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.

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Cover image: The figure on the cover (from Sondhi et al; pages 157–162) shows computed tomography of the abdomen indicating a 1.5 cm solid-appearing hypodense lesion in the right kidney interpolar region.

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CLINICOPATHOLOGIC CONFERENCE

Unveiling the Shadow: Unraveling the Cause of Blindness

Manush Sondhi, Iman Qaiser, Samina Hayat, Sarwat Umer, and Kinza Muzaffar

CASE PRESENTATION

Chief symptoms

A 71-year-old Black woman with a medical history of type 2 diabetes mellitus, hypertension, and asthma was admitted with complaints of painful bilateral vision loss. She reported right-sided vision loss for four months and left-sided vision loss since a week before admission. Additionally, she presented with fatigue and unintentional weight loss, having lost 50 pounds over seven months.

History of present illness

Four months before admission, the patient experienced acute right-sided vision loss. Although she reported a history of headaches, she did not exhibit jaw claudication, scalp tenderness, or muscle stiffness and pain. There was no joint pain or swelling reported, nor did she have a fever, photosensitive rashes, alopecia, mucosal ulcers, chest pain, dyspnea, cough, abdominal pain, numbness, or dry eyes/dry mouth. She was initially prescribed prednisone 60 mg daily by an ophthalmologist because of a suspicion of giant cell arteritis (GCA). A left-sided temporal artery biopsy was unremarkable. Despite this, she continued prednisone treatment for suspected biopsy-negative GCA; it was discontinued shortly after when no improvement was observed. A week before admission, she developed bilateral, progressive proptosis followed by acute vision loss in her left eye, leading to hospitalization.

The patient had been experiencing right-sided hearing loss for some time. A magnetic resonance imaging (MRI) of the brain performed a year before admission revealed a right-sided vestibular schwannoma, for which she underwent a gamma knife procedure. A follow-up MRI six months later showed no change in the right vestibular schwannoma, and the patient continued to experience right-sided hearing loss.

Medical and social/family history

The patient's medical history includes type 2 diabetes mellitus, hypertension, and asthma. The patient's social and family history is unremarkable.

Review of systems

The patient reported experiencing painful bilateral vision loss along with unintentional weight loss. The review of systems yielded negative findings otherwise.

Physical examination

On physical examination, the patient presented with a blood pressure reading of 105/60 mm Hg, a heart rate of 91 beats per minute, a respiratory rate of 17 per minute, a temperature of 36.3°C, and oxygen saturation of 98% on room air. Her body mass index was 23.56. Bilateral visual acuity indicated no light perception. Intraocular pressure was measured at 10 mm Hg in the right eye and 12 mm Hg in the left eye, within the normal range (10–20 mm Hg). Bilateral visual field assessments revealed total superior temporal, inferior temporal, superior nasal, and inferior nasal deficiencies, suggesting ophthalmoplegia. There was bilateral diffuse periorbital edema, more pronounced on the left side, and bilateral optic atrophy observed through fundus photography.

Lung auscultation revealed clear breath sounds without wheezing, rhonchi, or rales. Cardiovascular examination showed normal S1 and S2 heart sounds without murmurs, rubs, or gallops. The skin appeared warm and dry, with no signs of erythema or rash. The abdomen was nondistended, and normal bowel sounds were present. Radial pulses and dorsalis pedis pulses were 2+ bilaterally. The patient displayed a normal range of motion with the ability to fully move all limbs and joints without any limitations. She was alert and oriented to person, place, and time, with no deficits in cranial nerve function, sensory perception,

Manush Sondhi, MD, Iman Qaiser, MD, Samina Hayat, MD, Sarwat Umer, MD, Kinza Muzaffar, MD: Louisiana State University, Shreveport.
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Address correspondence via email to Manush Sondhi, MD, at manushsondhi@gmail.com.
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or coordination. Mood, thought content, and judgment were all within normal limits.

Laboratory evaluation

A complete blood count revealed a hemoglobin level of 10.5 g/dL (reference range 10.9–14.3 g/dL), a white blood cell count of 13.06 K/μL (reference range 3.9–12.7 K/μL) with an eosinophil count of 0.4% (reference range 0%–8%), and an elevated platelet count of 543 K/μL (reference range 150–450 K/μL). Thyroid function, indicated by thyroid-stimulating hormone at 1.1 μIU/mL (0.4–4 μIU/mL), falls within the normal range. Renal function markers, including creatinine at 0.64 mg/dL (reference range 0.5–1.4 mg/dL) and a glomerular filtration rate above 60 mL/min, suggest normal kidney function. Inflammatory markers show significant elevation, with an erythrocyte sedimentation rate of 75 mm/hr (reference range 0–20 mm/hr) and a C-reactive protein level of 1.03 mg/dL (reference range 0–0.9 mg/dL).

Complement levels demonstrate normal C3 at 145 mg/dL (reference range 50–180 mg/dL) and C4 at 35 mg/dL (reference range 11–44 mg/dL), and angiotensin-converting enzyme is within the normal range at 16 U/L (reference range16–85 U/L). Autoimmune markers reveal a negative antinuclear antibody titer (<1:80), perinuclear antineutrophil cytoplasmic antibody (P-ANCA) at <1:20, and cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA) at <1:20. Glomerular basement antibody is negative. The patient's immunoglobulin levels revealed IgG1 at 246 mg/dL (reference range 382–929 mg/dL), IgG2 at 214 mg/dL (reference range 242–700 mg/dL), IgG3 at 18 mg/dL (22–176 mg/dL), and IgG4 at 81 mg/dL (4–86 mg/dL).

Urinalysis shows negative results for proteins, glucose, ketones, occult blood, red blood cells, nitrite, and leukocytes. Flow cytometry results exhibit normal immunophenotyping without a monotypic B cell population or increased blasts, suggesting no evidence of hematological malignancies. Lumbar puncture findings include normal cerebrospinal fluid glucose at 70 mg/dL (reference range 40–70 mg/dL), elevated protein at 58 mg/dL (reference range 15–40 mg/dL), and an absence of white blood cells (reference range 0–5/cu mm). Tests for neuromyelitis optica and myelin oligodendrocyte glycoprotein antibodies are negative, and the IgG index is 0.75 (reference <0.85), indicating no evidence of central nervous system inflammation.

CLINICAL COURSE

The MRI of the orbit and brain depicted extensive areas of enhancement involving the posterior aspect of the intra- and extraconal space, extraocular muscles, orbital apices, infratemporal fossae, pterygopalatine fossae, and retro maxillary fat. Bilateral enlargement of the medial and superior rectus muscles was observed, along with pachymeningeal enhancement along the base of the frontal lobes and the falx. Pansinusitis was evident, and intrinsic and perineural contrast enhancement of the intraorbital optic nerves suggested bilateral optic neuritis/perineuritis, with evolving ischemic changes in the left optic nerve (Figure 1A). A vestibular schwannoma in the right internal auditory canal remained unchanged (Figure 1B). The computed tomography (CT) of the sinuses confirmed soft-tissue density and mass-like attenuation in various orbital and maxillofacial locations. A pan CT scan showed no evidence of ground-glass opacities or mediastinal or hilar lymphadenopathy in the lungs, but it detected a solid noncalcified pleural-based nodule measuring 17 mm in the left apical region, along with a 1.5 cm solid-appearing hypodense lesion in the right kidney interpolar region (Figures 2 and 3).

The patient was initiated on a treatment regimen of isavuconazonium, micafungin, vancomycin, and meropenem because of a suspicion of infectious etiology while concurrently maintaining a low dose of oral prednisone. Continuous application of frequent lubrication and ointments in the eyes was also maintained. Subsequently, after a day of starting antibiotics, the patient underwent right endoscopic sinus surgery, septoplasty, right external ethmoidectomy, and right orbital decompression. Pathological examination of sinus mucosa, bone, right orbital fat, right periorbital fascia, and aerobic, anaerobic, fungal, and acid-fast bacilli cultures were conducted. However, all cultures yielded negative results. Pathological findings indicated mucosal inflammation with arterial wall fibrinoid damage and giant cells suggestive of granulomatosis with polyangiitis (GPA) (Figure 4).

A CT-guided biopsy of the lung nodule further revealed acute granulomatous vasculitis, supporting a systemic vasculitis process. Despite three doses of pulse steroids and cyclophosphamide, the patient did not show significant improvement. Subsequently, she was started on oral prednisone (60 mg) with sulfamethoxazole and trimethoprim for *Pneumocystis jiroveci* prophylaxis and rituximab every 6 months. Prednisone was gradually tapered off, and rituximab treatment was continued; despite this, after a six-month follow-up, vision remained unchanged, although orbital swelling had improved. Active surveillance for the mass in the right kidney is continued because it has remained stable in size. The lung mass has reduced to 9 mm and is currently under follow-up by the pulmonology department.

CASE SUMMARY

A 71-year-old Black woman presented with a history of painful right-sided vision loss four months ago, followed by left-sided vision loss a week before admission, along with symptoms of fatigue and unintended weight loss. Orbital and brain MRI revealed pansinusitis and bilateral optic neuritis. A pan CT scan identified a 17-mm solid nodule in the left apical region and a 1.5-cm solid lesion in the right kidney. Laboratory results indicated normal complements, IgG4, urinalysis, and negative antibodies, including C-ANCA and P-ANCA. The patient was initially treated with antibiotics and a low dose of oral prednisone.

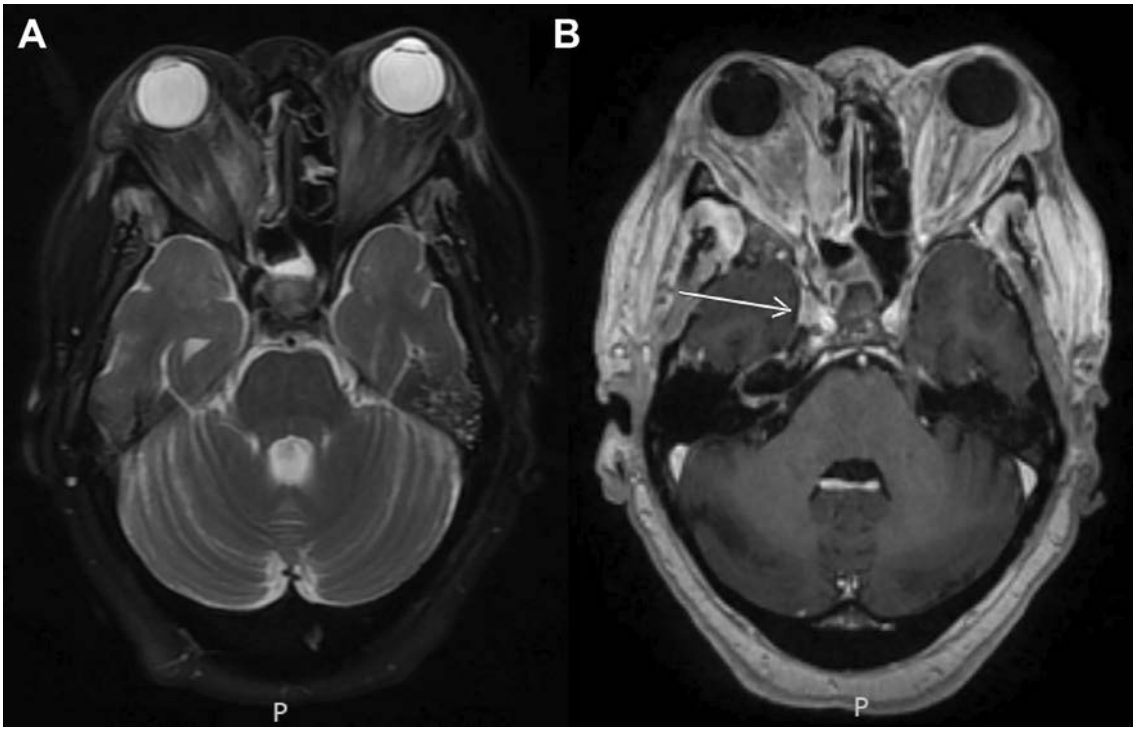

Figure 1. (A) Magnetic resonance imaging of the orbit and brain depicting extensive areas of enhancement along with the bilateral enlargement of the rectus muscles, pachymeningeal enhancement, and pansinusitis. (B) Magnetic resonance imaging of the brain showing right vestibular schwannoma (arrow).

Further, biopsy results of sinus tissues and lung nodule confirmed GPA. Despite receiving three doses of pulse steroids and cyclophosphamide, the patient did not exhibit significant improvement. Subsequently, she was prescribed oral prednisone (60 mg) and rituximab every six months. Although orbital swelling showed improvement, her vision remained unchanged.

DIFFERENTIAL DIAGNOSIS

GPA is a rare autoimmune vasculitis characterized by inflammation of small- to medium-sized blood vessels. The disease

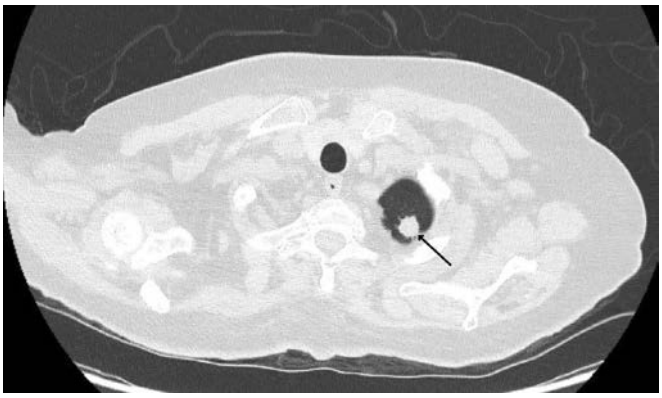

Figure 2. Computed tomography of the chest showing a solid noncalcified pleural base nodule measuring 17 mm in the left apical region (arrow).

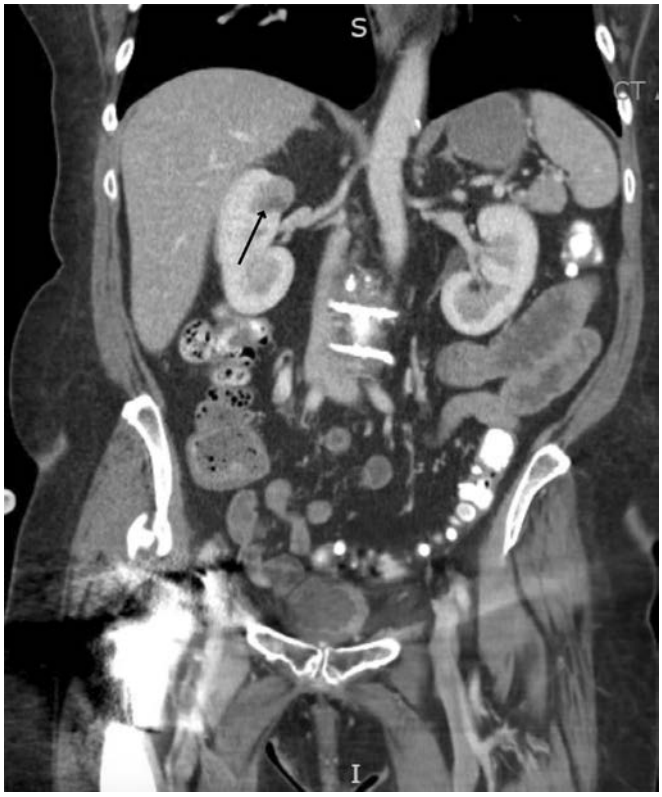

Figure 3. Computed tomography of the abdomen showing a 1.5-cm solid-appearing hypodense lesion in the right kidney interpolar region (arrow).

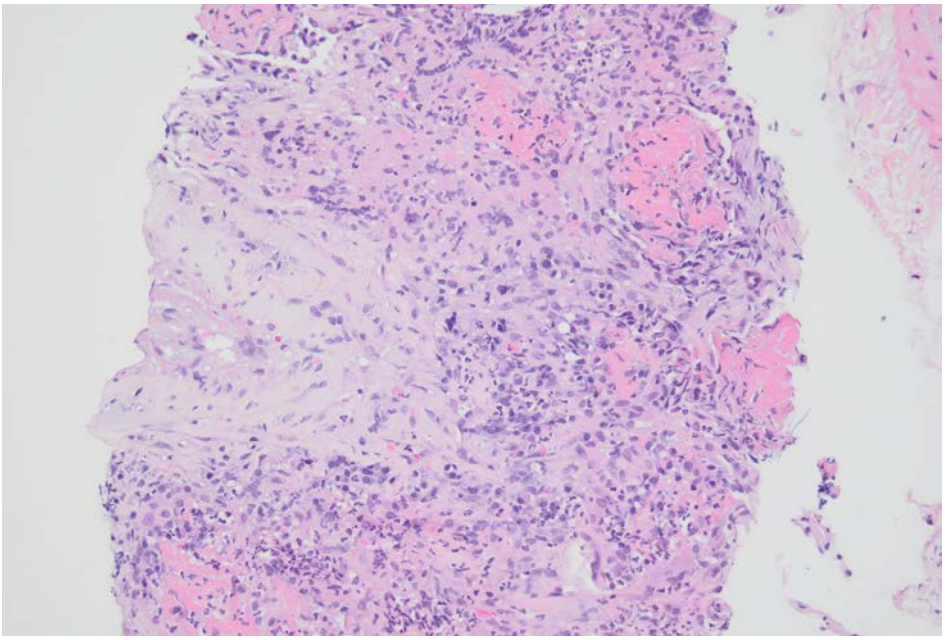

Figure 4. Right orbital and sinus region biopsy indicating mucosal inflammation with arterial wall fibrinoid damage and giant cells suggestive of granulomatosis with polyangiitis.

predominantly affects the upper and lower respiratory tract and kidneys but can involve virtually any organ system. There are several differential diagnoses to consider for orbital involvement in GPA (Table 1).

The patient meets five points for GPA according to the 2022 American College of Rheumatology/EULAR classification criteria, fulfilling required features like pulmonary nodule, granulomatous inflammation, and sinus inflammation for diagnosis, while microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) scored 0 points.[1] Granulomatous inflammation and the presence of granulomas helped exclude MPA, while the lack of eosinophilic infiltration and a normal eosinophil count indicated the absence of EGPA.

Orbital sarcoidosis and necrotizing sarcoid granulomatosis can also present with proptosis, periorbital swelling, ocular pain, and visual disturbances due to direct infiltration by sarcoid tissue. The absence of noncaseating granulomas or classic necrosis pattern favors GPA in this case.

IgG4-related disease is another important differential diagnosis that can present with periorbital swelling and proptosis. However, in this case, the biopsy did not show the characteristic features of a dense lymphoplasmacytic infiltrate, focal storiform fibrosis, or obliterative phlebitis. Additionally, the criteria for elevated serum IgG4 levels (>135 mg/dL), more than 10 IgG4+ plasma cells per high-power field, and an IgG4+/IgG+ cell ratio >40% on immunohistochemistry were not met. Inflammatory disorders like idiopathic orbital inflammation, including variants like the apical form of Tolosa-Hunt syndrome and a sclerosing form featuring chronic progressive fibrosis, pose another set of considerations. Ocular infections that resemble GPA often stem from fungal pathogens such as histoplasmosis, blastomycosis, and coccidioidomycosis, as well as from mycobacterial and bacterial agents like streptococcus. However, these were ruled out due to negative results from stains, cultures, and biopsy findings. Neoplastic conditions such as orbital lymphomas, head and neck squamous cell carcinomas, nasopharyngeal carcinoma, metastases, and schwannomas can mimic GPA, but biopsy ruled them out. Endocrine-related conditions, specifically thyroid ophthalmopathy, can manifest with orbital symptoms akin to those seen in GPA.

DISCUSSION

GPA features the presence of serum proteinase 3 (PR3)- or myeloperoxidase (MPO)-ANCA, which serves as a crucial serological marker. Studies emphasize the diagnostic importance of PR3-ANCA testing, demonstrating a sensitivity and specificity of 79.8% to 86.6% and 96.8% to 98.3%, respectively.[2] The ANCA titer may also serve as an indicator of disease activity or relapse after treatment, though its role in managing ANCA-associated vasculitis is still under investigation.

In the context of GPA, approximately 82% to 94% of patients display positive ANCA.[3] PR3-ANCA is the predominant subtype in 65% to 75% of cases, whereas 20% to 30% of patients with clinical GPA present with alternative ANCA.[4] Although most cases of ANCA-associated vasculitis (AAV) are identified by positive ANCA titers, there exists a less common subset of patients with ANCA-negative AAV. It is essential to recognize that a negative

Table 1. Differential diagnosis of orbital involvement in GPA*

Differential diagnosis	Diagnostic modalities	Key differentiating features	Prevalence
GPA	PR3-ANCA positivity in 65%–75% cases whereas MPO-ANCA in 20%–30% cases, imaging (CT, MRI), biopsy	Upper and lower respiratory tract and kidney involvement, pauci-immune necrotizing granulomatous inflammation	Approximately 3 cases per 100,000[10]
MPA	MPO-ANCA positivity in 50%–75% cases, imaging (CT, MRI), biopsy	Renal and pulmonary involvement sparing the upper airways, pauci-immune necrotizing nongranulomatous inflammation	Approximately 1.5 cases per 100,000[11]
EGPA	Eosinophil count, MPO-ANCA positivity in around 50% of cases, imaging (CT, MRI), biopsy	Eosinophilia (>1.5 × 10^9/L), asthma, sensorimotor peripheral neuropathy, mononeuritis multiplex, pulmonary and cardiac involvement, pauci-immune necrotizing granulomatous inflammation with eosinophilic infiltration	Approximately 18 cases per million[12]
IgG4-RD	Elevated serum IgG4 levels (>135 mg/dL), imaging (CT, MRI), biopsy	Dense lymphoplasmacytic infiltrate, storiform fibrosis with more than 10 IgG4+ plasma cells per high-power field, and an IgG4+/IgG+ cell ratio >40% on biopsy	Approximately 1–10 per 100,000[13]
Orbital sarcoidosis	Chest x-ray, elevated serum ACE levels, imaging (CT, MRI), biopsy	Multisystem involvement, noncaseating granulomas on biopsy	8.1 per 100,000[14]
Necrotizing sarcoid granulomatosis	Imaging (CT, MRI), biopsy	Pulmonary and/or systemic sarcoid features, epithelioid granulomas with necrosis foci on biopsy	Very rare
IOI	Imaging (CT, MRI), biopsy	Presents without systemic disease, chronic inflammatory infiltrate, composed of small mature lymphocytes, plasma cells, neutrophils, eosinophils, and occasionally histiocytes and macrophages on biopsy	Unknown, relatively rare
Neoplastic conditions (eg, orbital lymphomas)	Imaging (CT, MRI, PET), biopsy	Monoclonal cell population, distinct tumor morphology on biopsy	Variable, depending on type
Ocular infections (eg, fungal, mycobacterial)	Cultures, serological tests, PCR, imaging (CT, MRI), biopsy	Positive cultures or PCR for specific pathogens, history of exposure	Variable, depending on region
Thyroid ophthalmopathy	Thyroid function tests, TSH receptor antibody, imaging (CT, MRI)	Hyperthyroidism symptoms, extraocular muscle enlargement without tendon involvement	Approximately 19 per 100,000[15]

* ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgG4-RD, IgG4-related disease; IOI, idiopathic orbital inflammation; MPA, Microscopic polyangiitis; MPO, myeloperoxidase; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography; PR3, proteinase 3; TSH, thyroid-stimulating hormone.

ANCA assay does not definitively rule out GPA, because at least 10% of patients are ANCA-negative.[5] In these patients, the diagnosis often relies on clinicopathologic features rather than ANCA positivity, particularly in those with limited or nonrenal manifestations of AAV.[6] ANCA status may change over time, with patients initially testing negative and eventually testing positive, particularly as the disease becomes more generalized.

ANCA-negative AAV may involve undetectable ANCA antibodies, either because of a low levels in the blood or their presence solely in tissues. Alternatively, there could be ANCA antibodies with undiscovered specificities, targeting unique antigenic targets or posttranslational modifications. Also, pathological mechanisms unrelated to traditional antibody-mediated pathways, such as cell-mediated immunity or alternative autoantibodies, might contribute to the vascular inflammation observed in this condition. This underscores the complexity of the serological landscape and emphasizes the need for a comprehensive understanding of ANCA-related dynamics in the context of GPA.

Regarding clinical manifestations, ocular symptoms may serve as initial indicators of GPA in approximately 15% of patients.[7] Proptosis is the most common presentation of orbital GPA, often resulting from contiguous disease in the nasal and

paranasal sinuses, illustrating the interconnected nature of manifestations in this vasculitic disorder. Additionally, scleritis is a significant and early presentation of GPA, occurring in roughly 50% of patients. Episcleritis typically follows a milder course and tends to resolve independently, although topical glucocorticoids may expedite symptom relief. Approximately 20% to 50% of patients with orbital manifestations may experience significant visual impairment.[8]

Treatment for GPA varies depending on disease severity and patient condition, with regimens tailored accordingly. Initial assessment focuses on determining if GPA poses a threat to life or organs, guiding treatment decisions for first occurrences, refractory cases, relapses, or maintenance therapy. Azathioprine has become a prominent medication for managing mild disease, replacing methotrexate, and rituximab is now commonly used as the first-line treatment for severe disease instead of cyclophosphamide. In cases of ocular GPA, rituximab shows promise in inducing remission but requires close monitoring for symptom exacerbation.[9]

This case presented significant challenges because of the absence of ANCA antibodies, which might have been attributed to any of the previously mentioned reasons. Although the vestibular schwannoma was unrelated to the acute vision loss and systemic symptoms, and the right kidney lesion appeared atypical for GPA because it did not resemble hypodensity from ischemia potentially linked to vasculitis, the presence of these incidentalomas complicated the diagnostic process. The patient was initially suspected to have GCA and was promptly started on steroids. This treatment could have potentially aided in managing GPA and possibly delayed the onset of left eye blindness. However, the steroids were discontinued prematurely because of a lack of vision improvement and other suspected causes. The delayed restart of steroids and the gradual resolution of orbital pseudotumors might have exacerbated the outcome. Such cases necessitated intensive and aggressive measures from the outset. In summary, the interplay between serological markers, dynamic ANCA status, and diverse clinical presentations highlights the complexity of diagnosing and managing GPA, demanding a nuanced and multidisciplinary collaboration in clinical practice.

FINAL DIAGNOSIS

Seronegative granulomatosis with polyangiitis

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 Sondhi 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/Helsinki Declaration requirements.

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BRIEF REPORT

Patient Perceptions of Rheumatoid Arthritis Blood Work: A Cross-Sectional Survey in the ArthritisPower Registry

William B. Nowell,[1] Shilpa Venkatachalam,[1] Kelly Gavigan,[1] Michael D. George,[2] Johanna B. Withers,[3] Laura Stradford,[1] Esteban Rivera,[1] and Jeffrey R. Curtis[4]

Objective. To examine how patients with rheumatoid arthritis (RA) perceive RA-related laboratory testing and the potential utility of a blood test to predict treatment response to a new RA medication.

Methods. ArthritisPower members with RA were invited to participate in a cross-sectional survey on reasons for laboratory testing plus a choice-based conjoint analysis exercise to determine how patients value different attributes of a biomarker-based test to predict treatment response.

Results. Most patients perceived that their doctors ordered laboratory tests to check for active inflammation (85.9%) or assess medication side effects (81.2%). The most commonly ordered blood tests used to monitor RA were complete blood counts, liver function tests, and those measuring C-reactive protein (CRP) and erythrocyte sedimentation rate. Patients felt CRP was most helpful in understanding their disease activity. Most worried their current RA medication would eventually stop working (91.4%) and they would waste time trying a new RA medication that may not work for them (81.7%). For patients who would require a future change in RA treatment, a majority (89.2%) reported that they would be very/extremely interested in a blood test that could help predict whether such new medication would be effective. Highly accurate test results (improving the chance RA medication will work from 50% to 85–95%) were more important to patients than low out-of-pocket cost (<$20) or minimal wait time (<7 days).

Conclusions. Patients consider RA-related blood work important for monitoring of inflammation and medication side effects. They worry about treatment effectiveness and would undergo testing to accurately predict treatment response.

INTRODUCTION

Rheumatoid arthritis (RA), a debilitating, multisystem disease, is the most common autoimmune inflammatory arthritis, affecting 1.3 million US residents (1). Treatments include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) (2). American College of Rheumatology guidelines recommend a treat-to-target approach in RA, re-evaluating disease activity regularly, and changing DMARDs for patients who have not achieved low disease activity or remission (2). This approach is strongly recommended in those who are b/tsDMARD-naive and conditionally recommended in those with inadequate response to b/tsDMARDs (2). As drug and therapy development has progressed in recent years, treatment and management of patients with RA have improved, and there are now many treatment options available with different mechanisms of action. Decision making is important for treatment planning, and it includes physician clinical recommendations incorporating evidence from patient laboratory results, patient comorbidities, patient preferences, and other factors such as treatment side effect profile, tolerability, availability, and access. Unfortunately, the current paradigm of RA care consists of a somewhat arbitrary initial treatment selection, often motivated by insurance considerations rather than clinical or medical factors, with empiric switching thereafter, a "guess and adjust" approach.

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[1]William B. Nowell, PhD, MSW, Shilpa Venkatachalam, PhD, MPH, Kelly Gavigan, MPH, Laura Stradford, MPH, Esteban Rivera, MS: Global Healthy Living Foundation, Upper Nyack, New York; [2]Michael D. George, MD, MSCE: University of Pennsylvania, Philadelphia; [3]Johanna B. Withers, PhD: Scipher Medicine Corporation, Waltham, Massachusetts; [4]Jeffrey R. Curtis, MD, MS, MPH: University of Alabama at Birmingham and the Foundation for Advancing Science, Technology, Education and Research, Birmingham.

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Address correspondence via email to William B. Nowell, PhD, MSW, at bnowell@ghlf.org.

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SIGNIFICANCE & INNOVATIONS

- Identifying patients' perspectives on rheumatoid arthritis (RA)–related laboratory testing and the utility of a blood test to predict treatment response may help to facilitate better and targeted patient education, which in turn may help shared decision making for RA treatment.
- Most patients perceived that their doctor ordered laboratory testing for the following reasons: to check for active inflammation, assess side effects of medications, check for the presence of RA-related autoantibodies, whether medication is working, if vitamin levels are good, or if their RA is progressing.
- A test predicting RA treatment response is appealing to patients because they are concerned that their current medication may eventually stop working and worry that they would waste time trying RA treatments that would not work for them.
- In a conjoint analysis exercise to clarify patients' preferences and values regarding the attributes of a test predicting RA medication treatment response, accuracy (at least 85% or better) was more important to patients than either out-of-pocket cost or wait time to receive the results.

Laboratory tests are an important part of diagnosis, clinical assessment, and monitoring in RA. Unlike laboratory testing in other diseases, such as serum glucose in diabetes and hemoglobin levels in anemia, the various clinical, laboratory, and imaging findings are evaluated together for monitoring of DMARDs, inflammation, and disease progression in RA. Limited information is available for patients with RA regarding their interactions with or perceptions of laboratory data for their treatment decisions (3–5). Recent research has shown that patients with RA often find that laboratory reports do not provide enough information to help them interpret results, which is why there is a desire among patients for more in-depth explanations of results, particularly to contextualize laboratory results (6). Although patients typically look to their doctor to provide context for laboratory testing, there is no standard approach for sharing and discussing laboratory data with patients. To make up for the insufficiency of communication, most patients turn to online resources to supplement laboratory test report information, demonstrating a need for improved communication, which could in turn improve shared decision making for patients with RA in their diagnosis and treatment paths (6). Shared decision making describes a process by which physicians and patients work together to make treatment choices based on individual patient preferences and appropriate clinical evidence (7,8).

Because of the importance of patient comprehension of laboratory testing for shared decision making in RA, coupled with a lack of published studies on patients' perspectives on RA laboratory results, the objective of this study was to understand perspectives of patients on their RA-related blood work. We also examined whether a test that could predict treatment effectiveness of a new RA medication, one of the commercially available blood tests used for patients with RA, would be desirable to patients, and if so, what such a test's optimal attributes would be from their perspective.

MATERIALS AND METHODS

This study was conducted in the ArthritisPower research registry (Advarra Institutional Review Board [IRB] protocol no. 00026788), a patient-powered research network collaboration between the nonprofit Global Healthy Living Foundation (GHLF) and rheumatology researchers at the University of Alabama at Birmingham (9). Launched in 2015, ArthritisPower comprises members with a rheumatic and musculoskeletal disease diagnosis who have provided consent to participate in research studies.

A 27-item cross-sectional survey including a conjoint analysis was developed with input from patients, rheumatologists, researchers, and patient advocates. The survey was divided into three sections, which included questions related to reasons for laboratory testing (Part A, "Your Blood Work"), a choice-based conjoint analysis exercise to determine how patients value different attributes of a blood test that might predict future response to a new RA medication (Part B, "Predicting Your Response / Non-Response to Therapy"), and a patient self-report of demographic and clinical characteristics (Part C, "Demographic Questions"). For the choice-based conjoint, 48 different hypothetical test characteristics ("profiles") were created based on different combinations of three test attributes (accuracy, wait time, and cost), each with three to four levels (Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25187). The survey was designed to take approximately 15 minutes to complete.

Members of the ArthritisPower registry with a self-reported physician diagnosis of RA were invited via email to participate in the online survey after passing screening questions related to age, diagnosis, and current/past medication regimen. Participants were eligible for this survey if they were residents of the United States and its territories, age 19 years and above (21 years and above for Puerto Rico residents), had a self-reported physician diagnosis of RA, had ever taken a DMARD (bDMARD, csDMARD, or tsDMARD) for RA, and had access to a computer or smartphone. There was no cost to participants for participating in this study, and no compensation was offered. This ArthritisPower study was granted exemption by Advarra IRB (Pro00063028).

Analysis. Descriptive statistics were used to summarize data. Part-worth utility was calculated from the choice-based conjoint to determine relative value for each level of the three conjoint attributes (10). Preferred levels (relative utility) of each

attribute were calculated based on the average preference scores for each level and scaled so that the sum of all positive values equaled the absolute value of the sum of all negative values for each attribute. Higher scores indicate strongly preferred levels in comparison to lower-scored levels; scores have meaning only relative to other scores. Utility scores were also calculated to determine the weight an attribute carries in the decision-making process, indicating the importance of each attribute relative only to the other attributes included in the choice-based conjoint. Scores sum to 100% (10). Statistical tests used throughout corresponded to the data type and distribution. Significance was determined at the 5% level ($P < 0.05$), with 95% confidence intervals used to express the uncertainty in the data. SAS version 9.4 software (SAS Institute) was used for all statistical analyses.

RESULTS

During May and June 2022, 11,712 invitation emails with survey links were sent to eligible participants in ArthritisPower. Emails were opened by 38.5% (4,557 of 11,712) of those eligible, and the survey link was clicked by 12.8% (582 of 4,557) of those who opened the email. A total of 531 patients (91.2% of those who clicked on the survey link) started the survey, of whom 405 (76.3%) met the inclusion criteria and completed the survey. Among all 405 patients with RA who completed the survey, 86.7% were female, and 89.9% were White, with a mean ± SD age of 57.9 ± 11.6 years and mean ± SD years since RA diagnosis of 13.4 ± 11.4 (Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25187). Patients took the following medications (not mutually exclusive): csDMARD (75.1%), bDMARD (53.6%), and tsDMARD (17.8%) (Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25187). The reasons that most patients perceived for their rheumatologist ordering laboratory testing were to check for active inflammation (85.9%) or to assess side effects of medications (81.2%). Other reasons included checking for RA-related autoantibodies (68.4%) or assessing whether medication is working (59.3%), vitamin levels are good (56.3%), or their RA is progressing (54.6%).

Patients reported that their rheumatologists most often ordered complete blood count, liver function, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) tests to monitor RA, but they had less certainty about what information their physicians use when considering changing medications, with "None" or "Don't know" being the most common response (48.7%) (Table 1). Patients (48.6%) felt that CRP was most helpful to their understanding their disease activity (Table 1).

Most patients were somewhat or very concerned that their current RA medication would stop working for them in the future (91.4%) or that they would waste time trying an RA medication that may not work for them (81.7%). If they had to change RA treatments in the future, a majority (89.2%) would be very or extremely interested in taking a blood test that could help predict whether the medication their doctor suggests would work well for them.

In the choice-based conjoint, patients valued a highly accurate test more than both cost and wait time. Figure 1 shows the relative importance of features (attributes) in terms of measure of influence scores, which summed to 99.9 rather than 100 because of rounding, where the importance of a feature is calculated by the impact that attribute had on patients' choice of preferred test profile between the two options presented in each question. The accuracy of a laboratory test result to predict the future efficacy of a new RA medication had an influence score of 52.4, exerting >60% the amount of influence that either cost (32.3) or wait time (15.3) had on patients' choices (Figure 1). Figure 2 shows preferred levels (relative utility) of each attribute. Specifically, patients were most likely to select a test that was highly accurate (improving the chance that the next RA medication will work well from 50% to 85–95%), low

Table 1. Patient perceptions of utility of RA-related blood work, n = 405*

	Used by physicians to monitor RA, n (%)†	Used by physicians when considering changing medications, n (%)‡	Useful for patients to understand disease activity, n (%)§
CBC	322 (79.5)¶	170 (42.0)	128 (31.6)
Liver function tests, kidney tests, and/or complete metabolic panel	312 (77.0)	174 (43.0)	140 (34.6)
CRP	269 (66.4)	162 (40.0)	197 (48.6)¶
ESR	238 (58.8)	181 (37.3)	174 (43.0)
Vitamin levels (eg, vitamin D, iron, calcium)	118 (29.1)	66 (16.3)	63 (15.6)
None/I don't know	42 (10.3)	197 (48.7)¶	123 (30.4)
Vectra DA (multi-biomarker disease activity)	25 (6.2)	35 (8.6)	57 (14.1)

* CBC = complete blood count; CRP = C-reactive protein; DA = disease activity; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis.
† Patients were asked to select which test(s) their rheumatologist orders for routine RA monitoring.
‡ Patients were asked to select which test(s) their rheumatologist orders when considering changing RA medications.
§ Patients were asked to select which test(s) they consider most useful to understand their RA disease activity.
¶ Marked values are top selections for each column.

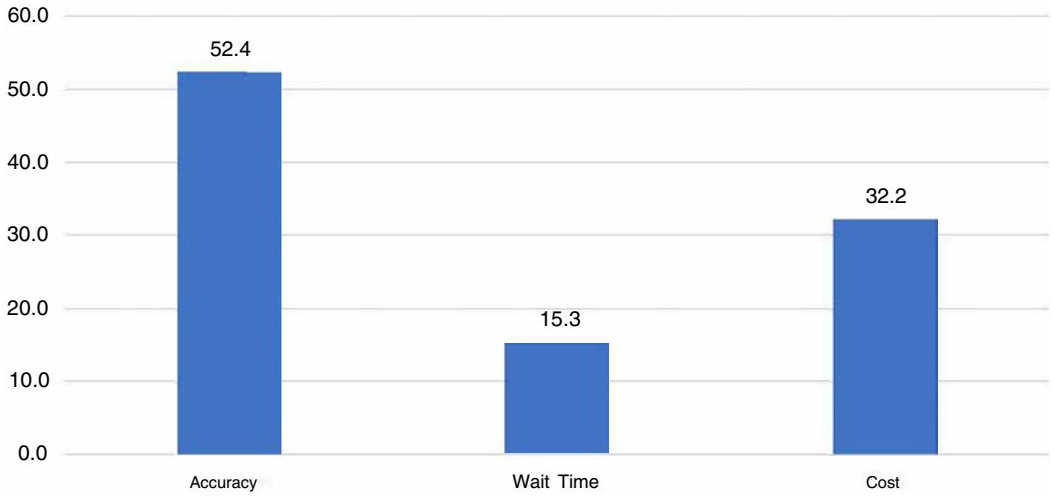

Figure 1. Measure of influence score for each attribute of a patient blood test to predict whether an RA medication will work well for them (n = 405). The measure of influence score is the measurement of influence an attribute has when the respondent is choosing their preferred bundle. The higher the score, the more weight it carries in the decision-making process. Scores add up to 99.9 rather than 100 due to rounding, in this case.

cost (≤$20), and fast (≤7 days for results). Patient preference was not very sensitive to wait time, although patients had some concerns about test results taking 2 weeks or more to return. For out-of-pocket cost, patients preferred tests that were low cost (≤$20) and were particularly concerned once their out-of-pocket laboratory test costs reached $75–125.

DISCUSSION

In this study, we found that most patients considered RA-related blood work to be important for their physician's ability to monitor active inflammation and RA medication side effects. Among various blood tests, CRP was the most helpful to patients themselves in understanding their disease activity. A decisive majority of patients worried that their current RA medication would stop working in the future and that they could waste time trying a new medication that may not effectively manage their RA. For a blood test predicting treatment response to a new RA medication, patients valued accuracy over cost or wait time, and approximately 9 in 10 patients surveyed indicated that they would be very or extremely interested in undergoing testing that could help predict whether the RA

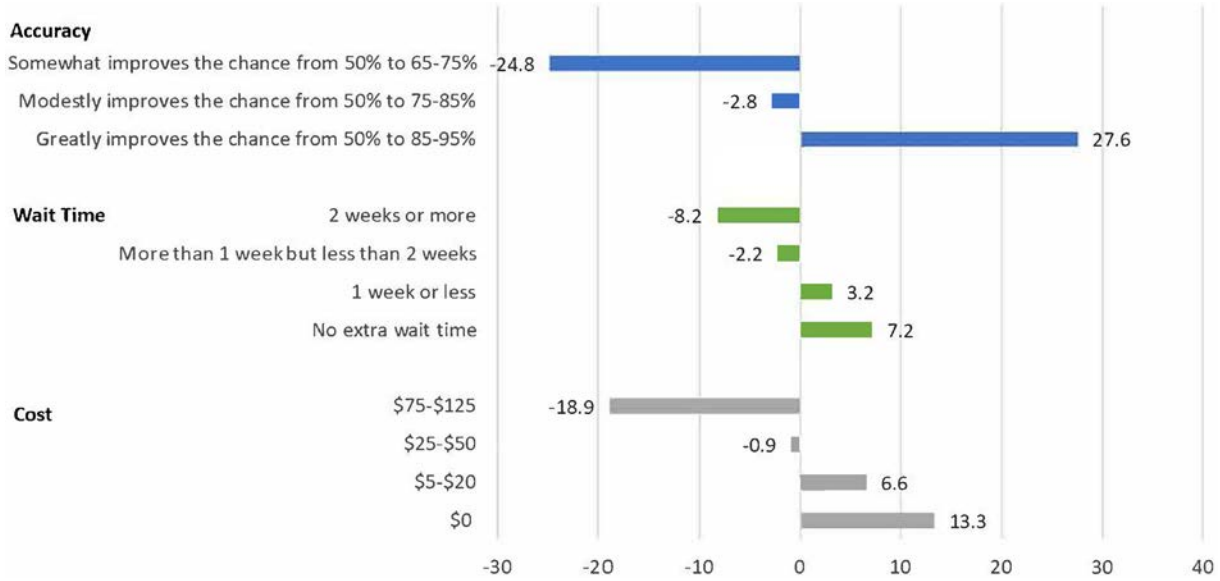

Figure 2. Relative utility value for each attribute of a patient blood test to predict whether an RA medication will work well for them (n = 405). The relative utility value is the measure of preference for each level of an attribute. The greater a level's relative utility value is, the more it enhances a bundle by being present. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25187/abstract.

medication their doctor suggests will work well for them in the future.

As in other conditions, such as diabetes, patients with RA in our sample knew that laboratory tests are useful in monitoring their condition over time and to indicate whether their disease is well-controlled. Moreover, patients with RA were aware that blood work is helpful in tracking potential medication side effects and checking for abnormalities in vitamin or liver enzyme levels. Such information can be used by patients and rheumatologists for shared decision making. In other health conditions, patients have similarly expressed a desire to understand their laboratory work and blood test results in order to participate in the decision-making process. For patients with prostate cancer, the Prolaris cell cycle progression test is used as a prognostic test of the aggressiveness of their tumor and assists in treatment decisions by relaying valuable information to patients (11); other diagnostic information such as the Gleason score and stage of cancer were valued by the patients, but they expressed problems with the way that biopsy and prostate specific antigen test results were conveyed to them by their physician (12). Patients further conveyed a desire for more personalized laboratory test result discussions and to comprehend the rationale for specific tests in order to evaluate and diagnose their prostate cancer (13). Such information allowed patients to engage in meaningful conversations about treatment options with their health care providers and encouraged medical adherence (13). Similarly, diabetes patients who knew their HbA1c values, a marker of disease control, reported a better understanding and assessment of their glycemic control than patients who did not (14). In short, it is not uncommon for patients to seek a deeper understanding of their laboratory results, the satisfaction of which may facilitate treatment decision making and adherence.

Patient understanding of laboratory results is particularly important in a disease like RA, which is often considered "invisible" to patients who experience it. Because the purpose and meaning of blood work and their results may not always be clear to patients, patient advocacy organizations and nurses or other providers can play an important role in developing and distributing patient education materials. Once developed, leaflets or booklets, videos, podcasts, or brief messages with simple explanations of RA blood tests can be disseminated to patients via patient organizations or provider websites, emails, social media, provider portals, rheumatology- or health-specific applications, or on paper during in-person encounters at clinics. Two such examples to promote a general understanding of RA blood work among patients include "A Patient's Guide to Understanding Rheumatoid Arthritis Testing & Monitoring – CRP, ESR, Vectra, and More: Learn about the main RA blood tests and what they can — and can't — reveal about your health," (15) from CreakyJoints of the US not-for-profit GHLF, and "Blood Matters: A guide to the blood tests used in managing rheumatoid arthritis and adult juvenile idiopathic arthritis," (16) developed by the United Kingdom's National Rheumatoid Arthritis Society.

A more thorough understanding of their own laboratory results may further enhance patients' comprehension of and confidence in prescribed treatment by making disease activity, and the positive impact of treatment, quantifiable ("visible") to patients. This could be done via personalized, contextualized, direct-to-patient reports coupled with in-person or telehealth discussions with providers to elaborate on laboratory results and respond to patient questions. US health law provides patients with the right to directly receive their health data, but unaided interpretation of raw laboratory results may prove confusing to many patients. Therefore, results should be formatted in alternative ways for patient viewing and comprehension.

Testing that can promote precision medicine is a major need in rheumatology for identifying what medications a patient is most likely to benefit from in the future, as opposed to using a trial-and-error strategy. The results of this study demonstrate that most patients express concern that their newly prescribed RA therapy may not work, which could waste time and unnecessarily prolong their symptoms while seeking a therapy that does. For patients, such wasted time is not inconsequential because it may permit disease progression, unresolved symptoms, and lower quality of life, burdening patients with RA and the health care system with mental health concerns (anxiety, depression) and higher costs (17). Thus, an accurate test predicting response/nonresponse to treatment was appealing. We found that patients highly valued the accuracy of such a test, with less enthusiasm shown for tests that provided more modest prediction of treatment response (ie, with accuracy less than 85%).

Several limitations of this study should be noted. The thresholds for different levels of accuracy of a laboratory test to predict the future efficacy of a new RA medication were somewhat arbitrary, and patient preference regarding accuracy as an attribute related to cost and wait time may be dependent upon the way this question was posed. However, we believe that the options of the attribute levels that we examined represent a range of options that may be feasible to achieve with a biomarker-based diagnostic test (18). Patients were recruited within an existing, voluntary research registry for RA and other conditions. As a result, there may be a lack of generalizability from these results among patients who completed our survey. For example, individuals who are more engaged in their care may be more likely to respond to a survey invitation regarding RA blood work, and their responses may not reflect the opinions of all patients with RA. Patients' clinical characteristics were based on participants' self-reported diagnosis, treatment, and experiences. Further, we asked patients to provide information about their preference for the use of a hypothetical test to predict treatment response rather than to report their actual experience having already undergone such testing. We also recognize that the value of predictive biomarker-based tests for RA that are more invasive (eg, requiring synovial biopsy) might be perceived differently by patients. Nevertheless, findings from this study help to fill an important gap in our understanding of patients' perceptions of

their RA-related laboratory test results and how such perceptions may be related to their treatment decision making.

Future research in this area should focus on a more ethnoculturally and globally representative group, specifically on patients with lower health literacy, to examine whether patient perceptions and understanding of RA blood work differ across ethnocultural groups and geographies, and whether such differences have an impact on disease self-management, medication adherence, and shared decision making. Future research should also examine the real-world experience of patients immediately following predictive laboratory testing, as well as several months out from new treatment initiation as guided by the predictive test, to determine whether patients notice an improvement in disease activity/symptoms, feel more confident about their new medication, and have improved adherence to treatment in relation to the experience of having received biomarker-based laboratory testing.

Patients consider RA-related blood work to be important for monitoring for active inflammation and medication side effects, but many are unsure which tests their physician uses when making treatment decisions. Deeper patient understanding of blood work is desired, and personalized patient laboratory results reports accompanied by discussions with a provider may improve treatment decision making and adherence. Given patients' fear that their current RA medication may stop working and that they may waste time trying a medication that may not work for them, a test predicting treatment response is appealing. In order to improve outcomes for patients with RA, further understanding of patient concerns regarding blood work and its role in treatment decision making and adherence is needed.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Nowell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Nowell, Venkatachalam, Gavigan, George, Withers, Stradford, Rivera, Curtis.

Acquisition of data. Nowell, Venkatachalam, Gavigan.

Analysis and interpretation of data. Nowell, Venkatachalam, Gavigan, George, Rivera, Curtis.

ROLE OF THE STUDY SPONSOR

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Association Between Rheumatoid Arthritis Disease Activity and Periodontitis Defined by Tooth Loss: Longitudinal and Cross-Sectional Data From Two Observational Studies

Katinka Albrecht,[1] Paola de Pablo,[2] Thorsten Eidner,[3] Guido Hoese,[4] Siegfried Wassenberg,[5] Angela Zink,[1] and Johanna Callhoff[6]

Objective. To analyze the effect of tooth loss/periodontitis on disease activity in early and established rheumatoid arthritis (RA).

Methods. Participants of the Course And Prognosis of Early Arthritis (CAPEA) early arthritis cohort reported their number of teeth at baseline. The number of teeth had been validated as a predictor of periodontitis. Clinical end points, including disease activity score (Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [ESR]), swollen joint count (SJC), ESR, and C-reactive protein level were collected at baseline, 3, 6, 12, 18, and 24 months. We used linear mixed regression models to estimate the association between tooth loss and clinical end points over time in early arthritis. For established RA, we analyzed cross-sectional data from the German National Database (NDB). All models accounted for age, sex, smoking, seropositivity, education level, and disease duration (only NDB).

Results. Among 1,124 CAPEA participants with early arthritis, those with higher tooth loss were older, more often male, smokers, and seropositive, and they had higher disease activity and inflammation markers at baseline. Tooth loss was associated with higher disease activity and ESR values over time. Inflammatory markers decreased comparably across tooth loss categories. Glucocorticoid use was higher among those with more tooth loss, whereas dose reduction was similar across tooth loss categories. Among 7,179 NDB participants with longstanding RA, disease activity and inflammation markers but not SJC were significantly higher in patients with more tooth loss.

Conclusion. Although we observed an association between tooth loss and disease activity scores and inflammation markers in early and established RA, longitudinal results suggest that tooth loss does not hamper treatment response.

INTRODUCTION

Rheumatoid arthritis (RA) and chronic periodontitis are common chronic inflammatory diseases linked by clinical and pathobiologic similarities (1). In patients with RA, tooth loss and periodontitis are highly prevalent (1–5). A population-based study resulted in a more than 2-fold increased rate of complete tooth loss in patients with RA compared with patients without RA after adjusting for confounders (3). Tooth loss, periodontitis, and arthritis have common underlying proinflammatory mechanisms, triggering inflammatory processes in the periodontium as well as in the synovium. Chronic periodontitis leads to the loss of the periodontal ligament and alveolar bone, which ultimately causes tooth loss. Several characteristics are found in the pathogenesis of RA

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[1]Katinka Albrecht, MD, Angela Zink, PhD: German Rheumatism Research Centre, Programme Area of Epidemiology and Health Care Research, Berlin, Germany; [2]Paola de Pablo, MD: University of Birmingham, Institute of Inflammation and Ageing, Research into Inflammatory Arthritis Center Versus Arthritis and MRC-Versus Arthritis Centre für Muskuloskeletal Ageing Research, Birmingham, West Midlands, UK; [3]Thorsten Eidner, MD: Jena University Hospital, Jena, Germany; [4]Guido Hoese, MD: Rheumatology practice, Stadthagen, Germany; [5]Siegfried Wassenberg, MD: Rheumatology Centre, Ratingen, Germany; [6]Johanna Callhoff, PhD: German Rheumatism Research Centre, Charité-Universitätsmedizin Berlin, Institute for Social Medicine, Berlin, Germany.

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Address correspondence via email to Katinka Albrecht, MD, at albrecht@drfz.de.

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SIGNIFICANCE & INNOVATIONS

- Tooth loss and/or periodontitis are frequent in patients with rheumatoid arthritis (RA).
- Increased disease activity scores and inflammation markers are associated with periodontitis as defined by tooth loss in both early and established RA.
- Response to therapy is not hampered by periodontitis as defined by tooth loss.
- Periodontitis/tooth loss has a clinical impact on RA and should be considered in the evaluation of RA disease activity.

as well as in periodontitis, including the presence of cytokine profiles, citrullinated proteins, peptide epitopes, and an association with HLA–DRB1, interleukin 1ß, and tumor necrosis factor-α polymorphisms (3). Various theories related to common risk factors, genetic links, bacterial citrullination, and cytokine imbalance exist to explain a biological link between RA and periodontitis (6). In terms of clinical relevance, results of cross-sectional studies suggest a relationship between the presence of tooth loss or periodontitis and disease activity in patients with RA (7,8). Tooth loss and the severity of periodontal disease were found to be associated with the presence and levels of anti–citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) (9,10). There is still insufficient evidence whether and how periodontitis influences the course of arthritis and response to therapy (11,12). Preliminary data from our study have shown a higher need for glucocorticoids in patients with RA and tooth loss. Using tooth loss as an indicator of periodontitis, we hypothesized that tooth loss is a predictor of higher inflammatory activity in early arthritis. The purpose of our study was to investigate the influence of the number of teeth on RA disease activity and individual disease activity markers within the first 2 years after symptom onset in patients with early arthritis enrolled in the Course And Prognosis of Early Arthritis (CAPEA) cohort study (13). To investigate this association in patients with established RA, we also used cross-sectional data from the German National Database (NDB) in which high numbers of real-life patients with RA are recorded annually (14).

PATIENTS AND METHODS

Data sources. We used longitudinal data from the CAPEA early arthritis cohort to analyze the effect of the number of teeth on disease activity markers within the first 2 years of early arthritis. CAPEA is a prospective, multicenter, longitudinal, observational study, conducted between 2010 and 2013 (13). Eligible patients had inflammatory arthritis for less than 6 months, confirmed by a physician at enrollment. They were consecutively enrolled in rheumatology clinics and practices in Germany and observed for 2 years in order to investigate the prognostic value of early symptoms for the development of persistent disease. Study visits were performed at 0, 3, 6, 12, 18, and 24 months. Ethical approval for the CAPEA study was obtained from the Ethics Committee of the Charité University Medicine, Berlin, in May 2009 (EA1/091/09).

Cross-sectional data of patients with established RA were derived from the NDB of the German Collaborative arthritis

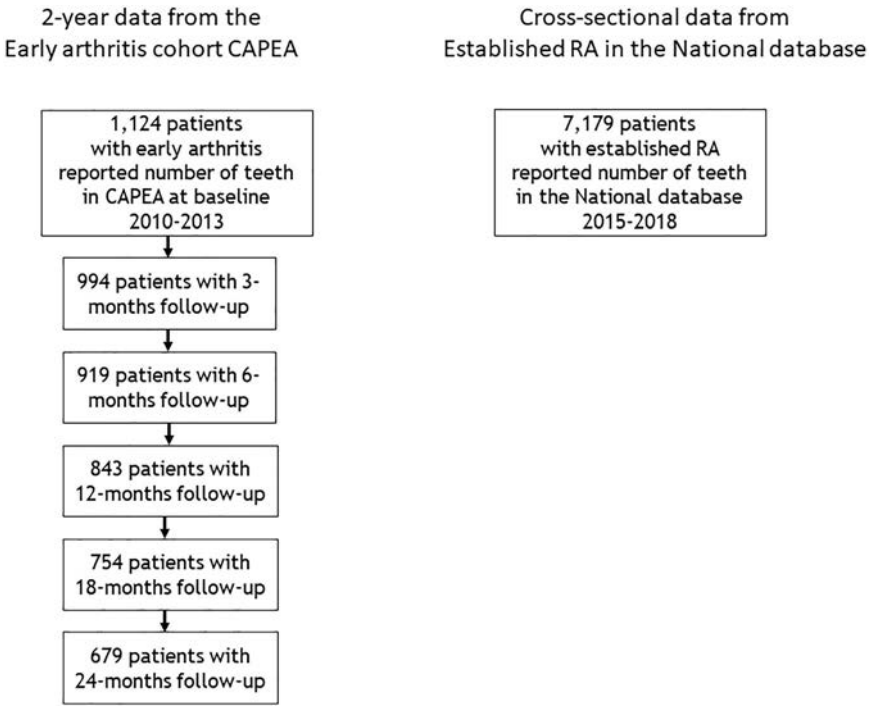

Figure 1. Flow chart. CAPEA = Course And Prognosis of Early Arthritis; RA = rheumatoid arthritis.

Table 1. Early arthritis cohort (CAPEA) baseline characteristics*

Characteristics	Number of teeth present				Total
	0	1–19	20–27	All 28	
N	89	315	452	268	1,124
Female, %†	57	65	64	69	65
Age, mean ± SD years†	69 ± 11	64 ± 10	54 ± 12	45 ± 15	56 ± 15
ESR, mm, mean ± SD‡	42 ± 28	38 ± 25	28 ± 20	24 ± 21	31 ± 23
Median (IQR)	32 (40)	32 (38)	23 (28)	18 (19)	24 (32)
CRP (mg/liter), mean ± SD§	25 ± 30	24 ± 41	15 ± 22	15 ± 33	19 ± 32
Median (IQR)	13 (26)	12 (25)	7 (15)	5 (11)	8 (17)
TJC, mean ± SD¶	9.4 ± 6.6	9.6 ± 6.8	7.6 ± 6.4	7.7 ± 6.7	8.3 ± 6.7
SJC, mean ± SD#	6.1 ± 4.9	6.9 ± 5.6	5.6 ± 4.9	5.2 ± 5.0	5.9 ± 5.2
DAS28-ESR, mean ± SD**	5.5 ± 1.2	5.2 ± 1.2	4.7 ± 1.2	4.5 ± 1.3	4.9 ± 1.3
Global Health, 0–10, mean ± SD†	5.7 ± 2.4	5.6 ± 2.3	5.1 ± 2.2	5.1 ± 2.3	5.3 ± 2.3
BMI, kg/m^2, mean ± SD††	28 ± 5	28 ± 5	27 ± 5	26 ± 5	27 ± 5
RF positive, %†	63	53	52	54	54
ACPA positive, %‡‡	45	36	39	41	39
GCs, %†	75	77	71	67	72
csDMARDs, %§§	56	60	54	60	58
Education, %¶¶					
≤8 years	80	58	35	21	42
9–10 years	16	30	43	46	38
11–13 years	4	12	22	33	20
Smoking (ever), %##	73	64	61	56	61

* N = 4 patients had initial biologic DMARD therapy. ACPA = anti-citrullinated peptide antibodies; BMI = body mass index; CAPEA = Course And Prognosis of Early Arthritis; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drug (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine A); DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; GC = glucocorticoid; IQR = interquartile range; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.
† Data are from 1,124 patients.
‡ Data are from 1,074 patients.
§ Data are from 1,069 patients.
¶ Data are from 1,121 patients.
# Data are from 1,120 patients.
** Data are from 983 patients.
†† Data are from 1,114 patients.
‡‡ Data are from 1,123 patients.
§§ Data are from 1,118 patients.
¶¶ Data are from 1,020 patients.
Data are from 1,102 patients.

centers. The NDB is a long-term monitoring database for German rheumatology practice. Participating rheumatologists from private practices and tertiary outpatient clinics consecutively include unselected patients with inflammatory rheumatic diseases. The database provides annually updated information on patients with inflammatory rheumatic diseases under rheumatologic care, covering data on laboratory test results, clinical and patient-reported outcomes, and antirheumatic therapy (14). Patients who had documented their tooth count between 2015 and 2018 were included, selecting the most recent data if several entries were available. Ethical approval for the NDB was obtained from the Ethics Committee of the Charité University Medicine, Berlin, in February 2007 (EA1/196/06), which was updated in May 2019. Both research projects were conducted in agreement with the Declaration of Helsinki.

Definition of periodontitis. We had previously developed a patient-reported questionnaire to assess periodontitis in patients with early arthritis, validated by radiographs and blinded dentists' assessment within CAPEA (15). A 6-item score turned out to be suitable for investigating periodontitis in RA with moderate diagnostic properties. However, missing teeth challenge the validity of self-reported periodontitis, especially in the case of increased occurrence as in RA (16). In CAPEA, 8% of the patients were edentulous and could not provide additional information on the periodontitis questionnaire. The periodontitis questionnaire was completed by a subset of patients (n = 353). During the validation process, we found that the number of teeth alone was a good predictor of periodontitis. We therefore used the number of teeth as a surrogate for periodontitis, as previously done by Coburn et al (16). The number of teeth has a further advantage because it can easily be included in additional data collections. As a result, we could use data from the NDB for a comparative sensitivity analysis.

Data assessment. Study participants reported the number of teeth at baseline in CAPEA and at the annual visit in the NDB,

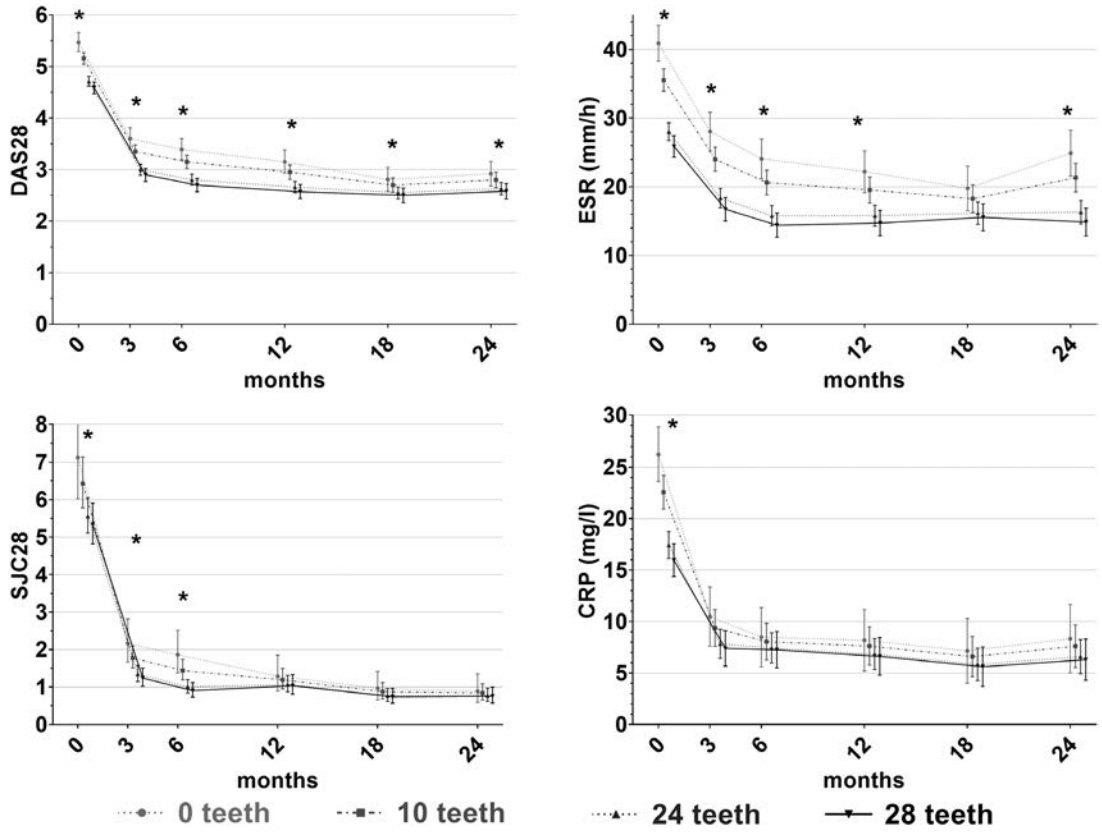

Figure 2. Disease activity and inflammatory markers during 2 year follow-up, stratified by number of teeth. CAPEA results from linear mixed models for DAS28, ESR, and CRP and from generalized linear models with negative binomial distribution for SJC28 adjusted for age, sex, smoking, RF, ACPA, and education level. Bars show 95% confidence intervals. * = $P < 0.05$ for the effect of number of teeth at this time point. Number of teeth was entered as a continuous variable in the models. For illustrative purposes, we show the least square means for selected number of teeth at all time points. ACPA = anti-citrullinated peptide antibodies; CAPEA = Course And Prognosis of Early Arthritis; CRP = C-reactive protein; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; SJC28 = swollen joint count for 28 joints.

based on the following questionnaire item: "How many of your own teeth do you have (including crowned teeth)," and a number between 0 to 28 was requested. For the NDB data analyses, the first recorded number of teeth that was available for a patient was used.

Baseline characteristics reported in both databases included age, sex, disease duration, smoking (no/current/ever), education (≤8/9–10/11–13 years of school), body mass index (in mg/kg^2), and the presence of RF and ACPA. Both were assessed and reported by the rheumatologists.

In both databases, rheumatologists reported disease activity markers at each visit, including erythrocyte sedimentation rate (ESR in mm/hour), C-reactive protein (CRP in mg/liter) level, the number of tender (TJC) and swollen joints based on 28 joints (SJC28), patient-reported global health (from 0–10, 10 being the worst rating), and the Disease Activity Score in 28 joints using the ESR (DAS28-ESR). Antirheumatic therapy, including conventional synthetic and biologic disease-modifying antirheumatic drugs (cs/bDMARDs) and glucocorticoid (GC) use, were reported at each visit (yes/no), with the daily prednisolone equivalent dose in mg/day.

Statistical analysis. Baseline data are reported as categories of the number of teeth (0, 1–19, 20–27, 28), based on Kim et al (17). The number of available data are reported for each parameter. Missing values from the NDB were replaced by multiple imputation using a fully conditional sampling method with 20 imputations.

For the CAPEA study, we used linear mixed models to assess the influence of the number of teeth at each study visit (0, 3, 6, 12, 18, and 24 months) on disease activity (DAS28) and inflammation markers (ESR and CRP). A generalized linear model with negative binomial distribution was used to assess the influence of number of teeth on swollen joint counts (SJC28), because this distribution models count data. The percentage of patients with GC use was estimated using a generalized linear mixed model, and the mean dosage of patients who were taking GCs was estimated with a linear mixed model. All models were adjusted for age, sex, RF positivity, smoking (ever vs. never) and education level, defined as years in education. The confounders were selected by clinical relevance as reported previously (3,8,16). The exposure, number of teeth, was entered as a

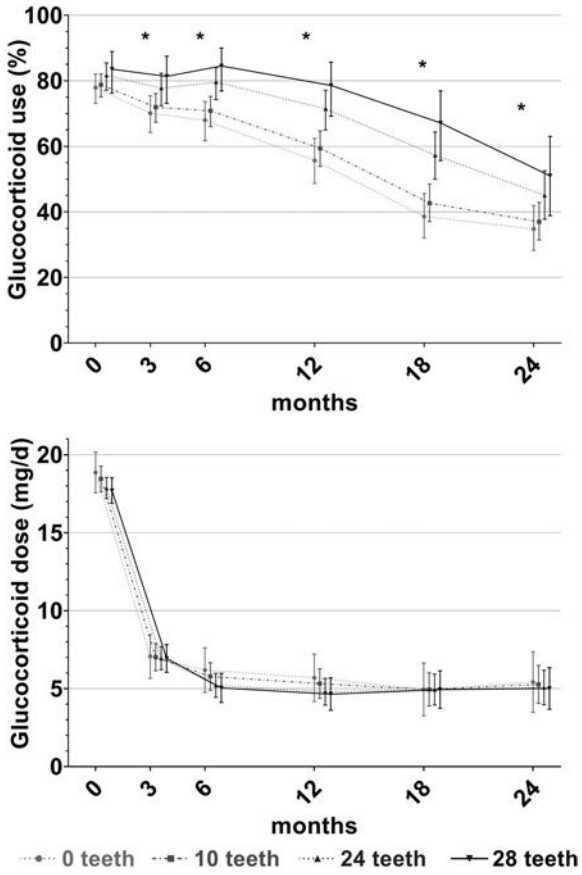

Figure 3. Glucocorticoid use during 2-year follow-up, stratified by number of teeth. CAPEA results from generalized linear mixed model and binomial distribution for the proportion of patients with glucocorticoid therapy and from a linear mixed model adjusted for age, sex, smoking, RF, and education level. Bars show 95% confidence intervals. * = $P < 0.05$ for the effect of number of teeth at this time point. Number of teeth was entered as a continuous variable in the models. For illustrative purposes, we show the least square means for selected number of teeth at all time points. CAPEA = Course And Prognosis of Early Arthritis; RF = rheumatoid factor.

continuous variable in all models. For visualization purposes, we chose to show least square means for selected number of teeth (0, 10, 24, and all 28). The influence of tooth loss on the outcomes was tested for each time point, and *P* less than 0.05 was considered statistically significant.

For the NDB data, linear regression models were used to adjust DAS28, ESR, and CRP level for age, sex, disease duration, RF, smoking, and education level. A generalized linear model with negative binomial distribution was used to adjust SJC28 for the same variables. We used box plots to illustrate the association between the number of teeth and DAS28, ESR, CRP, and SJC at the first time point the number of teeth was collected in this sample. Additionally, we used linear mixed models (for DAS28, CRP, and ESR) and a generalized linear mixed model with negetive binomial distribution for SJC to assess if tooth loss had an influence on these parameters over the course of up to 3 years. These models were adjusted for age, sex, presence of RF, presence of ACPA, smoking (ever vs. never), disease duration, and education level, defined as years in education.

The data sets analyzed in the current study are not publicly available because we respect our patients' right to privacy. Consent for publication of the data set was not obtained at the start of recruitment to the studies.

RESULTS

Early arthritis cohort (CAPEA) baseline characteristics. Among 1,124 CAPEA participants included, the mean disease duration was 13 ± 7 weeks, 65% were female, and the mean age was 56 years. Complete 24-month follow-up data were available for 679 patients (Figure 1).

RA diagnosis was confirmed in 91% of participants during follow-up via a clinical diagnosis by a rheumatologist. American College of Rheumatology (ACR)/European League Against Rheumatism 2010 criteria were fulfilled by 74% and ACR 1987 criteria by 57%. At baseline, of the 1,124 participants, 24% had all 28 teeth present, 40% had 20–27 teeth, 28% had 1–19 teeth, and 8% were edentulous. Those with higher tooth loss were older, more often male, more frequently smokers, and more often seropositive, and they had higher disease activity (DAS28-ESR) and inflammation marker (both ESR and CRP) values at baseline. In the edentulous group, 80% had less than 8 years of school education, whereas only 21% in the group with all teeth present had this level of education. Participants with early RA and complete dentition had the highest level of education. Tooth loss was associated with more GCs use (Table 1).

Disease activity and inflammatory markers during 2-year follow up. The number of teeth had a statistically significant influence on disease activity (DAS28) at every study visit during follow-up. There was a significant association between the number of teeth and ESR at every visit, except for the 18-month visit, and with CRP level at baseline. The influence on CRP level and SJC disappeared over time. There was a significant association between the number of teeth and SJC in the first 6 months of follow-up and no difference in the joint counts between groups afterward (Figure 2). The coefficients for the influence of tooth loss on the respective outcomes are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24799.

GC use during 2-year follow-up. Tooth loss was significantly associated with a higher percentage of GC use at all study visits after baseline, based on the generalized linear mixed model analysis. The mean adjusted starting doses were 18 mg/day in patients with all teeth and 19 mg/day in patients with no teeth. In general, GC doses were reduced to a mean dose of 5 mg/day in the first 3 months for all patients, independent of their number

of teeth. GC dose was not associated with tooth loss (Figure 3). The coefficients for the influence of tooth loss on GC use and GC dose are shown in Supplementary Tables 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24799.

NDB patient characteristics. Among 7,179 NDB participants included, mean disease duration was 13 years, 74% were female, and the mean age was 62 years. Of those, 21% had all 28 teeth, 41% had 20–27 teeth, 27% had 1–19 teeth, and 11% were edentulous. Patients with higher tooth loss were older, more often male, more frequently smokers, and more often seropositive, and they had higher ESR, CRP level, DAS28, TJC, SJC, and patient global assessments. In the edentulous group, 62% had up to 8 years of school education, whereas only 19% in the group with all teeth had this level of education. Participants with established RA and complete dentition had the highest level of education. Edentulous patients received GCs and csDMARDs more often, whereas bDMARDs were used less frequently (Table 2).

Association between tooth loss and disease activity markers in established RA. After adjusting for age, sex, disease duration, RF, smoking, and education level with generalized linear models, disease activity score and inflammatory markers were linearly associated with tooth loss categories (DAS28 no teeth 2.7, all teeth 2.4; ESR no teeth 23 mm/hour, all teeth 17 mm/hour). For all outcomes considered in Figure 4, there was a statistically significant association of tooth loss with the

Table 2. NDB patient characteristics*

	Number of teeth present				
	0	1–19	20–27	All 28	Total
N	793	1,922	2,928	1,536	7,179
Female, %†	69	72	74	80	74
Age, mean ± SD years†	73 ± 9	67 ± 12	62 ± 12	52 ± 16	62 ± 15
Disease duration, mean ± SD years†	15.2 ± 12	14.4 ± 11	12.8 ± 10	11.0 ± 9	13.1 ± 11
Median (IQR)	13.0 (16.2)	12.0 (15.3)	10.3 (14.4)	8.4 (11.7)	10.6 (14.4)
ESR, mm/hour, mean ± SD‡	26 ± 20	21 ± 17	18 ± 16	16 ± 14	19 ± 17
Median (IQR)	20 (25)	16 (20)	14 (18)	11 (14)	14 (19)
CRP, mg/liter, mean ± SD§	10 ± 17	8 ± 12	7 ± 21	7 ± 18	8 ± 18
Median (IQR)	5 (7)	4 (6)	4 (5)	3 (4)	4 (5)
TJC, mean ± SD¶	2.3 ± 3.9	2.2 ± 3.9	1.8 ± 3.6	1.5 ± 3.2	1.9 ± 3.7
SJC, mean ± SD#	1.4 ± 2.5	1.4 ± 2.8	1.1 ± 2.4	1.0 ± 2.4	1.2 ± 2.5
DAS28-ESR, mean ± SD**	3.5 ± 1.3	3.2 ± 1.2	3.0 ± 1.2	2.7 ± 1.2	3.0 ± 1.2
Patient global, 0–10, mean ± SD††	4.7 ± 2.3	4.3 ± 2.2	4.1 ± 2.2	3.5 ± 2.2	4.1 ± 2.3
BMI, kg/m^2, mean ± SD‡‡	27 ± 5	27 ± 5	27 ± 5	25 ± 5	26 ± 5
RF positive, %§§	61	60	56	54	57
ACPA positive, %¶¶	59	61	53	55	56
GCs, %##	49	47	40	33	41
csDMARDs, %***	72	70	70	67	70
bDMARDs, %†††	23	28	27	28	27
Education, %‡‡‡					
≤8 years	62	41	32	19	35
9–10 years	25	37	38	34	36
11–13 years	13	22	30	47	30
Smoking (ever), %§§§	61	58	56	46	55

* ACPA = anti-citrullinated peptide antibodies; bDMARDs = biologic disease-modifying antirheumatic drugs (TNF inhibitors, abatacept, rituximab, tocilizumab); BMI = body mass index; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine); DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; GC = glucocorticoid; IQR = interquartile range; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.
† Data are from 7,179 patients.
‡ Data are from 5,885 patients.
§ Data are from 6,845 patients.
¶ Data are from 6,881 patients.
# Data are from 6,880 patients.
** Data are from 5,718 patients.
†† Data are from 7,015 patients.
‡‡ Data are from 6,147 patients.
§§ Data are from 7,017 patients.
¶¶ Data are from 4,489 patients.
Data are from 7,133 patients.
*** Data are from 5,239 patients.
††† Data are from 7,134 patients.
‡‡‡ Data are from 6,340 patients.
§§§ Data are from 6,732 patients.

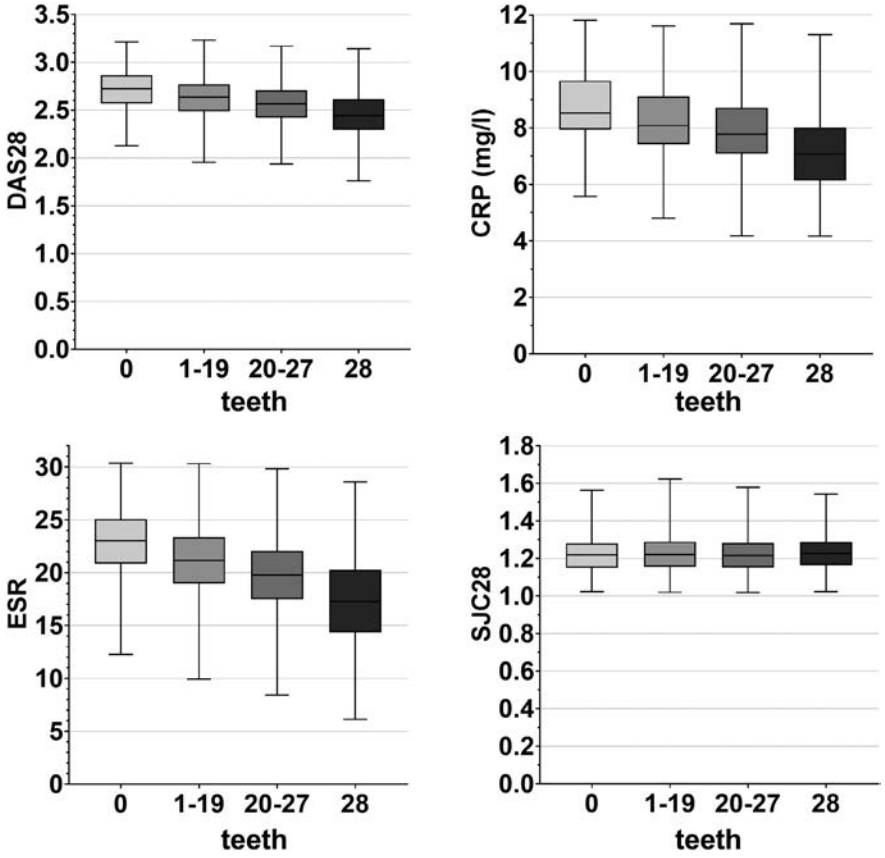

Figure 4. Association between number of teeth and disease activity and inflammatory markers in established RA. National database predicted values from generalized linear models, adjusted for age, sex, disease duration, RF, ACPA, smoking, and education level. Boxes show 25th percentile, median, and 75th percentile. Whiskers range from minimum to maximum. ACPA = anti-citrullinated peptide antibodies; CRP = C-reactive protein; DAS28 = disease activity score of 28 joints; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC28 = swollen joint count for 28 joints.

outcome. But there was no clinically meaningful association between groups of tooth loss and SJC (Figure 4).

DISCUSSION

To investigate the clinical relevance of a relationship between periodontitis and RA, we analyzed the impact of tooth loss on inflammatory markers and disease activity scores using data of two separate national cohorts, representing both participants with early and established RA. Our results show a significant association between tooth loss severity and increased inflammatory markers, in particular ESR, as well as higher disease activity scores over time. However, there was no relationship between tooth loss and joint swelling. Longitudinal data indicate successful reduction of disease activity, independent of tooth loss.

In early arthritis, tooth loss was differentially associated with various inflammatory markers. Whereas ESR values were significantly higher in patients with fewer teeth and remained higher throughout the 2-year course of treatment, a difference in CRP values was only present before the start of treatment. Increased ESR values do not necessarily reflect solely RA activity. The composite activity score DAS28-ESR reflected the association with ESR. Patients with fewer teeth had slightly more swollen joints in the first year, but there was no difference thereafter because disease activity levels were similar between groups, likely because of response to therapy. NDB data confirmed the association with elevated ESR and CRP levels and tooth loss categories, but no clinically relevant difference in the number of swollen joints in participants with long-standing RA, who have an average disease duration of more than 10 years. Ultimately, none of the differences are clinically important.

The relationship found between tooth loss and inflammatory markers or disease activity indices is in line with data from a recent case-control study by Rodríguez et al that confirmed a significant association between severe periodontitis, assessed by periodontal examination, and RA disease activity, as assessed by different disease activity indices (8). In a recent review, Manzo and Kechida suggested that severe periodontitis should always be treated before evaluating RA disease activity to avoid unnecessary therapeutic modifications (18). We partly agree on this point, because

the more frequent use of GC in patients with tooth loss, which was present in both cohorts, may have been caused not only by more active disease but also extra-articular inflammation. Further to a successful reduction of disease activity, GC tapering was achieved in almost all patients regardless of their number of teeth, so that we found no evidence of a worse response to therapy or refractory disease activity in relation to tooth loss. The lack of association between tooth loss and joint swelling also fits with the findings of Rodríguez et al in that functional disability, as measured by the Health Assessment Questionnaire, was not associated to presence of periodontitis in RA (8).

There have been discussions and studies on whether nonsurgical periodontitis therapy leads to an improvement in RA outcomes (19,20). Results of clinical studies suggest a beneficial effect of periodontitis therapy on RA disease activity (1). A meta-analysis of five clinical trials showed significant improvement in ESR values only. All studies had small case numbers with a study duration of no longer than 6 months (21). The effect shown on ESR matches our results suggesting that inflammatory activity from periodontitis is reflected in increased ESR but does not necessarily lead to increased activity in the joint. In a recent small randomized controlled trial (n = 22), periodontal treatment resulted in significant improvements of periodontal health but had no effects on the DAS28-ESR within 3 months (22).

Tachibana et al investigated the response to biologic therapy using fluorodeoxyglucose-positron emission tomography/computed tomography for periodontitis assessment (11). They found a negative correlation between periodontitis activity and DAS28-CRP reduction within 6 months, but correlations were not significant when adjusted for smoking and ACPA values.

A relative limitation of our study is that we used the patient-reported number of teeth as an indicator for periodontitis, and the periodontal/tooth status was not assessed by a dentist. However, self-reported number of teeth has been shown to be a valid indicator of the true number of teeth present on dental examination (23). Furthermore, we performed dental assessments and x-rays in a subset of CAPEA participants. When validating the periodontitis score, the number of remaining teeth was the item correlating best with the different assessments of periodontitis. Using age and the patient-reported number of remaining teeth resulted in a sensitivity of 86% to detect any periodontitis and a specificity of 78% to detect severe periodontitis (15). Major strengths of our study are that it includes data from two large national patient samples including both early as well as longstanding RA. Because of similar data collection strategies in both cohorts, important risk factors contributing both to periodontitis and RA, such as age, male sex, smoking, RF, and education level, were entered as confounders in all models. The CAPEA data were collected 10 years ago, and treatment options have improved since then. This should be taken into account in the interpretation.

To conclude, our data suggest a clear independent association between increased inflammation markers and periodontitis as defined by tooth loss but not with swollen joint counts as a measure of synovitis, in both patients with early arthritis and longstanding established RA over time. The patient-reported tooth count may be a helpful tool to consider periodontitis when evaluating RA disease activity and raised inflammatory markers. Longitudinal data suggest that periodontitis/tooth loss does not hamper response to therapy because reduction of disease activity and tapering of GCs were successful regardless of the number of teeth.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Callhoff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Increased Risk of Rheumatoid Arthritis in Patients With Asthma: A Genetic Association Study Using Two-Sample Mendelian Randomization Analysis

Jiyuan Yan,[1] Yi Zhang,[2] Xiaofei Zhang,[1] Ge Chen,[1] Daiqing Wei,[1] Ke Duan,[3] Zheng Li,[1] Lin Peng,[1] Jialin Liu,[4] Zhong Li,[1] and Yanshi Liu[1]

Objective. Observational studies have explored the association between asthma and some types of arthritis, including rheumatoid arthritis and osteoarthritis, but the results are largely contradictory. We aimed to investigate the causal effects of asthma on arthritis, including osteoarthritis, rheumatoid arthritis, gout, and ankylosing spondylitis.

Methods. Two-sample Mendelian randomization (MR) analysis was used to investigate the causal effects of asthma on each arthritis. The genetic instruments for asthma were obtained from a large genome-wide association study of asthma. The inverse-variance weighted (IVW) method was used as the main analysis of MR. Bonferroni-adjusted *P* value threshold was used to account for multiple comparisons.

Results. MR-IVW analysis suggested that adult-onset asthma (AOA) was associated with increased risk of rheumatoid arthritis. The odds ratio for rheumatoid arthritis associated with AOA and childhood-onset asthma (COA) were 1.018 (95% confidence interval [95% CI], 1.011–1.025; $P < 0.001$) and 1.006 (95% CI 1.001–1.012; $P = 0.046$), respectively. For osteoarthritis, gout, or ankylosing spondylitis, all the MR analyses showed no significant causal effects of AOA or COA on them. We also performed a reverse MR analysis to explore the causal effects of rheumatoid on all asthma, allergic asthma, or nonallergic asthma and found no significant causal effects on them.

Conclusion. Genetically predicted AOA predisposes patients to an increased risk of rheumatoid arthritis but has no causal effects on osteoarthritis, gout, and ankylosing spondylitis. The result of COA on rheumatoid arthritis is suggestive of potential causal relationship but needs to be confirmed in further studies.

INTRODUCTION

Asthma is the second most common chronic respiratory disease worldwide, with a prevalence rate of 3.57% of the population and a mortality rate of 6.48 per 100,000 people (1). According to the age of onset, asthma is defined as childhood-onset asthma (COA) and adult-onset asthma (AOA), which have distinct pathogenesis and clinical outcomes (2). Chronic airway inflammation, airway hyperresponsiveness, and variable airflow obstruction are typical features of asthma. Because of its high prevalence and the associated health burden, it represents a major threat to people's well-being and, in serve cases, greatly reduces the quality of life.

In addition to respiratory manifestations, asthma has also been reported to increase the risk of many other complications, including endocrine disorders and cardiovascular diseases (3,4). Some studies have suggested an association between asthma and arthritis, including osteoarthritis (5) and rheumatoid arthritis (6). Asthma also shares common genetic variants with ankylosing spondylitis (7,8). However, existing studies about the association between asthma and arthritis have yielded controversial results. For example, a population-based study found that asthma is significantly associated with the risk of diabetes mellitus and coronary heart disease but not with rheumatoid arthritis (9). This negative finding was further supported by another recently

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[1]Jiyuan Yan, MD, Xiaofei Zhang, MM, Ge Chen, MD, Daiqing Wei, MD, Zheng Li, MD, Lin Peng, MD, Zhong Li, MD, Yanshi Liu, MD: The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China; [2]Yi Zhang, MM: Southwest Medical University, Luzhou, Sichuan, China; [3]Ke Duan, MD: Sichuan Provincial Laboratory of Orthopaedic Engineering, Luzhou, Sichuan, China; [4]Jialin Liu, MD: The Affiliated Stomatology Hospital of Southwest Medical University, Luzhou, Sichuan, China.

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Address correspondence via email to Zhong Li, MD, at 545890312@qq.com, and Yanshi Liu, MD, at ortho-liuyanshi@swmu.edu.cn.

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SIGNIFICANCE & INNOVATIONS

- This is the first Mendelian randomization study to reveal a causal effect of adult-onset asthma (AOA), but not childhood-onset asthma, on rheumatoid arthritis.
- People with AOA are more likely to have rheumatoid arthritis than those without, whereas rheumatoid arthritis does not increase the risk of developing asthma.
- Both childhood-onset asthma and AOA have no causal effects on osteoarthritis, gout, and ankylosing spondylitis.

published cohort study (10). Most of these results are based on observational studies, which are susceptible to confounding factors. In addition to rheumatoid arthritis, there is still a lack of data to elucidate the association between asthma and the other three types of arthritis. Because rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis are all associated with substantial disabilities and health burden in the elderly, more data are needed to clarify the risk of arthritis associated with asthma.

In this study, we used a two-sample Mendelian randomization (MR) analysis to determine the causal effects of asthma on four major types of arthritis (eg, rheumatoid arthritis, osteoarthritis, gout, and ankylosing spondylitis). We divided asthma into COA and AOA and separately analyzed their effects on the risk of the four types of arthritis. We found that genetically predicted AOA is associated with a significantly higher risk of rheumatoid arthritis, but rheumatoid arthritis reversely has no effect on asthma. The findings of the current study provide a genetic understanding for asthma and its associated complications for future basic and clinical research.

MATERIALS AND METHODS

Study design. This is a two-sample MR analysis evaluating the causal effects of asthma on the incidence of osteoarthritis, rheumatoid arthritis, gout, and ankylosing spondylitis. The MR analysis uses genetic variants that are significantly associated with the exposure (eg, asthma) as proxy indicators to evaluate the causal effects on outcomes (11). Such an analysis can greatly reduce bias from potential confounders because the alleles are randomly assigned at insemination and will be not altered by environment factors during life.

Exposure, outcome, and data source. In this study, we analyzed the causal effects of asthma on osteoarthritis, rheumatoid arthritis, gout, and ankylosing spondylitis. Asthma was considered as the exposure, whereas the four types of arthritis were the outcomes. Clinically, asthma is divided into two: COA and AOA. The former is mostly an allergic disease and is less likely to persist into adulthood (12), whereas the latter is more likely to be caused by immunological and inflammation-related disorders (13). In the MR analysis, we used COA-specific single nucleotide polymorphisms (SNPs) and AOA-specific SNPs to separately explore their effects on the four types of arthritis. The SNPs were obtained from two large genome-wide association studies (GWAS) of asthma from the UK Biobank (14,15). The SNPs in the two GWAS studies were used in a previous study to reveal the causal effects of asthma on gastrointestinal disorders (16). The outcome datasets were obtained from GWAS by the European Bioinformatics Institute Consortium on rheumatoid arthritis (ebi-a-GCST90013534) (17) and osteoarthritis (ebi-a-GCST005814); or by the FinnGen Consortium on gout (finn-b-GOUT_STRICT), or on ankylosing spondylitis (finn-b-M13_ANKYLOSPON_STRICT). The characteristics of the exposure and outcome GWAS, as well as the number of employed SNPs and their F-statistic range, are described in Table 1. In addition, we also performed an MR analysis of rheumatoid arthritis on asthma. In this analysis, the SNPs used as instrumental variables for rheumatoid arthritis were obtained from a published large GWAS (18). The outcome datasets for all asthma (finn-b-J10_ASTHMA), allergic asthma (finn-b-ALLERG_ASTHMA), or nonallergic asthma (finn-b-ASTHMA_NONALLERG) were obtained from the recently released GWAS on different types of asthma by the FinnGen Consortium.

Selection of SNPs. To ensure the association with COA and AOA, we used SNPs that reached a GWAS significance threshold ($P < 5 \times 10^{-8}$) as the instrumental variables. We calculated the F-statistic ($F = \beta^2/SE^2$) for each instrumental SNP and excluded SNPs with an F-statistic less than 10 to preclude bias from week instruments (19). Then, we introduced the significant SNPs into the linkage disequilibrium test by setting the clumping r^2 cutoff to 0.001, and those SNPs showing linkage disequilibrium were excluded. When harmonizing the asthma and arthritis data sets, palindromic SNPs with intermediate allele frequencies were also excluded. A fundamental assumption of the MR analysis is that the causal effects of the genetic variables on the outcome are due to their association with the exposure and not via other potential causal pathways. This assumption may be violated by SNPs that have potentially confounding pathway—an effect called pleiotropy. Considering this, we used the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to detect outlier SNPs (20) and further removed them. The final SNPs used as instrumental variables for COA and AOA are presented in Supplementary Tables 1–8, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193, whereas the SNPs for rheumatoid arthritis were presented in Supplementary Table 9–11, at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193.

Statistical analysis. An ideal condition for the MR assumption is that the SNPs employed as instrumental variables have no heterogeneity and pleiotropy. The presence of substantial heterogeneity among SNPs will cast doubt on the assumption that all variants used as instrumental variables are valid and will

Table 1. General description on the instrumental SNPs of the exposures and the outcome GWAS dataset of the four arthritis outcomes*

Exposure	Number of instrumental SNPs for exposure	F-statistic range of instrumental SNPs	Outcome arthritis	Number of SNPs in the outcome GWAS	Cases in the outcome GWAS	Control in the outcome GWAS
Adult-onset asthma	25	29.69–85.71	Rheumatoid arthritis	13,108,512	14,361	43,923
Adult-onset asthma	28	28.25–120.85	Osteoarthritis	15,845,511	10,083	40,425
Adult-onset asthma	26	28.25–120.85	Ankylosing spondylitis	16,380,466	599	217,431
Adult-onset asthma	26	28.25–120.85	Gout	16,380,466	1,699	216,239
Child-onset asthma	43	29.5–263.22	Rheumatoid arthritis	13,108,512	14,361	43,923
	63	29.5–486.46	Osteoarthritis	15,845,511	10,083	40,425
	54	29.5–486.46	Ankylosing spondylitis	16,380,466	599	217,431
	54	29.5–486.46	Gout	16,380,466	1,699	216,239

* GWAS = genome wide association study; SNP = single nucleotide polymorphism.

affect the robustness of the MR results (21). We used Cochran's Q statistic to assess heterogeneity and the MR-Egger intercept test to evaluate pleiotropy (21). Using this method, the presence of pleiotropy was determined if an intercept term in the test was significantly different from zero (21).

The main MR analysis was performed using the inverse-variance weighted (IVW) methods. IVW is the most efficient MR analysis with the highest statistical power (22). It can be performed using a fixed-effect model or random-effect model. We used random-effect IVW because it can address the issue of heterogeneity among SNPs (23). However, the results of IVW with a random-effect model will be biased if the SNPs have horizontal pleiotropy. In such cases, we used the MR-Egger regression as a sensitivity analysis, because it can account for the presence of pleiotropy. Finally, we also used the weighted median approach as another sensitive analysis, which is more robust to invalid instrumental variables by allowing up to 50% of the SNPs to be invalid (24).

For the interpretation of MR results, the IVW was the preferred method if no pleiotropy existed (22). The MR-Egger regression has a low statistical power, and the results of this method were only considered when pleiotropy among SNPs could not be avoided. The results of the weighted median approach were used to further support the main IVW analysis. Because the causal effects of AOA or COA were analyzed on four types of arthritis with the same SNPs, we used the Bonferroni-adjusted *P* value threshold (0.05/4 = 0.0125) to determine the significance of each association. All statistical analyses were performed in the R software (R Core Team, Vienna, Austria, Version 4.1.3).

The raw data can be obtained via the corresponding email for noncommercial aims.

RESULTS

Causal effects of AOA on rheumatoid arthritis. The basic information about the number of exposure SNPs and the range of their F-statistic are shown in Table 1. The F-statistics of all the SNPs were greater than 10 in all MR analysis, indicating the validity of the selected SNPs as instrumental variables (Table 1). Cochran's Q test showed a high heterogeneity of SNPs in the analysis of AOA on rheumatoid arthritis (Supplementary Table 12, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193). In the first MR analysis, the odds ratio (OR) of AOA on rheumatoid arthritis was 1.019 (95% confidence interval [95% CI], 1.002–1.037; $P = 0.032$) by the IVW method and was 1.019 (95% CI 1.010–1.027; $P < 0.0001$) by the weighted median method. For COA on rheumatoid arthritis, the OR by IVW and weighted median was 1.003 (95% CI 0.990–1.015; $P = 0.682$) and 1.006 (95% CI 0.999–1.013; $P = 0.083$).

We used the MR-PRESSO test to identify outliers and then reanalyzed the association between AOA/COA on the incidence of rheumatoid arthritis after excluding the outliers. The results after removal of outlier SNPs are shown in Figure 1. AOA showed significant causal effects on the incidence of rheumatoid arthritis. The OR in the IVW analysis was 1.018 (95% CI 1.011–1.025), reaching a statistical significance of $P < 0.001$. The IVW result was further supported by the weighted median approach (OR 1.021; 95% CI 1.016–1.030; $P < 0.001$). The MR-Egger result showed an OR of 1.38 (95% CI 0.917–2.078), but the result was not statistically significant ($P = 0.136$). However, as there was no pleiotropy in the AOA to rheumatoid arthritis MR analysis (Supplementary Table 12, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193), the IVW results were preferred due to the stronger statistical power. These results indicate that genetically predisposed AOA is associated with an increased risk of developing rheumatoid arthritis. For the MR analysis of osteoarthritis, gout, and ankylosing spondylitis, all three MR methods failed to show significance for a causal effect of AOA on them (Figure 1).

No significant causal effect of COA on the four types of arthritis. The OR of COA on the incidence of rheumatoid

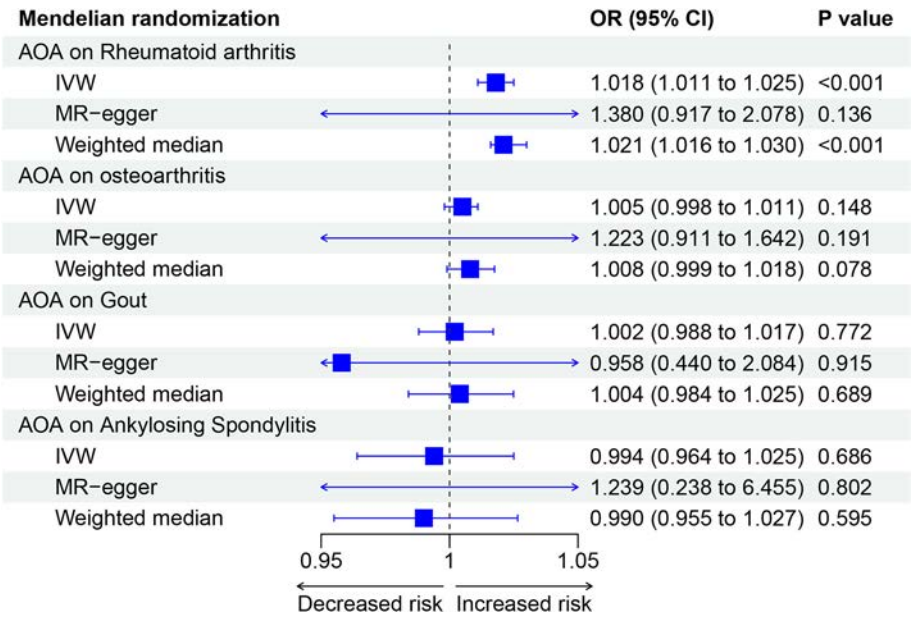

Figure 1. The association between adult-onset asthma (AOA) and four types of arthritis. 95% CI = 95% confidence interval; IVW = inverse-variance weighted; MR = Mendelian randomization; OR = odds ratio.

arthritis by IVW analysis in the first MR analysis was 1.003 (95% CI 0.990–1.015; P = 0.682) (Figure 2). Cochran's Q test showed high heterogeneity of the SNPs of AOA on rheumatoid arthritis (Supplementary Table 12, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193). We used the MR-PRESSO test to identify outliers and further removed them in the subsequent MR analysis. The OR associated with COA by the IVW method after removing the outliers was 1.006 (95% CI 1.001–1.012; P = 0.046). Using the Bonferroni-adjusted P value (0.0125) as the threshold, genetically predicted COA was unlikely to have a causal effect on rheumatoid arthritis. In addition, sensitivity analysis using the MR-Egger and weighted median methods also revealed no significant association between COA and rheumatoid arthritis. Similar to AOA, the MR analysis by all methods did not suggest a causal effect of COA on osteoarthritis, gout, and ankylosing spondylitis.

The two asthma GWAS studies have identified SNPs associated with AOA or COA. We reviewed these SNPs and found that

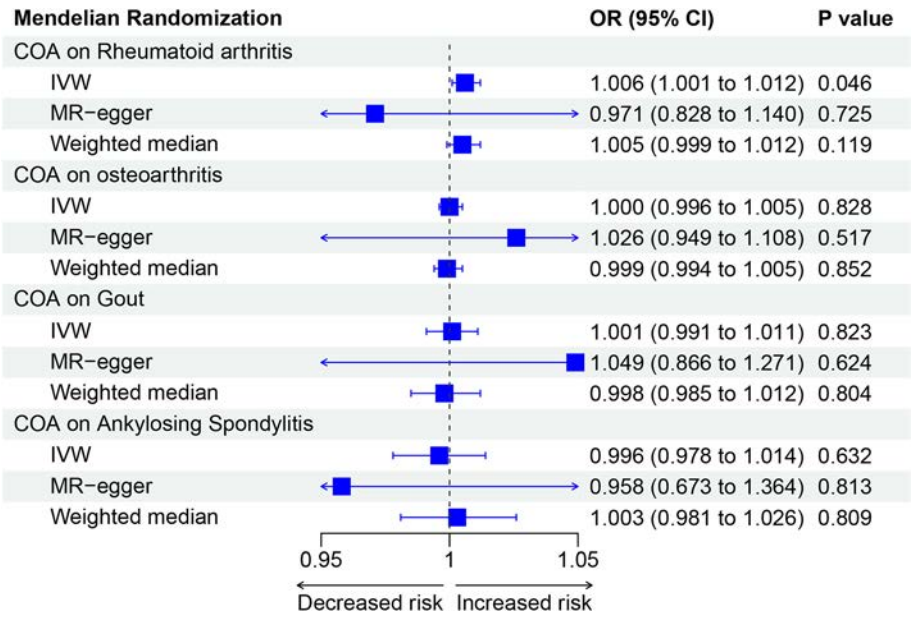

Figure 2. The association between child-onset asthma (COA) and four types of arthritis. 95% CI = 95% confidence interval; IVW = inverse-variance weighted; MR = Mendelian randomization; OR = odds ratio. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193/abstract.

some SNPs are shared by both AOA and COA (Supplementary Table 13, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193). In the main aforementioned MR analyses, we excluded these overlapping SNPs and used only AOA or COA-related SNPs for their associations to ensure specificity. To further enhance the robustness of the main MR findings, we performed a secondary analysis by including these overlapping SNPs as instrumental variables for AOA or COA. The significant association between AOA and rheumatoid arthritis was not changed by including the overlapping SNPs (Table 2). After removing the outliers identified by the MR-PRESSO test, the OR by IVW and weighted median was 1.012 (95% CI 1.006–1.019; $P < 0.001$) and 1.012 (95% CI 1.003–1.021; $P = 0.006$), respectively, both reaching significant difference under the Bonferroni-adjusted threshold. Similar results were observed in another analysis by including the SNPs that were in linkage disequilibrium with other variants in the initial MR analysis (Supplementary Table 14, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25193). However, we did not observe significant causal effects on the incidence of other asthma-arthritis associations. Therefore, these results continue to suggest that genetically predicted AOA has a causal effect on rheumatoid arthritis but does not affect the risk of the other three types of arthritis.

No causal effect of rheumatoid arthritis on asthma. As AOA is associated with an increased risk of rheumatoid arthritis, we asked here where rheumatoid arthritis has causal effects on asthma. We analyzed the ORs associated with rheumatoid arthritis on all asthma, allergic asthma, and on nonallergic asthma, using the GWAS by the FinnGen Consortium as the outcome datasets. The F-statistics of SNPs used as instrumental variables for rheumatoid arthritis were all greater than 10 (Table 3). After excluding outliers by the MR-PRESSO tests, the MR results by MR-Egger, weighted median, or IVW showed no significant causal effects of rheumatoid arthritis on any type of asthma (Table 3). These results indicate that patients with genetically predisposed higher risk of rheumatoid arthritis are unlikely to have an increased risk of developing asthma.

DISCUSSION

Among the various types of arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout are the four most common. Arthritis causes substantial disabilities each year and is a major global burden. Identifying risk factors of arthritis and revealing the associations between other diseases and arthritis will contribute to better care for this patient population. In this study, we explored the genetic causal effects of asthma, the second most common chronic respiratory disease worldwide, on the four major types of arthritis. Using two-sample MR analysis, we found that genetically predicted AOA can cause rheumatoid arthritis but has no effect on osteoarthritis, ankylosing spondylitis, and gout.

The association between asthma and rheumatoid arthritis has been observed in several observational studies. For example, the adjusted incidence rate of rheumatoid arthritis increased by 44% in patients with asthma in a cohort study (25), and this risk is even higher in female patients with asthma (26). Notably, the association between the two diseases is not consistent in previous studies. In one prospective study, asthma was not associated with rheumatoid arthritis (9). Another study found that asthma only affects the incidence of seropositive rheumatoid arthritis but not overall rheumatoid arthritis (10). This discrepancy may be due to the study design and potential confounding factors that cannot be fully addressed in the analysis. A meta-analysis found a significantly positive association between asthma and

Table 2. The causal effects of AOA or COA on the four types of arthritis by including the overlapping SNPs associated with both AOA and COA*

	AOA			COA		
Outcome arthritis	Number of SNPs	OR (95% CI)	*P* value	Number of SNPs	OR (95% CI)	*P* value
Rheumatoid arthritis						
IVW	30	1.012 (1.006–1.019)	<0.001	38	1.005 (0.998-1.011)	0.181
MR-Egger	30	0.879 (0.623–1.24)	0.47	38	0.895 (0.767–1.043)	0.165
Weighted median	30	1.012 (1.003–1.021)	0.006	38	1.006 (0.999–1.013)	0.114
Osteoarthritis						
IVW	34	1.003 (0.998–1.009)	0.251	71	1.001 (0.996–1.004)	0.897
MR-Egger	34	1.056 (0.814–1.37)	0.685	71	1.025 (0.953–1.102)	0.508
Weighted median	34	1.008 (0.999–1.016)	0.067	71	0.999 (0.994–1.005)	0.798
Ankylosing spondylitis						
IVW	32	0.99 (0.963–1.019)	0.499	65	0.993 (0.977–1.009)	0.375
MR-Egger	32	0.62 (0.151–2.541)	0.511	65	0.931 (0.685–1.264)	0.648
Weighted median	32	0.981 (0.95–1.014)	0.256	65	0.997 (0.975–1.018)	0.758
Gout						
IVW	32	0.999 (0.986–1.013)	0.922	65	0.998 (0.989–1.007)	0.657
MR-Egger	32	0.866 (0.451–1.66)	0.667	65	1.022 (0.865–1.208)	0.797
Weighted median	32	0.999 (0.981–1.016)	0.884	65	0.996 (0.983–1.009)	0.566

* 95% CI = 95% confidence interval; AOA = adult-onset asthma; COA = child-onset-asthma; IVW = inverse-variance weighting; MR = Mendelian randomization; OR = odds ratio; SNP = single nucleotide polymorphism.

Table 3. The association between rheumatoid arthritis and asthma by two-sample Mendelian analysis*

Outcome GWAS	OR (95% CI)	*P* value	Number of SNPs	F-statistic range of exposure SNPs
All asthma				
MR-Egger	1.009 (0.954–1.067)	0.757	29	96.7–29.8
Weighted median	0.995 (0.987–1.003)	0.214	29	96.7–29.8
IVW	0.994 (0.987–1.001)	0.121	29	96.7–29.8
Nonallergic asthma				
MR-Egger	1.031 (0.977–1.095)	0.33	32	29.8–678.3
Weighted median	0.994 (0.979–1.01)	0.483	32	29.8–678.3
IVW	0.995 (0.983–1.007)	0.425	32	29.8–678.3
Allergic asthma				
MR-Egger	1.037 (0.977–1.101)	0.242	28	29.8–678.3
Weighted median	1.001 (0.988–1.015)	0.866	28	29.8–678.3
IVW	0.997 (0.984–1.009)	0.613	28	29.8–678.3

* 95% CI = 95% confidence interval; GWAS = genome wide association study; IVW = inverse-variance weighted; MR = Mendelian randomization; OR = odds ratio; SNP = single nucleotide polymorphism.

the risk of rheumatoid arthritis but suggested the presence of publication bias (6). More convincing data are therefore needed on the association between asthma and rheumatoid arthritis.

Currently, there is a lack of studies to separately explore the risk of osteoarthritis, gout, or ankylosing spondylitis associated with AOA or COA. Asthma is clinically divided into AOA and COA, which have different pathogenesis. A previous study revealed a positive association between asthma and the risk of rheumatoid arthritis in women (26). COA is more likely to be a dysregulated allergic condition, and only a few patients will have persistent symptoms into adulthood (12). On the contrary, AOA is more likely to be a consequence of multiple disorders, of which immunological dysfunction plays a central role (27). In this study, we used the SNPs from two separate GWAS as instrumental variables of AOA or COA to analyze their effects on arthritis (14,15). The two studies used the genome sequencing data of participants from the UK Biobank but found different SNPs associated with AOA or COA. This is due to differences in the definition of AOA or COA between the two studies. We combined the results of the two studies and have excluded SNPs that are associated with both AOA and COA to perform the main MR analysis, and the results provided genetic data to support the causal effects of AOA, but not COA, on the risk of rheumatoid arthritis.

An inherent limitation of cohort studies is their ability to adjust for confounding factors. Although some studies using large samples have addressed a wide range of confounding factors when exploring the association between asthma and arthritis (10,28), the potential role of other undetected confounding factors may affect the results. Compared with these studies, the MR approach uses genetic determinants of asthma as the exposure, which are determined at insemination and are not affected by individual-level conditions. Therefore, this method can provide a reliable estimate of the association between two diseases. Using this method, we revealed a genetical causal of AOA on rheumatoid arthritis, whereas COA had no influence on the risk of rheumatoid arthritis. This result may be due to the common immunological pathogenesis of AOA and rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disorder, whereas AOA is also largely caused by immune dysfunction (13). Our findings are similar to those of other studies, which found that patients with AOA are more likely to develop other disorders, including cardiovascular diseases and metabolic disorders, than those with COA (29,30). However, the *P* value (<0.05) in the IVW implies a potential association between the two diseases. A previous study revealed that allergic diseases predispose people to increased risk of rheumatoid arthritis (28). Because COA is mostly an allergic disease, its effects on the risk of rheumatoid arthritis requires further exploration at the genetic and individual level.

Unlike rheumatoid arthritis, the MR analysis in this study suggested no causal effect of asthma on the other three types of arthritis. Despite these findings, a previous study has reported higher prevalence of osteoarthritis in patients with asthma than in those without or in those with chronic obstructive pulmonary disease. Another study suggested that the coexistence of osteoarthritis is more common in AOA than that in COA (31). These results suggest that asthma and osteoarthritis are not causally linked but are likely to coexist. Clinical attention should be paid to the coexistence of the two diseases. Studies exploring the individual-level association between asthma and gout, or between asthma and ankylosing spondylitis, are rare. Although our results suggested no association between asthma and the two diseases, further studies are warranted to explore their correlations at the individual level to help the clinical management of these conditions.

Our studies have several limitations. First, both the exposure and outcome data for the MR analysis were obtained from people of European descent. Because the genetic variants associated with disease vary widely between races, it remains unclear whether the association between asthma and arthritis in this study also exists in other races. Second, although we determined the causal risk of asthma on rheumatoid arthritis, the OR in the MR analysis is not the true risk at the population level. The increased risk of rheumatoid arthritis obtained in population studies is more reliable for clinical reference. Third, we found a

positive correlation between AOA and the risk of rheumatoid arthritis. Rheumatoid arthritis can be divided into seronegative and seropositive types. Because of the lack of related data, we could not determine the association by the types of rheumatoid arthritis. Finally, we divided asthma into AOA and COA in this study because of the study design of the original GWAS. There are many other endotypes of asthma besides AOA and COA, such as allergic and nonallergic asthma. It is necessary to analyze the effects of these endotypes on the risk of arthritis in future studies.

In this study, we explored the causal effects of asthma on the incidence of arthritis. We found that genetically predicted AOA has a causal effect on rheumatoid arthritis, but not on other arthritis, including osteoarthritis, gout, and ankylosing spondylitis. Clinically, we should pay attention to the risk of rheumatoid arthritis in patients with AOA to help guide better clinical care for these patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Drs. Zhong Li and Y. Lui had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Zhong Li, Y. Liu.

Acquisition of data. Yan.

Analysis and interpretation of data. Y. Zhang, X. Zhang, Chen, Wei, Duan, Zheng Li, Peng, J. Liu.

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Impact of Sex, Serostatus, and Smoking on Risk for Rheumatoid Arthritis–Associated Interstitial Lung Disease Subtypes

Gregory C. McDermott,[1] Keigo Hayashi,[2] Pierre-Antoine Juge,[3] Ritu Gill,[4] Suzanne Byrne,[1] Staci Gagne,[1] Xiaosong Wang,[2] Misti L. Paudel,[1] Matthew Moll,[5] Michael H. Cho,[1] Kathleen Vanni,[2] Emily Kowalski,[2] Grace Qian,[2] Katarina Bade,[2] Alene Saavedra,[2] Yumeko Kawano,[1] Michael DiIorio,[1] Taylor Wolfgang,[1] Edy Y. Kim,[1] Paul F. Dellaripa,[1] Michael E. Weinblatt,[1] Nancy Shadick,[1] Tracy J. Doyle,[1] and Jeffrey A. Sparks[1]

Objective. Rheumatoid arthritis–associated interstitial lung disease (RA-ILD) includes multiple subtypes with varying histopathology, prognosis, and potential treatments. Limited research has investigated risk factors for different RA-ILD subtypes. Therefore, we examined demographic, serologic, and lifestyle associations with RA-ILD subtypes.

Methods. We systematically identified RA-ILD cases and RA controls without ILD (RA-noILD) in the Brigham RA Sequential Study and Mass General Brigham Biobank RA cohort. We determined RA-ILD subtype (usual interstitial pneumonia [UIP], nonspecific interstitial pneumonia [NSIP], and other/indeterminate) through chest high-resolution computed tomography imaging pattern. We investigated associations of demographic, lifestyle, and serologic factors with major RA-ILD subtypes using multivariable logistic regression.

Results. Among 3,328 patients with RA, we identified 208 RA-ILD cases and 547 RA-noILD controls. RA-UIP was associated with older age (odds ratio [OR] 1.03 per year, 95% confidence interval [95% CI] 1.01–1.05), male sex (OR 2.15, 95% CI 1.33–3.48), and seropositivity (OR 2.08, 95% CI 1.24–3.48), whereas RA-NSIP was significantly associated only with seropositive status (OR 3.21, 95% CI 1.36–7.56). Nonfibrotic ILDs were significantly associated with smoking (OR 2.81, 95% CI 1.52–5.21). Having three RA-ILD risk factors (male, seropositive, smoking) had an OR of 6.89 (95% CI 2.41–19.7) for RA-UIP compared with having no RA-ILD risk factors.

Conclusion. Older age, seropositivity, and male sex were strongly associated with RA-UIP, whereas RA-related autoantibodies were associated with RA-NSIP. These findings suggest RA-ILD sex differences may be driven by RA-UIP and emphasize the importance of further studies to clarify RA-ILD heterogeneity and optimize screening and treatment approaches.

INTRODUCTION

Rheumatoid arthritis–associated interstitial lung disease (RA-ILD) is a serious extra-articular disease manifestation of rheumatoid arthritis (RA) and a major contributor to morbidity and mortality in patients with RA.[1–3] RA-ILD is a heterogeneous condition that includes multiple subtypes with different histopathology, prognosis, and treatment strategies. Although lung

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[1]Gregory C. McDermott, MD, MPH, Suzanne Byrne, MD, Staci Gagne, MD, Misti L. Paudel, PhD, Michael H. Cho, MD, MPH, Yumeko Kawano, MD, Michael DiIorio, MD, Taylor Wolfgang, MD, Edy Y. Kim, MD, PhD, Paul F. Dellaripa, MD, Michael E. Weinblatt, MD, Nancy Shadick, MD, Tracy J. Doyle, MD, MPH, Jeffrey A. Sparks, MD, MMSc: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Keigo Hayashi, MD, PhD, Xiaosong Wang, MS, Kathleen Vanni, BA, Emily Kowalski, BS, Grace Qian, BA, BSc, Katarina Bade, BS, Alene Saavedra, BA: Brigham and Women's Hospital, Boston, Massachusetts; [3]Pierre-Antoine Juge, MD, PhD: Brigham and Women's Hospital, Boston, Massachusetts, Université de Paris Cité, INSERM UMR 1152 and Hôpital Bichat-Claude Bernard, AP-HP, Paris, France; [4]Ritu Gill, MD: Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts; [5]Matthew Moll, MD, MPH: Brigham and Women's Hospital and Harvard Medical School, Boston, Department of Veterans Affairs Boston Healthcare System, West Roxbury, Massachusetts.

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

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SIGNIFICANCE & INNOVATIONS

- Rheumatoid arthritis–interstitial lung disease (RA-ILD) includes multiple subtypes with varying histopathology, prognosis, and potential treatments. Limited research has investigated risk factors for different RA-ILD subtypes.
- We identified patients with RA-ILD from two cohorts and investigated associations of clinical, demographic, and serologic risk factors with different RA-ILD subtypes.
- RA-ILD with a usual interstitial pneumonia pattern, the subtype with the worst prognosis, was associated with older age, male sex, and seropositivity for RA-related autoantibodies, whereas RA-ILD with a nonspecific interstitial pneumonia pattern was only associated with seropositivity.
- These findings suggest that RA-ILD subtypes have different risk factor profiles, which emphasizes the need for further studies that investigate RA-ILD heterogeneity.

biopsy remains the gold standard for subtype diagnosis, the pattern of radiologic abnormality on chest high-resolution computed tomography (HRCT) is frequently used to differentiate RA-ILD subtypes in the absence of a tissue diagnosis.[4,5] Despite recognition of important differences between RA-ILD subtypes, most previous research on risk factors has investigated RA-ILD as a single entity rather than as separate subtypes. To better understand the heterogeneity observed in RA-ILD, we investigated demographic, serologic, and lifestyle risk factors for RA-ILD and its major subtypes.

Previous research has demonstrated differences between RA-ILD subtypes. Two of the most common RA-ILD subtypes are usual interstitial pneumonia (UIP), which is characterized by basilar fibrosis and honeycombing, and nonspecific interstitial pneumonia (NSIP), characterized by extensive ground glass infiltrates and subpleural sparing.[5] Other subtypes seen in RA-ILD include organizing pneumonia (OP), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and respiratory bronchiolitis (RB), as well as indeterminate subtypes.[5] Among these subtypes, UIP has a particularly poor prognosis,[6,7] with median survival as short as 3.2 years,[8] but may be a target for treatment with antifibrotic therapy.[9–11] Additional research has demonstrated that the common promoter variant of *MUC5B* (rs35705950) is a genetic risk factor for the UIP subtype of RA-ILD but was not associated with other subtypes, suggesting that risk factor profiles and pathogenesis may vary between RA-ILD subtypes.[12] Despite the recognition of differences in prognosis and risk factors, there has been limited research investigating differences in risk factors for RA-ILD subtypes.

Therefore, we used data from two RA cohorts to investigate demographic, lifestyle, and serologic risk factors for RA-ILD and major RA-ILD subtypes, including UIP and NSIP. We identified RA-ILD cases and RA controls without ILD (RA-noILD) and performed a detailed assessment for RA-ILD subtypes using pattern of HRCT imaging findings. We hypothesized that male sex, smoking, and RA-related autoantibodies would be most strongly associated with RA-UIP in comparison with other subtypes.

METHODS

Study populations and design. We systematically identified RA-ILD cases and RA-noILD controls from two established RA cohorts in the Mass General Brigham (MGB) health care system, which were pooled to improve sample size and statistical efficiency. The MGB health care system is a large multihospital health care network in the greater Boston, Massachusetts area. One cohort was the Brigham Rheumatoid Arthritis Sequential Study (BRASS), which is a prospective registry of patients with RA receiving care at Brigham and Women's Hospital that started enrolling participants in 2003. The other cohort was the MGB Biobank RA cohort, which includes patients with RA enrolled in the MGB Biobank, a biospecimen and clinical data collection program that has recruited patients from inpatient and outpatient sites in the MGB health care system since January 1, 2010. In both cohorts, all patients with RA met either 1987 or 2010 American College of Rheumatology/EULAR classification criteria for RA.[13,14] This study was approved by the MGB Institutional Review Board (protocol 2016P000226). All participants provided informed consent.

Identification of RA-ILD cases and RA-noILD controls. We identified cases and controls from patients with RA in BRASS and the MGB Biobank RA cohort who had clinically performed HRCT chest imaging. We required chest HRCT imaging for all cases and controls to be confident in their RA-ILD status because subclinical RA-ILD is common.[15–18] All patients in BRASS and the MGB Biobank RA cohort with available HRCT chest imaging were reviewed for clinical evidence of RA-ILD, including a report of symptoms to rheumatologists or pulmonologists, pulmonary function testing, imaging reports, and, when available, pathology. We also performed a separate research review of HRCT chest imaging for each patient. For the research review, chest HRCT scans were reviewed by at least two thoracic radiologists (S.B., S.G, R.G) using a sequential reader method for the presence of interstitial lung abnormalities, which has been previously described.[19,20] The radiologists were masked to patient clinical details. One HRCT scan was selected for research radiology review per patient. For MGB Biobank patients, we reviewed the HRCT chest scan performed closest to Biobank

enrollment. For BRASS patients, we selected the scan closest to a study follow-up visit date.

All RA-ILD cases met published classification criteria for definite or probable RA-ILD based on a combination of imaging, pathology, and pulmonary function testing findings.[21] Patients with no evidence of RA-ILD on clinical review and no evidence of interstitial lung abnormalities on research review of HRCT chest imaging were defined as RA-noILD controls. Our primary analysis did not analyze patients with RA without a chest HRCT scan because they might have had subclinical RA-ILD. Patients with interstitial lung abnormalities on HRCT but no clinical evidence of RA-ILD and those with possible clinical evidence of RA-ILD but not meeting classification criteria for definite/probable RA-ILD[21] were also excluded.

RA-ILD subtypes. We further classified RA-ILD into subtypes (UIP, NSIP, OP, other/indeterminate) based on pattern of HRCT chest imaging findings. The sample size was too limited to investigate other subtypes separately. For the research radiology review, each scan was scored as non-UIP, typical/definite UIP, probable UIP, or indeterminate for UIP.[22] Evidence of non-UIP pattern ILD such as fibrotic NSIP, cellular NSIP, OP, or other ILD patterns (eg, hypersensitivity pneumonitis) was determined by thoracic radiologist interpretation following established guidelines and typical radiologic patterns.[23,24] Because many patients had multiple HRCT chest imaging studies performed, determination of subtype included both the research radiology review and review of clinical imaging reports. Patients with definite or probable UIP pattern on their clinical radiology report or research radiology review were considered to have UIP. Those with probable or definite NSIP in a fibrotic or cellular pattern were considered to have NSIP, and those with OP findings were considered to have OP. Those with other patterns or without clearly defined radiologic pattern were considered to have other/indeterminate subtypes based on thoracic radiologist interpretation. In cases in which multiple or progressive radiologic findings/patterns were present (eg, cellular NSIP progressing to fibrotic NSIP), the last available pattern was used.

To further investigate associations with fibrotic RA-ILD, we combined RA-ILD cases with UIP and fibrotic NSIP. RA-ILD cases with other subtypes were considered to have nonfibrotic RA-ILD.

Demographics, lifestyle factors, RA features, and *MUC5B* genotyping. The index date was defined as the date of RA-ILD diagnosis for cases, determined by medical record review. For controls, the index date was set as the date of research-reviewed HRCT chest imaging. The timing of index date for cases and controls as well as covariate ascertainment is detailed in Supplementary Figure 1. We extracted demographic data including sex, date of birth, and self-described race from the electronic health record. We performed medical record review to determine date of RA diagnosis. Body mass index (BMI) was extracted from the electronic health record. Smoking status and pack-years of smoking history were determined from questionnaires performed at study enrollment. RA-related autoantibody testing status for rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP) and autoantibody titers were extracted from the electronic health records. We considered a patient to be seropositive if they had positive RF and/or anti-CCP antibodies. Four patients were missing serostatus, and they were excluded from the models that included serostatus. A total of 14 cases and 11 controls were missing BMI data. There were no other missing covariate data.

To account for a potential impact of subclinical or undiagnosed RA-ILD on time-varying exposures, we chose a covariate assessment date of one year before index date for BMI. For supplementary analyses, we assessed medication use at the covariate assessment date with a look-back period of 12 months. We also investigated erythrocyte sedimentation rate and C-reactive protein measurements in the year before index date. For patients with multiple measures in that time period, we used the value closest to index date.

In supplementary analyses, we limited our analysis to patients and controls who had available genotyping of the *MUC5B* promoter variant (rs35705950). Genotyping methods used by the MGB Biobank have been previously described.[25]

Statistical analysis. We presented baseline characteristics between RA-ILD cases and RA-noILD controls using descriptive statistics. We also presented baseline characteristics for individual RA-ILD subtypes as well as fibrotic and nonfibrotic RA-ILD cases compared with RA-noILD controls. We used logistic regression to determine odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations among demographic, lifestyle, and serologic factors with RA-ILD and RA-ILD subtypes (UIP, NSIP, and OP as well as fibrotic and nonfibrotic), comparing RA-ILD cases with RA-noILD controls. We constructed multivariable models that included variables statistically significant in the univariable analyses and additionally adjusted for cohort.

Based on the results from the multivariable models, we identified key risk factors (male sex, seropositivity for RF and/or anti-CCP antibodies, and smoking history) and calculated the OR of having RA-ILD overall and by subtype per risk factor using multivariable logistic regression. These models were additionally adjusted for RA duration at index date and cohort. To further assess the impact of serostatus on RA-ILD and subtype risk, we created multivariable logistic regression models that investigated autoantibody titer as a continuous variable. Separately, we categorized the titer into normal (upper limit of normal or less), low (>1–3× upper limit of normal), and high (>3× upper limit of normal) and examined the association with RA-ILD and subtypes using multivariable logistic regression. In a supplementary analysis, we included patients who had both RF and anti-CCP measured and

examined the associations between dual-positive status (both RF and anti-CCP positive), single-positive status (RF and/or anti-CCP only), and RA-ILD and subtypes. For this analysis, patients who were seronegative were the reference group.

In supplementary analyses, we limited the cases and controls to patients who had available genotyping of the *MUC5B* promoter variant (rs35705950). We constructed multivariable models that adjusted for age, sex, serostatus, RA duration, smoking status, pack-years, presence versus absence of the *MUC5B* promoter variant, and the first three principal components of genetic ancestry. Finally, to assess the possibility that our use of imaged controls affected our results, we performed a sensitivity analysis with an expanded control group that included all patients with RA in both cohorts who did not have a RA-ILD diagnosis. This included the original "imaged" control group as well as patients with RA who did not have HRCT chest imaging. Patients with RA who had possible RA-ILD were excluded. In this analysis, the index date was date of RA diagnosis.

Two-sided *P* values of <0.05 were considered statistically significant. All analyses were performed using SAS v9.4. Patients and the public were not involved in the design or implementation of this study.

RESULTS

Study sample and characteristics. Out of a total of 3,328 patients with RA, including 976 with available HRCT imaging, we identified 208 RA-ILD cases and 547 RA-noILD controls. Baseline characteristics of the RA-ILD cases and RA-noILD controls are detailed in Table 1. The mean age ± SD at RA diagnosis was 50.7 ± 14.6 years for RA-ILD cases and 49.1 ± 14.8 years for RA-noILD controls. The median RA duration at index date was 9.0 years (interquartile range [IQR] 0.4–20.4) for RA-ILD

Table 1. Characteristics at index date for RA-ILD cases and RA-noILD controls*

Demographics	All RA-ILD cases (n = 208)	RA-UIP cases[a] (n = 99)	RA-NSIP cases[a] (n = 38)	RA-noILD controls (n = 547)
Age at RA diagnosis, mean ± SD, y	50.7 ± 14.6	53.1 ± 16.0	48.1 ± 14.2	49.1 ± 14.8
Age at index date, mean ± SD, y	62.8 ± 12.2	65.2 ± 10.7	59.3 ± 14.3	61.1 ± 12.9
Female, n (%)	140 (67.3)	60 (60.6)	28 (73.7)	427 (78.1)
Race, n (%)				
White	182 (87.5)	85 (85.9)	32 (84.2)	473 (86.5)
Black	14 (6.7)	8 (8.1)	3 (7.9)	36 (6.6)
Asian	3 (1.4)	2 (2.0)	0 (0.0)	7 (1.3)
Other	9 (4.3)	4 (4.0)	3 (7.9)	31 (5.7)
Lifestyle				
BMI, mean ± SD, kg/m^2	29.2 ± 6.3	29.4 ± 5.9	30.0 ± 7.6	28.6 ± 6.5
BMI category, n/total n (%)				
Underweight (<18.5)	2/194 (1.0)	0/94 (0.0)	0/38 (0.0)	9/536 (1.7)
Normal (18.5–24.9)	53/194 (27.3)	29/94 (30.9)	10/38 (26.3)	169/536 (31.5)
Overweight/with obesity (BMI >25)	139/194 (71.7)	65/94 (69.1)	28/38 (73.7)	358/536 (66.8)
Smoking status, n (%)				
Never	70 (33.7)	37 (37.4)	13 (34.2)	257 (47.0)
Past	123 (59.1)	55 (55.6)	21 (55.3)	247 (45.2)
Current	15 (7.2)	7 (7.1)	4 (10.5)	43 (7.9)
Median pack-years, median (IQR)	8.3 (0–25)	7.5 (0–25)	3.1 (0–20)	0.4 (0–16.5)
RA features				
Median RA duration at index date, median (IQR), y	9.0 (0.4–20.4)	8.2 (0.0–22.7)	4.3 (0.0–17.6)	8.9 (2.5–17.7)
Seropositive, n (%)	158/204 (77.5)	74/97 (76.3)	31/38 (81.6)	328 (60.0)
RF positive, n (%)	135/200 (67.5)	65/96 (67.7)	25/36 (69.4)	246/543 (45.3)
Median RF level, fold above ULN, median (IQR)	4.0 (1.0–20.2)	3.7 (1.0–25.8)	3.9 (1.0–18.9)	1.1 (1.0–6.2)
Anti-CCP positive, n (%)	133/193 (68.9)	67/92 (72.8)	26/36 (72.2)	270/519 (52.0)
Median anti-CCP level, fold above ULN, median (IQR)	7.4 (0.5–15.2)	9.7 (0.8–16.0)	9.5 (0.6–16.3)	1.5 (0.3–11.4)
MUC5B promoter variant (rs35705950) genotype, n/total n (%)				
GG allele	63/101 (62.4)	22/48 (45.8)	18/23 (78.3)	301/356 (84.6)
GT or TT allele	38/101 (37.6)	26/48 (54.2)	5/23 (21.7)	55/356 (15.4)

* Index date was date of RA-ILD for cases and date of HRCT for RA-noILD controls. Anti-CCP, anti–cyclic citrullinated peptide; BMI, body mass index; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; NSIP, nonspecific interstitial pneumonia; RA-noILD, RA controls without ILD; RA, rheumatoid arthritis; RF, rheumatoid factor; UIP, usual interstitial pneumonia; ULN, upper limit of normal.
[a] Other subtypes detailed in Supplementary Table 8.

cases and 8.9 years (IQR 2.5–17.7) for RA-noILD controls. The proportion of women was 67.3% in RA-ILD cases and 78.1% in the RA-noILD controls. The majority of patients were White in the group with RA-ILD (87.5%) and the RA without ILD group (86.5%). Ever smokers accounted for 66.3% of RA-ILD cases and 53.1% of RA-noILD controls. A total of 77.5% of RA-ILD cases were seropositive compared with 60.0% in RA-noILD controls. Among the cases and controls with available genotyping of the *MUC5B* promoter variant rs35705950 (Supplementary Table 1), 38 of 101 (37.6%) RA-ILD cases had at least one copy of the *MUC5B* promoter variant compared with 55 of 356 (15.4%) of RA-noILD controls (Table 1). A comparison of fibrotic RA-ILD cases, nonfibrotic RA-ILD cases, and RA-noILD controls is detailed in Supplementary Table 2. In these analyses, cases with UIP or fibrotic NSIP patterns were considered to be fibrotic RA-ILD, whereas other subtypes were considered nonfibrotic. Baseline medication use and markers of inflammation are detailed in Supplementary Table 3.

Associations with RA-ILD and major subtypes. Unadjusted logistic regression results investigating associations among demographics, sex, lifestyle factors, and serostatus are detailed in Supplementary Table 4. In multivariable models (Table 2), male sex (OR 1.57, 95% CI 1.08–2.28), seropositivity (OR 2.23, 95% CI 1.52–3.26), positive RF (OR 2.41, 95% CI 1.69–3.44), positive anti-CCP (OR 1.98, 95% CI 1.38–2.84), and ever smoker (OR 1.70, 95% CI 1.13–2.55) were each associated with an increased odds of RA-ILD.

RA-UIP was associated with older age at index date (OR 1.03 per year, 95% CI 1.01–1.05), male sex (OR 2.15, 95% CI 1.33–3.48), and seropositivity (OR 2.08, 95% CI 1.24–3.48) compared with RA-noILD controls. RA-NSIP was significantly associated with seropositivity (OR 3.21, 95% CI 1.36–7.56) compared with RA-noILD controls. Among patients with both RF and anti-CCP measured, the presence of both RF and anti-CCP positivity was associated with RA-ILD and UIP, NSIP, and fibrotic subtypes, as detailed in Supplementary Table 5. We also assessed for associations with demographic, lifestyle, and serologic factors and fibrotic and nonfibrotic RA-ILD patterns, as detailed in Table 2. Associations with RA-ILD and major subtypes by autoantibody titer are detailed in Supplementary Tables 6 and 7.

Figure 1 details ORs of RA-ILD, major subtypes, and fibrotic and nonfibrotic patterns. Patients with UIP and fibrotic NSIP were considered to have fibrotic RA-ILD in these analyses. These models dichotomized age at ≥60 years for visualization.

Associations with RA-ILD and major subtypes by number of risk factors. Based on the results from multivariable models, we identified male sex, seropositivity for RA-related autoantibodies, and ever smoker status as key risk factors for RA-ILD and the UIP subtype. We stratified cases and controls by number of RA-ILD risk factors present (eg, a seropositive, male, former smoker would have all three risk factors, whereas a seronegative, female, never smoker would have zero risk factors). Numbers of cases and controls by risk factor are detailed in Supplementary Table 8. We investigated the association of number of risk factors with all RA-ILD and key risk factors, with results detailed in Table 3. Among those with all three risk factors, the ORs were 6.89 (95% CI 2.41–19.7) and 4.35 (95% CI 1.14–16.6), with *P* for trend <0.0001 and 0.003 for RA-UIP and RA-NSIP, respectively.

Additional analyses. Baseline characteristics of patients with less common RA-ILD subtypes such as OP, RB-ILD, and other/indeterminate subtypes are shown in Supplementary Table 9. Unadjusted ORs for associations with OP are detailed in Supplementary Table 10. Because of the small number of patients with OP (n = 16) and lack of unadjusted associations,

Table 2. Multivariable adjusted ORs for RA-ILD and major subtypes compared with RA-noILD controls without ILD on HRCT chest imaging*

	Multivariable OR for all RA-ILD (95% CI)	Multivariable OR for RA-UIP (95% CI)	Multivariable OR for RA-NSIP (95% CI)	Multivariable OR for fibrotic[a] RA-ILD (95% CI)	Multivariable OR for nonfibrotic RA-ILD (95% CI)
Age at index date (per year)	1.00 (0.99–1.02)	**1.03 (1.01–1.05)**	0.98 (0.95–1.01)	**1.02 (1.00–1.04)**	0.98 (0.96–1.01)
Male (vs female)	**1.57 (1.08–2.28)**	**2.15 (1.33–3.48)**	1.15 (0.53–2.52)	**1.91 (1.23–2.95)**	1.15 (0.65–2.03)
Seropositive (vs seronegative)	**2.23 (1.52–3.26)**	**2.08 (1.24–3.48)**	**3.21 (1.36–7.56)**	**2.39 (1.49–3.83)**	**2.09 (1.19–3.67)**
RF+ (vs RF−)	**2.41 (1.69–3.44)**	**2.49 (1.54–4.03)**	**3.00 (1.41–6.39)**	**2.61 (1.70–4.02)**	**2.18 (1.29–3.69)**
Anti-CCP+ (vs anti-CCP−)	**1.98 (1.38–2.84)**	**2.45 (1.47–4.08)**	**2.55 (1.18–5.48)**	**2.51 (1.59–3.95)**	1.46 (0.86–2.46)
RA duration (per year)	0.99 (0.97–1.00)	0.98 (0.96–1.00)	0.99 (0.96–1.02)	0.99 (0.97–1.00)	0.99 (0.97–1.01)
Smoking status					
Never	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Ever	**1.70 (1.13–2.55)**	1.17 (0.68–2.02)	1.95 (0.86–4.42)	1.25 (0.77–2.03)	**2.81 (1.52–5.21)**
Pack-years (per 10 pack-years)	1.0 (0.92–1.09)	1.01 (0.90–1.12)	1.00 (0.84–1.19)	1.01 (0.92–1.11)	0.99 (0.87–1.13)

* ORs were adjusted for age at index date, sex, serostatus, RA duration at index date (RA-ILD diagnosis for cases or HRCT for RA-noILD controls), smoking status, pack-years, and cohort. Bolded values are statistically significant. Anti-CCP, anti–cyclic citrullinated peptide; CI, confidence interval; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; RA, rheumatoid arthritis; RA-noILD, RA controls without ILD; Ref, reference; RF, rheumatoid factor; UIP, usual interstitial pneumonia.
[a] Cases with UIP or NSIP were considered to have fibrotic RA-ILD in this analysis.

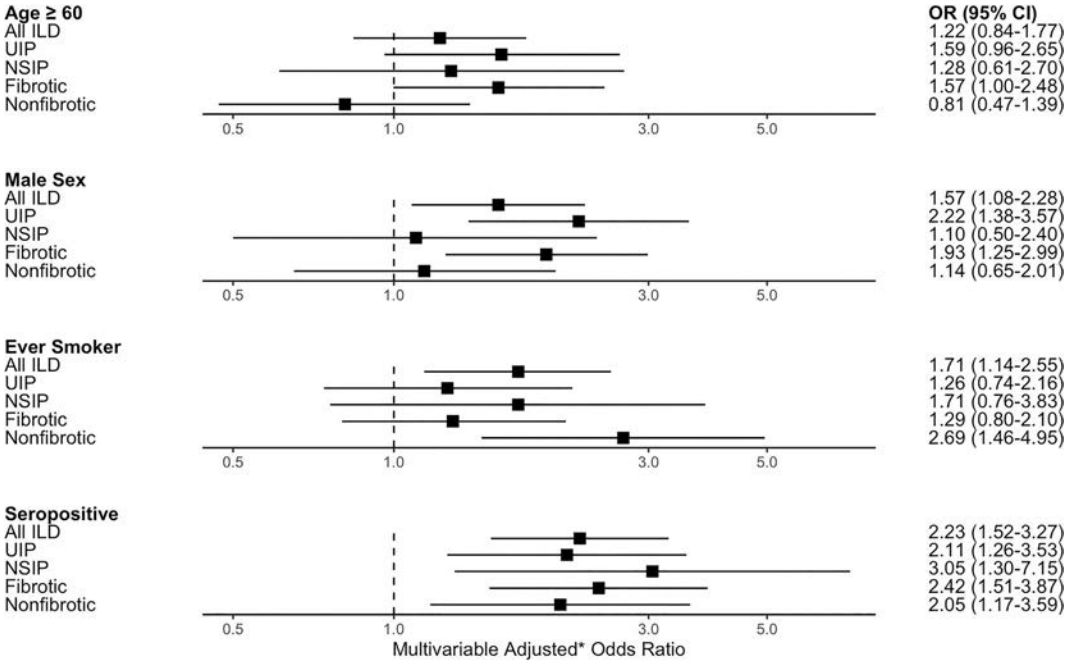

Figure 1. Multivariable ORs for RA-ILD and major subtypes by selected factors (age ≥60 years, male, ever smoker, and seropositivity). All models presented were adjusted for age at index date, sex, serostatus, RA duration at index date (RA-ILD diagnosis date for cases or HRCT date for RA-noILD controls), smoking status, pack-years, and cohort. Patients with UIP or fibrotic NSIP were considered to have fibrotic RA-ILD in this analysis. 95% CI, 95% confidence interval; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; RA, rheumatoid arthritis; RA-noILD, RA controls without ILD; UIP, usual interstitial pneumonia.

we did not investigate associations with OP using multivariable models.

Among patients with available *MUC5B* rs35705950 genotyping (Supplementary Table 1), the presence of the *MUC5B* promoter variant genotype was strongly associated with RA-ILD (OR 3.50, 95% CI 2.06–5.95) and in particular with UIP (OR 7.29, 95% CI 3.58–14.8). Full results of the models including *MUC5B* are detailed in Supplementary Table 11.

Results from our sensitivity analysis with an expanded control group are detailed in Table 4 and Supplementary Table 12. This analysis expanded the control group from 547 to 2,912 controls, as detailed in Supplementary Table 13. The associations we observed among male sex, seropositivity, and smoking status with RA-ILD and key subtypes were consistent with the previous analysis. Older age at RA diagnosis was significantly associated with RA-ILD and specifically the RA-UIP subtype.

DISCUSSION

In this study, we investigated risk factors for RA-ILD and specific RA-ILD subtypes using two large cohorts with RA and identifying patients with and without RA-ILD confirmed by HRCT. Male

Table 3. Association of male sex, seropositivity for RA-related autoantibodies, and smoking with risk of RA-ILD and major subtypes*

	Multivariable[a] OR for all RA-ILD (95% CI)	Multivariable[a] OR for RA-UIP (95% CI)	Multivariable[a] OR for RA-NSIP (95% CI)	Multivariable[a] OR for fibrotic[b] RA-ILD (95% CI)	Multivariable[a] OR for nonfibrotic RA-ILD (95% CI)
Zero risk factors (female, seronegative, never smoker)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
One risk factor	**1.93 (1.00–3.70)**	2.42 (0.91–6.47)	1.06 (0.31–3.58)	2.27 (0.97–5.28)	1.61 (0.62–4.17)
Two risk factors	**3.42 (1.79–6.53)**	**3.35 (1.26–8.90)**	2.89 (0.91–9.17)	**3.55 (1.53–8.21)**	**3.48 (1.37–8.86)**
Three risk factors (male sex, seropositive, ever smoker)	**5.94 (2.87–12.3)**	**6.89 (2.41–19.7)**	**4.35 (1.14–16.6)**	**6.62 (2.65–16.6)**	**5.52 (1.94–15.7)**
P for trend	**<0.0001**	**<0.0001**	**0.003**	**<0.001**	**<0.001**
Continuous risk score per risk factor	**1.79 (1.47–2.19)**	**1.73 (1.32–2.27)**	**1.85 (1.23–2.78)**	**1.77 (1.39–2.25)**	**1.85 (1.38–2.49)**

* Bolded values are statistically significant. 95% CI, 95% confidence interval; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; RA, rheumatoid arthritis; RA-noILD, RA controls without ILD; Ref, reference; UIP, usual interstitial pneumonia.
[a] Adjusted for age at index date, RA duration at index date (RA-ILD diagnosis for cases or HRCT for RA-noILD controls), and cohort.
[b] Cases with UIP or fibrotic NSIP were considered to have fibrotic RA-ILD in this analysis.

Table 4. Multivariable ORs for RA-ILD (n = 208) and major subtypes compared with RA-noILD and unimaged controls (n = 2,912)*

	Multivariable OR for all RA-ILD (95% CI)	Multivariable OR for RA-UIP (95% CI)	Multivariable OR for RA-NSIP (95% CI)	Multivariable OR for fibrotic[a] RA-ILD (95% CI)	Multivariable OR for nonfibrotic RA-ILD (95% CI)
Age at index date (per year)	**1.02 (1.01–1.03)**	**1.03 (1.02–1.05)**	1.01 (0.98–1.03)	**1.03 (1.01–1.04)**	1.01 (0.99–1.03)
Male (vs female)	**1.75 (1.25–2.44)**	**2.09 (1.33–3.29)**	1.42 (0.66–3.06)	**1.94 (1.30–2.91)**	1.48 (0.86–2.54)
Seropositive (vs seronegative)	**1.96 (1.38–2.79)**	**1.91 (1.17–3.13)**	**2.47 (1.07–5.73)**	**2.17 (1.39–3.39)**	1.68 (0.97–2.91)
RF+ (vs RF−)	**1.89 (1.36–2.61)**	**1.95 (1.23–3.08)**	1.96 (0.94–4.05)	**1.99 (1.33–3.00)**	**1.73 (1.03–2.88)**
Anti-CCP+ (vs anti-CCP−)	**2.05 (1.49–2.84)**	**2.69 (1.67–4.33)**	**2.42 (1.15–5.09)**	**2.71 (1.78–4.14)**	1.37 (0.84–2.24)
Smoking status					
Never	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Ever	**1.57 (1.10–2.24)**	1.24 (0.75–2.04)	1.63 (0.74–3.57)	1.26 (0.81–1.96)	**2.29 (1.29–4.09)**
Pack-years (per 10 pack-years)	**1.09 (1.01–1.17)**	1.10 (1.00–1.21)	1.07 (0.91–1.27)	**1.10 (1.00–1.20)**	1.07 (0.95–1.20)

* ORs were adjusted for age at index date, sex, serostatus, smoking status, pack-years, and cohort. ORs were adjusted for age at index date, sex, serostatus, RA duration at index date (RA-ILD diagnosis for cases or HRCT for RA-noILD controls), smoking status, pack-years, and cohort. Bolded values are statistically significant. 95% CI, 95% confidence interval; anti-CCP, anti–cyclic citrullinated peptide; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; RA, rheumatoid arthritis; RA-noILD, RA controls without ILD; Ref, reference; RF, rheumatoid factor; UIP, usual interstitial pneumonia.
[a] Cases with UIP or fibrotic NSIP were considered to have fibrotic RA-ILD in this analysis.

sex, older age, and seropositivity were associated with RA-UIP, whereas RA-NSIP was significantly associated with seropositivity. The combination of male sex, seropositivity, and smoking conferred nearly seven-fold increased risk of RA-UIP, a RA-ILD subtype with a particularly poor prognosis. These findings suggest that RA-ILD subtypes may have distinct risk factor profiles, which emphasizes the importance of further efforts to understand RA-ILD disease heterogeneity to inform screening and prognostication strategies.

Our study adds to the existing literature investigating differences between RA-ILD subtypes. Kim and colleagues investigated mortality differences between UIP and NSIP pattern RA-ILD and reported a median survival of 3.2 years in the RA-UIP group compared with 6.6 years in those without UIP pattern RA-ILD.[26] Similarly, Solomon and colleagues found that the UIP pattern was associated with higher mortality than NSIP and also detailed baseline factors in patients with RA-ILD and UIP and patients with RA-ILD and NSIP.[6] However, the sample sizes of these previous investigations were 82 and 137 patients, respectively, smaller than our sample of 208 patients with RA-ILD, and they investigated outcomes rather than risk factors. Other studies have also demonstrated increased mortality and morbidity, including hospitalizations and supplemental oxygen use in patients with RA-ILD with UIP pattern.[27,28] One recent study investigated differences in pulmonary function trajectory with different immunosuppressive treatments among patients with RA-ILD and classified subtypes into UIP and non-UIP patterns. In this study, RA-ILD subtype did not affect pulmonary function trajectory.[29] There has been limited investigation of other ILD subtypes in RA. A recent study from Japan detailed a high recurrence rate in a cohort of 33 patients with RA with OP.[30] These results also add to the small body of literature comparing RA-ILD subtypes with controls without ILD determined by HRCT chest imaging.

Notably, our study recapitulates the importance of several established RA-ILD risk factors.[31] Although RA is more common among women, the significant association between men and RA-ILD has been well-described.[32–35] Interestingly, we observed that the association between RA-ILD and men may be driven by the UIP pattern of RA-ILD, suggesting important sex differences in ILD risk that need further investigation. Among the subset of patients with available *MUC5B* genotyping, we confirmed strong associations between the presence of the rs35705950 promoter variant and the RA-UIP subtype of RA-ILD.[12] Additionally, previous research from several groups has established the important association between RA-related autoantibodies and RA-ILD risk.[32,33,36,37] Cigarette smoking has also been previously established as an important RA-ILD risk factor.[32,33,36–38] Notably, the associations we observed between smoking with RA-ILD and key subtypes in our study may have been attenuated because of our use of a control group with clinically performed HRCT chest imaging. Because smokers may be more likely to have HRCT chest imaging, this may have enriched the smoking prevalence in our control group. Furthermore, our inclusion of RB-ILD, a form of ILD strongly associated with smoking, may also influence our findings, but there were only six patients with this subtype.

Our study also raises several important clinical questions that will require future investigation. Currently, antifibrotic treatment options in RA-ILD are mainly used in UIP and other progressive fibrotic subtypes.[39,40] Whether differences in risk factor profiles may be able to help identify patients for RA-ILD screening or early treatment strategies remains unknown. In our study, despite distinct individual risk factor profiles for RA-ILD subtypes, the number of cumulative risk factors was strongly associated with RA-ILD across all subtypes. This suggests that a screening algorithm for RA-ILD based on counting risk factors may be a straightforward screening approach for clinicians to implement.

Additionally, given the importance of genetic risk factors in RA-ILD,[41] investigating RA-ILD screening strategies that incorporate both clinical and genetic risk factors, including the creation of a validated risk score, remains an important avenue of future research.

The mechanisms underlying RA-ILD subtype heterogeneity remain incompletely understood. The RA-UIP pattern shares many epidemiologic and genetic risk factors with idiopathic pulmonary fibrosis, including the *MUC5B* promoter variant, telomere length, and telomere-related gene mutations.[42,43] The latter associations suggests that aging and physiologic stresses may play an important role in disease pathogenesis of this subtype. Indeed, we saw that RA-UIP was associated with older age, an association that we did not observe for RA-NSIP. Additionally, the links between inflammation and dysbiosis in the pulmonary mucosa and the development of RA-related autoantibodies suggest a potential mechanism linking inflammatory subtypes of lung disease and high levels of RA-related autoantibodies.[44,45] Our findings regarding a sex difference in RA-ILD subtypes, which persisted after adjustment for smoking, adds further evidence to the importance of sex-related differences in RA pathogenesis and outcomes.[46] Whether the higher prevalence of RA-ILD among men is related to physiologic, lifestyle, or genetic mechanisms requires further investigation.

Our study has several strengths. By pooling two large RA cohorts consisting of 3,328 patients with RA, we were able to identify >200 RA-ILD cases, who all met stringent classification criteria for clinically apparent RA-ILD. Furthermore, we relied on HRCT imaging to identify and categorize cases and compared patients with RA-ILD to patients with RA who had no clinical evidence of RA-ILD on medical record review and no evidence of interstitial lung abnormalities on a research review of HRCT. Because of the nature of the data collected by the cohorts, we had detailed information on smoking history and intensity, which is a significant risk factor for both RA and lung disease.

Our study also has potential limitations to consider. First, we relied on clinically performed HRCT to be certain about the case and control groups related to ILD status as the outcome of interest. The use of clinically imaged controls may introduce the possibility of a selection bias within the control groups. However, when we performed a sensitivity analysis that included all patients with RA, with and without imaging, who did not have ILD, we observed similar findings. Although we are confident in the case/control status of those in our main analysis, we could not analyze other patients for possible subclinical RA-ILD in a broader patient population or perform time-to-event analyses. Research is ongoing to prospectively perform HRCT for research purposes and observe patients longitudinally to better investigate the natural history of RA-ILD before clinical onset.

Second, we used HRCT findings to classify RA-ILD subtypes because few patients had histopathologic results. Lung biopsy is rarely performed in patients with RA-ILD, and therefore, our use of HRCT aligns with common clinical practice. Additionally, categorization of RA-ILD subtypes by radiologic findings alone has been used in previous research investigating differences in RA-ILD outcomes by subtype.[6,8] However, additional research has demonstrated that HRCT pattern may misclassify ILD subtypes.[47,48] Third, RA disease activity measures are not available for the MGB Biobank RA cohort, and we were therefore not able to incorporate these data into our analyses. Although RA disease activity is available in BRASS, these data were not timed to RA-ILD onset. Because of the nature of the case–control study, we were limited in investigating the possible associations of RA medications on RA-ILD risk. Although trials are ultimately needed to firmly establish the pulmonary safety of disease-modifying antirheumatic drugs,[49] cohort studies using pharmacoepidemiologic methods, such as target trial emulation, should be pursued. However, we were able to identify multiple baseline factors associated with RA-ILD and key subtypes that may inform risk prediction and screening strategies.

Finally, although we used two separate cohorts, they were recruited from the same health care system and were predominantly White. Furthermore, most patients in both cohorts were evaluated and treated at academic rheumatology practices, and there was a high proportion of seronegative patients. This may limit generalizability to other populations with RA and health care systems in more diverse and different geographic settings. Independent validation of our findings in other RA-ILD cohorts with phenotyping of subtypes is an important area of future investigation.

In conclusion, we investigated risk factor profiles for RA-UIP and RA-NSIP and for fibrotic and nonfibrotic RA-ILD. RA-UIP was associated with older age and male sex, whereas NSIP was most strongly associated with RA autoantibodies. The combination of male sex, seropositivity, and smoking conferred nearly seven-fold risk of RA-UIP. These findings may help clarify RA-ILD heterogeneity and inform future screening strategies for RA-ILD.

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/Helsinki Declaration requirements.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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BRIEF REPORT

Power of Representation in Educational Materials: Teaching Cutaneous Lupus Across Skin Tones in an Interactive Module

Alex Tinianow,[1] Dana Sous,[2] Damien Abreu,[1] Trisha B. Scharff,[1] Michael Thomashow,[3] Susan Bayliss,[4] Sarah Goglin,[5] Joe R. Monroe,[6] Muithi Mwanthi,[1] Heather A. Jones,[7] and Lisa Zickuhr[1]

Objective. Clinicians report low confidence assessing cutaneous lupus erythematosus (CLE) lesions, especially for patients who identify as Black, Indigenous, and People of Color (BIPOC) who are historically excluded from educational materials. To address this, we created an online, interactive module teaching an approach to assessing CLE across skin tones and measured its impact on medical knowledge and confidence.

Methods. Our team created a module with case-based methods to introduce an approach to CLE, common mimicking rashes, and tips for photographing cutaneous lesions in BIPOC. Graduate medical trainees from five academic institutions completed the module. Using surveys and pre–post testing, we assessed changes in medical knowledge and clinical confidence along with learner satisfaction, comparing responses using Wilcoxon-signed rank tests and chi square analysis. We assessed the module's representation of light, medium, and dark skin tones with chi square analysis.

Results. The module represented light, medium, and dark skin tones ($\chi^2 = 4.788$, $P = 0.091$) among 102 images (77.5%, n = 79) were novel images from authors' personal libraries. Ninety-four participants completed the postmodule test and evaluation survey. Analyses revealed significant improvement in medical knowledge identifying serologic studies associated with subacute CLE ($\chi^2 = 14.035$, $P < 0.001$) and describing how to photograph rashes ($\chi^2 = 38.211$, $P < 0.001$). Participants reported improved confidence across all learning objectives after module completion ($P < 0.001$).

Conclusion. This module is the first to introduce an approach to assessing CLE across skin tones, effectively increasing medical knowledge and confidence among graduate medical trainees.

INTRODUCTION

Inclusive educational materials prepare clinicians to deliver equitable care. However, patients who identify as Black, Indigenous, and People of Color (BIPOC) historically have been excluded from medical materials (1,2). This shortcoming impairs clinicians' skills assessing rashes in BIPOC (3,4) and contributes to inferior outcomes in which BIPOC experience delays in diagnosis, more aggressive disease, and lower confidence in their providers (5,6).

Cutaneous lupus erythematosus (CLE) presents one example in which inequitable representation of BIPOC in medical education materials impairs clinicians' diagnostic acumen (3). CLE, consists of multiple patterns, namely, acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) (7), while manifesting differently across skin tones. Inflammatory cells infiltrate the dermis in CLE, reflecting red light and producing rashes with reddish coloration in light skin tones. Among BIPOC, additional melanin influences light's reflection, and CLE appears violaceous,

[1]Alex Tinianow, MD, Damien Abreu, MD, PhD, Trisha B. Scharff, MD, MPHS, Muithi Mwanthi, MD, PhD, Lisa Zickuhr, MD, MHPE: Washington University School of Medicine, St. Louis, Missouri; [2]Dana Sous, MD: Kansas University, Kansas City; [3]Michael Thomashow, MD: University of California - San Francisco, San Francisco, and Alameda Health System, Oakland, California; [4]Susan Bayliss, MD: Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri; [5]Sarah Goglin, MD: University of California, San Francisco; [6]Joe R. Monroe, PA, MPAS: Oklahoma City Veterans Affairs Health Center, Oklahoma City; [7]Heather A. Jones, MD: Meramec Dermatology, Arnold, Missouri.

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

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SIGNIFICANCE & INNOVATIONS

- Skin tone representation within medical education materials influences health care providers' clinical acumen in caring for Black, Indigenous, and People of Color (BIPOC).
- Providers are requesting learning opportunities that enhance their ability to care for BIPOC, including in the domain of cutaneous lupus erythematosus (CLE).
- Collaborations among educators facilitate representation of BIPOC in teaching materials.
- An inclusive, online, interactive module can effectively increase learners' confidence in assessing CLE across skin tones.

requiring clinicians to recognize nuanced manifestations across skin tones. Clinicians, recognizing this complexity, seek additional training assessing CLE in BIPOC (3).

Effective educational initiatives represent people equitably and use strategies grounded in learning theory. Piaget's cognitive learning theory posits that schema are the fundamental structure of knowledge and that people learn by restructuring them through educational experiences, such as case-based learning (8). As a unit of knowledge, the subtypes of CLE present a schema layered with additional nuance of the different manifestations of CLE among skin tones.

In response to clinicians' requests for training materials that improve their confidence assessing CLE in BIPOC, we created, implemented, evaluated, and refined an online, interactive module that introduces an approach to CLE across skin tones. We leveraged the cognitive learning theory, presenting educational content according to the CLE classification schema via case-based learning. Primarily, we aimed to improve learners' knowledge and confidence assessing CLE across skin tones. Secondarily, we sought to enhance learners' awareness of correlating CLE with serologic findings and risk for systemic lupus, as well as optimizing photodocumentation among BIPOC.

MATERIALS AND METHODS

Assembling our team. We assembled a team of medical educators from multiple specialties and professions with shared clinical and research interests in CLE among BIPOC. Clinical experts (SG, JRM, HAJ, and LZ) wrote learning objectives and outlined educational content. Each expert organized material for trainees (DS, DA, TBS, and MT) to build into the module. We leveraged team members' skills: As a dermatologist who specializes in autoimmune connective tissue diseases, HAJ oversaw content accuracy, as educators familiar with writing multiple-choice questions, SG and LZ organized assessments, and as the member with the most experience creating online modules, LZ directed the module structure.

Building and distributing the module. Our team created an online, interactive module using Rise360 (Articulate) to teach the assessment of CLE across skin tones. In keeping with learners' needs, the module was designed to take 30 to 60 minutes to complete and started with a premodule test, continued through five lessons, and concluded with a postmodule test (3). We structured the lessons around the CLE classification schema, reinforcing the fundamental structure of CLE knowledge to implement cognitive learning theory. We emphasized distinguishing the subtypes of CLE from their common mimics, differentiating the nuanced presentations of CLE among skin tones, and correlating the patterns of CLE with the differential risk of systemic disease. To convey these points, we used interleaving, in which different but related concepts are presented in close proximity to highlight distinguishing features (9). Our lessons also featured tips for photographing cutaneous lesions in BIPOC to improve learners' understanding of photodocumentation in health care.

We presented content using cases to help learners integrate knowledge of CLE into their pre-existing schema. Lessons incorporated branched logic, interactive images, and knowledge-check questions to actively engage learners. Summaries of three to five high-yield facts concluded each lesson.

Our team selected images from our personal libraries, using them in accordance with our institutions' policies for patient privacy. When needed, we incorporated images from the American College of Rheumatology Image Library and other sources under Creative Commons licensure (10,11). We intentionally represented light, medium, and dark skin tones throughout the module.

We distributed a link to the module via email to internal medicine residents and rheumatology fellows at participating training programs. Washington University in St. Louis School of Medicine (WUSM) assigned time in the didactic curriculum for learners to complete the module.

Evaluating and revising the module. We rated the skin tone represented in each image as light, medium, and dark against the Massey-Martin New Immigrant Survey using established methods and compared the number of light, medium, and dark skin tone images using chi square analysis (2,12).

We assessed the change in learners' medical knowledge of CLE across skin tones using premodule and postmodule tests. The premodule and postmodule tests contained the same five multiple-choice questions, which in aggregate assessed all the module's learning objectives. We wrote questions following the National Board of Medical Examiners' Item Writing Guide to gauge application of knowledge within the confines of multiple-choice assessment (13). We compared the percentage of correct premodule and postmodule responses for each question using chi square analysis.

We wrote an evaluation survey that appended the postmodule test. We assessed learners' self-reported confidence with CLE across skin tones using retrospective pre- and post-Likert scale questions, asking participants to rate their confidence for each of the learning objectives on a scale from 1 (not competent at all) to 4 (extremely competent). We compared premodule and postmodule responses using Wilcoxon-signed rank tests and calculated the effect size for each question.

We also assessed learners' satisfaction with the module using Likert scale questions targeting the quality of the module and the relevance of the content. We invited narrative comments for additional feedback. Lastly, learners provided demographic information and reported the amount of time taken to complete the module.

Learners submitted their responses to premodule and postmodule tests, as well as evaluation surveys anonymously via Qualtrics. We accepted data from partially completed tests and surveys. Evaluation surveys were linked to postmodule test data but were independent of premodule test responses. After synthesizing these evaluation data, our team edited the module to improve its quality. We performed statistical analyses using SPSS (IBM). The study protocol complied with the World Medical Association Declaration of Helsinki, and the Washington University School of Medicine Institutional Review Board approved our study with waived informed consent (#202201184).

Table 1. Demographics of learners, as submitted on the postmodule evaluation survey*

Demographics	Number of participants	Percentage
Total	94	100
Institution		
Albert Einstein College of Medicine	4	4.3
University of Alabama Birmingham–Heersink School of Medicine	3	3.2
University of California San Francisco School of Medicine	4	4.3
University of Texas Medical School at Houston	5	5.3
Washington University in St. Louis School of Medicine	74	78.7
Not specified	4	4.3
Training level		
Medical student	1	1.1
PGY-1	0	0
PGY-2	35	37.2
PGY-3	38	40.4
PGY-4	7	7.4
PGY-5	7	7.4
PGY-6 or above	3	3.2
Not specified	3	3.2
Specialty		
Internal medicine	72	76.6
Rheumatology	19	20.2
Not specified	3	3.2

* PGY = postgraduate year.

RESULTS

We created an online, interactive module using case-based instructional methods to teach health care providers how to assess cutaneous lupus rashes across skin tones (https://rheumatology.wustl.edu/fellowship-program/courses/). The module featured 102 images, with 77.5% (n = 79) representing images from authors' personal image libraries, 8.8% (n = 9) from American College of Rheumatology Image Library, 8.8% (n = 9) from journal publications, 2.9% (n = 4) from Wikimedia (https://www.wikimedia.org/), and 1.0% (n = 1) from Flickr (https://www.flickr.com/). Overall, the module equally represented light (40.2%), medium (36.3%), and dark (23.0%) skin tones ($\chi^2 = 4.788$, $P = 0.091$).

Although 132 learners completed the premodule test, 104 participants answered postmodule questions, and 94 participants completed the postmodule evaluation survey (Table 1), representing 78.8% postmodule test and 71.2% evaluation survey response rates. Most participants were from WUSM (78.7%) and identified as internal medicine residents (76.6%). The most common training level was the third postgraduate year (40.4%).

Table 2 shows the change in medical knowledge of CLE across skin tones compared between the premodule and postmodule tests. At baseline in the premodule test, there was a high percent of correct scores for identifying mimicking rashes of postinflammatory hyperpigmentation (88.6%) and dermatomyositis (85.6%). Participants demonstrated significant improvement in medical knowledge identifying serologic associations with SCLE ($\chi^2 = 14.035$, $P < 0.001$) and describing how to photograph rashes ($\chi^2 = 38.211$, $P < 0.001$). The change in participants' ability to discern the differential risk for systemic lupus improved after the module, but not significantly ($\chi^2 = 0.194$, $P = 0.660$). In a secondary analysis of this question's responses, we investigated if specialty field influenced this outcome by comparing the percentage of correct responses among rheumatology fellows (84.2%) with that of all other trainees (63.5%) to learn there was no significant difference between them ($\chi^2 = 2.703$, $P = 0.100$).

Data regarding learners' self-reported confidence in assessing CLE across skin tones from premodule to postmodule showed a significant increase across all learning objectives (Table 3). Effect sizes ranged between 0.706 and 0.825, representing the module's strong influence on learners' confidence. Participants' confidence identifying SCLE lesions improved the most ($r = 0.825$). Most participants (97.8%, n = 89 of 91) agreed that the content was relevant to their practice and that they will change their clinical approach to CLE after completing the module. All (100%, n = 91 of 91) participants agreed that the module was high quality and presented a variety of skin tones. The mean ± SD time to complete the module was 44.66 ± 15.45 minutes.

Many participants reflected positively on their experience with the module. Learners felt that it was an "excellent module"

Table 2. Change in medical knowledge between premodule and postmodule tests, presented as the percentage of correct responses and evaluated with chi-square analysis*

Focus of question	Premodule correct responses (N = 132) n (%)	Postmodule correct responses (N = 104) n (%)	χ^2	*P*
Identifying a mimicking rash (postinflammatory hyperpigmentation)	88.6 (117)	90.4 (94)	0.006	0.940
Identifying a mimicking rash (dermatomyositis)	85.6 (113)	96.2 (100)	0.549	0.459
Serologic association with SCLE	37.1 (49)	76.9 (80)	14.035	<0.001
How to photograph rashes	24.2 (32)	90.4 (94)	38.211	<0.001
Differential risk for systemic lupus	62.1 (82)	67.3 (70)	0.194	0.660

* SCLE = subacute cutaneous lupus.

that was "interesting and practical with high-yield teaching points." Others "loved the layout of the modules and the format" and how it "allowed you to test yourself while going through." One participant felt "the explanations for why an answer choice is wrong or right [was] also done much better than usual." Another participant said, "Overall, amazing content and I truly have an increased confidence due to developing an approach to lupus rashes in various skin tones as a result of this module. I am eager to put it to use and refine it as needed." Several participants also appreciated the examples of BIPOC, saying there were "very helpful picture examples including different skin tones," and that the module "[provided] a lot of education on a topic I knew minimal about before starting."

Narrative comments also highlighted areas of potential improvement. Some participants requested even more images representing BIPOC, saying that they "would have liked more dark skin examples." Others noted that sometimes "the images [were] too small." Some participants asked for a section on "specific treatments for the different types of lupus rashes," and to streamline the list of labs and tests needed "to secure the diagnosis" of each subset of CLE. Based on these comments, we reinforced diagnostic plans for each type of cutaneous lupus in the lessons' summaries, incorporated an overview of treatment options for the subtypes of CLE, and emphasized in each lesson that double clicking an image increases its size.

DISCUSSION

Our module is the first of its kind to introduce an approach to assessing CLE across skin tones. The module increased learners' medical knowledge and self-rated confidence evaluating CLE in people with fair skin and BIPOC. Secondarily, the module improved trainees' awareness of the asssociations between CLE manifestations with serologic studies and risk for systemic lupus, as well as techniques for photodocumentation in BIPOC.

Following cognitive learning theory, we used the CLE classification schema as a fundamental unit of knowledge and constructed the module around the characterization of ACLE, SCLE, and CCLE (8). We incorporated interactive instructional methods for learners to internalize CLE knowledge and apply it during assessment (14). Learners' medical knowledge and confidence addressing CLE across skin tones significantly improved after completing the module, and narrative comments described learners' appreciation for the interactive instructional methods, underscoring the success of our strategy.

Table 3. Change in mean scores of participants' self-reported competence fulfilling learning objectives before and after the module using a Likert Scale (1 = not competent at all; 2 = a little competent; 3 = moderately competent; 4 = extremely competent)*

Competency domain	Mean score before module†	Number of responses	Mean score after module	Number of responses	Z	Effect size (*r*)	*P*
Assessing CLE in fair skin	2.11	93	2.92	92	−7.374	0.765	<0.001
Assessing CLE in BIPOC	1.67	93	2.66	92	−7.725	0.801	<0.001
Identifying ACLE lesions	2.14	93	2.91	92	−6.812	0.706	<0.001
Identifying SCLE lesions	1.60	93	2.75	92	−7.961	0.825	<0.001
Identifying CCLE, discoid variant lesions	1.97	93	2.92	92	−7.258	0.753	<0.001
Differentiating CLE from common mimicking rashes	1.67	92	2.68	92	−7.758	0.809	<0.001
Correlating the pattern of CLE with the differential risk of SLE	1.67	91	2.92	91	−7.692	0.806	<0.001
Photographing rashes in patients with any skin tone	1.95	92	3.02	91	−7.448	0.781	<0.001

* ACLE = acute cutaneous lupus; BIPOC = Black, Indigenous, and People of Color; CCLE = chronic cutaneous lupus erythematosus; CLE = cutaneous lupus erythematosus; SCLE = subacute cutaneous lupus; SLE = systemic lupus erythematosus.
† Measured retrospectively.

The greatest investment of resources occurred upfront during module development, when team members sourced images, organized content, and infused their expertise into the module. Our team structure maximized members' contributions by leaning into strengths, assigning tasks to people with previous experience, and pairing clinical experts with trainees. The result is a self-contained, self-directed module available online free of charge that is easily sustainable and scalable. The module may be used in any graduate medical training program without needing to recruit local content experts to teach the material.

Our process highlights the importance of collaborations in education. Our team represents three geographic locations in the United States. We pooled our personal image libraries from treating patients in these regions and created a comprehensive module representing light, medium, and dark skin tones. Creative Commons, a nonprofit organization that provides licenses and public domain tools to help grant copyright permissions, and the American College of Rheumatology Image Library further enhanced this collaboration (9,10). The usefulness of resources available for free or to college members underlines their importance in supplementing and enhancing representation in educational materials.

Our module intentionally incorporated BIPOC into medical education materials, a necessity for preparing clinicians to deliver equitable care. Learners praised the module for the importance of its content, relevance to their practice, and inclusion of many skin tones. As a result, learners reported increased confidence assessing CLE in patients with fair skin and in BIPOC. However, learners requested even more images of dark skin tones, revealing the module's equal representation of skin tones did not achieve equity. Educators may need to overrepresent BIPOC in order to overcome knowledge gaps incurred from BIPOC's historic exclusion from education materials.

The most notable improvement in objective knowledge related to photographing rashes, with greater than 90% of participants answering correctly on the postmodule test. The knowledge of how to capture images of skin lesions in BIPOC lays the foundation for quality photodocumentation in the electronic health record and BIPOC representation in educational materials. Many educational initiatives overlook this topic, and we demonstrate the feasibility of its integration.

Our project has several limitations. First, our learners consisted of internal medicine residents, rheumatology fellows, and one medical student. The participation of only one medical student precludes generalizing results to undergraduate medical learners. Additionally, the majority of participants trained at WUSM, potentially oversampling learners from similar clinical backgrounds and baseline knowledge. Third, knowledge assessment was limited to five multiple-choice questions that, in the absence of validated questions, we wrote de novo. This strategy became further limited when two of the five questions tested previously secured medical knowledge with high rates of correct responses in the premodule test. Finally, multiple-choice questions and learner confidence do not equate to clinical skill, and our evaluation plan could not measure the module's impact on patient care because of limitations associated with time, financial resources, the targeted learner population, and confidentiality.

Future research can build on our successes. An online, interactive module proves effective at teaching an approach to CLE across skin tones, and this method can be applied to teaching other autoimmune dermatologic conditions in BIPOC. The population of learners can be expanded to continuing medical education and other clinical specialties, such as dermatology and nephrology. Furthermore, the module could be combined with clinical learning opportunities, including those found in dermatology-rheumatology clinics (15).

In conclusion, our module offers an effective, scalable, online, interactive learning activity that teaches an approach to assessing CLE across skin tones, as well as correlating serologic and systemic associations of CLE. It also demonstrates the power of collaboration among educators to represent BIPOC within teaching materials. Our approach can guide educators as they design materials inclusive of BIPOC, responding to clinicians' requests for additional training in this domain. The health care system must enact many changes to reverse its contributions to systemic racism against BIPOC. The reformation of medical education to represent and integrate BIPOC into materials contributes one step toward delivering equitable health care.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Zickuhr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tinianow, Sous, Abreu, Scharff, Thomashow, Bayliss, Goglin, Monroe, Mwanthi, Jones, Zickuhr.

Acquisition of data. Tinianow, Sous, Abreu, Scharff, Thomashow, Bayliss, Goglin, Monroe, Mwanthi, Jones, Zickuhr.

Analysis and interpretation of data. Tinianow, Sous, Abreu, Scharff, Thomashow, Bayliss, Goglin, Monroe, Mwanthi, Jones, Zickuhr.

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Training to Increase Minority Enrollment in Lupus Clinical Trials With Community Engagement: Enhancing Lupus Clinical Trial Recruitment Through Provider and Community Health Worker Engagement

Saira Z. Sheikh,[1] Tessa Englund,[1] Andrew Simkus,[2] Nicole Wanty,[2] Annie McNeill,[2] Kristen Holtz,[2] Tenesha Hood,[3] Starla Blanks,[3] Maria Allen,[4] Katherine Holben,[1] and Allen Anandarajah[4]

Objective. This study evaluates the effectiveness of the Training to Increase Minority Enrollment in Lupus Clinical Trials with Community Engagement (TIMELY) program on enhancing referrals of underrepresented patients to lupus clinical trials. TIMELY leverages two existing American College of Rheumatology online educational initiatives: Materials to Increase Minority Involvement in Clinical Trials (MIMICT), a continuing medical education activity for health care providers, and the community health worker (CHW) Lupus Clinical Trials Training (LuCTT). TIMELY introduced a unique roundtable meeting format to build on the existing online educational programs and facilitate discussions between local clinical trial sites and provider and CHW participants.

Methods. This study used an online pretest and posttest design to assess changes in theory-based behavioral predictors of lupus clinical trial referrals and engagement (ie, knowledge, attitudes, self-efficacy, and intentions) among providers and CHWs. Participants completed MIMICT or LuCTT and then were eligible to participate in roundtable meetings. Paired *t*-tests were used to assess changes in composite scores before and after the intervention for each of the outcomes.

Results. The final sample included 40 providers and 18 CHWs. Knowledge scores increased significantly for both providers ($P < 0.01$) and CHWs ($P < 0.001$) on completion of MIMICT and LuCTT, respectively. After participating in the TIMELY roundtable, providers' composite scores for self-efficacy and intentions significantly increased ($P < 0.001$). Provider self-efficacy gains were sustained at three months' follow-up ($P < 0.001$).

Conclusion. These promising findings highlight the potential and opportunities for the TIMELY program to improve behavioral predictors of trial referrals, including CHW knowledge and providers' knowledge, self-efficacy, and intentions to refer underrepresented patients to lupus clinical trials.

INTRODUCTION

Clinical trials in the United States have historically failed to adequately enroll participants that reflect the racial and ethnic diversity of the patient population.[1] This issue is clearly exemplified for clinical trials in systemic lupus erythematosus (hereafter, "lupus"), which disproportionately affects racial and ethnic minority groups, who experience higher prevalence and severity of the disease.[2] For example, the prevalence of lupus is much higher among Black and African American patients than White patients,[3] with Black patients representing about 43% of patients with prevalent lupus in the United States and White patients composing about 33% of patients with lupus.[4] However, between 1997 and 2017, Black patients only represented 14% of

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[1]Saira Z. Sheikh, MD, Tessa Englund, PhD, MPH, Katherine Holben, BA: University of North Carolina at Chapel Hill; [2]Andrew Simkus, MSc, Nicole Wanty, MA, Annie McNeill, MPH, Kristen Holtz, PhD: KDH Research & Communication, Atlanta, Georgia; [3]Tenesha Hood, MA, Starla Blanks, MBA, MPH: American College of Rheumatology, Atlanta, Georgia; [4]Maria Allen, LPN, Allen Anandarajah, MD, MS: University of Rochester Medical Center, Rochester, New York.

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Address correspondence via email to Saira Z. Sheikh, MD, at szsheikh@email.unc.edu.

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SIGNIFICANCE & INNOVATIONS

- The American College of Rheumatology's (ACR) Training to Increase Minority Enrollment in Lupus Clinical Trials with Community Engagement (TIMELY) program leverages two established educational interventions for providers and community health workers (CHWs) and incorporates a novel roundtable discussion component to improve representation of racially and ethnically diverse patients in lupus clinical trials.
- Participants received training on advancing representation of diverse participants in lupus clinical trials via one of two online courses developed by the ACR: the Materials to Increase Minority Involvement in Clinical Trials continuing medical education activity for health care providers and the CHW Lupus Clinical Trials Training program for CHWs.
- Community roundtable meetings were held for providers and CHWs and allowed for dynamic discussions of facilitators and barriers to lupus clinical trial enrollment.
- Findings from this evaluation highlight the TIMELY program's potential to improve behavioral predictors of provider and CHW engagement and referral of underrepresented patients to lupus clinical trials.

participants in lupus clinical trials, whereas White patients were overrepresented at 51% of enrolled participants.[4] Inadequate representation of diverse patients in clinical trials can exacerbate inequities in access to new and innovative treatments among underrepresented patient populations.[5]

Lupus symptoms vary widely and range from mild to severe. Typically, patients experience fatigue, rashes, arthritis, and fever, but they may also experience serious, life-threatening manifestations, including chronic inflammation and damage to the kidneys, heart, lungs, eyes, and brain.[6] There is currently no cure for lupus, but early diagnosis and proper treatment can mitigate lupus morbidity and mortality, allowing patients diagnosed with lupus to reduce the physical, psychological, social, and quality-of-life impact of lupus.[7] Black and Hispanic or Latino patients have increased disease symptom severity, experience more lupus-related complications, and have two- to three-fold higher mortality rates compared to non-Hispanic White patients.[4,8,9] Ensuring representation of racially and ethnically diverse patients in lupus clinical trials is essential to reduce the physical, psychological, and social impact of lupus on patients' quality of life. Increasing the representation of diverse populations, however, would require overcoming a plethora of challenges confronted by both patients and health care providers.

The majority of patients who participate in clinical trials learn about them from their health care provider (hereafter, "provider"),[10] highlighting the importance of providers in addressing disparities in clinical trial representation. However, providers face many barriers that hinder them from referring patients to clinical trials. These include lack of access to information about clinical trials, lack of familiarity with clinical trial sites and referral processes, implicit biases, and beliefs that clinical trials could negatively impact the patient or their relationship with their provider.[11] Patients also face many obstacles toward enrolling in clinical trials, such as lack of awareness of and access to clinical trial opportunities, meeting rigorous eligibility criteria, feelings of intimidation from the informed consent process, concerns about possible side effects of treatments, transportation difficulties, and mistrust of medical systems in the context of past and present structural racism and discrimination.[12]

Previous interventions have shown success in training trusted community members about lupus clinical trials and encouraging them to connect with patients.[13] One method of community engagement involves the use of community health workers (CHWs), frontline public health workers who have especially close connections to the communities they serve.[14] Engagement with CHWs has been shown to be effective at improving knowledge and awareness of clinical trials in general,[15] including through the *Promotora de Salud* (*promotor* [*a*]) model for Hispanic or Latino communities, in which *promotoras* provide culturally appropriate services and act as patient advocates, educators, mentors, outreach workers, and translators.[16] However, there is a dearth of research exploring community engagement approaches to improve participation of racially and ethnically diverse patients in lupus clinical trials.

To address provider-side barriers to recruitment of underrepresented patients into lupus clinical trials, the American College of Rheumatology (ACR) developed the Materials to Increase Minority Involvement in Clinical Trials (MIMICT) model. MIMICT has been shown to be effective in improving providers' knowledge of clinical trials as well as their self-efficacy and intentions to refer racially and ethnically diverse patients into clinical trials.[17] The educational components of MIMICT focus on disparities in lupus and barriers to clinical trial participation faced by African American and Latino patients with lupus. The educational content is tailored to the unique role that health care providers can play in engaging their own patients in discussions about lupus clinical trials and ensuring that patients have the information needed to make informed decisions about clinical trial participation. The ACR also developed the CHW Lupus Clinical Trials Training (LuCTT) program to address patient-reported barriers by educating and training CHWs to connect with African American and Latino patients with lupus. For a more detailed description of the online MIMICT and LuCTT training programs that the Training to Increase Minority Enrollment in Lupus Clinical Trials with Community Engagement (TIMELY) built on, see Table 1.

The ACR launched TIMELY initiative to reduce racial disparities in lupus clinical trials. The TIMELY program combines the existing MIMICT and LuCTT intervention models to address both provider- and patient-reported barriers to lupus clinical trial participation for African American and Latino patients, with the addition

Table 1. Description of ACR's MIMICT and LuCTT online training programs*

	MIMICT[a]	CHW LuCTT[b]
Target populations	Providers (primary care providers, rheumatologists, dermatologists, nephrologists)	CHWs
Goal	To develop providers' knowledge about, attitudes toward, self-efficacy, and behavioral intentions to educate and refer African American and Latino patients to lupus clinical trials.	To develop CHWs' knowledge and skills to effectively conduct outreach on lupus clinical trials and support African American and Latino patients and their families during recruitment, enrollment, and participation in lupus clinical trials.
Description	MIMICT is specifically designed to address provider- and patient-specific barriers[11] to overcoming disparities in lupus care and clinical trial enrollment among underrepresented patients with lupus.	LuCTT is a program that is designed to support recruitment and enrollment of underrepresented populations affected by lupus into clinical trials through an online and in-person training course for CHWs.
Online training component	A six module online continuing medical education activity; MIMICT presents key information about lupus in four modules and content focused on dermatologists and nephrologists in two modules.	Five online modules educate CHWs on barriers to lupus clinical trial participation faced by African American and Latino patients.

* ACR, American College of Rheumatology; CHW, community health worker; LuCTT, Lupus Clinical Trials Training; MIMICT, Materials to Increase Minority Involvement in Clinical Trials.
[a] https://thelupusinitiative.org/mimict-2/.
[b] https://thelupusinitiative.org/luctt/chw-organizations/.

of roundtable discussion sessions to promote community engagement and increase opportunities for providers and CHWs to refer underrepresented patients to clinical trials in their communities. The roundtable sessions were designed to be an opportunity for TIMELY participants to review the MIMICT (provider roundtables) and LuCTT (CHW roundtables) trainings and materials as well as facilitate engagement and discussion with local clinical trial sites about the importance of and opportunities to refer underrepresented patients to clinical trials in their community. The primary goals of the TIMELY program were to increase providers' and CHWs' knowledge on lupus clinical trials and methods to overcome barriers to enrollment using the MIMICT and LuCTT models. The program further aimed to increase providers' and CHWs' attitudes, self-efficacy, and intentions to refer racial and ethnic minority patients to lupus clinical trials through community roundtable discussions. The objective of this study was to explore the impact of the novel TIMELY program on behavioral predictors of provider and CHW engagement and referral of patients to lupus clinical trials.

MATERIALS AND METHODS

Participants. Recruitment of providers and CHWs took place from May 2022 to March 2023. Participants were recruited from two geographic areas served by the University of North Carolina at Chapel Hill (UNC) (providers) and Curamericas Global (CHWs) in North Carolina and by the University of Rochester Medical Center (URMC) (providers) and CHW Association of Rochester (CHWs) in New York. These locations were chosen based on their status as medically underserved areas, which are geographic areas and populations identified by the Health Resources and Services Administration as having a shortage of primary health care services.[18] Providers who participated in the study were required to have currently or previously cared for a patient with confirmed or suspected lupus and to have not previously participated in the ACR MIMICT continuing medical education (CME) activity. CHWs were eligible to participate if they reported conducting community outreach activities in the last 12 months and had not previously participated in the ACR LuCTT program. All participants were required to have internet access to complete the online surveys and training.

Study design and interventions. We obtained ethical approval for this study from the KDH Research & Communication Institutional Review Board (IRB) (FWA00011177, IRB 00005850), the UNC IRB (#22-1499), and the URMC IRB (FWA00009386). This study used a pretest and posttest study design to evaluate changes in four clinical trial–related cognitive outcomes theoretically related to behavior change around clinical trial referrals and engagement: knowledge, attitudes, self-efficacy, and intentions.[19] The outcome measures selected for this study were adapted from the approach taken in the initial evaluation of MIMICT, which was based on the theory of planned behavior,[19] as detailed in our previous article.[17]

Participating providers were instructed to complete MIMICT, a self-directed online CME activity with four core modules structured for primary care providers.[20] Subsequently, two modules, one for dermatologists and one for nephrologists, were developed. The MIMICT CME activity was developed to educate providers on the basics of clinical trials, discerning lupus symptoms and associated health disparities, understanding the clinical trial referral process, and applying strategies for culturally competent communication when engaging with diverse patient populations. CHWs who participated in the study completed the LuCTT five-

module online program, which consisted of interactive training to improve CHWs' skills in educating Black and Hispanic or Latino patients with lupus about clinical trials. MIMICT and LuCTT are described in more detail in Table 1.

Before completing the MIMICT or LuCTT online training, participants completed a pretest survey to assess their knowledge of lupus clinical trials. Immediately following their completion of the online training, participants took a posttest survey to measure change in knowledge. After completing the online training and associated surveys, provider and CHW participants were then invited to attend roundtable discussion sessions hosted by local clinical trial sites (UNC or URMC) (providers) or the ACR (CHWs). Those who were to attend the roundtable sessions completed an initial survey assessing their baseline attitudes toward lupus clinical trials as well as their self-efficacy and intentions to refer individuals to lupus clinical trials. Participants completed additional follow-up surveys approximately one month and three months after attending the roundtable session to assess changes in their attitudes, self-efficacy, and intentions. Roundtable sessions were held independently for providers and CHWs and facilitated by ACR staff and site leads from UNC and URMC.

TIMELY roundtable sessions were held between September 2022 and May 2023 and lasted no more than two hours. The roundtable discussions built on topics covered in the online training modules and allowed participants to learn about local clinical trial opportunities from the hosting sites. Providers also received information on local CHW organizations and resources to share with their patients (eg, MIMICT patient materials). CHWs also received information about TIMELY-trained providers in their area.

Measures. Online surveys were developed to assess changes in participant outcomes following participation in the TIMELY program. Questions were developed to assess knowledge and were adapted from established measures of attitudes,[21–23] self-efficacy,[24] and intentions.[25] Knowledge about, attitudes toward, self-efficacy with, and intentions to refer or engage underrepresented patients to lupus clinical trials were the primary outcomes for providers and CHWs. Likert-type questions that ranged from 1 (strongly disagree) to 10 (strongly agree) were used to assess attitudes, self-efficacy, and intentions regarding lupus clinical trial referrals. We averaged all survey responses into a single composite score for each outcome domain. Knowledge composite scores ranged from 0 to 100, with a score of 100 indicating a participant answered all knowledge questions correctly; missing answers were scored as incorrect. Nephrologist and dermatologist participants received different sets of newly developed knowledge questions for the MIMICT CME evaluation, and thus each were analyzed separately from the main knowledge outcome analyses. The knowledge questions for nephrologists and dermatologists covered similar content as the general providers' survey and included questions about identifying specialist-specific resources. Average composite scores were calculated for the attitude, self-efficacy, and intention outcome measures and included all participants who answered at least 80% of the questions within each domain.

We compared the differences between pretest and posttest scores to assess changes in knowledge associated with participation in the MIMICT CME activity and LuCTT and before and after roundtable participation to assess changes in attitudes, self-efficacy, and intentions associated with participation in the roundtables. All roundtable participants received a follow-up survey to be completed after the roundtable session and a second follow-up survey approximately three months after the follow-up survey, which assessed the same attitude, self-efficacy, and intention outcomes as the baseline survey. Participant satisfaction with the TIMELY program was assessed after completion of the MIMICT CME activity and LuCTT and after participation in the roundtable sessions.

Participating providers were eligible for one CME credit upon completing the MIMICT CME activity and a $100 e-gift card (Amazon or Walmart) upon completion of each roundtable survey, for up to $300 in total incentives. CHWs received a $35 e-gift card (Amazon or Walmart) after completing each roundtable survey, for up to $105 total in incentives.

Statistical analyses. All analyses were conducted using Stata/IC 16.1 statistical software. We used paired z tests to assess differences in the proportion of participants who answered correctly on each individual knowledge question at pretest and posttest. We used paired *t*-tests to assess differences in average composite knowledge scores at pretest and posttest (following completion of the MIMICT CME activity or LuCTT educational intervention). The primary outcomes were analyzed using *t*-tests to compare composite scores of attitudes, self-efficacy, and intentions before and after roundtable participation. Secondary analyses compared composite scores before and after roundtable participation for individual questions and before roundtable participation and at the three-month follow-up. To account for the number of *t*-tests performed with the attitudes, self-efficacy, and intentions composite scores, Bonferroni's adjusted significance threshold of $P < 0.0167$ was applied.

RESULTS

A total of 54 providers and 45 CHWs were enrolled in the study (Figure 1). From this provider count, we omitted one provider who was determined to be ineligible (specialty area of practice), one provider who was asked to be removed from the study, and eight providers who were lost to follow-up. For the final CHW count, we omitted the 14 CHWs who were lost to follow-up. The final sample consisted of 44 providers (including 11 dermatologists and 5 nephrologists) and 31 CHWs who completed the MIMICT CME activity and LuCTT posttest, of whom 40 providers and 18 CHWs participated in a roundtable discussion and

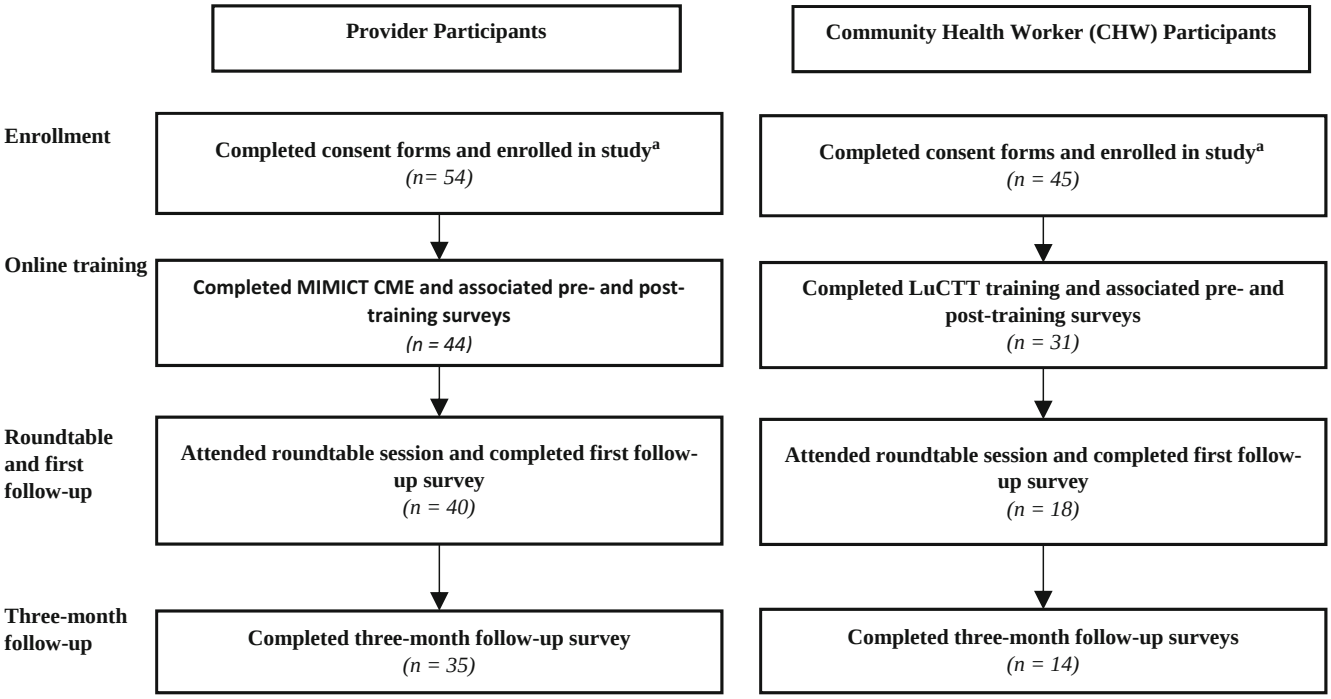

Figure 1. TIMELY study participant flowchart. [a]Providers and CHWs who enrolled in the study and were later found to be ineligible or who asked to be removed from the study are omitted from this count. CME, continuing medical education; LuCTT, Lupus Clinical Trials Training; MIMICT, Materials to Increase Minority Involvement in Clinical Trials; TIMELY, Training to Increase Minority Enrollment in Lupus Clinical Trials with Community Engagement

completed the first follow-up survey (Figure 1). Finally, 35 providers and 14 CHWs completed the three-month follow-up survey. TIMELY participant outcomes are outlined in the following sections for participants in the MIMICT CME activity and LuCTT and respective roundtables held for provider and CHWs. Secondary analyses of individual questions and follow-up comparisons are available in the Supplementary Material.

Health care provider participant outcomes. Among the 44 provider participants, most identified as female (68.2%) and White (63.6%) and were practicing physicians (84.1%); provider participants also included nurse practitioners (9.1%) and physician assistants (6.8%). Additional demographic characteristics of TIMELY provider participants are outlined in Supplementary Table 1. Most participating providers practiced in rheumatology (54.6%), dermatology (25%), nephrology (9.1%), or primary care (6.8%) practice settings. Half of participants (50%) reported that they had not referred any patients with lupus to a clinical trial in the past year.

Impact of MIMICT CME activity. From pretest to posttest (after completing the MIMICT training module), composite knowledge scores for providers significantly increased ($P < 0.01$) (Table 2). Composite knowledge scores also significantly increased among dermatologist and nephrologist provider participants from pretest to posttest ($P < 0.01$). Provider results for each individual knowledge question can be seen in Supplementary Table 2. The mean composite satisfaction rating for the MIMICT program was 4.47 ± 0.65 out of 5 possible points. Full provider satisfaction results for MIMICT can be seen in Supplementary Table 3.

Impact of TIMELY roundtable participation. From before to after roundtable participation, composite scores for self-efficacy ($P < 0.001$) and intentions ($P < 0.001$) increased significantly for providers (Table 3); these significant improvements were maintained for self-efficacy through the three-month follow-up survey (Table 4). There was no significant change in composite attitude scores ($P = 0.97$) from before to after roundtable participation. Provider results for each individual attitude, self-efficacy, and

Table 2. Knowledge composite score comparisons by MIMICT CME provider group*

MIMICT CME group	Pretest mean (SD)	Posttest mean (SD)	*P*
Core MIMICT modules (n = 28)	95.36 (5.76)	98.57 (3.56)	**<0.01**
Dermatology specialty module (n = 11)	84.85 (11.68)	98.48 (5.03)	**<0.01**
Nephrology specialty module (n = 5)	76.67 (9.13)	96.67 (7.45)	**<0.01**

* Nephrologist and dermatologist participants received different sets of newly developed knowledge questions for the MIMICT CME evaluation, and thus each were analyzed separately from the main knowledge outcome analyses. *P* values are derived from *t*-tests. Bold indicates statistical significance at $P \leq 0.0167$. CME, continuing medical education; MIMICT, Materials to Increase Minority Involvement in Clinical Trials.

Table 3. Provider composite score comparisons before and after roundtable participation (n = 40)*

Outcomes	Pretest mean (SD)	Posttest mean (SD)	*P*
Attitudes	6.79 (0.89)	6.78 (0.91)	0.97
Self-efficacy	6.53 (1.62)	7.44 (1.49)	**<0.001**
Intentions	7.12 (2.17)	8.34 (1.78)	**<0.001**

* *P* values are derived from *t*-tests. Bold indicates statistical significance at $P \leq 0.0167$.

Table 5. CHW composite score comparisons before and after roundtable participation (n = 18)*

Outcomes	Pretest mean (SD)	Posttest mean (SD)	*P*
Knowledge	63.44 (19.07)	79.93 (17.78)	**<0.001**
Attitudes	7.87 (1.08)	7.61 (0.87)	0.20
Self-efficacy	8.18 (2.21)	8.90 (1.03)	0.12
Intentions	8.46 (1.25)	9.00 (0.94)	0.08

* *P* values are derived from *t*-tests. Bold indicates statistical significance at $P \leq 0.0167$. CHW, community health worker.

intentions question can be seen in Supplementary Tables 4–6. TIMELY roundtable provider participants' mean satisfaction rating was 9.23 ± 1.10 out of 10 possible points (see Supplementary Table 7 for full provider satisfaction results after roundtable participation by question).

CHW participant outcomes. Among the 31 CHW participants, most identified as female (80.7%) and Black (54.8%) and/or Hispanic or Latino (35.5%) (see Supplementary Table 1 for CHW demographic characteristics). More than 40% of participants reported more than five years of experience working as a CHW (41.9%). Most CHWs reported that they had not received previous training about lupus (96.8%) but that they knew someone in their community who had lupus (71%).

Impact of LuCTT educational course. From pretest to posttest, composite knowledge scores for CHWs who completed the LuCTT training model increased significantly ($P < 0.001$). CHW results for each individual knowledge question can be seen in Supplementary Table 8. The mean composite satisfaction rating for LuCTT was 8.67 ± 1.24 (out of 10 possible points).

Impact of TIMELY roundtable participation. From before to after roundtable participation, there were no significant changes in CHWs' composite scores for attitudes, self-efficacy, or intentions, as outlined in Table 5 (see Supplementary Tables 9–12 for additional data). The mean composite satisfaction score for the CHW roundtables was 8.86 ± 1.19 out of 10 possible points (see Supplementary Table 13 for full CHW satisfaction after roundtable participation by question).

DISCUSSION

The results of this evaluation suggest that the TIMELY program's use of online education and roundtable components is a promising approach to educate providers and CHWs about lupus clinical trials. Both providers and CHWs showed significant increases in knowledge of lupus clinical trials after participation in the MIMICT CME activity and LuCTT. This was true for all three categories of providers (primary care providers and rheumatologists, dermatologists, and nephrologists); however, knowledge results for dermatologists and nephrologists should be interpreted cautiously given the small sample sizes. Additionally, providers demonstrated increased self-efficacy and intentions to refer patients to lupus clinical trials following participation in the TIMELY roundtables. Provider referral is one of the most commonly reported modalities for increasing participation of underrepresented patients in lupus clinical trials.[10] Thus, enhancing providers' understanding of lupus clinical trials, along with bolstering their intentions and self-efficacy in referring patients to lupus clinical trials, supports the potential of the TIMELY program to result in increased engagement of racially and ethnically minority patients in lupus clinical trials.

The TIMELY education component combined with roundtable sessions allowed providers and CHWs to discuss issues and strategies regarding recruitment of racially and ethnically diverse patients into lupus clinical trials. This novel approach of the TIMELY program resulted in improvements in provider participants' knowledge, self-efficacy, and intentions to engage underrepresented patients in lupus clinical trials. However, no change was noted for CHW participants' self-efficacy or intention outcomes, highlighting an opportunity for future research and refinement to improve the TIMELY program components for CHWs. The high levels of satisfaction with the roundtable sessions reported by both providers and CHWs indicate a need for similar opportunities for stakeholder discussion to be incorporated into the design of future programs.

The results of this study were consistent with those of the pilot study for the ACR's MIMICT program.[17] In both studies, providers had significant increases in composite scores for knowledge, self-efficacy, and intentions but no significant changes in

Table 4. Provider three-month follow-up comparisons with baseline and first follow-up*

	Baseline vs 3-mo follow-up			First follow-up vs 3-mo follow-up		
Outcomes	Baseline, mean (SD)	3-mo follow-up, mean (SD)	*P*	First follow-up, mean (SD)	3-mo follow-up, mean (SD)	*P*
Attitudes	6.74 (0.91)	6.83 (0.72)	0.43 (n = 33)	6.78 (0.90)	6.88 (0.65)	0.56 (n = 28)
Self-efficacy	6.46 (1.64)	7.69 (1.46)	**<0.001** (n = 35)	7.32 (1.50)	7.69 (1.46)	0.07 (n = 35)
Intentions	7.10 (2.01)	7.81 (2.06)	0.06 (n = 34)	8.32 (1.78)	7.81 (2.06)	0.11 (n = 34)

* *P* values are derived from *t*-tests. Bold indicates statistical significance at $P \leq 0.0167$.

attitude scores after being exposed to each study's interventions. The lack of significant changes in attitude scores before and after the roundtable sessions for both providers and CHWs may relate to the focus of TIMELY on education and engagement to improve knowledge and intentions to refer patients with online education and roundtable discussions; it may be helpful to incorporate additional time and discussions into future iterations of TIMELY to encourage providers and CHWs to consider their own attitudes toward clinical trials and how these relate to their personal beliefs and behaviors in practice. Additionally, most effect sizes for attitude change are small, as noted by Albarracin and Shavitt[26] in a review of attitudes and attitude change interventions. As such, the results of the present study were also consistent with previous studies aiming to increase provider engagement in clinical trials in fields outside lupus, such as the QuinteT program, which featured workshops with collaborative presentations and exercises,[27] and a study conducted by Jenkins et al[28] that used video training modules followed by mock interviews with patient actors. In both studies, providers showed improvements in outcomes similar to those assessed in our study (eg, significant improvements in knowledge about clinical trials and self-confidence in referring patients). However, provider attitudes toward clinical trials were not assessed in these studies, leading to difficulties in determining why TIMELY participants did not show improvements in attitude scores. Another study by Margevicius et al[29] used individualized interventions based on providers' responses about perceived barriers to clinical trial enrollment to improve provider attitudes toward clinical trials. Taken together, this work highlights an opportunity to enhance understanding of effective components to improve attitudes toward clinical trials in future iterations of the TIMELY program.

Including CHW participants was a novel aspect of the TIMELY program, as was the incorporation of roundtable sessions, an element that has scarcely been used in previous studies aiming to improve engagement in lupus clinical trials. Although CHWs participating in this study showed improvements in knowledge of lupus clinical trials, they did not demonstrate significant improvements in self-efficacy, intention to refer, or attitudes toward engaging patients in lupus clinical trials. One possible reason may be the small number of participants; in the future, recruiting a higher number of participants may increase the statistical power of our results. Additionally, a study from Schapira and Schutt[15] directly involved CHWs in the creation of a training program on clinical trials, which improved both knowledge of and attitudes toward clinical trials in CHW participants. Although the original LuCTT program was developed with CHW trainer and CHW input, the TIMELY adaptation of the LuCTT program may benefit from additional CHW input and incorporation of other LuCTT educational components, such as role play and other interactive opportunities.

This evaluation assessing preliminary outcomes of the TIMELY program had several limitations. Participants were limited to two specific geographic areas where TIMELY was implemented, so the results of this study may be difficult to generalize to other regions or contexts. Future iterations of the TIMELY program should focus on expanding outreach to include a broader sample of geographic locations. Additionally, the online enrollment and survey components of this study may have restricted participation of individuals with limited digital literacy or access. The self-reported outcome measures used in the TIMELY evaluation are subject to social desirability bias[30] and did not include objective measures of patient engagement and referrals around lupus clinical trials. Future studies are needed to examine objective measures of lupus clinical trial engagement and referral rates of underrepresented patients among TIMELY participants and sites. It should also be noted that the significant increase in providers' intentions to refer patients to clinical trials was not maintained at the three-month follow-up survey. Because the increase did approach significance, this could indicate that a larger sample size of participants would have improved these results. The TIMELY intervention did not include components to continue engagement with TIMELY participants after the roundtable discussions, which may have resulted in a lack of sustained effects for intentions scores between the one-month and three-month time points. There may be additional factors at work that were not explored by this study, such as professional identity and clinic-level factors that could impede or facilitate referrals, which have been shown to be important predictors of providers' intentions to recruit for clinical trials.[31] Finally, clinical trial knowledge was not reassessed at the three-month time point, so it cannot be determined from this study that the increases in knowledge shown by both groups of participants were sustained after the posttest.

In conclusion, this evaluation highlights the TIMELY program's potential to improve behavioral predictors of provider and CHW engagement and referral of underrepresented patients to lupus clinical trials. The combination of online training courses and roundtable discussion sessions used in this intervention shows promise in promoting involvement of both providers and CHWs in the recruitment process for lupus clinical trials. Additionally, future studies should incorporate approaches to build partnerships with patients to help overcome provider and patient barriers that limit participation of marginalized communities in lupus clinical trials. Findings from this study will be used to inform future iterations of TIMELY and other intervention programs focused on advancing representation of racially and ethnically diverse patients in lupus clinical trials.

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 Sheikh 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/Helsinki Declaration requirements.

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The Impact of Pregnancy Readiness on Lupus Activity, Maternal Mental Health, and Pregnancy Outcomes

Ceshae C. Harding,[1] Amanda M. Eudy,[1] Cathrine A. Sims,[1] Cuoghi Edens,[2] Mehret Birru Talabi,[3] Rosalind Ramsey-Goldman,[4] Laura Neil,[1] and Megan E. B. Clowse[1]

Objective. Among individuals with systemic lupus erythematosus (SLE) who became pregnant, we explored the impact of medical readiness for pregnancy and personal readiness for pregnancy on the following aspects of maternal health: (1) provider-reported disease activity, (2) patient-perceived disease activity, (3) mood symptoms, (4) pregnancy-related health behaviors, and (5) pregnancy outcomes.

Methods. All study participants were enrolled in a prospective registry, met Systemic Lupus Collaborating Clinics (SLICC) criteria for SLE, and had at least one pregnancy. Patient-reported outcomes were collected at the first rheumatology visit during pregnancy. "Medically ready" for pregnancy was defined as (1) <1 g of proteinuria, (2) no rheumatic teratogens at conception, and (3) continuing pregnancy-compatible SLE medications after conception. "Personally ready" was defined as planned pregnancy based on a London Measure of Unplanned Pregnancy score ≥10. Multivariable logistic regression models estimated the association of pregnancy readiness with each outcome of interest.

Results. Among the 111 individuals enrolled, lack of medical readiness for pregnancy was associated with significantly higher rates of active disease and worse pregnancy outcomes; however, these patients did not perceive themselves as having higher disease activity. Lack of personal readiness for pregnancy was associated with significantly higher patient-perceived disease activity. Although medical readiness did not impact depressive symptoms substantially, lack of personal readiness for pregnancy was associated with much higher maternal depressive symptoms.

Conclusion. To improve pregnancy outcomes among individuals with SLE, greater focus is needed on improving medical optimization before conception. For maternal mental health and quality of life, greater focus is needed on decreasing the incidence of unplanned pregnancy.

INTRODUCTION

Although maternal outcomes among individuals with systemic lupus erythematosus (SLE) are improving, pregnancy in SLE remains higher risk for the mother–infant dyad, with greater maternal and fetal death, preeclampsia, and cesarean sections.[1] Higher-risk pregnancy in this population is attributable to both the underlying pathophysiology of disease and the administration of teratogenic medications for management.[2–4] Unfortunately, the administration of reliable contraception and provider comfort with pregnancy planning discussions remain suboptimal, leaving many individuals with SLE at risk of unintended pregnancy.[5,6] Unplanned pregnancy may be associated with worse pregnancy outcomes in the general population and has been implicated in higher rates of adverse pregnancy outcomes and infant complications specifically in SLE.[7–12] In the general population, unplanned pregnancy has been shown to be associated with increased maternal depression and symptom burden, which may also hold true for the SLE population.[13–15] Among individuals with SLE, unplanned pregnancy is a potentially modifiable risk factor that

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[1]Ceshae C. Harding, MD, Amanda M. Eudy, PhD, Cathrine A. Sims, MD, Laura Neil, BA, Megan E. B. Clowse, MD, MPH: Duke University School of Medicine, Durham, North Carolina; [2]Cuoghi Edens, MD: University of Chicago Medicine, Chicago, Illinois; [3]Mehret Birru Talabi, MD, PhD: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [4]Rosalind Ramsey-Goldman, MD, DrPH: Northwestern University Feinberg School of Medicine, Chicago, Illinois.

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Address correspondence via email to Ceshae C. Harding, MD, at ceshae.harding@duke.edu.

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SIGNIFICANCE & INNOVATIONS

- In patients with systemic lupus erythematosus (SLE), not being "medically ready" for pregnancy was associated with significantly higher provider-reported disease activity and worse pregnancy outcomes.
- Lack of "personal readiness" for pregnancy was associated with significantly higher patient-perceived disease activity, higher maternal symptoms of depression, and lower self-reported maternal health.
- With mental health conditions being the leading cause of maternal death across much of the United States, avoiding unplanned pregnancy among individuals with SLE represents an important step in maternal mental health.
- To improve pregnancy outcomes among individuals with SLE, greater focus is needed on improving medical optimization before conception.

varies in prevalence across different demographics and is associated with lower administration of treatment-specific medications and higher disease activity.[7]

Medical optimization before pregnancy represents another potentially modifiable risk factor in SLE that impacts pregnancy outcomes and maternal health. The American College of Rheumatology's Reproductive Health Guideline recommends conceiving when SLE is well controlled for six months and continuing pregnancy-compatible medications for disease management.[7,16] Pregnancies conceived when the disease is not well controlled have higher rates of adverse pregnancy outcomes and maternal morbidity.[2,7] "Medical optimization" before pregnancy can be classified as "medical readiness" for pregnancy, whereas "pregnancy planning" can be classified as "personal readiness" for pregnancy. Applying these concepts, the impact of medical readiness for pregnancy, personal readiness for pregnancy, and the intersection of these two modifiable risk factors on maternal physical and mental health in SLE is poorly understood. We have also not yet characterized these findings in the context of pregnancy outcomes. In this study among individuals with SLE who became pregnant, we explored the association between medical readiness and personal readiness for pregnancy with the following aspects: (1) provider-reported disease activity, (2) patient-perceived disease activity, (3) mood symptoms, (4) pregnancy-related health behaviors, and (5) pregnancy outcomes.

MATERIALS AND METHODS

Study design. We conducted a prospective cohort study using data from the Maternal Autoimmune Disease Research Alliance (MADRA) Registry. MADRA is a prospective registry that has enrolled pregnant women with rheumatic disease seen in the Duke Autoimmunity & Pregnancy clinic since January 2018. Patients are enrolled following informed consent during the first rheumatology clinic visit in pregnancy (Duke Health Institutional Review Board [IRB] Pro00084014). All MADRA participants who met Systemic Lupus Collaborating Clinics (SLICC) criteria for SLE and completed the London Measure of Unplanned Pregnancy (LMUP) at baseline were included in this study. The study was approved by the Duke Health IRB (Pro00000775).

Measures and outcomes. Patient-reported outcomes, including the LMUP,[17] social determinants of health, patient-perceived SLE activity, and Edinburgh Postnatal Depression Scale (EPDS)[18] were collected during the first rheumatology visit of pregnancy. The LMUP is a six-question, self-reported survey assessing the extent to which an individual intended to become pregnant (Supplementary Materials A).[17] Patient Health Questionnaire-2 (PHQ-2) scores and clinical data, including medications, laboratory results, and provider-reported SLE activity, were obtained at each visit. Pregnancy outcomes of interest included miscarriage, stillbirth, termination, gestational age at delivery, preterm delivery, and preeclampsia.

Pregnancy intention was stratified into three categories: medically ready, personally ready, or both medically and personally ready. Medically ready was defined as <1 g of proteinuria, no rheumatic teratogens at conception, and continuing pregnancy-compatible SLE medications after conception. The definition for medically ready is based on the American College of Rheumatology's Reproductive Health Guideline, evidence-based guidelines from experts in rheumatic and musculoskeletal disease.[16] These three criteria are based on factors that are known key predictors of poor pregnancy outcomes among individuals with lupus. "Personally ready" was defined as a planned pregnancy based on a LMUP ≥10. Individuals were placed into four categories: (1) medically and personally ready, (2) not personally ready (medically ready), (3) not medically ready (personally ready), and (4) not medically or personally ready. For patients missing data on one of the LMUP components (n = 3), the value of the missing item was imputed based on the mean score for their completed items.[17] For patients with missing data on one of the components of EPDS, the study mode for each missing variable was used to impute the missing value (n = 6 patients for EPDS).

Analysis plan. Analyses estimated the association of pregnancy readiness with outcomes of interest. Differences in the prevalence of mood symptoms, patient-reported disease activity, and quality of life by pregnancy readiness were analyzed descriptively using Fisher's exact test or a two-sample *t*-test. Multivariable logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the association of pregnancy readiness with each binary outcome of interest. Multivariable linear regression models estimated β and 95% CIs for the association of pregnancy readiness with each continuous outcome of

interest. To account for correlation between multiple births in the same patient, we used generalized estimating equations with an unstructured correlation matrix. Confounders were assessed based on combined directed acyclic graph minimally sufficient set reduced based on a 10% change in β estimates.[19] Final models were adjusted for a composite variable of social disadvantage, including single or living alone, household income less than $50,000, or Medicare or Medicaid insurance. SAS 9.4. (SAS Institute, Inc) software was used for the analysis.

RESULTS

A total of 111 women were enrolled, with an average maternal age of 29.8 years at 12.7 weeks mean gestational age at entry (Table 1). Among the cohort, 42% self-identified as Black, 41% self-identified as White, and 14% self-identified as other; 11% self-identified as Hispanic. More than one-third of individuals had less than a college education and were insured by Medicare or Medicaid; 41% had an annual household income of less than $50,000 (Table 1). Most were taking hydroxychloroquine (79%), one-third were taking azathioprine, and eight patients had exposure to a teratogen. Across the various demographics, disparities in rates of pregnancy loss, preterm birth, and preeclampsia were greatest among those with a history of lupus nephritis, less than a college education, low social support, and those who self-identified as Black. Half of patients were both medically and personally ready, 20% were neither medically nor personally ready, 16% were medically ready but not personally ready, and 13% were personally ready but not medically ready (Table 1).

Demographics. Compared with individuals who were both medically and personally ready for pregnancy, individuals who were not medically and/or not personally ready for pregnancy were significantly younger, less likely to identify as White, and more likely to be single, live alone or only with children, have less educational attainment, lower annual household income, and more likely to be insured by Medicaid or Medicare (Table 1).

Compared with individuals who were both medically and personally ready for pregnancy, individuals who were not medically ready for pregnancy, regardless of personal readiness, had significantly higher rates of active SLE, including higher Systemic Lupus Erythematosus Pregnancy Disease Activity Index

Table 1. Baseline demographics and clinical characteristics (N = 111)*

	Total (N = 111)	Medically and personally ready (n = 57)	Not personally ready (medically ready) (n = 18)	Not medically ready (personally ready) (n = 14)	Not medically or personally ready (n = 22)	*P* value
Gestational age at entry, mean (SD), wk	12.7 (6.8)	12.2 (7.2)	10.9 (4.9)	14.5 (7.2)	14.3 (7.0)	0.3
Maternal age, mean (SD), y	29.8 (5.0)	31.5 (4.4)	28.6 (6.6)	29.2 (3.2)	26.9 (4.6)	0.001
Race n (%)						0.04
Asian	9 (8)	5 (9)	0 (0)	2 (14)	2 (9)	
Black	47 (42)	19 (33)	10 (56)	4 (29)	14 (64)	
Native American or American Indian	2 (2)	0 (0)	1 (6)	1 (7)	0 (0)	
White	46 (41)	30 (53)	7 (39)	4 (29)	5 (23)	
Other	6 (5)	3 (5)	0 (0)	2 (14)	1 (5)	
Unknown	1 (1)	0 (0)	0 (0)	1 (7)	0 (0)	
Ethnicity: Hispanic, n (%)	12 (11)	3 (5)	0 (0)	5 (36)	4 (18)	0.003
Education level: less than college, n (%)	42 (38)	13 (23)	11 (61)	5 (36)	13 (59)	0.003
Marital status: single, n (%)	24 (22)	4 (7)	2 (11)	3 (21)	15 (68)	<0.0001
Living alone or with children, n (%)	9 (8)	1 (2)	1 (6)	3 (21)	4 (18)	0.01
Medicaid, Medicare, or uninsured, n (%)	39 (35)	7 (12)	10 (56)	8 (57)	14 (64)	<0.0001
Annual household income <$50,000, n (%)	46 (41)	11 (19)	11 (61)	7 (50)	17 (77)	<0.0001
Social disadvantage, n (%)	56 (50)	15 (26)	13 (72)	10 (71)	18 (82)	<0.0001
Primigravida (n = 109), n (%)	38 (35)	18 (32)	7 (39)	4 (31)	9 (41)	0.9
Nulliparous (n = 109), n (%)	58 (53)	33 (59)	8 (44)	5 (38)	12 (55)	0.5
History of lupus nephritis, n (%)	37 (33)	11 (19)	5 (28)	8 (57)	13 (59)	0.003
History of APS n (%)	4 (4)	3 (5)	1 (6)	0 (0)	0 (0)	0.8
Baseline medications						
Teratogen exposure, n (%)	8 (7)	0 (0)	0 (0)	2 (14)	6 (27)	0.0001
Hydroxychloroquine, n (%)	88 (79)	55 (96)	18 (100)	6 (43)	9 (41)	<0.0001
Azathioprine, n (%)	38 (34)	26 (46)	6 (33)	4 (29)	2 (9)	0.02
Prednisone, n (%)	40 (36)	18 (32)	7 (39)	6 (43)	9 (41)	0.8
Average dosage, mean (SD), mg/day	12.9 (10.0)	6.7 (2.9)	12.1 (7.6)	19.6 (13.6)	21.7 (10)	0.0001
Aspirin, n (%)	42 (38)	23 (40)	8 (44)	4 (29)	7 (32)	0.7
Tacrolimus, n (%)	3 (3)	2 (4)	0 (0)	0 (0)	1 (5)	>0.99
Cyclosporin, n (%)	1 (1)	0 (0)	1 (6)	0 (0)	0 (0)	0.3

* APS, antiphospholipid syndrome.

Table 2. Association between pregnancy readiness and provider-reported systemic lupus erythematosus disease activity*

	Patients, n	Mean (SD) or n (%)	β or OR (95% CI)	Adjusted β or adjusted OR (95% CI)
SLEPDAI[a]				
Medically and personally ready	57	1.7 (2.2)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	18	1.8 (2.3)	0.17 (−0.92 to 1.26)	−0.25 (−1.47 to 0.97)
Not medically ready (personally ready)	14	5.5 (6.0)	**3.83 (0.73 to 6.93)**	**3.42 (0.54 to 6.31)**
Not medically or personally ready	22	5.7 (5.1)	**4.02 (1.85 to 6.18)**	**3.51 (1.19 to 5.83)**
SLEPDAI ≥6[b]				
Medically and personally ready	57	4 (7)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	18	1 (6)	0.78 (0.09 to 6.79)	0.54 (0.07 to 4.40)
Not medically ready (personally ready)	14	4 (29)	**5.30 (1.13 to 24.86)**	3.75 (0.87 to 16.17)
Not medically or personally ready	22	8 (36)	**7.57 (1.95 to 29.37)**	**4.99 (1.24 to 20.07)**
PGA[a]				
Medically and personally ready	57	0.3 (0.4)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	18	0.5 (0.6)	**0.27 (0.005 to 0.54)**	0.18 (−0.08 to 0.44)
Not medically ready (personally ready)	14	0.8 (0.7)	**0.52 (0.14 to 0.89)**	**0.43 (0.08 to 0.79)**
Not medically or personally ready	22	0.9 (0.7)	**0.66 (0.36 to 0.96)**	**0.55 (0.23 to 0.87)**
PGA ≥1.0[b]				
Medically and personally ready	57	3 (5)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	18	2 (11)	2.25 (0.34 to 14.94)	1.60 (0.25 to 10.39)
Not medically ready (personally ready)	14	4 (29)	**7.20 (1.39 to 37.31)**	**5.23 (1.06 to 25.80)**
Not medically or personally ready	22	10 (45)	**15.00 (3.50 to 64.33)**	**10.26 (2.17 to 48.47)**
Renal PGA[a]				
Medically and personally ready	57	0 (0)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	18	0.05 (0.1)	0.05 (−0.02 to 0.11)	0.05 (−0.03 to 0.13)
Not medically ready (personally ready)	14	0.3 (0.4)	**0.28 (0.06 to 0.50)**	**0.29 (0.07 to 0.50)**
Not medically or personally ready	22	0.6 (0.7)	**0.58 (0.27 to 0.89)**	**0.58 (0.28 to 0.88)**

* Bold indicates statistical significance values. Adjusted models include a composite variable of social disadvantage including single or living alone, household income <$50,000, Medicare or Medicaid insurance, or uninsured. CI, confidence interval; OR, odds ratio; PGA, Physician Global Assessment; Ref, reference; SLEPDAI, Systemic Lupus Erythematosus Pregnancy Disease Activity Index.
[a] The data for this section are represented as means (SDs), β (95% CIs), and adjusted β (95% CIs).
[b] The data for this section are represented as n (%), ORs (95% CIs), and adjusted ORs (95% CIs).

(SLEPDAI), Physician Global Assessment (PGA), and active nephritis (Table 2). Among the 36 individuals who were not medically ready, 8 had at least 1 g of proteinuria, 8 had been taking mycophenolate-containing medications, and 31 did not continue pregnancy-compatible SLE medications after conception.

Patient-perceived disease activity. Individuals who were not medically ready for pregnancy had similar rates of patient-reported SLE activity compared to those who were medically ready (Table 3). In contrast, those who were not personally ready for pregnancy had significantly higher patient-reported SLE activity, with five times the likelihood of reporting a moderate or severe flare compared with individuals who were personally and medically ready (Table 3).

Mood symptoms. Individuals who were neither medically nor personally ready for pregnancy had no increase in depressive symptoms, but were more likely to report feeling "overwhelmed" and "sad or miserable" compared with individuals who were both medically and personally ready for pregnancy (Table 4). Individuals who were not personally ready for pregnancy were twice as likely to have maternal depressive symptoms as measured by the EPDS compared with those who were personally ready (39% vs 18%, adjusted OR 2.73, 95% CI 0.85–8.82) and were more likely to report feeling overwhelmed (Table 4).

Pregnancy-related health behaviors. Compared with individuals who were personally ready for pregnancy, individuals who were not personally ready for pregnancy were less likely to report having done any preparatory changes in health behavior (eg, taking a prenatal vitamin, smoking cessation, changing medications, seeking medical advice). These findings were similar when comparing individuals who were both medically and personally ready for pregnancy with individuals who were not medically and/or not personally ready for pregnancy (Supplemental Table 1).

Pregnancy outcomes. Compared with individuals who were both medically and personally ready for pregnancy, individuals who were neither medically nor personally ready for pregnancy had higher rates of preeclampsia (adjusted OR 5.65, 95% CI 1.45–22.08) and delivered, on average, three weeks earlier

Table 3. Association between pregnancy readiness and patient-perceived systemic lupus erythematosus activity*

	Patients, n	Mean (SD) or n (%)	β or OR (95% CI)	Adjusted β or adjusted OR (95% CI)
Patient-reported activity[a,b]				
Medically and personally ready	51	2.5 (2.7)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	14	5.1 (1.9)	**2.63 (1.39 to 3.87)**	**1.85 (0.40 to 3.30)**
Not medically ready (personally ready)	12	3.5 (3.5)	0.94 (−1.10 to 2.99)	0.22 (−1.72 to 2.17)
Not medically or personally ready	18	3.6 (2.9)	1.12 (−0.44 to 2.68)	0.27 (−1.48 to 2.02)
Joint tenderness and swelling[a,b]				
Medically and personally ready	55	1.4 (2.3)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	15	3.9 (3.0)	**2.50 (0.94 to 4.06)**	**1.91 (0.13 to 3.68)**
Not medically ready (personally ready)	14	2.5 (3.0)	1.06 (−0.58 to 2.71)	0.57 (−1.16 to 2.29)
Not medically or personally ready	21	2.4 (3.0)	0.94 (−0.53 to 2.41)	0.34 (−1.48 to 2.17)
Arthritis pain[a,b]				
Medically and personally ready	56	1.3 (2.2)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	15	3.3 (2.7)	**2.05 (0.57 to 3.53)**	**1.70 (0.08 to 3.32)**
Not medically ready (personally ready)	14	2.1 (2.4)	0.79 (−0.61 to 2.18)	0.49 (−0.98 to 1.96)
Not medically or personally ready	21	1.7 (2.3)	0.43 (−0.81 to 1.67)	0.07 (−1.34 to 1.48)
Current pain[a,b]				
Medically and personally ready	55	2.4 (2.9)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	15	4.4 (2.9)	**2.08 (0.39 to 3.76)**	1.40 (−0.43 to 3.24)
Not medically ready (personally ready)	14	3.5 (3.4)	1.11 (−0.76 to 2.99)	0.55 (−1.30 to 2.40)
Not medically or personally ready	20	2.9 (2.8)	0.48 (−1.01 to 1.98)	−0.19 (−1.83 to 1.45)
Moderate to severe patient-reported flare[c]				
Medically and personally ready	57	7 (12)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	16	7 (44)	**5.56 (1.49 to 20.78)**	**5.10 (1.31 to 19.85)**
Not medically ready (personally ready)	14	3 (21)	1.95 (0.41 to 9.23)	1.81 (0.41 to 7.95)
Not medically or personally ready	21	6 (29)	2.86 (0.72 to 11.34)	2.62 (0.71 to 9.71)
Moderate to severe fatigue[c]				
Medically and personally ready	57	26 (46)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	16	10 (63)	1.99 (0.70 to 5.61)	2.14 (0.69 to 6.61)
Not medically ready (personally ready)	13	6 (46)	1.02 (0.30 to 3.48)	1.08 (0.30 to 3.96)
Not medically or personally ready	21	13 (62)	1.94 (0.67 to 5.61)	2.09 (0.63 to 6.90)

* Bold indicates statistical significance values. Adjusted models include a composite variable of social disadvantage including single or living alone, household income <$50,000, Medicare or Medicaid insurance, or uninsured. CI, confidence interval; OR, odds ratio; Ref, reference.
[a] Scale of 0 (least severe) to 10 (most severe).
[b] The data for this section are represented as means (SDs), β (95% CIs), and adjusted β (95% CIs).
[c] The data for this section are represented as n (%), ORs (95% CIs), and adjusted ORs (95% CIs).

(Table 5). There were no differences in pregnancy outcomes for those who were only medically ready or only personally ready.

DISCUSSION

This prospective study conducted among pregnant individuals with SLE had several notable findings. First, lack of medical readiness for pregnancy was associated with significantly higher rates of active disease and worse pregnancy outcomes; however, these patients did not perceive themselves as having higher disease activity. Furthermore, individuals lacking personal readiness for pregnancy had significantly higher perceived disease activity, despite not having higher provider-reported disease activity. Second, although medical readiness was not associated with substantially higher depressive symptoms, lack of personal readiness for pregnancy was associated with much higher likelihood of maternal depressive symptoms and feeling overwhelmed. Insufficient medical and personal readiness for pregnancy were both associated with a lack of preparatory health behaviors and social disadvantage.

As we know, SLE disease activity is an important predictor of poor pregnancy outcomes and fetal loss.[2,3,20] As a result, medical optimization before conception represents an important step in improving pregnancy outcomes among those with SLE.[2,3] Interestingly, individuals who were not medically ready for pregnancy did not perceive higher disease activity, a novel finding suggesting individuals may be unaware of their level of illness. This finding is concerning because if individuals are unable to accurately perceive their SLE disease activity, they are likely to be unaware of the associated risks with pursuing pregnancy. This demonstrates the critical need for patient–provider communication and the role providers can play in educating patients, which allows them to make informed decisions. Interventions to improve reproductive counseling, including provider education and electronic medical record–based reminders, have shown efficacy, with educational interventions ranging from simulations to websites and handouts.[21,22] Increasing provider engagement in

Table 4. Association between pregnancy readiness and maternal depressive symptoms*

	n (%)	OR (95% CI)	Adjusted OR (95% CI)
PHQ-2			
Medically and personally ready (n = 57)	4 (7)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 16)	3 (19)	3.06 (0.59–15.86)	2.62 (0.40–17.10)
Not medically ready (personally ready) (n = 13)	1 (8)	1.10 (0.11–10.81)	0.98 (0.11–9.10)
Not medically or personally ready (n = 18)	4 (22)	3.79 (0.72–19.93)	3.23 (0.61–17.18)
Depression (EPDS score ≥10)			
Medically and personally ready (n = 56)	10 (18)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 18)	7 (39)	2.93 (0.99–8.68)	2.73 (0.85–8.82)
Not medically ready (personally ready) (n = 14)	3 (21)	1.25 (0.29–5.37)	1.17 (0.28–4.89)
Not medically or personally ready (n = 22)	8 (36)	2.63 (0.82–8.43)	2.42 (0.72–8.11)
Anxious or worried for no good reason			
Medically and personally ready (n = 57)	25 (44)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 18)	11 (61)	2.01 (0.69–5.83)	1.84 (0.58–5.80)
Not medically ready (personally ready) (n = 14)	7 (50)	1.28 (0.40–4.12)	1.17 (0.33–4.18)
Not medically or personally ready (n = 22)	14 (64)	2.24 (0.80–6.28)	2.01 (0.64–6.27)
Felt scared or panicky for no good reason			
Medically and personally ready (n = 57)	17 (30)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 18)	6 (33)	1.18 (0.39–3.54)	1.26 (0.42–3.79)
Not medically ready (personally ready) (n = 14)	4 (29)	0.94 (0.26–3.41)	1.01 (0.28–3.57)
Not medically or personally ready (n = 22)	11 (50)	2.35 (0.84–6.62)	2.56 (0.86–7.58)
Things have been overwhelming			
Medically and personally ready (n = 56)	16 (29)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 18)	10 (56)	**3.13 (1.05–9.28)**	**2.91 (0.91–9.30)**
Not medically ready (personally ready) (n = 13)	3 (21)	0.68 (0.17–2.77)	0.63 (0.14–2.81)
Not medically or personally ready (n = 22)	13 (59)	**3.61 (1.26–10.34)**	**3.31 (1.04–10.59)**
Felt sad or miserable			
Medically and personally ready (n = 56)	3 (5)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready) (n = 18)	2 (11)	2.21 (0.34–14.47)	2.04 (0.24–17.13)
Not medically ready (personally ready) (n = 14)	1 (7)	1.36 (0.13–14.03)	1.26 (0.12–13.25)
Not medically or personally ready (n = 22)	7 (32)	**8.24 (1.82–37.25)**	**7.51 (1.36–41.39)**

* Bold indicates statistical significance values. Adjusted models include a composite variable of social disadvantage including single or living alone, household income <$50,000, Medicare or Medicaid insurance, or uninsured. CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; OR, odds ratio, PHQ-2, Patient Health Questionnaire 2; Ref, reference.

Table 5. Association between pregnancy readiness and pregnancy outcomes (n = 95)*

	Patients, n	n (%)	OR or β (95% CI)	Adjusted OR or adjusted β (95% CI)
Pregnancy loss[a]				
Medically and personally ready	49	6 (12)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	13	4 (31)	3.19 (0.73 to 13.97)	2.25 (0.39 to 13.04)
Not medically ready (personally ready)	12	1 (8)	0.65 (0.07 to 5.95)	0.46 (0.05 to 4.30)
Not medically or personally ready	21	6 (29)	2.87 (0.80 to 10.29)	1.85 (0.46 to 7.46)
Among pregnancies lasting ≥20 wk[a]				
Preeclampsia				
Medically and personally ready	41	8 (20)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	8	2 (25)	1.38 (0.22 to 8.64)	1.91 (0.27 to 13.34)
Not medically ready (personally ready)	10	3 (30)	1.77 (0.37 to 8.41)	2.24 (0.45 to 11.10)
Not medically or personally ready	18	9 (50)	**4.13 (1.19 to 14.34)**	**5.65 (1.45 to 22.08)**
Preterm delivery (<37 wk)[a]				
Medically and personally ready	45	11 (24)	1.0 (Ref)	1.0 (Ref)
Not personally ready (medically ready)	9	0 (0)	–	–
Not medically ready (personally ready)	10	3 (30)	1.32 (0.29 to 5.98)	1.54 (0.31 to 7.70)
Not medically or personally ready	19	9 (47)	2.78 (0.88 to 8.81)	3.35 (0.87 to 12.91)
Gestational age at delivery week[b]				
Medically and personally ready	45	36.8 (3.4)	0 (Ref)	0 (Ref)
Not personally ready (medically ready)	9	37.8 (1.0)	0.96 (−0.24 to 2.15)	1.30 (−0.84 to 3.45)
Not medically ready (personally ready)	10	36.2 (2.7)	−0.62 (−2.46 to 1.22)	−0.33 (−2.69 to 2.04)
Not medically or personally ready	19	33.3 (6.3)	**−3.56 (−6.59 to −0.53)**	−3.20 (−6.75 to 0.34)

* Bold indicates statistical significance values. Adjusted models include a composite variable of social disadvantage including single or living alone, household income <$50,000, Medicare or Medicaid insurance, or uninsured. CI, confidence interval; OR, odds ratio; Ref, reference.
[a] The data for this section are represented as n (%), ORs (95% CIs), and adjusted ORs (95% CIs).
[b] The data for this section are represented as means (SDs), β (95% CIs), and adjusted β (95% CIs).

discussions aimed at ascertaining reproductive goals and contraceptive counseling is important for all reproductive-aged individuals with SLE, with greatest benefit potentially among those lacking medical readiness for pregnancy.

Early in pregnancy, maternal symptoms of depression were higher among individuals who were not personally ready for pregnancy. Although previous studies have shown an association between unplanned pregnancy and maternal depression in the general population, our study supports this finding specifically among individuals with SLE.[13,14] In the general population, studies have demonstrated 14% to 21% of individuals with unplanned pregnancies experience depression.[8,9] In our study, about one-third of women who were not personally ready for pregnancy had depressive symptoms. Individuals with SLE have a higher incidence of depression at baseline and many independent clinical risk factors for depression, including chronic disease, pain, and fatigue.[15,23] As a result, patients with SLE who are not personally ready for pregnancy may represent a particularly vulnerable population. Tailored mental health interventions and increasing social support represent important potential steps for decreasing the development of psychologic distress among those with SLE experiencing an unplanned pregnancy.[24,25]

In addition to worsened mood symptoms, individuals not personally ready for pregnancy had significantly higher patient-perceived disease activity, despite not having higher provider-reported disease activity. At the same time, individuals who were not medically ready for pregnancy did not perceive higher disease activity. Among those who were not personally ready, depressive symptoms may have resulted in fatigue, weakness, and somatic symptoms, leading to a perceived increase in SLE activity.[26] The disconnect between pregnancy readiness and perceived disease activity may reflect the difference in patient-reported SLE activity experienced by patients with active Type 1 versus Type 2 SLE.[27,28] In this model, Type 1 SLE activity describes inflammation including lupus nephritis, some of which cause minimal physical symptoms and result in low patient-reported SLE activity. On the other hand, Type 2 SLE activity includes diffuse pain, fatigue, and brain fog, and can be exacerbated by stress. Type 2 SLE often results in higher patient-reported measures of SLE activity, which may elucidate our findings.

Our study also found an association between lack of readiness for pregnancy, both personal and medical readiness, and not having participated in preparatory health behaviors. Of particular importance is individuals' reports of not having changed medications for rheumatic disease. Risks of inappropriate medication administration during pregnancy are well documented in the literature and can be serious, including increased fetal malformations, spontaneous abortion, and maternal complications.[3,29,30] Continuing pregnancy-compatible SLE medications not only decreases medication-related risk, but also lowers the likelihood of disease flare during pregnancy.[3] Although many pregnancy-related health interventions around nutrition, smoking and alcohol cessation need additional study on long-term effectiveness, medication change represents a major intervenable step among those already engaged in clinical care.[3,31,32] Among preparatory health behaviors, these individuals also reported not having sought medical advice, which underscores the importance of provider-initiated discussions around pregnancy planning.

Regarding sociodemographic factors, individuals lacking pregnancy readiness had higher levels of social disadvantage, including lower income, higher enrollment in Medicare or Medicaid, younger age, and singleness. Higher rates of unintended pregnancy and lower medication adherence are well established among individuals with SLE affected by social disadvantage as well as in the general population.[7,33,34] Individuals with lower income and those enrolled in Medicare or Medicaid receive lower-quality care and experience greater difficulty accessing contraception and remaining engaged in care.[33,35,36] We also found lower rates of medical readiness before pregnancy among individuals who self-identified as Black and/or Hispanic, which is particularly important given higher rates of adverse pregnancy outcomes among minoritized populations with SLE.[37,38] Racial and ethnic health disparities in SLE highlight the need for multifaceted interventions aimed at tackling systemic racism and decreasing the incidence of discrimination within the health care system.[39] These findings underscore the need for an approach to reproductive health in SLE that addresses the social determinants of health and health inequity.

Limitations of this study include being conducted at a single center in the Southeastern United States. The center serves a large referral base across North Carolina. Because of the small sample size created by dividing across four categories of pregnancy readiness, some of our estimates for dichotomous outcomes may not have been adequately powered. However, we were sufficiently powered for all continuous outcomes. With the use of a prospective pregnancy registry, we are unable to account for women who experience first trimester pregnancy loss before enrollment, so our rates for early pregnancy loss may not reflect all individuals with SLE. Patient-reported outcomes collected at the first visit of pregnancy and depressive symptoms may evolve over the course of pregnancy, which we will assess in future studies. Future studies may also assess the impact of maternal mental health in SLE on pregnancy outcomes. Nonetheless, our study identifies potentially important and novel associations between pregnancy readiness and key maternal health and pregnancy outcomes among individuals with SLE.

In patients with SLE, not being medically ready for pregnancy was associated with significantly higher provider-reported disease activity and worse pregnancy outcomes. Not being personally ready for pregnancy, on the other hand, was associated with significantly higher patient-perceived disease activity, higher maternal symptoms of depression, and lower self-reported maternal health. To improve pregnancy outcomes among individuals with SLE, greater focus is needed on improving medical

optimization before conception. For maternal mental health and quality of life, greater focus is needed on decreasing the incidence of unplanned pregnancy in this higher-risk population.

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 Harding 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/Helsinki Declaration requirements.

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REVIEW ARTICLE

Strategies to Improve Equitable Access to Early Osteoarthritis Diagnosis and Management: An Updated Review

Angela Abenoja,[1] Madeline Theodorlis,[1] Vandana Ahluwalia,[2] Marisa Battistella,[1] Cornelia M. Borkhoff,[3] Glen Stewart Hazlewood,[4] Aisha Lofters,[4] Crystal MacKay,[5] Deborah Marshall,[4] and Anna R. Gagliardi[1]

Though osteoarthritis (OA) affects millions of people worldwide, many fail to access recommended early, person-centered OA care, particularly women who are disproportionately impacted by OA. A prior review identified few strategies to improve equitable access to early diagnosis and management for multiple disadvantaged groups. We aimed to update that review with literature published in 2010 or later on strategies to improve OA care for disadvantaged groups including women. We identified only 11 eligible studies, of which only 2 (18%) focused on women only. Other disadvantaged groups targeted in the largely US-based studies included patients who are Black, Spanish-speaking, rural, and adults aged 60 years and older. All studies evaluated interventions targeted to patients; 4 (36%) assessed video decision aids, and 7 (63.6%) assessed in-person, video, or telephone self-management education. Interventions were often multifaceted (n = 9, 82%), and most studies (n = 8, 73%) achieved positive outcomes in at least some outcomes measured. No studies evaluated clinician- or system-level strategies. Few studies (n = 5, 45%) described how they tailored strategies to disadvantaged groups or how they addressed person-centered care concepts apart from enabling self-management. Future research is needed to develop, implement, evaluate, and scale-up multilevel strategies to enhance equitable, person-centered OA care for disadvantaged groups including women.

Introduction

Osteoarthritis (OA) affects more than 300 million people worldwide, causing chronic joint pain and stiffness in areas such as the hands, lower back, neck, knees, hips, and feet, often impeding activities of daily living (1). OA is a debilitating disease that can lead to depression, diabetes, heart disease, and poor quality of life (2). Early diagnosis and management are key to preventing decline and optimizing patient health and quality of life. Though OA guidelines differ in treatment recommendations and what is considered early versus later intervention, first-line therapy for OA may include education, self-management (eg, physical activity and weight loss), pain management, and physiotherapy, and after trial of first-line therapies, second-line therapy may include injections and joint replacement (3,4).

Intersectional factors, including social determinants, are associated with having chronic diseases and receiving recommended management (5). This is also true of OA. In a systematic review, fewer than half of 16,103 patients with OA received early diagnosis or management (6). Another review found that, of patients undergoing joint replacement, only 36% had been prescribed or advised of first-line therapy (7). Considerable accumulated research shows that age, race, gender, and rurality contribute to inequitable OA care (8). Women are far more likely than men to develop hand, knee, and hip OA; experience greater OA severity, pain, and disability; and suffer from a greater number and prevalence of OA-related comorbidities such as depression or hypertension (9–12). Furthermore, women are less likely to receive guideline-concordant OA care. Reviews of published research and analysis of population-based data in Canada and the United States found that women, particularly women who are racialized with less education or income (henceforth, diverse women), were less likely than men to undergo physical

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[1]Angela Abenoja, MPH, Madeline Theodorlis, MPH, Marisa Battistella, PharmD, Anna R. Gagliardi, PhD: Toronto General Hospital Research Institute, Toronto, Ontario, Canada; [2]Vandana Ahluwalia, MD: University of Calgary, Calgary, Alberta, Canada; [3]Cornelia M. Borkhoff, PhD: West Park Healthcare Centre, York, Ontario, Canada; [4]Glen Stewart Hazlewood, MD, PhD, Aisha Lofters, MD, PhD, Deborah Marshall, PhD: University of Toronto, Toronto, Ontario, Canada; [5]Crystal MacKay, PhD: William Osler Health System, Brampton, Ontario, Canada.
Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25179.
Address correspondence via email to Anna R. Gagliardi, PhD, at anna.gagliardi@uhn.ca.
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therapy, be on a wait list for joint replacement, or undergo joint replacement (13–16). Hence, insight is needed on how to support equitable early diagnosis and management of OA among disadvantaged groups including diverse women.

Borkhoff et al (17) reviewed research published from 1950–2010 on strategies that could reduce inequities in OA care for any disadvantaged group, in which strategies referred to any type of intervention. The review included only 10 studies, all based in the United States. All studies evaluated educational strategies to improve self-management among people with OA who varied by racial and ethnic group (eg, African or Spanish-speaking Americans). One study compared the impact of self-management education between women and men, but participants were largely well-educated White persons.

Given the need to improve OA care for diverse women, the overall aim of this study was to identify research published subsequent to the review by Borkhoff et al (17) on strategies that support early diagnosis and management of OA among vulnerable groups, and in so doing, to also identify strategies that can be used to enhance OA care for women. Borkhoff et al noted that disadvantaged groups experience disparities in both access to care as well as in the delivery of care and accordingly defined a strategy as any treatment, program, intervention, or approach that was designed explicitly to reduce disparities in care or to improve the health care experience, thus encompassing strategies at the patient–provider, organization, and system level (17). Person-centered care (PCC) is one approach for improving access to and quality of care that has been advocated for people with OA (18–20). PCC involves tailoring care to a patient's clinical needs, life circumstances, and personal preferences and emphasizes partnership between patients and care providers (21). Domains that characterize PCC include fostering a healing relationship, exchanging information, addressing patient emotions, managing uncertainty, sharing decisions, and enabling patient self-management (22). Considerable research shows that PCC can improve multiple patient-important and clinical outcomes for many conditions in primary, emergency, acute, and intensive care settings (23–25). Thus, in updating the review by Borkhoff et al, we broadened the scope to include both an equity of access and PCC lens. The purpose of this study was to conduct a rapid review of research published from 2010 to now on strategies to support equitable, person-centered, and early OA diagnosis and management.

Methods

Approach

We adopted a rapid review approach because this was one component of a multicomponent study (also involving qualitative interviews with key informants followed by a consensus survey to prioritize equity strategies). If sufficient research was identified, we could then later conduct an expanded review. Though similar in rigour and methods to a systematic review, this rapid review was expedited by restriction to a single language (English), a short time frame (2010 and newer to include only indexed literature published after the study by Borkhoff et al [17]), and by refraining from critical appraisal and contacting the authors of included studies (26). We complied with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (27). The research team included a diverse 13-member women's advisory group, health care professionals (family physician, rheumatologists, physiotherapist, and pharmacist), and health services researchers with expertise in the topics of OA, PPC, equity, women's health, and synthesis methods. All contributed to conceptualization, study design, eligibility criteria, review and interpretation of data, and report preparation. We did not require institutional review board approval because data were publicly available and did not register a protocol.

Eligibility criteria. Supplementary File 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25179, details eligibility criteria. In brief, we included studies that developed or examined the use and impact of single-faceted (eg, educational workshop) or multifaceted strategies (eg, educational workshop plus a follow-up reminder phone call) to promote or support equitable or person-centered OA care. Strategies broadly referred to policies, programs, interventions, or tools. Participants or targets of the strategy included any disadvantaged persons aged 18 years and older with potential or confirmed OA of any body part based in any home, community, primary, ambulatory, or hospital care setting or clinicians (eg, family physicians, nurses or nurse practitioners, physical/occupational therapists, podiatrists, registered massage therapists, community pharmacists, exercise specialists, and diet counselors), policymakers, or managers of organizations that provide care or advice to persons with OA. Hence, strategies could be relevant at the patient, health care professional, or health care system level. Based on the review by Borkhoff et al (17), disadvantaged groups included women, specific racial and ethnic groups, those living in inner-city or rural areas, those with a lower socioeconomic status, and those aged 80 years and older. Given that what we found was a lack of standardization in defining "older adults" and aiming to be inclusive, we included studies where authors defined "older adults" as aged 65 years and older. We included studies of any research design published in the English language. Systematic reviews were not eligible, but if deemed relevant, we screened references. Eligible studies assessed strategy impact on outcomes including but not limited to awareness, knowledge, behavior, determinants (enablers/barriers), and clinical outcomes.

Searching and screening. Supplementary File 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.

wiley.com/doi/10.1002/acr.25179, shows the search strategy, based on that employed in the review by Borkhoff et al (17), that we used to search MEDLINE, Embase, CINAHL, Sociological Abstracts, PsycInfo, Joanna Briggs Institute, Cochrane Library, and Scopus for studies from 2010 inclusive to September 2022 (because the review by Borkhoff et al included studies published up to and including 2009). We used the search strategy by Borkhoff et al, which includes a combination of Medical Subject Headings and keywords to represent a range of intersectional factors that contribute to inequitable access to and quality of OA care and expanded the search with Medical Subject Headings and keywords for the concept of PPC (eg, patient-centered care) and with terms representing additional determinants of inequities (eg, women's health, race and ethnic groups) (see search strategy lines 23–47 in Supplementary File 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25179). We complied with the "Peer Review of Electronic Search Strategy" reporting guidelines (28). We did not search gray literature because it is proven to be costly and time-consuming with low yield, there are no standard methods of doing so, and gray information may be at high risk of bias (29).

Though screening in a rapid review is typically completed by only one person, to enhance rigor and for training purposes, three reviewers (AA, MT, and ARG) independently screened titles and abstracts for the first 125 search results and discussed discrepancies (this number was chosen as likely to include a wide range of eligible and ineligible studies to support training). Thereafter, AA independently screened remaining titles and abstracts, and MT and ARG resolved uncertainties with AA through discussion. We conducted full-text screening concurrent with data extraction. To identify studies pertaining to the aforementioned disadvantaged groups, we selected those in which the title or abstract (for initial screening) or the introduction or methods (for full-text screening) mentioned the disadvantaged, the vulnerable, inequity, disparity, or synonymous terms, or explicitly stated that they focused on or included women, specific racial and ethnic groups, those living in inner-city or rural areas, those with a lower socioeconomic status, or persons who are older.

Data extraction and analysis

To pilot test the data extraction process, AA, MT, and ARG independently extracted data from the same three studies and then compared and discussed discrepancies to achieve a common understanding of how to extract data. Thereafter, AA extracted and tabulated data on study characteristics (author, publication year, country, objective, research design, and participants [including number and specific disadvantaged group as identified in the article]) and results, including strategy design and outcomes assessed. Strategy design included information on intervention content, format, delivery, timing, and personnel (30). We categorized strategies as relevant to patients, health care professionals, or health care systems depending on the target of the strategy. We also mapped strategies to the six-domain PCC framework by McCormack et al (22), chosen over others because it addressed OA-specific PCC approaches proposed by others (18–20) and is more comprehensive than other PCC frameworks (31–33).

Patient and public involvement

Although our review was inclusive of any disadvantaged group, our primary interest is equitable access to and quality of care for women, so a 13-member advisory group of women with one or more types of OA, who also varied by age and ethnic and racial group, participated in all aspects of the study. These included orientation (individual meetings to discuss role and a group meeting to share OA experiences and discuss the study), planning (reviewed information about synthesis methods and shared strategies they viewed as needed to improve OA care), data collection and analysis (reviewed a summary of early data and met as a group to discuss final data), and dissemination (reviewed this manuscript).

Results

Search results

We identified a total of 6,353 search results, and after removing duplicates, 5,478 items remained. Screening of titles and abstracts eliminated 5,443 items. Among 36 full-text articles screened, we discarded 25 as ineligible because of population (14), lack of focus on equity or PPC (5), not being OA-specific (3), and publication type (3). We included 11 studies in this review (see Figure 1). Supplementary File 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25179, includes details extracted from the included studies (34–44).

Study characteristics

Studies were published from 2010 to 2021. Most (n = 7, 63.6%) were conducted in the United States (36–42), followed by South Korea (n = 2, 18.2%) (34,43), and then 1 (9.1%) each in Taiwan (44) and Thailand (35). All studies employed quantitative or mixed methods, with most being randomized trials (n = 9, 81.8%). With respect to setting, studies were based in specialist (n = 2, 18.2%) (37,39), outpatient (n = 2, 18.2%) (35,36), primary (n = 3, 27.3%) (38,41,42), or community care settings (n = 3, 27.3%) (34,43,44). Studies focused on either self-management (n = 7, 63.6%) (34–36,41–44) or treatment (n = 4, 36.4%) of OA (37–40). Four studies (36.4%) addressed OA in any body part (34,41–43), whereas 5 (63.6%) focused on only knee OA

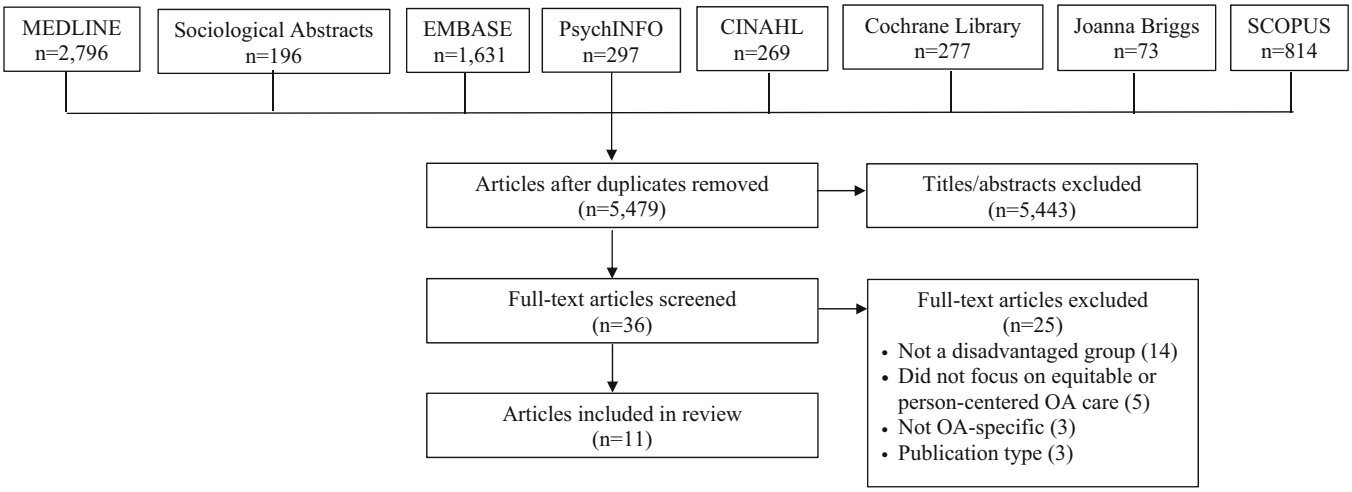

Figure 1. PRISMA flow diagram.

(35,37,38,40,44), and 2 (18.2%) focused on knee and hip OA (36,39).

Disadvantaged groups targeted

Overall, studies included a mean of 176.7 patients (median 147, range 18–493). Five (45.5%) studies targeted older adults, with three defining "older" as 65 years and older (34,43,44) and two defining "older" as 60 years and older (41,42). Three studies (27.3%) targeted Black persons with OAc (36–38), and one study (9.1%) included each of Spanish-speaking adults (42), diverse ethnic groups (39), and rural dwellers (44). Two studies (18.2%) focused on women only (34,35). Eight studies (72.7%) included at least 50% women (37–44), and of those, 6 (85.7%) analyzed and reported results by sex or gender (37,38,40,41,43,44). One additional study did not report sub-analyses, but 94.4% of the participants were women (39).

Strategies to support equitable OA care

Supplementary File 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25179, provides details of strategy design. Table 1 summarizes strategy type and design. All 11 (100%) studies evaluated the effectiveness of strategies targeting people with OA. Four (36.4%) studies evaluated decision aid strategies: three for knee OA and one for both knee and hip OA (37–40). All four studies evaluated video decision aids; one evaluated only the video decision aid (37), and three combined the video decision aid with either a personalized report (40), motivational interviewing (38), or an educational booklet (39). Seven studies (63.6%) evaluated self-management education, four for any type of OA, two for knee OA, and one for hip OA (34–36,41–44). One study involved a single strategy of group education sessions (43). Remaining studies evaluated multifaceted strategies including group education sessions, a booklet, and motivational interviewing (44); videos (35); or motivational interviewing and telephone follow-up (34).

Tailoring of strategies

Five studies (45.5%) described how they tailored strategies for disadvantaged groups. To increase accessibility of a self-efficacy and exercise program, Cho (34) employed stretching exercises that were suitable for community-dwelling older adults who had limited access to exercise facilities. The exercise program was held in locations that participants frequently visited. Bunsanong and Chaimongkol (35) consulted a panel of three experts (two orthopedists and a nurse specialized in women's health) to develop self-care education for older women, leading to a video that was short in length and in lay language. To develop pain coping self-management education, Allen et al (36) consulted 248 African Americans (49.2% women) with OA, who suggested changes to lay language and culturally relevant examples in the counseling session and handout. McDonald et al (42) adapted a virtual pain communication training strategy to Spanish-speaking older adults by offering the video and pain coaching in Spanish and by encouraging users to practice talking about their pain in Spanish. Lee and Cho (43) consulted community health workers with more than 10 years of experience to help develop lay language education content for older adults.

Impact of strategies

Of the four studies that evaluated decision aids, two achieved positive outcomes. None of the four studies described tailoring the strategy to the targeted disadvantaged group. Ibrahim et al (37) (video decision aid) reported a significantly increased number of Black patients (69.9% women) undergoing knee

Table 1. Summary of strategies to support equitable OA care evaluated in included studies*

Study, country, OA type	Target level	Study objective (and disadvantaged target group)	Strategy	
			Type	Design
Cho 2021 (34), South Korea, any	Patient	Evaluate impact of education on OA symptoms and exercise among women	Self-management	Twelve 60-minute group sessions on self-efficacy and exercises/ stretching, exercise time, booklet, motivational interviewing, and 13 telephone follow-up sessions
Bunsanong and Chaimongkol 2021 (35), Thailand, knee	Patient	Assess impact of education on OA self-care on OA symptoms and quality of life among women	Self-management	Eight 75-minute group sessions on OA symptom management, booklet, and videos
Allen et al 2019 (36), United States, hip	Patient	Assess impact of coping skills training program on pain and coping ability among Black patients	Self-management	Eleven 45-minute telephone counselling sessions on cognitive and behavioural pain coping skills, handout, and relaxation audio-recording
Ibrahim et al 2017 (37), US, knee	Patient	Assess impact of a decision aid on access to total knee replacement among Black patients	Decision aid	40-minute decision aid video outlining treatment options
Vina et al 2016 (38), US, knee	Patient	Assess impact of a decision aid on surgical referral rates and treatment preferences among Black patients	Decision aid	40-minute decision aid video on treatment options and 30-minute motivational interviewing session
Shue et al 2016 (39), US, hip/knee	Patient	Assess impact of a decision aid on OA knowledge and treatment preferences in ethnically diverse persons	Decision aid	Booklet and video decision aids on treatment options
Volkmann and FitzGerald 2015 (40), US, knee	Patient	Assess impact of decision aid on patient expectations and decision-making among men and women	Decision aid	45-minute decision aid video on treatment options and personalized arthritis report
McDonald et al 2013 (41), US, any	Patient	Assess impact of pain communication training on OA symptoms in older adults	Self-management	Three-minute educational video and virtual pain coach to practice communication
McDonald et al 2012 (42), US, any	Patient	Examine effects of virtual Spanish pain coach on OA-related symptoms	Self-management	Three-minute educational video and Spanish-speaking virtual pain coach
Lee and Cho 2012 (43), South Korea, any	Patient	Assess impact of education on OA and exercises on pain and self-care in older adults	Self-management	Six 120-minute group sessions on OA education, and exercises/stretching
Wu et al 2011 (44), Taiwan, knee	Patient	Assess impact of education on OA self-care on beliefs and self-efficacy in older adults	Self-management	Four 80-minute group sessions on OA and self-management, exercises, and stretching, booklet, and motivational interviewing

* OA = osteoarthritis.

replacement in the intervention group, and Volkmann and Fitzgerald (40) (video decision aid plus personalized report) reported significantly improved expectations about post–knee replacement pain, decision readiness, and reduced decisional conflict among women but not men. Vina et al (38) (video decision aid plus motivational interviewing) found no significant difference between intervention and control groups in referral to an orthopedic surgeon or in willingness to consider knee replacement among Black patients (51.0% women), and Shue et al (39) (video decision aid plus booklet) found no significant difference in knowledge about the risks and benefits of joint replacement or in willingness to participate in shared decision-making among ethnically diverse persons (53.0% women).

Of the seven studies that evaluated self-management strategies, four demonstrated strategy impact in all outcomes measured (34,35,43,44), and two demonstrated impact in some outcomes measured (36,41). Of the six studies that achieved at least some positive outcomes, four provided some details of how the strategy was tailored to the target disadvantaged groups (34–36,43). Cho (34) (group education, stretching, booklet, motivational interviewing, and telephone follow-up) reported significantly less joint stiffness, physical function disability, and depressive symptoms and reported significantly higher self-efficacy and quality of life among women aged 65 years and older in the experimental group. Bunsanong and Chaimongkol (35) (group education, booklet, and videos) reported better knee functional status and higher health-related quality of life among women in the intervention group. Lee and Cho (43) (group education plus exercises/stretching) reported a significantly lower number of painful joints and greater improvement in arthritis management skills in the experimental group of participants aged 65 years and older living in rural dwellings (91% women). Wu et al (44) (group sessions, booklet, and motivational interviewing) reported a significant improvement in arthritis self-efficacy, pain beliefs, and the number of unplanned medical consultations among the intervention group of participants aged 65 years and older (70% women). McDonald et al (41) (pain communication video plus virtual pain coach) reported a significant difference in communication about source of pain among adults aged 60 years and older in the intervention group compared with the control group, but not for pain intensity (82.6% women). Allen et al (36) (telephone counseling, handout, and relaxation audio recording) reported increased self-efficacy among African Americans in the intervention group but no significant difference in pain severity compared with those in the control group (49.2% women). In the only self-management study in which the intervention had no impact, McDonald et al (42) (Spanish language pain communication video plus virtual pain coach) reported no significant difference in communication about pain source or changes in pain treatment prescribing among Spanish-speaking adults aged 60 years and older in the intervention group compared with controls (94.4% women).

Strategies to support person-centered OA care

Supplementary File 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25179, includes data on PCC content extracted from included articles. Table 2 summarizes PCC content. All 11 studies included content related to at least one domain. The domain most frequently included was *enable self-management* (n = 8, 72.7%). About half of the studies addressed *share decisions* (n = 6, 54.5%), fewer still addressed the domain of *exchange information* (n = 3, 27.3%), and only one study each (9.1%) addressed *foster a healing relationship* and *address emotions*. No studies included content for the domain *manage uncertainty*.

Although all studies referred to at least one PCC domain, content was brief or vague and offered little to no tangible information on how to achieve PCC for the disadvantaged population in question. For instance, for the domain *share decisions*, one study offered brief advice: "Continued discussions between practitioners and patients might be needed until a treatment combination is achieved that reduces pain to an acceptable level and avoids adverse events from treatment changes" (41). In contrast, another study offered somewhat greater detail:

Shared decision-making (SDM) involves a two-way exchange of information between patient and physician to make an informed clinical decision that incorporates the patient's preferences and values to optimize outcomes. Evidence suggests that SDM strategies are effective in enhancing patient decision quality or the degree to which treatment decisions reflect the preferences of fully informed patients, especially for preference-sensitive procedures such as total joint arthroplasty. For this to happen, patients need to have adequate information to understand their disease and the treatment options, which can impact their treatment choice as well as their outcome. Nevertheless, there are concerns about the implementation of SDM in orthopedics, including lack of physician time to participate and its potential interference with clinical workflow (42).

Conclusions

Despite considerable evidence of gendered disparities in access to and quality of OA care for diverse women (7–16), this study identified only 11 studies published after 2009 on strategies to overcome inequities in OA care for any disadvantaged group, and only two (18.2%) of those focused solely on women. Other disadvantaged groups targeted in the largely US-based studies included Black, Spanish-speaking, rural, and older (aged 60 years and older) adults. All studies evaluated interventions targeted to patients: four (36.4%) assessed video decision aids, and seven (63.6%) assessed in-person, video, or telephone self-management education. Interventions were often multifaceted (n = 9, 81.8%), and most studies (n = 8, 72.7%) achieved positive outcomes in at least some outcomes measured. Though all

Table 2. Summary of person-centered care domains in included studies*

Domain anddefinition	Studies, n (%), references	Examples	
		Limited	Expanded
Foster a healing relationship: extend friendly greeting, make eye contact, speak in respectful manner, and avoid judgmental attitude	1 (9.1), ref. 42	When older adults were accompanied by a friend or family member, the companion was allowed to remain in the room if the older adult wished them to (42).	–
Exchange information: listen to concerns, prompt for additional details, understand needs, goals, circumstances, and preferences, use lay language, and ensure privacy	3 (27.3), refs. 35,41,42	Understanding how patients manage their symptoms is essential for health care providers to effectively support the needs of patients with knee OA, especially in middle-aged women (35).	The virtual pain coach orally instructed the older adults to practice talking with her about their pain. The coach asked the older adults to talk about their pain, detected and responded to pauses by encouraging the older adults to describe additional information, provided general positive feedback on the practice session, and concluded the coaching session by encouraging the older adults to share their important pain information with their practitioner. Older adults verbally interacted with the virtual pain coach as they practiced talking about their pain. The virtual pain coaching intervention reinforced the interpretability strategies taught in the videotape portion of the intervention and introduced two important discourse management strategies: practice in selecting relevant pain management topics to discuss with the practitioner; and practice in turn taking (41).
Address emotions: Actively inquire about feelings, acknowledge concerns, express empathy, note that such feelings are normal or common, and suggest strategies to cope or mitigate emotions	1 (9.1), ref. 34	The use of cognitive behavioral therapy and exercise therapy is effective in improving psychosocial factors (self-efficacy, depression, and psychological distress) and health-related and knee-related quality of life (34).	–
Manage uncertainty: offer rationale for tests or treatment, and describe likelihood of risks and benefits using words, statistics, or pictures	0 (0.0)	–	–
Share decisions: describe treatment or management options, assess interest in shared decisions, provide information to enable shared decisions, and suggest factors to consider in making decisions	6 (54.5), refs. 37–42	It is possible that a more frequent intervention and better access to a decision aid for patients could result in greater improvement in patient preference toward joint replacement (38).	Decision aids provide high-quality information on treatment options while also clarifying the outcomes of treatment choice. In this way, they empower patients and facilitate communication and decision making. Decision aids are associated with increased patient knowledge, more realistic patient perceptions about the disease or treatment, less decisional conflict, fewer patients who are passive decision makers, fewer patients who remain indecisive after counseling, and improved concordance between patient values and treatment choices. The National Quality Forum cited shared decision making, which decision aids promote, as one of the six health care reforms with the greatest potential to reduce disparities (37).
Enable self-management: set expectations for follow-up care, offer advice on self-care, provide take-home information, and refer to other sources of information or support	8 (72.7), refs. 34–36,38–40,43,44	For pain management decisions, 18% of all patients responded that they wanted to independently manage their hip or knee pain. Approximately 95% of patients rated the patient decision aids as "somewhat" to "extremely useful" in improving their understanding of OA, the available treatment options, and their personal values and in preparing them to talk further with their health care provider (39).	Coping skills training counselors received training in the protocol. Training also included issues related to cultural sensitivity. In particular, counselors were encouraged to use active listening to identify opportunities to demonstrate that pain coping skills are compatible with cultural, spiritual, religious, or other values. For example, in the context of cognitive restructuring, if a participant described religious beliefs or values, the counselor would explore how those beliefs could be integrated into new, more adaptive thoughts about pain coping (36).

* OA = osteoarthritis.

studies referred to at least one PCC domain, this was most often about self-management, and guidance was minimal. Few or no studies addressed other PCC domains.

The findings of this study were remarkably similar to the findings of the review by Borkhoff, which included only 10 studies conducted in the United States, all involving single-faceted or multifaceted interventions. These interventions involved decision aids or self-management education and targeted patients with low literacy and Spanish-speaking or Black persons, and only one study compared intervention impact between women and men (17). Prior research on the quality of OA care largely focused on describing OA treatment for compliance with OA clinical guidelines (5,6) or identifying barriers of access to timely, guideline-compliant care (45,46), but not how to improve OA care. This study confirms prior research in our group that revealed limited research on equitable PPC for women across many different health care concerns or how to achieve it (47,48). Thus, this study is unique in that it focused specifically on identifying strategies to improve OA care with both an equity and PCC lens, referring to strategies tailored to enhance access to services and to improve patient–provider communication for disadvantaged groups.

These findings reveal several implications for ongoing research. Overall, the lack of research, first identified by Borkhoff et al (17) and then confirmed by this review, on approaches for reducing disparities in OA care in general and beyond the United States is startling given the prevalence and profound negative impact of OA on health and wellbeing (1,2), international recognition of the need to improve care for diverse groups including women (49–53), and high rates of migration to developed countries (54). Hence, more research is needed to characterize the barriers faced by different disadvantaged groups and how to overcome those barriers.

All studies in this review, and in the prior review by Borkhoff et al (17), targeted patients. However, prior research shows that barriers of timely OA diagnosis and management are multilevel. For example, clinician-level barriers included lack of knowledge about OA management, OA was not considered serious, and there was a lack of time to fully assess patients, and system-level barriers included service availability and cost (45,46). Hence, continuing to only target patients with interventions meant to improve self-management will not overcome barriers at the clinician and system level, so further research is needed to verify barriers of OA care at those levels and to identify corresponding clinician- and system-level strategies to enhance OA care for disadvantaged groups.

This review revealed little insight on how to tailor strategies for disadvantaged groups. In studies that mentioned it, tailoring included language translation, offering interventions in frequently visited locations, or consulting representatives of target groups. In the review by Borkhoff et al, tailoring went beyond modifying the literacy level of existing content and involved consulting community members to plan or field-test the cultural acceptability of interventions and working with community leaders to deliver workshops at suitable times and places (17). Accumulating research underscores the benefit of culturally safe, community-based health promotion when targeting immigrant groups. A systematic review of 264 studies involving European immigrants found that community-oriented approaches were better than mass media or the internet at raising awareness about health promotion (55). Qualitative research in Canada with East and South Asian immigrant women revealed that culturally safe health promotion involved women only, addressed sociocultural/socioeconomic barriers, and was offered via familiar, local agencies such as settlement organizations and cultural groups or via pharmacists who can function as knowledge brokers (56,57). Coproduction of strategies is known to be an effective means of ensuring that programs are relevant to and adopted by target users (58), and partnerships with community agencies to develop health promotion programs tailored to the needs of those communities can improve health (59).

PCC represents an approach by which health care professionals can address the needs and preferences of diverse groups (22–25) and has been recognized as essential to OA care (18–20), but in this review, included studies did not directly discuss PCC or indirectly design or evaluate strategies based on PCC concepts. Hence, further research is needed to establish what constitutes PCC for racial and ethnic minority persons with OA, and multilevel strategies need to promote and support equitable, person-centered OA care. This could be based on many studies that characterized PCC (22–25,31–33) and, in the context of women, on our prior studies including review of published research, interviews with women of diverse racial and ethnic groups and health care professionals of various specialties, and prioritization of approaches that support PPC for women (47,48,60–63).

Our review featured many strengths. We employed rigorous review methods and complied with reporting criteria for reviews and review search strategies (26–29). To enhance reliability of the findings, multiple researchers undertook pilot-testing and data extraction. Throughout the entire research process, we consulted with our research team, which included researchers, clinicians, and a 13-member advisory group of diverse women with OA. Some limitations must also be mentioned. As with any type of review, we may not have identified all relevant studies because of possible limitations in our search strategy, including only English-language studies, and because we did not search grey literature as that is not typical of a rapid review (26), and due to the methodological challenges that have been identified by others (29,64). Ultimately, we generated limited insight on strategies to enhance equitable, person-centered OA care because few studies were included, they only tested patient-level strategies, and few described how strategies were tailored to disadvantaged groups or addressed PCC concepts. Thus, we lack insight on, in particular, the few studies focused on improving OA care for

women. Furthermore, relevant strategies at the organizational or system level may not be captured in published research. Because studies were largely conducted in the United States, the findings may not be transferrable to other jurisdictions with different health care systems or with differing disadvantaged groups from those in included studies.

Our review revealed little progress on identifying strategies to improve OA care for disadvantaged groups, and a prior review conducted more than a decade ago similarly identified a paucity of knowledge on this topic. We identified only 11 studies published in 2010 or later. Studies largely targeted Black, Spanish-speaking, or older Americans to improve OA self-management. It is notable that only two studies focused on women despite considerable evidence of gendered disparities in OA care, few studies integrated or assessed PCC concepts despite recognition of its importance to OA care, and no studies evaluated clinician- or system-level strategies despite considerable evidence of barriers to equitable, person-centered OA care at these levels. These gaps represent crucial areas that warrant future research.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Gagliardi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ahluwalia, Battistella, Borkhoff, Hazlewood, Lofters, MacKay, Marshall, Gagliardi.

Acquisition of data. Abenoja, Theodorlis, Gagliardi.

Analysis and interpretation of data. Abenoja, Theodorlis, Ahluwalia, Battistella, Borkhoff, Hazlewood, Lofters, MacKay, Marshall, Gagliardi.

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REVIEW ARTICLE

Prognostic Factors and Changes in Pain, Physical Functioning, and Participation in Patients With Hip and/or Knee Osteoarthritis: A Systematic Review

Bastiaan Cijs,[1] Ruben Stekelenburg,[2] Cindy Veenhof,[3] Jesper Knoop,[4] Tim Boymans,[5] Mariëtte de Rooij,[6] and Corelien Kloek[7]

Objective. This study aimed to systematically synthesize literature on prognostic factors of changes in either direction (ie, worsening or improvement) in pain, physical functioning, and participation in patients with knee and/or hip osteoarthritis (OA).

Methods. Studies included in two preceding reviews underwent full-text screening for inclusion in the current review. Additionally, an extensive literature search was conducted in five databases. Title/abstract screening was performed using an active learning program. Inclusion criteria comprised patients diagnosed with knee and/or hip OA, with the dependent variable assessing pain, physical functioning, or participation. Potential associated prognostic factors were measured as independent variables. The methodologic quality of studies was assessed with the Hayden criteria.

Results. A total of 31 studies were included in this systematic review. In patients with knee OA, pain worsening was associated with lower physical functioning (strong evidence) and with higher body mass index, ethnicity, and a higher comorbidity count (moderate evidence). Also, in patients with knee OA, pain improvement was associated with less pain at baseline (moderate evidence). In patients with knee and/or hip OA, worsening of physical functioning exhibited associations with higher body mass index, more pain, more hip pain, a higher comorbidity count, higher avoidance of activities (strong evidence), and ethnicity (moderate evidence). In patients with knee OA, improvement in physical functioning showed an association with higher vitality (moderate evidence). Regarding the remaining prognostic factors, there is weak, inconclusive, or inconsistent evidence for an association with the outcomes. In patients with hip OA, only weak evidence was found for three factors predicting a change in physical functioning.

Conclusion. This review encompasses prognostic factors associated with changes in either direction (ie, worsening or improvement) in pain, physical functioning, and participation. The results are consistent with other reviews. Future research should place a stronger emphasis on patients with hip OA and participation as an outcome.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder and is a leading cause of disability in older adults.[1,2] The knee joint is the most affected joint in individuals with OA, followed by the hand and the hip.[1] OA affects 7% of the global population.[2] There has been an increase of 114% since 1990.[3,4] The aging population and the increasing numbers of people with obesity

[1]Bastiaan Cijs, Msc: University Medical Centre Utrecht and Hogeschool Utrecht (HU) University of Applied Sciences Utrecht, Utrecht, The Netherlands; [2]Ruben Stekelenburg, Msc: HU University of Applied Sciences Utrecht, Utrecht, The Netherlands; [3]Cindy Veenhof, PhD: University Medical Centre Utrecht and HU University of Applied Sciences Utrecht, Utrecht, and Reade, Center for Rehabilitation and Rheumatology, Amsterdam, The Netherlands; [4]Jesper Knoop, PhD: University of Applied Sciences, Nijmegen, and Vrije Universiteit, Amsterdam, The Netherlands; [5]Tim Boymans, PhD: Maastricht University Medical Center, Maastricht, The Netherlands; [6]Mariëtte de Rooij, PhD: University Medical Centre Utrecht, and Reade, Center for Rehabilitation and Rheumatology, Amsterdam, The Netherlands; [7]Corelien Kloek, PhD: HU University of Applied Sciences Utrecht and Leidsche Rijn Julius Health Care Centers, Utrecht, The Netherlands.

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Address correspondence via email to Bastiaan Cijs, Msc, at bas.cijs@hu.nl.

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SIGNIFICANCE & INNOVATIONS

- In patients with knee osteoarthritis (OA), pain worsening was associated with lower physical functioning (strong evidence) and with higher body mass index, ethnicity, and a higher comorbidity count (moderate evidence), whereas pain improvement was associated with less baseline pain (moderate evidence).
- In patients with knee and/or hip OA, worsening of physical functioning exhibited associations with higher body mass index, more pain, more hip pain, a higher comorbidity count, higher avoidance of activities (strong evidence), and ethnicity (moderate evidence), whereas improvement in physical functioning showed an association with higher vitality (moderate evidence).
- We used a highly innovative active learning method for screening the studies. It saved time, which benefits the completeness of the systematic review, and it has contributed to knowledge and experience to be even more effective and efficient in future research.

contribute to this trend.[2] OA is already the most common cause of disability in the elderly.[5] The years of life lived with OA is 19.0, with a significant increase of 115% since 1990.[3]

Pain is the most experienced disabling symptom.[1,6] A characteristic of OA is that patients with it experience recurrent fluctuations in pain, with varying intensity, frequency, and durations.[7] Other symptoms are joint stiffness,[8,9] reduced range of motion, and crepitus.[1] However, symptoms can differ per joint.[6] Furthermore, a clinical diagnosis of knee or hip OA was associated with difficulties in self-care, mobility, performing activities, and participation.[9–11] OA therefore affects all domains of the International Classification of Functioning, Disability and Health (ICF).[12]

Because OA is a chronic condition with fluctuating symptoms, it is interesting to have insight into predictive factors for an increase or decrease in these symptoms.[7] This knowledge creates the potential to positively influence the course of OA progression. In 2016 and 2020, two systematic reviews in patients with knee and hip OA with a search strategy focused on the course of clinical outcomes were published.[13,14] These reviews reported several prognostic factors for a deterioration of pain and physical functioning. From those studies, we know that several clinical characteristics (eg, comorbidities) and psychosocial factors (eg, more depressive symptoms) predict worsening of pain and physical functioning.[13,14] Several reviews have been published since, but they only investigated factors associated with a worsening of pain[15,16] or physical functioning[15] or only imaging-based measurements were used[16] or the number of included articles was low due to a limited search strategy.[15] Since the previous systematic reviews, various studies have been published on prognostic factors for worsening pain and physical functioning. Only one systematic review has been conducted into prognostic factors on the course of pain and functional status in patients with knee and/or hip OA in 2006.[17] To provide an up-to-date overview, the literature will be systematically summarized on prognostic factors that can predict a change in pain, physical functioning, and participation in both the directions of worsening and improvement in patients with knee and/or hip OA.

MATERIALS AND METHODS

This systematic review was conducted following the steps outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023394827). The protocol was amended after adjustments on inclusion and exclusion criteria. These amendments have been passed to PROSPERO.

Search methods for identification of studies. Two paths were employed to search and include studies. First, two prior systematic reviews were leveraged[13,14] because the aims were similar and the methodologies were appropriate. Their search strategy covered studies addressing changes in all directions of pain or physical functioning. This allowed the search strategy to be limited in certain aspects. The included records from previous systematic reviews[13,14] were screened on full text in the current study. Second, a comprehensive literature search was conducted. The used search terms from the aforementioned reviews were supplemented with additional search terms.[13,14] Literature for pain and physical functioning was searched from July 9, 2015, because previous reviews have searched until then. Literature for participation was searched from inception. The literature search was performed in Embase, PubMed, CINAHL, PsycINFO, and SPORTDiscus. The search string (Supplementary Table 1) was collaboratively developed with a medical librarian. The literature search was performed on May 31, 2024.

Criteria for considering studies for systematic review. Studies underwent initial screening on title and abstract using redefined inclusion and exclusion criteria (Table 1). Inclusion criteria and exclusion criteria were refined before full-text screening (Table 1).

Screening process. All identified references were extracted from the databases, and duplicates were eliminated. Pilot tests screening 50 titles and abstract against the inclusion and exclusion criteria were independently conducted by two reviewers (BC and RS). Multiple screening sessions were required to establish sufficient interrater reliability, whereas after the third session, Cohen's kappa statistic was calculated at 0.792 (first session 0.433, second session 0.524).[18]

Table 1. Inclusion and exclusion criteria before screening on title/abstract and before screening on full text[75*]

Aspects of Research	Inclusion criteria	Exclusion criteria
Before screening on title/abstract		
Domain	Radiographically (K&L grades) and/or clinically (ACR criteria) diagnosed hip/knee OA or diagnosed by a physician	OA induced by hip dysplasia/posttraumatic OA/ femoroacetabular impingement
Determinant	At least one potential associated factor with pain, physical functioning, or participation	
Outcome	At least one measurement instrument evaluating pain, physical functioning, or participation on multiple timepoints	
Design	Prospective cohort study design or analyzed as a prospective cohort study when data were derived from a clinical trial	Review articles
Other	Full-text article is available	Articles written in another language than English or Dutch and articles published before July 10, 2015, on pain and physical functioning
Before screening on full text		
Domain	Radiographically (K&L grades ≥2) and/or clinically (ACR criteria) diagnosed hip/knee OA without TJR	OA induced by hip dysplasia/posttraumatic OA/ femoroacetabular impingement
Determinant	At least one potential associated factor with pain, self-reported physical functioning, or self-reported participation measured as an independent variable	An imaging-based potential associated factor, biomarker, or intervention
Outcome	At least one measurement instrument (dependent variable) evaluating pain, self-reported physical functioning, or self-reported participation on multiple timepoints with a minimum follow-up period of six months	
Design	Prospective cohort study design or analyzed as a prospective cohort study when data were derived from a clinical trial	A cohort exposed to an intervention, review articles, randomized controlled trials, or controlled clinical trials
Other	Full-text article available	Articles written in another language than English or Dutch, articles published before July 10, 2015, on pain and physical functioning or the number of participants in analyses <100

* ACR, American College of Rheumatology; K&L, Kellgren and Lawrence, OA, osteoarthritis; TJR, Total Joint Replacement.

To enhance screening efficiency, the first reviewer (BC) subsequently screened titles and abstracts using the active learning software program ASReview version 1.1.[19] ASReview is an iterative learning process in which the reviewer tells the software whether a reference is relevant or irrelevant. ASReview[19] arranges the remaining references based on this new information. This repeats itself continuously after each rating of a single reference. The ASReview team advised screening at least 25% of the references. When the last 100 reviewed papers were excluded, it is assumed that the remaining records were also irrelevant. Therefore, this was used as a stopping criterion. As a safeguard, a random subsample of 10% was screened by the second reviewer (RS) on the traditional way. The inclusions and exclusions were compared in SPSS version 29, and a Cohen's kappa statistic was calculated at 0.625, representing a moderate agreement between reviewers BC and RS.[18] In order to improve the active learning model, references that were assessed as relevant after the discussion were marked as relevant in ASReview. After this, BC continued screening titles and abstracts in ASReview for up to 35% of all references, which is above the general percentages of screened references in this software.[19] It was expected that this updated the active learning model in ASReview. Hereafter, due to continuing the screening process up to 35% of all references, there was a second cycle of discussion of conflicts between reviewers BC and RS. When a conflict remained after discussion, a third reviewer (CK) screened these references and made the decision. In the next step, full texts were screened whether they met the narrowed inclusion and exclusion criteria by BC and RS, including the studies included in previous reviews.[13,14] In the case of discussion, a third reviewer was consulted (CK).

Data extraction. The following information of the included studies was systematically extracted by BC: authors, year of publication, study design, follow-up period, population, diagnostic tool for OA, number of participants in analyses, outcomes, measurement instruments, prognostic factors, covariates, type of analysis, and statistical values and results. The threshold level of significance of a prognostic factor was set at P of 0.05 or less. The extracted data were verified by a second reviewer (RS), and

differences were adjusted or added when necessary. A variable can cause a worsening, an improvement, or neither of both of pain, physical functioning, and/or participation. There are three comments regarding this terminology:

1. In this study, terminology was reduced to "worsening," "improvement," or "stable." Indicated studies used different terminology for a change in pain, physical functioning, or participation.
2. It was assumed that the null hypothesis in an individual study means no change of the outcome pain physical functioning or participation. If a nonsignificant result was described in an individual study, this was described in the current study as "stable."
3. If a variable had an odds ratio or risk ratio <1, taking into account the 95% confidence interval, then this was regarded as a protective factor. In the current study, this was described as "improvement."

Methodologic quality. The methodologic quality of studies on prognosis and predictive factors was assessed by the Hayden criteria,[20] which were developed to assess the impact of biases in prognostic studies, which fit the inclusion criteria. Furthermore, the previous systematic reviews,[13,14] on which we continued build on, had also used the Hayden criteria, containing six domains of potential bias on the results: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement and account, and (6) analysis.[20] The risk of bias of confounding was not rated because the current study was focused on predictive variables. Confounding was not a consideration in prediction studies.[13,14,21] The methodologic quality of the included studies was assessed independently by two reviewers (BC and RS). Differences in assessment between review authors were discussed to reach consensus. The risk of bias in all five areas was rated as low, moderate, or high. As recommended,[20] studies were classified as high quality if in all five areas, there was a low or a moderate risk of bias. Studies with a high risk for at least one of the areas of bias were defined as low-quality studies.

Meta-analyses were considered when at least three studies were consistent in the measurement instrument for the outcome, as well as the prospective factor. The power of a meta-analysis was low with a small number of studies, and clinical heterogeneity should be low.[22] If not possible, a best-evidence synthesis was performed, classifying evidence into five levels (strong, moderate, weak, inconclusive, and inconsistent).[16,17] Consistency was determined if more than 66% of studies showed the same association direction. To determine the level of evidence, the number of studies, the methodologic quality, and the consistency were taken into account.

RESULTS

First, 53 studies were included in the previous systematic reviews of de Rooij et al.[13,14] After applying inclusion and exclusion criteria for full text, 15 of these studies were included in the current review. Second, the search strategy yielded 18,769 records (Figure 1). Following deduplication, 12,641 records underwent title/abstract screening, resulting in 399 references originating from the search strategy. Ultimately, 453 reports underwent full-text screening, with 54 studies originating from the previous systematic reviews and 399 studies originating from the search strategy. During the data extraction process, one record was excluded[23] because it appeared that pain and physical functioning were taken together as one outcome measure. Bottomline, 31 studies were included, of which 15 included studies originated from previous systematic reviews[13,14] and the remaining 16 included studies originated from the search strategy.

Study characteristics. A total of 27 studies employed a prognostic cohort design,[23–50] whereas the remaining used a retrospective cohort design.[51–54] A total of 24 studies included patients diagnosed with knee OA,[24–35,38–42,47–49,51–54] four studies included patients diagnosed with knee and hip OA and analyzed these patient groups separately,[36,37,45,46] three studies included patients with knee and/or hip OA,[43,46,50] and one study included patients with generalized OA.[44] In 20 studies, the included participants suffered from radiographic OA[24,26–29,32–35,38–42,44,47–49,53,54]; in 10 studies, there was a clinical diagnosis[25,30,36,37,43,50–52]; and in the remaining study, there was a combination of radiographic and clinical OA.[31] The mean follow-up period and number of participants in analyses were approximately 48 months (minimum [min] 12,[24] maximum [max] 120[47]) and 922 (min 159,[51] max 3,802[47]), respectively. For more specific details on the study characteristics regarding prospective factors, results, and analyses, see Supplementary Tables 2 to 4.[25,27,30,31,34–36,42,47,52,53]

Methodologic quality. There was a minimal agreement[18] (Cohen's κ 0.359) between the two reviewers (BC and RS) regarding methodologic quality. In a discussion session, both reviewers reached consensus on the conflicting nine studies. The major disagreements were in the domain of "study attrition." A study should correctly describe whether the loss to follow-up is associated with "key characteristics."[20] Discussion arose among the reviewers about whether "key characteristics" referred to those from the original study or from the current systematic review. It was agreed that this referred to the original study. A total of 11 studies[25,27,30,31,34–36,42,47,52,53] were of high quality, and the other remaining 20 studies[24,26,28,29,32,33,37,39–41,43–46,48–51,55,56] were of low quality (Supplementary Table 5). In multiple studies, the loss to follow-up was not (fully) described or the key

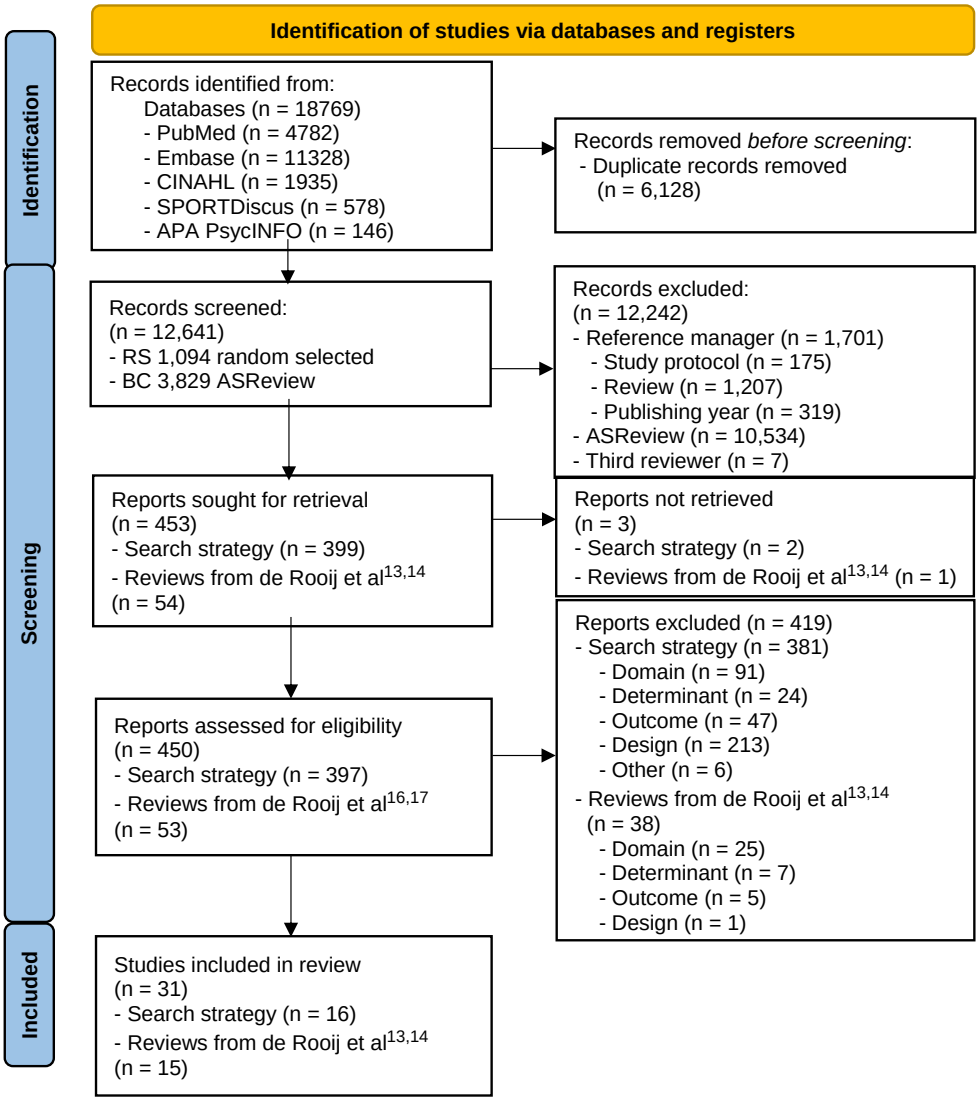

Figure 1. Screening for eligibility. APA, American Psychological Association; BC, author Bastiaan Cijs; RS, author Ruben Stekelenburg. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25428/abstract.

characteristics of participants who were lost to follow-up differed significantly from the other participants. Therefore, the most common domain of the Hayden criteria for potential bias in the low-quality studies was study attrition.

Associated factors with pain. In 19 studies, pain was an outcome, all of them in patients with knee OA.[24,25,28,29,31–35,38–41,47,49,51–54] In total, they assessed 50 different prognostic factors. Pain was assessed with the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index pain,[28,31,33,35,39–41,47,56] the Numeric Rating Scale,[24,25,32,47,49] the Visual Analog Scale,[51,52] the Knee Osteoarthritis Outcome Score-Pain the Intermittent and Constant Osteoarthritis Pain scale[29,55] or with scoring frequent knee pain.[34,41] The best-evidence synthesis showed that pain worsening was associated with a lower physical functioning (strong evidence),[25,53] higher body mass index,[25,29,41] ethnicity (African American),[41,47] and a higher number of comorbidities (moderate evidence).[25,40] Furthermore, there is an association between less pain at baseline and pain improvement (moderate evidence).[34,40] For other prognostic factors the evidence is weak, inconclusive or inconsistent (Tables 2 and 3). No studies were found for hip OA on the outcome of pain.

Associated factors with physical functioning. In 20 studies physical functioning was an outcome, these studies included patients with knee and/or hip OA.[24,26–28,30,31,36–38,40–48,50,52] In total they assessed 63 different prognostic factors. Of these, 13 studies only included patients with knee OA,[24,26–28,30,31,38,40–42,47,48,52] five studies[36,37,45,46,50] included patients diagnosed with knee and hip OA and four of them analyzed these patient groups separately,[36,37,45,46] one study there was a combination of

Table 2. Evidence levels for association with outcomes

Level	Evidence
Strong	Consistent (non)significant associations found in at least two high-quality studies
Moderate	Consistent (non)significant associations found in one high-quality study and at least one low-quality study
Weak	(Non)significant association found in one high-quality study or consistent (non)significant associations found in at least two low-quality studies
Inconclusive	(Non)significant association found in less than two low-quality studies
Inconsistent	Inconsistent significant findings irrespective of study quality

radiographic and clinical OA[43] and the remaining study included patients with generalized OA.[44] Physical functioning was assessed with the WOMAC physical functioning,[24,26–28,30,31,36,37,40–43,45–48,51,56] Late-Life Function and Disability Instrument, and the Disability Index[27] of the Stanford Health Assessment Questionnaire.[44] The best-evidence synthesis showed in patients with knee OA that worsening of physical functioning was associated with a higher body mass index,[30,41,42] a higher number of comorbidities,[30,36,40] a higher avoidance of activities[30,36,37] (strong evidence), and ethnicity (African American; moderate evidence).[41,47] Furthermore, in patients with knee and/or hip OA, worsening of physical functioning was associated with more pain[30,36,42–46] and more hip pain[30,36] (strong evidence). Furthermore, muscle strength of the hip abductors was not associated with worsening or improvement of physical functioning (strong evidence).[27,36,37] Moreover, an improvement of physical functioning was associated with a higher vitality (moderate evidence).[30,46] For other prognostic factors, the evidence was weak, inconclusive or inconsistent, including three factors that were studied in patients with hip OA only[36,43,45] (Tables 2 and 4).

Associated factors with participation. Only one study assessed participation.[27] This made a best-evidence synthesis impossible. In this study, the Late-Life Function and Disability Instrument was used for assessing participation.[27] This instrument can also be used for assessing physical functioning and was therefore included in the best-evidence synthesis to physical functioning.

DISCUSSION

We conducted a systematic review to identify prognostic factors predicting changes in pain, physical functioning, and participation in patients with knee and/or hip OA. A total of 19 variables were recognized as potential predictors of pain worsening in patients with knee OA. Among these, strong or moderate evidence was found for only four variables: higher body mass index, ethnicity (specifically African American), higher comorbidity count, and lower self-reported physical functioning. Additionally, 17 variables were associated with worsening in physical functioning in patients with knee OA, with strong or moderate evidence for six variables as follows: (higher) body mass index, ethnicity (African American), higher hip pain, higher comorbidities, and higher avoidance of activities). Five variables were associated with worsening in physical functioning in patients with hip OA, and for only two of these variables, there was strong evidence, higher pain, and higher hip pain. Furthermore, it applied to these prospective factors that they have been investigated in studies that included patients with knee and/or hip OA. Moreover, a total of 30 variables were associated with an improvement in pain (14) or physical functioning (16); however, only one of them (higher vitality) was of moderate evidence.

When compared with existing literature, this review found substantial consistent evidence. In patients with knee and hip OA, no new variables with strong evidence for an association with pain or physical functioning were identified compared to the reviews by de Rooij et al.[13,14] In patients with knee OA, with regard to the variables with a strong or moderate evidence for an association with pain or physical functioning, consistency with other studies was shown for body mass index,[23,57,58] ethnicity,[57] knee pain at baseline,[13,14] comorbidities,[13–15,57,59,60] and vitality.[23] There was also consistency regarding variables with a lower level of evidence (eg, higher stiffness,[57] severity of OA,[57] mental health,[13,14] smoking, pain coping skills,[13,14,58,60] self-efficacy,[61] and depressive symptoms[62]). On the other hand, in patients with knee OA, there was also some inconsistency regarding gender,[58] educational level,[57] bony tenderness,[57] quadriceps muscle strength,[13,14] duration of knee symptoms,[13,14] handgrip strength,[57] depressive symptoms,[13,14] and alcohol use.[13,14] The associations with pain and physical functioning of these variables were of low evidence. Possible reasons for these inconsistencies might be the use of different measuring instruments for the same constructs. Another reason for the differences between our findings and previous literature was a different population. Most studies included participants classified at high risk for OA, whereas we included participants with a clinical or radiographic diagnosis of OA. It cannot be ruled out that other variables played a role in a change in pain and physical functioning in people with OA or people who were at high risk of developing OA. In addition, it is possible that potential prognostic factors can be experienced differently by these groups. Overall, the results of this review are generally in line with previous studies. In patients with hip OA, there was consistency with previous studies regarding cardiovascular diseases, renal insufficiency, stroke, cognitive functioning,[63] and physical activity.[64] In contrast, there were inconsistent results regarding prognostic factors on pain[63] and limited range of motion of external hip rotation,[63] cardiac comorbidity,[59] and depressive symptoms.[62]

Table 3. Variables associated with outcome pain in patients with knee osteoarthritis

Predictor	Type of change	Significance	Level of evidence
Personal factors			
Higher body mass index	Worsening	Significant	Moderate
Lower achieved education[a]	Worsening	Significant	Weak
African American	Worsening	Significant	Moderate
Pain coping skill: praying/hoping	Worsening	Significant	Inconclusive
Pain coping skill: pain catastrophizing	Worsening	Significant	Inconclusive
Female	Stable	Nonsignificant	Inconclusive
Increased behavioral activities	Stable	Nonsignificant	Inconclusive
Smoking status	Stable	Nonsignificant	Weak
Cumulative lifetime smoking	Stable	Nonsignificant	Inconclusive
Alcohol use	Stable	Nonsignificant	Inconclusive
Advanced age	Improvement	Significant	Inconclusive
Gender (male)	Improvement	Significant	Inconclusive
Higher achieved education[a]	Improvement	Significant	Weak
White	Improvement	Significant	Inconclusive
Lower body mass index	–	–	Inconsistent
Body functions and structures			
Higher severity of osteoarthritis[a]	Worsening	Significant	Inconclusive
Higher joint space tenderness[a]	Worsening	Significant	Weak
Presence of foot/ankle symptoms			
Any[a]	Worsening	Significant	Weak
Ipsilateral[a]	Worsening	Significant	Weak
Contralateral[a]	Worsening	Significant	Weak
Bilateral[a]	Worsening	Significant	Weak
Higher comorbidities[a]	Worsening	Significant	Moderate
>10% weight gain	Worsening	Significant	Inconclusive
Persistence depressive symptoms	Worsening	Significant	Weak
Varus thrust[a]	Stable	Nonsignificant	Inconclusive
Calcium pyrophosphate deposition[a]	Stable	Nonsignificant	Inconclusive
History of renal insufficiency	Stable	Nonsignificant	Inconclusive
Catatonic depression (baseline)	Stable	Significant	Inconclusive
Asymptomatic depression (baseline)	Stable	Significant	Inconclusive
>–4.9% to <5% weight change	Stable	Nonsignificant	Inconclusive
Lower pain (baseline)	Improvement	Significant	Moderate
Anhedonic depression (baseline)	Improvement	Significant	Inconclusive
Melancholic depression (baseline)	Improvement	Significant	Inconclusive
Higher painful flexion of the knee[a]	–	–	Inconsistent
Presence of chondrocalcinosis[a]	–	–	Inconsistent
Higher Musculus Quadriceps Femoris strength	–	–	Inconsistent
Activities			
Lower self-reported physical functioning	Worsening	Significant	Strong
Lower performance-based physical functioning in women	Worsening	Significant	Weak
Regular walking	Worsening	Significant	Inconclusive
Lower performance-based physical functioning in men	Stable	Nonsignificant	Weak
Higher self-reported physical functioning	Improvement	Significant	Weak
Recreational activities	Improvement	Significant	Inconclusive
Higher physical activity	–	–	Inconsistent
Participation			
Sport	Improvement	Significant	Inconclusive
Runners[a]	Improvement	Significant	Inconclusive
Gardening	Improvement	Significant	Inconclusive
Other			
Pain medication use	Worsening	Significant	Inconclusive
Higher calorie intake	Worsening	Significant	Inconclusive
Higher magnesium intake	Improvement	Significant	Inconclusive
Higher fiber intake	Improvement	Significant	Inconclusive

[a] Measure of association used was odds ratio.

In the current study, the focus was not only on factors associated with deterioration but also on stability and/or improvement of pain and physical functioning. This had important added value because modifiable factors associated with an improvement were potential targets for intervention. However, the low number of participants in studies who showed stability or improved pain and physical functioning limited the level of evidence for associated factors for stability or improvement. Additionally, this study

Table 4. Variables associated with outcome physical functioning in patients with knee and/or hip OA*

Predictor	Type of change	Significance	Level of evidence
Personal factors			
Higher body mass index[a]	Worsening	Significant	Strong
Lower achieved education[b]	Worsening	Significant	Weak
African American	Worsening	Significant	Moderate
Pain coping skill: praying/hoping	Stable	Significant	Inconclusive
Pain coping skill: ignoring pain	Stable	Significant	Inconclusive
Lower achieved education[c]	Stable	Nonsignificant	Inconclusive
Smoking status	Stable	Nonsignificant	Inconclusive
Cumulative lifetime smoking	Stable	Nonsignificant	Weak
Male	Improvement	Significant	Inconclusive
White	Improvement	Significant	Inconclusive
Higher self-efficacy	Improvement	Significant	Weak
Higher age[a]	–	–	Inconsistent
Female	–	–	Inconsistent
Body functions and structures			
Higher pain[a,c]	Worsening	Significant	Strong
Higher hip pain[c]	Worsening	Significant	Strong
Higher severity of OA[c]	Worsening	Significant	Inconclusive
Higher stiffness[a]	Worsening	Significant	Inconclusive
Higher hip exorotation change[b]	Worsening	Significant	Inconclusive
Lower range of motion of the knee[b]	Worsening	Significant	Inconclusive
Duration of complaints	Worsening	Significant	Weak
Lower handgrip strength	Worsening	Significant	Inconclusive
Higher laxity[a]	Worsening	Significant	Weak
Higher comorbidities	Worsening	Significant	Strong
Higher comorbidities[b]	Worsening	Significant	Inconclusive
Cognitive impairment[a,c]	Worsening	Significant	Inconclusive
Lower cognitive functioning[a]	Worsening	Significant	Inconclusive
Chronic lung disease[a,c]	Worsening	Significant	Inconclusive
Peripheral artery disease[a]	Worsening	Significant	Inconclusive
>10% weight gain	Worsening	Significant	Inconclusive
Bilateral knee pain	Stable	Nonsignificant	Weak
Morning stiffness	Stable	Nonsignificant	Weak
Crepitus	Stable	Nonsignificant	Weak
Hip abductor muscle strength	Stable	Nonsignificant	Strong
Joint space narrowing	Stable	Nonsignificant	Weak
Varus thrust	Stable	Nonsignificant	Inconclusive
Presence of chondrocalcinosis	Stable	Nonsignificant	Weak
>–4.9% to <5% to weight change	Stable	Nonsignificant	Inconclusive
Comorbidities			
History of renal insufficiency	Stable	Nonsignificant	Inconclusive
Cardiovascular disease[a,c]	Stable	Nonsignificant	Inconclusive
Diabetes mellitus[a,c]	Stable	Nonsignificant	Inconclusive
Stroke[a,c]	Stable	Nonsignificant	Inconclusive
Cancer[a,c]	Stable	Nonsignificant	Inconclusive
Osteoporosis[a,c]	Stable	Nonsignificant	Inconclusive
Catatonic depression	Stable	Significant	Inconclusive
Asymptomatic depression	Stable	Significant	Inconclusive
Anxiety[a,c]	Stable	Nonsignificant	Inconclusive
Higher active knee flexion[a]	Improvement	Significant	Weak
>10% weight reduction	Improvement	Significant	Inconclusive
Anhadonic depression	Improvement	Significant	Inconclusive
Melancholic depression	Improvement	Significant	Inconclusive
Mental health	Improvement	Significant	Weak
Musculus quadriceps femoris strength	–	–	Inconsistent
Higher bony tenderness[a]	–	–	Inconsistent
Osteophytosis	–	–	Inconsistent
Depressive symptoms[b]	–	–	Inconsistent
Activities			
Higher avoidance of activities	Worsening	Significant	Strong
Walking time[a,c]	Stable	Nonsignificant	Inconclusive
Higher physical functioning (baseline)	Improvement	Significant	Inconclusive

(Continued)

Table 4. (*Cont'd*)

Predictor	Type of change	Significance	Level of evidence
Physical activity[a,c]	–	–	Inconsistent
Environmental factors			
Social isolation[a,c]	Improvement	Nonsignificant	Inconclusive
Medical and social care[a,c]	Improvement	Nonsignificant	Inconclusive
Income (capable of making it to the months end)[a,c]	Improvement	Nonsignificant	Inconclusive
Higher social support	Stable	Significant	Weak
Other			
Fiber intake	Worsening	Significant	Inconclusive
Pain medication use[a,c]	Worsening	Significant	Inconclusive
Higher vitality[a]	Improvement	Significant	Moderate
Higher magnesium intake	Improvement	Significant	Inconclusive
Higher calorie intake	Improvement	Significant	Inconclusive
Lower alcohol use	Improvement	Significant	Inconclusive

* OA, osteoarthritis.
[a] Measure of association used was odds ratio or risk ratio.
[b] Domain is hip OA only.
[c] Domain is hip/knee OA.

had identified prospective factors that were not associated with a change in both directions but only in one. There was not always an explanation for this. This was partly because it had not been studied but also because many prognostic studies had focused on an increase in pain and a decrease in physical functioning, possibly due to the natural course of OA progression. For example, a higher number of comorbidities was associated with a worsening of pain, but we found no evidence that a lower number of comorbidities was associated with improvement of pain. For some factors, there was a hypothesis or explanation as to why that factor influenced change in both directions. For example, a higher educational level was associated with an improvement of pain and a lower educational level with an increase of pain. Individuals with higher education levels may have had better health literacy.[65] This enabled them to understand and follow treatment plans more effectively and have healthier lifestyles then individuals with lower health literacy.[66]

Most associated factors with a change in pain or physical functioning were in the body functions and structures domain of the ICF.[12] The factors, with a moderate or strong level of evidence, associated with a change in pain and physical functioning were predominantly modifiable factors implicating potential for treatment of these factors in clinical practice. Nonsurgical interventions and the approach to influence modifiable factors had previously been described in international guidelines.[67] Body mass index, (hip) pain at baseline, self-reported physical functioning, avoidance of activities, and vitality were modifiable factors. For example, body mass index could be influenced by exercise therapy[66] and changing diet,[67] hip pain by medication[65] and exercise therapy,[66] self-reported physical functioning by behavioral change techniques[68] and exercise therapy,[66] and vitality by all of these interventions, although the long-term effects were not convincing. The factors that were not or less influenceable were ethnicity and the presence or the number of comorbidities. Furthermore, with the factors associated with a change in pain or physical functioning, a prediction model could be developed. A prediction model could be valuable for an individual patient to provide timely advice on modifiable factors, aiming to prevent an increase in pain or deterioration of physical functioning. A predictive model became even more valuable when it used continuous or more frequently measured data. We were possibly at a suitable juncture to develop a prediction model. Prediction models require continuous refinement and validation. Therefore, ongoing reviews and observational studies should focus on identifying new prospective factors and refining existing evidence.

An underresearched population in the existing knowledge are people with hip OA. For pain, there were no studies available, and for physical functioning, this group was also underrepresented. Findings from knee OA research cannot simply be applied to people with hip OA.[68] In addition to patients with hip OA being underrepresented in studies on physical functioning, the consistency of prognostic factors with previous studies varies. This increases the importance of future research on this group, aiming to develop effective prediction models specifically for patients with hip OA.[59,62–64] A second gap of knowledge is that participation was assessed in only one study. The used measurement instrument also fits physical functioning.[27,69] This could be because only a few validated questionnaires focused on participation. In addition, participation was often measured with a subscale of a measuring instrument.[70] In the current study, this made it not possible to summarize the literature on one of the outcomes as formulated in the aim of this study. Future research should focus on patients with hip OA, and participation as an outcome should receive more attention, especially given the increasing importance of participation, the approach from positive health,[71] and keeping people active for as long as possible, despite the aging population.[2] Furthermore, in many patients with OA, the symptoms and function manifested as episodes.[72] It is interesting to identify the factors that contributed to acute flares of deteriorating pain and physical functioning in patients with OA.[7] Innovative

measurement tools like applications (apps) and wearables provided possibilities to measure outcome measurements, as well as determinants, more frequently or even continuously. For future research, this allows stronger conclusions to be drawn about causal relationships.

As a major strength of our study, we used a highly innovative active learning method for screening the studies. Efficient and innovative methods to use during the screening process are desirable, especially in domains with large numbers of papers.[73] Naturally, there are ambiguities when using innovative methods and difficulties that have to be overcome. Using artificial intelligence (AI) is promising when appropriately used.[73] There is a lot of literature available on OA, and manual screening would be very time consuming. ASReview[19] therefore offered the solution for the current study with more than 9,000 records. Multiple reviews using ASReview[19] have already been published. In our experiences, it is very important to upload prior knowledge and label them (relevant or irrelevant) in the AI system to get the active learning program started as best as possible. Another important recommendation is that when an active learning program is used in future research, the stopping heuristics must be very clear. At the start of the screening process, no study had yet been published that described criteria for when the screening process can be terminated when AI is used, and it can be assumed that the remaining studies will be irrelevant. Currently, there is a study under review that developed the Screen, Apply, Find, Evaluatie procedure.[74] This is a practical and conservative set of stopping heuristics that offers a clear guideline for determining when to end the active learning process in screening software like ASReview.[19] Retrospectively, the current study meets all the criteria for ending the process. The use of ASReview[19] in the current study is unlikely to have influenced the results. It saved time, which benefits the completeness of the systematic review, and it has contributed to knowledge and experience to be even more effective and efficient in future research. Delving into an innovative method such as ASReview takes time, but we recommend using AI when carrying out systematic reviews because it ultimately saves time.

Despite the fact that the study was conducted with great care, there were some limitations. First, the list of prognostic factors of interest associated with pain, physical functioning, and participation may not be complete. There was a large number of studies that were eligible for full-text screening; hence, the decision was made to refine the inclusion and exclusion criteria. Due to this decision, possible prognostic factors were excluded, for example, joint space narrowing, inflammatory blood markers or performance-based measurement instruments. Second, intervention studies were excluded because the intervention influenced the course of symptoms and thereby the association between a potential associated factor and pain, physical functioning, or participation. The control groups, without intervention, were also not included in the current review. It is possible that information from control groups was relevant but was not included in this review. Third, only studies with a sample size of <100 participants were excluded. This size selection may have resulted in selection bias of included studies. Besides these limitations due to methodologic choices, it was not possible to conduct a meta-analysis due to heterogeneity in the prospective factors among included studies.

In this systematic review, the literature is summarized regarding prognostic factors on changes in either direction (ie, worsening or improvement) in pain, physical functioning, and participation in patients with hip/knee OA. Strong or moderate evidence was found for some personal factors and clinical factors. This was consistent with previous reviews. A valuable implication for clinical practice is that associated factors like body mass index, number of comorbidities, avoidance of activities, and higher vitality are modifiable factors. A prediction model can be valuable for an individual patient to provide timely advice on modifiable factors, aiming to prevent an increase in pain or deterioration of physical functioning. Future research should focus on patients with hip OA, the outcome participation, and causal relationships of these prospective variables on clinical outcomes of OA progression.

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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, author Cijs 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/Helsinki Declaration requirements.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Using Adaptive Choice-Based Conjoint Approach to Facilitate Shared Decision-Making in Osteoarthritis Management: A Patient Perception Study

Basem Al-Omari,[1] Joviana Farhat,[1] Mohanad Odeh,[2] Mumtaz Khan,[3] Hristo Grancharov,[4] Zaki Abu Zahr,[5] Sammy Hanna,[6] and Abdulla Alrahoomi[4]

Objective. This study examines the application of the adaptive choice-based conjoint (ACBC) method to facilitate the shared decision-making (SDM) process for osteoarthritis (OA) treatment.

Methods. The study recruited adult patients with OA attending the rheumatology/orthopedics clinics in a local urban hospital in Abu Dhabi, United Arab Emirates (UAE). Participants completed a questionnaire regarding who influences their decision in selecting OA medication, followed by an ACBC questionnaire about OA medication preferences and a questionnaire about the potential contribution of ACBC to the SDM process. A univariate analysis was used to investigate the relationships between participant variables and factors that influence their decision-making processes. The chi-squared test, Fisher's exact test, Cramér's V coefficient test, and multivariable logistic regression analysis were used. The primary outcome investigates the contribution of the ACBC method to the SDM process for OA treatment. Secondary outcomes measure the association between patient demographics and variables related to the SDM process and ACBC questionnaire.

Results. Five hundred patients participated in this study, with a response rate of 100%. Most study participants were 60 to 69 years old (34.8%), women (78.8%), and UAE nationals (90.4%). Patients' opinions and online or paper information influencing their decision in selecting OA medication had a statistically significant association with age, gender, education, and employment ($P = 0.001$, $P = 0.039$, $P = 0.002$, and $P = 0.001$, respectively). Employment status showed the strongest association (φc 0.170) with being independent in making the decision about OA medications, whereas education levels showed the strongest association (φc 0.24) with decisions impacted by online or paper information. The results of the multivariable logistic analysis showed that the only statistically significant variable for online or paper information that influenced the decision in selecting OA medication was education level ($P = 0.003$). Most participants agreed or strongly agreed that the ACBC predicted their preferences for OA treatment (96.8%) and that the questionnaire may help doctors understand patient preferences (93%), and they recommended the use of the ACBC tool in doctors' clinics to aid the SDM process (92.8%) between patients and their physicians.

Conclusion. An ACBC approach can facilitate doctors' understanding of patient preferences and aid the SDM process. Most patients with OA are independent or influenced by their physician when making decisions about OA medication. Higher education and employment among patients with OA are associated with a better involvement in the SDM process for available treatment.

INTRODUCTION

With health care expansion, the interest in shared decision-making (SDM) between physicians and patients has been largely increasing.[1] SDM has been defined as a process that allows clinicians to collaboratively help patients reach evidence-informed medical decisions, whether they are diagnostic, therapeutic, or preventive.[2,3] This process enables patients to

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[1]Basem Al-Omari, PhD, Joviana Farhat, PharmD: Khalifa University, Abu Dhabi, United Arab Emirates; [2]Mohanad Odeh, PhD: Department of Clinical Pharmacy and Pharmacy Practice Faculty of Pharmaceutical Sciences, The Hashemite University, Zarqa, Jordan; [3]Mumtaz Khan, MD: Khalifa University and Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates; [4]Hristo Grancharov, MD, Abdulla Alrahoomi, MD: Khalifa University and Healthpoint Hospital, Abu Dhabi, United Arab Emirates; [5]Zaki Abu Zahr, MD: Healthpoint Hospital, Abu Dhabi, United Arab Emirates; [6]Sammy Hanna, MD: Khalifa University and Healthpoint Hospital, Abu Dhabi, United Arab Emirates and Queen Mary University of London, London, United Kingdom.

SIGNIFICANCE & INNOVATIONS

- The implementation of the adaptive choice-based conjoint (ACBC) approach may improve physicians' understanding of patient preferences and facilitate an effective shared decision-making (SDM) process for osteoarthritis (OA) treatment.
- Education and employment status are associated with the level of engagement of patients with OA in the SDM process.
- The majority of Arab patients with OA may perceive themselves as independent in making decisions about their OA medication or their final choices often guided by their physicians.
- This study pioneers the application of ACBC specifically tailored for Arab patients with OA in the United Arab Emirates, making a unique contribution to the field.

share their preferences with physicians, exchange information, and discuss available treatment options.[4] Therefore, it provides a way of integrating evidence and patient preferences into health-related decisions.[5] In practice, using an SDM process has improved patients' knowledge, engagement, satisfaction, adherence, and outcome.[6–8] On the contrary, limiting the active participation of patients in clinical decisions could be associated with patients' dissatisfaction and the discontinuity of care.[9]

Clinically, rheumatologic conditions such as osteoarthritis (OA) are managed with multiple treatment options. Accordingly, the application of SDM has been considered an essential tool for patients with OA and their physicians.[10] OA is a chronic illness associated with multiple long-term complications along with a variable efficacy for the available treatment options among patients.[11,12] According to the National Institute for Health and Care Excellence OA guidelines, patients' preferences and beliefs should be considered when choosing the treatment for OA.[13] Furthermore, understanding patients' preferences can help physicians to individualize health care delivery based on patients' needs.[14] This is especially relevant when the treatment outcomes are variable, or when several treatment options may provide similar benefits and risk ratios.[15] Therefore, OA has been classified as a preference-sensitive condition.[16] Patients' preferences may also influence their adherence to OA treatment.[17,18] Hence, adopting an SDM model is essential for providing patients with OA with accurate information and encouraging their active participation in decision-making as part of patient-centered care.[18,19]

The SDM process has been facilitated using printed or online tools such as patient decision aids (PtDAs), which present evidenced information about treatment benefits, risks and other characteristics.[20] In addition to PtDAs, the conjoint analysis (CA) method has been used to measure individuals' preferences more accurately[21] to facilitate the SDM process.[22] In recent years, adaptive choice-based conjoint (ACBC) has been considered the most advanced CA technique applied for evaluating the preferences of patients.[23] In the OA setting, research findings showed that ACBC is a practical method to obtain patients' preferences for OA management options.[24–26] However, there is limited evidence regarding the potential contribution of ACBC as a tool to elicit patient preferences and improve the SDM process, especially in Arabic-speaking countries.

Despite the demanding need for SDM in health care, several constraints may obstruct its implementation. For example, the complexity of medical decisions, the availability of several treatment options, and time constraints can limit the use of SDM.[27] Patients may also be passive decision-makers, preferring that the clinician makes treatment decisions.[28] As a process, the SDM can be influenced by many patient-related factors, such as race, gender, socioeconomic status, language and health literacy, symptom severity, and previous medical care experience.[15,29] Therefore, patients may vary in their level of involvement in the SDM process.[30]

Arabic-speaking patients with chronic diseases may prefer a paternalistic decision-making model.[31] At the same time, some patient subgroups, including women or unemployed patients, may have increased preference for participating in decision-making. Population-based studies also reported that both patients and their health care professionals were positively oriented toward active patient involvement in SDM. These heterogeneous outcomes explain why the preference of Arab patients for SDM has gained a more significant concern in the research field. In the Gulf region, particularly in the United Arab Emirates (UAE), physicians strongly support patients' engagement in decision-making regarding their health.[32] Physicians partially engaged in SDM attributed their behaviors to uncontrollable factors, including patient attitudes, environment, and interpersonal dynamics.[32] Alameddine et al[32] reported that female physicians were more involved in SDM compared with male physicians across both male and female patients. This could be associated with the cultural, social, and religious limitations that may affect the physician–patient relationship.[32] To date, it can be suggested that there is still limited evidence on the preferences of patients with OA toward decision-making. Therefore, in line with the global mission to strengthen patients' active role in health care decision plans, this study aims to examine the ACBC method as a

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Address correspondence via email to Basem Al-Omari, PhD, at basem.alomari@ku.ac.ae.

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potential contributor to facilitate the SDM process between Arab patients with OA residing in the UAE and their physicians.

METHODS

Adaptive choice-based CA for OA treatment. Using Sawtooth Software Lighthouse Studio version 9.13.1, a web-based ACBC questionnaire tailored for Arabic speakers was developed. The ACBC task comprised three divisions. In the first division, labeled Build Your Own, participants were provided with the complete attributes and levels representing the available OA treatment options. They were requested to select their most favored level specific to each attribute. The second division, the screening section, consisted of several scenarios formulated by the software and personalized according to participants' earlier responses. Moreover, within this section, must-have and unacceptable questions were also presented. These questions aimed to further individualize scenarios per each participant's specific preferences. In the final task, participants were presented with choice-based questions in which they had to select their desired scenario from three sets of scenarios.

It is worth mentioning that the plan for developing the ACBC questionnaire followed the same previously applied process in UK-based studies using 9 attributes and 31 levels.[24–26] The current ACBC questionnaire included 10 attributes and 34 levels.[23] In particular, the cost attribute has been added because the UAE health care system has different insurance coverage plans that could impact patients' treatment preferences. Refer to Supplementary Table 1 for a complete list of attributes and levels used in the ACBC task.

Participants and settings. Patients with OA who were 18 years and above and attending the rheumatology or orthopedics outpatient clinics in a local urban hospital in Abu Dhabi, UAE, were recruited for this study. Patients were part of this study if they had a confirmed diagnosis of OA from their physician in at least one joint and reported symptomatic pain in joints for the last 12 months. This study excluded patients with OA with other illnesses that might affect their joint pain, such as rheumatoid arthritis, osteoporosis, or injuries.

Data collection. Research associates collected the data between March and August 2022. Patients who met the inclusion criteria had an explanation about the study, its objectives, and patient involvement. Consequently, patients willing to participate in the study signed an informed consent sheet. A touch screen laptop was supplied to each participant to complete the questionnaire. In the case of limited health literacy, the research associates assisted the patients in completing the required tasks.

Initially, participants were asked about their age, gender, country of origin, education, employment, years since diagnosis OA, affected joints, and their currently prescribed OA medications. The pain interference with everyday life was documented for each patient based on a Likert scale ranging from not at all to extreme. Then, participants were requested to complete a questionnaire comprising five Likert scale items

Table 1. Participant characteristics*

Characteristic	n (%)
Age, y	
20–29	1 (0.2)
30–39	16 (3.2)
40–49	52 (10.4)
50–59	161 (32.2)
60–69	174 (34.8)
70–79	85 (17)
>79	11 (2.2)
Gender	
Female	394 (78.8)
Male	106 (21.2)
Country of origin	
UAE	452 (90.4)
Yemen	11 (2.2)
Egypt	5 (1)
Jordan	5 (1)
Oman	6 (1.2)
Syria	3 (0.6)
Lebanon	4 (0.8)
Palestine	2 (0.4)
Other	12 (2.4)
Education	
Doctoral degree	5 (1)
Master's degree	11 (2.2)
Bachelor's degree	81 (16.2)
Diploma	35 (7)
High school certificate	89 (17.8)
Middle school	38 (7.6)
Primary school	48 (9.6)
Not educated	189 (37.8)
I prefer not to say	4 (0.8)
Employment	
Employed	68 (13.6)
Employed part-time	1 (0.2)
Self-employed	4 (0.8)
Unemployed	310 (62)
Retired	117 (23.4)
Affected joints	
Knee	429 (85.8)
Spine/back/neck	103 (20.6)
Shoulder	95 (19)
Feet	94 (18.8)
Hands	63 (12.6)
Hip	56 (11.2)
Elbow	28 (5.6)
Pain interference with normal life	
Not at all	22 (4.4)
A little bit	70 (14)
Moderately	140 (28)
Quite a bit	115 (23)
Extremely	153 (30.6)
Years since diagnosis of OA	
>5	196 (39.2)
5–10	180 (36)
>10	120 (24)
Unknown	4 (0.8)

* N = 500. OA, osteoarthritis; UAE, United Arab Emirates.

ranging from strongly agree to strongly disagree. It comprised four inquiries regarding who influences their decision in selecting OA medication (physician, family or friends, online information or brochures, and completely independent). Participants completed the Arabic version of the ACBC questionnaire locally in a private room during their clinic waiting time, with an average of 10 to 12 minutes for questionnaire completion. The ACBC questionnaire assessed patient preferences regarding their OA medication treatment. The ACBC tool yielded personalized results of OA treatment for each participant and received their report findings. As a next step, participants were scheduled for consultations with specialists, facilitating the discussion of individual preference outcomes with their respective physicians. After the consultation, each participant was administered a questionnaire with five Likert scale items, from strongly agree to strongly disagree, and composed of three inquiries. The first question queried whether the ACBC results, as predicted by the software, accurately represented their preferences for OA treatment. The second question assessed the potential of the ACBC questionnaire in aiding physicians' comprehension of patient preferences for OA treatment. The third question sought participants' recommendations regarding integrating the ACBC tool into doctors' clinics to enhance the SDM process between patients and their physicians.

Statistical analysis. Categorical variables and participants' responses were presented through descriptive statistics in terms of frequencies and percentages. The study data were investigated using Statistical Package for the Social Sciences, version 27. A univariate analysis was used to analyze the relationships between participant variables and factors influencing their decision-making processes. The chi-squared test was employed (when the anticipated count was below five, Fisher's exact test was used as an alternative). To enhance our comprehension of the relationships, the Cramér's V coefficient was computed to measure the strength of the association. A Cramér's V value of 1 signifies complete association, whereas 0 indicates no association. Values >0.25 suggest a very strong relationship, values >0.15 indicate a strong relationship, values >0.1 signify a moderate relationship, and values >0.05 indicate a weak relationship.[33]

Additionally, comparing Cramér's V coefficient values allows us to rank the variables based on the strength of their impact on the dependent variable. A multivariable logistic regression analysis was conducted to understand the variables influencing the online decision-making process regarding OA. The dependent variable was categorized as either agree or strongly agree versus other responses about the influence of online and paper brochures on the decision to select OA medication. Adjusted odds ratios (ORs) and corresponding *P* values were calculated, along with relative 95% confidence interval (95% CI) measures. The senior author may make data available upon reasonable request. This research was approved by the institutional review board of Khalifa University of Science and Technology (reference number H20-023) and the Healthpoint Research Ethics Committee (reference number MF2467-2020-4).

RESULTS

Participant profiles. Five hundred patients with OA participated in this study, achieving a 100% response rate without any loss of follow-up. The majority of study participants were women (78.8%). Many participating patients were 60 to 69 years old (34.8%), and patients who were 20 to 29 years old accounted only for 0.2% of participants. Arabic was the dominant first language (98.8%), whereas English and other languages accounted for 0.8% and 0.4%, respectively. This was expected because 90.4% of the participants were originally from the UAE. Most participants (37.8%) were uneducated (did not complete their primary school education), and 26.4% had post–high school education. Approximately 62% of the study population did not have employment, and only a small minority were involved in part-time work (0.2%) (Table 1).

The knee was the most frequently affected joint with OA (85.5%), whereas the elbow was the least affected joint (5.6%). Study participants exhibited variation in the duration of OA, with most patients having OA for less than five years (39.2%), whereas

Table 2. Patient agreement on factors that may influence their decision in selecting OA medication*

Statement	Frequency, n (%)				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
My doctor influences my decision in selecting my osteoarthritis medication.	225 (45)	151 (30.2)	43 (8.6)	78 (15.6)	3 (0.6)
My family or friends influence my decision in selecting my OA medication.	48 (9.6)	126 (25.2)	41 (8.2)	214 (42.8)	71 (14.2)
Online and paper brochures and information influence my decision in selecting my OA medication.	20 (4)	96 (19.2)	64 (12.8)	170 (34)	150 (30)
I am completely independent in making the decision in selecting my OA medication.	249 (49.8)	164 (32.8)	34 (6.8)	48 (9.6)	5 (1)

* N = 500. OA, osteoarthritis.

24% of patients had OA for more than 10 years. Of the participants, 30.6% conveyed that OA extremely affected their everyday lives, whereas 4.4% stated that joint pain did not affect their everyday lives at all (Table 1). The most used medications for OA before the study were paracetamol (63%) and ibuprofen (23.4%), and the least used medications were codeine or dihydrocodeine (0.2%) (Supplementary Table 2).

Factors influencing patients' decisions in selecting OA medication. Most participants (75.2%) agreed or strongly agreed that their doctor influences their decision in selecting OA medication. More than half of the participants (57%) disagreed or strongly disagreed that their family or friends influenced their decision in selecting OA medication. Some participants (23.2%) agreed or strongly agreed that online and paper brochures and

Table 3. Relationships between participant variables and online or paper information influencing their decision in selecting OA medications*

	Frequency, n (%)[a]							Multivariable regression adjusted for all variables			
										95% CI	
Characteristic	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	*P*	φc[b]	Adjusted *P*	OR	Lower	Upper
Age, y						**0.001**	0.15	0.07	0.84	0.69	1.015
30–39	3 (17.6)	5 (29.4)	5 (29.4)	2 (11.8)	2 (11.8)						
40–49	3 (5.8)	13 (25)	11 (21.2)	15 (28.8)	10 (19.2)						
50–59	6 (3.7)	36 (22.4)	23 (14.3)	58 (36)	38 (23.6)						
60–69	4 (2.3)	26 (14.9)	18 (10.3)	68 (39.1)	58 (33.3)						
70–79	4 (4.7)	16 (18.8)	7 (8.2)	22 (25.9)	36 (42.4)						
>79	0 (0)	0 (0)	0 (0)	5 (45.5)	6 (54.5)						
Gender						**0.018**	0.15	0.24	0.72	0.42	1.24
Male	3 (2.8)	25 (23.6)	13 (12.3)	46 (43.4)	19 (17.9)						
Female	17 (4.3)	71 (18)	51 (12.9)	124 (31.5)	131 (33.2)						
Country of origin						0.400	0.10	0.39	0.93	0.81	1.09
UAE	19 (4.2)	85 (18.8)	53 (11.7)	153 (33.8)	142 (31.4)						
Yemen	1 (9.1)	1 (9.1)	3 (27.3)	4 (36.4)	2 (18.2)						
Egypt	0 (0)	2 (40)	0 (0)	0 (0)	3 (60)						
Jordan	0 (0)	2 (40)	2 (40)	1 (20)	0 (0)						
Oman	0 (0)	2 (33.3)	2 (33.3)	2 (33.3)	0 (0)						
Syria	0 (0)	2 (66.7)	0 (0)	1 (33.3)	0 (0)						
Lebanon	0 (0)	0 (0)	1 (25)	2 (50)	1 (25)						
Palestine	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)						
Other	0 (0)	2 (16.7)	3 (25)	5 (41.7)	2 (16.7)						
First language						0.480	0.08	0.26	1.16	0.92	1.35
Arabic	20 (4)	95 (19.2)	63 (12.8)	167 (33.8)	149 (30.2)						
English	0 (0)	1 (25)	0 (0)	3 (75)	0 (0)						
Other	0 (0)	0 (0)	1 (50)	0 (0)	1 (50)						
Education						**<0.001**	0.24	–	–	–	–
No education	6 (3.1)	19 (9.8)	13 (6.7)	69 (35.8)	86 (44.6)			**0.003**	Ref	Ref	Ref
Secondary	6 (3.4)	40 (22.9)	17 (9.7)	67 (38.3)	45 (25.7)			0.860	1.1	0.26	4.9
BSc	5 (4.3)	37 (31.9)	28 (24.1)	29 (25)	17 (14.7)			0.001	3.37	1.7	6.7
Postgraduate	3 (18.8)	0 (0)	6 (37.5)	5 (31.3)	2 (12.5)			0.009	2.1	1.2	3.7
Employment						**<0.001**	0.20	0.71	0.93	0.64	1.36
Employed	5 (6.8)	16 (21.9)	19 (26)	19 (26)	14 (19.2)						
Unemployed	10 (3.2)	49 (15.8)	27 (8.7)	108 (34.8)	116 (37.4)						
Retired	5 (4.3)	31 (26.5)	18 (15.4)	43 (36.8)	20 (17.1)						
Years since diagnosis of OA						**0.009**	0.14	0.75	0.59	0.13	2.05
>5	11 (5.6)	47 (24)	28 (14.3)	68 (34.7)	42 (21.4)						
5–10	7 (3.9)	33 (18.3)	18 (10)	63 (35)	59 (32.8)						
>10	2 (1.7)	15 (12.5)	18 (15)	36 (30)	49 (40.8)						
Pain						0.160	0.09	0.26	1.12	0.92	1.35
Not at all	1 (4.5)	5 (22.7)	4 (18.2)	8 (36.4)	4 (18.2)						
A little bit	3 (4.3)	9 (12.9)	15 (21.4)	31 (44.3)	12 (17.1)						
Moderately	6 (4.3)	27 (19.3)	18 (12.9)	47 (33.6)	42 (30)						
Quite a bit	6 (5.2)	26 (22.6)	11 (9.6)	39 (33.9)	33 (28.7)						
Extremely	4 (2.6)	29 (19)	16 (10.5)	45 (29.4)	59 (38.6)						

* N = 500. Bolded *P* values are statistically significant. 95% CI, 95% confidence interval; BSc, Bachelor of Science; OA, osteoarthritis; OR, odds ratio; Ref, reference; UAE, United Arab Emirates.
[a] The statement measured by the Likert scale: "Online and paper brochures and information influence my decision in selecting my OA medication."
[b] Cramér's phi (φc).

information influenced their decision in selecting OA medication. Moreover, the vast majority of participants (82.6%) agreed or strongly agreed that they are independent in deciding while selecting OA medication (Table 2).

The univariate association analysis showed no significant associations between patient variables and doctors and family or friends influencing patients' decisions in selecting OA medication. Younger age (P = 0.001), male gender (P = 0.018), higher education (P < 0.001), being employed (P < 0.001), and having fewer years of OA symptoms (P = 0.009) had statistically significant associations with online and paper brochures and information influencing patients' decision in selecting OA medication (Table 3). Age (P = 0.010), gender (P = 0.039), education (P = 0.002), and employment (P = 0.001) had statistically significant associations with patients being independent in selecting OA medication (Table 3).

Table 4. Relationships between participant variables and being independent in their decision in selecting OA medications*

Demographic	Frequency, n (%)[a]					P	φc[b]
	Strongly agree	Agree	Neutral	Disagree	Strongly disagree		
Age, y						**0.010**	0.140
30–39	13 (76.5)	4 (23.5)	0 (0)	0 (0)	0 (0)		
40–49	26 (50)	17 (32.7)	4 (7.7)	5 (9.6)	0 (0)		
50–59	91 (56.5)	47 (29.2)	5 (3.1)	18 (11.2)	0 (0)		
60–69	82 (47.1)	63 (36.2)	14 (8)	14 (8)	1 (0.6)		
70–79	32 (37.6)	30 (35.3)	11 (12.9)	9 (10.6)	3 (3.5)		
>79	5 (45.5)	3 (27.3)	0 (0)	2 (18.2)	1 (9.1)		
Gender						**0.039**	0.140
Male	61 (57.5)	28 (26.4)	8 (7.5)	6 (5.7)	3 (2.8)		
Female	188 (47.7)	136 (34.5)	26 (6.6)	42 (10.7)	2 (0.5)		
Country of origin						0.080	0.150
UAE	224 (49.6)	148 (32.7)	31 (6.9)	45 (10)	4 (0.9)		
Yemen	7 (63.6)	3 (27.3)	0 (0)	1 (9.1)	0 (0)		
Egypt	1 (20)	3 (60)	0 (0)	1 (20)	0 (0)		
Jordan	3 (60)	1 (20)	1 (20)	0 (0)	0 (0)		
Oman	4 (66.7)	2 (33.3)	0 (0)	0 (0)	0 (0)		
Syria	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)		
Lebanon	3 (75)	0 (0)	0 (0)	0 (0)	1 (25)		
Palestine	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)		
Other	5 (41.7)	4 (33.3)	2 (16.7)	1 (8.3)	0 (0)		
First language						0.200	0.100
Arabic	248 (50.2)	161 (32.6)	32 (6.5)	48 (9.7)	5 (1)		
English	1 (25)	2 (50)	1 (25)	0 (0)	0 (0)		
Other	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)		
Education						**0.002**	0.150
Diploma or BSc	70 (60.3)	37 (31.9)	4 (3.4)	4 (3.4)	1 (0.9)		
No education	75 (38.9)	73 (37.8)	19 (9.8)	23 (11.9)	3 (1.6)		
Postgraduate	11 (68.8)	2 (12.5)	3 (18.8)	0 (0)	0 (0)		
Up to secondary	93 (53.1)	52 (29.7)	8 (4.6)	21 (12)	1 (0.6)		
Employment						**0.001**	0.170
Employed	48 (65.8)	14 (19.2)	7 (9.6)	3 (4.1)	1 (1.4)		
Unemployed	134 (43.2)	114 (36.8)	22 (7.1)	39 (12.6)	1 (0.3)		
Retired	67 (57.3)	36 (30.8)	5 (4.3)	6 (5.1)	3 (2.6)		
Years since diagnosis of OA						0.210	0.100
>5	108 (55.1)	56 (28.6)	13 (6.6)	18 (9.2)	1 (0.5)		
5–10	85 (47.2)	66 (36.7)	7 (3.9)	19 (10.6)	3 (1.7)		
>10	56 (46.7)	40 (33.3)	13 (10.8)	10 (8.3)	1 (0.8)		
Pain						0.300	0.090
Not at all	0 (0)	2 (50)	1 (25)	1 (25)	0 (0)		
A little bit	12 (54.5)	7 (31.8)	1 (4.5)	2 (9.1)	0 (0)		
Moderately	46 (65.7)	16 (22.9)	2 (2.9)	5 (7.1)	1 (1.4)		
Quite a bit	71 (50.7)	43 (30.7)	11 (7.9)	13 (9.3)	2 (1.4)		
Extremely	56 (48.7)	34 (29.6)	9 (7.8)	15 (13)	1 (0.9)		

* N = 500. Bolded P values are statistically significant. BSc, Bachelor of Science; OA, osteoarthritis; UAE, United Arab Emirates.
[a] The statement measured by the Likert scale was "I am completely independent in making the decision in selecting my OA medication."
[b] Cramér's phi (φc).

Online and paper brochures and information had a stronger influence on the decision to select OA medication in participants who were younger, male, highly educated, retired, and recently diagnosed with OA. Education levels showed the strongest association (φc 0.24) with decision-making affected by online resources, followed by employment status (φc 0.20). Age, gender, and years of diagnosis exhibited similar degrees of association (φc 0.15, 0.015, and 0.14, respectively) (Table 3). After multivariable analysis, we adjusted ORs and *P* values for all variables. The results revealed that education level was the only statistically significant variable for online or paper information influencing the decision to select OA, as determined by the multivariable model (*P* = 0.003). Individuals with a bachelor's degree exhibited a 3.37 times higher likelihood of being influenced by online and paper brochures than uneducated patients (OR 3.37, 95% CI 1.7–6.7, *P* = 0.001). This effect was followed by a 2.1 times higher likelihood for postgraduates (OR 2.1, 95% CI 1.2–3.7, *P* = 0.009), whereas the differences among those with a secondary education level and uneducated patients appeared to be not significant (OR 1.1, 95% CI 0.26–4.9, *P* = 0.86).

Age, gender, education, and employment had a statistically significant association with independence in selecting OA medications. Younger men as well as highly educated, and employed participants tend to exhibit stronger agreement toward making independent choices than other demographic groups. Employment status showed the strongest association (φc 0.170) with being independent in decision-making, followed by education level (φc 0.150), then age and gender (φc 0.150) (Table 4).

ACBC's contribution to the SDM process. The vast majority of participants agreed or strongly agreed that the ACBC predicted their preferences for OA treatment (96.8%). The questionnaire may help doctors understand patients' preferred characteristics for OA pharmaceutical treatment (93%), and participants recommended the use of ACBC tool in clinics to aid the SDM process between patients and their doctors (92.8%). Study participants did not show disagreement or strong disagreement with any of the questions in Table 5.

DISCUSSION

Most patients with OA believe that they are independent or affected by their physician in making decisions regarding OA medications. Patients' age, gender, education, and employment status had statistically significant associations with patients' independence in selecting OA medication and employment status revealed the strongest association. Regarding the contribution of ACBC to the SDM process, the great majority of participants in our study indicated that the ACBC questionnaire represented their preferences for OA treatment and recommended using the ACBC approach by doctors to aid the SDM process.

This study predominantly includes individuals of Arab ethnicity, with a majority being women and residing in the UAE. The majority of patients were over 60 years old, and a significant portion reported having no education and being unemployed. Older age and female dominance are expected, taking into consideration that the prevalence of OA is increasing in the Middle East and North Africa region, especially among the elderly and female population.[34,35] Because the majority of participants were UAE nationals over the age of 60, it was expected by the researchers that all of them are Arabs, and most of them are uneducated and unemployed because they were born before the UAE was established in 1971. Before the union of the UAE, the learning system had depended on educational circles and semiorganized education.[36] As expected, the knee emerged as the most frequently affected joint by OA, whereas the elbow was the least affected joint. This aligns with the worldwide prevalence pattern of OA affecting most commonly the knee joint and least commonly the elbow joint.[11,37]

This study showed that participants' decisions regarding OA medications are not influenced by their family members or friends, and online and paper brochures and information do not influence them. The vast majority of participants indicated that they were

Table 5. Participants' responses regarding ACBC contribution to the SDM process*

Statement	Frequency, n (%)				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The results predicted by the software represent my preference for osteoarthritis treatment.	206 (41.2)	278 (55.6)	16 (3.2)	0 (0)	0 (0)
This questionnaire may help doctors to understand patients' preferences for osteoarthritis treatment.	162 (32.4)	303 (60.6)	35 (7)	0 (0)	0 (0)
I recommend the use of the ACBC tool in doctors' clinics to aid the SDM process between patients and their doctors.	162 (32.4)	302 (60.4)	36 (7.2)	0 (0)	0 (0)

* N = 500. ACBC, adaptive choice-based conjoint; SDM, shared decision-making.

independent or influenced by the physician while selecting their OA medication. This may suggest that Arab patients with OA have good knowledge and experience in dealing with OA progression and management. Furthermore, this could be due to patients being empowered by their physicians to make decisions when given the opportunity.

Previous studies reported that patients must be empowered to make independent health decisions, especially when they know about their disease.[38] The role of family and friends in patients' decisions is still ambiguous. Some literature suggested that they can enhance patients' autonomy by adopting a supportive role in clarifying information,[39] and others indicated that they could hinder patients' independence, causing them to become passive and less involved than they would like.[40] Participants also indicated that physicians influence their decisions regarding OA medication. In other chronic illnesses, such as cancer, it was reported that patients ultimately prefer the health care practitioners to make the final decision regarding treatment despite their willingness to engage in decision-making with the practicioners.[41] This is particularly important in the context of chronic disease management. This could also indicate a dominance of the paternalistic approach within the SDM processes. This approach prioritizes doctors' role in taking charge of final treatment decisions rather than promoting a more cooperative perspective that requires patients to actively contribute to SDM.[42] Furthermore, this could also indicate the UAE's social and medical beliefs, in which the paternalistic decision-making model is the preferred approach for patients with chronic diseases.[31] Therefore, patients may still consider it unusual to take an active role in deciding their OA medication.

In this study, the univariate association statistical analysis revealed statistically significant associations among participants who were influenced by online or paper information and were independent in selecting OA medication and four patient characteristics (age, gender, education, and employment). Conversely, no significant associations were observed among those influenced by family or friends and doctors. The multivariable results revealed that education level had a statistically significant association with online or paper information influencing the decision to select OA medications. Our results align with prior research indicating that age, gender, education, and employment are factors associated with patients' involvement in the SDM process.[43–46] Younger men and highly educated participants tend to exhibit stronger agreement toward making independent choices and being influenced by online or paper information when selecting OA medication compared with other demographic groups. Education level revealed the strongest association with OA medication decisions being influenced by online or paper information.

In contrast, employment status revealed the strongest association with being independent in the decision regarding OA medications. Previous research reported age and gender as independent factors with significant differences in the intensity of OA, the expression of pain, and the emotional impact.[47] Younger age is also known to positively influence the decision of selecting medication in patients with arthritis.[48] Given the surge in online and printed health materials over the past 10 years, it is understandable that younger patients may be more convinced by this type of information. In turn, the gender difference revealed in our study constitutes vital new information. Tschon et al[49] suggested that in the era of precision medicine, revealing the gender-based determinants in the treatment of OA supports the definition of gender-oriented protocols. Furthermore, our finding is consistent with previous evidence reporting that patients with higher education are more involved and share the responsibility with the doctors throughout the decision-making process.[46]

In our study, participants agreed or strongly agreed that the ACBC questionnaire represented their preferences for OA treatment, and its use may help doctors understand patients' preferences for available treatment options. Previous studies by Al-Omari et al[24–26] reported on ACBC's ability to generate the actual preferences of patients for OA medical treatment. The area of preference studies is rapidly expanding to provide a greater chance for including patients' voices in medical decisions.[50] This may be highly relevant in patients with chronic illnesses such as OA who focus on treatment outcomes as well as the impact of the disease on their quality of life when making decisions concerning their health.[51] Therefore, stated-preference or CA methods have been increasingly applied to individualize patients' preferences and strengthen the SDM process.[52] However, it is worth mentioning that CA is still a relatively new application in decision tools; therefore, clinicians report time and effort challenges that may still be encountered.[53]

The study findings indicated that most participants recommended using the ACBC approach in clinical practices to aid SDM between patients and their doctors. This aligns with earlier research reporting that patients preferred their physician to present treatment choices and seek their viewpoints, favoring the use of an approach that focuses mainly on their needs.[31] According to a 2017 Cochrane Review, PtDAs were associated with enhanced knowledge and risk perceptions, allowing patients to be active and decisive to make aligned decisions with their needs and manage decisional conflicts if they encountered preference-sensitive choices.[54] This may help improve medication adherence because patients can make collaborative decisions with their physicians.[55] Studies suggest that patients are more willing to initiate and engage in treatments that match their preferences. However, a recently conducted research study reported that the majority of Arab patients diagnosed with chronic diseases prefer to delegate medical decisions directly to their doctors.[56] This might be correlated to the UAE-based cultural and health habits directing patients toward a paternalistic medical approach. In turn, the patients' active participation in decision-making regarding their health may still be an atypical idea.

To our knowledge, this study pioneers in the initial exploration of how the ACBC method can aid in promoting SDM and assessing the impact of various factors on patients choices regarding OA medication. Moreover, our study evaluated the associative correlation between participant variables and factors that may influence patients' decisions to select OA pharmaceutical treatment. Despite the strengths of our study, there are some limitations associated with this study. Our research was executed within a single health care facility, potentially constraining the extent to which the findings can be extrapolated. This can also limit the reflection of the broad spectrum of available treatment options and patient scenarios, potentially restricting the study's ability to capture the full complexity of decision-making.

Furthermore, the changes in health care practices and patient attitudes over time may not be adequately captured when assessed in an individual center. This study focused on a single group of patients; however, it would have been worthwhile to compare control patients who received usual care with the ones who used the ACBC tool to assess possible differences between both groups. Therefore, future research necessitates multiple health care clinics and dual comparative groups to ensure a more diverse patient population and generalized outcomes.

In the long term, health care professionals may need further training and education to directly apply ACBC, which can foster patient engagement in disease management and personalized care. This may include workshops or online modules to familiarize physicians with its functionality. Moreover, integrating the ACBC tool into electronic health records will ensure easy access to patients' preferences during consultation. Future research should focus on the influence of clinicians' attitudes and characteristics on the SDM process for comprehensive understanding and better health care outcomes. Future studies implementing ACBC to facilitate the SDM processes may investigate its effectiveness using the SDM questionnaire 9. Future research may also consider investigating the use of ACBC within other treatment options for OA, such as exercise, weight management, and surgical treatment.

More highly educated and employed patients with OA residing in the UAE are more involved in the SDM process for their treatment. Arab patients with OA believe that they are independent in their medication decisions, and they are mainly influenced by their physician. The strongest statistical association with OA medication decisions being influenced by online and paper brochures and information was the education level and for being independent was employment status. For OA treatment, our study findings recommend using the ACBC approach in clinical practices to assist doctors' understanding of patient preferences and aid the SDM process.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Al-Omari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Al-Omari, Farhat.

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American College of Rheumatology
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BRIEF REPORT

Comparison of Three Physician Global Assessment Instruments in Systemic Sclerosis

Laura Ross,[1] Dylan Hansen,[2] Susanna Proudman,[3] Jennifer Walker,[4] Kimti Kumar,[3] Wendy Stevens,[2] Nava Ferdowsi,[2] Joanne Sahhar,[5] Gene-Siew Ngian,[5] Diane Apostolopoulos,[5] Lauren V. Host,[6] Kathleen Morrisroe,[1] Gabor Major,[7] Murray Baron,[8] and Mandana Nikpour[9]

Objective. Physician global assessments (PhyGAs) are variably applied in systemic sclerosis (SSc) clinical trials. The comparability of different PhyGA results is unknown. We sought to assess the comparability of results from three different PhyGA instruments simultaneously applied in the Australian Scleroderma Cohort Study (ASCS).

Methods. Using data from 1,965 ASCS participants, we assessed the correlation between results of three PhyGA assessments: (1) overall health, (2) activity, and (3) damage. We evaluated the concordance of change in each PhyGA between study visits. Ordered logistic regression analysis was used to evaluate the clinical associations of each PhyGA.

Results. The absolute scores of each PhyGA were strongly correlated at individual study visits. Concordant changes of the PhyGA scores occurred between 50% of study visits. Only patient-reported breathlessness was associated with all three PhyGA scores (overall health: odds ratio [OR] 1.67, $P < 0.01$; activity: OR 1.44, $P < 0.01$; damage: OR 1.32, $P < 0.01$). Changes in physician-assessed activity scores were also associated with patient-reported worsening skin disease (OR 1.25, $P = 0.03$) and fecal incontinence (OR 1.23, $P = 0.01$), whereas damage scores were associated with respiratory disease (pulmonary arterial hypertension: OR 1.25, $P = 0.03$; chronic obstructive pulmonary disease: OR 1.37, $P = 0.04$), as well as skin scores (OR 1.02, $P < 0.01$) and fecal incontinence (OR 1.21, $P = 0.02$).

Conclusion. PhyGAs of overall health, activity, and damage are each associated with different SSc features, and changes in different PhyGA scores are discordant 50% of the time. Our findings suggest results of variably worded PhyGAs are not directly interchangeable and support the development of a standardized PhyGA.

INTRODUCTION

The physician global assessment (PhyGA) is a single-question instrument used in systemic sclerosis (SSc) clinical studies to provide an overall assessment of patient status. In the absence of specific biomarkers of certain organ systems, the PhyGA is a method of capturing global disease not assessed by other objective measures.[1,2] However, a standardized PhyGA has not been developed, and there is no consistent application of PhyGAs across SSc studies.[1] In randomized controlled trials

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[1]Laura Ross, MBBS, PhD, Kathleen Morrisroe, MBBS, PhD: The University of Melbourne, Melbourne, and St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [2]Dylan Hansen, MBiostat, Wendy Stevens, MMBS, Nava Ferdowsi, MBBS, MMed: St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [3]Susanna Proudman, MBBS, Kimti Kumar, MBBS: The University of Adelaide and Royal Adelaide Hospital, Adelaide, South Australia, Australia; [4]Jennifer Walker, MBBS, PhD: Flinders Medical Centre, Bedford Park, South Australia, Australia; [5]Joanne Sahhar, MBBS, Gene-Siew Ngian, MBBS, PhD, Diane Apostolopoulos, MBBS, PhD: Monash Health and Monash University, Clayton, Victoria, Australia; [6]Lauren V. Host, MBBS: Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [7]Gabor Major, MBBS: John Hunter Hospital, New Lambton Heights, New South Wales, Australia; [8]Murray Baron, MDCM: Jewish General Hospital, Montreal, Quebec, Canada; [9]Mandana Nikpour, MBBS, PhD: The University of Melbourne, Melbourne, Victoria, and the University of Sydney, Sydney Musculoskeletal Health Research Flagship Centre, and Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia.

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Address correspondence via email to Laura Ross, MBBS, PhD, at laura.ross@unimelb.edu.au.

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SIGNIFICANCE & INNOVATIONS

- Change in physician global assessment (PhyGA) scores of activity, damage, and overall health are only concordant 50% of the time.
- The disease-specific features that correlated with each of activity, damage, and overall health are different, indicating physicians assess each of these constructs differently.
- The results of physician assessments of activity, damage, and overall health are not directly interchangeable, highlighting the need to standardize the PhyGA instrument in systemic sclerosis clinical trials.

(RCTs), physicians are variably asked to assess disease activity, severity, damage, or overall health and make their assessment using various types of scales. Which disease construct should be assessed by the PhyGA has not been determined, and as such, the validity of the PhyGA has not been established.[1]

It is untested whether various wordings of a PhyGA influence the assessment made by the physician and whether a singular definition of an SSc-PhyGA is required. Despite current practice, it is unknown whether global assessment results obtained from differently worded instruments are directly comparable.[3] The evaluation of global assessments in other diseases indicate this should be interrogated in SSc. Assessment of the concordance of patient-rated dyspnea in acute heart failure assessed by three differently worded instruments showed that simultaneous application of all three instruments purporting to measure the same construct elicited discordant ratings of symptom severity.[4] Given the frequent use of the PhyGA in RCTs and the inclusion of the PhyGA in composite response measures,[1–3] it is timely to assess the validity of the PhyGA.

In the Australian Scleroderma Cohort Study (ASCS), treating physicians are asked to complete three PhyGAs assessing activity, damage, and overall health at each visit. We hypothesized that each global assessment would provide different clinical information, meaning that the results of each PhyGA would not be directly interchangeable. We evaluated the correlation of the PhyGA results and assessed the concordance of change in each of the PhyGAs between visits. Secondly, we evaluated the clinical associations of each global assessment to explore whether different SSc features were more strongly associated with individual PhyGAs.

PATIENTS AND METHODS

Study participants and data collection. The ASCS is a multicenter prospective cohort study. At annual study visits, demographic, clinical, and investigation findings are recorded. All ASCS participants who fulfilled American College of Rheumatology/EULAR criteria for SSc[5] and had a definable disease subclass[6] were eligible for inclusion. Disease duration was defined as the time from onset of the first non-Raynaud SSc manifestation. Participants had a modified Rodnan skin thickness score (MRSS) recorded at each visit. Joint contractures were considered present if there was at least one fixed flexion deformity present on examination. Patients were asked to report (yes or no) if they experienced any worsening of skin disease in the month preceding each study visit. Additionally, they were also asked to rate the presence of itch of their skin on a scale of 0 (no itch) to 10 (worst possible itch), with a score of 3 or higher (at least moderate itch) being considered positive for skin itch. Synovitis, tendon friction rubs, calcinosis, digital ulcers, and digital gangrene were present if observed on clinical examination. Digital amputation was recorded as present if at least one distal digital amputation of a minimum of loss of tissue distal to the nail bed (at least type I finger amputation[7]), attributable to SSc, was observed. Myositis was considered present if proximal weakness on manual muscle testing in combination with elevated serum creatine kinase was detected. Gastrointestinal symptoms were present if patients reported regular reflux symptoms, dysphagia, vomiting, postprandial bloating, diarrhea, constipation, or fecal incontinence. The presence of reflux esophagitis and esophageal and bowel dysmotility were recorded if confirmed by endoscopy and motility studies, respectively. Patients were asked if they had experienced worsening breathlessness (yes or no) in the month preceding each study visit. The presence of ischemic heart disease (angina or coronary artery bypass graft surgery), asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and peripheral vascular disease (PVD) were recorded based on patient reports and medical record review.

All participants had annual respiratory function tests (measuring forced vital capacity [FVC] and diffusing capacity for carbon monoxide [DLCO]) and transthoracic echocardiography to screen for interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). ILD was defined by the presence of typical lung parenchymal changes detected by high-resolution computed tomography of the chest (HRCT). Individuals were referred for HRCT at the discretion of the treating physician, based on abnormal examination or investigation findings. PAH was diagnosed by right-sided heart catheterization (RHC), with a mean pulmonary artery pressure ≥20 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg, and pulmonary vascular resistance ≥2 Wood units. Measurement of markers of inflammation was performed annually. Current medication treatment was recorded at each study visit. PAH treatment was considered administration of any of the following: ambrisentan, bosentan, epoprostinol, macitentan, riociguat, selexipag, sildenafil, or tadalafil. PAH treatment was used to assess the relationship between PhyGAs and the presence of PAH, as RHC results were recorded once at the time of RHC.

PhyGA. At each study visit, the physician was asked to rate each of the following on a 11-point Likert scale: (1) the patient's

overall health for the past week (0 = no disease, 10 = very severe disease), (2) how active the patient's SSc was in the past week (0 = no activity, 10 = very severe activity), and (3) the extent of damage from SSc (0 = no damage, 10 = very severe damage). No further description or instruction was provided to the physician. Each physician rated participants at their own discretion, according to their own interpretation of the constructs of overall health, disease activity, and damage. No formal training was provided in the completion of the PhyGAs. The ASCS is conducted in accordance with the *National Statement on Ethical Conduct in Research Involving Humans* and was approved by the Human Research Ethics Committee at St. Vincent's Hospital Melbourne (LRR 012/21). Written informed consent was provided before any study data were collected.

Statistical analysis. Data are presented as numbers (percentage) for categorical variables and means (SDs) or median (interquartile range [IQR]), as appropriate, for continuous variables. Spearman's rank correlation coefficient was calculated to assess the relationship between each global assessment at each study visit and to assess the correlation of change in each of the PhyGAs between study visits. The percentage agreement and kappa value of change in each PhyGA score between visits was calculated, applying a threshold of both 10% and 20% change (in either a positive or negative direction) of PhyGAs, in keeping with thresholds of change applied in other studies.[3]

The associations between clinical features of SSc, treatment, and comorbidities and each PhyGA as a discrete score (dependent variable) at each study visit were tested using univariate random effects ordered logistic regression. Univariate random effects ordered logistic regression analysis was then repeated assessing the association between disease features and comorbidities and a change in each of the PhyGA scores between each study visit. In the absence of a defined minimal clinically important difference of the PhyGA, change was defined as a ≥1 unit change in score between study visits. Three multivariable random effects ordered logistic regression models were developed for each of the PhyGAs. Variables that had a P value <0.25 in univariable analysis were considered for inclusion in the multivariable modeling, and variables that did not reach the 0.1 α level or that had a 15% confounding effect on any remaining parameter estimate were removed. FVC and right ventricular systolic pressure were omitted from multivariable modeling because of collinearity with DLco values. A subgroup analysis of patients with diffuse SSc (dcSSc) recruited within seven years of disease onset was performed. All statistical analyses were performed using STATA 17.0 (StataCorp).

RESULTS

This study included 1,965 participants, with a median follow-up of 4.46 years (IQR 1.40–8.91 years). One-quarter of patients (25.95%) had dcSSc. Patient characteristics are described in Supplementary Index 1. The median baseline PhyGA scores were 3 (IQR 2–5), 3(IQR 2–4), and 3 (IQR 2–4) for overall health, activity, and damage, respectively. The correlations between each of the PhyGA scores at each study visit were 0.70, 0.67, and 0.72 (all $P < 0.01$) between health and activity, health and damage, and activity and damage, respectively.

Change in PhyGA scores. A change (in either a positive or negative direction) in PhyGA scores, as compared to the previous study visit, was reported at 66.8%, 61.6%, and 62.6% of study visits for health, activity, and damage, respectively. Notably, a decrease in damage scores was observed between 29.4% of visits. The frequency and direction of change in each of the scores of activity, damage, and overall health were compared and are summarized in Figure 1. There was a moderate correlation

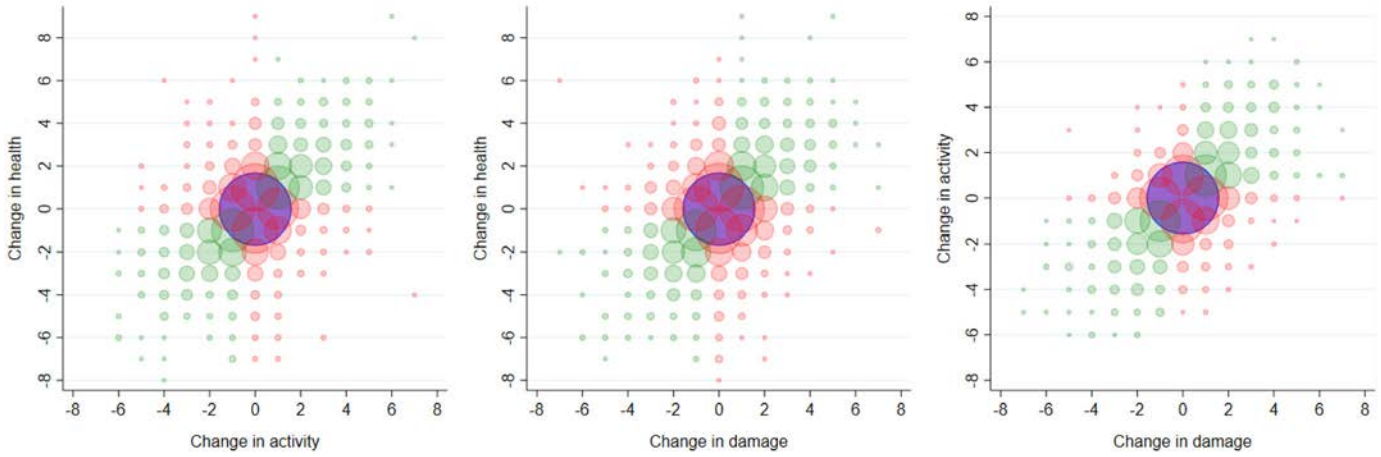

Figure 1. Scatter plot of change in physician global assessment scores between study visits. Size of marker proportional to frequency of recorded result. The purple circles represent no changes, the green circles represent concordant changes, and the red circles represent discordant changes. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25427/abstract.

Table 1. Percentage agreement between changes in PhyGA instruments*

PhyGA	10% change in PhyGA[a]			20% change in PhyGA[a]		
	Overall health, percentage agreement (kappa)	Activity, percentage agreement (kappa)	Damage, percentage agreement (kappa)	Overall health, percentage agreement (kappa)	Activity, percentage agreement (kappa)	Damage, percentage agreement (kappa)
Change in overall health	–	54.3 (0.32)	50.4 (0.26)	–	54.7 (0.32)	50.7 (0.26)
Change in SSc activity	54.3 (0.32)	–	56.7 (0.35)	54.7 (0.32)	–	56.2 (0.34)
Change in SSc damage	50.4 (0.26)	56.7 (0.35)	–	50.7 (0.26)	56.2 (0.34)	–

* PhyGA, physician global assessment; SSc, systemic sclerosis.
[a] Refers to 10% or 20% change in either a positive or negative direction.

between change in overall health and change in physician-rated disease activity (coefficient 0.48, $P < 0.01$) and damage (coefficient 0.40, $P < 0.01$), and there was a moderate correlation between change in disease activity and damage ratings (coefficient 0.53, $P < 0.01$). The percentage agreement between a change in each of the PhyGA at thresholds of 10% and 20% are presented in Table 1, showing that there was a concordant direction of change in the three PhyGA instruments in approximately 50% of study visits, with poor to moderate agreement.

Disease associations with PhyGAs. When considering each of the PhyGAs as a continuous variable, almost all disease manifestations, comorbidities, and symptoms were significantly associated with each of the three PhyGA scores, except left ventricular ejection fraction and diabetes. Minor differences were noted for calcinosis (which was only associated with damage), myositis (which was associated with overall health and activity, but not damage), and PVD (which was only associated with overall health scores) (Supplementary Index 2).

When evaluating the clinical associations of a change in PhyGA scores between study visits, there were variable clinical associations with changes in each of the global instruments. (Table 2, univariable analysis in Supplementary Index 3). Only patient-reported breathlessness was associated with worsening of all PhyGAs. An increase in damage was associated with a higher MRSS, PAH, fecal incontinence, and COPD, in addition to symptom of breathlessness. Only patient-reported worsening of skin and breathlessness were significantly associated with worsening of PhyGAs of activity.

Evaluation of PhyGAs in early dcSSc. The correlation of the three PhyGA scores in patients with early dcSSc showed similar results to the overall population, with Spearman's correlation coefficients of 0.70, 0.66, and 0.64 (all $P < 0.01$) between health and activity, health and damage, and activity and damage, respectively. A correlation coefficient of 0.59 ($P < 0.01$) between change in overall health and activity scores, of 0.53 ($P < 0.01$) for change in damage and activity scores, and a coefficient of 0.39 ($P < 0.01$) for change in damage and overall health scores was observed in patients with early dcSSc. Multivariable regression analysis showed that in early dcSSc, cutaneous symptoms were significantly associated with an increase in physician-rated activity, but pulmonary manifestations were less likely to influence PhyGAs as compared to the overall SSc cohort (Supplementary Indices 4 and 5).

DISCUSSION

In this study comparing the application of three PhyGA rating scales pertaining to overall health, activity, and damage, we have shown that the direction of change of each PhyGA is concordant only 50% of the time. Furthermore, we have demonstrated different patterns of disease associations with a change in each of the PhyGA scores. These results suggest the physician assessment of each of these three constructs is informed by the assessment of different disease manifestations, and each PhyGA is likely to give complementary rather than overlapping clinical information. This has implications when considering the use of the PhyGA in RCTs. Constructs measured in RCTs range from SSc disease activity to damage, overall health, or transition health questions.[1] It is current practice to compare global assessments between trials[3] without consideration given to the specific question being asked and whether PhyGA results between trials are directly comparable.

There is significant clinical heterogeneity in the presentation of SSc,[8] making overall disease assessment challenging. It is possible that clinical heterogeneity may, in part, account for the discordance of PhyGA results, in combination with the varying contribution of comorbidities to overall burden of ill-health. However, when our study population was restricted to only those with early dcSSc, a population more like that enrolled in RCTs, a similar pattern of PhyGA results was observed. There is only moderate concordance between global assessment results, and each of the PhyGAs is significantly influenced by different disease features and comorbidities. These results suggest that when presented with multiple PhyGA instruments, each targeting an individual disease construct, such as activity, damage and overall disease, physicians are adjusting their overall assessment. The lack of concordance between results of each of the PhyGA instruments indicates that when PhyGA questions are worded differently or are

Table 2. Clinical associations of change in physician global assessment rating*

Variable	Change in overall health rating		Change in activity rating		Change in damage rating	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics						
Disease duration	1.00 (1.00–1.01)	0.44	1.00 (0.99–1.01)	0.94	1.00 (0.99–1.01)	0.80
Diffuse SSc	0.90 (0.78–1.04)	0.16	0.90 (0.77–1.05)	0.18	0.80 (0.67–0.96)	0.02
Female	0.97 (0.82–1.16)	0.75	1.03 (0.86–1.23)	0.76	0.95 (0.80–1.14)	0.59
Cutaneous manifestations						
MRSS	–	–	–	–	1.02 (1.01–1.03)	<0.01
Skin worse in the last month	–	–	1.25 (1.03–1.53)	0.03	–	–
Vascular manifestations						
Gangrene	–	–	–	–	1.93 (0.95–3.96)	0.07
Respiratory manifestations						
More breathless in the last month	1.67 (1.42–1.96)	<0.01	1.44 (1.22–1.71)	<0.01	1.32 (1.13–1.54)	<0.01
DLco (corrected, percentage predicted)	1.00 (0.99–1.00)	<0.01	1.00 (0.99–1.00)	0.02	–	–
PAH treatment	–	–	–	–	1.25 (1.03–1.52)	0.03
Gastrointestinal manifestations						
Fecal incontinence	–	–	1.23 (1.05–1.44)	0.01	1.21 (1.03–1.41)	0.02
Serum biomarkers						
CRP	–	–	–	–	1.05 (1.00–1.10)	0.07
Comorbidities						
COPD	–	–	–	–	1.37 (1.02–1.85)	0.04
Ischemic heart disease	–	–	0.61 (0.44–0.85)	<0.01	–	–

* All results presented in this table are random effects ordered logistic regression. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DLco, diffuse capacity of carbon monoxide; MRSS, modified Rodnan skin thickness score; OR, odds ratio; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

addressing different disease constructs, results are not directly comparable and should be each be considered as individual instruments rather than directly compared as results of "the physician global."

Our results indicate there is at least some effect of specific comorbidities on certain global assessments. The ASCS does not collect data pertaining to comorbid mental health disorders or other musculoskeletal conditions, such as osteoarthritis or back pain. Given the known impact of these common conditions on overall health, function, and well-being,[9–11] it is reasonable to presume that they, too, would have an impact on a physician's assessment of overall health. No specific instruction is provided to ASCS investigators about the inclusion or exclusion of comorbidities from their assessments. Whether any global assessment of SSc should include consideration of treatments and their side effects and whether assessments of overall health should include an evaluation of comorbidities remain unresolved. However, in the context of an RCT, in which the aim is to demonstrate treatment efficacy, careful consideration needs to be paid to any instrument that is significantly influenced by other chronic comorbidities. An instrument that is significantly affected by the concurrent presence of, for example, osteoarthritis, a condition that is unlikely to respond to antifibrotic or immunosuppressive therapy, is unlikely to have the necessary sensitivity to change to measure the efficacy of targeted SSc therapies.

This study is not without limitations. It is not known if physicians are masked to their previous assessments when making a global assessment at each ASCS visit. ASCS data are collected in a database separate to participants' clinical notes, with data entered in a form distinct to the medical record and not routinely carried forward in clinical notes from one visit to the next. PhyGA records from previous visits are available to physicians within the ASCS database; however, it is not recorded whether these results are referenced by the physician when they report their global assessments at each study visit. Furthermore, patients may be assessed by a different physician at each visit, introducing interobserver variability in ratings for each patient. Each physician applies the PhyGAs using their clinical judgment. This is consistent with the current approach applied to RCTs, in which there is no standardized or protocolized approach to the application of the PhyGA.

The physician understanding and interpretation of each of the global constructs assessed by the three PhyGAs included in the ASCS protocol are untested. Although we were able to observe some variation in pattern of disease associations with each individual PhyGA, we were unable to draw any conclusions as to the specific meaning any individual construct has to physicians performing the assessment. However, we did note that between almost one-third of study visits, the PhyGA of damage decreased. Damage is considered unidirectional, with damage accruing over time, meaning damage scores should only increase with longer disease duration.[12] That damage scores were frequently observed to decrease over time may indicate limited content validity of a PhyGA of damage. The PhyGA of damage may be capturing components of activity (hence the decrease in scores over time), as well as being potentially limited by high intra- and interrater variability of the instrument.

Any subgroup analysis is limited by low participant numbers, which limits the statistical power of any analyses. Although the subgroup of patients with early dcSSc assessed in this study is similar in size to the study population of many phase 3 RCTs, it is possible that different clinical associations with the PhyGA would be seen in a true RCT patient population, particularly if studies have been enriched for disease features, such as ILD.

In conclusion, our results show there is a statistically significant relationship between different PhyGAs; however, results from each PhyGA are not identical. At least half of the time, there is a discordant change in direction of PhyGA, indicating that the results of differently worded PhyGA instruments are not interchangeable. Assessments of SSc disease activity, damage, and overall health are associated with a varying degree with different disease manifestations suggesting that physicians consider different features of SSc when making each of these assessments. These results support efforts currently underway to standardize a SSc-specific PhyGA to improve the methodologic rigor of SSc clinical trials and comparability of study results and to ensure the validity of composite outcome measures.

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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 Ross 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/Helsinki Declaration requirements.

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Tricuspid Annular Plane Systolic Excursion/Systolic Pulmonary Artery Pressure Ratio and Cardiorenal Syndrome Type 2 in the Systemic Sclerosis EUSTAR Cohort

Amalia Colalillo,[1] Chiara Pellicano,[1] Lidia P. Ananyeva,[2] Eric Hachulla,[3] Giovanna Cuomo,[4] Andrea-Hermina Györfi,[5] László Czirják,[6] Jeska de Vries-Bouwstra,[7] Luc Mouthon,[8] Hadi Poormoghim,[9] Francesco Del Galdo,[10] Nicolas Hunzelmann,[11] Julia Spierings,[12] Masataka Kuwana,[13] and Edoardo Rosato,[1] and the EUSTAR Collaborators

Objective. The aim of the study was to evaluate the association between the tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio and estimated glomerular filtration rate (eGFR) and their association with mortality in the European Scleroderma Trials and Research (EUSTAR) cohort.

Methods. Patients with systemic sclerosis (SSc) from the EUSTAR database with TAPSE, sPAP, and parameters required to calculate eGFR were included. Logistic regression and Cox regression analysis were performed to evaluate TAPSE/sPAP as a risk factor for chronic kidney disease (CKD) and overall survival.

Results. A total of 2,370 patients with SSc were included; 284 (12%) patients had CKD stage 3a–5. TAPSE/sPAP (odds ratio [OR] 0.479; 95% CI 0.310–0.743; $P < 0.001$), arterial hypertension (OR 3.118; 95% CI 2.173–4.475; $P < 0.001$), diastolic dysfunction (OR 1.670; 95% CI 1.148–2.428; $P < 0.01$), and N-terminal pro-B-type natriuretic peptide (OR 1.165; 95% CI 1.041–1.304; $P < 0.01$) were associated with CKD stage 3a–5. TAPSE/sPAP ≤0.32 mm/mm Hg (hazard ratio [HR] 3.589; 95% CI 2.236–5.761; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 2.818; 95% CI 1.777–4.468; $P < 0.001$), and age (HR 1.782; 95% CI 1.348–2.356; $P < 0.001$) were the most significant predictive factors for all-cause mortality. A total of 276 patients with SSc had pulmonary hypertension (PH) confirmed by right-sided heart catheterization, with 69 (25%) having CKD stage 3a–5. No difference was found in eGFR between patients with PH with reduced or normal cardiac index.

Conclusion. Reduced TAPSE/sPAP ratio is independently associated with CKD. TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 are prognostic factors for all-cause mortality. In patients with SSc with PH, eGFR is independent by reduced cardiac output.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease associated with a high burden of morbidity and mortality due to organ-based complications (1). SSc is characterized by an increased risk of subclinical and overt cardiopulmonary involvement, including heart failure (HF) (2,3). Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by pulmonary vascular remodeling resulting in increased pulmonary vascular resistance and pulmonary artery pressure, chronic right ventricle (RV) pressure overload and RV dysfunction and, eventually, right HF (4). A common comorbidity in PAH is chronic kidney disease (CKD), with a reported prevalence ranging from 4% to 36% (5–9). CKD is often present at PAH diagnosis, and/or a decline in kidney function may occur in the course of the disease. CKD is strongly and independently associated with mortality in patients

[1]Amalia Colalillo, MD, Chiara Pellicano, MD, Edoardo Rosato, PhD: Sapienza University of Rome, Rome, Italy; [2]Lidia P. Ananyeva, PhD: V.A. Rheumatology Russian Federation, Moscow, Russia; [3]Eric Hachulla, PhD: Hôpital Claude Huriez and University of Lille, Lille, France; [4] Giovanna Cuomo, MD: University of Campania Luigi Vanvitelli, Naples, Italy; [5]Andrea-Hermina Györfi, MD: University Hospital Düsseldorf and Heinrich-Heine University, Düsseldorf, Germany; [6]László Czirják, PhD: University of Pécs, Pécs, Hungary; [7]Jeska de Vries-Bouwstra, MD: Leiden University Medical Center, Leiden, The Netherlands; [8]Luc Mouthon, MD: Hôpital Cochin, Assistance Publique Hôpitaux de Paris, and Université Paris Cité, Paris, France; [9]Hadi Poormoghim, PhD: Firoozgar Hospital and Iran University of Medical Sciences, Tehran, Iran; [10]Francesco Del Galdo, PhD: University of Leeds, West Yorkshire, UK; [11]Nicolas Hunzelmann, PhD: University of Cologne, Köln, Germany; [12]Julia Spierings, MD: University Medical Centre Utrecht, Utrecht, The Netherlands; [13]Masataka Kuwana, MD: Nippon Medical School Graduate School of Medicine, Tokyo, Japan.

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Address correspondence via email to Edoardo Rosato, PhD, at edoardo.rosato@uniroma1.it.

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SIGNIFICANCE & INNOVATIONS

- The tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio is independently associated with chronic kidney disease (CKD), irrespective of left ventricle ejection fraction.
- Abnormal right ventricular–pulmonary arterial coupling is associated with cardiorenal syndrome type 2.
- In patients with pulmonary hypertension, CKD is not due to a reduced cardiac output.
- TAPSE/sPAP ≤0.32 mm/mm Hg and CKD are significant predictors for all-cause mortality.

with PAH (5–9). The complex and bidirectional interactions between heart and kidneys represent potential mechanisms explaining the high prevalence of kidney dysfunction in PAH. HF or CKD progression results in the activation of a cascade of events often accelerating cardiac and renal dysfunction. Cardiorenal syndrome (CRS) type 2 describes CKD as a consequence of chronic HF. A reduced cardiac output resulting in renal hypoperfusion has long been considered the only mechanism explaining the development of CKD in HF. However, more recently, several studies have shown that an increased right atrial pressure (RAP) leading to renal venous congestion and downstream impact on renal hemodynamics is involved in the loss of renal function in HF (10,11). Navaneethan et al. found a significant correlation between estimated glomerular filtration rate (eGFR) and RAP, but not between eGFR and cardiac index, in all groups of patients with pulmonary hypertension (PH) (7). In a previous study, we demonstrated that a reduced tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio is predictive of PH diagnosis and is associated with all-cause mortality in patients with SSc (12). The TAPSE/sPAP ratio is the noninvasive measure of right ventricular–pulmonary arterial (RV-PA) coupling and describes the continuum of the RV contractility adaptation to the afterload and, therefore, is strictly related to right-sided heart hemodynamics (4,13). No study to date has investigated the TAPSE/sPAP ratio as a clinical index of renal dysfunction in patients with SSc.

Thus, the primary aim of the study was to evaluate the association between RV-PA coupling, assessed by TAPSE/sPAP ratio, and CKD, assessed by eGFR, in the SSc European Scleroderma Trials and Research (EUSTAR) cohort. The secondary aim of the study was to assess the association of TAPSE/sPAP ratio and eGFR with overall survival and mortality in the SSc EUSTAR cohort.

MATERIALS AND METHODS

Study design and population. A post hoc analysis of prospectively collected data from the multinational EUSTAR database was completed. The structure of the online database, the collected data set, and definitions of clinical variables have been described in detail previously (1,14).

All patients included in the EUSTAR database since 2010 (start of the online version), aged at least 18 years, fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria (15), and with at least one visit recording TAPSE, sPAP, and parameters required to calculate the eGFR (age, sex, and serum creatinine) were selected.

The TAPSE/sPAP ratio is not recorded in the EUSTAR database and was calculated for all patients with SSc as the ratio between TAPSE and sPAP measurements. sPAP was reported in millimeters of mercury, and a cutoff of >36 mm Hg was regarded as increased (16,17). TAPSE/sPAP ratio was expressed in millimeters per millimeters of mercury. A value of <0.55 mm/mm Hg was the cutoff selected to define the TAPSE/sPAP ratio reduced and suggestive of PH (12,16). A value of TAPSE/sPAP ratio ≤0.32 mm/mm Hg was the cutoff selected to define the intermediate-high risk of mortality (12,16).

eGFR is not recorded in the EUSTAR database and was calculated for all patients with SSc by the 2021 Chronic Kidney Disease Epidemiology Collaboration equation, expressed as a single equation as follows:

$$\text{eGFR} = 142 \times \min(S_{Cr}/k, 1)^{\alpha} \times \max(S_{Cr}/k, 1)^{-1.200} \times 0.9938^{\text{Age}} \times 1.012\,[\text{if female}],$$

where S_{Cr} is serum creatinine in mg/dL, age is in years, k is 0.7 for female and 0.9 for male individuals, α is –0.241 for female and –0.302 for male individuals, min indicates the minimum of S_{Cr}/k or 1, and max indicates the maximum of S_{Cr}/k or 1 (18,19).

CKD was defined as an eGFR <60 mL/min per 1.73 m^2 for more than 3 months (20). Patients were classified into CKD stages based on eGFR values of eGFR ≥60 mL/min per 1.73 m^2 (normal or stages 1–2), eGFR 45–59 mL/min per 1.73 m^2 (Stage 3a), eGFR 30–44 mL/min per 1.73 m^2 (Stage 3b), eGFR 15–29 mL/min per 1.73 m^2 (stage 4), and eGFR <15 mL/min per 1.73 m^2 (stage 5) (20).

All-cause mortality was evaluated in all included patients with SSc. The time interval (months) between the visit date recording TAPSE, sPAP, parameters required to calculate eGFR, and date of death was calculated.

The outcomes evaluated in this population were the association between the TAPSE/sPAP ratio and eGFR and the predictive value of TAPSE/sPAP ratio and eGFR for all-cause mortality.

Patients with right-sided heart catheterization. Patients with SSc with available right-sided heart catheterization (RHC) data (mean PAP [mPAP]) were selected among all patients included. PH was defined by a mPAP >20 mm Hg (16). Patients

with SSc with available cardiac index data were selected among patients with PH confirmed by RHC. Cardiac index was reported in liters per minute per meter squared, and a cutoff of <2.5 L/min per m^2 was used to define reduced cardiac index (16). Patients with PH were further classified in precapillary PH and postcapillary PH, according to the 2022 PH guidelines (16).

The outcomes evaluated in this population were as follows: 1) evaluate the difference in eGFR mean values between patients with and without PH; 2) evaluate the difference in eGFR mean values between patients with PH with and without a reduced cardiac index; and 3) evaluate the difference in eGFR mean values between patients with precapillary PH and postcapillary PH.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics version 26. Shapiro–Wilk was used to evaluate the normal distribution of data. Data were reported as mean ± SD; categorical data were represented as frequencies and proportions. Pearson's correlation coefficient was applied to evaluate the linear relationship between continuous variables. Student's *t*-test was used to evaluate between-group differences. Multiple regression analysis was used to evaluate the correlation between eGFR and independent variables (TAPSE, sPAP, TAPSE/sPAP ratio, left ventricle ejection fraction [LVEF]).

Univariate and multivariate binary logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) were performed to analyze the association between dependent variable (eGFR [<60 versus ≥60 mL/min per 1.73 m^2]) and independent variables (TAPSE, sPAP, TAPSE/sPAP ratio [mm/mm Hg], arterial hypertension [yes or no], LVEF [%], diastolic dysfunction [DD; yes or no], N-terminal pro-B-type natriuretic peptide [NT-proBNP; pg/mL], disease subset [limited cutaneus SSc; lcSSc]/diffuse cutaneus SSc; dcSSc]).

Kaplan–Meier curves and log-rank test were used to illustrate and compare the survival difference between different risk groups. Univariate Cox regression analysis was used to identify the independent prognostic factors for overall survival. Multivariate Cox regression analysis was performed on the significant variables in univariate Cox regression analysis. Hazard ratios (HRs) and 95% CIs were reported. All continuous variables were standardized with Z-score. Listwise deletion was used to handle missing data. Moreover, the multivariate imputation by chained equations was used to handle missing data (we used the function mice of the R package mice). The response variable eGFR was not used in the prediction. Five imputed data sets were produced. A *P* of less than 0.05 was considered statistically significant for all tests.

RESULTS

Within the EUSTAR database, 2,370 patients with SSc met the inclusion criteria for this study. Demographic and clinical characteristics of patients with SSc are shown in Table 1. TAPSE/sPAP ratio mean value was 0.84 ± 0.30 mm Hg. Serum creatinine and eGFR mean values were 0.86 ± 0.51 mg/dL and 86 ± 22 mL/min per 1.73 m^2, respectively. In total, 2,086 (88%) patients had an eGFR of ≥60 mL/min per 1.73 m^2, and 284 (12%) patients had CKD stage 3a–5.

Evaluation of the association of TAPSE/sPAP ratio with eGFR. A slightly positive correlation was found between eGFR and TAPSE/sPAP ratio (r = 0.271, $P < 0.001$) (Figure 1A), TAPSE (r = 0.137, $P < 0.001$), and LVEF (r = 0.104, $P < 0.001$); a slightly negative correlation was observed between eGFR and sPAP (r = –0.253, $P < 0.001$). A slightly positive correlation was found between forced vital capacity (FVC) and TAPSE/sPAP ratio (r = 0.238, $P < 0.001$). On multiple linear regression analysis,

Table 1. Demographic and clinical characteristics of 2,370 patients with systemic sclerosis*

Characteristics	Results	N
Age, years	62 ± 14	2,370
Male	388 (16.4)	2,370
Disease duration, years	14 ± 10	2,063
lcSSc/dcSSc	1,386 (70.7)/575 (29.3)	1,961
ACA	761 (43.7)	1,742
ATA	580 (32.9)	1,763
ARA	134 (9.9)	1,360
mRSS	6 ± 7	1,816
Digital ulcers history	981 (44.5)	2,206
FVC, % predicted	92 ± 22	2,065
FVC <70% predicted	294 (14.2)	2,065
DL_{CO}, % predicted	66 ± 23	1,962
Interstitial lung disease	768 (53.9)	1,425
Arterial hypertension	623 (27.4)	2,274
LVEF, %	60.8 ± 6.6	2,164
LVEF <50%	74 (3.4)	2,164
Diastolic dysfunction	574 (28.5)	2,011
TAPSE, mm	21.8 ± 4.2	2,370
sPAP, mm Hg	30 ± 14	2,370
sPAP >36 mm Hg	452 (19.1)	2,370
TAPSE/sPAP, mm/mm Hg	0.84 ± 0.30	2,370
TAPSE/sPAP <0.55 mm/mm Hg	406 (17.1)	2,370
TAPSE/sPAP ≤0.32 mm/mm Hg	134 (5.7)	2,370
NT-proBNP, pg/mL	636 ± 3,534	1,486
Serum creatinine, mg/dL	0.86 ± 0.51	2,370
eGFR, mL/min per 1.73 m^2	86 ± 22	2,370
eGFR ≥90 mL/min per 1.73 m^2	1,216 (51.3)	2,370
eGFR 60–89 mL/min per 1.73 m^2	870 (36.7)	2,370
CDK Stage 3	242 (10.2)	2,370
CDK stage 4	27 (1.1)	2,370
CDK stage 5	15 (0.6)	2,370

* Percentages are calculated on the number of available data. Values are the mean ± SD or n (%) unless indicated otherwise. ACA = anti-centromere antibodies; ARA = anti-RNA polymerase III antibodies; ATA = anti-topoisomerase I antibodies; CKD = chronic kidney disease; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; dsSSc = diffuse cutaneous systemic sclerosis; eGFR = estimated glomerular filtration rate; FVC = forced vital capacity; lcSSc = limited cutaneous systemic sclerosis; LVEF = left ventricular ejection fraction; mRSS = modified Rodnan skin score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

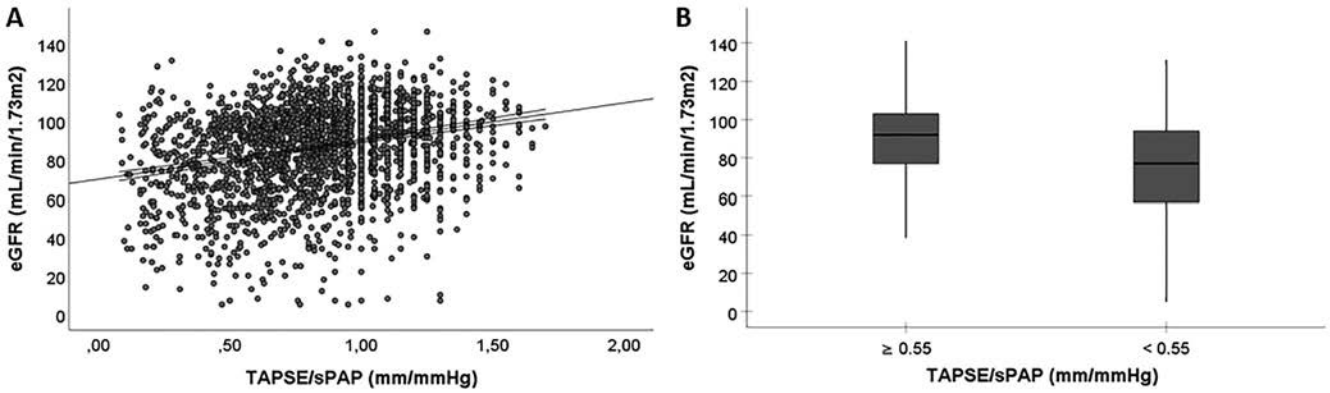

Figure 1. Tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio and estimated glomerular filtration rate (eGFR) in systemic sclerosis patients. **(A)** Correlation between TAPSE/sPAP ratio and eGFR; **(B)** eGFR in patients with and without TAPSE/sPAP ratio <0.55 mm/mm Hg.

eGFR was significantly correlated with TAPSE/sPAP ratio (β coefficient = 0.183; $P < 0.001$), sPAP (β coefficient = –0.092; $P < 0.05$), and LVEF (β coefficient = 0.072; $P < 0.01$). No correlation was found between eGFR and TAPSE (β coefficient = –0.022; $P = 0.505$). The eGFR mean value was significantly lower in patients with SSc with sPAP >36 mm Hg than in patients with SSc with sPAP ≤36 mm Hg (74 ± 23 mL/min per 1.73 m^2 versus 89 ± 21 mL/min per 1.73 m^2; $P < 0.001$) and in patients with SSc with TAPSE/sPAP <0.55 mm/mm Hg than in patients with SSc with TAPSE/sPAP ≥0.55 mm/mm Hg (74 ± 24 mL/min per 1.73 m^2 versus 89 ± 21 mL/min per 1.73 m^2; $P < 0.001$) (Figure 1B).

The eGFR mean value was significantly lower in patients with SSc with arterial hypertension than in normotensive patients (75 ± 23 mL/min per 1.73 m^2 versus 91 ± 20 mL/min per 1.73 m^2; $P < 0.001$). In patients with SSc with DD, eGFR mean value was significantly lower than in patients with normal diastolic function (78 ± 23 mL/min per 1.73 m^2 versus 90 ± 21 mL/min per 1.73 m^2; $P < 0.001$). The eGFR mean value was significantly lower in patients with lcSSc than in patients with dcSSc (84 ± 22 mL/min per 1.73 m^2 versus 91 ± 22 mL/min per 1.73 m^2; $P < 0.001$) and in patients with SSc with anticentromere antibodies (ACA) than in patients with SSc with antitopoisomerase I antibodies (ATA) (83 ± 20 mL/min per 1.73 m^2 versus 92 ± 21 mL/min per 1.73 m^2; $P < 0.001$). The eGFR mean value was significantly lower in patients with SSc with anti-RNA polymerase III antibodies (ARA) than in patients with SSc with ATA (82 ± 24 mL/min per 1.73 m^2 versus 92 ± 21 mL/min per 1.73 m^2; $P < 0.001$). No difference was found in eGFR mean value between patients with SSc with ACA and ARA.

The univariate binary logistic regression analysis showed that TAPSE (OR 0.662; 95% CI 0.583–0.752; $P < 0.001$), sPAP (OR 1.572; 95% CI 1.426–1.734; $P < 0.001$), TAPSE/sPAP ratio (OR 0.496; 95% CI 0.434–0.566; $P < 0.001$), arterial hypertension (OR 3.959; 95% CI 3.069–5.107; $P < 0.001$), LVEF (OR 0.761; 95% CI 0.673–0.860; $P < 0.001$), DD (OR 2.468; 95% CI 1.913–3.184; $P < 0.001$), NT-proBNP (OR 1.317; 95% CI 1.034–1.678; $P < 0.05$), and lcSSc (OR 1.580; 95% CI 1.154–2.163; $P < 0.01$) were significantly associated with CKD stage 3a–5 (Table 2). The multivariate binary logistic regression analysis showed that only TAPSE/sPAP ratio (OR 0.479; 95% CI 0.310–0.743; $P < 0.001$), arterial hypertension (OR 3.118; 95% CI 2.173–4.475; $P < 0.001$), DD (OR 1.670; 95% CI 1.148–2.428; $P < 0.01$), and NT-proBNP (OR 1.165; 95% CI 1.041–1.304; $P < 0.01$) were significantly associated with CKD stage 3a–5 (Table 2). The pooled results obtained from the analysis of the five imputed data sets showed that TAPSE/sPAP ratio (OR 0.621; 95% CI 0.457–0.843; $P < 0.01$), arterial hypertension (OR 3.105; 95% CI 2.377–4.057; $P < 0.001$), DD (OR 1.707; 95% CI 1.298–2.245; $P < 0.001$), lcSSc (OR 1.589; 95% CI 1.141–2.213; $P < 0.01$), and LVEF (OR 0.876; 95% CI 0.768–0.998; $P < 0.05$) were significantly associated with CKD stage 3a–5 (Table 2).

Mortality. All-cause mortality was analyzed in 2,271 (95.8%) patients with SSc, after excluding 99 (4.2%) patients lost at follow-up. Ninety-six (4.2%) patients died after a follow-up of 24 ± 21 months. Kaplan–Meier curves showed a higher mortality in patients with SSc with a TAPSE/sPAP ratio ≤0.32 mm/mm Hg (log-rank $\chi^2 = 85.8$, $P < 0.001$) (Figure 2A), in patients with SSc with eGFR <60 mL/min per 1.73 m^2 (log-rank χ^2 68.6, $P < 0.001$) (Figure 2B), in patients with SSc with FVC <70% predicted (log-rank χ^2 23.7, $P < 0.001$), and in patients with SSc with LVEF <50% (log-rank χ^2 6.8, $P < 0.05$). In univariate Cox regression analysis, TAPSE/sPAP ratio ≤0.32 mm/mm Hg (HR 6.302; 95% CI 4.030–9.855; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 4.826; 95% CI 3.196–7.288; $P < 0.001$), FVC <70% predicted (HR 2.998; 95% CI 1.954–4.600; $P < 0.001$), LVEF <50% (HR 2.828; 95% CI 1.421–5.627; $P < 0.01$), age (HR 1.948; 95% CI 1.532–2.476; $P < 0.001$), and dcSSc (HR 2.030; 95%

Table 2. Univariate and multivariate binary logistic regression analysis with listwise deletion (n = 1,486) and multiple imputation (n = 2,370) in patients with systemic sclerosis with categorization of estimated glomerular filtration rate in two groups: <60 vs. ≥60 mL/min per 1.73 m^2*

	Univariate analysis		Multivariate analysis (n = 1,486)		Multivariate analysis (n = 2,370)	
Parameters	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
lcSSc	1.580 (1.154–2.163)	<0.01	1.045 (0.683–1.598)	0.840	1.589 (1.141–2.213)	<0.01
Arterial hypertension	3.959 (3.069–5.107)	<0.001	3.118 (2.173–4.475)*	<0.001	3.105 (2.377–4.057)	<0.001
LVEF	0.761 (0.673–0.860)	<0.001	0.897 (0.765–1.052)	0.181	0.876 (0.768–0.998)	<0.05
Diastolic dysfunction	2.468 (1.913–3.184)	<0.001	1.670 (1.148–2.428)	<0.01	1.707 (1.298–2.245)	<0.001
NT-proBNP	1.317 (1.034–1.678)	<0.05	1.165 (1.041–1.304)	<0.01	1.101 (0.994–1.219)	0.065
TAPSE	0.662 (0.583–0.752)	<0.001	1.015 (0.791–1.303)	0.907	0.971 (0.812–1.161)	0.750
sPAP	1.572 (1.426–1.734)	<0.001	0.898 (0.672–1.200)	0.467	1.056 (0.864–1.290)	0.596
TAPSE/sPAP	0.496 (0.434–0.566)	<0.001	0.479 (0.310–0.743)	<0.001	0.621 (0.457–0.843)	<0.01

* lcSSc = limited cutaneous systemic sclerosis; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

CI 1.346–3.061; $P < 0.01$) were predictive factors for all-cause mortality. In multivariate Cox regression analysis, TAPSE/sPAP ratio ≤0.32 mm/mm Hg (HR 3.589; 95% CI 2.236–5.761; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 2.818; 95% CI 1.777–4.468; $P < 0.001$), dcSSc (HR 2.680; 95% CI 1.717–4.185; $P < 0.001$), and age (HR 1.782; 95% CI 1.348–2.356; $P < 0.001$) were the most significant predictive factors for all-cause mortality (Table 3). The pooled results obtained from the analysis of the five imputed data sets was reported in Table 3.

Patients with RHC. RHC data were available in 394 patients with SSc. Hemodynamic parameters are reported in Table 4. A total of 276 (70.1%) patients with SSc had PH confirmed by RHC. The eGFR mean value was significantly lower in patients with PH than in patients without PH (76 ± 23 mL/min per 1.73 m^2 versus 82 ± 23 mL/min per 1.73 m^2; $P < 0.05$). In the group of patients with SSc with PH, the prevalence of CKD was 25% (n = 69).

Cardiac index data were available in 221 patients with SSc with PH confirmed by RHC. Of these, 58 (26.2%) patients had a cardiac index <2.5 L/min per m^2, and 58 (26.2%) patients had an eGFR <60 mL/min per 1.73 m^2. No difference was found in eGFR mean value between patients with PH with a reduced cardiac index and patients with PH with normal cardiac index (77 ± 24 mL/min per 1.73 m^2 versus 75 ± 23 mL/min per 1.73 m^2; $P = 0.734$).

Pulmonary arterial wedge pressure and PVR data were available only in 215 patients with SSc with PH. Of these, 169 (78.6%) patients with SSc had precapillary PH. No difference was found in eGFR mean value between patients with precapillary PH and patients with postcapillary PH (77 ± 22 mL/min per 1.73 m^2 versus 70 ± 22 mL/min per 1.73 m^2; $P = 0.065$).

DISCUSSION

This is the first study to analyze the relationship between the noninvasive measure of RV-PA coupling and renal dysfunction.

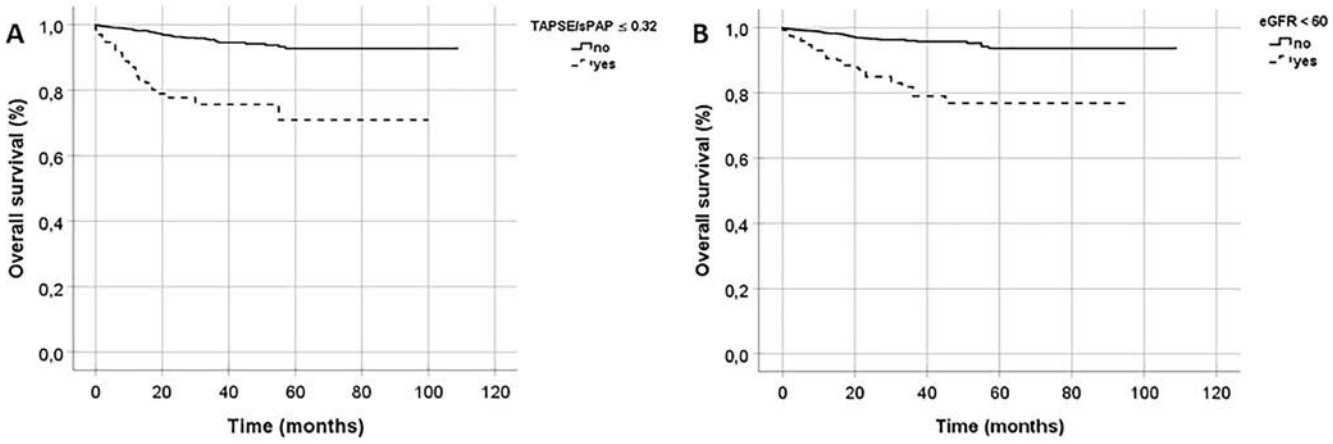

Figure 2. Overall survival in 2,271 patients with systemic sclerosis (SSc). **(A)** Overall survival in patients with SSc with tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio ≤0.32 mm/mm Hg (dotted line) and TAPSE/sPAP ratio >0.32 mm/mm Hg (continuous line); **(B)** overall survival in patients with SSc with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 (dotted line) and eGFR ≥60 mL/min per 1.73 m^2 (continuous line).

Table 3. Univariate and multivariate Cox regression analysis for overall survival with listwise deletion (n = 2,065) and multiple imputation (n = 2,271) in patients with systemic sclerosis*

Parameters	Univariate analysis		Multivariate analysis (n = 2,065)		Multivariate analysis (n = 2,271)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
TAPSE/sPAP ≤0.32 mm/mm Hg	6.302 (4.030–9.855)	<0.001	3.589 (2.236–5.761)	<0.001	3.725 (2.290–6.060)	<0.001
eGFR <60 mL/min per 1.73 m^2	4.826 (3.196–7.288)	<0.001	2.818 (1.777–4.468)	<0.001	2.879 (1.796–4.616)	<0.001
FVC <70% predicted	2.998 (1.954–4.600)	<0.001	2.085 (1.317–3.300)	<0.01	1.880 (1.160–3.046)	<0.05
LVEF <50%	2.828 (1.421–5.627)	<0.01	1.259 (0.617–2.566)	0.527	1.131 (0.544–2.348)	0.739
Age	1.948 (1.532–2.476)	<0.001	1.782 (1.348–2.356)	<0.001	1.771 (1.336–2.348)	<0.001
Male sex	1.300 (0.786–2.152)	0.307	–	–	–	–
dcSSc	2.030 (1.346–3.061)	<0.01	2.680 (1.717–4.185)	<0.001	2.808 (1.785–4.417)	<0.001

* CI = confidence interval; dsSSc = diffuse cutaneous systemic sclerosis; eGFR = estimated glomerular filtration rate; FVC = forced vital capacity; HR = hazard ratio; LVEF = left ventricular ejection fraction; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

Our data, derived from a large cohort of patients with SSc, showed that the TAPSE/sPAP ratio was independently associated with CKD, and patients with SSc with a reduced TAPSE/sPAP ratio and CKD were characterized by a decreased survival. CKD was frequent in patients with SSc with PH, and the eGFR did not seem to depend on cardiac output.

Heart and kidneys are tightly linked, and the dysfunction in one organ may result in the dysfunction of the other. In CRS type 2, chronic HF results in the onset or progression of CKD. Renal congestion, rather than renal hypoperfusion, has been identified as the leading underlying cause for kidney dysfunction in HF (11). These mechanisms also apply to right HF due to PAH (21). Although RHC is the gold standard to directly measure right cardiac pressures and cardiac output, echocardiographic parameters can be used to estimate hemodynamic parameters that can be obtained from RHC. The TAPSE/sPAP ratio is a echocardiographic parameter of RV dysfunction strictly related to pulmonary and right-sided heart hemodynamics (4,13).

This is the first study to show a positive linear correlation between TAPSE/sPAP ratio and eGFR. Patients with SSc with a TAPSE/sPAP ratio <0.55 mm/mm Hg had lower eGFR than patients with higher values. The 2022 PH guidelines include TAPSE/sPAP ratio <0.55 mm/mm Hg among signs suggestive of PH (16). Recently, we demonstrated that a TAPSE/sPAP ratio <0.55 mm/mm Hg was a predictive risk factor for PH confirmed by RHC in patients with SSc (12). These results seems to suggest that patients who are most likely to have PH may also have kidney dysfunction. In the present study, TAPSE/sPAP ratio was independently associated with CKD stages 3a–5 and was more strongly associated with CKD than NT-proBNP. To date, there are no specific diagnostic biomarkers for CRS. Biomarkers of cardiac and kidney injury may be useful to detect early cardiac or renal dysfunction in the clinical context of CRS (10). Natriuretic peptides (NPs), as biomarkers of myocardial wall stress, have both diagnostic and prognostic value in HF, PH, and CRS (10,16,22). Patients with CKD have higher NP levels (particularly NT-proBNP) not only due to reduced renal clearance but also because of chronic pressure/volume overload and CKD-associated cardiomyopathy (23). Patients with CRS have higher B-type natriuretic peptide (BNP) levels than patients with HF without renal impairment (24). TAPSE/sPAP ratio was a better predictive factor of PH diagnosis than NT-proBNP in our previous study (12). We may hypothesize that the TAPSE/sPAP ratio, detecting early mild right-sided heart hemodynamic changes, could also be an index of renal dysfunction in the context of PH and CRS. Moreover, our results showed that TAPSE/sPAP ratio and DD were more strongly associated with CKD than LVEF. CKD has been associated with abnormal longitudinal strain parameters in patients with HF and preserved LVEF (25). DD has been associated with increased risk of CKD progression (26).

Table 4. Right-sided heart catheterization parameters of 394 patients with systemic sclerosis*

Parameters	Results	N
mPAP, mm Hg	27 ± 11	394
mPAP >20 mm Hg	276 (70.1)	394
PAWP, mm Hg	11 ± 5	315
PVR, WU	3.6 ± 3.2	225
CO, L/min	4.7 ± 1.5	223
Cardiac index, L/min per m^2	3.1 ± 1	313
Cardiac index <2.5 L/min per m^2	83 (26.5)	313

* Values are in mean ± SD or n (%) unless indicated otherwise. CO = cardiac output; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WU = Wood units.

TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 were independently associated with all-cause mortality, even when adjusted for known risk factors for increased mortality in patients with SSc, including age, male sex, diffuse disease subset, FVC <70% of the predicted value, and LVEF <50% (1). Moreover, TAPSE/sPAP ratio ≤0.32 mm/mm Hg, eGFR <60 mL/min per 1.73 m^2, and age were the most significant predictive factors for mortality. In two previous distinct studies, we found that TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 were associated with mortality in patients with SSc (12,27). The 2022 European Society of Cardiology/European Respiratory Society three-strata risk-

assessment tool includes TAPSE/sPAP ratio as a risk factor for death in patients with PAH (16), whereas the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 risk score and its abridged version REVEAL Lite 2 include eGFR <60 mL/min per 1.73 m^2 as a prognostic factor in patients with PAH (28,29). Future studies are needed to evaluate these two parameters in a multiparametric risk-assessment tool to improve risk stratification in patients with SSc.

Our study also showed that patients with SSc with PH, irrespective if precapillary or postcapillary PH, had lower eGFR mean values than patients without PH. The prevalence of CKD in patients with SSc with PH confirmed by RHC was 25%. Our results are consistent with previous studies. Data from the REVEAL registry, including only patients with PAH, reported a prevalence of CKD of 28% (8). In all groups of patients with PH was found a prevalence of 36% (7). Moreover, in our study, no difference was found in eGFR between patients with PH with reduced or normal cardiac index. Bitker et al. showed that increased RAP and reduced cardiac index were both independently associated with a decline in renal function in 179 patients with PAH (9), whereas Navaneethan et al. found a significant correlation between eGFR and RAP but not between eGFR and cardiac index in 1,088 patients with all PH groups (7). Several studies reported no association between cardiac index and eGFR in HF, supporting the hypothesis that low cardiac output is not the primary driver for renal dysfunction in patients with HF (30–33). This seems to support our findings that a parameter strictly related to an abnormal right-sided heart hemodynamics could also be a valuable index of kidney dysfunction. In patients with SSc with CRS type 2, the renal function should be monitored frequently because the vasoactive drugs, used to improve Raynaud's phenomenon, could reduce renal blood flow.

A major strength of the study is the large sample size. However, the study has some limitations. Patient selection was based on available data. Data about proteinuria and albuminuria and/or other functional or structural markers of kidney disease were not provided by the EUSTAR database. Therefore, patients with an eGFR of ≥90 and of 60–89 mL/min per 1.73 m^2 could not be further classified as having normal renal function or CKD stage 1 or 2. Data on pre-existing renal disease are not available in EUSTAR registry. Also, we did not have data on diabetes and other pre-existing comorbidities potentially involved in kidney dysfunction, and there were no data on therapy potentially affecting volume status, serum creatinine levels, and eGFR. Furthermore, biomarkers of CRS were not included in the EUSTAR database. The cause of death for patients with SSc was missing in many patients, and mortality due to PH was not registered in the EUSTAR database. Many RHC data were missing and RAP was not provided by the EUSTAR database.

In conclusion, our results show that TAPSE/sPAP ratio is an echocardiographic parameter associated with CKD in patients with SSc, independently of LVEF. Abnormal RV-PA coupling is associated with CRS type 2 in patients with SSc, irrespective of PH diagnosis. In a subgroup analysis of patients with SSc with PH confirmed by RHC, our data confirm that CKD is not due to a reduced cardiac output. Our results strengthen previous findings that TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 are the most significant predictive factors for all-cause mortality in patients with SSc.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rosato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Colalillo, Pellicano, Ananyeva, Hachulla, Cuomo, Györfi, Czirják, de Vries-Bouwstra, Mouthon, Poormoghim, Del Galdo, Hunzelmann, Spierings, Kuwana, Rosato.

Acquisition of data. Colalillo, Pellicano, Ananyeva, Hachulla, Cuomo, Györfi, Czirják, de Vries-Bouwstra, Mouthon, Poormoghim, Del Galdo, Hunzelmann, Spierings, Kuwana, Rosato.

Analysis and interpretation of data. Colalillo, Pellicano, Ananyeva, Hachulla, Cuomo, Györfi, Czirják, de Vries-Bouwstra, Mouthon, Poormoghim, Del Galdo, Hunzelmann, Spierings, Kuwana, Rosato.

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APPENDIX: EUSTAR COLLABORATORS

Members of the EUSTAR Collaborators Group are as follows: Antonietta Gigante (Roma, Italy); Danilo Alunni Fegatelli (Roma, Italy); Ludmila Garzanova (Moscow, Russia); David Launay (Lille, France); Claudio Di Vico (Napoli, Italy); Christina Bergmann (Erlangen, Germany); Cecilia Varju (Pécs, Hungary); HU Scherer (Leiden, The Netherlands); Benjamin Chaigne (Paris, France); Elham Andalib (Tehran, Iran); Begonya Alcacer-Pitarch (Leeds, United Kingdom); Pia Moinzadeh (Köln, Germany); Jacob Van Laar (Untrecht, The Netherlands); Shinji Watanabe (Tokyo, Japan); Oliver Distler (Zurich, Switzerland); Suzana Jordan (Zurich, Switzerland); Gabriela Riemekasten (Lübeck, Germany); Gabriele Marschner (Lübeck, Germany); Patricia E. Carreira (Madrid, Spain); Maria Martin (Madrid, Spain); Elise Siegert (Berlin, Germany); Claudia Kedor (Berlin, Germany); Carmen-Pilar Simeón-Aznar (Barcelona, Spain); Alfredo Guillén Del Castillo (Barcelona, Spain); Antonella Marcoccia (Roma, Italy); Armando Gabrielli (Roma, Italy); Mickaël Martin (Poitiers, France); Cédric Landron (Poitiers, France); Vanessa Smith (Gent, Belgium); Paolo Airò (Brescia, Italy); Maria-Grazia Lazzaroni (Brescia, Italy); Peter Villiger, Sabine Adler (Bern, Switzerland); Florenzo Iannone (Bari, Italy); Luca Idolazzi (Verona, Italy); Ulf Müller-Ladner (Bad Nauheim, Germany); Juan Jose Alegre-Sancho (Valencia, Spain); Marie-Elise Truchetet (Bordeaux, France); Lorenzo Dagna (Milano, Italy); Marco Matucci Cerinic (Florence, Italy); Ana Maria Gheorghiu (Bucharest, Romania); Ana-Maria Ramazan (Constanta City, Romania); Alberto Cauli (Monserrato, Cagliari, Italy); Ivan Castellví (Barcelona, Spain); Michele Iudici (Geneva, Switzerland); Kamal Solanki (Hamilton, New Zealand); Tomas Soukup (Hradec Kralove, Czech Republic); Yannick Allanore (Paris, France); Massimiliano Limonta (Bergamo, Italy); Magda Pârvu (Bucharest, Romania); Gianluca Moroncini (Ancona, Italy); Elisabetta Zanatta (Padova, Italy); Enrico Selvi (Siena, Italy); Yoshiya Tanaka (Kitakyushu, Japan); Carlo Francesco Selmi (Rozzano, Milano, Italy); Otylia Kowal Bielecka (Bialystok, Poland); Maurizio Cutolo (Genova, Italy); Simona Rednic (Cluj-Napoca, Romania); Jörg Henes (Tübingen, Germany); Sarah Kahl (Bad Bramstedt, Germany); Nicoletta Del Papa (Milano, Italy); Christopher Denton (London, United Kingdom); Tim Schmeiser (Wuppertal-Elberfeld, Germany); Marek Brzosko (Szczecin, Poland); Petros Sfikakis (Athens, Greece); Ulrich Walker (Basel, Switzerland); Simone Negrini (Genova, Italy); Valeria Riccieri (Roma, Italy); Nihal Fathi (Assiut, Egypt); Mislav Radic (Split, Croatia); Stefan Heitmann (Stuttgart, Germany); Francesco Paolo Cantatore (Foggia, Italy); Carolina de Souza Müller (Curitiba, Brasil); Rosario Foti (Catania, Italy); Maura Couto (Viseu, Portugal); Elena Rezus (Lasi, Romania);

Alexandra Balbir-Gurman (Haifa, Israel); Dorota Krasowska (Lublin, Poland); Daniela Opris-Belinski (Bucharest, Romania); Martin Aringer (Dresden, Germany); Branimir Anic, Marko Baresic, Miroslav Mayer (Zagreb, Croatia); Sule Yavuz (Altunizade-Istanbul, Turkey); Svetlana Agachi (Chisinau, Republic of Moldova); Fahrettin Oksel (Bornova, Izmir, Turkey); Zbigniew Zdrojewski (Gdansk, Poland); Ignasi Rodriguez-Pinto (Barcelona, Spain); Marija Geroldinger-Simic (Linz, Austria); Gema Maria Lledó-Ibañez (Barcelona, Spain); Torsten Kubacki (Köln, Germany); Anastas Batalov (Plovdiv, Bulgaria).

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Endothelial Biomarkers of Systemic Sclerosis–Associated Pulmonary Hypertension

Matthew R. Lammi,[1] Kathleen D. Kolstad,[2] Lesley Ann Saketkoo,[3] Avani Khatri,[4] Paul J. Utz,[4] Virginia D. Steen,[5] and Lorinda Chung[6]

Objective. Despite efforts at early detection, patients with systemic sclerosis (SSc) pulmonary hypertension (PH) present with advanced disease. We sought to determine whether endothelial biomarkers (asymmetric dimethylarginine [ADMA], soluble endoglin [sEng], and pentraxin-3 [PTX-3]) can determine SSc-PH risk or differentiate between SSc-PH subgroups.

Methods. ADMA, sEng, and PTX-3 were measured by enzyme-linked immunosorbent assay in four groups: 1) 18 healthy controls, 2) 74 patients with SSc-PH, 3) 44 patients at high risk for PH features, and 4) 10 patients with low risk for PH features. High-risk features included a diffusion capacity (DLco) less than 55% with a forced vital capacity (FVC) greater than 70%, an FVC/DLco ratio of >1.6, or a right ventricular systolic pressure on an echocardiogram greater than or equal to 40 mm Hg. ADMA, sEng, and PTX-3 were compared between these four groups as well as stratified based on the three SSc-PH clinical classification groups (pulmonary arterial hypertension [PAH], left-heart disease, and interstitial lung disease [ILD]).

Results. PTX-3 was significantly lower in subjects with SSc at low risk for PH (median 27.0 pg/ml [interquartile range (IQR) 19.0–47.3]; $P < 0.003$) than the other groups. The area under the receiver operating characteristic curve was 0.87 (95% confidence interval 0.76–0.98, $P = 0.0002$) to differentiate low risk from high risk for patients with PH. PTX-3 was significantly lower in SSc-PH from disease of the left side of the heart (57.5 pg/ml [IQR 39.8–79.0]; $P < 0.01$) compared to SSc-PH from either PAH (85.5 pg/ml [IQR 56.3–104.5]) or ILD (90.3 pg/ml [IQR 74.9–111.0]). Neither ADMA nor sEng differed between the four groups.

Conclusion. PTX-3 is a promising biomarker of PH risk status in patients with SSc as well as a possible marker of precapillary PH, which should be validated in an external cohort.

INTRODUCTION

Systemic sclerosis (SSc) is a debilitating and deadly autoimmune disease characterized by fibrosis of the skin and internal organs. Pulmonary arterial hypertension (PAH) occurs in approximately 12% of patients with SSc, and almost one third of those with high-risk features have elevated pulmonary artery pressure on right-sided heart catheterization (RHC) (1). Pulmonary hypertension (PH) in patients with SSc may either be characterized as precapillary, in which the pulmonary artery wedge pressure (PAWP) is less than or equal to 15 mm Hg (ie, PAH and PH from interstitial lung disease [ILD]), or postcapillary, in which the PAWP is greater than 15 mm Hg (ie, PH from disease of the left side of the heart). Although there is no current cure for PAH, early identification of PH in patients with SSc is associated with improved survival (2). Therefore, ongoing PH screening is recommended in patients with SSc. Despite this, many patients present with newly recognized PH at advanced stages (3). Current screening strategies are limited by the overreliance on echocardiographic estimates of pulmonary artery pressure, necessitating

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[1]Matthew R. Lammi, MD, MSCR: Louisiana State University Health Sciences Center, University Medical Center-New Orleans, and New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, Louisiana; [2]Kathleen D. Kolstad, MD, PhD: University of California Los Angeles, Los Angeles; [3]Lesley Ann Saketkoo, MD, MPH: University Medical Center-New Orleans, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, and Tulane University School of Medicine, New Orleans, Louisiana; [4]Avani Khatri, MS, Paul J. Utz, PhD: Stanford University School of Medicine, Palo Alto, California; [5]Virginia D. Steen, MD: Georgetown University Medical Center, Washington, DC; [6]Lorinda Chung, MD, MS: Stanford University School of Medicine and Palo Alto VA Health Care System, Palo Alto, California.

Drs. Lammi and Kolstad contributed equally to this work.

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Address correspondence via email to Matthew R. Lammi, MD, MSCR, at mlammi@lsuhsc.edu.

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SIGNIFICANCE & INNOVATIONS

- Pentraxin-3 (PTX-3), a long pentraxin released from endothelial cells in response to inflammatory stimuli, was an accurate biomarker of pulmonary hypertension (PH) risk in subjects with systemic sclerosis (SSc), with the lowest values of PTX-3 in subjects at low risk for PH.
- PTX-3 also differentiated subjects with SSc with PH due to disease of the left side of the heart from those with PH related to pulmonary arterial hypertension or interstitial lung disease.

improvements in our ability to detect the presence of, and predict the future development of, PH.

Because both SSc (4) and PH are inherently disorders of the vascular endothelium, circulating biomarkers of endothelial damage or dysfunction (hereafter referred to as "endothelial biomarkers") may be able to identify patients with SSc with PH or those at higher risk for PH development. Pentraxin-3 (PTX-3) is a long pentraxin that is produced locally in the endothelium, among other sites, in response to inflammatory signals; circulating PTX-3 levels are reported to be higher in patients with PAH (5), although conflicting data exist in SSc-PH (6,7). Soluble endoglin (sEng) interferes with the binding of transforming growth factor β to its receptor, impairing angiogenesis. sEng was found to be a more sensitive indicator of PAH than N-terminal pro–brain natriuretic peptide (NT-proBNP) (8), but there is an uncertain relationship between PH and sEng in SSc (9,10). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that is elevated in idiopathic PAH (11) and may also be higher in patients with SSc-PH compared to patients with SSc without PH (12,13).

We used biospecimens from the multicenter US Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry and the Stanford Scleroderma Biobank to investigate the following hypotheses: endothelial biomarkers are higher in 1) patients with SSc with PH and those at high risk for PH compared to those at low risk for PH features; 2) patients with SSc with limited cutaneous disease, because they are at higher risk of PH development, compared to those with diffuse cutaneous disease; and 3) patients with SSc with precapillary forms of PH (PAH and those with ILD) compared to those with postcapillary forms of PH (from disease of the left side of the heart).

PATIENTS AND METHODS

Patient selection. Subjects were selected from the PHAROS (ClinicalTrials.gov identifier: NCT00377949) Registry, a US-based multicenter registry enrolling patients with SSc with PH and those at high risk for but without PH (14). Data were collected from 2005 to 2016 and included demographics, SSc subtype and duration, autoantibody status, pulmonary function testing, echocardiography, RHC variables, and exercise capacity. This analysis was approved by the Louisiana State University Health Sciences Center Institutional Review Board (protocol #250). The cohort of interest was the subset of subjects who had blood samples collected and biobanked as part of the PHAROS Registry, recruited from seven enrolling sites (Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180). Comparators included SSc subjects at low risk for PH features (see Definitions) and healthy controls from the Stanford Rheumatology-Dermatology clinic. Healthy controls were free of autoimmune disease (mean age 60 years, 75% female). Portions of this article were previously reported in abstract form (15).

Definitions. PH was defined as a mean pulmonary artery pressure (mPAP) of greater than 20 mm Hg (16). Group 1 (PAH) PH was defined as an mPAP greater than 20 mm Hg with a PAWP less than or equal to 15 mm Hg and a pulmonary vascular resistance (PVR) of greater than or equal to 3 Wood units, with no significant ILD. Group 2 (associated with disease of the left side of the heart) PH was defined as an mPAP greater than 20 mm Hg and a PAWP greater than 15 mm Hg. Group 3 (ILD associated) PH was defined as an mPAP greater than 20 mm Hg, a PAWP less than or equal to 15 mm Hg, and significant ILD, defined as a forced vital capacity (FVC) less than 65%, or moderate to severe ILD on a high-resolution computed tomography scan (14).

"High risk" for patients with PH in the PHAROS Registry was defined as the absence of known PH but the presence of one of the following high-risk features: 1) diffusion capacity for carbon monoxide (DL_{CO}) less than 55% of predicted with an FVC of greater than 70% predicted, 2) a FVC/DL_{CO} ratio greater than 1.6, or 3) estimated right ventricular systolic pressure (RVSP) greater than or equal to 40 mm Hg on an echocardiogram (14). Patients at "low risk for PH" were recruited from the Stanford University Rheumatology clinic and did not have known PH, had a DL_{CO} greater than or equal to 80% predicted, an FVC greater than or equal to 80% predicted, and an RVSP less than or equal to 35 mm Hg or a normal echocardiogram result if the tricuspid jet velocity was unobtainable. Subjects with SSc were also classified as having diffuse or limited cutaneous subtypes based on the Leroy classification (17). SSc disease duration was defined as the time of first non–Raynaud's phenomenon symptom until registry enrollment. Race and ethnicity were self-reported based on a fixed list of categories.

Biomarker measurement. Serum samples were collected in red top blood tubes at the time of registry enrollment; for the subjects with PH from the PHAROS Registry, this was within 6 months of their diagnostic RHC. The samples were

centrifuged for 20 minutes at 1,100 to 13,000*g* at room temperature across the study sites in a standardized fashion and stored in aliquots at −80°C. The prechosen endothelial biomarkers were measured using commercial enzyme-linked immunosorbent assay kits (ADMA: Enzo Life Sciences ALX-850-323-KI01; sEng: R&D Systems DNDG00; PTX-3: Abcam ab202537). Samples were run in duplicate for each subject and healthy controls with appropriate positive and negative controls.

Statistical analysis. Data were assessed for normality and are expressed as median (interquartile range [IQR]), mean ± SD, and frequencies, as appropriate. Baseline characteristics were compared between those with and without blood samples in the PHAROS Registry. The same characteristics were compared between the PH groups and the high risk for PH PHAROS groups using the Mann-Whitney U test or Fisher's exact test.

Biomarkers (PTX-3, sEng, and ADMA) were compared between the four groups (healthy controls [n = 18], SSc with low risk for PH [n = 10], SSc with high risk for PH [n = 44], and SSc-PH [n = 74]) using the Kruskal-Wallis test with Dunn's post test for pairwise comparisons. Similar methods were used to compare biomarkers between group 1, group 2, and group 3 SSc-PH. Lastly, biomarkers were compared between subjects with limited and diffuse cutaneous SSc (including both high risk for PH and SSc-PH groups from the PHAROS Registry) using the Mann-Whitney U test. The Kruskal-Wallis test with Dunn's post test was used to compare four subgroups, stratified based on cutaneous subtype as well as PH status (SSc-PH and high risk for PH). Biomarkers were also compared between those with and without an anticentromere antibody. In a post hoc analysis, a receiver operating characteristic curve analysis was conducted with 1,000 bootstraps for PTX-3 to distinguish between 1) low risk and high risk for PH in subjects with SSc and 2) precapillary (groups 1 and 3) and postcapillary (group 2) SSc-PH. The *P* value threshold was *P* less than 0.05. Correlations were assessed between the three biomarkers and between each biomarker and age, DLco, 6-minute walking distance (6MWD), and mPAP. Because of multiple comparisons, the *P* value threshold for a statistically significant correlation was predefined as *P* less than or equal to 0.003 using the Bonferroni correction.

RESULTS

Participant characteristics. One hundred eighteen subjects with SSc with available blood samples were included, and 432 PHAROS subjects were excluded because blood samples were not collected. Included subjects were more likely to be male and White and had lower 6MWD and higher NT-proBNP levels (Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180); those with blood samples were more likely to have PH (63%) compared to excluded participants (60%; $P < 0.0001$), and NT-proBNP levels, but not 6MWD, were similar after adjustment for PH status.

Table 1. Participant characteristics*

Variable	Low risk for PH (n = 10)	High risk for PH (n = 44)	PH (n = 74)	*P* value (high risk vs. PH)
Age, mean ± SD years	52 ± 11	58 ± 11	58 ± 12	0.90
Sex (female), %	90	91	70	0.01
Race, %				
Non-Hispanic White	30	80	85	0.37
Black	0	9	10	
Other	70	11	5	
SSc subtype, %				
Limited	50	82	65	0.13
Diffuse	50	16	31	
Unclassified	0	2	4	
Anticentromere antibody positive, %	60	16	30	0.12
SSc disease duration, median (IQR) years	5.1 (1.3–15.3)	6.2 (3.7–16.4)	6.3 (3.2–11.3)	0.59
FVC, median (IQR) % predicted	96 (84–112)	90 (77–100)	70 (58–81)	<0.0001
DLco, median (IQR) % predicted	99 (80–128)	49 (40–59)	37 (30–51)	0.0001
6-minute walk distance, median (IQR) meters	n/a	371 (300–454)	331 (232–400)	0.13
NT-proBNP, median (IQR) pg/ml	n/a	150 (74–270)	533 (84–1282)	0.02
Echo-PASP, median (IQR) mm Hg	28 (18–35)	38 (36–42)	52 (40–71)	<0.0001
Functional class, %				
One	n/a	66	18	<0.0001
Two		25	49	
Three		9	26	
Four		0	7	

* *P* value represents statistical testing (unpaired *t*-test, Fisher's exact test, and Mann-Whitney U test) to compare subjects at high risk for pulmonary hypertension (PH) vs. those with PH. DLco = diffuse capacity for carbon monoxide; Echo-PASP = echocardiogram-estimated pulmonary artery systolic pressure; FVC = forced vital capacity; IQR = interquartile range; NT-proBNP = N-terminal pro–brain natriuretic peptide; SSc = systemic sclerosis.

Compared to subjects with SSc at high risk for PH (n = 44), those with PH (n = 74) were more likely to be male and had a lower FVC and DLco, higher NT-proBNP levels, and worse functional class (Table 1). There was no significant difference in cutaneous subtype, SSc disease duration, or presence of anticentromere antibody between the two groups. Patients with PH were predominantly group 1 PAH (46%), whereas 24% had PH due to disease of the left side of the heart (group 2 PH) and 30% had PH due to ILD (group 3 PH). The median mPAP was 32 mm Hg (IQR 28–43), with a PAWP of 12 mm Hg (IQR 9–15), a cardiac output of 5.2 liters/minute (IQR 4.0–6.2), and a PVR of 3.8 Wood units (IQR 2.8–6.8).

Endothelial biomarkers according to PH status and risk. PTX-3 was significantly lower in the subjects with SSc at low risk for PH (median 27.0 pg/ml [IQR 19.0–47.3]; Figure 1A) than those with PH (83.5 pg/ml [IQR 55.8–103.8]; $P = 0.0001$) or subjects with SSc at high risk for PH (68.3 pg/ml [IQR 48.5–104.5]; $P = 0.0008$). Interestingly, subjects with SSc at low risk for PH also had lower PTX-3 levels compared to healthy controls (77.0 pg/ml [IQR 51.0–91.0]; $P = 0.003$). PTX-3 was not significantly different between subjects with SSc with PH and those at high risk for PH ($P = 0.19$). When investigating PTX-3 as a biomarker to differentiate between low risk and high risk for PH, the area under the receiver operating characteristic curve (AUROC) was 0.87 (95% confidence interval [CI] 0.76–0.98, P=0.002; Figure 1B). A PTX-3 level less than 51.5 pg/ml was 100% specific for the low risk for PH cohort (95% CI 59%–100%; Supplemental Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180). ADMA and sEng were not significantly different between any of the three patient groups or the healthy controls (all $P > 0.05$; Figure 1C and D).

In subjects with SSc-PH, PTX-3 was significantly different between clinical classification groups. Subjects with PAH (group 1 [n = 34], 85.5 pg/ml [IQR 56.3–104.5]) and ILD-PH (group 3 [n = 20], 90.3 pg/ml [IQR 74.9–111.0]) had significantly higher PTX-3 levels compared to those with disease of the left side of the heart with PH (group 2 [n = 17], 57.5 [IQR 39.8–79.0];

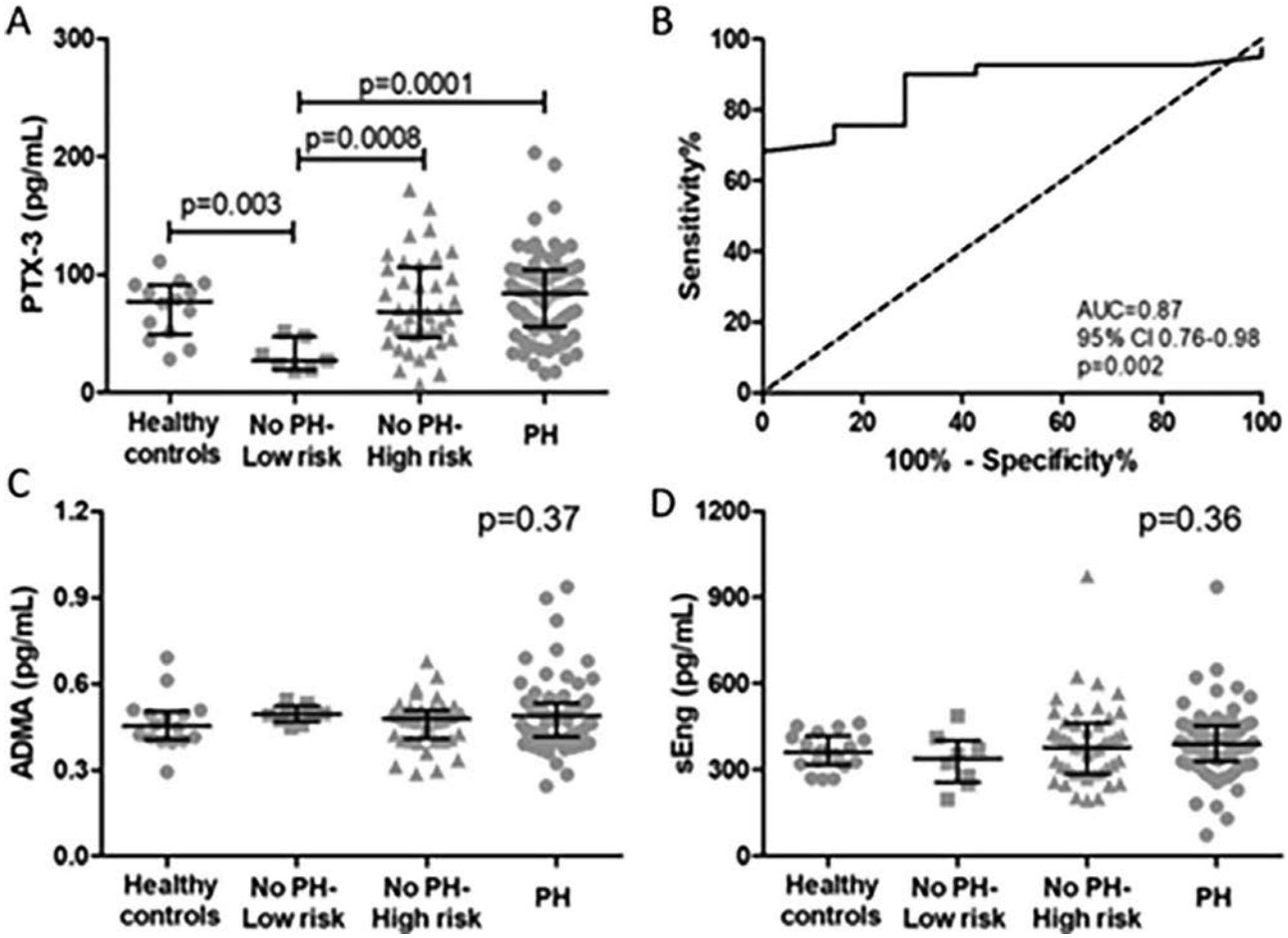

Figure 1. Endothelial biomarkers between healthy controls, subjects with systemic sclerosis with pulmonary hypertension (PH), and subjects with systemic sclerosis without PH at low or high risk for PH. **A,** Pentraxin-3 (PTX-3). **B,** Receiver operating characteristic curve of PTX-3 to distinguish between subjects with systemic sclerosis at low risk and those at high risk for PH. **C,** Asymmetric dimethylarginine (ADMA). **D,** Soluble endoglin (sEng). AUC = area under the curve; 95% CI = confidence interval.

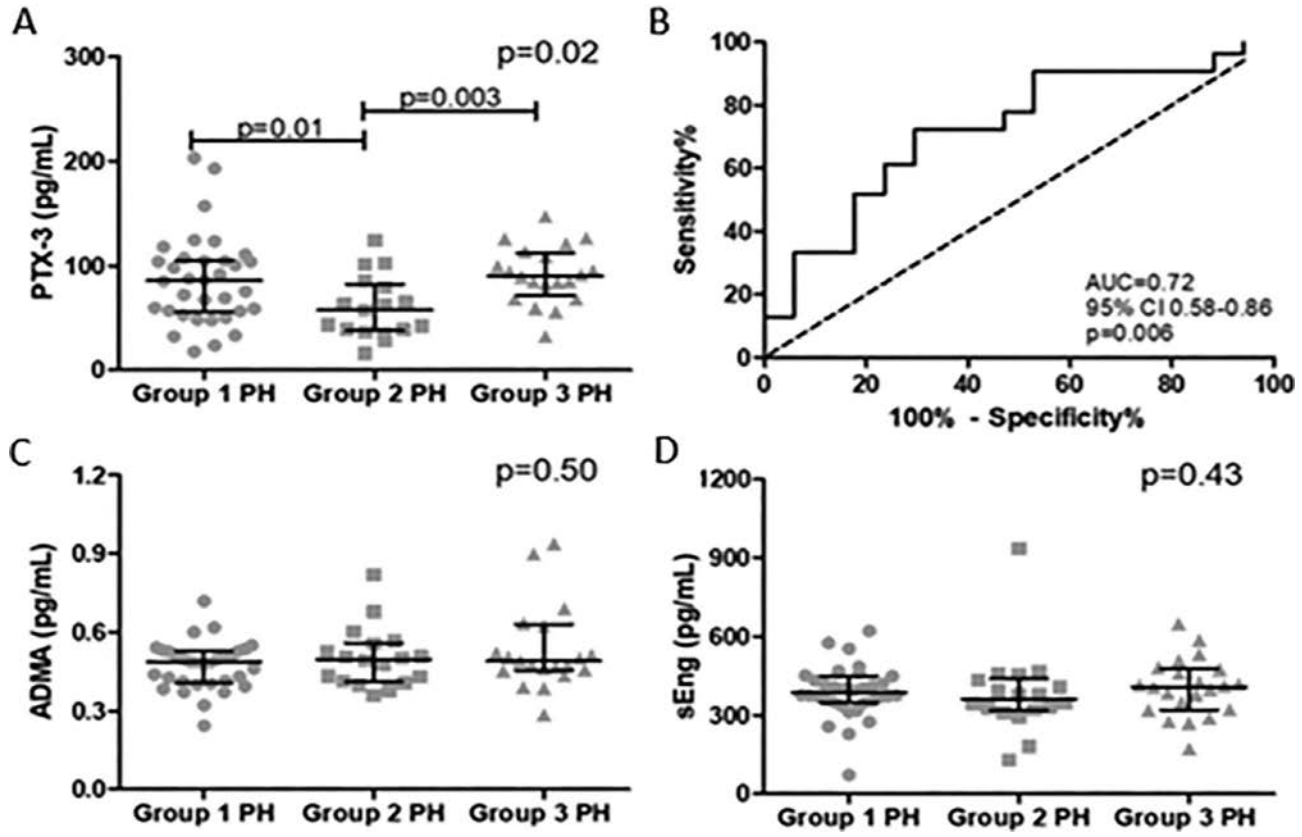

Figure 2. Endothelial biomarkers between subjects with systemic sclerosis with pulmonary hypertension (PH), stratified by PH classification group (see Methods for definitions). **A,** Pentraxin-3 (PTX-3). **B,** Receiver operating characteristic curve of PTX-3 to distinguish between precapillary (groups 1 and 3) and postcapillary (group 2) PH. **C,** Asymmetric dimethylarginine (ADMA). **D,** Soluble endoglin (sEng). AUC = area under the curve; 95% CI = confidence interval.

$P = 0.01$ and $P = 0.003$, respectively) (Figure 2C). The AUROC for PTX-3 to distinguish between precapillary PH (groups 1 and 3) and postcapillary PH (group 2) was 0.72 (95% CI 0.58–0.86, $P = 0.006$; Figure 2D and Supplemental Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180). Neither ADMA nor sEng was significantly different across the PH clinical classification groups (all $P > 0.05$; Figure 2A and B).

Endothelial biomarkers according to SSc subtype and other clinical characteristics. There were no differences between any of the three endothelial biomarkers when subjects with SSc were dichotomized by limited or diffuse cutaneous subtype (all $P > 0.05$; Figure 3), and biomarkers were similar between subjects with SSc with and without anticentromere antibody. Subjects at high risk for PH with limited cutaneous disease tended to have higher PTX-3 levels than the subjects at high risk for PH with diffuse cutaneous disease, although this was not statistically significant (70.2 pg/ml [IQR 50.8–106.1] vs. 50.3 [IQR 38.3–82.4], respectively; $P = 0.25$) (Supplemental Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180).

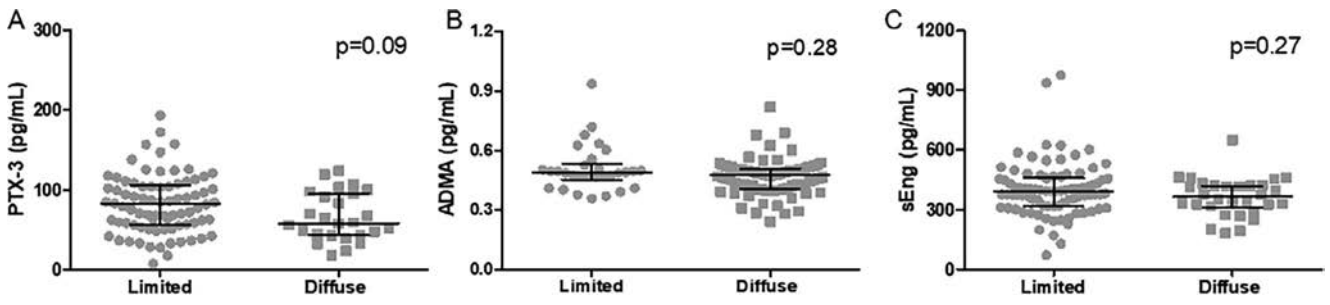

Figure 3. Endothelial biomarkers between subjects with systemic sclerosis, dichotomized by cutaneous subtype (see Methods for definitions). **A,** Pentraxin-3 (PTX-3). **B,** Asymmetric dimethylarginine (ADMA). **C,** Soluble endoglin (sEng).

None of the three biomarker levels correlated with each other in individual patients ($r \leq 0.07$, all $P > 0.44$; Supplemental Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25180). None of the biomarkers differed based on sex. Soluble endoglin weakly correlated to age ($r = 0.27$, $P = 0.003$) and NT-proBNP ($r = 0.36$, $P = 0.009$).

DISCUSSION

In this analysis of a multicenter prospectively collected registry, we found that PTX-3 levels were significantly lower in subjects with SSc with low risk for PH features and that PTX-3 levels also differed within the PH group, with higher levels in those with precapillary PH (clinical classification groups 1 and 3). Neither ADMA nor sEng was able to distinguish between groups based on PH presence or risk, type of PH, or cutaneous subtype.

PTX-3 is a soluble pattern recognition molecule that is released locally in endothelial cells (among other cell types) in response to inflammatory stimuli. PTX-3 prevents the binding of FGF2 to its receptor on endothelial cells (ECs), leading to less EC proliferation and angiogenesis. Therefore, lower levels of PTX-3 could correspond to an enhanced ability for angiogenesis. Our finding of reduced PTX-3 levels in the low risk for PH SSc group (even lower than normal controls) is complementary to results published by members of our group using the same patient samples. In a previous article, the low risk for PH group had a significantly different cytokine profile characterized by lower levels of brain-derived neurotrophic factor (BDNF), plasminogen activator inhibitor 1 (PAI-1), and epidermal growth factor (EGF), among others (18). Similar to PTX-3, lower levels of PAI-1 (19) and BDNF (20) have been associated with increased capacity for angiogenesis. Interestingly, PTX-3 appears to directly interact with BDNF (21) and EGF (22) in vitro. Although speculative, it is plausible that lower levels of PTX-3 in the patients at low risk for PH may correspond to an improved ability to regenerate damaged ECs and blood vessels, making the development of PH less likely (23).

Our findings share some similarities as well as differences from findings of previous endothelial biomarkers publications in SSc. One study of 171 patients, 12% of whom had PAH on RHC, found that PTX-3 levels were higher in patients with SSc-PH compared to patients with SSc without PH and that PTX-3 levels did not differ based on SSc cutaneous subtype (7). However, the authors did not characterize the patients without PH based on their risk profile, as we did in our study, so it is unknown whether the differences seen between patients with and without PH may have been driven by lower levels of PTX-3 in low-risk subjects. Another single-center study did not find a difference in PTX-3 between subjects with SSc with and without PH, although only 6.7% of their population had PH diagnosed by RHC (6). Prior studies of sEng have shown conflicting results, with one demonstrating a moderate correlation between echocardiogram-estimated pulmonary artery pressure and sEng (10), although another did not find a difference when PH was defined by RHC (9). Whereas the same group did not find a difference in ADMA between subjects with SSc with and without PH (9), others found that the ADMA level was elevated in SSc-PH when defined either by echocardiogram (12) or the gold standard RHC (13). It is unclear why our results differ, but it may be related to cohort differences between the studies, such as the much longer disease duration in the article by Thakkar et al (13) (mean disease duration of more than 19 years) compared to our cohort (median of 6.3 years).

We are the first to demonstrate that PTX-3 may have utility as a biomarker differentiating precapillary from postcapillary PH in patients with SSc. This is important because predicting PAWP prior to RHC may be challenging, patients with SSc have a high rate of diastolic dysfunction (24), and there are treatment options for group 1 and group 3 PH, whereas group 2 PH is generally considered not treatable with PH-specific medications. Therefore, a noninvasive biomarker that can be combined with echocardiographic and clinical data to select patients for diagnostic RHC would be clinically useful, although our findings have to be replicated in a larger external cohort.

Our article has both strengths and limitations that we should acknowledge. Most prior investigations of endothelial biomarkers were single-center studies, whereas we used the robust multicenter PHAROS Registry as well as a cohort of patients from the Stanford biobank. Another strength of our study is that we were able to stratify the patients with SSc based on their risk profile for PH. This allowed us to describe the novel finding that PTX-3 is significantly reduced in subjects at low risk for PH SSc, a finding that would have been lost if they were combined with the participants at high risk for PH. Our conclusion is limited by the small sample size of the low risk for PH cohort and lack of a validation cohort. Despite this limitation, there was a clear separation between groups in PTX-3, with no overlap in the IQR between subjects at low risk for PH and the three other groups. Lastly, not all patients in the high risk for PH PHAROS cohort underwent diagnostic RHC to fully rule out PH. Therefore, it is possible that differences between biomarkers were obscured by inclusion of some patients with PH in the high risk for PH group.

PTX-3 may be a possible biomarker of PH risk status in patients with SSc as well as a marker of precapillary PH. If these findings are replicated in a larger prospective SSc cohort, PTX-3 may be useful for PH risk stratification as well as selection for RHC.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lammi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lammi, Saketkoo, Steen, Chung.
Acquisition of data. Lammi, Kolstad, Utz, Chung.
Analysis and interpretation of data. Lammi, Kolstad, Saketkoo, Khatri, Utz, Steen, Chung.

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Implementation of a Best Practice Advisory to Improve Infection Screening Prior to New Prescriptions of Biologics and Targeted Synthetic Drugs

Hailey Baker,[1] Rebecca Fine,[1] Fenn Suter,[2] Heather Allore,[3] Betty Hsiao,[3] Vaidehi Chowdhary,[3] Elizabeth Lavelle,[4] Ping Chen,[4] Richard Hintz,[4] Lisa G. Suter,[5] and Abhijeet Danve[3]

Objective. Use of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in patients with preexisting tuberculosis (TB), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection can have serious consequences. Although various society guidelines recommend routine screening for these infections before initiating certain b/tsDMARDs, adherence to these recommendations varies widely. This quality improvement initiative evaluated local compliance with screening and assessed whether an automated computerized decision support system in the form of a best practice advisory (BPA) in the electronic health record could improve patient screening.

Methods. Established patients with autoimmune rheumatic disease (ARD) aged 18 years or older with at least one visit to our rheumatology practice between October 1, 2017, and March 3, 2022, were included. When prescribing a new b/tsDMARD, clinicians were alerted via a BPA that showed the most recent results for TB, HBV, and HCV. Screening proportions for TB, HBV, and HCV before BPA initiation were compared with those of eligible patients after the BPA implementation.

Results. A total of 711 patients pre-BPA and 257 patients post-BPA implementation were included in the study. The BPA implementation was associated with statistically significant improvement in screening for TB from 66% to 82% ($P \leq 0.001$), HCV from 60% to 79% ($P \leq 0.001$), hepatitis B core antibody 32% to 51% ($P \leq 0.001$), and hepatitis B surface antigen from 51% to 70% ($P \leq 0.001$).

Conclusion. Implementation of a BPA can improve infectious disease screening for patients with ARD who are started on b/tsDMARDs and has potential to improve patient safety.

INTRODUCTION

Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are widely used by rheumatologists and other specialists to treat patients with various autoimmune inflammatory diseases. Initiating a b/tsDMARD in patients with unknown preexisting latent tuberculosis (TB), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection can lead to significant morbidity and mortality (1–4). Adverse outcomes can be prevented by appropriate screening and treatment of underlying infection before initiation of or concurrently along with b/tsDMARD therapy (5).

Many national and international societies recommend screening for infections before the initiation of certain b/tsDMARDs (6–13). Adherence to these guidelines, however, is suboptimal (14–21). In a study of 2,027 patients prescribed new biologics, only 62% of patients were screened for latent TB, 42% for HBV, and 33% for HCV, and only 26% of patients were screened appropriately for all three infections (21). The American College of Rheumatology (ACR) recommends TB screening (tuberculin skin test or QuantiFERON) within 12 months before starting b/tsDMARDs for all patients with rheumatoid arthritis (RA) (22). The ACR advises treatment and monitoring of HBV and HCV in patients with RA but does not give clear recommendations for screening for HBV or HCV diseases before the initiation of b/tsDMARDs (7–10). Other professional societies, such as the American Association for the Study of Liver Diseases

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[1]Hailey Baker, MD, MS, Rebecca Fine, MD: Yale New Haven Health System, New Haven, Connecticut; [2]Fenn Suter: Georgetown University, Washington, DC; [3]Heather Allore, PhD, Betty Hsiao, MD, Vaidehi Chowdhary, MD, Abhijeet Danve, MD, MHS: Yale University, New Haven, Connecticut; [4]Elizabeth Lavelle, BSN, Ping Chen, MS, Richard Hintz, MS: Yale New Haven Hospital, New Haven, Connecticut; [5]Lisa G. Suter, MD: Yale University and West Haven Veterans Affairs Medical Center, New Haven, Connecticut.

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Address correspondence via email to Hailey Baker, MD, MS, at haileybaker08@gmail.com.
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SIGNIFICANCE & INNOVATIONS

- In patients with autoimmune rheumatic disease taking biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), pretreatment screening for latent tuberculosis and hepatitis infections, followed by appropriate prophylactic treatment, is recommended as standard of care by many national and international societies.
- Clinician adherence to these recommendations is low across rheumatology practices.
- Computerized decision support tools have the potential to improve screening proportions by automated capture of patient data in the electronic health record.
- Appropriate use of these tools can help prevent infectious complications in immunosuppressed patients with autoimmune rheumatic disease taking b/tsDMARDs.

(AASLD) and United States Preventive Services Task Force, recommend that all adults 18 years or older be screened for HCV at least once but do not give recommendations for patients starting immunosuppressive medications (23,24). The AASLD guidelines state that HCV RNA testing may be considered for immunosuppressed individuals but do not offer screening guidelines for patients starting immunosuppressive medications (23). The American Gastroenterological Association (AGA) offers guidelines for HBV testing before immunosuppressive medications but does not define an acceptable time interval for HBV testing before initiation of b/tsDMARDs (11). Moreover, the AGA recommends screening for HBV [hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb)] in patients at moderate or high risk before initiating immunosuppressive therapy but recommends against routinely screening for HBV in low-risk patients. This places the burden onto the clinician to categorize each patient's risk and identify which patients need to be screened. These disjointed and vague guidelines may contribute to the poor screening compliance that is seen across multiple specialties (14–21), thus posing risk of serious complications in patients. Patients with autoimmune rheumatic diseases (ARDs) are often treated with more than one b/tsDMARD over the course of disease, and pretreatment screening for HBV, HCV, and TB can help in avoiding the risk of these complications.

Electronic health records (EHRs) have the capacity to improve adherence to clinical practice guidelines by incorporating computerized decision support systems (CDSSs) (25,26). Clinical decision support tools have been described in the literature as ways to improve patient safety, clinical management, cost containment, administrative functions, and diagnostic support (27–30). A best practice advisory (BPA) is one type of CDSS that can be used in the EHR to provide a quick review of current laboratory test results and easy placement of orders. Within the field of rheumatology, studies have shown a direct correlation between CDSS in EHRs and improvement in RA quality metrics, clinician efficiencies, and productivity (31–33). Before December 2020, we did not have a system in place at our institution to efficiently ensure that all patients are screened for TB and hepatitis B and C before initiating b/tsDMARDs. Without CDSSs, clinicians and pharmacists must review individual patients' records to look for the results and separately order the test if required; both these tasks require spending sizable time during busy clinical encounters.

This quality improvement (QI) initiative focused on assessing the baseline screening proportions of TB, HBV, and HCV before initiation of b/tsDMARDs among patients with an ARD. We implemented a BPA that alerted clinicians to the need for TB, HBV, and HCV screening before signing new prescriptions of b/tsDMARDs and provided links within the BPA for ordering of necessary tests. Our main objective was to assess the impact of our BPA intervention by comparing pre-BPA and post-BPA screening proportions for TB, HBV, and HCV among patients with ARDs who were started on a new b/tsDMARD.

PATIENTS AND METHODS

Population and setting. The study was conducted at outpatient rheumatology practices in the Yale New Haven Health (YNHH) system. Patients aged 18 years or older with an ARD and at least one visit with a rheumatology clinician (including attending physicians, fellows, and advance practice registered nurses [APRNs]) who prescribed a new b/tsDMARD in the designated time frame were included in the study. Patient demographics were collected (age, sex, ARD diagnosis, and self-reported race or ethnicity from a set of categories). Implementation of the BPA begun on December 1, 2020. Data were extracted from the EHR (Epic systems) for the duration of October 1, 2017, to November 30, 2020 (pre-BPA period) and after implementation of BPA from December 1, 2020, to March 3, 2022 (post-BPA period). We included patients with an ARD who had documentation of initiation of tumor necrosis factor (TNF) inhibitors, interleukin-17 (IL-17) inhibitors, interleukin-6 (IL-6) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-immunoglobulin G1 fusion protein modulators, anti-CD20 antibody, Janus kinase (Jak) inhibitors, and other b/tsDMARDs (full list of medications included in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25181). Only patients who were naive to b/tsDMARDs or who were switched from one b/tsDMARD to another were included in the study. For patients with multiple new prescriptions in either the pre-BPA or post-BPA periods, we only analyzed screening data before the first new prescription. Repeat or renewed prescription orders were not considered "new" in either the pre-BPA or post-BPA

periods. Patients included in the pre-BPA cohort were excluded from the post-BPA cohort. Patients with new b/tsDMARD prescriptions written within 30 days of the last data extraction were excluded because we allowed for a 30-day window for screening labs to be collected after a new prescription was written. We only included clinicians who were practicing in both pre-BPA and post-BPA periods.

TB, HBV, and HCV screening. To define appropriate screening and capture complete data, we extracted the following test results from the EHR on all eligible patients: QuantiFERON Gold, HBsAg, total hepatitis B core antibody (HBcAb), HBsAb, hepatitis C antibody (HCV Ab), and quantitative hepatitis C viral load (HCV RNA). Although other tests exist for TB (ie, skin testing or T-spot), they are not used regularly in our health system or documented in an easily extractable way from the EHR. For the clinical relevance, we did not include HBsAb in the BPA because this is not necessary screening before initiation of a b/tsDMARD, although we did extract HBsAb data from the EHR.

Because current guidelines do not consistently specify exact timeframes for HBV and HCV screenings, we conducted a survey among 18 rheumatology clinicians (including faculty and senior rheumatology fellowship trainees) and two specialty pharmacists to determine what timeframes most clinicians would consider reasonable and appropriate. Based on this survey, we considered patients adequately screened if they had a QuantiFERON Gold, HBsAg, and HBcAb within 1 year before or 30 days after a new b/tsDMARD prescription and HCV Ab or HCV viral load testing within 3 years before or 30 days after a new b/tsDMARD prescription. If the patient was not present in the physician's office at the time the prescription was written, the 30-day window allows patients the time to get to a laboratory and the test results to be reviewed by the prescriber. If patients had either HBsAg or HBcAb within these timeframes, then we considered these partially adequate for HBV screening. We considered screening for HBsAg and HBcAb as complete HBV screening. Typically, HCV viral load is only collected for HCV-antibody-positive patients, but we considered patients who had testing for HCV RNA adequately screened for HCV regardless of antibody results, which is consistent with methods in similar previous studies and AASLD guidance on HCV testing in immunocompromised individuals (17,23).

Initial development of BPA. We leveraged existing literature to inform our BPA development (27,34–37). The BPA was designed by professional information technology specialists and informed by iterative clinician input (Figures 1 and 2). Upon ordering a new b/tsDMARD prescription, clinicians are alerted via the BPA. The BPA was built with a rule that excludes reordered medications, so the BPA only initiated when a new medication was

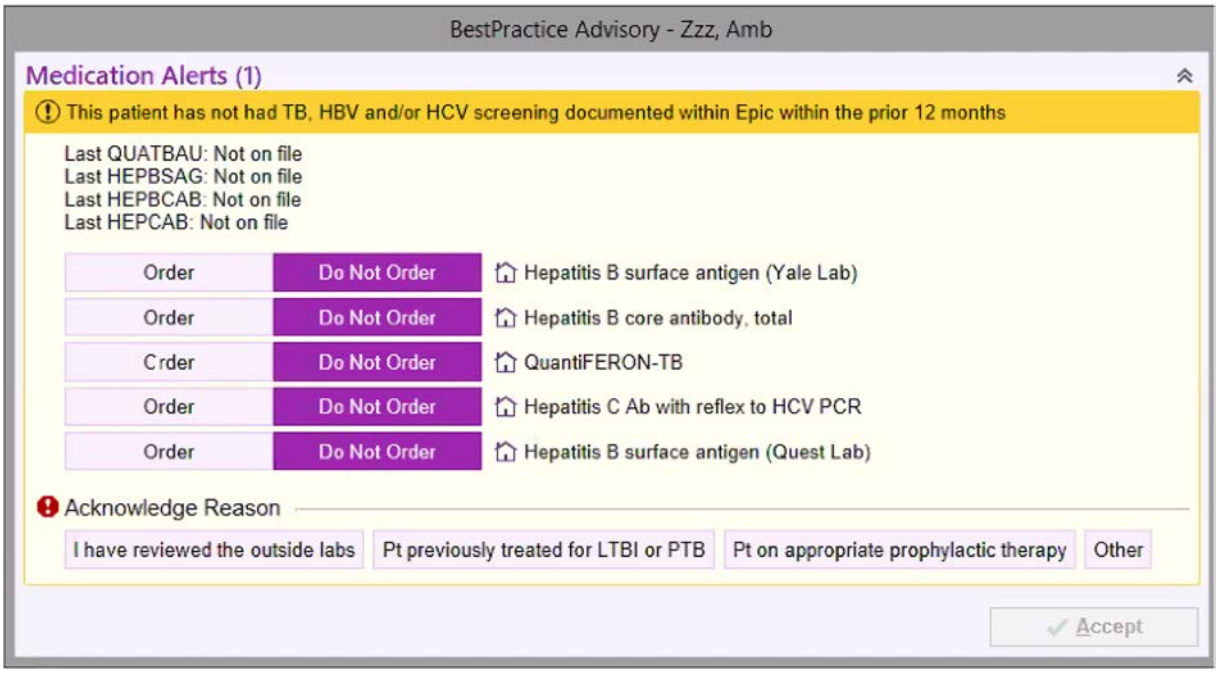

Figure 1. Original BPA notification as of December 1, 2020. Figure 1 is a visualization of the original design of the BPA that appeared on provider screens when ordering a new bDMARD for a patient. This version of the BPA includes four laboratory result components at the top, five options for quick ordering of tests, and four acknowledgment reasons. bDMARD = biologic disease-modifying antirheumatic drug; BPA = best practice advisory; HCV = hepatitis C virus; HEPBCAB = hepatitis B core antibody; HEPCAB = hepatitis C antibody; HEPBSAG = hepatitis B surface antigen; LTBI = latent tuberculosis infection; PCR = polymerase chain reaction; PTB = pulmonary tuberculosis; QUATBAU = TB QuantiFERON Gold; TB = tuberculosis.

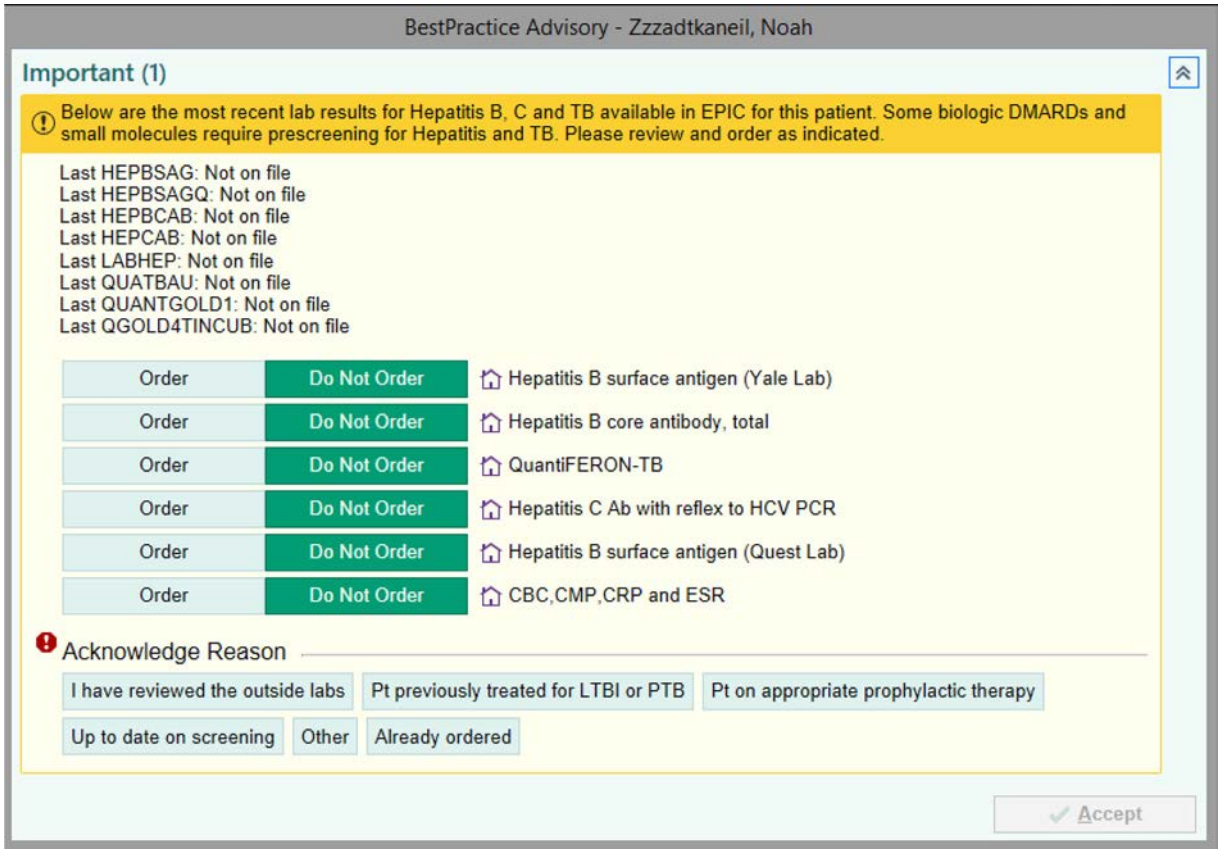

Figure 2. Finalized BPA notification as of March 21, 2021. Figure 2 is a visualization of the finalized BPA after subsequent PDSA cycles identified areas of improvement in the clinical decision support system. This final version of the BPA includes seven laboratory result components at the top, five options for quick ordering of infectious disease screening, four laboratory components for general monitoring while on drug therapy (CBC, CMP, CRP, and ESR), and five acknowledgment reasons for why a clinician is or is not ordering the labs. BPA = best practice advisory; CBC = complete blood count; CMP = comprehensive metabolic panel; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HCV = hepatitis C virus; HEPBCAB = hepatitis B core antibody; HEPBSAG = hepatitis B surface antigen; HEPBSAGQ = hepatitis B surface antigen, Quest Diagnostics; HEPCAB = hepatitis C antibody; LABHEP = represents multiple test components for hepatitis C; LTBI = latent tuberculosis infection; PCR = polymerase chain reaction; PDSA = Plan-Do-Study-Act; PTB = pulmonary tuberculosis; QUATBAU = TB QuantiFERON Gold; QUANTGOLD1 = TB QuantiFERON Gold; QGOLD4TINCUB = TB QuantiFERON Gold; TB = tuberculosis. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25181/abstract.

prescribed. The BPA informs the clinician about available prior test results for TB, HBV, and HCV in our EHR but does not extract data from clinical notes or scanned documents. The BPA provides embedded order set links for easy ordering of screening tests and commonly used monitoring labs (Figures 1 and 2). Screening labs were performed in-house in the YNHH system as well as at commercial laboratories (Quest Diagnostics). Both laboratory systems result directly in the EHR. There were no changes to workflows of how to order labs or how labs were documented in the EHR throughout the study period. Acknowledgment reasons were available at the bottom of the BPA (Figures 1 and 2) where clinicians could select reasons for not ordering tests included in the BPA. Selecting an acknowledgment reason was not required. Clinicians could not select more than one acknowledgment reason. For example, if patients had labs at an outside facility and clinicians documented this information in clinical notes, then the clinician could select "reviewed outside labs" in the BPA. However, we were unable to extract outside data from clinical notes in the EHR to validate that any outside labs were indeed completed within our specified period; therefore, charts labeled as "reviewed outside labs" were considered not adequately screened as a conservative analytical approach.

Yale School of Medicine has a Joint Data Analytics Team (JDAT) that supports researchers by assisting with data extraction from the EHR. We worked with JDAT to extract patient demographics, ARD diagnosis, prescription medication, date of prescription, and TB/HBV/HCV screening test results and dates.

PDSA cycles and BPA iteration. We performed multiple iterative Plan-Do-Study-Act (PDSA) cycles throughout this QI project to evaluate changes and improve on study interventions. We chose to track screening proportions as our metric. The goal of the first PDSA cycle was to ensure accuracy and completeness of the JDAT data extractions for all parameters. With the first extraction, a sample

of 20 charts was randomly selected and reviewed by two researchers (H.B. and R.F.) to ensure accuracy of data extracted. Inconsistencies were largely due to coding gaps for tests ordered through different labs. These efforts also enabled refinement of the BPA to capture eligible patients and screening tests more accurately. Chart review was only performed to ensure EHR data validity and reliability; no data elements were abstracted from the charts from chart review. We performed three iterative PDSA cycles to improve JDAT extractions and BPA design. Screening proportion outcomes were measured with each PDSA cycle and showed similar results with each data extraction (data not shown). The BPA was revised on July 22, 2021, August 19, 2021, and September 20, 2021, to ensure that accurate labs and clinician input were included. At the end of the study period, we surveyed faculty to receive feedback on the BPA.

Statistical analysis. Data were extracted from the EHR into Excel files, de-identified, and stored in REDCap. Descriptive statistics of patients were calculated in Excel and R statistical software. Chi-square tests were used to analyze pre-BPA and post-BPA screening proportions for TB, HBsAb, HBcAb, HBsAg, and HCV Ab. To preserve the familywise Type I error of 0.05, we applied Bonferroni corrections for multiple comparisons to determine statistical significance (presented as Q values). We conducted a post-BPA survey to assess BPA use, alert fatigue, and other feedback.

We used chi-square tests for categorical variables and adjusted for multiple comparisons using Bonferroni corrections. We performed multivariable logistic regression for receipt of each test including patient age, sex, and race and ethnicity and clinician level of training to assess for potential confounding variables. Yale School of Medicine Institutional Review Board approved this study.

RESULTS

Nine hundred sixty-eight patients met the inclusion criteria, with 711 patients in the pre-BPA period and 257 patients in the post-BPA period (Table 1). These represented prescriptions by 22 attending physicians, 5 fellows-in-training, and 2 APRNs. The two patient populations (pre- and post-BPA) were similar in age, race and ethnicity, ARD diagnosis, and having a new b/tsDMARD prescription (Table 1). Patient sex was found to be statistically different between the pre-BPA and post-BPA periods, although this observation was nonsignificant after Bonferroni correction. The mean age of the entire study population was 54 years (SD 14 years) with 70% female and the majority (77%) self-identifying as White. The most common rheumatic diseases were inflammatory arthritis (86%) and connective tissue disease (8%). TNF inhibitors (52%) and IL-17 inhibitors (15%) were the most common b/tsDMARDs prescribed. Demographic comparisons of the pre-BPA and post-BPA periods are in Table 1.

The BPA implementation was associated with statistically significant improvement in screening proportions for TB (pre-BPA 467 of 711 [66%] vs. post-BPA 210 of 257 [82%]; $P \leq 0.001$), HCV Ab or HCV viral load (pre-BPA 424 of 711 [60%] vs. post-BPA 202 of 257 [79%]; $P \leq 0.001$), HBsAg (pre-BPA 362 of 711 [51%] vs. post-BPA 181 of 257 [70%]; $P \leq 0.001$), and HBcAb (pre-BPA 224 of 711 [32%] vs. post-BPA 132 of 257 [51%]; $P \leq 0.001$, Table 2). Partial hepatitis B testing (screening for HBcAb or HBsAg but not both) was significantly improved after BPA (pre-BPA 364 of 711 [51%] vs. post-BPA 186 of 257 [72%]; $P \leq 0.001$). Complete hepatitis B testing (screening for both HBcAb and HBsAg) improved after BPA (pre-BPA 222 of 711 [31%] vs. post-BPA 127 of 257 [49%]; $P < 0.001$). No change was observed in the HBsAb, which was extracted from charts but not included in the BPA (pre-BPA 196 of 711 [28%] vs. post-BPA 73 of 257 [28%]; $P = 0.80$). A total of 154 patients (22%) in the pre-BPA and 117 patients (46%) in the post-BPA periods were appropriately screened for all three infectious diseases (QuantiFERON Gold, HBsAg, HBcAb, and HCV Ab or HCV quantitative RNA), which was a statistically significant change ($P < 0.001$).

We performed multivariable logistic analyses including patient characteristics (age, sex, and race and ethnicity) and clinician training level (attending, fellow, or APRN). In the pre-BPA period, relative to attending physicians, fellows were significantly more likely to order testing (HBcAb $P \leq 0.001$, HBsAb $P \leq 0.001$, HBsAg $P = 0.005$, partial hepatitis B testing $P = 0.006$, complete hepatitis B testing $P \leq 0.001$, HCV Ab or HCV RNA $P = 0.002$, all four tests $P \leq 0.001$) after accounting for multiple comparisons. In the pre-BPA period, each year of age decreased the adjusted odds of TB testing by 2% (odds ratio [OR] 0.98; 95% confidence interval [95% CI] 0.97–1.0; $P = 0.006$), and males had lower adjusted odds for HBcAb testing than females (OR 0.58; 95% CI 0.39–0.85). In the post-BPA period, there were no statistically significant findings for any patient or clinician variable. Implementation of the BPA increased the adjusted odds of screening by 2.2 to 2.5 times when adjusted for age, sex, and clinician training level (HBcAb OR 2.37 [95% CI 1.76–3.20], HBsAg OR 2.32 [95% CI 1.71–3.19], HCV Ab or HCV RNA OR 2.55 [95% CI 1.83–3.61], partial HBV testing OR 2.54 [95% CI 1.86–3.50], complete HBV testing OR 2.21 [95% CI 1.64–2.99], TB OR 2.32 [95% CI 1.63–3.34], all four tests OR 2.22 [95% CI 1.64–3.00]).

Clinicians selected an acknowledgment reason in 82 charts (32% of total post-BPA charts). Of those that selected an acknowledgment reason, most clinicians selected that the patient was already up to date on screening (53 of 82 charts with an acknowledgment reason, 65%). However, of the patients that clinicians felt were up to date on screening, only 34 (64%) had all the appropriate screening tests (TB, HBV, and HCV) collected within our specified periods. Eighteen clinicians (22%) stated that they had reviewed outside labs. Two clinicians (2%) stated they had already ordered the labs, and nine clinicians (11%) selected "other" for their acknowledgment reason. These "other" reasons are not able to be extracted from the EHR; thus, they are not known.

Table 1. Description of study population pre- and post-BPA*

	Pre-BPA (N = 711)	Post-BPA (N = 257)	*P* value	Q value
Mean age, years (SD)	54 (14)	54 (15)	0.77	>0.9
Female, N (%)	517 (73)	165 (64)	0.013	0.065
Race and ethnicity			0.81	>0.9
American Indian or Alaska Native, N (%)	2 (0)	2 (1)		
Asian, N (%)	12 (2)	4 (2)		
Black or African American, N (%)	67 (9)	24 (9)		
Other or unknown, N (%)	79 (11)	33 (13)		
Other Pacific Islander, N (%)	2 (0)	0 (0)		
White or Caucasian, N (%)	549 (77)	194 (75)		
Rheumatic disease			0.4	>0.9
Inflammatory arthritis, N (%)	305 (43)	141 (55)		
Connective tissue disease, N (%)	25 (4)	14 (5)		
Vasculitis, N (%)	16 (2)	12 (5)		
Other, N (%)	3 (0)	0 (0)		
Missing diagnosis, N (%)	362 (51)	90 (35)		
Class of medication prescribed			0.37	>0.9
TNF inhibitors, N (%)	373 (52)	130 (51)		
IL-17 inhibitors, N (%)	113 (16)	34 (13)		
Anti-CD20, N (%)	1 (0)	1 (0)		
IL-6, N (%)	42 (6)	22 (9)		
JAK, N (%)	118 (17)	40 (16)		
CTLA-4 agonists, N (%)	25 (4)	9 (4)		
Other, N (%)	39 (5)	21 (8)		

* Table 1 includes descriptive statistics of the study population pre-BPA (October 1, 2017, to November 11, 2020) and post-BPA (December 1, 2020 to March 3, 2022) implementation. A Bonferroni correction was used to correct for multiple comparisons and reduce risk of false positive results, which is represented by the Q values. Inflammatory arthritides included rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and adult-onset Still's disease. Connective tissue diseases included were systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disease, and systemic sclerosis. Vasculitides included ANCA-associated vasculitis, Bechet's disease, giant cell arteritis, and Takayasu arteritis. The "Other" category included diagnoses for polymyalgia rheumatica and Familial Mediterranean Fever. ANCA = antineutrophil cytoplasmic autoantibody; BPA = best practice advisory; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IL-17 = interleukin-17; IL-6 = interleukin-6; JAK = Janus kinase inhibitor; TNF = tumor necrosis factor.

We received nine responses to our post-BPA survey of faculty to assess for clinician perception of the BPA. Most responders routinely used the BPA (six of nine responders), felt it helped them manage their patients more efficiently (five of nine responders), and felt it did not add to their work burden (five of nine responders). When asked if this BPA was adding to their alert fatigue, four of nine responders stated "yes," four of nine responders stated "no," and one of nine responders stated "not sure."

DISCUSSION

This QI project was performed to understand our local current screening practices and determine whether implementation

Table 2. Comparison of screening rates of TB, HBV and HCV tests captured pre-BPA and post-BPA*

	Pre-BPA (N = 711)	Post-BPA (N = 257)	*P* value
TB, N (%)	467 (66)	210 (82)	<0.001†
HBsAb, N (%)	196 (28)	73 (28)	0.8‡
HBcAb, N (%)	224 (32)	132 (51)	<0.001†
HBsAg, N (%)	362 (51)	181 (70)	<0.001†
HCV Ab or HCV RNA, N (%)	424 (60)	202 (79)	<0.001†
Partial hepatitis B, N (%)	364 (51)	186 (72)	<0.001†
Complete hepatitis B, N (%)	222 (31)	127 (49)	<0.001†
All four tests, N (%)	154 (22)	117 (46)	<0.001†

* Table 2 displays observed screening rates of TB, HBV, and HCV before and after the initiation of the BPA on December 1, 2020. Partial hepatitis B testing was defined as having either HBsAg or HBcAb, but not both. Complete hepatitis B testing was defined as having both HBsAg and HBcAb. To be considered as having testing of "all four tests," a patient had to have QuantiFERON Gold, HBsAg, HBcAb, and HCV Ab or HCV quantitative RNA performed within the specified time. We used a Bonferroni correction to correct for multiple comparisons and reduce risk of false positive results, which is represented by Q values. BPA = best practice advisory; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis.
† Q value ≤0.001.
‡ Q value ≥0.9.

of a BPA could improve local compliance with TB, HBV, and HCV screening before initiation of b/tsDMARDs. This study accords with the existing literature that supports the use of CDSS to improve quality of care and adds to the current literature by confirming the successful impact of a BPA intervention on screening for HBV and HCV and TB. Many studies have looked at infectious disease screening proportions (38–40), but few have looked at all three infectious agents (HBV, HCV, and TB) (17). We are unaware of studies that assessed the efficacy of an intervention to address low screening proportions before b/tsDMARD use. Our pre-BPA screening proportions were very low (ranging from HBcAb of 32% pre-BPA to TB of 66% pre-BPA). Adequate screening proportions for all three diseases (TB, HBV, HCV) were only 22% pre-BPA and 46% post-BPA. Individual screening tests ranged from 51% for HBcAb to 82% for TB post-BPA, which mirrors screening proportions in a similarly designed nationwide study (17). We observed statistically significant improvements in screening for all tests, TB, HBV (both partial and complete), and HCV after implementation of a BPA (Table 2).

Ambiguous and disjointed screening guidelines may contribute to confusion and low screening proportions before initiation of b/tsDMARDs. Not all b/tsDMARDs pose the same risk of reactivation of TB or hepatitis B, which adds to the complexity of when to screen. For example, anti-CD20 medications have a lower risk of TB reactivation compared with TNF inhibitors. Conversely, there is a high risk of hepatitis B reactivation with anti-CD20 medications compared with IL-17 or IL-23 inhibitors (41). Despite these nuances between several b/tsDMARDs and screening indications, our institution prioritized universal screening before new b/tsDMARD therapy given the risks of TB, HBV, and HCV reactivation and because a patient with an ARD is likely to receive several b/tsDMARDs during the course of disease, thus ultimately necessitating screening for all three infections. We designed a BPA to reach this institutional goal and observed significant improvement in screening post-BPA implementation. Additionally, we observed significant influence of patient age, patient sex, and clinician fellowship status on pre-BPA screening proportions, which were eliminated after implementation of the BPA. Thus, demonstrating implementation of an electronic BPA in the EHR has the potential to not only improve screening proportions for patients with ARD being started on b/tsDMARDs but also potentially help correct disparities in screening.

There are multiple limitations to this study. Because screening intervals for all three tests (HBV, HCV, and TB) are not clearly specified in current society guidelines, clinicians may not screen patients that they feel are low risk or if they feel screening is not indicated for certain b/tsDMARDs despite the BPA, which may have underestimated our pre-BPA baseline screening and overestimated the impact of the BPA. We used generous screening windows to reduce this possibility. This study was an observational study, so it has all the standard biases associated with observational data, including potential confounding factors and inability to determine a causal relationship between the improvements we found and the BPA. We performed multivariable logistic analysis to assess potential confounding factors, which we controlled for, and still observed statistically significant findings. Moreover, HBsAb was not included in the BPA, but this information was extracted from the EHR, and we found no change in HBsAb pre- and post-BPA even though HBsAb is often ordered along with other HBV screening tests. The observation that HBcAb and HBsAg screening improved, whereas HBsAb did not, supports that the changes seen are likely related to the BPA intervention itself and not from confounding factors. At this time, BPA is only able to capture laboratory results ordered and reported within the EHR. Patients may have had outside labs documented in clinical notes, but we considered these patients not adequately screened as we could not verify the test results. Thus, our findings may underreport screening. Furthermore, during our PDSA cycle chart review, we found inconsistencies in which (eg, patient- vs. encounter-level) orders are captured in the EHR, leading to the potential risk of missing data capture, again possibly underreporting screening. We were able to correct this through iterative PDSA cycles and a cross-disciplinary team that included clinicians and EHR coders.

Although this is a single institutional study, it was conducted at a large multihospital health system with a diverse patient population and many outpatient clinics, which increases the generalizability of this study across other similar health systems. We use Epic as the EHR of our health system and all health systems that use Epic can institute similar CDSS alerts. We have not tested the external validity of our specific BPA, but many studies at other institutions that have found similar positive impacts of BPA on their intended outcomes (34–37). Thus, the positive outcomes observed with our BPA intervention may be generalizable to other large health systems. However, our findings may not be as generalizable to smaller, community medical sites with fewer CDSS tools available in their EHRs.

Some disadvantages of using CDSS include information overload and pop-up alert fatigue. Studies have shown that frequent CDSS alerts can contribute to alert fatigue, which may lead to clinicians ignoring these alerts (42–44). We worked with clinicians to create a parsimonious BPA to reduce burden and links within the BPA for ordering to facilitate efficiency. We performed a post-BPA implementation survey to assess alert fatigue, which overall had a low response number (nine total respondents) but was informative. Survey respondents were split 50/50 on whether this survey contributed to alert fatigue. Although it may have contributed to some alert fatigue, most survey responders did say it helped make their screening practices more efficient, which is encouraging. Moreover, we need to weigh the potential alert fatigue with the significant improvements in TB, HCV, and HBV screening post-BPA and their effect on avoiding adverse outcomes. Other disadvantages of CDSS include duplicate test ordering, but the BPA offers an "acknowledgment reason"

opt-out response to avoid excess use. Only 82 clinicians (32% of total post-BPA charts) chose an acknowledgment reason, and the most common reason was "patient up to date on screening" (N = 53, 65%). Interestingly, of the 53 charts that clinicians noted as "up to date on screening" only 34 of those (64%) patients had TB, HBsAg, and HBcAb within the last year and HCV Ab or HCV RNA within the last 3 years. This supports that many of the clinicians may consider patients adequately screened when they may not be. It is possible that these patients had outside labs that the BPA could not recognize, and then we would expect the clinician to have selected "I have reviewed outside labs," but only 18 clinicians (22% of those with acknowledgment reasons and 8.5% of total clinicians in the post-BPA period) selected "I have reviewed the outside labs" as their reasoning for not ordering testing, suggesting that few patients have outside labs.

Given our institutional directive for universal screening, we chose to screen broadly and refine the BPA if future data emerge to inform better practice. Although we considered patient safety our primary objective, the cost effectiveness of screening all patients remains unclear, and a potential future direction. Efforts are underway to extend the use of BPA beyond rheumatology to other specialties such as dermatology, gastroenterology, neurology, and immunology to improve screening proportions across specialties.

Overall, our study showed that a BPA can significantly improve screening for infectious diseases before initiation of new b/tsDMARDs and potentially reduce screening discrepancies in an efficient manner.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Baker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Baker, Fine, Hsiao, Chowdhary, L Suter, Danve.

Acquisition of data. Baker, Fine, F Suter, Allore, Hsiao, Chowdhary, Lavelle, Chen, Hintz, L Suter, Danve.

Analysis and interpretation of data. Baker, Fine, F Suter, Allore, Hsiao, Chowdhary, L Suter, Danve.

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