

MRI Contributes to Accurate and Early Diagnosis of Non-Radiographic HLA-B27 Negative Axial Spondyloarthritis

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Research

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Abstract

Background

Structural changes to sacroiliac joints cannot be adopted to confirm active sacroiliitis on magnetic resonance imaging in the absence of bone marrow edema (BME). However, less than half of Asian patients with axial spondyloarthritis were characterized by BME. We aim to define the best methodology for accurate diagnosis, especially in the area with less common bone marrow edema and serum human leukocyte antigen-B27 (HLA-B27).

Methods

We included 103 patients with inflammatory back pain and morning stiffness in this prospective study. No radiograph met the definition of positive modified New York criteria. Inflammation and structural damage on magnetic resonance imaging were evaluated. Serum c-reactive protein and HLA-B27 levels were collected. Correlations between the various collected variables were analyzed.

Results

We demonstrated a positive association between inflammatory lesions and structural damage in the 58 ASAS-defined nr-axSpA subjects. BME on magnetic resonance imaging is moderately correlated with sclerosis and focal joint space widening (fJSW) (phi score of 0.372 and 0.319, $p = 0.005$ and 0.015 , respectively). A moderately positive correlation between either the severity of BME and fJSW ($p = 0.004$) in 36 patients who had BME and met Assessment of Spondyloarthritis international Society criteria. There is a positive correlation between BME and fJSW across the whole cohort (phi score of 0.389; $p < 0.001$). We also identified a positive correlation between fJSW and BME in patients with non-radiographic axial spondyloarthritis and normal serum c-reactive protein levels (phi score of 0.362 and $p = 0.001$).

Conclusion

Severe erosions like fJSW on MRI-SIJs is positively correlated with development of BME on MRI and helps contribute to accurate diagnosis of non-radiographic axial spondyloarthritis either in the absence of HLA-B27 or normal serum inflammatory biomarkers, which might be used alternatively for early diagnosis of non-radiographic axial spondyloarthritis in Asian people who are characterized by less prevalence of BME and HLA-B27.

Background

Spondyloarthropathies (SpAs) are a group of chronic inflammatory rheumatic diseases that share overlapping features such as sacroiliitis, enthesitis, extra-articular manifestations including acute anterior uveitis, psoriasis, and inflammatory bowel disease (IBD), HLA-B27 positivity and familial aggregation [1-3]. Axial SpA (axSpA), describing a spectrum of predominant symptoms of chronic inflammatory back pain (IBP), can be diagnosed as either radiographic axSpA, such as ankylosing spondylitis (AS), or nonradiographic axSpA (nr-axSpA), depending on the presence or absence of radiographic sacroiliitis, respectively [4-5]. AxSpAs includes inflammation of the sacroiliac joints (SIJs), facet joints, and spinal entheses, which result in IBP, fatigue, stiffness, and ankyloses [6]. The classification criteria of the Assessment of Spondyloarthritis international Society (ASAS) have been widely used for diagnosis of axSpA [7-8].

Magnetic resonance imaging (MRI) is able to detect both inflammatory lesions like bone marrow edema (BME) and structural damage at SIJs and spines in patients with radiographic axSpA and is capable of depicting inflammatory lesions before the development of detectable structural changes on radiography or computed tomography (CT) of SIJs [7-8, 31]. The benefits of MRI-SIJs are that the high soft tissue and bone marrow contrast facilitates detecting BME, that help confirm the diagnosis of the nr-axSpA. MRI-SIJs has been enrolled for imaging criteria in the ASAS classification criteria for axSpA [9-10]. However, limitations of MRI-SIJs include the unpredictable interval between the development of structural damage visible on radiographs and the clinical diagnosis [11-15].

Experts generated the ASAS definition of axSpA based only on inflammatory lesions, while structural damage at SIJs has not yet been employed. Nonetheless, BME can be found in healthy people, running enthusiasts, and women postpartum [34-36]. Remission of inflamed bone marrow induced structural damage on MRI-SIJs. The question of whether structural damage should be added to this definition remains controversial. Literatures indicate MRI-SIJs can detect bone erosion early in the disease course [16]. Previous data indicated that less than half of axSpA patients were positive for active sacroiliitis on MRI-SIJs [17-19, 31], which is consistent with our real-world experience. In addition, in patients with an early phase of axSpA, HLA-B27 is associated with more prominent inflammation on MRI-SIJs, whereas serum inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are incapable of predicting early sacroiliitis. Whether HLA-B27 is associated with structural damage to SIJs remains unknown. All of these factors contribute to the difficulty in defining nr-axSpA patients with ethnicity who might have less common prevalence of BME on MRI-SIJs and serum HLA-B27. In the clinic, we often noticed that patients with chronic IBP did not have abnormal serum CRP or ESR either in the presence or absence of HLA-B27, even those who demonstrated multiple clinical characteristics of axSpA, which causes the prevalence of nr-axSpA to be underestimated.

The goals of this study were (1) to demonstrate the incidence of BME and structural damage on MRI-SIJs in the local population with clinical IBP and suspected nr-axSpA; (2) to identify whether structural damage on MRI-SIJs help contribute to an accurate diagnosis of nr-axSpA either in the presence or absence of HLA-B27 since we hypothesized that structural damage should be relevant to the inflammation on MRI-SIJs and capable of being applied as a diagnostic tool for axSpA; and (3) to determine the best imaging modality for an accurate diagnosis of nr-axSpA in the absence of serum HLA-B27, which might be warranted in certain ethnicity.

Methods

This prospective cohort study was conducted from 2014 to 2017 and all patients are Taiwanese. Patients ≥ 16 years with chronic IBP (duration ≥ 3 months, onset < 45 years, origins unknown) and morning stiffness were recruited into the cohort in clinics of the division of rheumatology at a medical center. This study has been approved by the Institutional Review Board of Tri-Service General Hospital with waiving of the informed consent form, No. 2-106-05-106. Weight-bearing issues, over-exercise, trauma events, and postpartum effects were excluded. Ethics committee approval was obtained, and all patients gave their written informed consent. Patients were examined by rheumatologists for the presence of SpA features according to the ASAS criteria [20]. The imaging arm of SpA criteria included radiographic sacroiliitis [modified New York criteria (mNY)] [21], or sacroiliitis on MRI-SIJs [10, 22]. Clinical evaluation of disease activity included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Scores (ASDAS) [23-24]. All participants had been presented and discussed on the basis of examinations by two experienced radiologists and eight rheumatologists with an interest and experience in both axSpA, conventional radiographs and MRI-SIJs.

All 103 patient participants were clinically suspected as having axSpA and none of them met mNY criteria on conventional radiographs [5, 10, 21]. 36 patients (group 1) had "positive MRI-SIJs" [MRI(+)/mNY(-)] and ≥ 1 SpA feature and fulfill the ASAS criteria for axSpA. Among these 67 MRI(-)/mNY(-) patient participants, there was a subgroup of 22 HLA-B27-positive patients with ≥ 2 additional clinical SpA features (group 2) [MRI(-)/mNY(-)/HLA-B27(+)], who met the ASAS criteria for axSpA. 45 patients were classified into a triple-negative subgroup [MRI(-)/mNY(-)/HLA-B27(-)] (group 3). Patient participants in group 3 had a high possibility of axSpA because of the presence of both IBP and a good response to NSAIDs, plus at least one more SpA feature from the clinical arm (psoriasis, dactylitis, uveitis, heel enthesitis, peripheral arthritis, or positive family history for SpA). A complete and detailed description on how patient participants were classified is presented in Table 1.

MRI assessment

Patients underwent MRI-SIJs performed using a 1.5 T scanner. Multiple sequences (coronal and axial T1-weighted spin echo, coronal and axial short-tau inversion recovery (STIR)) were performed with a slice thickness of 4 mm. The MRI-SIJs were acquired in an oblique coronal plane [25]. Two well-trained musculoskeletal radiologists independently scored all MRIs with both sequences viewed simultaneously. BME and structural damage to SIJs were evaluated based on ASAS and OMERACT definitions [7, 22]. We adopted the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system to evaluate the severity of inflammation on MRI-SIJs [16]. Sclerosis and erosions were defined as previously published [10, 26-28]. We noticed that some patients in the cohort showed bone erosions at SIJs, which lead to focal joint space widening (fJSW) (Figure 1), which was not noted on conventional radiographs by reconfirmation. For intrareader reliability, the MRI interpretation was measured with Fleiss kappa coefficients [29-30]. Kappa values of both site of SIJs were higher than 0.6.

Statistical analyses

Patient demographic information and characteristics are summarized as frequencies and percentages for categorical values, and are presented as the mean and standard deviation, as appropriate, for continuous variables. An association between the severity of BME and structural damage on MRI-SIJs was calculated using Spearman's rho scores for small population. Differences between categories of structural damage and presence or absence of HLA-B27 on grades of BME on MRI-SIJs (SPARCC scores) and ASDAS-CRP scores were calculated using a Mann-Whitney *U* test. Associations and strength between categories of structural damage and presence or absence of HLA-B27 were calculated using Pearson chi-square and phi coefficient scores. Analyses were performed using SPSS for Windows, version 15.0.1.1 (SPSS Inc, Chicago, IL).

Results

Demographics and disease activity scores of patients are listed in Table 1.

Imaging of SIJs

Average BME SPARCC scores in group 1 were 6.73 ± 7.725 (Table 1). HLA-B27 positive subjects in group 1 had higher mean SPARCC scores than those without HLA-B27 ($p = 0.015$). In group 1, 97.2%, and 44.4% patients had erosions, or fJSW. There were significant positive correlations between SPARCC scores and sclerosis, fJSW, or the triple positive of sclerosis, erosion, and fJSW ($p = 0.001, 0.004, \text{ and } 0.001$, respectively, Table 2). In group 2, we identified 100% and 13.6% of patients with erosions, and focal JSW, respectively (Table 1). In the present cohort, 58 patients (from groups 1 and 2) fulfilled ASAS classification criteria; 98.3%, and 32.8% of these patients had erosions, or fJSW, respectively (Table 1). Between inflammatory lesions and structural damage in these 58 ASAS-defined nr-axSpA subjects, BME on MRI-SIJs is moderately correlated with sclerosis and fJSW (phi score of 0.372 and 0.319, $p = 0.005$ and 0.015, respectively). BME was positively correlated with triple-positive signs of structural damage including sclerosis, erosions, and focal fJSW (phi score of 0.294, $p = 0.025$). Thus, we demonstrated a significantly positive correlation between either the presence or the severity of BME and fJSW in patients with nr-axSpA meeting the ASAS definition. Moreover, a similar positive correlation was found when patients were characterized by simultaneous presence of sclerosis, erosions, and fJSW.

	Age (yr)	Gender Male (%)	BASDAI	ASDAS-CRP	ASDAS-ESR	Abnormal serum CRP (%)	Abnormal serum ESR (%)	BME of MRI-SIJs (SPARCC scores)	Structural damage of MRI-SIJs				
									Sclerosis	Erosion	fJSW	Double positive [†]	Triple positive [‡]
Group 1 (n = 36)	31.3 ± 11.99	75%	2.47 ± 1.50	2.19 ± 0.66	1.90 ± 0.81	30.6%	33.3%	6.73 ± 7.73	77.8%	97.2%	44.4%	33.3%	30.6%
Group 2 (n = 22)	31.59 ± 12.51	86.4%	1.98 ± 0.82	1.86 ± 0.85	1.60 ± 0.60	22.7%	18.2%	NA	40.9%	100%	13.6%	27.3%	13.6%
Group 3 (n = 45)	30.09 ± 13.78	66.7%	2.36 ± 0.89	2.03 ± 0.59	1.73 ± 0.59	20%	24.4%	NA	51.1%	93.3%	8.9%	37.8%	8.9%
Group 1+2 [#] (n = 58)	31.41 ± 12.08	79.3%	2.28 ± 1.27	2.06 ± 0.75	1.79 ± 0.75	27.6%	27.6%	4.83 ± 6.85	63.8%	98.3%	32.8%	32.8%	31.0%
Group 1+2+3 (n = 103)	32.15 ± 12.81	73.8%	2.32 ± 1.12	2.05 ± 0.68	1.76 ± 0.68	24.3%	26.2%	2.49 ± 5.46	58.3%	96.1%	22.3%	35.0%	21.4%

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Scores; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BME, bone marrow edema; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; fJSW, focal joint space widening; ASAS, Assessment of Spondyloarthritis international Society; nr-axSpA, nonradiographic spondyloarthritis; Group 1, [MRI(+)/ mNY(-)]; Group 2, [MRI(-)/ mNY(-)/ HLA-B27(+)]; Group 3, [MRI(-)/ mNY(-)/ HLA-B27(-)]; NA, not applicable; [†]Double positive, dual presence of sclerosis and erosion on MRI-SIJs; [‡]Triple positive, simultaneously presence of sclerosis, erosion, and fJSW on MRI-SIJs; [#]group 1+2, ASAS defined nr-axSpA

	nr-axSpA (n = 103) (p value)	HLA-B27(+) (n = 41) (p value)	HLA-B27(-) (n = 62) (p value)	BME(+)/mNY(-) (group 1: n = 36) (p value)
Sclerosis (+) vs. (-)	3.98 vs. 0.40 (<0.001)***	5.77 vs. 0.67 (0.002)**	2.62 vs. 0.25 (0.161)	8.54 vs. 2.13 (0.001)**
Erosion (+) vs. (-)	2.57 vs. 0.50 (0.663)	3.90 vs. 0.00 NA (all (+))	1.62 vs. 0.50 (1.000)	7.26 vs. 2.00 (0.500)
fJSW (+) vs. (-)	7.52 vs. 1.04 (<0.001)***	8.58 vs. 1.97 (< 0.001)***	6.36 vs. 0.51 (0.005)**	1.81 vs. 4.15 (0.004)**
Double positive [†] (sclerosis/erosion) vs. (-)	2.82 vs. 1.86 (0.942)	3.36 vs. 4.19 (0.734)	0.91 vs. 1.90 (0.422)	5.15 vs. 8.22 (0.474)
Triple positive [‡] (sclerosis/erosion/fJSW) vs. (-)	7.82 vs. 1.04 (< 0.001)***	8.58 vs. 1.97 (0.001)**	6.90 vs. 0.52 (0.005)**	11.47 vs. 4.00 (0.001)**

Scores were evaluated by two experienced radiologists by consensus. For intrareader reliability, the MRI interpretation was measured with Fleiss kappa coefficients. SPARCC, Spondyloarthritis Research Consortium of Canada; fJSW, focal joint space widening; NA, not applicable; [†]Double positive, dual presence of sclerosis and erosion on MRI-SIJs; [‡]Triple positive, simultaneously presence of sclerosis, erosion, and fJSW on MRI-SIJs; **p value < 0.01; ***p value < 0.001

Among 45 patients in group 3; 93.3%, and 8.9% had erosions, and fJSW, respectively (Table 1). In the entire cohort, all had clinical IBP and at least one abnormal finding on MRI-SIJs, including BME or structural damage. Sixteen of 23 patients with fJSW had BME, while 20 of 80 patients without fJSW had BME ($p < 0.001$). 22 patients had sclerosis, erosions, and fJSW, and 15 had BME on MRI-SIJs. Of the other 81 patients, 22 had BME ($p < 0.001$). There is a positive

correlation between BME and sclerosis or fJSW (phi score of 0.290 and 0.389; $p = 0.003$ and < 0.001 , respectively). There is also positive correlation between BME and the simultaneous presence of sclerosis, erosions, and fJSW (phi score of 0.363; $p < 0.001$; Table 3).

Table 3 Associations and strengths between the presence of BME and structural damage of MRI-SIJs in 103 nr-axSpA subjects (Pearson Chi-Square & phi scores)										
	Sclerosis		Erosion		JSW		Double positive (sclerosis/erosion)		Triple positive (sclerosis/erosion/JSW)	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
BME (+) (%)	28/60 (47.7%)	8/43 (18.6%)	35/99 (45.4%)	1/4 (25%)	16/23 (69.6%)	20/80 (25%)	13/36 (36.1%)	23/67 (34.3%)	15/22 (68.2%)	21/81 (25.9%)
χ^2 p value	0.004**		0.670		< 0.001***		0.856		< 0.001***	
phi scores p value	0.290		0.042		0.389		0.018		0.363	
BME, bone marrow edema; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; nr-axSpA, nonradiographic spondyloarthritis; JSW, joint space widening; ** p value < 0.01; *** p value < 0.001; phi scores were used for association measure between binary variables										

In addition, there is a positive correlation between SPARCC scores and sclerosis (0.4 in sclerosis negative subjects vs. 3.98 in sclerosis positive subjects, $p < 0.001$) in the entire cohort. We also identified positive correlation between SPARCC scores and fJSW (1.04 in fJSW negative subjects vs. 7.52 in fJSW positive subjects, $p < 0.001$). There was positive correlation between SPARCC scores and the simultaneous triple-positive presence of sclerosis, erosions, and fJSW ($p < 0.001$) (Table 4). The data indicate that not only is BME correlated with fJSW, but also the severity of BME is positively correlated with fJSW.

Patients in the entire cohort with fJSW had higher ASDAS-CRP scores ($p = 0.01$, respectively). Subjects with both sclerosis and erosions had higher ASDAS-CRP scores ($p = 0.04$). Subjects triple positive for sclerosis, erosions, and fJSW had significantly higher ASDAS-CRP scores ($p = 0.02$, respectively) (Table 4).

Table 4 Difference between structural damage and the presence/absence of HLA-B27 on the severity of BME (SPARCC scores) or ASDAS-CRP level in nr-axSpA subjects (Mann-Whitney U test)			
Presence (+) vs. absence (-) of structural damage	HLA-B27(+) n = 41	HLA-B27(-) n = 62	nr-axSpA n = 103
SPARCC scores			
Sclerosis (+) vs. (-)	5.77 vs. 0.67 (0.002)**	2.62 vs. 0.25 (0.161)	3.98 vs. 0.40 (<0.001)***
Erosion (+) vs. (-)	3.90 vs. 0.00 NA [#]	1.62 vs. 0.50 (1)	2.57 vs. 0.50 (0.663)
JSW (+) vs. (-)	8.58 vs. 1.97 (< 0.001)***	6.36 vs. 0.51 (0.005)**	7.52 vs. 1.04 (<0.001)***
Double positive [†] (sclerosis/erosion) vs. (-)	3.36 vs. 4.19 (0.734)	0.91 vs. 1.90 (0.422)	2.82 vs. 1.86 (0.942)
Triple positive [‡] (sclerosis/erosion/JSW) vs. (-)	8.58 vs. 1.97 (0.001)**	6.90 vs. 0.52 (0.005)**	7.82 vs. 1.04 (< 0.001)***
ASDAS-CRP scores			
Sclerosis (+) vs. (-)	2.04 vs. 2.02 (0.678)	2.03 vs. 2.09 (1)	2.04 vs. 2.06 (0.848)
Erosion (+) vs. (-)	2.03 vs. 0.00 NA	2.04 vs. 2.23 (0.308)	2.04 vs. 2.23 (0.270)
fJSW (+) vs. (-)	2.38 vs. 1.89* (0.034)	2.31 vs. 2.00 (0.074)	2.34 vs. 1.96* (0.010)
Double positive [†] (sclerosis/erosion) vs. (-)	1.76 vs. 2.18 (0.108)	1.91 vs. 2.14 (0.199)	1.85 vs. 2.15 (0.050)
Triple positive [‡] (sclerosis/erosion/fJSW) vs. (-)	2.38 vs. 1.89* (0.034)	2.27 vs. 2.02 (0.173)	2.33 vs. 1.97* (0.020)
BME, bone marrow edema; SPARCC, Spondyloarthritis Research Consortium of Canada; ASDAS, Ankylosing Spondylitis Disease Activity Scores; CRP, C-reactive protein; fJSW, focal joint space widening; nr-axSpA, nonradiographic spondyloarthritis; NA, not applicable; [†] Double positive, dual presence of sclerosis and erosion on MRI-SIJs; [‡] Triple positive, simultaneously presence of sclerosis, erosion, and fJSW on MRI-SIJs; [#] All HLA-B27 (+) patients have erosions on MRI-SIJs; *p value < 0.05; ** p value < 0.01; *** p value < 0.001			

Correlations between disease activity, inflammatory biomarkers, and MRI-SIJ imaging

Our data showed that 30.6%, 22.7%, and 20% subjects in groups 1, 2, and 3 had increased serum CRP levels, respectively (Table 1), and that 25 of 36 patients in group 1 had BME and normal serum CRP levels, which indicated that symptomatic nr-axSpA subjects with acute inflammation of bone marrow would still have normal serum CRP levels, and mirrored the other challenge of accurately diagnosing nr-axSpA with IBP, but normal CRP. We also demonstrated the same phenotype using serum ESR level in this cohort (Table 1). We noticed that some patients with IBP, who met ASAS criteria in the presence of mNY criteria, did not have abnormal serum CRP and ESR in our clinical practice. In the clinic, we also found some patients with nr-axSpA who met ASAS criteria had normal serum CRP and ESR levels. According to the policy of the health insurance system in some countries, these radiographic and nr-axSpA patients cannot be prescribed biological agents, which might predispose axSpA patients with normal serum CRP to radiographic progression. We classified all 103 patients with nr-axSpA into groups with either normal or increased CRP levels. Patients with increased serum CRP levels had higher ASDAS-CRP levels ($p < 0.001$). Patients with higher serum CRP levels had higher ASDAS-ESR scores ($p < 0.001$). There is no association between serum CRP and BASDAI ($p = 0.08$) (data not shown here). We classified the cohort into HLA-B27 positive and negative groups and demonstrated the same correlation in each group (data not shown here). In addition, serum CRP or ESR level was not associated with either BME, SPARCC scores, or structural damage, including sclerosis, erosions, and fJSW (data not shown here).

Difference between HLA-B27 positive and negative nr-axSpA

We classified 103 nr-axSpA patients into two groups; serum HLA-B27 positive ($n = 42$) and negative ($n = 61$). Higher prevalence and greater severity of BME were noticed in HLA-B27 positive patients, compared with those without HLA-B27 ($p = 0.049$ and 0.006 , respectively). We analyzed whether inflammation is

correlated with structural damage in each group. Among HLA-B27-positive patients, more severe BME was identified in patients with sclerosis on MRI-SIJs ($p = 0.001$). In both HLA-B27-positive and -negative groups, BME was more common in the presence of fJSW (phi scores of 0.370 and 0.377, $p = 0.018$ and 0.003, respectively). BME was significantly prevalent in triple-positive patients with sclerosis, erosions, and fJSW ($p = 0.018$ and 0.012, respectively) (Table 5). In the HLA-B27-positive group, higher SPARCC scores were noted in patients with sclerosis ($p = 0.002$). In both HLA-B27-positive and -negative groups, SPARCC scores were higher in patients with fJSW ($p < 0.001$ and $= 0.005$). For subjects triple positive for sclerosis, erosions, and fJSW, SPARCC scores were significantly higher in the groups of both HLA-B27-positive and -negative patients ($p = 0.001$ and 0.005, respectively) (Table 4).

In the HLA-B27-positive group, patients with increased serum CRP level had significantly higher BASDAI scores compared with those with normal serum CRP levels ($p = 0.016$). In both HLA-B27-positive and -negative groups, patients with increased CRP levels had higher ASDAS-CRP scores (both $p < 0.001$, respectively). In the HLA-B27-positive group, patients with fJSW had significantly higher ASDAS-CRP scores ($p = 0.034$). In the HLA-B27-negative group, patients with fJSW had higher BASDAI scores ($p = 0.028$). In the HLA-B27-positive group, patients triple positive for sclerosis, erosions, and fJSW had significantly higher ASDAS-CRP scores ($p = 0.034$) (Table 4).

Table 5 Associations and strengths of the presence of BME and structural damage on MRI-SIJs in HLA-B27(+) and HLA-B27(-) nr-axSpA subjects, respectively (Pearson Chi-Square & phi scores)				
	Structural damages	BME (+) vs. BME (-)	<i>p</i> value	phi scores
HLA-B27(+) n = 42	Sclerosis (+)	65.4% vs. 34.6%	0.001**	0.503
	Erosion (+)	100% vs. 0%	NA	NA
	JSW (+)	75% vs. 25%	0.018*	0.370
	Double positive [†]	57.1% vs. 42.9%	0.318	0.156
	Triple positive [‡]	75% vs. 25%	0.018	0.370
	Abnormal serum CRP	35.7% vs. 64.3%	0.429	0.100
	Abnormal serum ESR	63.6% vs. 36.4%	0.179	0.210
HLA-B27(-) n = 61	Sclerosis (+)	32.4% vs. 67.6%	0.337	0.122
	Erosion (+)	27.6% vs. 72.4%	0.911	0.014
	fJSW (+)	63.6% vs. 36.4%	0.003**	0.377
	Double positive [†]	22.7% vs. 77.3%	0.539	-0.078
	Triple positive [‡]	60% vs. 40%	0.012*	0.320
	Abnormal serum CRP	54.5% vs. 45.5%	0.524	0.100
	Abnormal serum ESR	31.3% vs. 68.7%	0.690	0.051

BME, bone marrow edema; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; nr-axSpA, nonradiographic spondyloarthritis; fJSW, focal joint space widening; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; NA, not applicable; [†]Double positive, dual presence of sclerosis and erosion on MRI-SIJ; [‡]Triple positive, simultaneously presence of sclerosis, erosion, and fJSW on MRI-SIJ; * p value < 0.05 ; ** p value < 0.01 ; phi scores were used for association measure between binary variables

Discussion

In the present study, we aimed to determine the best imaging methodology to help confirm the accurate diagnosis of nr-axSpA in the presence or absence of bone marrow edema on MRI-SIJ and in the absence of HLA-B27, because BME and HLA-B27 are less common in Asia. Published data indicate increasingly that structural lesions such as fat dysplasia and bone erosions of MRI-SIJ are relevant to axSpA [32-33, 38-39]. Thus, clarification of the definition of a positive MRI and whether we can utilize structural damage of MRI-SIJ in diagnosing axSpA is urgent. Bone erosions on MRI-SIJ such as fJSW (Figure 1) are moderately correlated with the presence and the severity of BME in patients with nr-axSpA meeting the ASAS definition. Thus, we propose fJSW is associated with BME and contributes to accurate diagnosis in patients with clinically suspected nr-axSpA and have supported this hypothesis. We showed a moderately positive correlation between fJSW and the presence or the severity of BME in our entire cohort of patients with clinically suspected nr-axSpA. Sclerosis, erosion, and fJSW simultaneously presenting in patients are positively correlated with BME on MRI-SIJ. In addition, BME can be found in healthy people, running enthusiasts, and women postpartum [34-36]. Because BME seems unspecific to patients with axSpA, we recommend that fJSW is an additional imaging criteria for diagnosing nr-axSpA, especially in Asian people, who were characterized by less prevalence of BME.

In our clinical experience, we have noticed normal serum inflammatory biomarkers such as CRP and ESR among patients with radiographic axSpA or nr-axSpA, which challenges the accurate diagnosis of SpA, no matter the presence or absence of HLA-B27. If we focus our attention on nr-axSpA, it is more difficult to confirm the diagnosis. Our cohort showed that patients with nr-axSpA who have either normal serum CRP or ESR may still have BME or fJSW on MRI-SIJ. Indeed, all patients with nr-axSpA in our cohort with increased CRP levels had greater disease activity, such as ASDAS-CRP and ASDAS-ESR, compared with those with normal CRP. We showed similar positive correlations between abnormal CRP level and disease activity in both HLA-B27-positive and

HLA-B27-negative patients. Among patients with nr-axSpA and normal serum CRP levels, we demonstrated higher SPARCC scores, higher BASDAI scores, and ASDAS-CRP scores in HLA-B27-positive patients with nr-axSpA, than in patients who were HLA-B27 negative. We also identified a positive correlation between fJSW and BME in patients with nr-axSpA and normal CRP levels, which indicates that we can still apply fJSW to the identification of nr-axSpA patients in the absence of systemic biomarkers, and that the presence of severe structural damage of fJSW contributes to accurate and early diagnosis of nr-axSpA.

Additionally, in our clinical practice, we often noticed that some patients with chronic IBP, who might carry factors predisposing to BME or chronic non-inflammatory back pain, such as mechanical injury, weight-bearing, and postpartum effects, had been excluded. We aimed to determine the best imaging modality for an accurate diagnosis of nr-axSpA in the absence of serum HLA-B27. Our data demonstrated that patients with nr-axSpA who were HLA-B27 positive, not only had higher prevalence of BME, but also more severe BME on MRI-SIJs than patients who were HLA-B27 negative. Our observation of fJSW was able to confirm nr-axSpA in patients who were HLA-B27 positive in the absence of BME on MRI-SIJs. Furthermore, we demonstrated that fJSW contributes to accurate early diagnosis of nr-axSpA in patients without HLA-B27, because there is a moderate correlation between fJSW and BME. For patients with clinically suspected nr-axSpA who do not carry HLA-B27, do not have BME on MRI-SIJs, and do not meet mNY criteria, we can still use fJSW on MRI-SIJs to confirm the diagnosis. There are similar positive correlations between fJSW and BME in HLA-B27-positive and -negative groups, which indicates that using fJSW for diagnosis criteria is not influenced by the presence or absence of HLA-B27 and is a useful additional tool for all patients with nr-axSpA. Together, these findings indicate that bone erosion-related fJSW, might be an additional imaging criteria to indicate nr-axSpA on MRI, either in the presence or absence of HLA-B27, which may help to identify patients with nr-axSpA who are HLA-B27 negative, such as Japanese, who have a lower prevalence of HLA-B27 [37]. Definition and quantitation of the severity of fJSW at SIJs on CT in patients with nr-axSpA are warranted, because we know that the resolution of MRI is too limited to determine the severity of fJSW precisely.

There are some limitations to our study. First, it is difficult to determine the severity of fJSW on MRI. In the future, we will apply a combination of MRI and CT scan of SIJs to determine the extension of fJSW for accurate diagnosis of nr-axSpA. Second, based on published data [34], it is even difficult to identify normal joints in healthy controls because healthy control people might still have BME and structural damage even if they simply run for leisure [36]. Rheumatologists still cannot fully understand how to determine whether BME and structural changes are associated with SpA in the presence or absence of radiographic features. In our cohort, we had excluded people with weight-bearing, postpartum, and old age effects, which may have biased our data and also explained the reason why this study did not enroll healthy people as a control group. The most important of all, people without inflammatory back pain were rarely diagnosed with axSpA and are not necessary to receive MRI-SIJs, which would not help contribute to accurate diagnosis.

In conclusion, our data indicates that fJSW is positively correlated with development of BME on MRI in this cohort who had clinical IBP and highly suspected nr-axSpA. We can hypothesize that fJSW is able to be used as a diagnostic tool for nr-axSpA. HLA-B27-positive patients showed more severe disease activity on MRI. Structural changes including sclerosis and fJSW are related to more severe bone marrow inflammation in symptomatic patients with normal serum ESR or CRP.

Abbreviations

bone marrow edema (BME)

human leukocyte antigen-B27 (HLA-B27)

focal joint space widening (fJSW)

Spondyloarthropathies (SpAs)

Axial SpA (axSpA)

bowel disease (IBD)

inflammatory back pain (IBP)

ankylosing spondylitis (AS)

nonradiographic axSpA (nr-axSpA)

sacroiliac joints (SIJs)

Assessment of Spondyloarthritis international Society (ASAS)

Magnetic resonance imaging (MRI)

bone marrow edema (BME)

computed tomography (CT)

C-reactive protein (CRP)

erythrocyte sedimentation rate (ESR)

Ankylosing Spondylitis Disease Activity Index (BASDAI)

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Review Board of Tri-Service General Hospital (2-106-05-106).

Consent for publication:

All authors have agreed with the manuscript in all respects for publication.

Competing interests:

There are no competing interests declared by all authors.

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Obtained funding: Chun-Chi Lu;

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Study supervision: Deh-Ming Chang, Hsiang-Cheng Chen

Submission: Sin-Yi Lyu. All authors have read and approved the draft of manuscript.

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Figures



Figure 1

Severe bone erosions at sacroiliac joints lead to focal joint space widening.