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Why Do Some Patients Have Severe Sacroiliac Disease But No Syndesmophytes in Ankylosing Spondylitis? Data From a Nested Case-Control Study

Lauren K. Ridley[1], Mark C. Hwang[2], John D. Reveille[2], Lianne S. Gensler[3], Mariko L. Ishimori[4], Matthew A. Brown[5], Mohammad H. Rahbar[6], Amirali Tahanan[7], Michael M. Ward[8], Michael H. Weisman[9], and Thomas J. Learch[10]

ABSTRACT. ***Objective.*** Sacroiliac (SI) joint and spinal inflammation are characteristic of ankylosing spondylitis (AS), but some patients with AS have been identified who have discordant radiographic disease. We studied an AS subgroup with long-standing disease and fused SI joints. We identified factors associated with discrepant degrees of radiographic damage between the SI joints and spine.

Methods. From the Prospective Study of Outcomes in AS (PSOAS) cohort, patients with a disease duration ≥ 20 years and fused SI joints were included in a nested case-control design. Patients with and without syndesmophytes were used as cases and controls for analysis. We used classification and regression tree (CART) analysis to determine risk factors for syndesmophytes presence and reexamined the validity of the risk factors using univariable logistic regression models.

Results. There were 354 patients in the subgroup, 23 of whom lacked syndesmophytes. CART analysis showed females were less likely to have syndesmophytes. The next important predictor was age of symptom onset in males, with age of onset ≤ 16 years being less likely to have syndesmophytes. Univariable analysis confirmed females were less likely to have syndesmophytes (odds ratio [OR] 0.17, 95% CI 0.07-0.41). Syndesmophyte presence was associated with HLA-B27 positivity (P = 0.03) and age of symptom onset > 16 years old (OR 2.72, 95% CI 1.15-6.45). All 23 patients who lacked syndesmophytes were HLA-B27 positive.

Conclusion. Using CART analysis and univariable modeling, women were less likely to have syndesmophytes despite advanced disease duration and SI joint disease. Patients with younger age of symptom onset were less likely to have syndesmophytes. All patients without syndesmophytes were HLA-B27 positive, indicating HLA-B27 positivity may be more associated with SI disease than spinal disease.

Key Indexing Terms: ankylosing spondylitis, cohort studies, spondyloarthropathy

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[1]L.K. Ridley, MD, John P. and Katherine G. McGovern Medical School, University of Texas Health Center at Houston, Houston, Texas, USA; [2]M.C. Hwang, MD, J.D. Reveille, MD, Division of Rheumatology and Clinical Immunogenetics, Department of Internal medicine, John P. and Katherine G. McGovern Medical School, University of Texas at Houston, Houston, Texas, USA; [3]L.S. Gensler, MD, Department of Medicine/Rheumatology, University of California San Francisco, San Francisco, California, USA; [4]M.L. Ishimori, MD, Division of Rheumatology, University of California San Francisco, San Francisco, California; [5]M.A. Brown, MD, PhD, Guy's & St Thomas' NHS Foundation Trust, and King's College London NIHR Biomedical Research Centre, London, UK; [6]M.H. Rahbar, PhD, Center for Clinical and Translational Studies, University of Texas at Houston Medical School, Houston, Texas, USA; [7]A. Tahanan, MS, Center for Clinical and Transnational Science, University of Texas Health Science Center at Houston, Texas, USA; [8]M.M. Ward, MD, MPH, National Institutes of Health, NIAMS/IRP, Bethesda, Maryland, USA; [9]M.H. Weisman, MD, Cedars-Sinai Medical Center, Los Angeles, California, USA; [10]T.J. Learch, MD, Department of Radiology, Cedars-Sinai Medical Center, Los Angeles, California, USA.

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Address correspondence to Dr. L.K. Ridley, 6431 Fannin Street, MSB 5.270, Houston, TX 77030, USA. Email: lauren.k.ridley@uth.tmc.edu.

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Ankylosing spondylitis (AS) is characterized by inflammation and subsequent damage to both the spine and sacroiliac (SI) joints. Spinal damage is manifested by the creation of bony bridges called syndesmophytes; bony fusion of the SI joints occurs as well. Nevertheless, there is a wide variety in eventual outcomes for these patients; some develop aggressive spinal inflammation hypothesized to lead to syndesmophytes, which in advanced disease can culminate in the prototypical "bamboo" spine. Yet, expert clinicians and radiologists are aware of patients in their practice who display fused SI joints with minimal radiographically demonstrated spinal damage. Further, there is little known about relationships in individual patients between the spine and the SI joint sites regarding the severity of inflammation and damage. Do the sites progress together or independently? Why do some patients have severe SI disease but no spinal disease, or marked spinal disease but little or no SI disease? Finally, are there risk factors or predictors for differences in progression between these 2 anatomic sites?

A number of factors have been proposed in previous publications as potential associations or even markers of spinal radiographic progression or severity. Longer disease duration and advanced sacroiliitis have been more associated with spinal fusion and not just syndesmophytes alone, and an elevated C-reactive protein (CRP) has been consistently correlated with spinal radiographic damage.[1,2] A study by Deminger et al revealed differences in predictors of spinal radiographic progression between men and women.[3] Baseline radiographic disease is an independent predictor for both genders, whereas high CRP and smoking were predictors in men.[3,4] HLA-B27 positivity has not been associated with spinal radiographic progression.[4] A study from a Chinese cohort of patients with AS revealed that age of onset, BMI, smoking, symptom duration, and hip involvement were significant predictors of spinal damage.[5] Increased dynamic stress or a blue-collar occupation has also been associated with increased radiographic damage.[6]

The Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) is a large, well-characterized longitudinal cohort with consistent standardized data collections of radiographic findings that has enabled investigators to observe what appear to be regional dissociations between radiographic disease severity in the spine vs the SI joints of subjects with AS. The size and scope of this cohort, with the long-term follow-up of subjects, has provided us with a relatively small subset of patients with long-standing disease and fused SI joints but comparatively little radiographic spinal disease. We examined this uncommon subset of patients with AS and compared them to participants with similar long-standing disease and fused SI joints who had definite radiographic syndesmophytes; the results of these studies and the exploration of risk factors for the findings are reported herein.

METHODS

Study population. The PSOAS cohort is an observational study of subjects with AS, initiated in 2002, that collected and examined predictors of severity and outcome in AS. Patients were included if they fulfilled modified New York (mNY) criteria for AS,[7] were at least 18 years old, and gave their written informed consent to participate. It includes patients with AS from 5 centers, each having study approval from their respective institutional review boards (approval number): Princess Alexandria Hospital in Brisbane, Australia (2005/221), Cedars-Sinai Medical Center in Los Angeles (CR00004630), the National Institutes of Health (03-AR-0131), the University of California at San Francisco (H63075-35456-01), and the University of Texas Health Science Center at Houston (HSC-MS-07-0022), USA. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients were recruited from a wide variety of sources including the investigators' clinics at academic medical centers, referrals from community rheumatologists, and patient support groups.

Data collection. A standard protocol was used for the clinical evaluation of the study patients. Demographic, social, and comorbidities were recorded. Comorbidities included cardiovascular disease, diabetes mellitus, and hypertension, as well as patients who currently smoke or previously smoked tobacco. Study visits were conducted every 4 to 6 months by the study site investigator and included disease activity and functional impairment questionnaires, CRP and erythrocyte sedimentation rate levels, and all medications and medication changes. For nonsteroidal antiinflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs, biologic agents, corticosteroids, analgesics, and muscle relaxers, changes in the dosage, frequency, and duration were recorded at each study visit. All data and medications were entered into REDCap.[8] Radiographs of the pelvis, lumbar spine, and cervical spine were taken at the baseline visit and every 2 years thereafter. Radiographic severity was measured using the Bath AS Radiology Index (BASRI) and the modified Stoke AS Scoring System (mSASSS).[9,10] Quality assurance for the data was performed by the Data Management and Statistical Core personnel. Details of the data collection and management have been published previously, including information on inter- and intraobserver reliability for radiograph assessment.[11]

Study design. This study is a nested case-control design within the prospectively followed PSOAS cohort. We selected as cases the subgroup of patients with bilateral grade IV SI joint disease who developed syndesmophytes. The controls were the subgroup of patients with bilateral grade IV SI joint disease but who did not have syndesmophytes.

Determination of variables and statistical analysis. We used classification and regression tree (CART) analysis to study the effect of different predictors on syndesmophyte formation in our selected subgroup population, that is, patients with at least 20 years disease duration and possessing bilateral grade IV (or fused) SI joint disease. The selection of this subgroup was based on the assumption that if we were to examine the presence of syndesmophytes in relation to radiographic severity and damage in the SI joint, those patients with at a minimum of 20 years of disease duration would have had sufficient time to develop syndesmophytes if this was going to happen at all. To create our study population as specific as we could to examine the relationship between the spine and the SI joints, we delineated the presence of syndesmophytes as mSASSS $\geq$ 2 at all levels of the cervical and lumbar spine. Lack of syndesmophytes in an individual patient was defined as mSASSS < 2 at all levels of the cervical and lumbar spine. Table 1 and Table 2 have the baseline characteristics for the study group subpopulation at the time of the last radiograph, or at the last study visit if the information was not available at the time of the last radiograph. We used R package to run CART analysis with ANOVA method for regression. We developed a univariable logistic regression model to reexamine those factors associated with syndesmophytes for this subgroup of patients. P values < 0.05 were considered significant.

For the creation of our models, we examined a number of possible predictors of syndesmophyte formation that were based on known and potential associations with joint damage. Binary (yes or no) variables were self-reported gender, HLA-B27 status, history of uveitis, presence of peripheral arthritis, smoking, presence of enthesitis (using the University

Table 1. Cross-sectional characteristics of the subgroup of participants with disease duration ≥ 20 years and grade IV SI joint disease at the time of the last radiograph (N = 354).

	Syndesmophytes, n = 331	No Syndesmophytes, n = 23
History of PsO, n (%)		
Yes	29 (8.8)	2 (8.7)
No	302 (91.2)	21 (91.3)
DMARD used, n (%)		
Yes	27 (8.2)	5 (21.7)
No	304 (91.8)	18 (78.3)
DMARD types, n (%)		
LEF	0 (0)	0 (0)
SSZ	12 (3.6)	1 (4.3)
AZA	3 (0.9)	1 (4.3)
MTX	10 (3)	2 (8.7)
HCQ	1 (0.3)	1 (4.3)
MMF	3 (0.9)	0 (0)
Auranofin (oral gold therapy)	0 (0)	0 (0)
Other	2 (0.6)	0 (0)
TNFi used, n (%)		
Yes	109 (32.9)	7 (30.4)
No	222 (67.1)	16 (69.6)
TNFi type, n (%)		
ETN	50 (15.1)	4 (17.4)
IFX	13 (3.9)	1 (4.3)
ADA	39 (11.8)	2 (8.7)
GOL	7 (2.1)	0 (0)
CZP	3 (0.9)	0 (0)
NSAIDs used, n (%)		
Yes	127 (38.4)	10 (43.5)
No	204 (61.6)	13 (56.5)
Comorbidities,[a] n (%)		
HTN	149 (45)	4 (17.4)
DM	36 (10.9)	0 (0)
Depression	66 (19.9)	7 (30.4)
Any CVD[b]	75 (22.7)	4 (17.4)
ESR, mean (SD)	16.3 (19.2)	10.9 (9.5)
CRP, mean (SD)	1.1 (1.7)	0.5 (0.6)
BASFI total score, mean (SD)	44.96 (25.8)	31.2 (27.7)
BASDAI total score, mean (SD)	3.9 (2.3)	3.3 (1.7)
mSASSS total score, mean (SD)	44.5 (22.0)	2.1 (2.4)
Disease duration, yrs, mean (SD)	41.97 (23.5)	46 (33.4)
BASRI score, mean (SD)	2.1 (2.7)	1.8 (2.2)

[a] Assessed at the participants' last available visit. [b] Including heart attack, coronary artery disease, congestive heart failure, atrial fibrillation, coronary artery bypass, pacemaker in place. ADA: adalimumab; AZA: azathioprine; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiological Index; CRP: C-reactive protein; CVD: cardiovascular disease; CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; ETN: etanercept; GOL: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; LEF: leflunomide; MMF: mycophenolate mofetil; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; PsO: psoriasis; SI: sacroiliac; SSZ: sulfasalazine; TNFi: tumor necrosis factor inhibitor.

of California, San Francisco Enthesitis Index),[12] presence of inflammatory bowel disease, and presence of hip disease (scored using the BASRI). The presence of hip disease was defined as a total BASRI score > 0. We examined BMI (calculated as weight in kilograms divided by height in meters squared) and divided it into normal (BMI of 18.5 to < 25), overweight (BMI of 25 to < 30), and obese (BMI of ≥ 30) based on standard values. Ethnicity was divided by non-Hispanic vs Hispanic. In the cohort, race was separated into the following groups: Black or African American, White, Asian, Native American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and mixed. Education level was dichotomized to high school graduation or less vs college level education or more. We also examined age of onset and divided this variable among age ≤ 16 years at symptom onset, 17 to 45 years at symptom onset, and > 45 years at symptom onset considering the juvenile idiopathic arthritis definition.[13] All of the variables and radiographs for this study were assessed at the participants' last available visit.

Table 2. Factors associated with syndesmophytes for patients with disease duration ≥ 20 years and grade IV SI joint disease based on univariable logistic regression model (N = 354).

	Syndesmophytes, n = 331	No Syndesmophytes, n = 23	OR (95% CI)	*P*
	n (%)			
Gender				
Male	286 (86.4)	12 (52.2)	5.83 (2.43-14.00)	< 0.01
Female	45 (13.6)	11 (47.8)	0.17 (0.07-0.41)	
Race				
White	288 (87)	18 (78.3)	1.86 (0.66-5.27)	0.24
Racial and ethnic minority groups[a]	43 (13)	5 (21.7)	0.54 (0.19-1.52)	
HLA-B27				
Positive	278 (84)	23 (100)	NA[b]	0.03
Negative	53 (16)	0 (0)	NA[b]	
Education level[c]				
High school or less	60 (18.1)	6 (26.1)	1.59 (0.60-4.21)	0.35
College or more	271 (81.9)	17 (73.9)	0.63 (0.24-1.66)	
Age of onset, yrs				
≤ 16	42 (13.7)	6 (31.6)	0.41 (0.15-1.10)	0.08
17-45	258 (84.3)	13 (68.4)	2.72 (1.15-6.45)	0.02
> 45	6 (2)	0 (0)	NA[d]	0.02
BMI[c]				
Normal (18.5 to < 25)	34 (28.6)	5 (45.4)	0.41 (0.14-1.18)	0.10
Overweight (25 to < 30)	42 (35.3)	4 (36.4)	0.69 (0.22-2.13)	0.52
Obese (≥ 30)	43 (36.1)	2 (18.2)	1.57 (0.36-6.92)	0.55
Smoker[c]				
Yes	32 (10.2)	4 (18.2)	0.51 (0.16-1.60)	0.25
No	282 (89.8)	18 (81.8)	1.96 (0.62-6.14)	
IBD[c]				
Yes	21 (6.5)	2 (9.5)	0.66 (0.14-3.03)	0.60
No	302 (93.5)	19 (90.5)	1.51 (0.33-6.94)	
Ever uveitis				
Yes	141 (43.8)	10 (45.5)	0.94 (0.39-2.23)	0.88
No	181 (56.2)	12 (54.6)	1.07 (0.45-2.55)	
Presence of hip disease[c,e]				
Yes	181 (55)	11 (47.8)	1.33 (0.57-3.11)	0.50
No	148 (45)	12 (52.2)	0.75 (0.32-1.75)	
Presence of enthesitis[c]				
Yes	66 (20.1)	5 (21.7)	0.91 (0.33-2.53)	0.85
No	262 (79.9)	18 (78.3)	1.10 (0.40-3.08)	
Presence of peripheral arthritis[c]				
Yes	76 (23)	4 (17.4)	1.42 (0.47-4.30)	0.54
No	254 (77)	19 (82.6)	0.70 (0.23-2.13)	

No. of missing data in each of the 2 groups (Syndesmophytes and No Syndesmophytes, respectively): age at onset: 25, 4; BMI: 212, 12; smoker: 17, 1; IBD: 8, 2; ever uveitis: 9, 1; presence of hip disease: 2, 0; presence of enthesitis: 3, 0; presence of peripheral arthritis: 1, 0. [a] Includes Hispanic or Latino, Black, Asian, Native American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or mix. [b] All patients with no syndesmophytes were HLA-B27 positive. [c] Assessed at the participants' last available visit. [d] All patients with age of onset > 45 years have syndesmophytes. [e] Presence of hip disease is defined as total BASRI score > 0. BASRI: Bath Ankylosing Spondylitis Radiological Index; IBD: inflammatory bowel disease; NA: not applicable; OR: odds ratio; SI: sacroiliac.

RESULTS

Patient population. From the March 2019 dataset of the PSOAS cohort, 1289 patients qualified for the study. Of these, 136 were excluded because of lack of complete important information (no baseline Background Information Questionnaire [BIQ] data, radiographic data on SI joints or vertebral corners, or disease duration data). BIQ included demographic information, patient education, employment status, affected joints, medication information, and smoking information. Of the remaining 1153 patients, only those patients with bilateral grade IV SI joint disease were included; of these 556 patients, an additional 202 were excluded with disease duration (from the time of inflammatory back pain onset) < 20 years. The remaining 354 patients were divided into those that had syndesmophytes and those without syndesmophytes as per the above definition. This is summarized in Figure 1.

Statistical analysis. Using data from cases and controls, we performed logistic regression to examine factors associated with syndesmophytes. The analysis included computation of odds ratios (OR) and 95% CI. Using univariable logistic regression modeling for the 354 patients with ≥ 20 years duration of disease, we confirmed females were less likely to have syndesmophytes

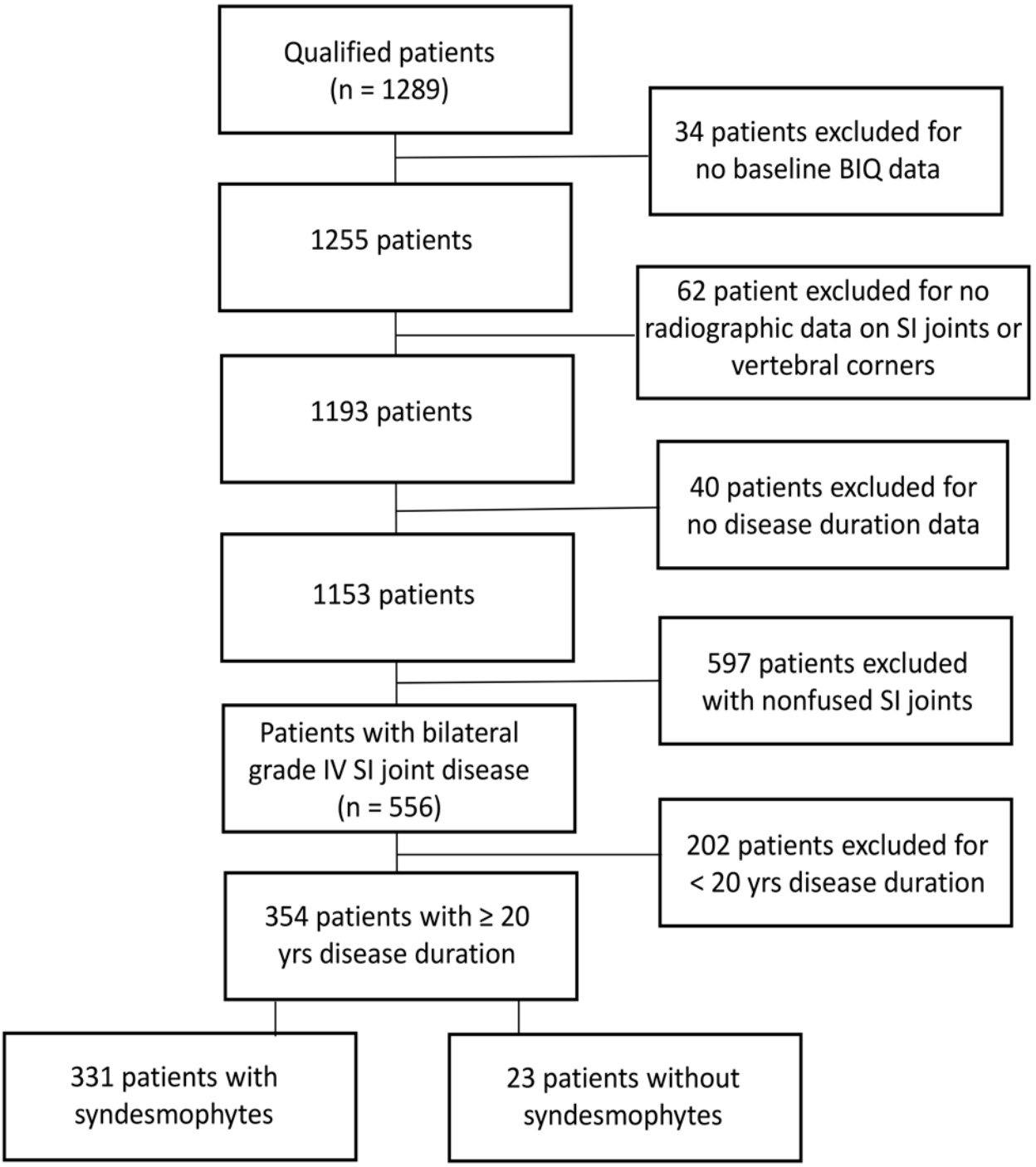

Figure 1. Flow diagram of the numbers of patients used for analysis, from the March 2019 dataset from the PSOAS cohort. BIQ: Background Information Questionnaire; PSOAS: Prospective Study of Outcomes in Ankylosing Spondylitis; SI: sacroiliac.

(OR 0.17, 95% CI 0.07-0.41; Table 2). Univariable analysis also showed that there was a greater risk of syndesmophyte presence with HLA-B27 positivity ($P = 0.03$) and age of symptom onset > 16 years old (age 17-45 yrs [OR 2.72, 95% CI 1.15-6.45] and age > 45 yrs [$P = 0.02$]; Table 2).

In this subgroup of 354 patients with fused SI joints accompanied by long disease duration, there were 23 patients, or 7% of the subgroup, who lacked syndesmophytes. Using CART analysis (Figure 2), we found that gender was the strongest predictor of either presence or absence of syndesmophytes. Male gender accounted for 84% of the 354 patients, with only 4% lacking syndesmophytes (Figure 2). Age of symptom onset was the next most important factor for the male subgroup on the CART analysis. Ten percent of males had age of symptom onset 16 years old or less, and of these, 11% lacked syndesmophytes. For age of symptom onset over 16 years old, this was 74% of males and only 3% of these lacked

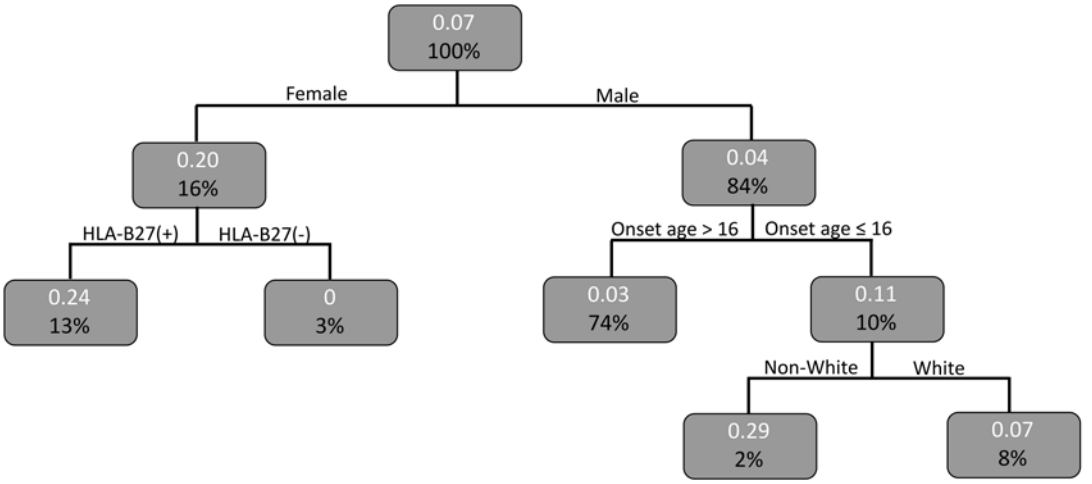

Figure 2. CART analysis. Values in white represent the likelihood of not having syndesmophytes. Values in black are the percentages of the total subgroup population. CART: classification and regression tree.

syndesmophytes (Figure 2). For age of onset ≤ 16 years, 2% of this subgroup were non-White but 29% lacked syndesmophytes.

Female gender accounted for 16% of the group. Of these 56 women, 20% did not have syndesmophytes despite fused SI joints and long disease duration (Figure 2). The next best association for female gender was HLA-B27 status, with HLA-B27 positivity being 13% of the subgroup and 24% of them lacking syndesmophytes (Figure 2).

Interestingly, all 23 participants who did not have syndesmophytes were HLA-B27 positive.

The only examined variable where there was a significant amount of missing data was BMI; this occurred in 234 of the 354 patients (weight was only collected consistently for visits after 2012). There were no underweight patients, that is, patients with a BMI < 18.5.

DISCUSSION

In this study, we examined associations and predictors for a small but unique subgroup of patients with AS with SI joint fusion and at least 20 years of disease duration, but who do not have radiographic syndesmophytes. Of our subgroup, 7% of patients lacked syndesmophytes. Using CART analysis and logistic regression modeling, we found that gender was the most important variable in this phenotype, with women being less likely to have syndesmophytes despite having complete SI fusion. Age of symptom onset may also be an important variable in this subgroup in particular, as males who had a younger age of symptom onset (≤ 16) were less likely to have syndesmophytes.

Comparing male and female gender subjects regarding radiographic severity has revealed inconsistent findings across studies. Greater spinal radiographic severity in men compared to women has been reported in a number of studies, independent of other variables.[14,15,16] Previous studies have also shown that women tend to have a younger age of onset[15,17] but not how age of onset can affect radiographic damage in concert with gender. In addition, other groups have shown that, compared to men, women are more likely to be diagnosed with nonradiographic axial disease.[18,19] In one study of female patients with AS, the development of new syndesmophytes was associated with long disease duration, older age, severe sacroiliitis, and baseline presence of syndesmophytes.[20] However, no study that we know of has examined the unique population who have fused SI joints with absent syndesmophytes after long disease duration.

Because of the sheer size of our database, our study is distinct in the ability to assess this subpopulation, but there are several limitations. First, we selected for comparison purposes a subtype with limited spinal involvement vs that with overt spinal involvement; it is possible that there may be other ways to separate cases using different criteria. In addition, there is an inherent bias in this cohort because in order to qualify, participants are required to meet mNY criteria for AS, which consist of bilateral SI joint damage that is recognizable and visible on plain radiographs. Thus, by definition they must have a level of severity manifested by recognizable radiographic disease in their SI joints to even be entered into the study. Another limitation is the use of mSASSS, which, as a scoring tool to look at radiographic changes over time in the cervical and lumbar spines, unfortunately does not include radiographic changes in the thoracic spine or zygapophyseal joints, both of which were not included in this dataset. Finally, we chose to create these subtypes for examination of our hypothesis because it was assumed that having fused SI joints and at least 20 years of disease duration would include only those subjects who would not be expected to have syndesmophytes as part of their AS. Therefore, this was a relatively small sample size, with only 23 participants of the 354 in the subgroup who did not have syndesmophytes. Use of NSAIDs or tumor necrosis factor inhibitors have been shown to possibly alter radiographic progression,[21,22] but because of the cross-sectional nature of this study, we were unable to assess for their influence. Additionally, radiographs have their own limitations to identify the presence of syndesmophytes, and it is unknown if spinal magnetic resonance imaging or computed tomography in the participants who lacked syndesmophytes would have revealed more spinal disease.

Women appear to have a different phenotype in AS; we found that they are less likely to form syndesmophytes despite fused SI joints with at least 20 years of disease duration. We do not understand the reasons behind these differences among the possibilities of genetic, hormonal, and biomechanical factors. Intriguingly, all in the nonsyndesmophyte group were HLA-B27 positive. There is likely a complex interplay of factors leading to differences in radiographic damage between the SI joints and the spine in AS, and it is interesting to consider if HLA-B27 may have more effect on SI joint damage than spinal damage. This was a small study, and further studies are needed to elucidate why AS disease may behave differently in this and other subgroups.

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