Rheum to Diagnosis: A Mixed Methods Study to Uncover Impediments to Accurate Diagnosis of Nonradiographic Axial Spondyloarthritis in the United States

Sonam Kiwalkar (✉ skiwalkar@tvc.org)

Vancouver Clinic <https://orcid.org/0000-0002-9507-9617>

Richard Howard

Spondylitis Association of America

Dongseok Choi

Oregon Health & Science University

Atul Deodhar

Oregon Health & Science University

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Abstract

Background

Delayed diagnosis of axial spondyloarthritis (axSpA) is well documented, but little is known about the distinct diagnostic journey and impediments for US patients with nonradiographic axSpA (nr-axSpA).

Methods

Interviews of adults with rheumatologist-diagnosed nr-axSpA and of rheumatologists explored the diagnostic journey and barriers to diagnosis. Emerging themes were further explored in an online patient survey. Patients were recruited through Spondylitis Association of America outreach and patient panels.

Results

Interviews were conducted with 25 patients (mean age, 45 years; 80% female) and 16 rheumatologists. Survey responses from 186 eligible patients (median age, 40 years; 67% female) were analyzed. Among surveyed patients, median time from symptom onset to nr-axSpA was 3.25 years. In multivariable analysis, delayed diagnosis was significantly more likely for women and people in rural areas. Most patients consulted ≥ 4 different types of healthcare providers (HCPs) before seeing a rheumatologist and consulted ≥ 2 rheumatologists before nr-axSpA diagnosis.

Identified impediments to timely diagnosis included the insidious onset of bothersome but tolerable chronic pain; episodic rather than persistent symptom patterns that seemed related to activity; symptoms other than chronic lumbosacral back pain that were dominant and required medical consultation; and widespread unfamiliarity with and misperceptions about nr-axSpA among frontline HCPs, radiologists, and rheumatologists.

Conclusions

Delayed nr-axSpA diagnosis is common and reflects HCP knowledge gaps as well as frequent patient presentation with dominant nonaxial symptoms. Targeted HCP education, further research into early disease patterns, and interventions sensitive to the broader spectrum of nr-axSpA manifestations are needed to improve timely diagnosis.

Trial Registration

Not applicable.

Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease preferentially involving the sacroiliac (SI) joints and spine. It typically manifests with chronic back, neck, or buttock pain beginning before 45

years, with features such as morning stiffness and pain that improve with exercise but not rest. AxSpA is frequently accompanied by enthesitis, psoriasis, inflammatory bowel disease, and uveitis.

People with definitive radiographic sacroiliitis are classified as having radiographic axSpA, also known as ankylosing spondylitis (AS). Those without radiographic sacroiliitis but with characteristic features of axSpA plus either human leukocyte antigen B27 (HLA-B27) positivity or magnetic resonance imaging (MRI) evidence of active SI inflammation are classified as having nonradiographic axSpA (nr-axSpA).(1) Disease activity and burden are substantial and comparable for patients in both groups.(2–4)

In the United States, the estimated population prevalence of axSpA in adults is 0.9–1.4%.(5) By contrast, the estimated prevalence of diagnosed axSpA is 0.2%.(6) This discrepancy suggests that most people with axSpA have not been clinically identified. Delays of up to 14 years between symptom onset and axSpA diagnosis have been observed and highlight the challenges of timely recognition.(7) This considerable delay translates into greater functional impairment, lesser quality of life, and substantial healthcare costs.(8)

Detection and diagnosis of axSpA are hindered by the very high prevalence of back pain in the general population.(9) In addition, validated diagnostic criteria and biomarkers that discriminate axSpA from other causes of back pain are currently lacking.(10) However, those with nr-axSpA likely face additional barriers. This entity has been defined relatively recently and remains unfamiliar to many healthcare providers (HCPs). Although nr-axSpA is at least as common in women as in men,(2) lingering misperceptions of AS being a predominantly male disease may diminish the recognition of axSpA in women.(11) At the same time, while a growing number of therapies have been shown to improve outcomes for this patient population,(12–17) delayed diagnosis is a major impediment to timely receipt of effective therapies. Prior studies of diagnostic delay have largely focused on patients with AS or axSpA overall.(18–25) Studies exploring the distinct obstacles to nr-axSpA diagnosis are lacking. The present study addresses this gap and aims to better understand patient experiences and the specific barriers that contribute to delay in nr-axSpA diagnosis in the United States.

Methods

In order to better understand patient experiences and contributions to delay in nr-axSpA diagnosis, this study used a mixed-methods design with qualitative and quantitative components. The study was approved by the Oregon Health & Science University institutional review board.

Qualitative Component

Patient Interviews

Adults diagnosed with nr-axSpA by rheumatologists were invited via the January 2020 eSun newsletter of the Spondylitis Association of America (SAA) to share their diagnostic journey during a 45-minute interview. To diversify the sampling frame, participants were also recruited from general population and

back pain market research panels. Interested respondents completed an online screener to confirm rheumatologist-diagnosed nr-axSpA. Individuals who met the primary eligibility criteria (Table 1) and had previously undergone MRI to evaluate their back or pelvic pain were invited to interview.

Table 1
Patient Eligibility Criteria for Qualitative and Quantitative Study Components

<ul style="list-style-type: none">• Age ≥ 18 years• United States resident• Diagnosed with nr-axSpA by a rheumatologist• Back, hip, or buttock pain ≥ 3 months• Back, hip, or buttock pain onset before age 45 years <p><i>AND affirmation of:</i></p> <p><i>EITHER</i></p> <p>≥ 3 of the following 4 criteria:</p> <ul style="list-style-type: none">o Gradually developing paino Pain improves with physical activityo Pain worsens with resto Pain causes nighttime awakening <p><i>OR</i></p> <p>≥ 1 of the following 7 criteria:</p> <ul style="list-style-type: none">o Pain significantly improves with nonsteroidal anti-inflammatory drugso Heel paino Psoriasiso Inflammatory bowel diseaseo Uveitis/iritiso Unexplained joint pain and swellingo Unexplained swelling of entire fingers or toes
Eligibility was determined by patients’ self-reported responses to a short screening questionnaire (qualitative interviews) or to questions contained in the survey instrument (quantitative component). Screening questions are in Additional file 1 .

The semistructured interviews explored patients’ sequential experiences and perceptions from initial symptom onset to nr-axSpA diagnosis by a rheumatologist (see **Additional file 2**). Interviews were

primarily conducted via GoToMeeting, a web-based conferencing and recording platform that allowed participants to view the interviewer's screen. Interviewers illustrated the diagnostic journey (see **Additional file 3**) on a template as participants described their experience. Participants were invited to correct and validate what was documented.

Rheumatologist Interviews

Board-certified US rheumatologists in the SAA database who treat patients with nr-axSpA were invited to participate in 30-minute interviews through email and telephone outreach in February 2020. The semistructured interviews focused on nr-axSpA in the rheumatologist's practice, diagnosis of nr-axSpA, and strategies to improve the diagnostic process (see **Additional file 4**).

Interview Team and Analysis

All interviews and analyses were conducted by 2 masters-level professionals—1 male, 1 female—with expertise in qualitative and quantitative research methods. Interview content was analyzed using a grounded theory approach to identify recurrent themes.

Quantitative Patient Survey Component

An online patient survey was fielded between April and July 2020 to further explore themes arising from qualitative analysis. Patients were invited to participate and share their nr-axSpA experience via SAA's electronic eSun newsletter (April and May 2020 issues), on social media channels, and through market research databases on the general population and on people with back pain. Initial survey questions assessed respondents' eligibility (see **Additional file 1**). Subsequent items explored patients' healthcare experiences leading up to and after their initial rheumatology consultation, barriers and facilitators affecting their nr-axSpA diagnosis, and demographic characteristics.

Statistical Analysis

Time to nr-axSpA diagnosis was a variable calculated from 2 separate, open-ended questions that asked for approximate month and year of symptom onset and of nr-axSpA diagnosis.

A multiple logistic regression analysis of patient survey data was undertaken using R statistical language (v3.6.3) to evaluate factors that might increase time to nr-axSpA diagnosis. Analyses centered on a new binary variable, delayed diagnosis (defined as greater than, or less than or equal to, median time to nr-axSpA diagnosis). The initial model included the following dichotomized independent variables: sex (male vs female), location (rural vs nonrural), race (white vs nonwhite), education (bachelor's degree or higher vs less than a bachelor's degree), work status (employed full-time vs not employed full-time), and income (<\$75,000 a year vs ≥\$75,000 a year). Independent variables with no significant association were removed from the final model.

Results

Qualitative Interview Component

Patient Interviews

Interviews were conducted with 24 of 165 respondents recruited from SAA outreach and 1 of 1425 respondents recruited via market research panels (Fig. 1). Mean age of interviewed patients was 45 years, and 80% were female. Time to nr-axSpA diagnosis was > 6 years (68%), 3 to 5 years (24%), and 1 to 2 years (8%). All but 3 patients had been treated with biologic therapy, and nearly a third worked in healthcare settings.

Early Symptoms Did Not Necessarily Prompt Medical Attention

Several barriers were revealed in interviews. Themes and illustrative quotes are shown in Table 2 and the more-detailed **Additional file 5**. Interviewed patients had diverse experiences with early nr-axSpA symptoms. For some, early symptoms caused pain or functional impairment that was severe enough for them to quickly seek medical attention. Another subset described an insidious background of chronic pain that waxed and waned and was often perceived as normal or an unremarkable wear-and-tear response. Yet others experienced episodic symptom flares. For a few patients, flares seemed random, but more commonly they coincided with exertional activities. Unless symptoms interfered with their activities, young and athletic patients often tolerated these episodes, having learned that flares eventually resolved.

Table 2

Impediments to nr-axSpA Diagnosis: Themes and Selected Illustrative Quotes From Qualitative Patient Interviews

<p>The insidious onset of early axSpA symptoms leads many patients to perceive their pain as bothersome but not alarming. Patients tolerate it without necessarily seeking medical care.</p>
<p>"My first symptoms started in my late 20s. I just thought it was normal back pain. It started in my SI joints....And what I did was go to a chiropractor. I didn't go to a doctor." (Patient 107)</p> <p>"I developed back pain in my teen years. It wasn't horrible. It wasn't like the full-on 'I can't sleep at night' back pain. It was 'this is uncomfortable,' I couldn't sleep in certain positions, an ongoing achy pain...but it was a low-level pain. So, I just assumed I'd hurt myself or something and I'd just have to live with it." (Patient 198)</p>
<p>Patients' chief complaints may not reflect the ASAS axSpA paradigm of insidious and persistent chronic low back pain. Rather, patients' most troubling symptoms often involve the neck or nonaxial sites, flare episodically, or seem associated with strenuous activity or trauma.</p>
<p>"Starting in middle school and all through high school, I saw an orthopedic doctor for my knees, never my back, cause my knees would always cause a problem—and they could never figure out what the cause was—they said it was probably just growing pains, but my knees would give out on me, be achy all the time." (Patient 211)</p> <p>"I first starting having issues in high school. My back would go out....I would be walking into school... and all of a sudden, I would have sciatic pain and I could hardly walk. But it would come and go. And we never really did anything about it." (Patient 103)</p> <p>"If I'd decided to vacuum...that would have put me out [with back pain] for a few days." (Patient 103)</p> <p>"All of a sudden my neck is stiff. It didn't occur to me to go to a doctor that first time. And go, 'Hey—my neck's stiff; let's figure this out.' It was stiff and I thought, well it will go away. And it did....and then it came back, [...but I knew] it went away last time." (Patient 172)</p> <p>"As a kid, I was slightly conscious of the fact that I would injure myself and the injury would kinda persist longer than it seemed like it should. I remember falling and hitting my heel as a young child of age 7-ish. That heel was sensitive for probably a year or so. I couldn't play basketball because every time I hit my fingers with the ball, my finger joints would swell up." (Patient 172)</p> <p>"In my senior year of high school, I would have to go to physical therapy before or after soccer games. I don't know why I never thought to not do those things, but I loved soccer and tennis, so I continued to play them. When I would play tennis, I would play my match, and then my doubles partner would have to carry me off the court because I couldn't walk anymore." (Patient 103)</p>
<p>HCPs are often unaware of and have poor understanding of axSpA, hindering detection and interpretation of nr-axSpA manifestations.</p>
<p>"They were just treating the symptoms and not figuring out what was wrong." (Patient 123)</p> <p>"I was told everything is normal by 4 specialists." (Patient 167)</p> <p>"I was told, 'You can't have AS. That is a man's disease.'" (Patient 151)</p> <p>"[The rheumatologist] dismisses AS right away because I am not HLA + and my x-rays show no evidence....Now I know this is wrong...and this rheumatologist is teaching this!" (Patient 241)</p> <p>"I had tested positive for the HLA-B27, but the rheumatologist told me, 'you just need to lose weight and you'll feel better.'" (Patient 103)</p>

<p>The insidious onset of early axSpA symptoms leads many patients to perceive their pain as bothersome but not alarming. Patients tolerate it without necessarily seeking medical care.</p>
<p>Patients presenting with nr-axSpA symptoms often lack definitive abnormalities that explain their symptoms, leading to counterproductive clinical encounters and skepticism, particularly toward young and female patients.</p>
<p>“Most orthos—because I was young and female—thought I was making it up.” (Patient 167)</p> <p><i>[When the x-ray result was normal],</i> “The doctor told me, “Your pain can’t be that bad.” (Patient 151)</p> <p>“I got referred to spine and bone specialists. I was about 21 or 22...and they made me feel like a hypochondriac. So, I stopped going and just dealt with it.” (Patient 103)</p> <p>“If a woman has symptoms that can’t be explained, they just assume she has emotional problems.” (Patient 165)</p>
<p>Patients face numerous barriers to satisfactory rheumatology care and a definitive diagnosis.</p>
<p>“I was seeing my general family doctor. He fought me pretty hard on referring me. Back in 2002, I requested that he test me for HLA-B27. He fought me pretty hard on that [too], but I threatened to go to another doctor. He finally ran that test, and it came back positive. So in 2012, he finally set me up with a referral to a rheumatologist.”</p> <p>“[My doctor didn’t want to order the test] because I wasn’t a guy. Women can’t have AS. That’s what I was told.”</p> <p>“Part of the problem was that where we lived, we didn’t have a rheumatologist. I would have had to travel to see a specialist. We had one finally in 2012.”</p> <p>“My diagnosis changed last year. I’ve seen 3 rheumatologists, and this last one changed my diagnosis [to nr-axSpA].” (Patient 213)</p> <p>“At some point I saw just about every rheumatologist in the metropolitan area, because I wasn’t getting anywhere. They sort [of] didn’t know what to do, and it didn’t seem like they knew much about spondylitis.” (Patient 156)</p>
<p>ASAS, Assessment of SpondyloArthritis International Society.</p>

Chronic Back Pain, Central to the axSpA Definition,(26) Was Often Not the Dominant Symptom

All interviewed patients reported low back, hip, or SI joint pain at some point; however, for nearly half of this group, peripheral joints, neck pain, enthesitis, uveitis, and gastrointestinal symptoms caused greater distress and were the initial focus of medical care.

Early Medical Encounters Were Often Unsatisfying

Patients with early disease typically sought medical care for specific troublesome symptoms, which they sometimes found difficult to describe. HCPs typically performed narrowly focused evaluations at initial visits. When physical examination, imaging studies, and laboratory tests were unremarkable, as was common, HCPs frequently offered reassurance and recommendations that patients found unsatisfying.

To patients returning with persistent pain symptoms, HCPs often expressed skepticism if symptoms could not be medically explained. In particular, patients who were young and/or female were often questioned about the validity of their pain complaints and motivations. Numerous women reported that their symptoms were attributed to stress, depression, pregnancy, or weight. Further, women repeatedly encountered HCPs who believed that axSpA was a “man’s disease.” This misperception was a significant barrier to HLA-B27 testing and rheumatology referral. Even when women were found to be HLA-B27 positive or received an axSpA diagnosis, many HCPs disputed the diagnosis.

Physicians, Including Rheumatologists, Lack Knowledge About axSpA

Most patients saw multiple HCPs before axSpA was considered. These HCPs often knew little about spondyloarthritis and did not recognize indications for rheumatology referral. To fill this void, patients often turned to the internet for answers. Although information on axSpA and especially nr-axSpA has been scarce until recently, when found, it empowered patients to communicate more effectively and advocate for testing and rheumatology care.

Frequent Barriers to Effective Rheumatology Care

Once referred to a rheumatologist, patients often faced long waits for an appointment. Patients encountered wide variation in rheumatologists, and several expressed alarm at their clinician’s limited knowledge of nr-axSpA. When researching potential rheumatologists, patients found few clues about the prospective rheumatologist’s spondyloarthropathy expertise and frequently consulted multiple rheumatologists before finding a “good” one. The most satisfying rheumatologists were often found at tertiary centers or through SAA.

Rheumatologist Interviews

Of 190 invited physicians, 26 completed the qualifying questionnaire, and 16 board-certified US rheumatologists were interviewed (Fig. 1); all had been in practice for ≥ 7 years and cared for multiple people with nr-axSpA. Five rheumatologists were in academic practices; 1 was a pediatric rheumatologist.

Awareness of nr-axSpA Is Low Among Physicians

Rheumatologists viewed poor recognition of inflammatory back pain (IBP) as a major factor contributing to diagnostic delay, noting that it is commonly missed by primary care physicians (PCPs), orthopedists, pain specialists, and even some rheumatologists. Patient age and sex may also play a role. Young, seemingly healthy patients often lack a sustained PCP relationship and are less skilled in self-advocacy. Women’s pain complaints are frequently dismissed as mechanical back pain by PCPs and specialists. However, rheumatologists also sensed rising awareness of nr-axSpA.

Varied and Latent Symptoms of nr-axSpA Hinder Diagnosis

Although some of the group perceived nr-axSpA diagnosis as straightforward, others described challenges posed by varied clinical presentations or seemingly unrelated symptoms. Understanding often emerged only after several encounters with a patient.

Several Factors Constrain the Utility of Diagnostic Imaging

Rheumatologists varied in their reliance on diagnostic imaging when evaluating patients for axSpA. They felt that most radiologists were inadequately trained in reading SI joint radiographs and that many rheumatologists lacked local access to experienced musculoskeletal radiologists. Rheumatologists have greater confidence in MRI, but their radiologists often lack key skills in interpreting axSpA features in this modality. Furthermore, less-experienced rheumatologists may not know how to adequately specify their MRI request to evaluate axSpA. Several interviewed rheumatologists had pursued informal training to improve their own MRI skills.

Quantitative Patient Survey Results

Of those recruited by SAA outreach, 88 of 252 respondents affirmed rheumatologist-diagnosed nr-axSpA and were deemed eligible, while 98 of 16,031 market research panel respondents were found eligible (Fig. 1). The resulting analysis sample (n = 186) was primarily female (67%), white (81%), and college educated (62%). Median age was 40 years (Table 3). At least 85% of patients had undergone MRI imaging, and nearly 80% had undergone HLA-B27 testing, with 59% reporting positive status.

Table 3
 Characteristics of Patients in Quantitative (Survey)
 Study Component (N = 186)

Sex	
Female	67%
Age, years	
Median	40.0
(interquartile range)	(34.0-51.8)
Race^a	
Asian	4%
Black	4%
Hispanic	6%
White	81%
Multiracial	3%
Other	1%
Education	
High school or less	8%
Trade/technical school	4%
Some college	26%
Bachelor's degree	39%
Advanced degree	23%
Work status (prepandemic)	
Student	2%
Work full-time	59%
Work part-time	11%
Stay-at-home parent	9%
Retired	9%
On disability	10%
Unemployed	5%

^a Percentages may not total 100 due to rounding.

Sex	
US region	
Northwest	14%
Northeast	26%
Southwest	20%
Southeast	18%
Central	22%
Community type	
Large city	28%
Suburb	38%
Small city or town	23%
Rural	11%
Household income	
<\$25000	9%
\$25000 to \$49999	15%
\$50000 to \$99999	28%
\$100000 to \$149999	31%
≥\$150000	12%
Prefer not to answer	6%
MRI to evaluate back, hip, or buttock pain	
Yes, back or pelvis	75%
Yes, site uncertain	11%
No	13%
Unsure	1%
HLA-B27 status	
Positive	59%
Negative	22%
Not tested	13%
^a Percentages may not total 100 due to rounding.	

Sex	
Unsure	6%
^a Percentages may not total 100 due to rounding.	

Median time from symptom onset to nr-axSpA diagnosis was 3.25 years (interquartile range, 1.5-8.0 years) (Fig. 2). While 49% of patients received their diagnosis within 2 years of symptom onset, 23% of patients experienced symptoms for longer than 11 years before their nr-axSpA diagnosis. Mean age at diagnosis was 37 years.

Patients typically sought care from multiple HCPs before seeing a rheumatologist, with 51% seeing at least 4 different types of clinicians (see **Additional file 6**). The most common providers seen were PCPs (70%), chiropractors (43%), and physical therapists (40%) (see **Additional file 6**). Although 59% of patients received a rheumatology referral for axSpA, 17% self referred, and 5% were already seeing a rheumatologist for another condition. Seeing a rheumatologist did not necessarily provide diagnostic clarity or satisfaction. Almost half of patients received their nr-axSpA diagnosis only after consulting multiple rheumatologists (see **Additional file 6**), and 84% sought care for their symptoms from 2 or more rheumatologists.

Factors Contributing to Diagnostic Delay

When asked which of several patient factors were most impactful in preventing timely nr-axSpA diagnosis, patients most frequently pointed to their own initial perceptions that “joint pains were due to activity or injury” (45%) or that their “back pain was due to aging” (18%). The two most impactful healthcare factors that hindered nr-axSpA diagnosis were “healthcare providers [who] attributed my symptoms to activity or injury” (22%), and “healthcare providers [who] thought my symptoms were ‘in my head’” (18%) (Fig. 3 and **Additional file 7**).

Nondiagnostic studies were additional confounding factors, with normal x-ray or MRI results (36%) and negative HLA-B27 status (58% of patients were known to be HLA-B27 negative) identified as contributing to diagnostic delay. Patients also indicated multiple barriers to seeing a rheumatologist. Thirty-two percent reported that “medical professionals didn’t know to refer me to a rheumatologist,” 11% “requested a rheumatology referral [that] was denied,” and 25% reported “limited access to rheumatologists.”

Even after getting to a rheumatologist, recognition and diagnosis of nr-axSpA were not always straightforward. Twenty-two percent of patients indicated that “rheumatologist(s) I saw gave me conflicting diagnoses,” and 16% indicated “rheumatologist(s) I saw were unaware of nr-axSpA.” Among women, 25% were told that “nr-axSpA was a ‘man’s disease’” and cited this misperception as a barrier.

Misdiagnosis was reported by 25% of patients, with greater frequency among women than men (33% vs 10%). Fibromyalgia was the most frequently cited alternative diagnosis and was reported exclusively by

women (12 of 124).

Facilitators of nr-axSpA Diagnosis

Seeing a rheumatologist who recognizes the signs and symptoms of nr-axSpA facilitates a timely diagnosis, but this scenario was not experienced by most surveyed patients (see **Additional file 8**). Only 26% indicated “I was quickly referred to a rheumatologist,” and 42% reported that “the first rheumatologist diagnosed me quickly and confidently.” Patients advocating for themselves (45%), researching the cause and/or disease on their own (44%), and referring themselves to a rheumatologist (24%) were factors that facilitated nr-axSpA diagnosis. For 20% of patients, their family history helped them recognize the need for rheumatology care.

Predictors of nr-axSpA Diagnostic Delay

Multiple logistic regression analysis of patient survey data indicated that race and income had nonsignificant associations with delayed nr-axSpA diagnosis and were removed from the final model. Patients were significantly more likely to have delayed diagnosis (see **Additional file 9**) if they were female (OR, 3.75; 95% CI, 1.88–7.69), lived in a rural location (OR, 3.56; 95% CI, 1.20-10.55), had completed college (OR 2.87; 95% CI, 1.38–5.95), or did not have full-time employment (OR 2.84; 95% CI, 1.41–5.71).

Discussion

To the best of our knowledge, this study is the first to use both qualitative and quantitative methods to evaluate impediments to nr-axSpA diagnosis in the United States.

Median time to nr-axSpA diagnosis was 3.25 years (mean, 7.9 years) among surveyed patients. Although half of patients were diagnosed within 2 years of symptom onset, more than 20% lived with undiagnosed or misdiagnosed symptoms for more than a decade. Diagnostic delay was significantly greater among patients who were women, lived in rural areas, were highly educated, and were not working full-time. The delay revealed in this study is consistent with the mean diagnostic delay of 6.7 years for patients with axSpA in a recent systematic review.(27)

This study identified additional factors that contribute to delay. A critical finding is HCPs’ poor awareness and understanding of axSpA. Patients commonly encountered outdated perceptions of axSpA that biased HCPs against this diagnosis in women and people who were HLA-B27 negative. More than a third of surveyed patients also indicated that seemingly normal imaging studies contributed to diagnostic delay. In 2009, the Assessment of SpondyloArthritis International Society (ASAS) developed classification criteria for axSpA that deliberately recognize that axSpA can be present without definitive radiographic sacroiliitis.(1) However, our findings suggest that many frontline HCPs are not yet familiar with nr-axSpA.

Several factors limit the utility of imaging studies in facilitating axSpA diagnosis. Radiologists often lacked skill in evaluating x-ray and MRI images of the SI joints and likely missed subtle abnormalities. These findings support a recent survey of radiologists demonstrating prevalent knowledge gaps related

to axSpA imaging.(28) Studies have shown that the bone marrow edema observed in the MRI of the SI joints in axSpA patients is not specific to the disease but can also occur in athletes, postpartum women, and other healthy populations.(29, 30) Furthermore, degenerative spinal disease frequently coexists with axSpA(31, 32) and may diminish attention to less-familiar axSpA-related abnormalities, particularly when axSpA is not suspected. These issues highlight the importance of close collaboration between radiologists and rheumatologists.

Symptoms described by study patients reflect the marked heterogeneity of nr-axSpA. Current efforts to increase awareness of axSpA often emphasize chronic IBP,(19, 33, 34) and for many patients in this study, persistent back pain was an early and dominant symptom. Yet numerous patients did not have this classic symptom pattern (see **Additional file 10**). Several patients described acute flares of back pain during their teen years and early adulthood. For other patients, the most painful and disabling symptoms occurred at nonaxial sites, consistent with growing evidence that manifestations of axSpA and peripheral spondyloarthropathy have considerable overlap.(35) Given HCPs' limited understanding of spondyloarthritis, it seems unlikely that they would recognize these diverse presentations of axSpA. Thus, axSpA campaigns that were centered on the timely recognition and referral of the patient with IBP may be overly narrow. Rather, it may be important to bring attention to the broader phenomena associated with spondyloarthritis and the common underlying pathophysiology.(36) Doing so may help HCPs better discern axSpA in patients with varied, asynchronous, and seemingly unrelated manifestations.

Study patients and their physicians often perceived a connection between axSpA symptoms and preceding physical activities or trauma. These perceptions led some patients to initially self manage symptoms in expectation of gradual resolution. In clinical settings, these perceptions likely led patients and physicians to narrowly focus on the chief complaint, overlooking other relevant signs or symptoms.

Patients' perceptions that their strenuous activities and axSpA symptoms are linked has been reported in a separate study(37) and may have validity. It is increasingly understood that spondyloarthritis arises, at least in part, from an exaggerated inflammatory response to biomechanical stress in predisposed individuals.(38, 39) Several studies have shown a positive association between physically demanding occupations and axSpA progression;(40, 41) however, few studies have explored the temporal relationship between axSpA symptoms and exertional activity or minor trauma. Further research into these associations is warranted and may facilitate early axSpA detection.

Women in this study were significantly more likely than men to experience delayed nr-axSpA diagnosis, supporting findings from a recent systematic review.(42) The present study identified several factors that likely contribute to this disparity. For example, women were more likely to indicate that normal imaging studies, negative HLA-B27 status, and HCP perceptions of axSpA as a "man's disease" hindered their diagnosis. Women were also more than 3 times as likely to report that their nr-axSpA symptoms was misdiagnosed, and more than 40% of women reported their HCP making disparaging remarks about their symptoms.

These findings are consistent with a study demonstrating striking sex-specific differences in how rheumatologists documented symptoms of patients with axSpA and showing that men were 3 times more likely to receive an axSpA diagnosis at their first rheumatology visit.(24) The authors concluded that HCPs held gender biases that influenced their clinical assessment, thereby affecting time to diagnosis at multiple time points.

Sex-related differences in the experience of pain may likewise contribute to disparate diagnostic delay. A recent study of axSpA pain found that women had significantly higher rates of pain in the cervicothoracic junction and thoracic spine, as well as higher rates of widespread axial and peripheral articular pain.(43) Biological sex differences that affect the brain's response to pain signals are apparent in infancy and may predispose women to more widespread pain.(44) Psychological and cultural factors also impact how men and women respond to and communicate about pain. These factors collectively influence doctor-patient interactions that center on pain. These disparities were demonstrated by Global Assessment pain and disability ratings that were discordantly higher among nearly 60% of women, but just 40% of men, compared with their physician's rating.(45) Women's disparate diagnostic journey is not unique to axSpA but reflects a broader phenomenon seen with medically inexplicable chronic pain.(46)

Finally, patients in this study faced numerous barriers to rheumatology care that hindered timely nr-axSpA diagnosis. Even when patients explicitly requested referral, their HCPs often resisted. These obstacles stem in part from HCPs' failure to recognize IBP and other indicators of rheumatological disease; however, local scarcity of rheumatology services can also be a factor.(47) In this study, rural location was independently associated with diagnostic delay, and several regions of the United States are underserved by rheumatologists.(48) Patients in this study were further hampered by the lack of rheumatologists with contemporary knowledge of nr-axSpA, indicating a continuing need for education on this topic. Patients and referring clinicians need mechanisms to more easily identify rheumatologists skilled in spondyloarthritis care. Strategies to improve the timeliness of nr-axSpA diagnosis must also anticipate regional variation in rheumatology access and be tailored accordingly.

Our study has some limitations. We used a convenience sampling approach that recruited almost all of the qualitative study participants, and more than half of survey respondents, through SAA outreach. These individuals were predominantly female and may not be representative of the broader population living with nr-axSpA. To diversify the sample, participants were also recruited from patient panels. This strategy was inefficient and required additional quality checks but increased male and nonwhite survey participation. In both study phases, the determination that respondents had rheumatology-diagnosed nr-axSpA and were eligible relied on self-reported survey responses and could not be independently confirmed.

The qualitative study component revealed patterns in early symptoms and care seeking that may significantly influence time to nr-axSpA diagnosis. These findings were not anticipated and thus were not systematically assessed. Further qualitative and quantitative research into patients' preclinical symptoms and experiences is indicated.

Conclusions

In this mixed-methods study of impediments to nr-axSpA diagnosis in the US, delayed diagnosis was common. Among surveyed patients, median time to diagnosis was 3.25 years, yet more than 20% had undiagnosed symptoms for over a decade. Diagnostic delay disproportionately affected women and patients living in rural areas. Barriers to timely diagnosis included patient tolerance for chronic pain, symptoms other than hallmark chronic low back pain prompting care, and episodic symptom flares seemingly related to strenuous activity. Furthermore, HCPs are typically unfamiliar with axSpA or hold outdated perceptions that contribute to delayed diagnostic testing and rheumatology referral, and qualified rheumatologists who understand axSpA are limited in number.

Further research into early nr-axSpA manifestations and associations with physical activity and minor trauma is needed, as well as education to improve knowledge of nr-axSpA and address misperceptions among frontline HCPs, radiologists, and rheumatologists. Interventions that consider the broader spectrum of presentations beyond lumbosacral IBP seem warranted.

Abbreviation

AS, ankylosing spondylitis

ASAS, Assessment of SpondyloArthritis International Society

axSpA, axial spondyloarthritis

CI, confidence interval

HCP, healthcare provider

HLA-B27, human leukocyte antigen B27

IBP, inflammatory back pain

MRI, magnetic resonance imaging

nr-axSpA, nonradiographic axSpA

OR, odds ratio

PCP, primary care physician

SAA, Spondylitis Association of America

SI, sacroiliac

Declarations

Ethics approval and consent to participate

This study was approved by the Oregon Health & Science University institutional review board (reference # 00020788).

Consent for publication

All study participants provided their consent for participation. Consent forms are available upon request.

Availability of data and methods

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

SK declares that she has no competing interests.

RH declares that he has the following competing interests:

- *Consulting/advisory board:* Novartis, GSK
- *Stock:* AbbVie, Amgen, Bristol Myers Squibb, GSK, Johnson & Johnson, Lilly, Merck, Novartis, Pfizer, Teva, UCB, Viatrix

DC declares that he has no competing interests.

AD declares that he has the following competing interests:

- *Consulting/advisory boards:* AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, GSK, Eli Lilly, Janssen, Novartis, Pfizer, UCB
- *Research grants:* AbbVie, Lilly, Novartis, Pfizer, UCB

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Authors' contributions

SK was integral in developing the study design, analyzing and interpreting the study datasets, and liaison with the statistician on dataset analysis. RH was integral in developing the study design, recruitment and enrollment of patients into the study, and analyzing and interpreting study datasets. DC provided statistical analysis on all datasets and verified data accuracy. AD was integral in development of the study design and analyzing and interpreting study datasets. All authors read and approved the final manuscript.

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Figures

Figure 1

Participant Recruitment and Enrollment for Qualitative and Quantitative Study Components

Figure 2

Time to Diagnosis of nr-axSpA Footnote: a Data missing for 1% of respondents.

Figure 3

Factors Contributing to Prevention of Timely or Accurate nr-axSpA Diagnosis Legend: Patients were queried as to which factors were most impactful in(Most contributed), and which factors contributed to (Contributed), preventing timely or accurate nr-axSpA diagnosis. These factors were later assessed as patient-related factors (A) or healthcare provider–related factors (B). Footnotes: a Themes identified in open-ended “Other Patient Factor” responses. b Based on responses for individuals indicating HLA-B27 negative status only. c Based on responses for women only.

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