Article

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Independent Determinants of Diagnostic Delay in Female Patients With Axial Spondyloarthritis and Its Impact on 12-Month Disease Outcomes

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Background: Axial spondyloarthritis (axSpA) often presents atypically in female patients, leading to prominent issues of diagnostic delay. However, the specific determinants of diagnostic delay in women and their impact on 12-month outcomes following treatment initiation remain understudied. This study aimed to identify independent factors associated with diagnostic delay in female axSpA patients and evaluate the independent effect of diagnostic delay on disease activity outcomes at 12 months post-diagnosis.

Methods: This was a single-center retrospective cohort study. We consecutively enrolled 156 female patients diagnosed with axSpA between January 1, 2020, and June 30, 2024. Demographic, clinical, and care pathway data were extracted from medical records. Diagnostic delay was defined as the interval (in years) from symptom onset to definitive diagnosis, analyzed after natural logarithmic transformation. The primary outcome was disease activity at 12 months post-diagnosis, measured by the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP). Univariate and multivariable linear regression analyses were used to identify factors influencing diagnostic delay. Multivariable linear regression (adjusted for baseline ASDAS-CRP, disease phenotype, treatment regimen, and age at onset) assessed the independent impact of diagnostic delay on the outcome.

Results: The median diagnostic delay was 5.90 years (interquartile range: 4.40–7.46). Multivariable linear regression identified that initial consultation with a non-rheumatologist [Beta coefficient (β) = 0.589, 95% confidence interval (95% CI): 0.493–0.686, $p < 0.001$], prior misdiagnosis (β = 0.218, 95% CI: 0.144–0.292, $p < 0.001$), non-radiographic axSpA (nr-axSpA) phenotype (β = 0.132, 95% CI: 0.059–0.206, $p < 0.001$), and concomitant uveitis (β = 0.182, 95% CI: 0.108–0.257, $p < 0.001$) were independent risk factors for prolonged diagnostic delay. Outcome analysis revealed that, after adjusting for confounders, longer diagnostic delay (β = 0.649, 95% CI: 0.450–0.848, $p < 0.001$), use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) compared to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) monotherapy (β = 0.157, 95% CI: 0.011–0.302, p = 0.036), and higher baseline ASDAS-CRP score (β = 0.481, 95% CI: 0.384–0.578, $p < 0.001$) were independent predictors of poorer disease control (higher ASDAS-CRP score) at 12 months post-diagnosis.

Conclusion: In female axSpA patients, suboptimal care pathways, misdiagnosis, and atypical clinical manifestations are major contributors to diagnostic delay. A longer diagnostic delay independently predicts worse 12-month treatment outcomes. These findings underscore the urgent need to enhance early recognition capabilities among non-rheumatologists and optimize referral pathways to shorten diagnostic delay.

Keywords: spondylarthritis; delayed diagnosis; women; disease progression; risk factors

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease primarily affecting the sacroiliac joints and spine, with a clinical spectrum encompassing both non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA, also known as ankylosing spondylitis) stages [1]. Advances in imaging technologies, particularly magnetic resonance imaging (MRI), along with updated classification criteria, have improved the identification of patients in the early, non-radiographic stage [2]. Despite these improvements, significant diagnostic delay remains a pervasive global challenge [3]. Multiple international studies report mean diagnostic delays for axSpA ranging from 6 to 8 years [4,5]. This delay is not merely a procedural issue; longer diagnostic delays are associated with worse long-term outcomes, including more severe radiographic structural damage, higher disease activity, greater functional impairment, and reduced quality of life [6].

The clinical presentation of axSpA exhibits notable sex differences. While historically considered a male-predominant disease, newer reports indicate a less pronounced sex distribution disparity [7]. Female patients more frequently present with atypical features, such as a higher prevalence of nr-axSpA, broader peripheral and cervical spine involvement, and lower levels of acute-phase reactants [7,8]. These manifestations often resemble common conditions like fibromyalgia or degenerative low back pain, leading to misdiagnosis and delayed referral when patients initially present to non-rheumatology specialties (e.g., orthopedics, rehabilitation medicine) [9,10]. A systematic review showed that diagnostic delay in axSpA was higher in women [11].

Recently, research on the determinants of delay and its adverse consequences has been conducted in general axSpA populations, yet critical gaps persist. First, most studies have not performed sex-stratified analyses, lacking depth in systematically exploring unique determinants of delay specifically within the female population, especially in cohorts explicitly including both nr-axSpA and r-axSpA phenotypes [12]. Second, and more importantly, the direct impact of diagnostic delay on disease activity outcomes following the initiation of guideline-recommended treatment, within a sex-specific context, remains underexplored [12]. It is currently unclear whether a prolonged, untreated inflammatory period independently predicts poorer treatment response in female patients, even after adjusting for baseline disease severity and treatment modalities.

To address these gaps, we conducted a retrospective cohort study focusing exclusively on female patients with axSpA. The study had two primary objectives: (1) First, to identify the independent determinants of diagnostic delay in this population. Here, we investigated which demographic, clinical, and healthcare pathway factors were causally associated with a longer delay from symptom onset to diagnosis; (2) Second, to evaluate whether the length of diagnostic delay itself serves as an independent predictor of treatment outcomes. Specifically, we assessed if a longer delay predicts higher disease activity (measured by ASDAS-CRP) at 12 months post-diagnosis, after controlling for baseline activity and treatment regimens.

Methods

Study Population

This was a single-center, retrospective cohort study conducted in our hospital. We reviewed the clinical records of 156 female patients diagnosed with axSpA between January 1, 2020, and June 30, 2024. The study was approved by the institutional ethics review board of The First Affiliated Hospital of Soochow University (approval number: 20251237) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before inclusion.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Female patients meeting the Assessment of Spondyloarthritis International Society (ASAS) 2009 classification criteria for axSpA [13]; (2) Aged $\geq$18 years; (3) Availability of complete medical records from the first physician visit, enabling precise calculation of diagnostic delay; (4) Regular follow-up at our center for $\geq$12 months after diagnosis, with complete baseline and follow-up disease activity assessments.

Exclusion criteria: (1) Coexisting systemic autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus); (2) Presence of severe comorbidities (including active malignancy, severe chronic kidney or liver disease); (3) Pregnant patients; (4) Incomplete clinical data.

Study Variables and Outcome Definitions

Diagnostic Delay: Defined as the time interval (in years, calculated precisely to the month) between the patient's self-reported date of onset of chronic inflammatory back pain symptoms and the date when an ASAS-certified rheumatologist definitively established the diagnosis of axSpA. Due to its typically skewed distribution, the natural logarithm of the delay in years (Ln [delay in years]) was used in all regression analyses to meet linear model assumptions. The normality of the residuals of the transformed model was significantly improved. Finally, the validity of the model was evaluated through the residual histogram and P-P plot (see **Supplementary Figs. 1–4**).

Disease Activity: Disease activity was assessed using the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP), developed and validated by the ASAS association. This score is calculated using the standard formula: ASDAS-CRP = 0.12 $\times$ Back Pain + 0.11 $\times$ Patient's Global Assessment + 0.07 $\times$ Peripheral Joints Score + 0.06 $\times$ Morning Stiffness Duration + 0.58 $\times$ Ln (CRP + 1) [14]. Assessment time points: (1) Baseline activity: ASDAS-CRP assessed at diagnosis or during the first evaluation immediately following diagnosis. (2) Follow-up endpoint activity: ASDAS-CRP assessed at approximately 12 months ($\pm$ 1 month) after diagnosis, while receiving standardized treatment (which included regular nonsteroidal anti-inflammatory drugs (NSAIDs) monotherapy, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), or biologic agents.

Candidate Determinants: Patient-level: Age at symptom onset [15], age at diagnosis, education level [16], smoking history [17], family history [18]; Disease phenotype: nr-axSpA vs. r-axSpA based on sacroiliac joint X-rays or MRI; Clinical manifestations: Peripheral arthritis [19], enthesitis, anterior uveitis [15], inflammatory bowel disease [20]; Auxiliary examinations: Human leukocyte antigen B27 (HLA-B27) status (positive/negative) [21], baseline CRP levels [22], extra-articular manifestations; Care pathway-level: First consultation department being non-rheumatology (Orthopedics/Rehabilitation

Table 1. Baseline characteristics of patients [median (Q1, Q3), n (%)].

Characteristics	Patients (n = 156)
Age at diagnosis	36.15 (31.98, 42.03)
Age of onset	29.50 (25.42, 35.25)
Smoking history (yes)	34 (21.79%)
Family history (yes)	39 (25.00%)
Level of education	
Primary school or below	25 (16.03%)
Junior high school	42 (26.92%)
Senior high school/Secondary vocational school/Vocational high school	44 (28.21%)
College diploma/Bachelor's degree or above	45 (28.85%)
nr-axSpA	70 (44.87%)
r-axSpA	86 (55.13%)
HLA-B27 positive	117 (75.00%)
Accompanied by uveitis	62 (39.74%)
Accompanied by enthesitis	53 (33.97%)
Accompanied by peripheral arthritis	29 (18.59%)
Accompanied by inflammatory bowel disease	22 (14.10%)
Diagnostic delay (years)	5.90 (4.40, 7.46)
Number of departments visited before definitive diagnosis	3.00 (2.00, 4.00)
First visit to a non-rheumatology specialty	23 (14.74%)
History of misdiagnosis	99 (63.46%)
Baseline ASDAS-CRP score	3.20 (2.60, 3.60)
Treatment regimen after diagnosis	
NSAIDs monotherapy	55 (35.26%)
Use of csDMARDs	62 (39.74%)
Use of biologic agents	39 (25.00%)

nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; HLA-B27, Human leukocyte antigen B27; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; NSAIDs, Non-Steroidal Anti-inflammatory Drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

Medicine/Pain clinic/Other specialties) [23], number of departments visited before diagnosis [24], history of misdiagnosis before definitive diagnosis (e.g., misdiagnosed as "lumbar muscle strain", "disc herniation", "fibromyalgia") [16], and post-diagnosis treatment regimen (only using NSAIDs/csDMARDs/biologic agent) [25].

Post-diagnosis treatment regimens were categorized based on the dominant therapy recorded in the medical records within the first 12 months following diagnosis, and in accordance with the ASAS-EULAR management recommendations for axSpA [26]. The categories were defined as follows: (1) NSAID monotherapy: Continuous or on-demand use of any non-steroidal anti-inflammatory drug, without concomitant use of csDMARDs or biologic agents. (2) csDMARD therapy: Treatment including any conventional synthetic disease-modifying antirheumatic drug, regardless of concomitant NSAID use. In this study, this category specifically comprised patients prescribed sulfasalazine and/or methotrexate, which are the csDMARDs with evidence for use in peripheral SpA and are most commonly used in our clinical setting. Patients receiving csDMARDs in combination with biologic agents were analyzed within the biologic agent group. (3) Biologic agent therapy: Treatment including any biologic DMARD (e.g., TNF inhibitors, IL-17 inhibitors), with or without concomitant NSAIDs or csDMARDs.

Statistical Analysis

The statistical analyses were conducted using IBM SPSS Statistics software (Version IBM SPSS 27, IBM SPSS, Armonk, IL, USA). The Kolmogorov-Smirnov test was applied to assess the normality of continuous variables. Non-normally distributed data were expressed as median (interquartile range) [IQR: Q1, Q3]. To identify independent factors associated with diagnostic delay, univariate linear regression analysis was initially conducted. Variables with a p-value < 0.05 in the univariate analysis and deemed clinically important were included in the multivariable linear regression model using an enter method. Variance inflation factor (VIF) was used to assess for multicollinearity. To evaluate the independent impact of diagnostic delay on disease activity outcomes, a multivariable linear regression model was constructed. The ASDAS-CRP score at 12 months post-diagnosis was the dependent variable, with

Table 2. Univariate linear regression analysis of diagnostic delay.

Variable	Category/Unit	Univariate Analysis	
		β (95% CI)	p-value
Age at diagnosis	Each additional year of age	0.011 (0.003, 0.019)	0.005
Age of onset	Each additional year of age	–0.007 (–0.015, 0.001)	0.070
Smoking history	No (reference)		
	Yes	0.035 (–0.118, 0.189)	0.649
Family history	No (reference)		
	Yes	–0.023 (–0.170, 0.123)	0.753
Level of education	Primary school or below (reference)		
	Junior high school	–0.046 (–0.190, 0.097)	0.522
	Senior high school/Secondary vocational school/Vocational high school	0.042 (–0.099, 0.183)	0.560
	College diploma/Bachelor's degree or above	0.027 (–0.113, 0.167)	0.702
Disease phenotype	r-axSpA (reference)		
	nr-axSpA	0.427 (0.318, 0.535)	<0.001
HLA-B27	Negative (reference)		
	Positive	0.064 (–0.082, 0.211)	0.388
Accompanied by uveitis	No (reference)		
	Yes	0.464 (0.357, 0.571)	<0.001
Accompanied by enthesitis	No (reference)		
	Yes	0.003 (–0.132, 0.137)	0.969
Accompanied by peripheral arthritis	No (reference)		
	Yes	–0.074 (–0.237, 0.089)	0.371
Accompanied by inflammatory bowel disease	No (reference)		
	Yes	–0.045 (–0.228, 0.137)	0.626
Number of departments visited before definitive diagnosis	For each additional unit	0.102 (0.062, 0.141)	<0.001
First visit to a non-rheumatology specialty	No (reference)		
	Yes	0.822 (0.700, 0.945)	<0.001
History of misdiagnosis	No (reference)		
	Yes	0.452 (0.342, 0.563)	<0.001

β indicates unstandardized regression coefficients; CI, confidence interval.

log-transformed diagnostic delay as the primary independent variable. This model was adjusted for baseline ASDAS-CRP, axSpA subtype, post-diagnosis treatment regimen, and age at symptom onset. The above regression analysis results were all presented as non-standardized β coefficients and 95% confidence intervals (CI). For the descriptive results, the median and IQR of the original, untransformed delay time were reported to facilitate clinical interpretation. A two-sided p-value < 0.05 was considered statistically significant.

Sample Size Considerations

As a retrospective, observational study encompassing all eligible patients from a defined period, a formal prospective sample size calculation was not performed. The sample size was determined by the number of consecutive female patients who met the inclusion criteria during the study period. To justify the adequacy of our sample for the planned multivariable linear regression analyses, we conducted a post-hoc power analysis using G*Power 3.1 software (Heinrich-Heine-Universitat Dusseldorf, Dusseldorf, Germany). For the primary outcome model (predicting disease activity at 12 months), with an observed adjusted R^2 of 0.763 (corresponding to a large effect size $f^2 = 3.22$), a sample size of 156, 6 predictors, and an α level of 0.05, the achieved statistical power exceeded 99.99%. This indicates that the study sample was more than sufficient to provide highly reliable estimates for the primary analyses.

Results

Patient Characteristics

A total of 156 female patients with axSpA were included in this study. The median diagnostic delay was 5.90 years (IQR: 4.40–7.46). Of these, 70 patients (44.9%) had nr-axSpA and 86 (55.1%) had r-axSpA, also known as ankylosing spondylitis. At diagnosis, the median ASDAS-CRP score was 3.20 (IQR: 2.60–3.60). Details are provided in Table 1.

Univariate Analysis of Factors Influencing Diagnostic Delay

Univariate linear regression analysis, using log-transformed diagnostic delay as the dependent variable, showed that older age at diagnosis (β = 0.011, 95% CI: 0.003–0.019, p = 0.005), nr-axSpA phenotype (β = 0.427, 95% CI: 0.318–0.535, $p < 0.001$), concomitant uveitis (β = 0.464, 95% CI: 0.357–0.571, $p < 0.001$), a greater number of departments visited before diagnosis (β = 0.102, 95% CI: 0.062–0.141, $p < 0.001$), initial consultation with a non-rheumatologist (β = 0.822, 95% CI: 0.700–0.945, $p < 0.001$), and history of misdiagnosis (β = 0.452, 95% CI: 0.342–0.563, $p < 0.001$) were significantly associated with longer diagnostic delay (Table 2).

Multivariable Analysis of Factors Influencing Diagnostic Delay

Variables with $p < 0.05$ in the univariate analysis were entered into the multivariable linear regression model. The full model included the following candidate variables for mutual adjustment: nr-axSpA phenotype (vs. r-axSpA), concomitant uveitis, initial consultation with a non-rheumatologist, history of misdiagnosis, age at diagnosis, and the number of departments visited before diagnosis. After adjusting for other factors, nr-axSpA phenotype (vs. r-axSpA) (β = 0.132, 95% CI: 0.059–0.206, $p < 0.001$), concomitant uveitis (β = 0.182, 95% CI: 0.108–0.257, $p < 0.001$), initial consultation with a non-rheumatologist (β = 0.589, 95% CI: 0.493–0.686, $p < 0.001$), and history of misdiagnosis (β = 0.218, 95% CI: 0.144–0.292, $p < 0.001$) were identified as independent risk factors for prolonged diagnostic delay. The adjusted R^2 for the model was 0.763, and all VIFs were less than 1.5, indicating no serious multicollinearity. See Table 3.

Impact of Diagnostic Delay on Disease Activity Outcomes

Multivariable linear regression analysis confirmed that a longer diagnostic delay (β = 0.649, 95% CI: 0.450–0.848, $p < 0.001$) and a higher baseline ASDAS-CRP score (β = 0.481, 95% CI: 0.384–0.578, $p < 0.001$) were independent risk factors for a higher ASDAS-CRP score at 12 months post-diagnosis. Additionally, the use of csDMARDs after diagnosis (compared to NSAIDs alone) was associated with poorer disease control at 12 months post-diagnosis (β = 0.157, 95% CI: 0.011–0.302, p = 0.036). The adjusted R^2 for this model was 0.624, and all VIFs were less than 2.0, indicating no serious multicollinearity. See Table 4.

Discussion

This study is the first to systematically evaluate the independent factors associated with diagnostic delay in a cohort of Chinese female patients with axSpA, and confirms that longer diagnostic delay is an independent risk factor for poor disease control at 12 months post-diagnosis. Key findings indicate that initial presentation at non-rheumatology departments, history of misdiagnosis, nr-axSpA phenotype, and concomitant uveitis are independent predictors of prolonged diagnostic delay. Furthermore, longer diagnostic delay combined with higher baseline disease activity constitutes an independent prognostic factor for unsatisfactory therapeutic outcomes.

The current study reveals that the healthcare pathway represents a core determinant of diagnostic delay. Initial consultation at non-rheumatology departments and prior misdiagnosis emerge as the most significant independent contributors, aligning with findings from a single-center study of 1295 Chinese axSpA patients demonstrating that

Table 3. Multivariate linear regression analysis of diagnostic delay.

Variable	Category/Unit	Multivariate analysis	
		β (95% CI)	p-value
Age at diagnosis	Each additional year of age	0.003 (–0.001, 0.007)	0.091
Disease phenotype	r-axSpA (reference)		
	nr-axSpA	0.132 (0.059, 0.206)	<0.001
Accompanied by uveitis	No (reference)		
	Yes	0.182 (0.108, 0.257)	<0.001
Number of departments visited before definitive diagnosis	For each additional unit	0.012 (–0.011, 0.035)	0.319
First visit to a non-rheumatology specialty	No (reference)		
	Yes	0.589 (0.493, 0.686)	<0.001
History of misdiagnosis	No (reference)		
	Yes	0.218 (0.144, 0.292)	<0.001

β indicates unstandardized regression coefficients; CI, confidence interval.

Table 4. Multivariate linear regression analysis of disease activity outcome.

Variable	Category/Unit	Multivariate analysis	
		β (95% CI)	p-value
Duration of diagnostic delay	For each additional unit	0.649 (0.450, 0.848)	<0.001
Disease phenotype	r-axSpA (reference)		
	nr-axSpA	–0.070 (–0.221, 0.081)	0.363
Age of onset	Each additional year of age	–0.002 (–0.010, 0.006)	0.665
Baseline ASDAS-CRP score	For each additional unit	0.481 (0.384, 0.578)	<0.001
Treatment regimen after diagnosis	NSAIDs monotherapy (reference)		
	Use csDMARDs	0.157 (0.011, 0.302)	0.036
	Use of biologic agents	–0.010 (–0.177, 0.156)	0.901

β indicates unstandardized regression coefficients; CI, confidence interval.

misdiagnosis history substantially increases delay risk [16]. This observation critically highlights systemic bottlenecks within healthcare systems - particularly the cognitive and referral gap between primary care and specialty care. Female axSpA patients frequently manifest atypical inflammatory back pain, a higher proportion of nr-axSpA, and more peripheral joint involvement, rendering their symptoms easily confused with fibromyalgia or degenerative lumbar spine disease, which forms the pathophysiological basis for misdiagnosis [27]. Large-scale international survey data further corroborate that female sex and an increased number of non-rheumatology consultations before diagnosis significantly correlate with prolonged delay [7]. Consequently, enhancing awareness among orthopedists, rehabilitation physicians, and general practitioners regarding atypical axSpA manifestations in women, coupled with establishing efficient referral pathways, represent the potential key intervention directions for reducing diagnostic latency [28]. To operationalize this, multifaceted interventions are needed. First, educational initiatives for primary care and non-rheumatology specialists should specifically highlight "red flags" for axSpA in women, including: insidious-onset back pain before age 45, marked morning stiffness, improvement with exercise but not with rest, alternating buttock pain, and a high index of suspicion even in the presence of normal acute-phase reactants [29]. Second, the implementation of simple screening tools in these settings should be encouraged. For example, the use of brief questionnaires addressing inflammatory back pain features (e.g., based on ASAS criteria) or the "2-question screen" (chronic back pain starting before age 40 and improvement with exercise) can efficiently identify patients warranting rheumatologic evaluation [30]. Finally, developing and disseminating clear local referral algorithms that specify when to order HLA-B27 testing or sacroiliac joint MRI, and when to refer directly to a rheumatologist, could standardize and expedite the diagnostic pathway [31].

Notably, this investigation establishes the nr-axSpA phenotype as another independent risk factor for diagnostic prolongation. This inversely reflects current clinical practice, where definitive radiographic sacroiliitis (i.e., r-axSpA) remains the strongest diagnostic driver [7]. Diagnosing nr-axSpA patients lacking characteristic X-ray alterations, particularly females, presents greater challenges. This underscores the imperative need for wider implementation of sacroiliac joint MRI for early inflammation detection in suspicious populations [32]. MRI enables identification of active inflammation (e.g., bone marrow edema) preceding structural damage, which is crucial for improving early diagnosis rates [33].

Furthermore, this study is the first to identify concomitant uveitis as an independent risk factor for prolonged diagnostic delay in a Chinese female cohort. This finding aligns with recent results from a large-scale retrospective U.S. study [34]. Potential explanations include: uveitis patients may present with milder or underappreciated arthritis symptoms, leading to delayed rheumatology referral; alternatively, ophthalmologists might miss opportunities to screen for chronic back pain during consultations [34,35]. Therefore, proactive inquiry about chronic back pain history and subsequent referral to rheumatology for screening among uveitis patients represent crucial clinical strategies for reducing axSpA diagnostic delays [15].

The most clinically significant finding of this investigation is that longer diagnostic delay remains an independent predictor of poor disease control (higher ASDAS-CRP scores) at 12 months post-diagnosis, even after rigorous adjustment for baseline disease activity, disease phenotype, and therapeutic regimen. This discovery rests on solid pathophysiological grounds: prolonged uncontrolled inflammation during diagnostic latency may induce irreversible microstructural damage and immune system dysregulation, thereby diminishing subsequent treatment responsiveness [36]. This association was established in an exclusively female cohort, underscoring the critical importance of shortening delays for improving the prognosis of female patients. It suggests that the trend towards poorer long-term functional outcomes observed in female patients within mixed-gender studies may be partly attributed to the more prolonged and uncontrolled inflammatory phase they experience [37]. A systematic review has demonstrated associations between diagnostic delay and greater functional impairment, worse quality of life, and increased healthcare burden [6]. Our study extends these correlations from long-term radiographic outcomes to mid-term disease activity metrics, providing direct evidence for the "time is joint" concept and establishing a complete causal chain from diagnostic prolongation to adverse outcomes.

This study employed the ASDAS-CRP score as the primary outcome measure. ASDAS-CRP integrates objective inflammation biomarkers (CRP) and has demonstrated superior sensitivity to treatment response compared to patient-reported Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) alone, representing the internationally recommended gold standard that enhances result reliability and cross-study comparability [38]. Notably, baseline ASDAS-CRP emerged as one of the strongest prognostic factors in our cohort, highlighting the concept of "disease activity inertia"—where patients presenting with high inflammatory burden at diagnosis predictably exhibit diminished therapeutic responsiveness, necessitating longer time-to-target or intensified treatment regimens [39]. This suggests clinicians should adopt more aggressive therapeutic approaches and establish closer monitoring schedules for female patients with elevated baseline scores.

The observed association between csDMARDs (versus NSAID monotherapy) and poorer disease control at 12 months warrants careful interpretation and should not be construed as indicating a lack of efficacy of csDMARDs. This finding is most plausibly explained by significant treatment selection bias (also known as confounding by indication). In real-world clinical practice, csDMARDs are typically not the first-line therapy for active axial disease per current ASAS-EULAR management recommendations [40]. Instead, they are often prescribed in specific scenarios that are inherently associated with a more challenging disease course: for instance, in patients with predominant peripheral arthritis, those who have contraindications or insufficient response to NSAIDs, or as a bridging therapy while awaiting approval or initiation of biologic agents. Consequently, the csDMARD group in our study likely represents a patient subset with a higher baseline disease burden, more complex phenotypes, or suboptimal responses to prior therapies, all factors that contribute to a worse prognosis, independent of the csDMARD treatment itself. Our data thus reinforce the importance of adhering to evidence-based treatment sequences and highlight that in observational studies, treatment type is a potent marker of disease severity. Future prospective studies are needed to delineate the specific role of csDMARDs in female axSpA patients, after adequately accounting for these baseline differences.

Several limitations should be acknowledged. First, the single-center retrospective design carries inherent selection bias, necessitating multicenter prospective studies to validate findings and explore natural disease history. Second, diagnostic delay reliance on retrospective documentation introduces potential recall bias; future research could incorporate objective biomarkers or big-data modeling for precision assessment. Third, despite adjusting for known confounders, unmeasured variables like treatment adherence and psychosocial factors may constitute residual confounding, warranting systematic collection in subsequent investigations. Future research should prioritize multicenter prospective cohort designs tracking patients from symptom onset, which would not only mitigate referral bias but also enable comprehensive documentation of full diagnostic-therapeutic trajectories, thereby establishing stronger causal evidence for diagnostic delay-related outcomes.

Conclusion

In conclusion, this study demonstrates that in Chinese female patients with axSpA, suboptimal care pathways and misdiagnosis constitute the primary modifiable factors contributing to diagnostic delay, while longer delays independently predict poorer mid-term therapeutic outcomes. Based on this, we propose the following specific recommendations to shorten diagnostic delays and improve prognosis: (1) Promote education among orthopedists, rehabilitation specialists, and general practitioners regarding atyp-

ical symptoms in women and mandate the use of simple screening tools; (2) Establish and promote structured referral pathways that specify timely sacroiliac joint MRI and rheumatology referral when patients show poor response to first-line analgesic therapy or exhibit "red flag" signs of inflammatory back pain; (3) At the healthcare system level, explore incorporating sacroiliac joint MRI into early imaging evaluation protocols for suspected axSpA patients, particularly where primary care settings permit, to overcome the limited sensitivity of conventional radiography. Future multicenter prospective studies are warranted to validate these discoveries and explore the implementation of interventions based on our research findings, aiming to improve long-term outcomes for female axSpA patients.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

HCZ, ZJS, WHW and HLY designed the research study and wrote the first draft. JYZ, GYY and BHZ performed the research. XH and WHW analyzed the data. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the institutional ethics review board of The First Affiliated Hospital of Soochow University (approval number: 20251237) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before inclusion.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638205.40.

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