research Consortium. Patterns of joint involvement in juvenile idiopathic arthritis and prediction of disease course: a prospective study with multilayer non-negative matrix factorization. PLoS Med 2019;16(2):e1002750.
6. Colebatch-Bourn AN, Edwards CJ, Collado P, et al. EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. Ann Rheum Dis 2015;74(11):1946–1957.
7. Malattia C, Tolend M, Mazzoni M, et al. Current status of MR imaging of juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 2020;34(6):101629.
8. Tarsia M, Zajc Avramovič M, Gazikalović A, et al. A clinical perspective on imaging in juvenile idiopathic arthritis. Pediatr Radiol 2024;54(4):490–504.
9. Borocco C, Anselmi F, Rossi-Semerano L. Contribution of ultrasound in current practice for managing juvenile idiopathic arthritis. J Clin Med 2022;12(1):91.
10. Wittoek R, Decock C, Dewaele N, et al. Structural ultrasound of joints and tendons in healthy children: development of normative data. Pediatr Rheumatol Online J 2023;21(1):105.
11. Collado P, Vojinovic J, Nieto JC, et al; Omeract Ultrasound Pediatric Group. Toward standardized musculoskeletal ultrasound in pediatric rheumatology: normal age-related ultrasound findings. Arthritis Care Res (Hoboken) 2016;68(3):348–356.
12. Trauzeddel R, Lehman H, Trauzeddel RF, et al. Age dependent ultrasound B-mode findings of the elbow joint in healthy children and adolescents. Rheumatol Int 2019;39(6):1007–1018.
13. Rosendahl K, Bruserud IS, Oehme N, et al. Normative ultrasound references for the paediatric wrist; dorsal soft tissues. RMD Open 2018;4(1):e000642.
14. Collado P, Windschall D, Vojinovic J, et al; OMERACT ultrasound subtask force on pediatric. Amendment of the OMERACT ultrasound definitions of joints' features in healthy children when using the DOPPLER technique. Pediatr Rheumatol Online J 2018;16(1):23.
15. Rossi-Semerano L, Breton S, Semerano L, et al. Application of the OMERACT synovitis ultrasound scoring system in juvenile idiopathic arthritis: a multicenter reliability exercise. Rheumatology (Oxford) 2021;60(8):3579–3587.
16. Roth J, Jousse-Joulin S, Magni-Manzoni S, et al; Outcome Measures in Rheumatology Ultrasound Group. Definitions for the sonographic features of joints in healthy children. Arthritis Care Res (Hoboken) 2015;67(1):136–142.
17. Rossi-Semerano L, Ravagnani V, Collado P, et al. Validity of ultrasonography in detecting enthesitis in children: a systematic literature review. Joint Bone Spine 2023;90(4):105538.
18. Collado P, Martire MV, Lanni S, et al; OMERACT Ultrasound Group. OMERACT International Consensus for ultrasound definitions of tenosynovitis in juvenile idiopathic arthritis: systematic literature review and Delphi process. Arthritis Care Res (Hoboken) 2023;75(11):2277–2284.
19. Vega-Fernandez P, Ting TV, Pratt L, et al. Ultrasonography in pediatric rheumatology. Rheum Dis Clin North Am 2022;48(1):217–231.
20. Vega-Fernandez P, Ting TV, Oberle EJ, et al; CARRA Musculoskeletal Ultrasound Workgroup. Musculoskeletal ultrasound in childhood arthritis limited examination: a comprehensive, reliable, time-efficient assessment of synovitis. Arthritis Care Res (Hoboken) 2023;75(2):401–409.
21. Sande NK, Bøyesen P, Aga AB, et al. Development and reliability of a novel ultrasonographic joint-specific scoring system for synovitis with reference atlas for patients with juvenile idiopathic arthritis. RMD Open 2021;7(2):e001581.
22. Vojinovic J, Magni-Manzoni S, Collado P, et al. SAT0636 Ultrasonography definitions for synovitis grading in children: the OMERACT pediatric ultrasound task force. Ann Rheum Dis 2017;76(Suppl 2):1015.
23. Vega-Fernandez P, Esteban Y, Oberle E, et al; CARRA JIA Ultrasound Workgroup. Reliability of the pediatric specific musculoskeletal ultrasound scoring systems for the elbow, wrist, and finger joints. J Rheumatol 2023;50(2):236–239.
24. Collado P, Naredo E, Calvo C, et al; ECO-JIA Study Group. Reduced joint assessment vs comprehensive assessment for ultrasound detection of synovitis in juvenile idiopathic arthritis. Rheumatology (Oxford) 2013;52(8):1477–1484.
25. Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31(2):390–392.
26. Malattia C, Damasio MB, Pistorio A, et al. Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis. Ann Rheum Dis 2011;70(3):440–446.
27. Hemke R, Doria AS, Tzaribachev N, et al. Selecting magnetic resonance imaging (MRI) outcome measures for juvenile idiopathic arthritis (JIA) clinical trials: first report of the MRI in JIA special interest group. J Rheumatol 2014;41(2):354–358.
28. Mazzoni M, Pistorio A, Magnaguagno F, et al. Predictive value of magnetic resonance imaging in patients with juvenile idiopathic arthritis in clinical remission. Arthritis Care Res (Hoboken) 2023;75(1):198–205.
29. Østergaard M, Peterfy CG, Bird P, et al. The OMERACT rheumatoid arthritis magnetic resonance imaging (MRI) scoring system: updated recommendations by the OMERACT MRI in arthritis working group. J Rheumatol 2017;44(11):1706–1712.

30. Østergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003;30(6):1385–1386.
31. Haavardsholm EA, Østergaard M, Ejbjerg BJ, et al. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis 2007;66(9):1216–1220.
32. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15(2): 155–163.
33. Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. Malawi Med J 2012;24(3):69–71.
34. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5(9):1315–1316.
35. Hemke R, Nusman CM, van der Heijde DMFM, et al. Frequency of joint involvement in juvenile idiopathic arthritis during a 5-year follow-up of newly diagnosed patients: implications for MR imaging as outcome measure. Rheumatol Int 2015;35(2):351–357.
36. Vega-Fernandez P, Oberle EJ, Henrickson M, et al; Childhood Arthritis and Rheumatology Research Alliance Investigators. Musculoskeletal ultrasound and the assessment of disease activity in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2023;75(8):1815–1820.
37. Takase-Minegishi K, Horita N, Kobayashi K, et al. Diagnostic test accuracy of ultrasound for synovitis in rheumatoid arthritis: systematic review and meta-analysis. Rheumatology (Oxford) 2018;57(1):49–58.
38. Szkudlarek M, Klarlund M, Narvestad E, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. Arthritis Res Ther 2006;8(2):R52.
39. Joshua F, Lassere M, Bruyn GA, et al. Summary findings of a systematic review of the ultrasound assessment of synovitis. J Rheumatol 2007;34(4):839–847.
40. Malattia C, Consolaro A, Pederzoli S, et al. MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis. Ann Rheum Dis 2013;72(3):363–368.
41. van Dijkhuizen EHP, Vanoni F, Magnano GM, et al; OMERACT Working Group MRI in JIA. Effect of the inclusion of the metacarpophalangeal joints on the wrist magnetic resonance imaging scoring system in juvenile idiopathic arthritis. J Rheumatol 2018;45(11):1581–1587.

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 914–924
DOI 10.1002/acr.70001

Sex Differences in Medication Discontinuation in Axial Spondyloarthritis

Rachael Stovall,[1] Cinthia Blat,[2] Eric Roberts,[2] Jean W. Liew,[3] Katherine Wysham,[1,4] Namrata Singh,[1] Janna Friedly,[1] Lianne S. Gensler,[2] Gabriela Schmajuk,[2,5,6] and Jinoos Yazdany[2]

Objective. We examined sex differences in medication discontinuation among patients with axial spondyloarthritis (axSpA) initiating tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), or JAK inhibitors (JAKi).

Methods. Using data from the Rheumatology Informatics System for Effectiveness (RISE) Registry (2003–2025), we assessed medication discontinuation by sex among new users of TNFi, IL-17i, and JAKi. Cox regression models were used to evaluate associations between sex and treatment discontinuation, adjusting for sociodemographic and clinical factors. We also examined medication continuation by sex and age group (18–64 vs ≥65 years) using Kaplan-Meier curves and tested for interactions between sex and age, race, and area deprivation index (ADI).

Results. Among 7,200 individuals, the mean ± SD age was 52.7 ± 14.7 years; 58.3% were female and 68.7% were non-Hispanic White. Among TNFi users (N = 6,256), women had a 24% higher risk of discontinuation compared to men (hazard ratio [HR]: 1.24; 95% confidence interval [CI]: 1.16–1.32). Among IL-17i users (n = 693), women had a 25% higher risk of discontinuation (HR: 1.25; 95% CI: 1.01–1.54). No significant sex differences were observed among JAKi users (N = 251). Among TNFi users, women under 65 years had the lowest probability of treatment continuation. There was no statistically significant interaction between sex and age, race or ADI.

Conclusions. In a large US registry, women with axSpA were more likely to discontinue TNFi and IL-17i than men. Larger studies with longer follow-up since treatment approval are needed to confirm the lack of sex differences in JAKi discontinuation as this group could be underpowered.

INTRODUCTION

Axial spondyloarthritis (axSpA) is an inflammatory disease primarily affecting the axial skeleton but may also involve peripheral joints and extramusculoskeletal manifestations. Although early evidence mistakenly suggested that axSpA primarily affects men, it is now recognized that the disease occurs with equal prevalence in both men and women.[1] Despite this, women often experience longer diagnostic delays, report worse symptoms, and exhibit greater functional impairment than men.[1,2] These differences highlight the potential influence of sex on disease manifestations, treatment response, and outcomes in axSpA.

Tumor necrosis factor inhibitors (TNFi) have long been a second-line treatment in axSpA,[3] after nonsteroidal anti-inflammatory drugs

Data collection was supported by the American College of Rheumatology's (ACR) Rheumatology Informatics System for Effectiveness registry. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the ACR, the Department of Veterans Affairs, or the United States government.

Funding for this project was provided by Dr Stovall's Spondyloarthritis Research & Treatment Network (SPARTAN) Early Career Investigator Award. Dr Stovall's work was also supported by the Spondylitis Association of America Jane Bruckel Early Career Investigator Award. Dr Liew's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH (grant K23-AR-082938); the Rheumatology Research Foundation Investigator Award; a SPARTAN pilot grant; and the Spondylitis Association of American Jane Bruckel Early Career Investigator Award. Dr Singh's work was supported by the NIAMS, NIH (award K23-AR-079588), and by the National Institute on Aging, NIH (award R03-AG-082857). Dr Friedly's work was supported by the UW Clinical Learning, Evidence And Research Center, which is funded by the NIAMS, NIH (award 2P30-AR-072572-07). Dr Yazdany's work was supported by the NIAMS, NIH (grant K24-AR-074534).

[1]University of Washington, Seattle; [2]University of California, San Francisco; [3]Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts; [4]VA Puget Sound Health Care System, Seattle, Washington; [5]San Francisco VA Health Care System, San Francisco, California; [6]University of California, San Francisco Institute for Health Policy Research.

The American College of Rheumatology (ACR) owns the data in the Rheumatology Informatics System for Effectiveness (RISE) registry, and University of California, San Francisco, as a Data Analytic Center for the ACR, has access to the data for specific research projects, including this one, but is contractually obligated through data use agreements with practices to not share these data, even in a deidentified state. Researchers interested in performing additional analyses from these data are invited to submit proposals to the ACR RISE registry.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70001).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70001.

Address correspondence via email to Rachael Stovall, MD, MAS, at stovall@uw.edu.

Submitted for publication June 2, 2025; accepted in revised form November 3, 2025.

SIGNIFICANCE & INNOVATIONS

- This study is one of the first to evaluate sex differences in medication discontinuation in axial spondyloarthritis beyond tumor necrosis factor inhibitor (TNFi) use using real-world data.
- In the TNFi and interleukin-17 inhibitor (IL-17i) groups, women had a 24% and 25% higher risk of discontinuation, respectively, compared to men.
- There was no medication discontinuation difference by sex in JAK inhibitor use, although the sample size was smaller.
- These results inform our understanding of real-world use of these medications so that in future research, we can better understand sex differences in medication use and efficacy, ascertain ways to bridge any identified gaps, and aid in individualized-treatment shared-decision-making between patients and clinicians.

(NSAIDs), and most existing literature on sex-based treatment differences derives from studies of this drug class. Women appear less likely than men to achieve clinical response, demonstrating higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, lower remission rates, and greater functional impairment during TNFi therapy.[1,4–7] Observational data further suggest that women are more likely to discontinue or switch TNFi earlier than men.[4,7] Pooled analyses from four etanercept clinical trials stratified by sex also showed lower response—measured by Ankylosing Spondylitis Disease Activity Score and BASDAI—and lower adherence in women.[8] Collectively, these findings point to meaningful sex-based differences in TNFi treatment persistence and response.

With the expansion of newer therapeutic options, including interleukin-17 inhibitors (IL-17i) and JAK inhibitors (JAKi), the treatment landscape for axSpA has broadened considerably.[9] These newer agents have demonstrated efficacy in randomized controlled trials (RCTs) and are now routinely used in clinical practice.[10,11] However, it remains unclear whether the sex-based differences observed with TNFi extend to these newer drug classes.

Real-world evidence is well suited to address this knowledge gap. Although RCTs provide critical efficacy and safety data, they often underrepresent women with axSpA, lack sufficient power to detect sex-specific differences in treatment outcomes, and infrequently report sex-stratified outcomes.[12] Meta-analyses of RCTs confirm that sex-stratified data are inconsistently reported and, when available, suggest men derive greater benefit from TNFi and IL-17i.[12,13] In contrast, real-world studies encompass broader and more diverse patient populations, including those from racial and ethnic minorities, those with lower socioeconomic status (SES) or health literacy, those with multiple comorbidities, and pregnant or breastfeeding individuals. These groups may have different treatment responses, tolerability, or adherence barriers not captured in clinical trials. Therefore, large observational studies are needed to better understand treatment differences beyond clinical trials by sex in axSpA.

To address these gaps, we conducted a large national study using the Rheumatology Informatics System for Effectiveness (RISE) registry, a US-based electronic health record (EHR) registry of patients with rheumatic diseases, to examine sex differences in treatment discontinuation among individuals with axSpA treated with TNFi, IL-17i, or JAKi. We aimed to include a diverse population with respect to race, ethnicity, SES, and comorbidities. We hypothesized that women would have a higher rate of medication discontinuation across all three medication classes compared to men.

METHODS

Data source. We conducted a retrospective cohort study using data from the RISE registry from 2003 to 2025. RISE captures EHR data from routine outpatient care in participating rheumatology practices across the United States. Through the end date of this study, the registry included data from more than 1,100 providers representing approximately 20% of the national clinical rheumatology workforce.[14] Most RISE practices are community-based single or multi-rheumatologist private practices. Designed to integrate seamlessly into clinical workflows, RISE does not require additional data entry into a separate database. Instead, it extracts structured EHR data—such as diagnoses, medications, laboratory results, and patient-reported outcomes—along with clinical notes. The registry is compatible with most certified EHR systems, with NextGen, eClinicalWorks, AllScripts, and Practice Fusion being the most commonly used platforms.

Study sample. To identify individuals with prevalent axSpA, we used International Classification of Diseases (ICD) 9th and 10th Revision codes (720.0, M45.x, M46.8) in the RISE registry from January 1, 2003, to March 31, 2025. Individuals were eligible for cohort inclusion if they were ≥18 years of age at the time of the study start, had two or more ICD codes for axSpA recorded ≥30 days apart in the RISE registry, and had a medication-free period of at least six months followed by at least two prescriptions for the same medication within the TNFi, IL-17i, or JAKi classes between 2003 and 2025. The ICD codes for axSpA were linked to a rheumatology clinic visit, ensuring that all patients had documented visits before follow-up in the study. We employed a new-user design, meaning patients were considered to be initiating treatment with a TNFi, IL-17i, or JAKi after six months with none of these medications prescribed (also known as a washout period). We chose 6 months, as opposed to 12 months, because many patients are started on a biologic within the first year of seeing a rheumatologist, and requiring a longer washout period would significantly reduce our sample size and bias our sample

toward the healthiest patients. The requirement of at least two prescriptions for the same medication ensured that patients had truly started therapy, as initial prescriptions are frequently abandoned due to barriers such as prior authorization issues, cost, or patient preferences. This design allowed us to focus on individuals who initiated and continued treatment. Supplementary Table 1 describes the number of patients in RISE that met criteria for our study based on our inclusion and exclusion criteria.

Validation of administrative definition in RISE data. In our prior research within the RISE registry on ankylosing spondylitis (AS), also referred to as radiographic axSpA, we conducted a detailed review of a sample of available RISE clinical notes to confirm AS diagnoses (gold standard) among individuals with two or more ICD-9 or ICD-10 codes, which was the definition applied in the current study. This analysis yielded a positive predictive value of 88%.[15] Additionally, 3 of 50 patients (6%) were found to have an alternative diagnosis in RISE, resulting in a sensitivity of 88%.

Outcomes. The outcome of interest was time to medication discontinuation, defined as a documented stop date or gap of ≥90 days without a medication prescription or refill. For infliximab, we defined discontinuation as a documented stop date or gap of ≥60 days without a prescription or infusion encounter, as this medication is commonly dosed every 60 days. In other words, assuming a 90-day supply, patients were classified as having discontinued a medication if they had more than 180 days without a prescription. Assuming a 60-day supply for infliximab, more than 120 days without a prescription indicated medication discontinuation.

Study design. This was a retrospective longitudinal analysis. After patients met study entry criteria, covariates were measured during the six-month baseline period before the earliest medication record (Figure 1). Participants were observed from the second medication record until (1) a prescription gap of ≥60 days for infliximab, or ≥90 days for all other medications, was observed, in which case the participant was assumed to have stopped at the stop date for the last medication record before the gap; or (2) close of the study period (March 2025). Participants meeting condition (2) were classified as censored. Participants with a gap in medication use were further assessed to determine whether they had discontinued the medication or had dropped out of care from the facility. For these patients, we reviewed the EHR for a visit within the year following the gap. Patients with a medication gap and no further visits were presumed to have dropped out of care or to have switched to another facility. Because we could not track their medication use, we classified them as censored. Patients with a medication gap and at least one follow-up within the year were considered discontinued. For medication records missing a stop date, the stop date was estimated as 60 days from the record start date for infliximab and 90 days from the medication start date for all other medications.

Covariates. Our primary covariate of interest was sex. Given that RISE includes multisite EHR data, we classified sex as either female or male based on available data, while recognizing that EHR data in the RISE registry did not support gender

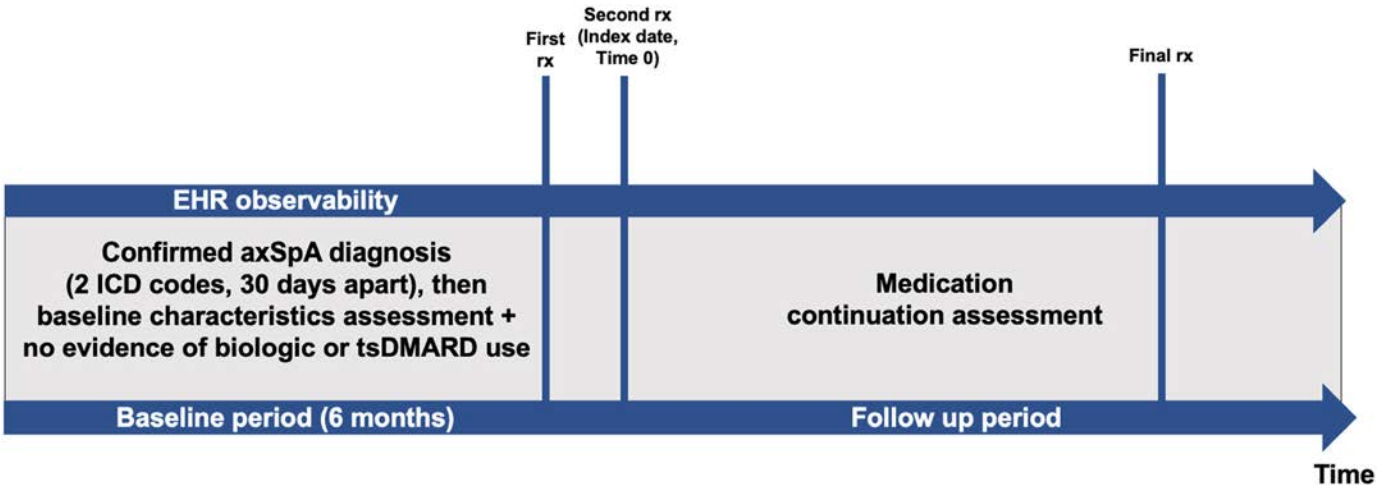

Figure 1. Study design: Participant recruitment, collection of baseline characteristics, and outcome assessment. Patients were followed until censored or until they were believed to have discontinued the drug, whichever came first. We considered a patient to have discontinued a drug if their next start date on the medication was greater than an allowable gap since the previous medication stop date (estimated or known). The allowable gap was 60 days for infliximab and 90 days for all other drugs. axSpA, axial spondyloarthritis; EHR, electronic health record; ICD, International Classification of Diseases; rx, prescription; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

analysis. Additional covariates included age, race or ethnicity (African American, Asian, Hispanic, non-Hispanic White, other or mixed, unknown), body mass index (BMI; <18.5, 18.5–24.9, 25–29.9, 30+), smoking status (ever/never), and area deprivation index (ADI). ADI, a ZIP code–based measure for neighborhood poverty and proxy for SES, was categorized into quintiles, with quintile 1 representing the highest SES category and quintile 5 representing the lowest SES category.[2,16] To further characterize our study population, we documented insurance type (private, Medicare, Medicaid, other, or unknown) and calculated the median number of patient visits during the baseline period as a measure of health care use. We also assessed disease activity using the Multidimensional Health Assessment Questionnaire (MDHAQ; range: 0–10 [lower to higher health status]) and described patterns of oral glucocorticoid and opioid use, as these treatments can potentially impact medication persistence. NSAID use could not be reliably assessed as many patients buy these over the counter, limiting the ability to adequately capture usage via prescriptions in the EHR.

Statistical analysis. We generated descriptive statistics for patient demographics, ADI, smoking status and biologic and targeted synthetic disease-modifying antirheumatic drug use. We then fit Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for medication discontinuation in men and women adjusted for age, race/ethnicity, insurance status, BMI, ADI, baseline visit count, oral glucocorticoid use, and opioid use. We assessed whether the assumption of proportional hazards was met for sex by visual inspection of plots of scaled Schoenfeld residuals over time. We then constructed Kaplan-Meier curves to examine medication continuation stratified by sex and age (<65 and ≥65 years) and compared survival functions using the log-rank test. We selected 65 years as the age cutoff because individuals aged ≥65 are typically eligible for Medicare, and we hypothesized that differences in cost-sharing structures and care access within this population might influence treatment discontinuation patterns. We observed the patients until they had a drug prescription gap or reached the new administrative censorship date of March 31, 2025. Data were missing for covariates race/ethnicity, BMI, insurance status, and ADI in 16.4%, 17.6%, 9.8%, and 6.5% of records, respectively, and we imputed the values using iterative chained equations with 165 imputations. The number of imputations needed to achieve stable standard errors for all analyses was estimated using the HowManyImputations package in R.[17]

Sensitivity analyses. To evaluate the reliability of our main findings, we conducted additional sensitivity analyses. In our primary analysis, our cohort included only patients with two or more prescriptions of the medication of interest. As a sensitivity analysis, to assess the robustness of our findings to this design decision, we included all patients with at least one medication prescription. In a second sensitivity analysis, we limited our analysis to only the subset of patients with a medication stop date recorded in the EHR. Then, we repeated the primary analysis in those with an MDHAQ score to adjust for disease activity where available; although not as extensively used to assess disease activity in axSpA, this outcome has been shown to correlate with more commonly used measures.[18] Next, we adjusted for calendar period of drug initiation with the following intervals to ensure groups had similar numbers of patients: 2003–2009, 2010–2015, 2016–2020, and 2021–2025. Afterwards, we adjusted for methotrexate use. All sensitivity analyses were adjusted for the covariates in the primary analysis. Lastly, we tested for statistical interactions ($P < 0.05$) by serially adding sex by age, race or ethnicity, and ADI cross-product terms to the primary adjusted analysis.

This study was approved by the Western Institutional Review Board and the University of California, San Francisco Committee on Human Research. We followed the STROBE guidelines to enhance the reporting of this observational study.[19] We did not use large language models.

RESULTS

We identified 7,200 adults with axSpA, with a mean ± SD age of 52.7 ± 14.7 years, 58.3% of whom were female, and 68.7% of whom were non-Hispanic White (Table 1). The median number of visits during the baseline period (interquartile range) per patient was 2.0 (1.0–3.0).

Among patients prescribed a TNFi, 4,213 of 6,256 or 67.3% discontinued during the study period. Median time until TNFi discontinuation was 416 days (95% CI: 392–434). After adjusting for covariates, female sex was associated with a 24% higher risk of TNFi discontinuation (adjusted HR [aHR]: 1.24, 95% CI: 1.16–1.32) (Table 2). There was a 19% higher risk of TNFi discontinuation among those aged 51 to 60 years (aHR: 1.19, 95% CI: 1.04–1.36) compared to those aged 18 to 29 years. Other age groups did not have a statistically significant difference in TNFi discontinuation. Compared to patients with obesity (BMI 30+), those in the overweight category (BMI 25–29.9) had a lower risk of TNFi discontinuation (aHR: 0.91, 95% CI: 0.84–0.98). Race/ethnicity, insurance type, ADI, visit count, glucocorticoid use, and opioid use were not associated with TNFi discontinuation. When we studied the probability of TNFi continuation stratified by sex and age (18–64 vs ≥65 years), we found that women aged 18 to 64 years had the lowest probability of TNFi continuation (Figure 2A).

Among those prescribed an IL-17i, 435 of 693 or 62.8% discontinued the medication within the study period. Median time until discontinuation was 274 days (95% CI: 231–314). Women had a 25% higher risk of treatment discontinuation (aHR: 1.25,

Table 1. Baseline characteristics of patients with axSpA prescribed TNFi, IL-17i, or JAKi treatment*

Characteristic	Overall (N = 7,200)	Female (n = 4,200)	Male (n = 3,000)
Age ± SD, y	52.7 ± 14.7	52.2 ± 14.3	53.3 ± 15.2
18–29	485 (6.7)	275 (6.5)	210 (7.0)
30–40	1,086 (15.1)	646 (15.4)	440 (14.7)
41–50	1,626 (22.6)	1,014 (24.1)	612 (20.4)
51–60	1,716 (23.8)	1,032 (24.6)	684 (22.8)
61–70	1,391 (19.3)	744 (17.7)	647 (21.6)
71–80	745 (10.3)	416 (9.9)	329 (11.0)
>80	151 (2.1)	73 (1.7)	78 (2.6)
Race and ethnicity			
African American	296 (4.1)	195 (4.6)	101 (3.4)
Asian	129 (1.8)	59 (1.4)	70 (2.3)
Hispanic	351 (4.9)	223 (5.3)	128 (4.3)
Non-Hispanic White	4,949 (68.7)	2,861 (68.1)	2,088 (69.6)
Other or mixed	293 (4.1)	186 (4.4)	107 (3.6)
Unknown	1,182 (16.4)	676 (16.1)	506 (16.9)
Body mass index			
Underweight: <18.5	72 (1.0)	51 (1.2)	21 (0.7)
Normal weight: 18.5–24.9	1,314 (18.3)	863 (20.5)	451 (15.0)
Overweight: 25–29.9	1,799 (25.0)	896 (21.3)	903 (30.1)
Obese: 30+	2,751 (38.2)	1,764 (42.0)	987 (32.9)
Unknown	1,264 (17.6)	626 (14.9)	638 (21.3)
Ever smoker			
Ever	1,171 (16.3)	610 (14.5)	561 (18.7)
Never	2,516 (34.9)	1,578 (37.6)	938 (31.3)
Unknown	3,513 (48.8)	2012 (47.9)	1,501 (50.0)
National area deprivation index,[a] median (Q1, Q3)	44.8 (25.7)	47.0 (25.6)	41.7 (25.4)
Quintile 1 (1–19)	1,337 (18.6)	679 (16.2)	658 (21.9)
Quintile 2 (20–33)	1,258 (17.5)	700 (16.7)	558 (18.6)
Quintile 3 (34–49)	1,408 (19.6)	801 (19.1)	607 (20.2)
Quintile 4 (50–70)	1,360 (18.9)	862 (20.5)	498 (16.6)
Quintile 5 (71–100)	1,366 (19.0)	884 (21.0)	482 (16.1)
Unknown	471 (6.5)	274 (6.5)	197 (6.6)
Insurance category			
Private	4,158 (57.8)	2,372 (56.5)	1,786 (59.5)
Medicare	1,810 (25.1)	992 (23.6)	818 (27.3)
Medicaid	367 (5.1)	275 (6.5)	92 (3.1)
Other insurance	160 (2.2)	98 (2.3)	62 (2.1)
Unknown	705 (9.8)	463 (11.0)	242 (8.1)
MDHAQ,[b] mean ± SD	3.3 ± 3.0	3.6 ± 3.0	3.0 ± 2.9
Unknown	4,529	2,598	1931
Visit count during baseline period, median (Q1, Q3)	2 (1, 3)	2 (1, 3)	1 (1, 2)
Oral glucocorticoid use	1,153 (16.0)	715 (17.0)	438 (14.6)
Opioid use	624 (8.7)	379 (9.0)	245 (8.2)
TNFi	6,256 (86.9)	3,589 (85.5)	2,667 (88.9)
IL-17i	693 (9.6)	443 (10.5)	250 (8.3)
JAKi	251 (3.5)	168 (4.0)	83 (2.8)

* Values are expressed as n (%) unless otherwise indicated. axSpA, axial spondyloarthritis; IL-17i, interleukin-17 inhibitor; JAKi, JAK inhibitor; MDHAQ, Multidimensional Health Assessment Questionnaire; Q, quintile; TNFi, tumor necrosis factor inhibitor.
[a] Range 1–100, lower to higher disadvantage.
[b] Range 0–10, higher to lower health status.

95% CI: 1.01–1.54) (Table 3). When stratifying by sex and age (18–64 vs ≥65 years), men aged 18 to 64 had the lowest probability of discontinuing treatment (Figure 2B).

In the JAKi group, 165 of 251 or 65.7% discontinued the medication. Median time until discontinuation was 342 days (95% CI: 270–437). The JAKi group did not have a difference in medication discontinuation by sex (aHR: 0.89, 95% CI: 0.62–1.27) (Table 4), nor was there a difference in treatment continuation when stratifying by age and sex (Figure 2C). Given the smaller size of the JAKi group, the analysis may be underpowered.

Sensitivity analyses. In a series of sensitivity analyses, we found that the risk of TNFi discontinuation remained higher in women than men. This included when we expanded our sample to include participants with one or more prescription for TNFi instead of two or more prescriptions (n = 10,426, aHR: 1.14, 95% CI: 1.09–1.20) (Supplementary Table 2). Risk of

Table 2. Risk of TNFi discontinuation among patients with axSpA*

Characteristic	Primary analyses (imputed data[a])			
	Crude analysis		Adjusted analysis[b]	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Gender				
Female	1.26 (1.19–1.34)	<0.001	1.24 (1.16–1.32)	<0.001
Male	—		—	
Age, y				
18–29	—		—	
30–40	1.06 (0.92–1.22)	0.42	1.06 (0.92–1.22)	0.45
41–50	1.10 (0.96–1.26)	0.17	1.07 (0.93–1.22)	0.35
51–60	1.19 (1.04–1.36)	0.009	1.19 (1.04–1.36)	0.014
61–70	1.10 (0.96–1.26)	0.17	1.12 (0.97–1.30)	0.13
71–80	0.92 (0.79–1.07)	0.29	0.95 (0.80–1.13)	0.55
>80	0.76 (0.58–1.00)	0.049	0.80 (0.61–1.06)	0.13
Race and ethnicity				
African American	0.99 (0.85–1.15)	0.90	0.94 (0.81–1.10)	0.45
Asian	1.05 (0.85–1.31)	0.65	1.13 (0.91–1.41)	0.28
Hispanic	1.10 (0.96–1.27)	0.18	1.06 (0.92–1.22)	0.43
Non-Hispanic White	—		—	
Other or mixed	1.17 (0.99–1.38)	0.072	1.16 (0.99–1.37)	0.074
National area deprivation index				
Quintile 1 (1–19)	—		—	
Quintile 2 (20–33)	1.06 (0.96–1.17)	0.29	1.04 (0.94–1.15)	0.44
Quintile 3 (34–49)	1.10 (1.00–1.21)	0.047	1.09 (0.99–1.20)	0.10
Quintile 4 (50–70)	1.08 (0.98–1.19)	0.14	1.04 (0.94–1.15)	0.45
Quintile 5 (71–100)	1.17 (1.06–1.30)	0.002	1.11 (1.00–1.23)	0.054
Insurance category				
Private	—		—	
Medicare	0.92 (0.86–0.98)	0.016	0.95 (0.87–1.04)	0.30
Medicaid	1.15 (1.00–1.32)	0.054	1.08 (0.94–1.25)	0.28
Other insurance	0.91 (0.73–1.12)	0.37	0.89 (0.72–1.10)	0.29
Body mass index				
Underweight: <18.5	0.80 (0.59–1.08)	0.14	0.81 (0.60–1.10)	0.18
Normal weight: 18.5–24.9	0.92 (0.85–1.00)	0.058	0.94 (0.86–1.03)	0.19
Overweight: 25–29.9	0.87 (0.80–0.94)	<0.001	0.91 (0.84–0.98)	0.016
Obese: 30+	—		—	
Visit count during baseline period	1.01 (0.99–1.02)	0.22	1.00 (0.99–1.02)	0.63
Oral glucocorticoid use	1.09 (1.01–1.18)	0.031	1.07 (0.99–1.16)	0.10
Opioid use	0.99 (0.89–1.11)	0.88	0.97 (0.87–1.08)	0.58

* aHR, adjusted HR; axSpA, axial spondyloarthritis; CI, confidence interval; HR, hazard ratio; TNFi, tumor necrosis factor inhibitor.
[a] Data imputed through multiple imputation by iterative chained equations.
[b] Adjusted for age, race/ethnicity, insurance status, body mass index, area deprivation index, baseline visit count, oral glucocorticoid use and opioid use.

discontinuation was still higher in women when we restricted the sample to include only those with documented medication stop dates (n = 2,488, aHR: 1.33, 95% CI: 1.21–1.46). This was also the case when we repeated our primary analysis adjusting for MDHAQ in the subset of patients with an observed value for MDHAQ (n = 2,292, aHR: 1.22, 95% CI: 1.01–1.35), when adjusting for calendar period of drug start (n = 6,256, aHR: 1.20, 95% CI: 1.13–1.28), and when adjusting for methotrexate use (n = 6,256, aHR: 1.27, 95% CI: 1.19–1.36). Among those on IL-17i, risk of treatment discontinuation remained higher among women when we expanded our sample to patients with one or more prescription (n = 1,383, aHR: 1.18, 95% CI: 1.03–1.35) and restricted it to patients with documented stop dates only (n = 347, aHR: 1.44, 95% CI: 1.09–1.91). There was no sex difference in IL-17i discontinuation with adjustment for MDHAQ (n = 285, aHR: 1.34, 95% CI: 0.94–1.93) or with adjustment for calendar period of drug start (n = 693, aHR: 1.22, 95% CI: 0.99–1.51). When we additionally adjusted for methotrexate use, women still had a higher risk of IL-17i discontinuation compared to men (n = 693, aHR: 1.28, 95% CI: 1.04–1.57). With JAKi use, there was no sex difference in medication discontinuation when studying those with one or more prescription (n = 577, aHR: 0.94, 95% CI: 0.76–1.17) or when adjusting for methotrexate use (n = 251, aHR: 0.88, 95% CI: 0.62–1.26), and the sample was too small to fit models for documented medication stop dates, MDHAQ adjustment or calendar period of drug start.

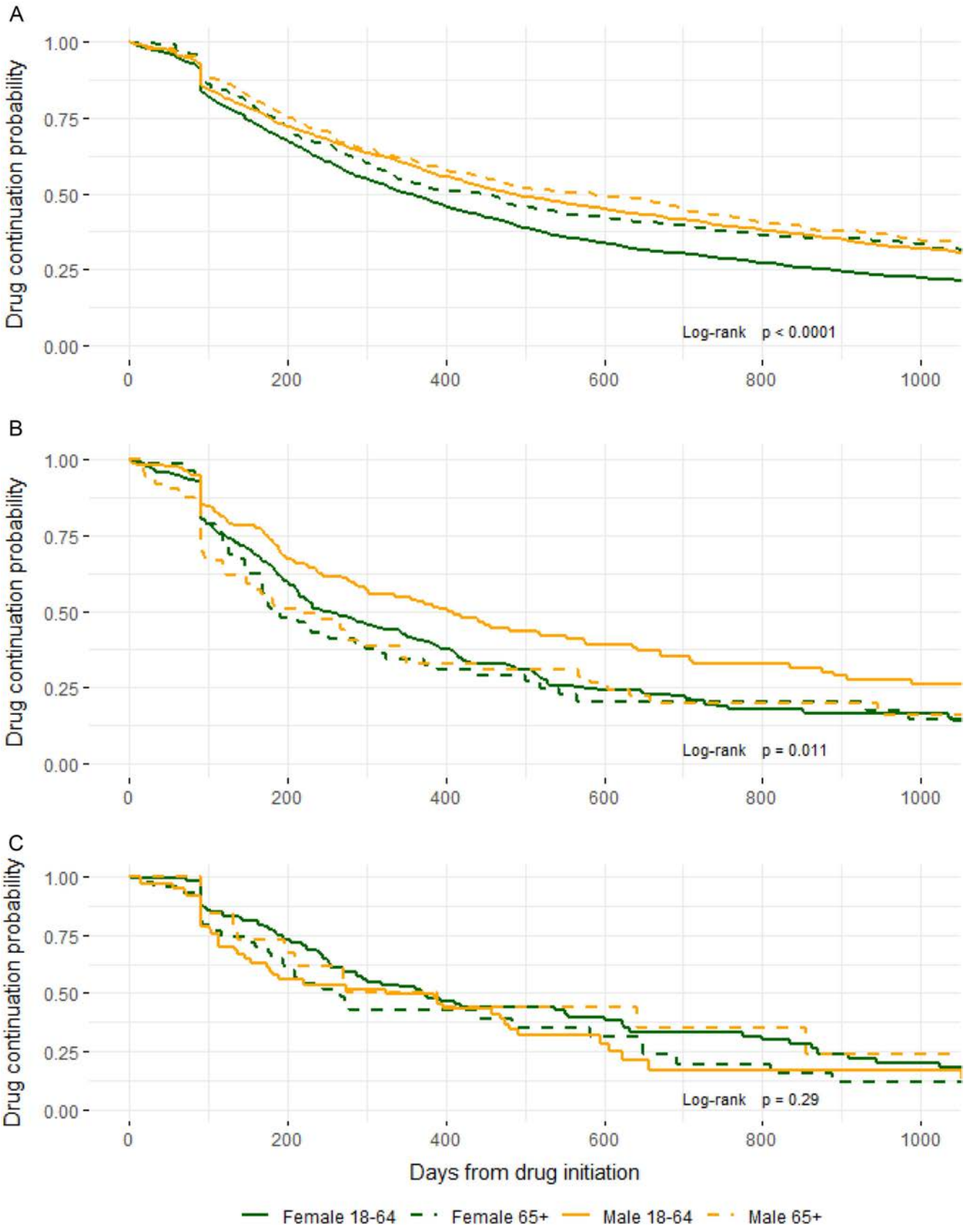

Figure 2. Probability of mediation continuation by sex and age in axial spondyloarthritis. (A) Drug continuation among patients prescribed tumor necrosis factor inhibitors. (B) Drug continuation among patients prescribed interleukin-17 inhibitors. (C) Drug continuation among patients prescribed JAK inhibitors. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.70001/abstract.

Table 3. Risk of IL-17i discontinuation among patients with axSpA*

Characteristic	Primary analysis (imputed[a])			
	Crude analysis		Adjusted analysis[b]	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Gender				
Female	1.24 (1.02–1.52)	0.030	1.25 (1.01–1.54)	0.038
Male	—		—	
Age, y				
18–29	—		—	
30–40	1.13 (0.66–1.94)	0.65	1.14 (0.66–1.97)	0.63
41–50	1.17 (0.70–1.95)	0.54	1.20 (0.71–2.03)	0.49
51–60	1.11 (0.68–1.83)	0.68	1.15 (0.69–1.92)	0.58
61–70	1.19 (0.72–1.96)	0.51	1.17 (0.68–2.00)	0.57
71–80	1.48 (0.86–2.55)	0.16	1.30 (0.70–2.42)	0.40
>80	1.55 (0.67–3.58)	0.31	1.57 (0.63–3.93)	0.33
Race and ethnicity				
African American	0.94 (0.58–1.54)	0.81	0.93 (0.56–1.56)	0.79
Asian	0.86 (0.36–2.05)	0.73	1.01 (0.40–2.51)	0.99
Hispanic	1.07 (0.63–1.83)	0.80	1.13 (0.64–1.98)	0.68
Non-Hispanic White	—		—	
Other or mixed	0.79 (0.49–1.28)	0.34	0.81 (0.49–1.33)	0.40
National area deprivation index				
Quintile 1 (1–19)	—		—	
Quintile 2 (20–33)	1.20 (0.88–1.63)	0.25	1.24 (0.89–1.71)	0.20
Quintile 3 (34–49)	1.37 (0.99–1.90)	0.06	1.42 (1.01–1.99)	0.044
Quintile 4 (50–70)	1.10 (0.80–1.52)	0.54	1.10 (0.78–1.54)	0.58
Quintile 5 (71–100)	1.21 (0.87–1.66)	0.25	1.27 (0.90–1.79)	0.17
Insurance category				
Private	—		—	
Medicare	1.22 (0.98–1.51)	0.078	1.09 (0.81–1.48)	0.56
Medicaid	1.13 (0.73–1.76)	0.59	1.08 (0.69–1.72)	0.73
Other insurance	0.64 (0.29–1.41)	0.27	0.56 (0.25–1.26)	0.16
Body mass index				
Underweight <18.5	1.72 (0.50–5.97)	0.39	1.92 (0.52–7.03)	0.32
Normal weight: 18.5–24.9	0.99 (0.75–1.29)	0.92	1.02 (0.77–1.36)	0.86
Overweight: 25–29.9	1.02 (0.80–1.30)	0.89	1.08 (0.84–1.40)	0.53
Obese: 30+	—		—	
Visit count during baseline period	1.06 (1.01–1.12)	0.024	1.05 (0.99–1.11)	0.10
Oral glucocorticoid use	1.29 (1.03–1.63)	0.028	1.23 (0.96–1.57)	0.10
Opioid use	1.00 (0.71–1.40)	>0.99	0.9 (0.63–1.31)	0.59

* aHR, adjusted HR; axSpA, axial spondyloarthritis; CI, confidence interval; HR, hazard ratio; IL-17i, interleukin-17 inhibitor.
[a] Data imputed through multiple imputation by iterative chained equations.
[b] Adjusted for age, race/ethnicity, insurance status, body mass index, area deprivation index, baseline visit count, oral glucocorticoid use, and opioid use.

Last, we explored interactions between sex and age, race, and ADI. We did not see interactions between sex and any sociodemographic factors in the TNFi, IL-17i or JAKi groups.

DISCUSSION

In this national study, we examined sex differences in treatment discontinuation among new users of TNFi, IL-17i, and JAKi in axSpA. We found across multiple analyses that women consistently had earlier medication discontinuation of TNFi than men. These findings underscore the importance of understanding why women discontinue these medications earlier, so that we can develop strategies to improve their clinical outcomes. Discontinuation rates for IL-17i were also higher among women, but when adjusting for MDHAQ or calendar period, rate of drug discontinuation was similar across sexes. There were no sex differences in JAKi discontinuation. This study is novel in that it goes beyond a focus on TNFi to also include IL-17i and JAKi, and it uses real-world data to study all three of these medication classes rather than data from RCTs.

Our findings are consistent with the growing literature to suggest that women stop TNFi early.[4] There are several explanations for why women may be less likely to continue medications for axSpA long term. First, women are more likely to experience TNFi drug side effects.[20] Second, it is possible women could be more likely to develop drug antibodies to adalimumab and infliximab, both TNFi, which could lessen their efficacy and also place them at higher risk of adverse events

Table 4. Risk of JAKi discontinuation among patients with axSpA*

Characteristic	Primary analyses (imputed)			
	Crude		Adjusted[a]	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Gender				
Female	0.89 (0.64–1.23)	0.48	0.89 (0.62–1.27)	0.51
Male	—		—	
Age, y				
18–29	—		—	
30–40	0.61 (0.25–1.49)	0.27	0.53 (0.20–1.41)	0.21
41–50	0.47 (0.22–1.04)	0.061	0.45 (0.19–1.06)	0.068
51–60	0.47 (0.21–1.02)	0.056	0.44 (0.18–1.06)	0.067
61–70	0.75 (0.35–1.61)	0.46	0.80 (0.34–1.87)	0.61
71–80	0.68 (0.30–1.56)	0.36	0.67 (0.24–1.87)	0.44
>80	0.29 (0.08–1.11)	0.07	0.23 (0.05–0.99)	0.048
Race and ethnicity				
African American	1.05 (0.35–3.19)	0.93	1.52 (0.42–5.57)	0.52
Asian	1.91 (0.73–4.97)	0.18	2.15 (0.69–6.73)	0.19
Hispanic	0.91 (0.48–1.72)	0.76	0.98 (0.49–1.96)	0.96
Non-Hispanic White	—		—	
Other or mixed	1.06 (0.48–2.35)	0.89	1.03 (0.42–2.52)	0.94
National area deprivation index				
Quintile 1 (1–19)	—		—	
Quintile 2 (20–33)	1.10 (0.66–1.83)	0.72	1.26 (0.71–2.22)	0.43
Quintile 3 (34–49)	0.82 (0.51–1.31)	0.40	0.89 (0.53–1.50)	0.66
Quintile 4 (50–70)	0.94 (0.60–1.48)	0.80	1.10 (0.65–1.85)	0.73
Quintile 5 (71–100)	1.09 (0.66–1.79)	0.73	1.37 (0.77–2.41)	0.28
Insurance category				
Private	—		—	
Medicare	1.24 (0.87–1.76)	0.23	1.19 (0.73–1.94)	0.49
Medicaid	0.96 (0.44–2.09)	0.92	1.05 (0.44–2.50)	0.91
Other insurance	0.41 (0.06–2.77)	0.35	0.27 (0.03–2.20)	0.22
Body mass index				
Underweight: <18.5	0.57 (0.14–2.33)	0.43	0.42 (0.09–1.88)	0.26
Normal weight: 18.5–24.9	1.36 (0.86–2.15)	0.19	1.43 (0.86–2.37)	0.16
Overweight: 25–29.9	1.18 (0.79–1.76)	0.41	1.20 (0.77–1.87)	0.42
Obese: 30+	—		—	
Visit count during baseline period	1.02 (0.94–1.10)	0.61	1.03 (0.93–1.14)	0.60
Oral glucocorticoid use	0.85 (0.60–1.21)	0.37	0.83 (0.54–1.26)	0.37
Opioid use	1.02 (0.70–1.48)	0.92	1.07 (0.69–1.65)	0.76

* aHR, adjusted HR; axSpA, axial spondyloarthritis; HR, hazard ratio; CI, confidence interval; JAKi, JAK inhibitor.
[a] Adjusted for age, race/ethnicity, insurance status, body mass index, area deprivation index, baseline visit count, oral glucocorticoid use, and opioid use.

from these medications.[21–23] It is unclear how hormonal differences could play a role, and there is active research in this area including the role of menopause.[24] These reasons have been suggested for earlier TNFi discontinuation among women with rheumatoid arthritis as well.[25] Women with axSpA are more likely to have extra-axial manifestations including peripheral arthritis and enthesitis and therefore may report more pain and functional difficulties, which could lead to treatment discontinuation.[1] One meta-analysis of RCTs in axSpA found that there was a larger difference in treatment efficacy among women with nonradiographic axSpA compared to men and those with radiographic axSpA suggesting this subgroup could be different.[13] Few patients were pregnant during the study, and therefore we do not think this is a major reason for medication discontinuation. Moreover, TNFi are generally safe in pregnancy.[26] Lastly, cost-related issues may impact long term medication use. Women tend to have lower income than men and therefore may have less ability to afford these expensive medications.[27]

When stratified by age, TNFi treatment discontinuation rates were similar between men and women older than 65 years. However, among those under 65 years, women were significantly more likely to discontinue treatment than men. Although the reason for this is unclear, we speculate that younger women may have a higher prevalence of nonradiographic axSpA, which has been associated with lower treatment efficacy in other studies.[13]

We found that women had a higher risk of IL-17i discontinuation than men, consistent with findings from two meta-analyses of RCTs.[12,13] However, this association was no longer observed after adjusting for MDHAQ or calendar period. Because only a

small number of patients had MDHAQ data available (n = 285), we suspect that this attenuation reflects limited sample size rather than a true absence of effect. Similar factors that contribute to higher TNFi discontinuation among women may also underlie earlier IL-17i discontinuation.

We did not find a difference by sex in JAKi discontinuation. However, the number of patients receiving JAKi was smaller compared to those on TNFi and IL-17i, which likely limited the precision of our estimates. This difference in sample size is expected, given that TNFi such as etanercept have been available since 2003 for the treatment of AS (radiographic axSpA),[28] whereas IL-17i such as secukinumab and ixekizumab were approved more recently (2016[29] and 2019,[30] respectively), and tofacitinib (a JAKi) was approved in 2021,[31] indicating there was a longer time to follow-up patients on TNFi than IL-17i and JAKi. Consequently, the longer follow-up time available for patients on TNFi may partly explain the more robust findings in that group. A larger sample of patients on JAKi could help confirm our findings and provide more precise estimates of the effect of sex on discontinuation of these therapies. One important distinction is that, unlike TNFi and IL-17i, JAKi do not provoke antidrug antibody formation,[32] a phenomenon that could affect response to TNFi and IL-17i therapy and is more common among women.[21,33]

We noticed that women were more likely to seek medical care than men and had on average two visits per year, whereas men had one visit on average, consistent with the literature in spondyloarthritis.[34] We controlled for number of visits in our analysis, as this could affect the timing of when a medication is marked as discontinued in patient's EHR.

This study has several strengths. First, using multisite EHR data from the RISE registry with e-prescriptions allowed us to study a large number of patients with axSpA from diverse geographic locations across the United States. Second, our cohort is enriched with women, who made up more than half of our study sample, making RISE an important data source to study sex differences in axSpA. Per our validation study,[15] we were reasonably certain that individuals assigned an axSpA diagnosis based on ICD codes truly had the disease, in addition to the fact that patients were evaluated by a rheumatologist and had at least two prescriptions for a biologic or targeted synthetic disease modifying antirheumatic drug. Reassuringly, many of the sensitivity analyses did not significantly change our results.

Our study also has some limitations. The RISE registry variable for sex/gender includes information gathered on >40 EHRs, all of which may collect data differently. Most EHRs did not distinguish between sex and gender until recently, and because most patients are not new to rheumatology practice, these data were likely collected for most patients before EHRs started asking separate questions for sex and gender. Sex-related differences may stem from both biological as well as sociocultural differences. We do not have data on trans and nonbinary patients. We do not know which patients were biologic naïve before the start of the study (ie, never taken a biologic before), nor do we know how many prior medications a patient was prescribed for axSpA before the baseline period of the study. We used e-prescriptions rather than prescription fill data and studied continuation rather than medication adherence. Some patients did not have a medication stop date and we had to assume a stop date based off of their last prescription. Only a small portion (14.7%) of patients had data on disease activity score as measured by the MDHAQ, thus limiting the precision of that sensitivity analysis. Lastly, outside of a sensitivity analysis adjusting for methotrexate use, we did not study other conventional synthetic disease modifying antirheumatic drugs, as they do not treat axial inflammation. Future studies should look at this since these drugs may improve persistence by reducing antidrug antibodies in a subset of patients.

In conclusion, in this large US sample of adults with axSpA, women were less likely to continue TNFi and IL-17i compared to men with axSpA. Although there were no sex differences in JAKi discontinuation, a larger sample could confirm these findings and estimate the effect with more precision. Future research should investigate the underlying reasons for sex differences in TNFi and IL-17i discontinuation.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Stovall confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Stovall R, van der Horst-Bruinsma IE, Liu SH, et al. Sexual dimorphism in the prevalence, manifestation and outcomes of axial spondyloarthritis. Nat Rev Rheumatol 2022;18(11):657–669.
2. Stovall R, Li J, Fitzpatrick J, et al. Low socioeconomic status and female sex are associated with worse functional status in axial spondyloarthritis. Arthritis Care Res (Hoboken) 2025;77(3):376–384.
3. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019;71(10):1599–1613.
4. Rusman T, Ten Wolde S, Euser SM, et al. Gender differences in retention rate of tumor necrosis factor alpha inhibitor treatment in ankylosing spondylitis: a retrospective cohort study in daily practice. Int J Rheum Dis 2018;21(4):836–842.
5. van der Slik B, Spoorenberg A, Wink F, et al. Although female patients with ankylosing spondylitis score worse on disease activity than male patients and improvement in disease activity is comparable,

male patients show more radiographic progression during treatment with TNF-α inhibitors. Semin Arthritis Rheum 2019;48(5):828–833.
6. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum 2017; 47(3):343–350.
7. Rusman T, Nurmohamed MT, Hoekstra S, et al. Disease activity in women with ankylosing spondylitis remains higher under tumour necrosis factor inhibitor treatment than in men: a five-year observational study. Scand J Rheumatol 2022;51(6):506–512.
8. van der Horst-Bruinsma IE, Zack DJ, Szumski A, et al. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. Ann Rheum Dis 2013;72(7):1221–1224.
9. Bittar M, Deodhar A. Axial spondyloarthritis: a review. JAMA 2025; 333(5):408–420.
10. Yin Y, Wang M, Liu M, et al. Efficacy and safety of IL-17 inhibitors for the treatment of ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Res Ther 2020;22(1):111.
11. Lee YH. Comparative efficacy and safety of Janus kinase inhibitors and secukinumab in patients with active ankylosing spondylitis: a systematic review and meta-analysis. Pharmacology 2022;107(11-12): 537–544.
12. Gao A, Pardo Pardo J, Dang S, et al. Sex-related differences in efficacy and safety outcomes in axial spondyloarthritis randomized clinical trials: a systematic literature review and meta-analysis. Arthritis Care Res (Hoboken) 2025;77(7):813–826.
13. Xie Y, Liu Y, Wu Q. Effect of gender and age on bDMARD efficacy for axial spondyloarthritis patients: a meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2024;63(11):2914–2922.
14. RISE for research. American College of Rheumatology website. Accessed March 29, 2023. https://rheumatology.org/rise-for-research
15. Stovall R, Kersey E, Li J, et al. Incidence rate and factors associated with fractures among Medicare beneficiaries with ankylosing spondylitis in the United States. Arthritis Care Res (Hoboken) 2023;76(2): 265–273.
16. Kind AJ, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. Ann Intern Med 2014;161(11):765–774.
17. von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. Sociol Methods Res 2020;49(3): 699–718.
18. García-Valle A, Andrés-de Llano JM, Fariña-González AJ, et al. Construct validity of the routine assessment of patient index data 3 (RAPID3) in the evaluation of axial spondyloarthritis. J Rheumatol 2022;49(1):36–43.
19. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014;12(12): 1500–1524.
20. Gosselt HR, van Lint JA, Kosse LJ, et al. Sex differences in adverse drug reactions from Adalimumab and etanercept in patients with inflammatory rheumatic diseases. Expert Opin Drug Saf 2023;22(6): 501–507.
21. Balsa A, Sanmarti R, Rosas J, et al. Drug immunogenicity in patients with inflammatory arthritis and secondary failure to tumour necrosis factor inhibitor therapies: the REASON study. Rheumatology (Oxford) 2018;57(4):688–693.
22. Hambardzumyan K, Hermanrud C, Marits P, et al; SWEFOT study group. Association of female sex and positive rheumatoid factor with low serum infliximab and anti-drug antibodies, related to treatment failure in early rheumatoid arthritis: results from the SWEFOT trial population. Scand J Rheumatol 2019;48(5):362–366.
23. Strand V, Goncalves J, Isaacs JD. Immunogenicity of biologic agents in rheumatology. Nat Rev Rheumatol 2021;17(2):81–97.
24. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018;20(6):35.
25. Lauridsen KB, Duch KS, Mortensen AS, et al. Sex differences in treatment response in patients with rheumatoid arthritis treated with tumour necrosis factor inhibitor: a cohort study from the DANBIO registry. Scand J Rheumatol 2025;54(4):252–262.
26. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2020;72(4):529–556.
27. Fry R, Aragão C. Gender pay gap in U.S. hasn't changed much in two decades. Pew Research Center. March 4, 2023. https://www.pewresearch.org/short-reads/2023/03/01/gender-pay-gap-facts/.
28. Enbrel is first biologic to receive FDA approval for the treatment of ankylosing spondylitis Amgen. July 14, 2003. https://www.amgen.com/newsroom/press-releases/2003/07/enbrel-is-first-biologic-to-receive-fda-approval-for-the--treatment-of-ankylosing-spondylitis
29. Novartis receives two new FDA approvals for Cosentyx to treat patients with ankylosing spondylitis and psoriatic arthritis in the US. Novartis. January 15, 2016. https://www.novartis.com/news/media-releases/novartis-receives-two-new-fda-approvals-cosentyx-treat-patients-ankylosing-spondylitis-and-psoriatic-arthritis-us
30. Lilly Receives U.S. FDA Approval for Taltz® (ixekizumab) for the Treatment of Active Ankylosing Spondylitis (Radiographic Axial Spondyloarthritis). Lilly Investors. August 26, 2019. https://investor.lilly.com/news-releases/news-release-details/lilly-receives-us-fda-approval-taltzr-ixekizumab-treatment
31. U.S. FDA approves Pfizer's XELJANZ® (tofacitinib) for the treatment of active ankylosing spondylitis. Pfizer. December 14, 2021. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-xeljanzr-tofacitinib-treatment-0
32. Núñez P, Quera R, Yarur AJ. Safety of Janus kinase inhibitors in inflammatory bowel diseases. Drugs 2023;83(4):299–314.
33. Mease PJ, McInnes IB, Kirkham B, et al; FUTURE 1 Study Group. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373(14):1329–1339.
34. Garrido-Cumbrera M, Poddubnyy D, Sommerfleck F, et al. Regional differences in diagnosis journey and healthcare utilization: results from the International Map of Axial Spondyloarthritis (IMAS). Rheumatol Ther 2024;11(4):927–945.

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 925–935
DOI 10.1002/acr.25693

A Qualitative Analysis of Patient Perspectives and Preferences in Lupus Management to Guide Lupus Guidelines Development

Shivani Garg,[1] Izzy Hartel,[1] Lisa R. Sammaritano,[2] Anca Askanase,[3] Bonnie L. Bermas,[4] Maria Dall'Era,[5] Alí Duarte-García,[6] Victoria P. Werth,[7] Brad Rovin,[8] Reem A. Mustafa,[9] Amy S. Turner,[10] Bené Williams,[11] Brian L. Ung,[11] Hiya Bhavsar,[11] Monique C. Gore-Massy,[11] Nahirannette Pulido,[11] Natacha Guerrero,[11] Natalie M. Smith,[11] Wambui Machua,[11] Linda T. Hiraki,[12] and Mary Beth Son[13]

Objective. A patient-centered approach for chronic disease management, including systemic lupus erythematosus (SLE), aligns treatment with patients' values and preferences, leading to improved outcomes. This paper summarizes how patient experiences, perspectives, and priorities informed the American College of Rheumatology (ACR) 2024 Lupus Nephritis (LN) and 2025 SLE screening, treatment guidelines.

Methods. We completed a cross-sectional qualitative study using content analysis of two Patient Panel meetings for the ACR LN and SLE guidelines. Key themes were presented by Patient Panel representatives during Voting Panel Meetings along with evidence for each recommendation, to ensure comprehensive discussions and align treatment recommendations with patients' priorities and values.

Results. Nineteen people (90% women) with diagnoses of SLE and/or LN participated in the Patient Panels and 17 consented to use their feedback for analysis. Thematic analysis of their discussions revealed nine patient-reported key themes in three domains: (1) treatment and monitoring of LN and SLE: medication side effects, daily function, treatment goals, and monitoring and screening; (2) clinical communication: strategies to optimize communication and provider and structural impediments to effective communication; and (3) improving transparency and information sharing: clinical trial participation, and medical costs and insurance coverage. These themes were actively incorporated into discussions during the Voting Panels for the ACR LN and SLE guidelines.

Conclusion. This work supported the integration of patient experiences in the clinical practice guideline development process and aligned recommendations with real-world patient experiences and priorities, thereby enhancing the clinical applicability of the ACR LN and SLE guidelines.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease, with lupus nephritis (LN) as one severe manifestation.[1–15] SLE and LN are chronic diseases characterized by disease flares, heterogeneity in disease severity, and significant impact on quality of life.[1–15] Treatment is commonly aimed at controlling the disease and minimizing target organ damage. However, there is discordance between disease activity indices and patient reported outcomes, underscoring the importance of aligning treatment with patients' values and preferences.[16–21] Incorporating patient perspectives in clinical practice guidelines can assist in balancing benefits with potential harms of treatments as well as include patients' values and preferences.[22–24] This approach acknowledges that the lived experiences of individuals with SLE extend beyond standardized measures and encompass a spectrum of physical, emotional, and social challenges, and support a patient-centric treatment

[1]University of Wisconsin School of Medicine and Public Health, Madison; [2]Hospital for Special Surgery, Weill Cornell Medicine, New York, New York; [3]Columbia University, New York, New York; [4]UT Southwestern Medical Center, Dallas, Texas; [5]University of California, San Francisco; [6]Mayo Clinic, Rochester, Minnesota; [7]University of Pennsylvania and Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia; [8]Ohio State University, Columbus; [9]University of Kansas, Kansas City; [10]American College of Rheumatology, Atlanta, Georgia; [11]Patient Advisory Panel Members; [12]The Hospital for Sick Children, Toronto, Ontario, Canada; [13]Boston Children's Hospital, Boston, Massachusetts.

Drs. Hiraki and Son contributed equally and are co-senior authors.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25693).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25693.

Address correspondence via email to Shivani Garg, MD, PhD, at shivanigargup@gmail.com.

Submitted for publication June 26, 2025; accepted in revised form October 13, 2025.

SIGNIFICANCE & INNOVATIONS

- This paper summarizes key themes of patient experiences, perspectives, and priorities to support shared decision-making and align treatment recommendations in lupus nephritis and systemic lupus erythematosus guideline development.
- Three thematic domains emerged: treatment and monitoring; clinical communication; and improving transparency and information sharing.
- We highlight strategies to engage patients with diverse experiences to inform guideline recommendations per patient perspectives.

plan. Finally, including patient voices in clinical guidelines improves feasibility and acceptability of using guideline recommendations during routine visits.[25]

Since 2015, the American College of Rheumatology (ACR) has prioritized formal patient involvement in guideline development.[24,26] Clinical guideline development experts have highlighted the need to ensure patients' values are taken into consideration when evidence is systematically evaluated and graded to make recommendations. The goals of patient engagement in this setting are to: 1) identify patient values and priorities to inform clinical practice recommendations, particularly about therapies that carry potential harms; and 2) foster a collaborative approach to care, enhance patient engagement and adherence, and provide a more holistic and patient-centered approach for chronic disease care.

To inform the 2024 and 2025 ACR guidelines for the screening, monitoring, and treatment of LN and SLE respectively, the ACR convened two Patient Panels. The objectives of this manuscript are to highlight key themes that emerged during the Patient Panel discussions and illustrate how patient engagement can be actively incorporated into guideline development.

MATERIALS AND METHODS

Study design. We completed a cross-sectional qualitative study using content analysis of Patient Panel meetings that were held to inform ACR LN and SLE guideline development. This approach has been successfully used in ACR interstitial lung disease (ILD) and other guidelines to identify complex latent constructs that are not easily measured.[24,26] The consolidated Criteria for Reporting Qualitative Research was used to design this study (Supplementary Table 1).[28,29]

Setting and participants. National surveys, recommendations from the ACR SLE and LN guideline committee members, communications through the Lupus Foundation of America patient support groups, and previous Patient Panel member lists were used to identify participants for the Patient Panel meetings. Patients completed a screening checklist to report their diagnosis, disease type (SLE or LN), disease control (good or partial control with or without immunosuppressive medicines), rheumatologist, region, and ethnic group. All patients (n = 28) who reported a diagnosis of SLE with disease type as SLE or LN regardless of good or partial disease control and not actively followed by the clinician facilitators leading the Patient Panel meetings were invited to participate in the Patient Panels. Among all invited patients, 15 individuals participated in LN panel meeting and 13 participated in the SLE panel meeting; 9 individuals participated in both LN and SLE Patient Panel meetings.[27] In total 19 unique individuals participated in at least one Patient Panel meeting and 17 out of 19 consented for using their feedback to develop this manuscript. Sample size selection and the number of focus groups were determined based on prior guidelines, feedback from the guideline leadership (Core Team), and expert facilitators. Participants for the Patient Panels were purposefully recruited to represent different cultural, social and ethnic backgrounds, disease duration, and age of onset to capture different patient perspectives and values and to ensure that the findings were generalizable and applicable to different populations with lupus. Two separate Patient Panels, one for LN and one for SLE, were convened to identify key themes on patient experiences, values, perceptions, and priorities.

Patient panel meetings. Three Core Team rheumatologists (SG, LTH, MBS), supported by two ACR staff members experienced with ACR guideline development processes (AST and RP), facilitated the two four-hour virtual Patient Panel meetings. Prior to the virtual meetings, patients received a synopsis of the evidence that had been compiled to create each guideline. Additionally, the facilitators created and shared a semi-structured outline of the topics covered by the recommendations. Lastly, patients participated in an orientation webinar that provided information and guidance on interpreting the evidence report before the Patient Panel meeting. Participants were encouraged to consider the recommendations in the context of their preferences, values and priorities in regard to monitoring and management of SLE or LN. A facilitated discussion started with open-ended, guiding questions (Supplementary File 1). The facilitators provided definitions and gave details whenever necessary. Questions and prompts were kept open-ended by the facilitators to expand discussion points and engage panel members. To reduce participant fatigue during the four-hour Patient Panel meetings, facilitators incorporated scheduled breaks (every 60 minutes) and participants were encouraged to take additional breaks as needed. Facilitators also monitored engagement and ensured equal participation throughout the meetings.

The Patient Panel meetings were recorded by the ACR team (AST and RP), and quotes and comments made by Patient Panel members were documented. Text transcripts were developed

from the recordings and discussions. All identifiers and identifiable comments were redacted from the text transcripts. Text transcripts were independently reviewed by the facilitators for accuracy and to achieve immersion. Key themes were noted by each facilitator, and discrepancies in coding and generated themes were resolved via discussion to enhance trustworthiness and rigor. Key themes were reviewed with the Patient Panel members to obtain feedback on the findings. Given this was a secondary use of de-identified transcripts originally generated for the ACR guidelines development work, an institutional review board approval was not required.

Voting Panel meetings. The ACR uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework during guideline development. GRADE provided a structured framework for rating the quality of evidence and determining the strength of recommendations based on a careful assessment of benefits, harms, and patient perspectives. The published literature was reviewed by the Literature Review Team, which also designated the quality of evidence for each recommendation, per GRADE. This evidence was then presented during the Voting Panel meetings by the meeting chair and Literature Review Team leader. The Voting Panel meetings occurred virtually over two days for LN and over three days for SLE. Two Patient Panel members were selected to be patient representatives on the Voting Panels for the 2025 ACR SLE and 2024 LN Guidelines to highlight and share perspectives and key themes that emerged from the Patient Panel meetings around each recommendation and/or topic discussed.

During the Voting Panel meetings, the chair presented data detailing the quality of evidence for each recommendation and started the discussion by inviting patient representatives to share their comments. Following detailed discussion, Voting Panel members, both patients and health care providers, voted on each recommendation.

Content analysis. Transcripts from Patient Panel meetings were analyzed using content analysis. Key themes informed the coding scheme for the content analysis. Content analysis was performed by two independent reviewers (including 1 facilitator, SG, and 1 non-facilitator, IH).[28,30–32] The data were organized into meaningful thematic clusters pertaining to patient preferences. Adjustments to the coding scheme were made iteratively between each reading until thematic saturation was reached.[26,28,30–32] After key themes were generated, the reviewers and facilitators met to discuss themes and coding. Using validated qualitative methods, any discrepancies in coding and generated themes were resolved via discussion and consensus to enhance trustworthiness and rigor. Transcripts were coded using NVivo software.[33] This research triangulation was employed to enhance credibility of the findings and ensure that the analysis reflects the full breadth and depth of the data. Using member checking, we assured that patient preferences were associated with placement in the respective themes and code categories. The listed frequencies of each coded theme and subcategories within each theme for patient preferences and priorities regarding SLE and LN monitoring and treatment were summarized in tables. Following this, themes and subcategories under each theme were ranked in descending order of the listed frequencies. This step helped us identify highly ranked or high priority themes and subcategories within each theme. Finally, highly ranked themes with subcategories within each theme (informed by their listed frequency) were summarized in final tables included in this manuscript.

RESULTS

Patient panel member characteristics. Among 19 unique individuals participated (attended) in one or two Patient Panels, 17 patients provided consent to use their feedback for analysis and inclusion in aggregate data for this paper; 88% were female, 55% were Black and 77% had LN (Table 1). Regarding representation across US geographic regions, 47% of the Patient Panel members were from the South, followed by 35% from the East.

Table 1. Summary of patient panel characteristics

Characteristics	Patients (n = 17)[a], n (%)
Age, median (range), in yrs	38 (22–50)
Female	15 (88.2)
Race/Ethnicity	
Black	9 (52.9)
Asian	3 (17.6)
White	3 (17.6)
Hispanic	2 (11.8)
Region	
South	8 (47.1)
East	6 (35.3)
West	3 (17.6)
Disease control[b]	
Good control with 1 or more immunosuppressive medicines[b]	7 (41.2)
Partial control requiring multiple immunosuppressive medicines[c]	10 (58.8)
Disease experience	
Arthritis	16 (94.1)
Skin manifestations	13 (76.5)
Lupus nephritis diagnosis	14 (82.3)
Lupus affecting blood cell counts	11 (64.7)
Ever requiring hospitalization for lupus flare	9 (52.9)
Serositis	5 (29.4)
Childhood-onset lupus	1 (5.88)

[a] Table shows data from 17 patients who provided consent to use their feedback for analysis for this manuscript among 19 unique individuals who attended 1 or more patient panel meetings.
[b] Patient-reported information.
[c] Requiring multiple medicines or failed several medicines for lupus.

Thematic analysis. Across the two Patient Panels for LN and SLE, four common themes emerged regarding treatment and monitoring of LN and SLE (Domain 1) including medication side effects, daily function, treatment goals, and monitoring and screening (Table 2). Next, two key themes were generated around clinical communication (Domain 2), including strategies to optimize clinical communication and effective, respectful communication (Table 3). Finally, two themes surfaced around improving transparency and information sharing (Domain 3), including clinical trial participation, and medical costs and insurance coverage (Table 4). As described in our methods, common and key themes were identified based on the ranking informed by the listed frequency of each coded themes and subcategories in our content analysis.

Domain 1. Treatment and monitoring of LN and SLE (Table 2)

Theme 1: Medication side effects. The most common theme highlighted by Patient Panel members was the negative impact of treatment on quality of life. A patient taking mycophenolic acid stated that *"Food is a big part of [my] background and culture, and [I] love to cook, so having GI [stomach] issues [with medicine] really decreases [my] quality of life… this is important [to me]…"* Additionally, patients noted that balancing side effects with efficacy is important to them: *"Side effects of therapies do affect quality of life, but I am willing to take all of these side effects over kidney failure."* Other subcategories that were emphasized included the impact of treatment on mental health (eg, depression, suicidal ideation, social withdrawal) and pill fatigue potentially resulting in nonadherence: *"I have pill fatigue, sometimes I just can't do it… It is mentally overwhelming resulting in pill fatigue…*"

Theme 2: Daily function. Maximizing daily function was a key priority for many patients. The ability to perform required or valued daily activities, such as cooking, being physically active with the family, were included under daily function by the patients. A patient stated, *"…My goal is to survive and have the best daily functioning as possible."* Another patient quoted, "*Quality of life is my number 1 wish, but in reality, this doesn't seem possible."* Next, patients prioritized avoiding flares and preventing organ damage to maintain their daily activities: *"Each flare has led to a major "failure" (eg, loss of sight, going to [the] hospital), so avoiding the flare is most important to me."* An additional theme emerged regarding including patient preferences on the route of administration and number of medicines needed to maintain daily function, "*Mode of administration should be considered […] [Discuss] what is easier for the patient or preferred by them…"* Another patient mentioned, "*Start with one medicine, then add others, because then you have a better understanding of side effects and response to each one…"*

Theme 3: Treatment goals. Patients discussed that their main goal was survival, when it was in question. A patient said, *"First priority was survival at time of diagnosis because I was in [a] coma – so I just wanted to live."* Additionally, patients highlighted that treatment goals should align with patient values and change based on disease severity and life phases, focusing on long-term outcomes as disease progression allows. To elaborate, a patient stated, *"In the past, everything was failing, so some questions were more critical than others. When you are really sick, your goals are different. You can have other conversations when your illness slows down a little."*

Theme 4: Monitoring and screening. Patients discussed the importance of frequent lab monitoring and how helpful it is to carefully monitor organ function and response to current therapy. They shared some concerns regarding undergoing invasive procedures (eg, kidney biopsy) but agreed that initial kidney biopsy for diagnosis was acceptable, assuming that proper sedation and anesthesia were administered: *"[I] had a kidney biopsy and was told that it would hopefully tell that [I] had LN…"* However, most patients were concerned about getting a repeat kidney biopsy: *"I would not likely want to do another biopsy because of other possible side effects like bleeding. I would only do it again if there was something going on with…labs or there was some other clear reason."* Additionally, patients highlighted that receiving sedation did improve their overall experience of undergoing an invasive procedure like kidney biopsy compared to not receiving sedation or anesthesia. A patient mentioned that *"I was not sedated and it [kidney biopsy] was painful…"*

Domain 2. Themes regarding clinical communication (Table 3)

Theme 1: Optimizing clinical communication. Patients suggested several strategies that could improve clinical care. A highly ranked strategy was supporting shared decision-making during their disease course to foster trust and built strong relationships with patients. A patient quoted, "*Risks are very different to you over time, so doctors must continue to check in with their patients regularly over disease course to discuss risks vs. benefits."* Another patient stated that "*Every side effect, severe or mild, should be discussed…This helps with decision-making and being prepared*." Additionally, offering a personalized, compassionate, and collaborative team-based approach, such as including a pharmacist in the care team, was considered extremely valuable. A patient stated, "*My pharmacist also suggested where I could reduce certain medications, all of which was helpful and made things easier to manage."* Another patient said, "*The best decision depends on the drug sometimes, and the trust the patient has in their doctor…health care team…"*

Table 2. Domain 1: Treatment and monitoring of systemic lupus erythematosus and lupus nephritis*

Themes	Theme subcategories	Illustrative quotes (1–3)
Theme 1: Medication side-effects	Impact on quality of life	"*One of the biggest challenges is fatigue that affects quality of life, which some medicines worsen, and nothing can be done…*" "*Some side effects are unbearable, some are tolerable…I think the discussion should be personalized based on each patient's preferences and tolerability…*"
	Balancing side effects vs. efficacy	"*Side effects of therapies do affect quality of life, but I am willing to take all of these side effects over kidney failure.*" "*Prednisone can destroy your bones and teeth […] but when I am in a flare, I know prednisone will definitely help me…*" "*Sad we're still having this fertility conversation as I am unable to have children because of the medication [cyclophosphamide] I was given…*" "*Immunosuppressives causing infections has also been a big issue. This should be discussed with patients more regularly.*" "*Hydroxychloroquine messed up my vision, but I am back on it now as I need it.*"
	Pill fatigue	"*I have pill fatigue, sometimes I just can't do it… It [pill burden] is mentally overwhelming resulting in pill fatigue.*" "*Pill burden is a real problem; providers must remember this and prescribe accordingly, so patients have as few pills to take…*" "*At one point, I was on 14 pills… I am a pre-med student… I just could not do it…*"
Theme 2: Daily function	Maximizing daily function	"*…My goal is to survive and have the best daily functioning as possible.*" "*Quality of life is my #1 wish but in reality, this doesn't seem possible.*" "*Maximum quality of life… I like to be physically active… I miss time with family…*"
	Avoiding flares	"*Avoiding a flare is very important to be able to achieve … normalcy in life.*" "*Prevent disease flare because [flare] leads to extreme joint pain, finger swelling, [and] inability to walk, which affects daily activities.*" "*Each flare has led to a major 'failure' [loss of sight, going to hospital], so avoiding the flare is most important to me.*"
	Preventing organ damage	"*Kidney [function] preservation was very important initially and still is today.*" "*Protecting organ function is a priority*" "*… I am willing to take all of these side effects over kidney failure…*"
	Medicine preferences (number, route, and type)	"*Mode of administration should be considered […] [Discuss] what is easier for the patient or preferred by them…*" "*Start with one medicine, then add others, because then you have a better understanding of side effects and response to each one…*" "*Pill burden is a real issue… It affects cost and adherence…*"
Theme 3: Treatment goals	Survival	"*My goal is to survive…*" "*First priority was survival at time of diagnosis because I was in coma – so I just wanted to live.*"
	Aligning treatment with patient values	"*Understand the patient as a whole person instead of just a disease […] Consider … [what] communities a person is in… all affect goals of treatment.*" "*I was a med student trying to go into residency. It was scary to think of the environment I was getting into. There was no discussion about adjusting my steroids to better manage that risk.*"
	Changes based on disease severity	"*Treatment goals depend on the point in the journey, particularly how severe and active the disease is…*" "*At certain levels of illness, I am more willing to accept potential harms, if options are limited…*" "*When you are really sick, your [goals] are different. You can have other conversations when your illness slows down a little.*"
	Changes with age or life phases	"*I would avoid stomach side effects more when I was younger because I was trying to go out and socialize. As I get older, I'm worried about risk of infection, so I would sit at home with stomach issues, if needed…*" "*Fertility is also important, as lupus attacks women in their prime; need to discuss egg preservation as well as other organ damage issues…*" "*My kidney function has gotten a lot better, so now I am more concerned about fertility and cancer risks and considering my quality of life when I am 40 or older*"
	Long-term outcomes	"*Doctors can help by really talking with patients about options and plans that look ahead and provide hope, especially about stages of treatment to try to achieve longer-term goals…*" "*In the beginning, you're still learning and not worried as much about longer term outcomes, but they become more important as you go on.*"

(Continued)

Table 2. (*Cont'd*)

Themes	Theme subcategories	Illustrative quotes (1–3)
Theme 4: Monitoring and screening	Frequency of blood and urine monitoring	"*I watch liver and kidney function carefully. Can't always get organ transplanted.*" "*I don't mind doing blood work every 3 months, especially if labs are more local to me. I don't prefer to drive 2 hours to do a blood draw.*" "*Over the years, I have come to prefer monthly bloodwork, because it educates me to see my blood levels.*"
	Invasive procedures (eg, diagnostic kidney biopsies)	"*Kidney biopsy was the best method to identify [lupus nephritis]…*" "*[I] Had a kidney biopsy and was told that it would hopefully tell that [I] had LN…*" "*I was put under sedation so I did not have much issues [with the kidney biopsy]…*"
	Repeat invasive procedures	"*I would not likely want to do another biopsy because of other possible side effects like bleeding. I would only do it again if … there was a clear reason.*" "*If I need a biopsy again, I will have to be convinced that it is vital…*" "*I was not sedated and it [kidney biopsy] was painful…*"

* Themes arranged from most common to least commonly listed frequency. Only key subcategories with higher listed/coded frequencies for each theme are shown. LN, lupus nephritis.

Theme 2: Provider and structural impediments to effective communication. Many patients reported experiencing a significant power differential in their interactions with health care providers, a dynamic that can be reinforced or even exacerbated by the language some providers use. Judgmental communication, for instance, negatively impacted patients' mental health and resulted in mistrust. As one patient advised, "*Don't be judgmental, but be curious about why they [the patient] may decline certain treatment options.*" Another patient described the impact of such communication, stating, "*Being dismissive…makes [a] patient feel worse and less open or willing to listen to their doctor.*" Beyond individual interactions, broader negative communication patterns, such as experiencing structural racism, also fostered mistrust and negatively affected patients' feelings and care. To elaborate, a patient stated, "*…patients are often dismissed, even more so for people of color and women.*"

Domain 3. Improving transparency and information sharing (Table 4)

Theme 1: Clinical trial participation. Patients highlighted a need for building trust among communities to ensure broader clinical trial recruitment and representation from diverse communities. They recommended that providing more detailed information about the medication, placebo, inclusion criteria and research outcomes could help build trust. A patient reported, "*Companies should answer questions and explain things to the community to build trust. Things need to be translated to communities so you can get them to participate in the trials.*" Moreover, patients suggested that the involvement of patients in clinical trial design and engaging patient advocates as research coordinators or on research teams could help build trust and ensure broader representation. A patient stated, "*Having someone from the community who is part of team, is involved [in] clinical trials, [and] can deliver the information honestly, not ambiguously, is important to maintain trust of the patients.*" A suggestion was made to offer a visit with a research coordinator and culturally appropriate materials to reassure possible research participants and increase participation across communities. Finally, they shared concerns about discontinuing key therapies to enroll in clinical trials: "*…has brought up research opportunities, but in some cases, [I] would have had to come off my meds for 3 months…*"

Theme 2: Medical costs and insurance coverage. Beyond clear communication about their medical conditions and treatment options, patients strongly emphasized their need for practical assistance in navigating the complex landscape of health care costs and insurance coverage. Many expressed feeling overwhelmed or stressed with managing these financial aspects, highlighting it as a barrier to accessing and adhering to care, and had a negative impact on their mental health. For example, one patient articulated this need clearly, stating, "*Doctors must discuss ALL therapeutic options and their side effects with patients so patients can make their own care plans, especially in context of their insurance, costs, and more.*" Other patients supported this sentiment and expressed a desire for transparency and partnership, where clinicians actively help patients understand the financial impact of their health care choices. Without support, patients expressed they may face unexpected out-of-pocket expenses, struggle to afford prescribed medications or procedures, or even delay or forego necessary care, ultimately impacting their health outcomes and overall well-being. One patient noted, "*Patients are paying for things out of pocket if they have a high deductible…*"

Aligning treatment guidelines and evidence-based recommendations with patients' priorities and values. During the Voting Panel discussions, following the presentation of the graded evidence for each potential recommendation, Patient Panel representatives were invited to share the key themes and patient perspectives that had emerged from the two Patient Panel meetings. Such discussions helped align guideline recommendations with patients' preferences. For example, when

Table 3. Domain 2: Themes regarding clinical communication*

Themes	Theme subcategories	Illustrative quotes (1–3)
Theme 1: Optimizing clinical communication	Shared decision-making	"*Risks are very different to you over time, so doctors must continue to check in with their patients regularly over disease course to discuss risks vs. benefits.*" "*A clear discussion and understanding between the doctor and patient to understand what is being recommended is recommended.*" "*Every side effect, severe or mild, should be discussed… This helps with decision-making and being prepared.*"
	Showing empathy and compassion	"*This [compassion] is important for treatment success, overall. The doctor should be genuine and see the whole patient.*" "*Emphasizing importance of compassionate care and understanding that this is a gateway for trust and better outcomes.*" "*That [compassionate care] let me know that I didn't have to stick with a medication because it 'worked', helped be more confident about speaking up.*"
	Multidisciplinary or collaborative care team approach	"*My pharmacist also suggested where I could reduce certain medications, all of which was helpful and made things easier to manage.*" "*The best decision depends on the drug sometimes, and the trust the patient has in their doctor… health care team…*" "*[Doctors] should refer the patient to mental health specialists, social worker.*" "*It would be very helpful to have a referral from the rheumatologist to other areas where we are affected, like GI and cardiology.*"
	Personalized approach	"*Hopefully, over time, we can get to personalized lupus care with more precision in the future […] every patient is different…*" "*The doctor should ask what the patient's most important priority for the visit is, to address the limited time and to be sure they get to that issue.*"
	Offer telehealth and enroll in pharmacy mail delivery services	"*Having a virtual appointment option is very helpful […] This has allowed for better adherence…*" "*Virtual appointments mean better control of my disease…*"
	Building trust and rapport	"*Doctors need to emphasize the importance of compassionate care and understand that this is a gateway for trust and better outcomes.*" "*The best decision depends on the drug… and the trust [the] patient has in [the] doctor…*"
Theme 2. Provider and structural impediments to effective communication	Impact on mental health	"*[I] feel hopeless and experience post-traumatic stress disorder for all we go through with treatments…*" "*Mental health is one of the most severe side-effects and should be assessed…*" "*Depression is a basic thing for chronic illness; recognize [this] and do not be dismissive.*"
	Judgmental care team	"*Don't be judgmental, but be curious about why they [the patient] may decline certain treatment options.*" "*Please explain [treatments] and be kind in the way the message is delivered – 'this is how we think it will help you' rather than treating the patient like a science experiment.*"
	Structural racism and need for cultural competency	"*Understand the patient as a whole person instead of just a disease such as the concept of fertility as a Black woman and a person with lupus…*" "*Medical school doesn't teach interpersonal skills, cultural competence, and intersectionality but should…*" "*Education for patients & providers about this [cultural competency]-patients are often dismissed, even more so for people of color & women.*"
	Mistrust in health care team and system	"*… Some rheumatologists are so focused on the numbers that it's like the patient is not even there. This is dismissive, which makes patient feel worse and less open or willing to listen to their doctor.*" "*We [lupus patients] want to know and be assured that we are not disposable human subjects to pharmaceutical companies.*" "*At this stage of my life, thinking about possibly having to go to a facility several times per week gives me a sense of sadness and grief.*"
	Lack of collaborative approach	"*Sometimes doctors will send patients to another specialist to deal with issues that come up; know that the rheumatologist's referral has more impact…*" "*Pharmacists… I wish we had them there all the time… their input is valuable.*"

* Themes arranged from most common to least commonly listed frequency. Only key subcategories for each theme are shown. GI, gastrointestinal.

Table 4. Domain 3: Improving transparency and information sharing*

Theme 1: Clinical trial participation	Building trust among communities	"*Companies should answer questions and explain things to the community to build trust. Things need to be translated to communities so you can get them to participate in the trials.*" "*I mistrust clinical trials because of the history within the Black community. When you ask, the doctor or company say they don't know how many Black women have participated in the trials. People asking people to be involved [in clinical trials] need to know the details.*" "*The rheumatologists who are doing clinical trials don't always tell all of their patients that they are doing the trials […] all potential research opportunities should be provided to all patients.*"
	Additional details on medicines, inclusion criteria, placebo	"*Also, when involved in a clinical trial, the patient doesn't know if they are receiving the drug or a placebo and could get pulled off the trial mid-way through – so, be upfront with all relevant details, as all of this creates uncertainty for the patients involved…*" "*The rheumatologists who are doing clinical trials don't always tell all of their patients that they are doing the trials*" "*Also, need to explain to patients all the details of what the research is about; this helps with the trust issues.*"
	Dedicated research coordinator visits	"*Having someone from the community who is part of team, is involved [in] clinical trials, [and] can deliver the information honestly, not ambiguously, is important to maintain trust of the patients.*" "*Details on what a visit will look like can help…*"
	Being off therapy	"*… has brought up research opportunities, but in some cases, [I] would have had to come off my meds for 3 months…*" "*Back and forth on medicines that needed to be stopped.. Had abnormal PAP… But then PAP was normal but was on meds again… make sure your professionals are well trained in their roles so this doesn't happen…*"
Theme 2: Medical costs and insurance coverage	Financial resources	"*Doctors should tell patients about options like copay programs, if available…*" "*I try to find other 3rd party networks that can do administration of drugs.*"
	Insurance coverage and appeals	"*Patients are paying for things out of pocket if they have a high deductible…*" "*Insurance doesn't always want to pay for MRIs or CT scans… sometimes it is covered better if recommended by rheumatologists…*"
	Transparency of cost	"*Doctors must discuss ALL therapeutic options and their side effects with patients so patients can make their own care plans, especially in context of their insurance, costs, and more.*" "*I do agree, there should be cost transparency. However, sometimes the rheumatologist has limited time, so this doesn't happen as much as it could.*"
	Patient and provider advocacy	"*Tell the patient about options so they know they are there, and tell them you will advocate for them with the insurance company, if needed.*" "*Rheumatologists should try to help patients. Don't disregard or not recommend something just because the doctor assumes [their] insurer won't cover.*"

* Themes arranged from most common to least common listed frequency. Only key subcategories for each theme are shown. CT, computerized tomography; MRI, magnetic resonance imaging.

discussing repeat kidney biopsy to monitor treatment response, the panel heard a strong patient preference to limit invasive procedures, or at least to have a dedicated discussion on the specific benefits of repeating the biopsy versus empiric treatment escalation. Giving primacy to patient preferences likely influenced the voting on guideline recommendations.

In several instances during the Voting Panel meetings, physicians and patients worked together to clarify recommendations on complex topics, such as glucocorticoid use, balancing treatment efficacy with side effects, tailoring treatment per individual patient priorities, life phase, and values. For example, there was substantial variability regarding glucocorticoid dosing and tapering among the physician Voting Panel members. A nuanced discussion between physicians and Patient Panel representatives highlighted the need to minimize glucocorticoid exposure over time to limit side effects. However, Patient Panel representatives also conveyed their willingness to accept higher doses of glucocorticoids to gain disease control, provided that the benefits and harms were thoroughly discussed and a clear tapering plan was established.

Next, discussions highlighted the importance of contextualizing therapeutic choices within patients' broader life circumstances, including life stage and family planning. The Voting Panel's guidance to favor mycophenolate over cyclophosphamide, or to use the Euro-Lupus low-dose cyclophosphamide regimen if cyclophosphamide was deemed necessary, directly addresses the significant concerns raised by both physicians and Patient Panel members regarding the potential for cyclophosphamide-induced infertility. This approach moves beyond simply treating the primary condition (SLE or LN) and

demonstrates a patient-centered commitment to proactively mitigate long-term impacts on reproductive health and future family planning desires. It's a clear example of how broader therapeutic strategies must thoughtfully weigh treatment efficacy alongside individual patient priorities and life goals during different stages of life (eg, during reproductive years), ensuring that counseling and treatment choices support not just immediate health needs but also long-term quality of life and personal aspirations.

The systematic approach that was adopted to align guideline recommendations with the Patient Panel's feedback informed our conceptual framework (Figure 1). This framework or approach can be used by other groups to develop clinical practice guidelines and potentially better align care with patient values and preferences.

DISCUSSION

This study summarizes the processes employed to identify and incorporate patients' experiences, perspectives, and priorities in the development of ACR LN and SLE screening, monitoring and treatment guidelines. These themes that arose from those discussions included input from Patient Panel members who participated on the Voting Panel, and were pivotal for aligning final guideline recommendations with patient perspectives, priorities, and values. Additionally, this work underscores the importance of tailoring treatment choices with patients' broader life circumstances, including life stage—recognizing that these will change over time so should be continually reassessed. Finally, integrating patient experiences helped broaden perspectives of the Voting Panel and develop treatment and management recommendations based on real-world patient experiences, enhancing the clinical applicability of LN and SLE guideline recommendations.

Engaging patients in developing treatment and management guidelines is important.[34] Several studies have explored patient experiences in SLE and LN.[10,19,35,36] Yet, this work was distinct as it was one of the first to directly integrate patient perspectives and patient members in the voting process to inform clinical guideline development aligned with real-world patient experiences for SLE and LN.[37,38] Many previous efforts have documented patient priorities separately or retrospectively; our approach established a partnership where patient-defined themes actively shaped recommendation discussions in real-time. This work adapted an approach used by the 2023 ACR/CHEST ILD and other ACR guidelines to gather patient values and perspectives and integrate them into the Voting Panel decision-making instead of only independently reviewing population, intervention, comparator, and outcomes (PICO) questions with the Patient Panel.[26] This approach helped our team gather and share perspectives that spanned multiple PICO questions and clinical scenarios, including challenging and complex topics like family planning and treatment choices, personalized care, building trust, and effective, respectful communication. Moreover, the diversity of our Patient Panel, encompassing varied racial and ethnic backgrounds, socioeconomic statuses, and disease experiences and durations, was a strength. This heterogeneity likely contributed to the richness and breadth of themes identified, particularly concerning structural racism and health care access disparities, which may be less prominent in some cohorts.

The themes emerging from our panel resonate with much of the existing literature on patient experiences with chronic illness, including the significant burden of treatment side effects, the

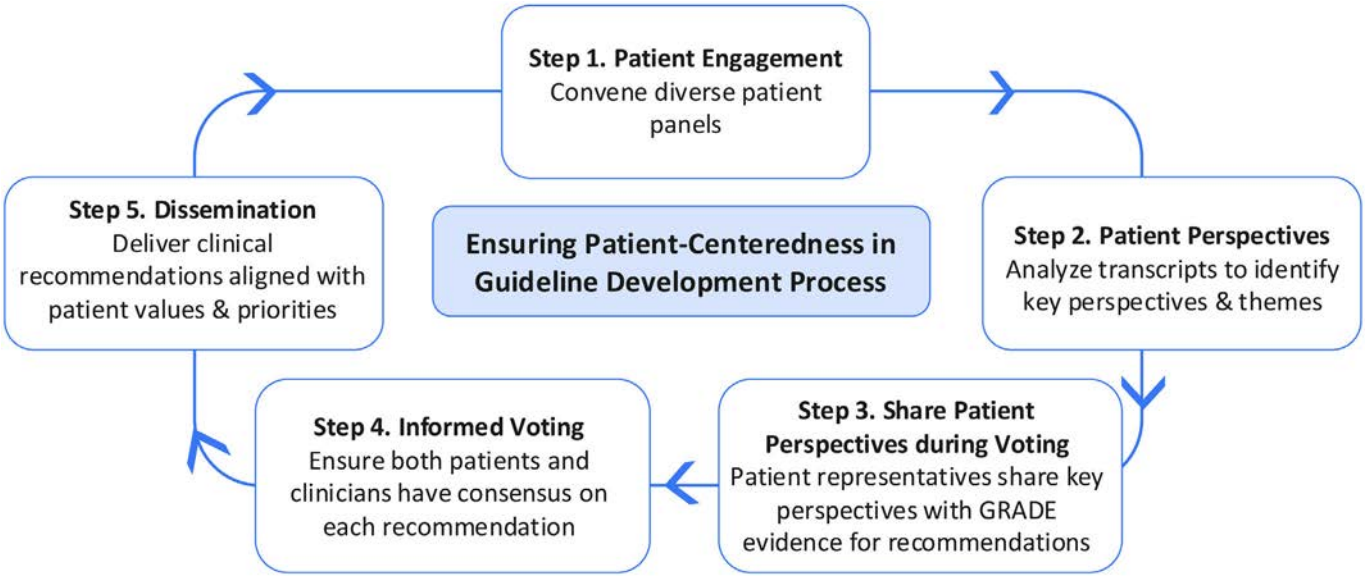

Figure 1. A framework to ensure the development of patient-centered approach in clinical guideline development and potential improving clinical care.

desire for shared decision-making, and challenges with health care communication.[10,19,35,36] Particularly, patients highlighted the importance of survival as the key priority and tailoring treatment per individual patient preferences, life phases, and disease severity using a multidisciplinary, team-based approach.[26,39–41] This highlights the importance of ongoing communication supported by shared decision-making strategies to ensure that management is aligned to patients' evolving priorities based on disease severity and life phases.[20,42,43] The emphasis on preserving organ function to prolong survival and improve quality of life while minimizing medication side effects reflected a desire of patients to support their overall well-being and ensure better long-term outcomes and survival. The explicit linkage of these patient-articulated needs to the formulation of guideline recommendations distinguishes this study and provides a clear pathway for translating patient voices into actionable clinical guidance.

Additionally, effective communication and a strong patient-physician relationship were noted as crucial elements of patient-centered care. Further, cost and insurance issues were widely acknowledged, and our findings underscore the profound need for proactive, clinician-guided navigation of these complexities, a theme that may be particularly pronounced in the US health care context represented by our panel.[44–47]

Our study had a number of strengths including having a diverse group of Patient Panel participants, and the triangulation of data sources to enhance credibility and rigor. We also acknowledge some study limitations. First, although our Patient Panel included multiple perspectives, certainly not all possible perspectives were included. Second, it is important to consider that the experiences and challenges highlighted by patients, particularly those related to navigating care and costs, may be significantly influenced by the specific structure and complexities of the US health care system, and the regions of the United States with higher representation in the Patient Panels (eg, 47% of the Patient Panel members were from the South followed by 35% from the East). Consequently, some findings may have limited generalizability to patient experiences in countries with different health care models. Third, the data on the duration of disease (SLE or LN) and history of being on dialysis or undergoing a kidney transplantation were not collected. Therefore, some patient perspectives could have been missed in our analysis and could limit generalizability of our findings. Finally, significant differences in patient perspectives were not identified among patients with and without LN. However, it is important to note that majority of patients (77%) had LN. Therefore, future research should further explore these differences, particularly in patients without LN who have a less aggressive disease course and may be on less immunosuppression.

In conclusion, this study provides valuable insights into the experiences, perspectives, and priorities of patients with SLE and LN. The findings underscore the importance of patient-centered care, effective communication, and addressing systemic barriers using multidisciplinary team-based and patient-centered approaches. By integrating patient perspectives into guideline development, we can continue towards a truly collaborative and patient-centered approach for people with LN and SLE.

ACKNOWLEDGMENTS

We would like to thank Regina Parker for her integral support in conducting this work and developing this manuscript. We would also like to thank Brandi Rollins, Jolanda Jackson, LaKeisha Coach, Maria Martines, Toya Jules, Michael Okechuku, and Rashelle Howell for their valuable contributions during the Patient Panels. Microsoft Co-pilot, a Large Language Model (LLM), was minimally used in the preparation of this manuscript and its use was limited to check spelling and grammar of this paper.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Garg confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Buie J, McMillan E, Kirby J, et al. Disparities in lupus and the role of social determinants of health: current state of knowledge and directions for future research. ACR Open Rheumatol 2023;5(9):454–464.
2. Hocaoğlu M, Valenzuela-Almada MO, Dabit JY, et al. Incidence, prevalence, and mortality of lupus nephritis: A population-based study over four decades using the Lupus Midwest Network. Arthritis Rheumatol 2023;75(4):567–573.
3. Hailu GT, Hussen SU, Getachew S, Berha AB. Management practice and treatment outcomes of adult patients with Lupus Nephritis at the Renal Clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. BMC Nephrol 2022;23(1):214.
4. Ke SR, Liu CW, Wu YW, et al. Systemic lupus erythematosus is associated with poor outcome after acute myocardial infarction. Nutr Metab Cardiovasc Dis 2019;29(12):1400–1407.
5. Živković V, Mitić B, Stamenković B, et al. Analysis on the risk factors for organ damage in patients with systemic lupus erythematosus: a cross-sectional single-center experience. Sao Paulo Med J 2019; 137(2):155–161.
6. Peng W, Tang Y, Tan L, et al. Clinicopathological study of male and female patients with lupus nephritis: a retrospective study. Int Urol Nephrol 2018;50(2):313–320.
7. Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. Rheumatology (Oxford) 2017;56(suppl_1):i67–i77.
8. Tazi Mezalek Z, Bono W. Challenges for lupus management in emerging countries. Presse Med 2014;43(6 Pt 2):e209–e220.
9. Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther 2012;14 Suppl 4(Suppl 4):S4.
10. Chambers SA, Raine R, Rahman A, Isenberg D. Why do patients with systemic lupus erythematosus take or fail to take their prescribed

medications? A qualitative study in a UK cohort. Rheumatology (Oxford) 2009;48(3):266–271.
11. Fernández M, Alarcón GS, Calvo-Alén J, et al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Rheum 2007;57(4):576–584.
12. Contreras G, Lenz O, Pardo V, et al. Outcomes in African Americans and Hispanics with lupus nephritis. Kidney Int 2006;69(10):1846–1851.
13. Petri M, Purvey S, Fang H, et al. Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. Arthritis Rheum 2012;64(12):4021–8.
14. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore) 2006;85(3):147–156.
15. Alarcón GS, McGwin G, Jr., Petri M, et al. Baseline characteristics of a multiethnic lupus cohort: PROFILE. Lupus 2002;11(2):95–101.
16. Drenkard C, Fuentes-Silva Y, Parente Costa Seguro L, et al. Let's Talk About Lupus. Overview of an innovative, high-reach, online program to fill the education gaps of Latin Americans living with lupus. J Clin Rheumatol 2022;28(2):e368–e374.
17. Twumasi AA, Shao A, Dunlop-Thomas C, et al. Exploring the perceived impact of the chronic disease self-management program on self-management behaviors among African American women with lupus: A qualitative study. ACR Open Rheumatol 2020;2(3):147–157.
18. Drenkard C, Bao G, Lewis TT, et al. Physician-patient interactions in African American patients with systemic lupus erythematosus: Demographic characteristics and relationship with disease activity and depression. Semin Arthritis Rheum 2019;48(4):669–677.
19. Garg S, Chewning B, Gazeley D, et al. Patient and healthcare team recommended medication adherence strategies for hydroxychloroquine: Results of a qualitative study informing intervention development. Lupus Sci Med 2022;9(1):e000720.
20. Garg S, Ferguson S, Chewning B, et al. Clarifying misbeliefs about hydroxychloroquine (HCQ): developing the HCQ benefits versus harm decision aid (HCQ-SAFE) per low health literacy standards. Lupus Sci Med 2023;10(2):e000935.
21. Singh JA, Fraenkel L, Green C, et al. Individualized decision aid for diverse women with lupus nephritis (IDEA-WON): A randomized controlled trial. PLoS Med 2019;16(5):e1002800.
22. Kim C, Armstrong MJ, Berta WB, et al. How to identify, incorporate and report patient preferences in clinical guidelines: A scoping review. Health Expect 2020;23(5):1028–1036.
23. Kelley M, James C, Alessi Kraft S, et al. Patient perspectives on the learning health system: The importance of trust and shared decision making. Am J Bioeth 2015;15(9):4–17.
24. Johnson SR, Turner AS, Goodman SM. How the American College of Rheumatology develops guidelines. Rheum Dis Clin North Am 2022;48(3):579–588.
25. Brunelli C, Borreani C, Caraceni A, et al. PATIENT VOICES, a project for the integration of the systematic assessment of patient reported outcomes and experiences within a comprehensive cancer center: a protocol for a mixed method feasibility study. Health Qual Life Outcomes 2020;18(1):252.
26. Mirza RD, Bolster MB, Johnson SR, et al. Assessing patient values and preferences to inform the 2023 American College of Rheumatology/American College of Chest Physicians interstitial lung disease guidelines. Arthritis Care Res (Hoboken) 2024;76(8):1083–1089.
27. Sammaritano LR, Askanase A, Bermas BL, et al. 2024 American College of Rheumatology (ACR) guideline for the screening, treatment, and management of lupus nephritis. Arthritis Rheumatol 2025;77(9):1115–1135.
28. Patton M. Qualitative research and evaluation methods. Vol 3. Sage Publications; 2002.
29. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349–357.
30. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs 2008;62(1):107–15.
31. Bloor M, Wood F. Keywords in qualitative methods: A vocabulary of research concepts. 1st ed. Sage Publications; 2006.
32. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15(9):1277–88.
33. NVivo (Version 12). 2018. Accessed November 2020. https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home
34. Duda-Sikuła M, Kurpas D. Enhancing chronic disease management: Personalized medicine insights from rural and urban general practitioner practices. J Pers Med 2024;14(7):706.
35. Chambers S, Raine R, Rahman A, et al. Factors influencing adherence to medications in a group of patients with systemic lupus erythematosus in Jamaica. Lupus 2008;17(8):761–9.
36. Chambers SA, Rahman A, Isenberg DA. Treatment adherence and clinical outcome in systemic lupus erythematosus. Rheumatology 2007;46(6):895–898.
37. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64(6):797–808.
38. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78(6):736–745.
39. Katz PP, Barber CEH, Duarte-García A, et al. Development of the American College of Rheumatology patient-reported outcome quality measures for systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2024;76(6):777–787.
40. Basta F, Fasola F, Triantafyllias K, et al. Systemic lupus erythematosus (SLE) therapy: The old and the new. Rheumatol Ther 2020;7(3):433–446.
41. Liu X, Jia X, Wang X, et al. Mental health conditions in patients with systemic lupus erythematosus: A systematic review and meta-analysis. Rheumatology (Oxford) 2024;63(12):3234–3242.
42. Coylewright M, Keevil JG, Xu K, et al. Pragmatic study of clinician use of a personalized patient decision aid integrated into the electronic health record: An 8-year experience. Telemed J E Health 2020;26(5):597–602.
43. Espinoza Suarez NR, LaVecchia CM, Ponce OJ, et al. Using shared decision-making tools and patient-clinician conversations about costs. Mayo Clin Proc Innov Qual Outcomes 2020;4(4):416–423.
44. Wisniewski JM, Walker B. Association of simulated patient race/ethnicity with scheduling of primary care appointments. JAMA Netw Open 2020;3(1):e1920010.
45. Widdifield J, Bernatsky S, Thorne JC, et al. Wait times to rheumatology care for patients with rheumatic diseases: a data linkage study of primary care electronic medical records and administrative data. CMAJ Open 2016;4(2):E205–12.
46. Kaplan G, Hamilton Lopez M, McGinnis JM, editors. Transforming Health Care Scheduling and Access: Getting to Now. National Academies Press; 2015.
47. Ward MM. Access to care and the incidence of endstage renal disease due to systemic lupus erythematosus. J Rheumatol 2010;37(6):1158–63.

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 936–945
DOI 10.1002/acr.25703

Three Practical Methods for Estimating Preoperative Cardiorespiratory Fitness in Patients With Severe Hip or Knee Osteoarthritis: A Cross-Sectional Study

Brendon H. Roxburgh,[1,2] Holly A. Campbell,[1,2] James D. Cotter,[1,2] Ulla Reymann,[1] Michael J. A. Williams,[1,2,3] David Gwynne-Jones,[1] and Kate N. Thomas[1,2]

Objective. Low preoperative cardiorespiratory fitness is associated with poorer functional and subjective recovery following hip or knee arthroplasty. The objective of this study was to evaluate the ability of simple, indirect assessment tools (the Duke Activity Status Index, daily step count, and timed up and go test) to estimate directly measured cardiorespiratory fitness and identify patients with low preoperative fitness (<15 mL/kg/min) among those with severe hip or knee osteoarthritis.

Methods. Ninety-one patients with severe hip or knee osteoarthritis who were scheduled for total joint arthroplasty were recruited. Within 1 week before surgery, participants performed symptom-limited maximal cardiopulmonary exercise testing, the Duke Activity Status Index questionnaire, accelerometry to determine daily step count, and the timed up and go test.

Results. All three indirect tools provided strong estimates of peak oxygen consumption ($\dot{V}O_2$) ($r^2 \geq 0.61$). The Duke Activity Status Index slightly underestimated peak $\dot{V}O_2$ by 0.9 mL/kg/min. All three metrics performed strongly in their ability to accurately identify patients without a peak $\dot{V}O_2 < 15$ mL/kg/min; however, their accuracy to positively predict peak $\dot{V}O_2 > 15$ mL/kg/min was only fair.

Conclusion. These simple, practical, cost-effective tools have utility for estimating preoperative fitness to rule out low fitness. These tools could be used by perioperative clinicians for identifying patients who may not require preoperative cardiopulmonary exercise testing, thereby optimizing resource allocation.

INTRODUCTION

Cardiorespiratory fitness is a measure of the integrated capacity of the cardiovascular, respiratory, and muscular systems to use and deliver oxygen to the working muscles and remove metabolites during exertion.[1,2] Cardiorespiratory fitness is recognized as a clinical vital sign,[3] and as such, it functions as a predictor of risk for developing cardiovascular and metabolic diseases as well as some cancers and psychological disorders.[4–9] It is playing an increasingly important role in preoperative evaluation of patients because of its utility identifying patients at higher risk of surgical complication.[10,11] Given this context, it is imperative that cardiorespiratory fitness can be measured or estimated easily, accurately, and reliably.

Cardiorespiratory fitness can be assessed either directly or indirectly, depending on whether oxygen consumption ($\dot{V}O_2$) is measured or predicted from a surrogate such as work rate. Cardiopulmonary exercise testing (CPET), a direct measure of cardiorespiratory fitness that involves direct measurement of $\dot{V}O_2$ and usually to maximal exertion, is considered the "gold standard."[10,12] Despite its strengths, it is a very resource-intensive form of assessment, requiring specialized and expensive equipment, skilled personnel (eg, an exercise physiologist, sometimes with clinical oversight), and 30 to 60 minutes to perform the test. It is also onerous for patients. Furthermore, accurate measures are frequently not possible in patients with physical or psychological limitations that prevent a true "maximal" effort.

There are also indirect measures of cardiorespiratory fitness, such as maximal or submaximal exercise tests, (eg, exercise tolerance testing or the YMCA cycle test) in which select physiological measures are collected and used to estimate fitness. Although this

ACTRN: 12618001358235.

Dr Thomas's work is supported by Health Research Council of New Zealand (grant 18/636) and a Health Research South Start-Up Award of University of Otago.

[1]University of Otago, Dunedin, New Zealand; [2]HeartOtago, Dunedin, New Zealand; [3]Te Whatu Ora Southern, Dunedin, New Zealand.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25703).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25703.

Address correspondence via email to Brendon H. Roxburgh, PhD, at brendon.roxburgh@otago.ac.nz.

Submitted for publication July 7, 2025; accepted in revised form October 23, 2025.

SIGNIFICANCE & INNOVATIONS

- The Duke Activity Status Index (DASI) questionnaire showed excellent agreement with directly measured peak oxygen consumption ($\dot{V}O_2$), demonstrating its potential as a reliable nonexercise estimate of cardiorespiratory fitness.
- DASI, daily step count, and the timed up and go (TUG) test all had high negative predictive value, effectively identifying patients unlikely to have very low fitness (peak $\dot{V}O_2$ < 15 mL/kg/min).
- Combining estimated fitness measures (DASI, step count, or TUG) with clinical and demographic data significantly improved the prediction of peak $\dot{V}O_2$, offering a low-cost, accessible alternative to cardiopulmonary exercise testing.

approach can have a lower cost and generally does not require expensive equipment or the same level of physiologist/clinical oversight, the error associated with many cardiorespiratory fitness estimates is too large to be of practical value (≥20% difference between estimated and directly measured peak $\dot{V}O_2$).[13]

Osteoarthritis is the most common joint disease, with an estimated prevalence of 151 million worldwide, and is increasing at 2% per annum.[14,15] Patients living with lower-limb osteoarthritis on average have 30% lower cardiorespiratory fitness than age- and sex-matched healthy controls.[16] Low peak $\dot{V}O_2$ is associated with poorer functional and subjective recovery following hip or knee arthroplasty.[17] For example, a single-center observational study found that patients scheduled for hip or knee arthroplasty with a preoperative peak $\dot{V}O_2$ < 15 mL/kg/min had significantly poorer functional and subjective recovery at 6 weeks after the operation.[17] Specifically, less fit patients performed approximately 50% (n = 5) fewer sit to stand reps in a 30-second test, took approximately 60% (n = 3,500) fewer daily steps, and were approximately 2 seconds slower during the timed up and go (TUG) test at 6 weeks after the operation; they also had poorer perceived surgical recovery at 7 days and 6 weeks after the operation. Despite this prognostic significance, objectively assessing preoperative fitness in this population remains difficult as conventional exercise testing can be painful, time-consuming, or infeasible for some patients. Developing practical and accurate ways to identify patients with low cardiorespiratory fitness could enable targeted prehabilitation or optimization strategies, with the potential to improve both clinical and subjective postoperative outcomes.

Three simple alternative methods have been shown to correlate with peak $\dot{V}O_2$ and show potential to be used in routine clinical practice. The Duke Activity Status Index (DASI) is a reliable 12-question survey for estimating peak $\dot{V}O_2$, making it an inexpensive, quick, and easily administered method for estimating fitness. Previous work has shown it to correlate well with directly measured peak $\dot{V}O_2$ (ie, via CPET) in healthy adults (r = 0.80),[18] and it has strong prognostic validity in multiple cohorts.[19,20] Accelerometry (eg, daily step count) is an objective measure of physical activity that is correlated with peak $\dot{V}O_2$ and has been associated with postoperative complications[21–23] in gastrointestinal surgery patients. The TUG test is another quick and easily performed clinical test, relying on only simple equipment that all clinical spaces would have access to (chair, marker, and stopwatch).[24] Although the TUG test was originally developed to assess mobility, balance, and walking ability and to identify individuals at increased risk of falls, there is a negative correlation between TUG time and both peak $\dot{V}O_2$ and the anaerobic threshold in older adults.[25] Furthermore, performance in the TUG test is associated with postoperative complications and 1-year mortality in patients undergoing colorectal or cardiac surgery.[26]

It is unclear how well these measures correlate with directly measured cardiorespiratory fitness in patients with end-stage hip and knee osteoarthritis who experience significant exercise limitations. Therefore, the purpose of this study was to (1) determine whether estimated peak $\dot{V}O_2$ from the DASI provides a valid approximation of directly measured peak $\dot{V}O_2$ (ie, via CPET); (2) evaluate the relationship of DASI, daily step count, or TUG time with directly measured peak $\dot{V}O_2$ and anaerobic threshold; and (3) evaluate the ability of these tools to identify patients with low preoperative cardiorespiratory fitness in patients with severe hip or knee osteoarthritis.

PATIENTS AND METHODS

Study design and ethical approval

This was a secondary cross-sectional analysis of a previously published multiarm, parallel design, randomized, controlled trial.[27] The original study was a 12-week prehabilitation study comparing high-intensity interval training, hot-water immersion, or home-based exercise on preoperative fitness, health, and physical function; the data used in this secondary analysis were collected at baseline (ie, before randomization for prehabilitation). This study was registered with the Australia New Zealand Clinical Trial Registry (ACTRN12618001358235), and ethical approval was granted by the Health and Disability Ethics Committee of New Zealand (ref: 18/NTA/148). Written, informed consent was obtained for all participants, and all procedures conformed to the standards set by the Declaration of Helsinki.

Participants

Eligible patients with end-stage hip or knee osteoarthritis were identified from the arthroplasty waiting list at Dunedin Public Hospital (Dunedin, New Zealand) between September 2019 and April 2021. Participants who were scheduled to have surgery within 4 months and able to attend the study location for the

purposes of the original trial were recruited. Participants who provided informed consent were medically screened for study participation by an anesthetist or cardiologist. Participants were excluded if they met any of the following criteria: (1) a contraindication to non–physician-supervised maximal exercise testing,[28] (2) stable or unstable angina, (3) a recent myocardial infarction (ie, <3 months before), (4) an implantable cardioverter defibrillator or pacemaker, (5) revision arthroplasty, (6) staged bilateral total joint replacement, (7) pathology limiting upper-limb exercise (ie, shoulder-joint osteoarthritis), (8) living outside the study area or unable to regularly attend study sessions, and (9) any other medical condition deemed a significant risk to study participation.

Experimental design

Screened participants completed a single assessment session. Ethnicity was self-reported, and participants could select more than one; an option for "other" with free text was available. Height (stadiometer; Wedderburn WS-HRP, Auckland, New Zealand), body mass (scales; Seca, Hamburg, Germany), and resting supine blood pressure (methods described elsewhere[29]) were measured before performing a symptom-limited incremental CPET. All testing was performed on either an electromagnetically braked cross trainer or arm ergometer (dependent on participant tolerance, mobility, and joint pain). Participants completed a 3- to 5-minute warm-up before exercise intensity was increased 5 to 20 W every minute until volitional fatigue, aiming for an exercise duration of 8 to 12 minutes; tests were terminated by the supervising researcher if any termination criteria were present (eg, onset of complex arrythmia, moderate-to-severe angina, or participant desire to stop).[30] After a rest following the CPET, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was completed to characterize osteoarthritis severity.[31] Participants completed the DASI questionnaire, which was scored with the point value for all "yes" answers summed. Peak $\dot{V}O_2$ was estimated using the equation DASI score × 0.43 + 9.6.[18] Participants then performed the TUG test using a 43-cm high chair (without arm rests) and a cone placed 3 m directly in front of the chair.[24] On the command ("go"), the timer started and participants stood up and walked (without walking aids) as quickly as possible around the cone and returned to the chair; the timer was stopped when the participant was seated. Lastly, participants were provided with an accelerometer (activPAL3c; Glasgow, Scotland) that was fitted anteriorly at the mid-thigh using Hypafix tape and worn for the following 7 consecutive days.

Standardization

Testing was conducted in a climate-controlled room (mean ± SD temperature: 22 ± 0°C at 42 ± 10% relative humidity). Participants were asked to abstain from moderate- or high-intensity exercise for 24 hours before, alcohol and caffeinated beverages for 12 hours before, and cigarette smoking for 4 hours before the assessment session. Participants were reminded to take their medication as prescribed.

Data analysis

Breath-by-breath data from the CPET were exported from the software package (Quark CPET v1.6.7; COSMED) as a 20-second average to aid interpretation. All CPET analyses were performed in duplicate independently by two researchers (BHR and HAC). The maximum 20-second average value was used to determine peak $\dot{V}O_2$ for each participant. The V-slope method was used to determine anaerobic threshold,[12,32] and this was confirmed using plots of ventilatory efficiency and end-tidal carbon dioxide and oxygen as functions of $\dot{V}O_2$.[12] Accelerometry data were downloaded from the device and analyzed using manufacturer software (PALbatch v8.10; PAL Technologies, Glasgow, Scotland).

Statistical analysis

GraphPad Prism (version 10.1.1 for Mac; Boston, MA, USA) and SPSS (version 30.0.0; Chicago, IL, USA) were used for statistical analysis. This analysis was a secondary analysis of a prospective cohort, therefore no a priori sample size calculation was performed. Instead, we report effect estimates with 95% confidence intervals (CIs) and provide post hoc detectable-effect calculations to indicate the precision and power of the available sample. Descriptive data are expressed as mean ± SD or number (proportion). Normality was assessed using the Shapiro-Wilk test, and variables that violated this assumption were log-transformed before analysis. Univariate analysis of variance was used to compare continuous variables between the hip and knee arthroplasty groups and to compare estimated peak $\dot{V}O_2$ (via the DASI) and directly measured peak $\dot{V}O_2$; bias and 95% limits of agreement were also assessed using a Bland-Altman plot. Simple linear regression and Pearson correlation coefficients were used to explore associations between estimated peak $\dot{V}O_2$ (via the DASI), daily step count, or TUG time and directly measured peak $\dot{V}O_2$ and anaerobic threshold. To aid in the interpretation of the correlation coefficients, 0.9 to 1.0 was considered a very high correlation, 0.7 to 0.9 high correlation, 0.5 to 0.7 moderate correlation, 0.3 to 0.5 low correlation, and 0.0 to 0.3 negligible correlation.[33] Multiple linear regression assessed the combined predictive capacity of the DASI questionnaire, daily step count, and TUG time on peak $\dot{V}O_2$. These analyses were adjusted for age, sex, body mass index (BMI), and osteoarthritis severity (ie, WOMAC score), chosen based on their potential influence on peak $\dot{V}O_2$

while mitigating multicollinearity concerns. EasyROC[34] was used to generate area under the receiver operating characteristic curve (AUROC), which assessed the capacity of estimated peak $\dot{V}O_2$ via the DASI, daily step count, and TUG time to stratify participants into low and normal fitness groups based on previously defined thresholds in noncardiac surgery patients (ie, peak $\dot{V}O_2$: 15 mL/kg/min; anaerobic threshold: 11 mL/kg/min[11]; no previously defined thresholds available for total joint arthroplasty patients). The Youden index determined the optimal cut-off points. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated for each cut-off point.

RESULTS

Ninety-one participants (54% female) completed the assessment session and were included in this study (Figure 1; Table 1). Total hip arthroplasty participants had greater osteoarthritis impact (ie, WOMAC: +8; 95% CI 1–15) and were slower on the TUG test (+2.4 seconds; 95% CI 0.3–4.4) compared with total knee arthroplasty participants.

Directly measured and estimated peak $\dot{V}O_2$

No CPETs were stopped prematurely because of the presence of any termination criteria. Participants awaiting hip or knee arthroplasty had similar cardiorespiratory fitness, whether directly measured or estimated via the DASI ($P \geq 0.825$; Table 1). Fifteen (37%) and 13 (26%) participants awaiting hip or knee arthroplasty had peak $\dot{V}O_2 < 15$ mL/kg/min. The DASI tended to underestimate peak $\dot{V}O_2$ by a mean of 0.9 mL/kg/min (95% CI −2.1 to 0.4; $P = 0.187$) (Figure 2). This bias was similar for patients awaiting hip (−1.0 mL/kg/min; 95% CI −10.0 to 12.0) and knee (−0.8 mL/kg/min; 95% CI −12.0 to 13.1) arthroplasty.

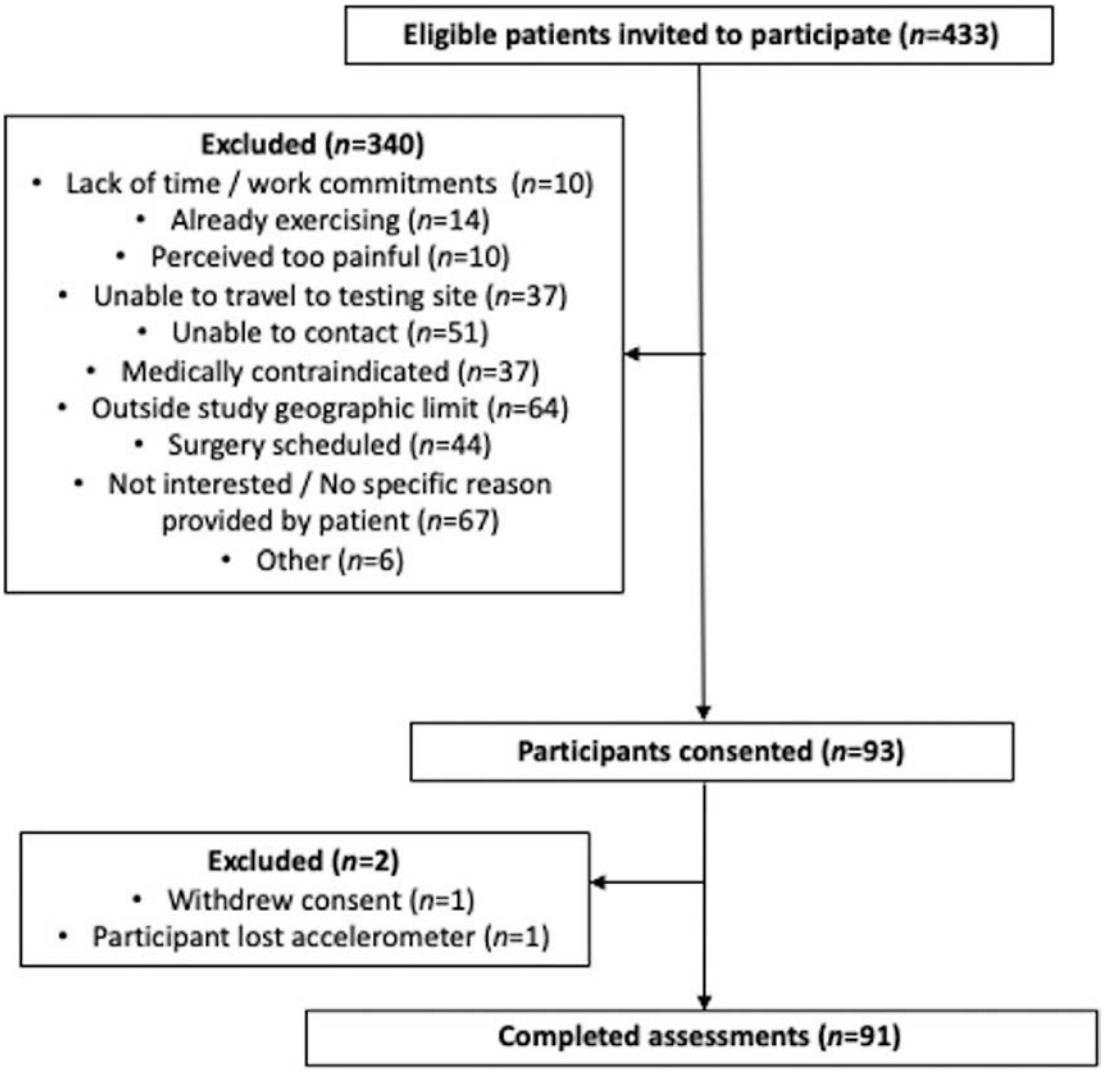

Figure 1. Study flow diagram.

Table 1. Descriptive statistics of participants*

Variable	Overall (N = 91)	THA (n = 41)	TKA (n = 50)
Age, mean (SD), y	68 (9)	69 (10)	68 (9)
Male/female sex, n (%)	41 (46)/50 (54)	19 (46)/22 (54)	22 (45)/28 (55)
BMI, mean (SD), kg/m^2	32.1 (6.8)	30.1 (5.1)	33.8 (7.6)
Ethnicity, n (%)			
NZ European/European	86 (93)	39 (95)	47 (92)
Māori	5 (5)	2 (5)	3 (6)
Cook Island Māori	1 (1)	0	1 (2)
African	1 (1)	0	1 (2)
Comorbidity, n (%)			
Asthma/COPD	18 (20)	7 (14)	11 (19)
CVD			
Previous myocardial infarct	9 (10)	4 (8)	5 (10)
Atrial arrhythmia	4 (4)	2 (4)	2 (4)
Previous stroke	5 (5)	3 (6)	2 (4)
Dyslipidemia	38 (41)	15 (29)	23 (45)
Hypertension	60 (65)	25 (49)	35 (69)
Obesity	50 (54)	18 (44)	32 (63)
Diabetes mellitus/prediabetes	17 (18)	8 (16)	9 (18)
Physiologic variables, mean (SD)			
Relative peak $\dot{V}O_2$, mL/kg/min	18.7 (6.9)	18.5 (6.3)	18.9 (7.3)
Absolute peak $\dot{V}O_2$, L/min	1,656 (645)	1,572 (585)	1,724 (688)
DASI-estimated peak $\dot{V}O_2$, mL/kg/min	17.8 (4.5)	17.6 (4.7)	18.0 (4.4)
Anaerobic threshold, mL/kg/min	12.3 (4.5)	12.1 (3.7)	12.5 (5.0)
SBP_{rest}, mm Hg	129 (13)	130 (14)	128 (13)
DBP_{rest}, mm Hg	77 (7)	76 (7)	78 (7)
Daily steps	6,066 (3,218)	5,920 (3,351)	6,183 (3,136)
TUG(s)	10.6 (4.5)	11.9 (4.9)	9.5 (3.9)
Questionnaires, mean (SD)			
DASI-estimated peak $\dot{V}O_2$, mL/kg/min	17.8 (4.5)	17.6 (4.7)	18.0 (4.4)
DASI score	19.4 (10.3)	19.2 (10.7)	19.6 (10.0)
WOMAC	58 (17)	62 (16)	54 (16)

* Continuous variables were compared between THA and TKA participants using univariate analysis of variance. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DASI, Duke Activity Status Index; DBP_{rest}, resting diastolic blood pressure; NZ, New Zealand; peak $\dot{V}O_2$, peak oxygen consumption; SBP_{rest}, resting systolic blood pressure; THA, total hip arthroplasty; TKA, total knee arthroplasty; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Correlation and regression analysis: preoperative peak $\dot{V}O_2$ and the anaerobic threshold with DASI, daily step count, and TUG test

Both criterion measures of fitness (ie, peak $\dot{V}O_2$ and the anaerobic threshold) showed similar correlations for all three surrogate measures (Table 2; Supplementary Figures S1 and S2; Supplementary Table S1). The highest correlation (r = 0.56; 95% CI 0.39–0.69) was observed between preoperative peak $\dot{V}O_2$ and preoperative daily step count. In regression analysis, every additional 1,000 steps/day was associated with approximately a 1 mL/kg/min higher peak $\dot{V}O_2$ (r^2 = 0.32). The predictive ability of daily step count was approximately doubled (r^2 = 0.62) (Supplementary Table S2) with the inclusion of age, sex, BMI, and osteoarthritis severity (ie, WOMAC score) in the model (Figure 3).

Peak $\dot{V}O_2$ was moderately correlated with the predicted value from DASI (r = 0.50; 95% CI 0.33–0.64). Correlations were similar between hip and knee arthroplasty participants for estimated peak $\dot{V}O_2$ (r = 0.49 and 0.52, respectively) (Supplementary Table S1) and total step count (r = 0.51 and 0.59, respectively) with directly measured peak $\dot{V}O_2$. Almost two-thirds of the variability in peak $\dot{V}O_2$ was accounted for within a multiple regression incorporating estimated peak $\dot{V}O_2$ from the DASI, age, sex, BMI, and WOMAC score (r^2 = 0.63).

ROC curve

Diagnostic performance of the DASI questionnaire, daily step count, and TUG test for predicting a peak $\dot{V}O_2$ < 15 mL/kg/min or anaerobic threshold < 11 mL/kg/min are outlined in Table 3.

DASI. AUROC for estimated peak $\dot{V}O_2$ from the DASI questionnaire to predict a directly measured peak $\dot{V}O_2$ < 15 mL/kg/min and anaerobic threshold < 11 mL/kg/min was 0.74 for both.

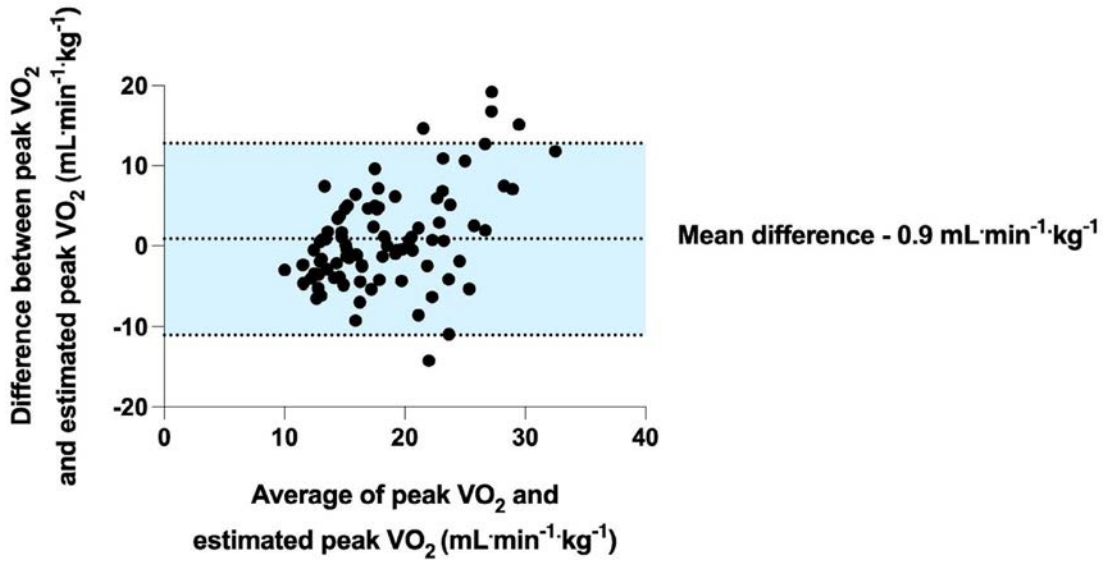

Figure 2. Bland-Altman analysis (mean difference and 95% limits of agreement [blue shaded area]) between directly measured and estimated peak $\dot{V}O_2$ from the Duke Activity Status Index questionnaire (mL/kg/min). The solid line represents the mean bias (–0.9 mL/kg/min), and the shaded area shows the 95% limits of agreement, illustrating that the Duke Activity Status Index slightly underestimates peak $\dot{V}O_2$ with acceptable individual variability. Peak $\dot{V}O_2$, peak oxygen consumption.

Table 2. Pearson correlation coefficient and simple linear regression analysis of preoperative peak $\dot{V}O_2$ and anaerobic threshold with other preoperative assessments*

Predictors	Correlation coefficient, *r* (95% CI)	Slope	Standardized coefficient	y-intercept	r^2	*P* value
Peak $\dot{V}O_2$						
Daily step count	0.56 (0.39 to 0.69)	0.001	0.572	11.41	0.32	<0.001
TUG test	−0.55 (−0.69 to −0.37)	−0.83	−0.573	27.00	0.30	<0.001
DASI-estimated peak $\dot{V}O_2$, mL/kg/min	0.50 (0.33 to 0.64)	0.77	0.508	4.90	0.25	<0.001
Anaerobic threshold						
Daily step count	0.45 (0.27 to 0.60)	324	0.449	2,085	0.20	<0.001
TUG test	−0.46 (−0.62 to −0.26)	−0.45	−0.506	16.59	0.21	<0.001
DASI-estimated peak $\dot{V}O_2$, mL/kg/min	0.48 (0.30 to 0.63)	0.001	0.480	8.50	0.23	<0.001

* Preoperative peak $\dot{V}O_2$ or anaerobic threshold were used as the predictor. CI, confidence interval; DASI, Duke Activity Score Index; peak $\dot{V}O_2$, peak oxygen consumption; TUG, timed up and go.

Peak $\dot{V}O_2$ = 51.28 + 0.283 × (estimated peak $\dot{V}O_2$ via DASI) + 5.177 × (1 if male; 0 if female) −0.334 × (Age) −0.412 × (BMI) -0.066 × (WOMAC score)

Peak $\dot{V}O_2$ = 51.33 + 0.0004 × (daily step count) + 5.165 × (1 if male; 0 if female) −0.298 × (Age) −0.356 × (BMI) −0.085 × (WOMAC score)

Peak $\dot{V}O_2$ = 56.91 + 5.116 × (1 if male; 0 if female) −0.301 × (Age) −0.404 × (BMI) −0.067 × (WOMAC score) −0.304 × (TUAG time)

Figure 3. Multiple regression equations to predict peak $\dot{V}O_2$ using estimated peak $\dot{V}O_2$ (via DASI) or daily step count or TUAG time, with sex, age, BMI, and WOMAC score. BMI, body mass index; DASI, Duke Activity Status Index; peak $\dot{V}O_2$, peak oxygen consumption; TUAG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3. Diagnostic performance of the DASI, daily step count, and TUG test time for predicting peak $\dot{V}O_2$ < 15 mL/kg/min and anaerobic threshold < 11 mL/kg/min*

	Peak $\dot{V}O_2$ < 15 mL/kg/min			Anaerobic threshold < 11 mL/kg/min		
Variable	DASI	Daily step count	TUG	DASI	Daily step count	TUG
AUROC	0.74 (0.74–0.85)	0.84 (0.76–0.92)	0.84 (0.76–0.92)	0.74 (0.64–0.84)	0.76 (0.66–0.86)	0.79 (0.69–0.88)
Threshold	17.3	5,181	9.7	18.5	5,009	8.6
Sensitivity	0.84 (0.66–0.95)	0.87 (0.63–0.84)	0.77 (0.69–0.96)	0.85 (0.70–0.94)	0.70 (0.54–0.83)	0.75 (0.59–0.87)
Specificity	0.66 (0.53–0.78)	0.71 (0.59–0.82)	0.79 (0.67–0.88)	0.60 (0.46–0.74)	0.76 (0.62–0.86)	0.70 (0.56–0.82)
PPV	0.55 (0.42–0.81)	0.59 (0.45–0.85)	0.65 (0.50–0.84)	0.62 (0.48–0.83)	0.68 (0.53–0.82)	0.65 (0.50–0.81)
NPV	0.89 (0.76–0.94)	0.92 (0.80–0.95)	0.88 (0.75–0.93)	0.84 (0.69–0.91)	0.77 (0.62–0.87)	0.79 (0.64–0.88)
PLR	2.5 (1.7–3.6)	3.0 (2.0–4.6)	3.7 (2.2–6.2)	2.1 (1.5–3.1)	2.85 (1.71–4.77)	2.5 (1.6–3.9)
NLR	0.24 (0.11–0.56)	0.2 (0.1–0.5)	0.29 (0.15–0.56)	0.25 (0.12–0.54)	0.40 (0.24–0.65)	0.4 (0.2–0.6)

* DASI, Duke Activity Score Index; NLR, negative likelihood ratio; NPV, negative predictive value; peak $\dot{V}O_2$, peak oxygen consumption; PLR, positive likelihood ratio; PPV, positive predictive value; AUROC, area under the receiver operating characteristic curve; TUG, timed up and go. Data are absolute value or value (95% CI).

The DASI questionnaire had optimal cut-off points of 17.3 mL/kg/min and 18.5 mL/kg/min. Both cut-offs had good negative predictive values (0.84 and 0.89), however, positive predictive values were low (0.55 and 0.62).

Daily step count. AUROC for daily step count to predict peak $\dot{V}O_2$ < 15 mL/kg/min was 0.84 (95% CI 0.76–0.92) and to predict anaerobic threshold < 11 mL/kg/min was 0.76 (95% CI 0.66–0.86). A daily step count of 5,181 steps/day was the optimal cut-off point for predicting directly measured peak $\dot{V}O_2$ < 15 mL/kg/min and 5,009 steps/day for anaerobic threshold < 11 mL/kg/min. At these thresholds, daily step count demonstrated a high negative predictive value (0.92 for peak $\dot{V}O_2$ and 0.77 for anaerobic threshold) but only modest positive predictive values (0.59 and 0.68, respectively).

TUG test. AUROC for the TUG test to predict peak $\dot{V}O_2$ < 15 mL/kg/min was 0.84 and 0.79 for anaerobic threshold < 11 mL/kg/min. A TUG test time slower than 9.7 seconds was the optimal cut-off point for peak $\dot{V}O_2$ and 8.6 seconds for anaerobic threshold. The peak $\dot{V}O_2$ cut-off had a high negative predictive value (0.88), however, positive predictive values were low for both (0.65).

DISCUSSION

The DASI questionnaire provided an excellent estimate of directly measured peak $\dot{V}O_2$. The DASI, daily step count, and TUG test all performed strongly in their ability to accurately identify patients who did not have a peak $\dot{V}O_2$ < 15 mL/kg/min (ie, high negative predictive value); however, their accuracy to positively predict peak $\dot{V}O_2$ < 15 mL/kg/min was only fair. Estimated fitness (via DASI or daily step count) or TUG time when combined with demographic and clinical variables provided strong estimates of peak $\dot{V}O_2$. These low-cost, easily implemented tools provide an appropriate way to predict patient peak $\dot{V}O_2$ when CPET is not available.

To our knowledge, this is the first study to investigate the utility of the DASI questionnaire in patients scheduled for total hip or knee arthroplasty. The DASI questionnaire slightly underestimated peak $\dot{V}O_2$ by 0.9 mL/kg/min for patients with severe hip or knee osteoarthritis. This estimate of bias is considerably lower than the commonly reported measurement error associated with direct measurement of peak $\dot{V}O_2$ (1.0–2.0 mL/kg/min)[35] and the bias reported by Li et al[36] for DASI-estimated peak $\dot{V}O_2$ (8 mL/kg/min) in a smaller cohort (n = 45) of patients scheduled for major cancer surgery. Chemotherapy is known to reduce peak $\dot{V}O_2$, and it is possible that this, as well as the underlying pathology of cancer, contributed to these larger discrepancies.

A moderate correlation was observed between objectively measured preoperative peak $\dot{V}O_2$ via CPET and estimated peak $\dot{V}O_2$ via the DASI (r = 0.50). The largest multicenter trial investigating preoperative CPET reported a lower correlation with DASI scores (r = 0.41).[37] A subanalysis of that multicenter trial showed that in the preoperative setting the DASI had utility to detect a peak $\dot{V}O_2$ > 16 mL/kg/min (AUROC = 0.71) and the anaerobic threshold > 11 mL/kg/min (AUROC = 0.66)[38] as compared with 0.74 in the present study. The DASI showed utility for accurately identifying patients who did not have a low peak $\dot{V}O_2$, with a negative predictive value of 0.89; that is, only 11% patients who have a peak $\dot{V}O_2$ < 15 mL/kg/min would be missed with the DASI. This highlights the DASI as an extremely valuable tool for screening patients who do not require further preoperative assessment, thereby saving resources for those who may benefit the most from a preoperative CPET.

The time taken to complete and score the questionnaire is quick (<1 minute), and an even shorter five-question version of the DASI questionnaire has recently been validated.[38] The DASI is also more discriminate at risk-stratifying patients than relying

on clinician assessment alone.[37] Therefore, the data from the present study further support the routine use of the DASI in the preoperative assessment of functional capacity, particularly when CPET is not available or feasible. It may play a role as a resource-saving tool, allowing clinicians to triage who would most benefit from a further assessment like CPET.

A daily step count of at least 5,000 steps per day had an excellent discriminatory ability to rule out a low peak $\dot{V}O_2$ or low anaerobic threshold; specifically, only 8% of patients with a daily step count >5,000 steps per day would be incorrectly classified as having low fitness. Preoperative daily step count had the highest correlation with preoperative peak $\dot{V}O_2$ of the three tools (r = 0.56). Jones et al[39] similarly showed in patients scheduled for major elective intra-abdominal surgery that daily step count had a moderate association with preoperative peak $\dot{V}O_2$ (r = 0.59) but not the anaerobic threshold (r = 0.39). Preoperative physical activity tracking is an attractive alternative to CPET because of the relatively lower cost and ease of administering; not least, a large proportion of the population already own these trackers and their popularity is increasing with the technology now being incorporated in mobile phones. One potential concern is the number of days required to obtain a valid measure. Although 7-day monitoring was used in the present study, others have reported reliable measurements from 3-day measurements in patients scheduled for major abdominal surgery.[40] Future work should explore if shorter monitoring periods (ie, <7 days) can provide as accurate estimates.

The TUG test demonstrated similarly strong positive and negative predictive abilities for peak $\dot{V}O_2$ above or below 15 mL/kg/min. A TUG time of <9.7 seconds accurately predicted 88% of the time that an individual did not have a low peak $\dot{V}O_2$. Furthermore, peak $\dot{V}O_2$ could be estimated by combining the TUG test result with demographic (ie, age and sex) and clinical variables (BMI and osteoarthritis severity). However, despite having the highest positive predictive value (0.65), the test still had a false positive rate of 35% (ie, 35% of individuals who have a TUG time >9.7 seconds do not actually have a low peak $\dot{V}O_2$). An advantage of the TUG test is that it can be quickly administered by any health care professional and requires minimal equipment. Although the TUG test would not replace most of the functions of CPET, based on the results of this study it could be used to estimate peak $\dot{V}O_2$ and may help triage preoperative CPET.

Preoperative fitness is a predictor of postoperative functional and subjective recovery following hip or knee arthroplasty.[17] However, formal CPET is often impractical for widespread preoperative screening because of cost, time, and accessibility constraints. This study demonstrates that simple low-burden tools, such as the DASI, daily step count, or TUG time can provide strong estimates of directly measured peak $\dot{V}O_2$. Incorporating these tools into preoperative pathways could enable clinicians to efficiently screen for low fitness, identifying patients who may benefit most from targeted prehabilitation, enhanced perioperative monitoring, or tailored postoperative rehabilitation. Importantly, these assessments are not intended as exclusion criteria for surgery but rather as a practical means to optimize perioperative care and recovery. Future research should evaluate whether improving preoperative fitness in patients with low fitness leads to better postoperative outcomes and whether integration of such screening tools improves clinical decision-making and resource allocation.

The findings of this study should be considered in light of several limitations. A potential limitation of this study is that it is a secondary analysis of a previously conducted trial. As such, the trial was not originally designed to test the specific hypotheses addressed here. Additionally, the original trial inclusion/exclusion criteria may restrict the applicability of the results to broader populations. Exercise testing was performed on either an arm ergometer or an elliptical cross trainer, and based on previous work this will have influenced directly measured peak $\dot{V}O_2$.[41] However, given the similarities between directly measured and estimated peak $\dot{V}O_2$ via the DASI, this does not appear to have had a large influence on the comparisons in this study. Although these preoperative assessment tools have shown an association with preoperative peak $\dot{V}O_2$, they may not be suitable for detecting *changes* in preoperative peak $\dot{V}O_2$. For example, Roxburgh et al[27] reported large improvements in cardiorespiratory fitness; however, this did not translate to improvement in TUG time or estimated peak $\dot{V}O_2$ via the DASI. Therefore, these preoperative assessment tools may be used to estimate peak $\dot{V}O_2$ or as a risk-stratification tool but not necessarily for detecting changes in peak $\dot{V}O_2$ over time. Lastly, the participants in this study had severe hip or knee osteoarthritis, potentially limiting the generalizability of the determined cut-off points. However, given that exercise testing can be challenging to perform in patients with lower-limb conditions (eg, osteoarthritis, peripheral arterial disease, or amputation), these findings may have utility for estimating fitness with a broad range of physical disabilities or limitations.

Clinicians can be confident that the DASI, daily step count, or the TUG test combined with easily captured demographic and clinical data are effective for predicting peak $\dot{V}O_2$. Although all tools had good negative predictive value, indicating their efficacy at identifying patients unlikely to have low peak $\dot{V}O_2$, their positive predictive value was low, indicating limitations identifying patients who have low peak $\dot{V}O_2$. This suggests they might be better as screening tools to rule out low fitness, aiding perioperative clinicians in identifying patients who may or may not require preoperative CPET, thereby optimizing resource allocation.

ACKNOWLEDGMENTS

The authors would like to thank all participants for the time and effort associated with study participation. Additionally, the authors would

like to thank Professor Andre van Rij for his expertise and advice related to this study and Ruth Ford for her assistance with participant recruitment.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Roxburgh confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Saltin B, Strange S. Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. Med Sci Sports Exerc 1992; 24(1):30–37.
2. Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc 2000;32(1):70–84.
3. Ross R, Blair SN, Arena R, et al; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation 2016;134(24):e653–e699.
4. Taylor AH, Cable NT, Faulkner G, et al. Physical activity and older adults: a review of health benefits and the effectiveness of interventions. J Sports Sci 2004;22(8):703–725.
5. Lee DC, Artero EG, Sui X, et al. Mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol 2010;24(4)(suppl):27–35.
6. Myers J, McAuley P, Lavie CJ, et al. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. Prog Cardiovasc Dis 2015;57(4):306–314.
7. Sawada SS, Lee IM, Naito H, et al. Cardiorespiratory fitness, body mass index, and cancer mortality: a cohort study of Japanese men. BMC Public Health 2014;14(1):1012.
8. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009;301(19): 2024–2035.
9. Williams SE, Carroll D, Veldhuijzen van Zanten JJ, et al. Anxiety symptom interpretation: A potential mechanism explaining the cardiorespiratory fitness-anxiety relationship. J Affect Disord 2016;193:151–156.
10. Roxburgh BH, Cotter JD, Campbell HA, et al. Physiological relationship between cardiorespiratory fitness and fitness for surgery: a narrative review. Br J Anaesth 2023;130(2):122–132.
11. Moran J, Wilson F, Guinan E, et al. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth 2016;116(2): 177–191.
12. Levett DZH, Jack S, Swart M, et al; Perioperative Exercise Testing and Training Society (POETTS). Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth 2018; 120(3):484–500.
13. Malek MH, Berger DE, Housh TJ, et al. Validity of VO_2max equations for aerobically trained males and females. Med Sci Sports Exerc 2004;36(8):1427–1432.
14. World Health Organization. The Global Burden of Disease: 2004 Update. World Health Organization; 2008.
15. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38(10):1500–1505.
16. Philbin EF, Groff GD, Ries MD, et al. Cardiovascular fitness and health in patients with end-stage osteoarthritis. Arthritis Rheum 1995;38(6): 799–805.
17. Roxburgh BH, Campbell HA, Cotter JD, et al. The effect of preoperative cardiorespiratory fitness on functional and subjective outcomes following total hip and knee arthroplasty: a single centre, observational study. N Z Med J 2025;138(1614):19–41.
18. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64(10):651–654.
19. Wijeysundera DN, Beattie WS, Hillis GS, et al; Measurement of Exercise Tolerance before Surgery Study Investigators; International and National Coordinators; Central Project Office Operations Committee; CPET Methods Committee; Outcome Adjudication Committee; International Steering Committee. Integration of the Duke Activity Status Index into preoperative risk evaluation: a multicentre prospective cohort study. Br J Anaesth 2020;124(3):261–270.
20. Silvapulle E, Darvall J, De Silva A. Association between the Duke Activity Status Index and complications after noncardiac surgery: a systematic review. J Clin Anesth 2025;103:111808.
21. Richards SJG, Jerram PM, Brett C, et al. The association between low pre-operative step count and adverse post-operative outcomes in older patients undergoing colorectal cancer surgery. Perioper Med (Lond) 2020;9(1):20.
22. Nakajima H, Yokoyama Y, Inoue T, et al. How many steps per day are necessary to prevent postoperative complications following hepatopancreato-biliary surgeries for malignancy? Ann Surg Oncol 2020; 27(5):1387–1397.
23. Sobejana M, van den Hoek J, Metsios GS, et al. Cardiorespiratory fitness and physical activity in people who have rheumatoid arthritis at an increased risk of cardiovascular disease: a cross-sectional study. Rheumatol Int 2021;41(12):2177–2183.
24. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil 1986;67(6):387–389.
25. Boereboom CL, McGuinness RB, Herrod PJ, et al. Using a quick timed-up-and-go test to predict surgical risk. JCSM Rapid Commun 2021;4(2):159–165.
26. Robinson TN, Wu DS, Sauaia A, et al. Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. Ann Surg 2013;258(4):582–588.
27. Roxburgh BH, Campbell HA, Cotter JD, et al. Upper-limb high-intensity interval training or passive heat therapy to optimize cardiorespiratory fitness prior to total hip or knee arthroplasty: a randomized controlled trial. Arthritis Care Res (Hoboken) 2024;76(3):393–402.
28. Fletcher GF, Ades PA, Kligfield P, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128(8):873–934.

29. Roxburgh BH, Campbell HA, Cotter JD, et al. Acute and adaptive cardiovascular and metabolic effects of passive heat therapy or high-intensity interval training in patients with severe lower-limb osteoarthritis. Physiol Rep 2023;11(11):e15699.
30. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on exercise testing). J Am Coll Cardiol 1997;30(1): 260–311.
31. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12): 1833–1840.
32. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60(6): 2020–2027.
33. Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. Malawi Med J 2012;24(3):69–71.
34. Goksuluk D, Korkmaz S, Zararsiz G, et al. easyROC: an interactive web-tool for ROC curve analysis using R language environment. R J 2016;8(2):213–230.
35. Beltz NM, Gibson AL, Janot JM, et al. Graded exercise testing protocols for the determination of VO_2max: historical perspectives, progress, and future considerations. J Sports Med (Hindawi Publ Corp) 2016;2016:3968393.
36. Li MH, Bolshinsky V, Ismail H, et al. Comparison of Duke Activity Status Index with cardiopulmonary exercise testing in cancer patients. J Anesth 2018;32(4):576–584.
37. Wijeysundera DN, Pearse RM, Shulman MA, et al; METS study investigators. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet 2018; 391(10140):2631–2640.
38. Riedel B, Li MHG, Lee CHA, et al; METS Study Investigators. A simplified (modified) Duke Activity Status Index (M-DASI) to characterise functional capacity: a secondary analysis of the Measurement of Exercise Tolerance before Surgery (METS) study. Br J Anaesth 2021; 126(1):181–190.
39. Jones L, Tan L, Carey-Jones S, et al. Can wearable technology be used to approximate cardiopulmonary exercise testing metrics? Perioper Med (Lond) 2021;10(1):9.
40. Haveman ME, van Melzen R, El Moumni M, et al. Determining the reliable measurement period for preoperative baseline values with telemonitoring before major abdominal surgery: pilot cohort study. JMIR Perioper Med 2022;5(1):e40815.
41. Roxburgh BH, Campbell HA, Cotter JD, et al. Cardiopulmonary exercise testing in severe osteoarthritis: a crossover comparison of four exercise modalities. Anaesthesia 2021;76(1):72–81.

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 946–955
DOI 10.1002/acr.70007

Characterizing Metabolic Signatures of Air Pollution and Their Association With the Risk of Gout: A Population-Based Cohort Study

Peng Hu, PhD,[1] Shengtao Wei, PhD,[1] Shanshan Ran, PhD,[1] Dashan Zheng, PhD,[1] Fei Tian, PhD,[1] Lan Chen, PhD,[1] Manting Rao, MD,[1] Zhonghua Ai, PhD,[1] Zhenhe Huang, MD,[2] and Hualiang Lin, PhD[1]

Objective. This study aimed to identify metabolic signatures reflecting air pollution and further explore their associations with gout risk.

Methods. We retrieved 207,908 gout-free participants from a large cohort study. Annual average concentrations of fine particulate matter ($PM_{2.5}$), inhalable particulate matter (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) were estimated using bilinear interpolation based on the residential address. Elastic net regression was used to identify air pollutant–related metabolites and construct metabolic signatures. Cox regression models were performed to evaluate the association between air pollutants, related metabolic signatures, and the risk of gout. Mediation analyses were performed to explore how metabolites mediate the relationships linking air pollutants to gout.

Results. During a median follow-up of 12.56 years, 2,474 incident gout cases were identified. We identified metabolite biomarkers reflecting air pollutants, including 87 metabolites for $PM_{2.5}$, 76 for PM_{10}, 68 for NO_2, and 71 for NO_x. Air pollution–related metabolic signatures were associated with elevated gout risk, with hazard ratios of 1.10 (95% confidence interval [CI] 1.05–1.14) for $PM_{2.5}$, 1.12 (95% CI 1.08–1.17) for PM_{10}, 1.09 (95% CI 1.04–1.13) for NO_2, and 1.11 (95% CI 1.06–1.15) for NO_x. Consistently, per-interquartile range increase in $PM_{2.5}$, PM_{10}, NO_2, and NO_x was associated with 17%, 15%, 6%, and 6% increased gout risk, respectively. Additionally, metabolic signatures mediated the air pollutants–gout associations, with the mediation proportions varying from 2.36% for $PM_{2.5}$ to 4.30% for NO_x.

Conclusion. Our study indicated that air pollutants and metabolic signatures were associated with elevated gout risk, with metabolomic signatures playing a mediating role in the air pollutants–gout relationship.

INTRODUCTION

Gout is a rheumatic immune disease characterized by the accumulation of monosodium urate crystals in joints and surrounding tissues,[1,2] with the age-standardized incidence rate of gout increasing by 41% over the past three decades.[3] Gout flares, marked by debilitating joint pain, not only impact quality of life but also heighten susceptibility to metabolic comorbidities and death.[4–7] Apart from some well-known modifiable lifestyle behaviors, such as purine-rich food intake,[8] alcohol drinking,[9] and obesity,[10] air pollution has also been regarded as a vital risk factor in gout development.[11] Recently, the links between air pollution and a higher gout risk have been reported.[12–15] Nevertheless, the mechanisms linking air pollutants to gout have not yet been thoroughly elucidated.

Metabolomic profiling has shown great potential in providing objective metrics for evaluating one's metabolism responses to genetic and environmental factors. Blood-based metabolites could serve as objective downstream biomarkers in the gene transcription and translation processes, which could provide insightful information by revealing the interaction between environmental and genetic exposures.[16,17] Prior research has explored the associations between metabolites and gout risk.[18] One study identified metabolites to discriminate hyperuricemia from gout, revealing distinct metabolic signatures for gout and hyperuricemia.[19] Another study identified distinct metabolites and pathways in individuals with frequent gout flares compared

Supported by the National Natural Science Foundation of China (grant 82373534).

[1]School of Public Health, Sun Yat-sen University, Guangzhou, China; [2]Affiliated Nanshan Hospital of Shenzhen University, Shenzhen, China.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.70007).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70007.

Address correspondence via email to Zhenhe Huang, MD, at hzh932@126.com; or to Hualiang Lin, PhD, at linhualiang@mail.sysu.edu.cn.

Submitted for publication July 24, 2025; accepted in revised form November 12, 2025.

SIGNIFICANCE & INNOVATIONS

- Air pollution (fine particulate matter, inhalable particulate matter, nitrogen dioxide, and nitrogen oxides) and related metabolic signatures were associated with increased risk of gout.
- Metabolic signatures partially mediated the air pollutants–gout associations.
- This study established a potential air pollution–metabolism–gout association, offering new insights for gout prevention.

to those with infrequent gout flares, including 439 differential metabolites with the pathways of amino acids, nucleotide metabolism, carbohydrates, and bile acids.[20] Furthermore, it is reported that exposure to air pollution may cause metabolome fluctuation and lead to an imbalance in the expression process of metabolites.[21,22] Thus, it is reasonable to hypothesize that metabolomic changes might mediate the air pollutants–gout associations.

To verify the hypothesis, we identified the metabolic signatures most closely related to air pollutants and investigated their prospective association with gout risk. We further investigated whether these metabolic signatures of air pollutants might mediate their association with gout. Our research integrates metabolomics with air pollution studies, offering new insights for gout prevention.

METHODS

Study populations. The UK Biobank (UKB) is a longitudinal study that enrolled over 500,000 participants ranging in age from 37 to 73 years during 2006 to 2010. More details of UKB have been described in prior publications.[23] At baseline, all participants provided individual-level information through verbal interviews and touchscreen questionnaires and provided biologic and physical measurements. The study was approved by the North West Multicenter Research Ethics Committee (no. 21/NW/0157). The data sets generated and analyzed during the current study are available upon reasonable request to the Access Management System through the UKB website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

At baseline, 502,411 participants were recruited. Of them, 7,387 participants with prevalent gout were excluded. The participants without available data on metabolic biomarkers or air pollution were further excluded from the analysis (n = 287,116). Finally, 207,908 participants were included in the study (Fig S1).

Metabolomics profiling. Detailed procedures of metabolomics profiling have been described previously.[24] Briefly, Plasma samples from around 280,000 participants at baseline (2006–2010) and 16,000 participants during follow-up (2012–2013) were analyzed using high-throughput nuclear magnetic resonance spectroscopy via Nightingale Health's metabolic biomarker platform (Nightingale Health Ltd). In total, 251 metabolites were assessed, comprising 81 composite ratio indexes and 170 metabolites detected using absolute levels. The metabolic measures span a wide range of pathways, encompassing fatty acids, fatty acid compositions, and lipoprotein lipids with 14 subclasses, etc (Table S1).

Air pollution exposure assessment. The UK Department for Environment, Food and Rural Affairs supplied longitudinal data on atmospheric pollutants, including annual average concentrations of fine particulate matter ($PM_{2.5}$), inhalable particulate matter (PM_{10}), nitrogen oxides (NO_x), and nitrogen dioxide (NO_2). These geospatial records feature exceptional granularity through 1 × 1 km grid mapping, systematically documenting ground-level pollution patterns across in United Kingdom spanning the period from 2002 to 2022.

Each participant's residential address history, including the particular dates they lived in each location, was recorded to determine the individual-level exposure to air pollutants. The air pollutant data from the four closest grids at the exposure sites were interpolated using a bilinear method to calculate the weighted averages.[25] The annual average air pollution levels for individuals were determined based on their geocoded address and the associated grid cells. If individuals had changed their residential address, we calculated a time-weighted average exposure to air pollutants, with the duration spent at each address used as the weights.[26] In the current study, we evaluated average exposure levels from the four years before enrollment.

Ascertainment of incident gout. Incident gout was identified through the inpatient admission records sourced from Hospital Episode Statistics, Scottish Morbidity Record Data, and the Patient Episode Database, and the records with the *International Classification of Diseases, Tenth Revision* (ICD-10) codes M10.0, M10.2, M10.3, M10.4, and M10.9 were determined as gout cases.[12,13] Participants were observed from enrollment until the date of incident gout, loss to follow-up, death, or the latest date of available data (February 28, 2018, in Wales; July 31, 2021, in Scotland; and September 30, 2021, in England), whichever occurred earlier.

Assessment of covariates. We included some important factors as covariates according to prior knowledge and literature. Potential covariates included age, sex, ethnicity, body mass index (BMI), education level, household income, smoking status, alcohol consumption, healthy diet score, and physical activity. Ethnicity was grouped into the categories non-White (Asian, Black, Mixed, and Other) and White. Education level was grouped into the categories college degree or higher, vocational qualifications and other, and any school degree. Household income was classified into five levels (>£100,000, £52,000–£100,000, £31,000–£51,999, £18,000–£30,999, and <£18,000). BMI was computed by dividing

weight in kg by height in m^2 and further grouped into the categories obese (>29.9 kg/m^2), overweight (25–29.9 kg/m^2), underweight (<18.5 kg/m^2), and normal weight (18.5–24.9 kg/m^2). There were three categories for smoking status (never smoking, former smoking, and current smoking) and four groups for alcohol consumption (never, occasional, moderate, and heavy) based on the daily quantity and frequency of alcohol intake. Increased intake of vegetables, fruits, and fish, as well as reduced intake of red meats and processed meats, was used to compute the combined diet score, which varied from 0 to 5, with 1 point given for each beneficial diet element.[27] Physical activity was classified as low (<600 metabolic equivalents [MET] min/week), moderate (600–3,000 MET min/-week), and high (≥3,000 MET min/week) based on the total volume of physical activity.[28,29]

Statistical analysis. *Characterization of air pollution–related metabolite signatures.* All 251 metabolites were log-transformed and standardized before analysis. An elastic net regression model was used to determine the related metabolites and metabolic signatures reflecting air pollutants through the "glmnet" package. The elastic net regression model leverages both the characteristics of lasso and ridge penalties, offering a regularized approach method to address multicollinearity and prevent model overfitting.[30] The best lambda value was then derived using 10-fold cross-validation. The selected lambda value was the largest one yielding a mean squared error within 1 SD of the minimum. Metabolic signatures were generated by applying regression-derived weights to a sum of metabolites with nonzero coefficients. The total metabolic signatures reflected the synthetic impacts of the weighted sum of the chosen metabolic indicators.

Associations of air pollutants and metabolic signatures with gout risk. A linear regression model was used to evaluate the relationships of chosen individual metabolites with air pollution. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained by evaluating the relationships between air pollutants and associated metabolic signatures and gout risk using Cox proportional hazard models. Model 1 and model 2 were adjusted for sociodemographic and behavioral factors. In model 3, air pollution and metabolic signatures were mutually adjusted for at the same time to explore their independent associations. To assess the potential nonlinear relationships, a three-knotted (at the 10th, 50th, and 90th percentiles) restricted cubic spline model was applied. Additionally, we assessed the joint impacts of air pollutants and metabolic signature mixtures using quantile-based g-computation.

Mediation analysis and pathway analysis. We further performed a mediation analysis using the "mediation" package to explore the proportional contribution of individual metabolites and overall metabolic signatures to the air pollutants–gout associations. A quasi-Bayesian approach was used to assess variance in the mediation analysis (100 simulations), and the mediation effects were limited to 0 to 1. Taking into account the entire exposure–outcome relationship, the analysis could evaluate the proportionate direct effects and indirect effects within the air pollution–gout relationship through mediators. The same covariates were adjusted in the incident gout outcome models and the mediator models. Furthermore, pathway analyses were conducted on statistically significant metabolites of the air pollution–gout association through MetaboAnalyst 6.0, which used the KEGG database to investigate possible biologic pathways involved.

Stratified analysis and sensitivity analysis. Stratified analyses were conducted according to age (<60 years, ≥60 years) and sex (male, female). To determine whether the results of the subgroups were statistically different, likelihood ratio tests were computed for the interaction terms.

To further assess the robustness of our findings, we conducted several sensitivity analyses. First, to prevent potential reverse causality, we eliminated individuals who experienced incident gout during the first two years of follow-up. Second, repeated analyses were conducted by eliminating participants without complete information on covariates. Third, we further varied the exposure window to one-, two-, and three-year durations. Fourth, a time-varying Cox proportional hazard model, with the annual average levels of air pollution at a one-year scale, was employed to assess the air pollutants–gout association. Finally, we included hypertension and diabetes as covariates to verify the stability of the results.

All analyses were conducted using R (version 4.2.2). A two-sided *P* value below 0.05 was regarded as statistically significant. Bonferroni corrections were used in the analysis to address possible errors from multiple testing.

RESULTS

Characteristics of the included participants. We included 207,908 participants with an average age of 56.19 years (Table 1). During a median follow-up of 12.56 years, 2,474 participants developed incident gout. Participants who developed gout tended to be male and older, have lower income and educational levels, be inactive and obese, and have an unhealthy diet, a history of smoking, and heavy alcohol use ($P < 0.05$). The mean annual average concentrations for $PM_{2.5}$, PM_{10}, NO_2, and NO_x were 10.65 (SD 1.92), 16.77 (SD 2.71), 20.82 (SD 6.51), and 31.53 (SD 12.70) μg/m^3, respectively (Table S2).

Characterizing metabolic signatures of air pollutants. After conducting elastic net regression, 87, 76, 68, and 71 metabolites with nonzero coefficients were chosen to compute the metabolic signature scores reflecting $PM_{2.5}$, PM_{10}, NO_2, and NO_x, respectively. As shown in Figure 1, lipids, lipoprotein subclasses, amino acids, fatty acids, ketone bodies, triglycerides, metabolites linked to glycolysis, fluid balance, and inflammation are the primary components that make up the metabolic signatures. Moreover, we found that the linoleic acid to total

Table 1. Baseline characteristics of participants by gout incidence*

Characteristics	Total (N = 207,908)	Without gout (n = 205,434)	With gout (n = 2,474)	*P* value
Age, mean (SD), y	56.19 (8.09)	56.14 (8.09)	60.31 (7.07)	<0.001[a]
Sex, n (%)				<0.001[b]
Female	107,685 (51.79)	107,222 (52.19)	463 (18.71)	
Male	100,223 (48.21)	98,212 (47.81)	2011 (81.29)	
Ethnicity, n (%)				0.215[b]
Non-White	8,835 (4.25)	8,717 (4.24)	118 (4.77)	
White	199,073 (95.75)	196,717 (95.76)	2,356 (95.23)	
Education level, n (%)				<0.001[b]
College degree or higher	70,711 (34.01)	70,103 (34.12)	608 (24.58)	
Any school degree	79,733 (38.35)	78,898 (38.41)	835 (33.75)	
Vocational qualifications and other	56,555 (27.20)	55,536 (27.03)	1,019 (41.19)	
Missing	909 (0.44)	897 (0.44)	12 (0.49)	
Income, n (%)				<0.001[b]
<£18,000	48,345 (23.25)	47,592 (23.17)	753 (30.44)	
£18,000–£30,999	53,804 (25.88)	53,119 (25.86)	685 (27.69)	
£31,000–£51,999	53,861 (25.91)	53,277 (25.93)	584 (23.61)	
£52,000–£100,000	41,048 (19.74)	40,698 (19.81)	350 (14.15)	
>£100,000	10,219 (4.92)	10,135 (4.93)	84 (3.40)	
Missing	631 (0.30)	613 (0.30)	18 (0.73)	
BMI, n (%)				<0.001[b]
Underweight	903 (0.43)	902 (0.44)	1 (0.04)	
Normal weight	65,900 (31.70)	65,646 (31.95)	254 (10.27)	
Overweight	89,724 (43.16)	88,637 (43.15)	1,087 (43.94)	
Obese	50,696 (24.38)	49,576 (24.13)	1,120 (45.27)	
Missing	685 (0.33)	673 (0.33)	12 (0.49)	
Physical activity, n (%)				0.001[b]
Low	33,339 (16.04)	32,872 (16.00)	467 (18.88)	
Moderate	70,872 (34.09)	70,047 (34.10)	825 (33.35)	
High	69,457 (33.41)	68,685 (33.43)	772 (31.20)	
Missing	34,240 (16.47)	33,830 (16.47)	410 (16.57)	
Healthy diet score, n (%)				<0.001[b]
0–1	44,182 (21.25)	43,526 (21.19)	656 (26.52)	
2–3	116,459 (56.01)	115,058 (56.01)	1,401 (56.63)	
4–5	46,937 (22.58)	46,524 (22.65)	413 (16.69)	
Missing	330 (0.16)	326 (0.16)	4 (0.16)	
Smoking, n (%)				<0.001[b]
Never	113,322 (54.51)	112,347 (54.69)	975 (39.41)	
Previous	72,447 (34.85)	71,202 (34.66)	1,245 (50.32)	
Current	22,139 (10.65)	21,885 (10.65)	254 (10.27)	
Alcohol drinking, n (%)				<0.001[b]
Heavy	41,846 (20.13)	41,128 (20.02)	718 (29.02)	
Moderate	103,822 (49.94)	102,654 (49.97)	1,168 (47.21)	
Occasional	46,835 (22.53)	46,413 (22.59)	422 (17.06)	
Never	15,309 (7.36)	15,145 (7.37)	164 (6.63)	
Missing	96 (0.05)	94 (0.05)	2 (0.08)	
$PM_{2.5}$, mean (SD), μg/m^3	10.65 (1.92)	10.65 (1.93)	10.84 (1.83)	<0.001[a]
PM_{10}, mean (SD), μg/m^3	16.77 (2.71)	16.77 (2.71)	17.02 (2.63)	<0.001[a]
NO_2, mean (SD), μg/m^3	20.82 (6.51)	20.82 (6.51)	21.20 (6.53)	0.004[a]
NO_x, mean (SD), μg/m^3	31.53 (12.70)	31.52 (12.70)	32.27 (12.71)	0.004[a]

* BMI, body mass index; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter; PM_{10}, inhalable particulate matter; Non-White catrgory includes Asian, Black, Mixed, and other.
[a] *P* value by *t*-test.
[b] *P* value by chi-square test.

fatty acids percentage and lactate made the most pronounced contribution to the positive coefficient of the metabolic signature associated with $PM_{2.5}$ and PM_{10} (Figure 2, Tables S3–S6). Additionally, cholesterol in medium very low-density lipoprotein (M-VLDL-C) and the phospholipids to total lipids in small low-density lipoprotein (LDL) percentage significantly influenced the negative coefficient of the metabolic signatures reflecting $PM_{2.5}$ and PM_{10}. Furthermore, the degree of unsaturation and triglycerides in large LDL exhibited the strongest positive correlation with metabolic signatures reflecting NO_2 and NO_x. Meanwhile, triglycerides in large high-density lipoprotein and M-VLDL-C contributed the most for the reverse coefficient.

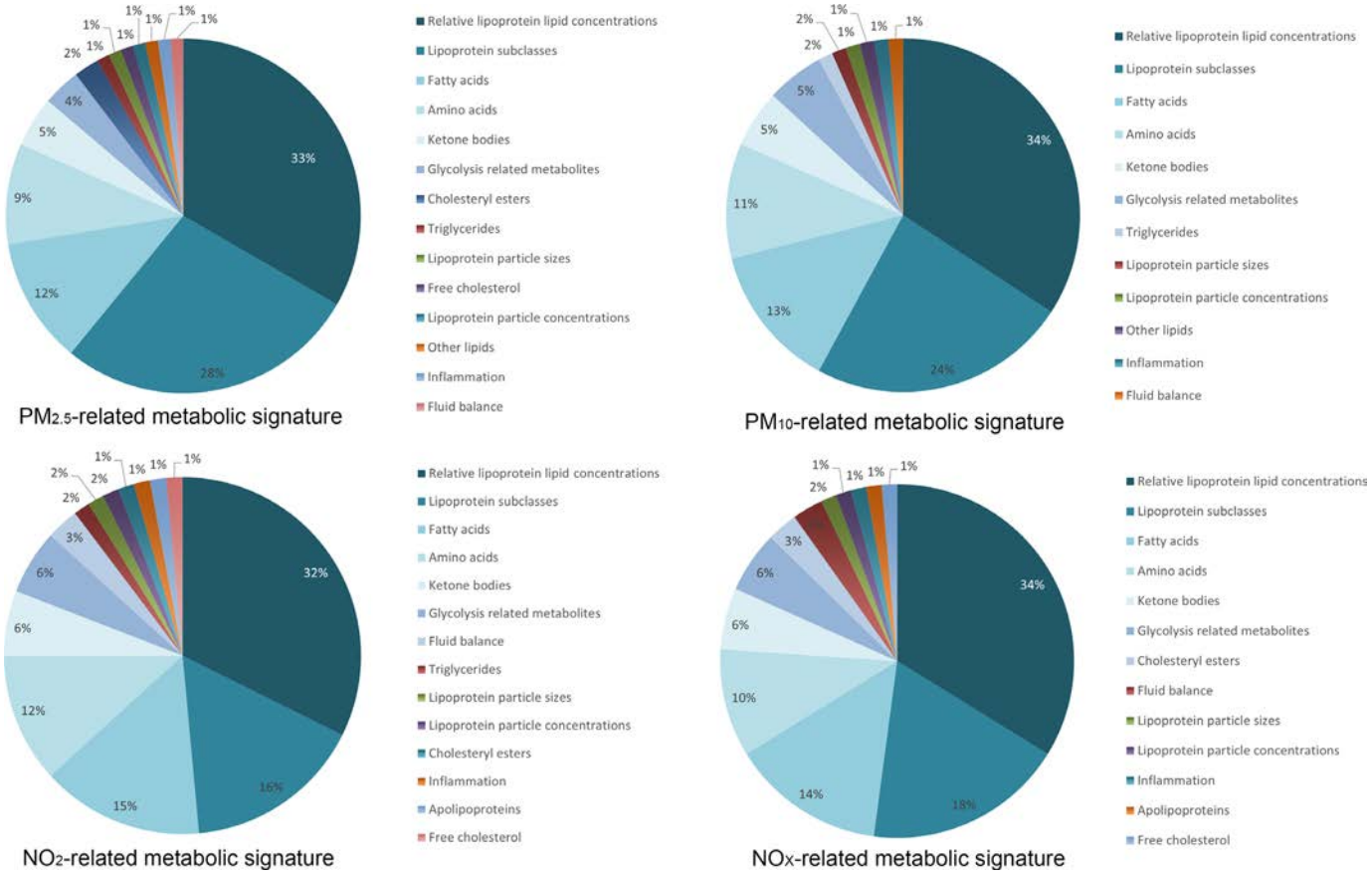

Figure 1. The composition of air pollution–related metabolic signatures. NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter; PM_{10}, inhalable particulate matter.

Association of air pollutants and metabolic signatures with gout. As shown in Table 2, per-interquartile range increase in air pollution was significantly associated with elevated gout risk in the fully adjusted models, with HRs of 1.17 (95% CI 1.11–1.23) for $PM_{2.5}$, 1.15 (95% CI 1.09–1.21) for PM_{10}, 1.06 (95% CI 1.01–1.11) for NO_2, and 1.06 (95% CI 1.01–1.11) for NO_x. Additionally, a higher risk of developing gout was positively associated with per-SD increase in metabolic signatures linked to air pollution, with the estimates of 1.10 (95% CI 1.05–1.14) for $PM_{2.5}$, 1.12 (95% CI 1.08–1.17) for PM_{10}, 1.09 (95% CI 1.04–1.13) for NO_2, and 1.11 (95% CI 1.06–1.15) for NO_x. The dose–response analysis indicated a higher gout risk with increments of air pollutants and related metabolic signatures (Fig S2). Similarly, we found the joint mixing effect of four air pollutants was 1.16 (95% CI 1.06–1.28) on gout risk, and the joint mixing effect of metabolic signatures was 1.27 (95% CI 1.16–1.39) on gout risk, each one quartile variation of exposures (Table S7).

Mediation analysis and pathway analysis. As shown in Figure 3, Metabolic signatures significantly mediated the associations between four air pollutants and gout. The mediation proportions were 2.36%, 3.76%, 3.58%, and 4.30% for $PM_{2.5}$, PM_{10}, NO_2, and NO_x, respectively. Furthermore, we estimated the associations of metabolites in mediating gout risk (Figs S3–S6). We found that lipoprotein subclass–related metabolites played crucial mediating roles. Among these, M-VLDL-C, cholesteryl esters in M-VLDL, free cholesterol in M-VLDL, the concentration of intermediate-density lipoprotein (IDL) particles, free cholesterol in IDL, and the concentration of small LDL particles mediated this process for all air pollutants, and cholesterol in IDL mediated the process for all air pollutants. Fig S7 displayed the metabolic pathways involving the metabolic biomarkers that significantly mediated the relationship between air pollutants and gout. We observed that the most prominent pathways were alanine, aspartate, and glutamate metabolism; glyoxylate and dicarboxylate metabolism; and linoleic acid metabolism.

Stratified analyses and sensitivity analyses. Stratified analyses showed that NO_2- and NO_x-related metabolic signatures had a stronger association with gout in women than in men and that older individuals (≥60 years) had stronger associations with metabolite signatures ($PM_{2.5}$, NO_2, and NO_x) than younger individuals (<60 years) ($P < 0.05$) (Fig S8). Similar results were found in the sensitivity analyses when we varied the exposure window to one-, two-, and three-year durations

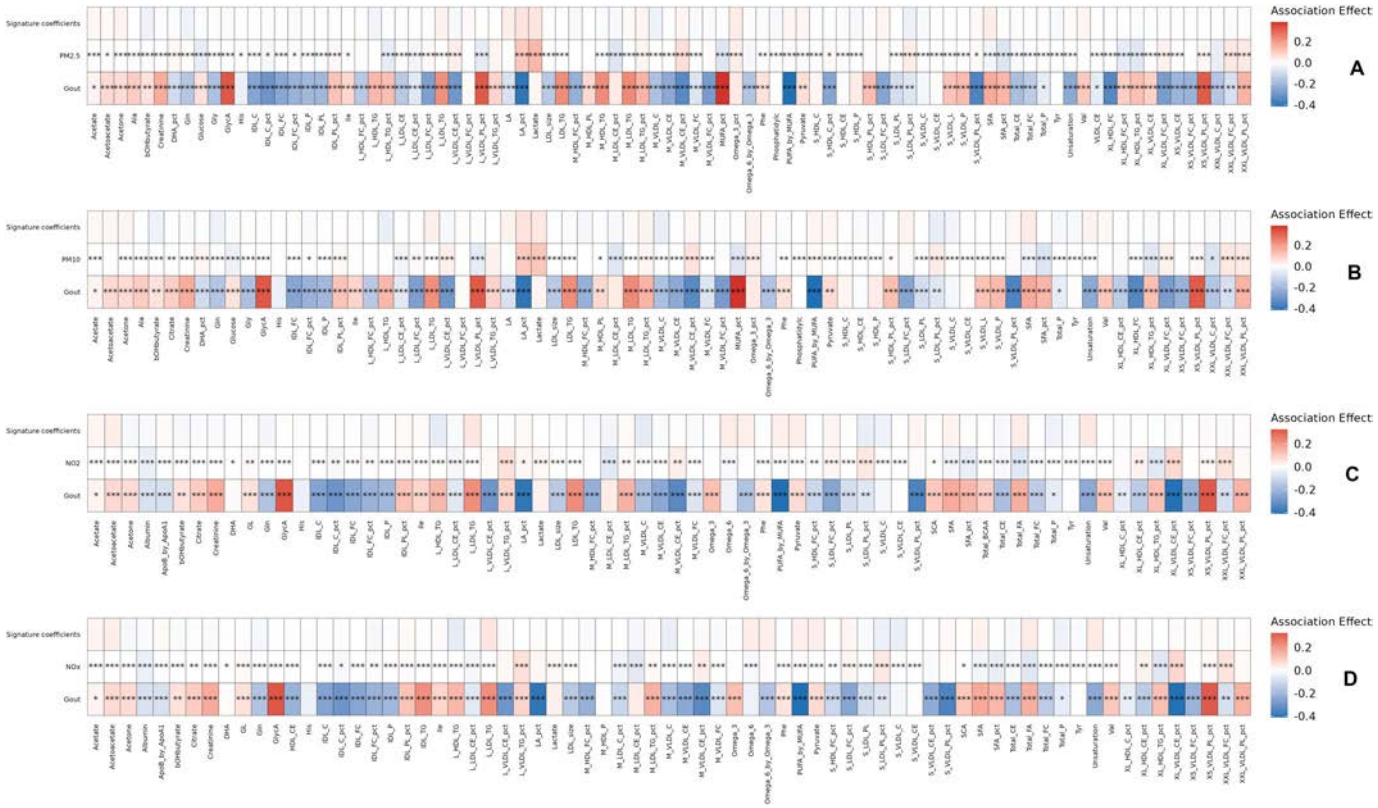

Figure 2. Associations of metabolites constituting the metabolic signatures with air pollutants and gout risk. (A) $PM_{2.5}$. (B) PM_{10}. (C) NO_2. (D) NO_x. In each panel, presented from top to bottom are the metabolites' coefficients (weights) in the metabolic signature and associations with air pollution and subsequent gout risk. Coefficients for associations with air pollution show the changes in metabolites per IQR increment in air pollution. Coefficients for the gout risk indicate ln (HR) per SD increment in metabolites. Colors reflect the direction (red for positive, blue for inverse) and strength (darker colors indicate stronger effects). *$P < 0.05$; **Bonferroni-corrected $P < 0.05$; ***$P < 0.001$. HR, hazard ratios; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter; PM_{10}, inhalable particulate matter. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.70007/abstract.

Table 2. Associations of air pollution and metabolic signatures with risk of gout (N = 207,908)*

Analysis model	Air pollutants		Metabolic signatures	
	HR (95% CI)[a]	*P* value	HR (95% CI)[b]	*P* value
$PM_{2.5}$				
Model 1	1.17 (1.11–1.23)	<0.001	1.11 (1.07–1.16)	<0.001
Model 2	1.17 (1.11–1.23)	<0.001	1.10 (1.06–1.15)	<0.001
Model 3	1.17 (1.11–1.23)	<0.001	1.10 (1.05–1.14)	<0.001
PM_{10}				
Model 1	1.17 (1.11–1.23)	<0.001	1.16 (1.12–1.21)	<0.001
Model 2	1.16 (1.10–1.22)	<0.001	1.13 (1.08–1.17)	<0.001
Model 3	1.15 (1.09–1.21)	<0.001	1.12 (1.08–1.17)	<0.001
NO_2				
Model 1	1.09 (1.04–1.14)	<0.001	1.15 (1.10–1.20)	<0.001
Model 2	1.06 (1.01–1.11)	0.016	1.09 (1.05–1.13)	<0.001
Model 3	1.06 (1.01–1.11)	0.024	1.09 (1.04–1.13)	<0.001
NO_x				
Model 1	1.10 (1.05–1.15)	<0.001	1.15 (1.10–1.19)	<0.001
Model 2	1.06 (1.01–1.12)	0.011	1.11 (1.06–1.15)	<0.001
Model 3	1.06 (1.01–1.11)	0.017	1.11 (1.06–1.15)	<0.001

* Model 1: adjustment for age and sex; model 2: additional adjustment for ethnicity, education level, household income, smoking status, alcohol consumption, body mass index, healthy diet score, and physical activity; model 3: mutual adjustment for both air pollutants and metabolic signatures. CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter; PM_{10}, inhalable particulate matter.

[a] Results are shown as each IQR increase in air pollutants.

[b] Results are shown as each SD increase in metabolic signatures.

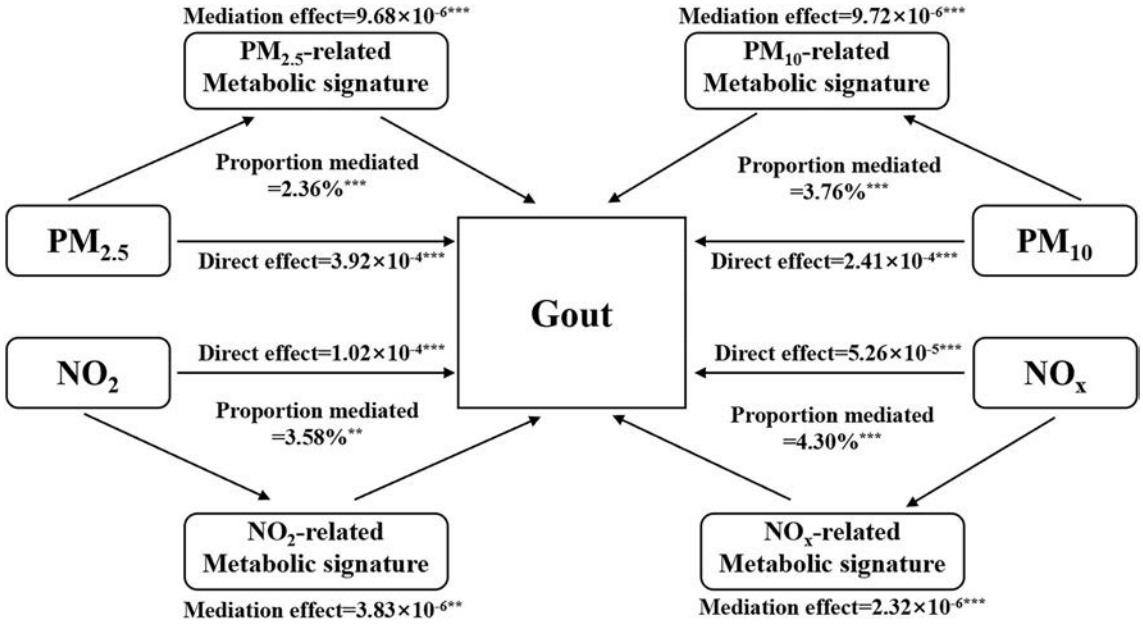

Figure 3. Mediation analyses for metabolic signatures on the association between air pollutants and gout. $^{**}P < 0.01$. $^{***}P < 0.001$. NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter; PM_{10}, inhalable particulate matter.

(Tables S8–S10), eliminating participants who experienced incident gout during the two-year follow-up period (Table S11), excluding participants without complete information on covariates (Table S12), and including hypertension and diabetes as covariates to examine the robustness of the results (Table S13). Similar results using the time-varying Cox proportional hazard model were observed (Table S14).

DISCUSSION

This is the first investigation examining the associations of air pollutants and their reflecting metabolic signatures with gout risk. In this large cohort investigation, we established the metabolic signatures linked to air pollution and demonstrated their association with elevated gout risk. Stratified analyses demonstrated that these relationships were more pronounced in women and older individuals. Additionally, mediation analyses suggested that metabolic signatures played an important role in mediating the link between air pollutants and gout risk.

Evidence suggests that air pollution exposure influences the blood metabolome.[31–36] For example, a study from the Rotterdam study indicated that long-term exposure to air pollutants was significantly related to metabolites mostly belonging to lipid and amino acid subclass metabolites.[31] Recent research has identified specific metabolites associated with air pollution, including energy metabolism, key inflammatory, and nucleic acid damage and repair pathways.[32] One study from California showed that air pollution may alter key metabolic pathways involving amino acid and fatty acid metabolism, adversely affect lipid homeostasis, and influence health.[36] Prior studies have also shown that NO_2 exposure was associated with various amino acid metabolites, such as tyrosine, phenylalanine, and tryptophan.[34,35] In line with prior research, our study also demonstrated that air pollution may alter several crucial metabolites, such as lipids, lipoprotein subclasses, fatty acids, amino acids, etc. Furthermore, the associations between metabolites and gout risk have also been demonstrated in previous research. Metabolites are metabolic end products or intermediates that impact cell function and respond to environmental exposures. However, no research has yet illustrated the air pollution–metabolism–gout relationship. In this study, we identified air pollution–related metabolic signatures and found that these signatures were associated with higher gout risk. Our findings emphasize the need for further research on the air pollution–metabolic signature–gout relationship, which provides new insights for the precise prevention and control of gout.

The air pollutants–gout associations have been explored in several investigations. For example, time-series studies suggested that short-term exposure to PM_{10} and NO_2 was found to be strongly linked to an elevated incidence of acute gout flares.[15,37] A study comprising 170,318 participants revealed a correlation between $PM_{2.5}$ exposure and increased gout risk.[14] Research conducted in the United Kingdom demonstrated that long-term exposure to air pollution evaluated from land use regression models was related to elevated gout risk.[12,13] Although our findings were mostly in line with established studies, the underlying biologic processes are still unknown. Our findings revealed a significant mediating pathway through metabolic markers in the air pollutants–gout associations, suggesting a potential mechanism through which air pollutants increase gout

risk by altering metabolism. Given metabolic signature could provide an objective reflection of air pollution exposure, the findings may provide a more thorough insight into metabolic alterations related to air pollution.

It is reported that some metabolic pathways are closely related to the development of gout, such as the dysfunction of lipid metabolism and amino acid metabolism.[38] Metabolites from lipoprotein subclasses were found to play crucial mediating roles. Previous studies have indicated VLDL levels could induce activation of inflammation and result in a persistent inflammatory condition.[39] Meanwhile, VLDL is metabolized in adipose and muscle tissue, forming IDL, which may further metabolize to LDL.[40] Furthermore, VLDL can be taken up by the VLDL receptor in adipocytes and the endothelium, promoting fat accumulation and contributing to obesity, which would enhance nucleic acid metabolism and increase uric acid synthesis.[41,42] In addition, several studies have also shown that amino acid metabolism is highly associated with gout.[20,38,43] A prospective cohort study found 107 metabolites were associated with hospitalized gout, including glutamine and glycine.[43] Another study indicated that amino acid metabolism is one of the main dysregulated pathways, which involves alanine and glutamate metabolism.[20] Consistent with prior studies, in this study, amino acid metabolism was also evidenced as an important pathway in the air pollution–gout association, especially alanine and glutamine metabolism. We observed similar findings in populations in the United Kingdom and further determined metabolic signatures linked to air pollution increased gout risk. We indicated some important pathways in the air pollution–gout associations, including alanine, aspartate, and glutamate metabolism; glyoxylate and dicarboxylate metabolism; and linoleic acid metabolism. In line with our findings, a recent study found that glyoxylate and dicarboxylate metabolism was one of the $PM_{2.5}$-related metabolic pathways; another study suggested that linoleic acid metabolism was a key metabolic pathway of $PM_{2.5}$ and PM_{10}.[44,45] It is proven that linoleic acid metabolism is closely related to inflammatory activation, and its metabolites regulate inflammatory signaling pathways through multiple molecular mechanisms.[46] Furthermore, the metabolic biomarkers in glyoxylate and dicarboxylate metabolism could further regulate the immune response.[47] The results of mediation analyses established an air pollution–metabolic signature/metabolites–gout relationship for further exploring potential biologic mechanisms of gout development.

It is important to note that participants who developed incident gout during follow-up had significantly different baseline characteristics compared to those who did not, as expected. Although this reflects the natural history of gout, it also introduces potential for confounding. We addressed this through extensive multivariable adjustment in our primary models, which yielded consistent results. This strengthens the inference that the association of exposure with gout is independent of these traditional risk factors. We observed a stronger association of metabolic signatures reflecting air pollution with gout risk in older participants and women, which could also be supported by several studies.[12,13] This could be explained by the aging-related immune system deterioration that makes older participants more vulnerable to environmental pollutants.[48] Moreover, we also found the HRs of NO_2/NO_x-related metabolic signatures on gout risk were higher in women than in men. This discrepancy could be attributed to social behavior variations, metabolism, and physiologic distinctions.[49,50]

Our study has several strengths. We used elastic net regularized regressions to find metabolic signatures linked to air pollution and observed that gout risk was associated with both air pollution and metabolic signatures. Meanwhile, we found a significant partial mediation impact of metabolism and established a potential air pollution–metabolism–gout relationship. In addition, we applied data from a large cohort study with substantial follow-up duration, and we also obtained various confounders and residence-based air pollution assessments.

Several limitations should also be acknowledged. First, some lifestyle covariates were collected using self-reported measures at baseline, which may unavoidably result in misclassification bias. However, earlier studies have suggested agreement between self-reported information and primary care records, demonstrating the accuracy of the self-reported covariates in the UKB.[51] Second, due to inadequate follow-up data on potential confounders, we only considered baseline factors. Third, although metabolite measurements were comprehensive, measurement errors were unavoidable in the study; meanwhile, the measurement of metabolites at baseline limits our understanding of metabolic variations and their effects on gout risk. Fourth, in this study, we identified gout cases using inpatient records with ICD codes, which may inevitably lead to misclassification bias; the data on gout cases in the outpatient and emergency departments were not taken into account in the study, which may lead to underestimation of the results. Finally, although the 10-fold cross-validation approach was applied to minimize overfitting, potential bias could not be avoided entirely. An independent cohort should be used for external validation to confirm the generalizability of these findings.

In conclusion, this study identified metabolic signatures reflecting long-term air pollution exposure ($PM_{2.5}$, PM_{10}, NO_2, and NO_x) and indicated that air pollutants with metabolic signatures were linked to elevated gout risk. Metabolic signatures partially mediated the air pollutants–gout relationship. The findings emphasize the advantages of precision prevention focused on mitigating metabolic imbalances to decrease gout risk among individuals exposed to air pollution and provide valuable insights for the prevention of gout.

ACKNOWLEDGMENTS

This research was conducted using the UKB (application no. 69550). This work uses data provided by patients and collected by the NHS as part of their care and support. The authors appreciate all UKB participants and all staff for their contribution to these studies.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding authors, Drs Huang and Lin confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Dalbeth N, Gosling AL, Gaffo A, et al. Gout. Lancet 2021;397(10287):1843–1855. doi:https://doi.org/10.1016/S0140-6736(21)00569-9
2. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16(7):380–390. doi:https://doi.org/10.1038/s41584-020-0441-1
3. Guan SY, Zheng JX, Sam NB, et al. Global burden and risk factors of musculoskeletal disorders among adolescents and young adults in 204 countries and territories, 1990-2019. Autoimmun Rev 2023;22(8):103361. doi:https://doi.org/10.1016/j.autrev.2023.103361
4. Hansildaar R, Vedder D, Baniaamam M, et al. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol 2021;3(1):e58–e70. doi:https://doi.org/10.1016/S2665-9913(20)30221-6
5. Choi HK, McCormick N, Yokose C. Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care. Nat Rev Rheumatol 2022;18(2):97–111. doi:https://doi.org/10.1038/s41584-021-00725-9
6. Cipolletta E, Tata LJ, Nakafero G, et al. Association between gout flare and subsequent cardiovascular events among patients with gout. JAMA 2022;328(5):440–450. doi:https://doi.org/10.1001/jama.2022.11390
7. Fisher MC, Rai SK, Lu N, et al. The unclosing premature mortality gap in gout: a general population-based study. Ann Rheum Dis 2017;76(7):1289–1294. doi:https://doi.org/10.1136/annrheumdis-2016-210588
8. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350(11):1093–1103. doi:https://doi.org/10.1056/NEJMoa035700
9. Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004;363(9417):1277–1281. doi:https://doi.org/10.1016/S0140-6736(04)16000-5
10. Karlsson T, Hadizadeh F, Rask-Andersen M, et al. Body mass index and the risk of rheumatic disease: linear and nonlinear mendelian randomization analyses. Arthritis Rheumatol 2023;75(11):2027–2035. doi:https://doi.org/10.1002/art.42613
11. Wu ZD, Yang XK, He YS, et al. Environmental factors and risk of gout. Environ Res 2022;212(Pt C):113377. doi:https://doi.org/10.1016/j.envres.2022.113377
12. Li A, Zhang Q, Zhou L, et al. Long-term exposure to ambient air pollution and incident gout: a prospective cohort study in the UK Biobank. Environ Pollut 2024;345:123540. doi:https://doi.org/10.1016/j.envpol.2024.123540
13. Liu W, Ye L, Hua B, et al. Association between combined exposure to ambient air pollutants, genetic risk, and incident gout risk: a prospective cohort study in the UK Biobank. Semin Arthritis Rheum 2024;66:152445. doi:https://doi.org/10.1016/j.semarthrit.2024.152445
14. Hu WS, Lin CL. Effect of air pollution on gout development: a nationwide population-based observational study. QJM 2021;114(7):471–475. doi:https://doi.org/10.1093/qjmed/hcaa286
15. He YS, Wang GH, Wu Q, et al. The relationship between ambient air pollution and hospitalizations for gout in a humid subtropical region of China. J Inflamm Res 2021;14:5827–5835. doi:https://doi.org/10.2147/JIR.S329706
16. Liu Y, Aryee MJ, Padyukov L, et al. Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. Nat Biotechnol 2013;31(2):142–147. doi:https://doi.org/10.1038/nbt.2487
17. Wishart DS. Metabolomics for investigating physiological and pathophysiological processes. Physiol Rev 2019;99(4):1819–1875. doi:https://doi.org/10.1152/physrev.00035.2018
18. Li Y, Han X, Tong J, et al. Analysis of metabolites in gout: a systematic review and meta-analysis. Nutrients 2023;15(14):3143. doi:https://doi.org/10.3390/nu15143143
19. Shen X, Wang C, Liang N, et al. Serum metabolomics identifies dysregulated pathways and potential metabolic biomarkers for hyperuricemia and gout. Arthritis Rheumatol 2021;73(9):1738–1748. doi:https://doi.org/10.1002/art.41733
20. Wang M, Li R, Qi H, et al. Metabolomics and machine learning identify metabolic differences and potential biomarkers for frequent versus infrequent gout flares. Arthritis Rheumatol 2023;75(12):2252–2264. doi:https://doi.org/10.1002/art.42635
21. Yao Y, Schneider A, Wolf K, et al. Longitudinal associations between metabolites and long-term exposure to ambient air pollution: results from the KORA cohort study. Environ Int 2022;170:107632. doi:https://doi.org/10.1016/j.envint.2022.107632
22. Zhu X, Zhang Q, Du X, et al. Respiratory effects of traffic-related air pollution: a randomized, crossover analysis of lung function, airway metabolome, and biomarkers of airway injury. Environ Health Perspect 2023;131(5):57002. doi:https://doi.org/10.1289/EHP11139
23. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3):e1001779. doi:https://doi.org/10.1371/journal.pmed.1001779
24. Würtz P, Kangas AJ, Soininen P, et al. Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: a primer on -omic technologies. Am J Epidemiol 2017;186(9):1084–1096. doi:https://doi.org/10.1093/aje/kwx016
25. Hu P, Shen L, Chen G, et al. Long-term exposure to fine particulate matter constituents and the prognosis of oral cancer patients: a prospective study in southeastern China. J Hazard Mater 2025;487:137304. doi:https://doi.org/10.1016/j.jhazmat.2025.137304
26. Huang K, Liang F, Yang X, et al. Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project. BMJ 2019;367:l6720. doi:https://doi.org/10.1136/bmj.l6720
27. Tian F, Wang Y, Qian ZM, et al. Plasma metabolomic signature of healthy lifestyle, structural brain reserve and risk of dementia. Brain 2025;148(1):143–153. doi:https://doi.org/10.1093/brain/awae257
28. Tian F, Wang Y, Huang Z, et al. Metabolomic profiling identifies signatures and biomarkers linking air pollution to dementia risk: a prospective cohort study. J Hazard Mater 2024;480:136498. doi:https://doi.org/10.1016/j.jhazmat.2024.136498
29. Chen L, Wang C, Zhang S, et al. Habitual physical activity and all-cause mortality among individuals with and without impaired lung function: findings from a prospective cohort study. Green Health 2025;1(2):6. doi:https://doi.org/10.3390/greenhealth1020006
30. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Stat Soc Series B Stat Methodol 2005;67(2):301–320. doi:https://doi.org/10.1111/j.1467-9868.2005.00503.x

31. Ginos BNR, de Crom TOE, Ghanbari M, et al. Long-term air pollution exposure and the blood metabolome: the Rotterdam study. Environ Res 2024;263(Pt 2):120131. doi:https://doi.org/10.1016/j.envres.2024.120131
32. Liang D, Tang Z, Diver WR, et al. Metabolomics signatures of exposure to ambient air pollution: a large-scale metabolome-wide association study in the Cancer Prevention Study-II nutrition cohort. Environ Sci Technol 2025;59(1):212–223. doi:https://doi.org/10.1021/acs.est.4c09592
33. Nassan FL, Wang C, Kelly RS, et al. Ambient $PM_{2.5}$ species and ultrafine particle exposure and their differential metabolomic signatures. Environ Int 2021;151:106447. doi:https://doi.org/10.1016/j.envint.2021.106447
34. Yao Y, Schneider A, Wolf K, et al. Longitudinal associations between metabolites and immediate, short- and medium-term exposure to ambient air pollution: results from the KORA cohort study. Sci Total Environ 2023;900:165780. doi:https://doi.org/10.1016/j.scitotenv.2023.165780
35. Liao J, Gheissari R, Thomas DC, et al. Transcriptomic and metabolomic associations with exposures to air pollutants among young adults with childhood asthma history. Environ Pollut 2022;299:118903. doi:https://doi.org/10.1016/j.envpol.2022.118903
36. Liao J, Goodrich J, Walker DI, et al. Metabolic pathways altered by air pollutant exposure in association with lipid profiles in young adults. Environ Pollut 2023;327:121522. doi:https://doi.org/10.1016/j.envpol.2023.121522
37. Ryu HJ, Seo MR, Choi HJ, et al. Particulate matter (PM_{10}) as a newly identified environmental risk factor for acute gout flares: a time-series study. Joint Bone Spine 2021;88(2):105108. doi:https://doi.org/10.1016/j.jbspin.2020.105108
38. Wu X, You C. The biomarkers discovery of hyperuricemia and gout: proteomics and metabolomics. PeerJ 2023;11:e14554. doi:https://doi.org/10.7717/peerj.14554
39. Huang JK, Lee HC. Emerging evidence of pathological roles of very-low-density lipoprotein (VLDL). Int J Mol Sci 2022;23(8):4300. doi:https://doi.org/10.3390/ijms23084300
40. Feingold KR. Lipid and lipoprotein metabolism. Endocrinol Metab Clin North Am 2022;51(3):437–458. doi:https://doi.org/10.1016/j.ecl.2022.02.008
41. Dlugosz P, Nimpf J. The reelin receptors apolipoprotein E receptor 2 (ApoER2) and VLDL receptor. Int J Mol Sci 2018;19(10):3090. doi:https://doi.org/10.3390/ijms19103090
42. Cong R, Zhang X, Song Z, et al. Assessing the causal effects of adipokines on uric acid and gout: a two-sample Mendelian randomization study. Nutrients 2022;14(5):1091. doi:https://doi.org/10.3390/nu14051091
43. McCormick N, Joshi AD, Yokose C, et al. Prediagnostic amino acid metabolites and risk of gout, accounting for serum urate: prospective cohort study and mendelian randomization. Arthritis Care Res (Hoboken) 2024;76(12):1666–1674. doi:https://doi.org/10.1002/acr.25420
44. Wang Y, Tian F, Qian ZM, et al. Air pollution, metabolic signatures, and the risk of idiopathic pulmonary fibrosis. Sci Total Environ 2025;964:178409. doi:https://doi.org/10.1016/j.scitotenv.2025.178409
45. Zhuo B, Ran S, Qian AM, et al. Air pollution metabolomic signatures and chronic respiratory diseases risk: a longitudinal study. Chest 2024;166(5):975–986. doi:https://doi.org/10.1016/j.chest.2024.06.3809
46. Alzoghaibi MA, Walsh SW, Willey A, et al. Linoleic acid, but not oleic acid, upregulates the production of interleukin-8 by human intestinal smooth muscle cells isolated from patients with Crohn's disease. Clin Nutr 2003;22(6):529–535. doi:https://doi.org/10.1016/S0261-5614(03)00083-9
47. Li Q, Jin H, Liu Y, et al. Determination of cytokines and oxidative stress biomarkers in cognitive impairment induced by methylmalonic acidemia. Neuroimmunomodulation 2021;28(3):178–186. doi:https://doi.org/10.1159/000511590
48. Ran S, Zhang J, Tian F, et al. Association of metabolic signatures of air pollution with MASLD: observational and Mendelian randomization study. J Hepatol 2025;82(4):560–570. doi:https://doi.org/10.1016/j.jhep.2025.04.001
49. Liao M, Braunstein Z, Rao X. Sex differences in particulate air pollution-related cardiovascular diseases: a review of human and animal evidence. Sci Total Environ 2023;884:163803. doi:https://doi.org/10.1016/j.scitotenv.2023.163803
50. Gill TK, Mittinty MM, March LM, et al; GBD 2021 Other Musculoskeletal Disorders Collaborators. Global, regional, and national burden of other musculoskeletal disorders, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2023;5(11):e670–e682. doi:https://doi.org/10.1016/S2665-9913(23)00232-1
51. Darke P, Cassidy S, Catt M, et al. Curating a longitudinal research resource using linked primary care EHR data-a UK Biobank case study. J Am Med Inform Assoc 2022;29(3):546–552. doi:https://doi.org/10.1093/jamia/ocab260

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 78, No. 7, July 2026, pp 956–958

LETTER

DOI 10.1002/acr.70014

Methodologic and conceptual limitations in moderator and mediator analyses of knee osteoarthritis trials: comment on the article by Farivar et al

To the Editor:

The recent secondary analysis by Farivar et al,[1] which examined moderators and mediators of a randomized controlled trial evaluating a new service delivery model for knee osteoarthritis, represents a meaningful effort to advance personalized care. Although the investigation of for whom and how the intervention worked is highly relevant, several methodologic and conceptual limitations merit critical discussion to guide future research.

First, the overreliance on a priori statistical significance in moderation analysis raises concerns. The identification of baseline pain and function as the only significant moderators, although clinically intuitive, may result from the notoriously low statistical power of traditional regression-based interaction tests.[2] This increases the risk of Type II errors, potentially overlooking influential moderators such as depression or comorbidity. Future studies should either be prospectively powered to test specific moderator hypotheses or employ machine learning techniques (eg, causal forests) to better detect complex interactions in high-dimensional data without incurring severe multiple testing penalties.[2,3]

Second, the null findings for physical activity and weight loss as mediators likely reflect conceptual underspecification of the theoretical model. The tested pathways assumed direct, linear relationships among the intervention, behavioral changes, and outcomes, neglecting the established nonlinear and reciprocal dynamics in chronic pain.[4] A more plausible model would position psychosocial variables—such as reduced kinesiophobia—as primary mediators, enabling subsequent increases in physical activity and ultimately improving pain and function. Testing isolated behavioral mediators without incorporating psychological drivers limits interpretability and likely leads to null results. The field should prioritize testing prespecified serial mediation models grounded in contemporary biopsychosocial theory.[3,4]

Third, methodologic gaps in mediator measurement further constrain the validity of the findings. The use of self-reported physical activity introduces recall and social desirability biases, particularly in an unblinded trial. Objective measures such as accelerometers are necessary to accurately capture behavioral constructs.[5] Moreover, assessing mediators at a single time point (eg, 3 months) fails to account for their dynamic nature and impedes causal inference. Longitudinal modeling approaches, such as latent growth curve models within a structural equation framework, would better capture trajectories of change in both mediators and outcomes.[4,5]

In conclusion, although Farivar et al[1] have addressed critical questions in personalized knee osteoarthritis management, their study underscores the need for greater methodologic rigor in moderator and mediator analyses. Future mechanism research should incorporate adequately powered and theory-driven moderator plans, specify and test sequential mediation pathways that include psychosocial mechanisms, and employ longitudinal, objective measures of putative mediators. These steps are essential to avoid accumulating misleading null findings and to advance toward truly mechanism-informed personalized care.

Supported by The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Biomechanical research on cartilage transplantation based on the theory of "equal emphasis on muscle and bone" (grant 2023ZYQJ02).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70014.

Yao Liu, MR
DuJiang Yang, MD
GuoYou Wang, MD, PhD
wang_guoyou1981@163.com
Department of Joint Surgery
The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University
Longmatan District, Luzhou, Sichuan Province, China

1. Farivar A, Bowden JL, Bennell KL, et al. Moderators and mediators of pain and function outcomes in a new service delivery model for management of knee osteoarthritis in primary care: secondary exploratory analysis of a randomized controlled trial. Arthritis Care Res (Hoboken) 2025;77(10):1204–1213. doi:https://doi.org/10.1002/acr.25564
2. Hurley M, Dickson K, Hallett R, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. Cochrane Database Syst Rev 2018;4(4):CD010842. doi:https://doi.org/10.1002/14651858.CD010842.pub2
3. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22(3):363–388. doi:https://doi.org/10.1016/j.joca.2014.01.003
4. Chua SKK, Lim CJ, Pua YH, et al. Is kinesiophobia associated with quality of life, level of physical activity, and function in older adults with knee osteoarthritis? Clin Orthop Relat Res 2025;483(4):667–676. doi:https://doi.org/10.1097/CORR.0000000000003278
5. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1(1):CD004376. doi:https://doi.org/10.1002/14651858.CD004376.pub3

DOI 10.1002/acr.70013

Reply

To the Editor:

We thank you for the opportunity to respond to a letter by Liu et al regarding our recently published article, "Moderators and mediators of pain and function outcomes in a new service delivery model for management of knee osteoarthritis in primary care: Secondary exploratory analysis of a randomized controlled trial."[1] We would like to clarify and expand on some aspects of this work.

It is important to note that this study was a secondary analysis of a complex intervention, namely a new model of service delivery for people with knee osteoarthritis (OA).[2,3] Reducing pain and improving physical function are key goals for many people attending OA management programs, and the study design was powered to detect change in these outcomes. Although exercise and physical function were key components of the intervention, it was a multifaceted approach to OA care. Understanding any potential moderators and mediators for these outcomes is valuable for planning and delivering future services but complex to measure and interpret. As per best practice, potential moderators and mediators were identified a priori, were based on both clinical and theoretical rationales available at the time of the protocol development, and have been described in detail in both the original published protocol[2] and the supplementary data of the secondary analyses article.[1]

Regarding the first concern raised by the authors of the letter, as we stated in the Introduction section and emphasized in the Methods section, although the PARTNER study model showed significant improvements in knee pain and function compared to usual general practitioner care, the magnitude of improvement was not clinically meaningful for pain and was uncertain for function.[1,2] In this instance, in which the intervention has a weak impact on the desired outcome, the use of secondary analysis to explore potential moderators and mediators has even greater justification.[4] Change in knee pain and function were the primary outcomes of interest, and the preidentified potential moderators of these outcomes included age, sex, body mass index, pain duration, living arrangements, level of education, and employment status. Back pain, as the most common comorbidity, was also considered a potential moderator. Although we agree that depression may be a moderator of effect in some trials, people with depression were not a specific target for our study, and the number of people presenting with depression was very low. Therefore, this was not an appropriate factor for the analysis and was unlikely to show any effect. Because the only identified moderator was age, we performed only univariate regression analysis, and multivariable analysis was not justified. Powering trials to test-specific moderator hypotheses in addition to the primary analyses would likely result in an unfeasible recruitment target, adding considerable cost to the running of the trial. Analyses may be assisted by artificial intelligence machine learning to identify multiple interactions; however, this analysis method may be better used within large systematic reviews or individual participant data meta-analysis frameworks.

The second suggestion was to consider a serial mediation effect in the PARTNER study. The effects of mediators are indirect and potentially impact the outcome variables through other mediators. In our secondary analysis, we identified that elevated satisfaction levels in three domains were significant mediators of only the PARTNER study intervention effect on knee pain and function. It should be noted that several psychosocial variables were included in our mediator analyses, including fear of movement, pain catastrophizing, and self-efficacy, and were not shown to influence the pain or function response in our trial context. We acknowledge that our study might not have captured all the potential mediators and the effect could be exerted through the impact of the satisfaction of other potential mediators, such as the physical activity levels, along with other explanations we suggested in the Discussion section. However, our secondary analysis was performed within the set of variables and data collected in the PARTNER trial,[3] and they should therefore be interpreted within this context. We agree that more complex, serial mediation models incorporating psychosocial variables would provide an improved assessment of pathways.

The third comment by Liu et al concerned the methodology of the main PARTNER study. They proposed to use objective measures for the physical activity level rather than the main study's measurement tool, which was the Physical Activity Scale for the Elderly questionnaire.[5] We agree that the use of objective measures collected with accelerometers may increase the accuracy of the results. However, the PARTNER study aimed to deliver the knee OA management program remotely, with assessment tools available and validated at the time of protocol development. It should be noted that from a trial delivery perspective, use of these devices comes with its own challenges, including the digital literacy of our cohort, the costs and practicalities associated with providing and mailing the devices, and the collection and retrieval of data. There has been considerable advancement in the accuracy and usability of these devices in the last 15 years, and we now regularly include wearable devices in many of our clinical trials. We thank Liu et al for their feedback on our trial and analyses, and we will consider it for future work.

Abdolhay Farivar, MD, FRACP
Jocelyn L. Bowden, BHMSc, BSc(Hons), PhD
David J Hunter, MBBS, PhD, FRACP
david.hunter@sydney.edu.au
Royal North Shore Hospital
and Kolling Institute, The University of Sydney
St Leonards, New South Wales, Australia
Venkatesha Venkatesha, BSc, MSc, PhD
Northern Sydney Local Health District
St Leonards, New South Wales, Australia

1. Farivar A, Bowden JL, Bennell KL, et al. Moderators and mediators of pain and function outcomes in a new service delivery model for management of knee osteoarthritis in primary care: secondary exploratory analysis of a randomized controlled trial. Arthritis Care Res (Hoboken) 2025;77(10):1204–1213. doi:https://doi.org/10.1002/acr.25564
2. Hunter DJ, Hinman RS, Bowden JL, et al; PARTNER Study Team. Effectiveness of a new model of primary care management on knee pain and function in patients with knee osteoarthritis: protocol for THE PARTNER STUDY. BMC Musculoskelet Disord 2018;19(1):132. doi:https://doi.org/10.1186/s12891-018-2048-0
3. Hunter DJ, Bowden JL, Hinman RS, et al; PARTNER Study Team. Effectiveness of a new service delivery model for management of knee osteoarthritis in primary care: a cluster randomized controlled trial. Arthritis Care Res (Hoboken) 2023;75(6):1320–1332. doi:https://doi.org/10.1002/acr.25037
4. Memon M, Cheah J-H, Ramayah T, et al. Moderation analysis: issues and guidelines. J Appl Struct Equ Model 2019;3(1):i–xi.
5. Quicke JG, Foster NE, Croft PR, et al. Change in physical activity level and clinical outcomes in older adults with knee pain: a secondary analysis from a randomised controlled trial. BMC Musculoskelet Disord 2018;19(1):59. doi:https://doi.org/10.1186/s12891-018-1968-z

DOI 10.1002/acr.70000

Residual confounding in a study of acetaminophen risk: errors resulting from dichotomized variables: comment on the article by Kaur et al

To the Editor:

The study by Kaur et al attempts to assess risk of acetaminophen use in an observational cohort using propensity score matching to minimize confounding.[1] There are very large differences in risk in the unadjusted data for those in the cohort who received acetaminophen and those who did not, because those prescribed acetaminophen were nearly three times more likely to take nonsteroidal anti-inflammatory drugs (NSAIDs). The reason for this difference is probably related to the likely indication, pain. Those in pain were presumably more likely to get both NSAIDs and acetaminophen. In the propensity score matching analysis, NSAID use was treated as a dichotomous variable.

In reality, the dose–response relationship between NSAID dose and the risk of serious adverse events is nearly linear, rather than dichotomous.[2] To ignore the dose dependence is likely to create a Type I error (in this case concluding that acetaminophen has dangerous side effects) when the confounder is unbalanced in the original data,[3] as in the current study. That is, if far more of those patients who got acetaminophen also got NSAIDs, then among all patients who got NSAIDs, those in the acetaminophen arm probably got more NSAIDs than those in the no acetaminophen arm. Because the dose of NSAID is a risk factor for adverse events, then even after matching for plus or minus NSAID use, the patients who use acetaminophen will have more adverse events than the patients not using acetaminophen, and this result will have nothing to do with the inherent risk of acetaminophen.

The building momentum emphasizing alternatives to randomized, controlled trials has both practical and scientific rationale,[4] but limitations in observational data sets force many potential confounders to be treated as dichotomous when this is not the case. Particularly, when drug choices are influenced by prevailing risk assumptions, as those associated with NSAID use, physicians' decisions become nuanced by their assessment of the degree of risk. In those cases, the severity of the potential confounder, such as diabetes, hypertension, obesity, heart failure, renal insufficiency, dyspepsia or the frequency of NSAID or opioid use, then becomes a key driver in physician choice. Yet published literature employing observational data nearly uniformly treats these variables as dichotomous, in many cases with resulting erroneous conclusions.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.70000.

Michael R. Bubb, MD
bubbmr@medicine.ufl.edu
University of Florida College of Medicine
Gainesville, FL

1. Kaur J, Nakafero G, Abhishek A, et al. Incidence of side effects associated with acetaminophen in people aged 65 years or more: a prospective cohort study using data from the Clinical Practice Research Datalink. Arthritis Care Res (Hoboken) 2025;77(5):666–675.
2. Wilcox CM, Allison J, Benzuly K, et al; American Gastroenterological Association. Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. Clin Gastroenterol Hepatol 2006;4(9):1082–1089.
3. Barnwell-Ménard J-L, Li Q, Cohen AA. Effects of categorization method, regression type, and variable distribution on the inflation of Type-I error rate when categorizing a confounding variable. Stat Med 2015;34(6):936–949.
4. Frieden TR. Evidence for health decision making - beyond randomized, controlled trials. N Engl J Med 2017;377(5):465–475.