Original Article

Role of Diffusion-weighted and Contrast-enhanced Magnetic Resonance Imaging in Differentiating Activity of Ankylosing Spondylitis

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Abstract

Background: Previous studies showed that combining apparent diffusion coefficient (ADC) value with the Spondyloarthritis Research Consortium of Canada (SPARCC) index value might provide a reliable evaluation of the activity of ankylosing spondylitis (AS), and that contrast-enhanced (CE) magnetic resonance imaging (MRI) is unnecessary. However, the results were based on confirming only a small random sample. This study aimed to assess the role of CE-MRI in differentiating the disease activity of AS by comparing ADC value with a large sample.

Methods: A total of 115 patients with AS were enrolled in accordance with Bath AS Disease Activity Index and laboratory indices, and 115 patients were divided into two groups, including active group (n = 69) and inactive group (n = 46). SPARCC, ΔSI, and ADC values were obtained from the short tau inversion recovery (STIR), diffusion-weighted imaging (DWI), and CE-MRI, respectively. One-way analysis of variance and receiver operating characteristic analysis were performed for all parameters.

Results: The optimal cutoff values (with sensitivity, specificity, respective area under the curve, positive likelihood ratio, and negative likelihood ratio) for the differentiation between active and inactive groups are as follows: SPARCC = 6 (72.06%, 82.61%, 0.836, 4.14, 0.34); ΔSI (%) = 153 (80.6%, 84.78%, 0.819, 5.3, 0.23); ADC value = 1.15×10^{-3} mm^2/s (72.73%, 81.82%, 0.786, 4, 0.33). No statistical differences were found among the predictive values of SPARCC, ΔSI, and ADC. Multivariate analysis showed no significant difference between the combination of SPARCC and ADC values with and without ΔSI.

Conclusions: Using large sample, we concluded that the combination of STIR and DWI would play significant roles in assessing the disease activity, and CE-MRI sequence is not routinely used in imaging of AS to avoid renal fibrosis and aggravation of kidney disease.

Key words: Activity; Ankylosing Spondylitis; Diffusion-weighted Imaging; Enhanced Magnetic Resonance Imaging

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the spine, causing lower back pain, and presents as a persistent alternation of active and inactive stages.[1] Bone marrow edema (BME) of sacroiliitis has been considered to be used to diagnose AS and to be the important indicator of different AS stages.[2] In general, the more accurate of active and inactive changes are distinguished; the better treatment on patients could be achieved.[3] Magnetic resonance imaging (MRI) is increasingly utilized to observe the activity of sacroiliitis through quantifying BME of sacroiliitis in patients with AS,[4-8] which is more sensitive

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than other modalities in monitoring the activity of AS.[7,8] Recommended sequences for MRI of the sacroiliac joint included turbo spin echo (TSE), T1-weighted (T1W) with fat saturation (FS) pre- and post-contrast, short tau inversion recovery (STIR), and diffusion-weighted imaging (DWI).

However, all of MRI sequences for evaluation of AS used to detect the activity of AS could result in the scan time prolonged and inconvenient, and the application of contrast agent might lead to myelofibrosis or aggravate existing kidney disease. The previous studies showed that the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index, combined with apparent diffusion coefficient (ADC) values, is a validated semiquantitative measure of sacroiliac inflammation[9] and that contrast enhancement (ΔSI) based on postcontrast T1W FS was not be needed.[10] However, the conclusion was only testified by a small sample. The aim of this study was to compare SPARCC and ADC with and without ΔSI in discriminating active from inactive AS in terms of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio by a large sample. Our results will direct at profiting from the elimination of redundant sequences, increasing patient comfort, and decreasing cost savings.

Methods

Ethical approval

This prospective study was reviewed by the Ethics Committee in our hospital, and the approval with written informed consent was obtained from each participant.

Participants

According to the criteria of the modified New York classification criteria for AS,[11] 115 patients were diagnosed with AS who underwent MRI of the sacroiliac joints from May 2011 to September 2014 (99 male, 16 female; mean age, 27.2 years, range 15-57 years). Patients with cardiac pacemakers, metallic implants, or pregnancy for the past 6 months were excluded from the study. Within a 2-week interval, MRI and laboratory inflammatory markers were achieved. The criteria of clinical and laboratory tests were served as the standard for determining the active and inactive group, including Bath AS Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). These criteria for active and inactive groups are as follows:[12] (1) active group: BASDAI average score ≥6, a score between 4 and 6 with ESR ≥20 mm/h (Westergren method), or CRP ≥3 mg/L; (2) inactive group: BASDAI average score <4.0 or a score between 4 and 6 with ESR <20 mm/h or CRP <3 mg/L.

The patients were differentiated into 69 patients with active AS (mean age, 27.2 years; range, 15–57 years; symptom duration 4.57 ± 4.38 years) and 46 with inactive AS (mean age, 33.2 years; range, 16–69 years; symptom duration 5.5 ± 5.34 years). The active group was significantly different from inactive group in ESR and CRP ($F = 38.93$, $P < 0.001$ and $F = 15.72$, $P = 0.003$), whereas there was no significant difference in BASDAI ($F = 0.045$, $P = 0.834$).

Magnetic resonance imaging techniques

All patients underwent MRI of bilateral sacroiliac joints using a 1.5-T MR system (Philips Healthcare, Netherlands). Imaging sequences included as shown in Table 1: (a) coronal oblique (parallel to the long axis of the sacrum) T1W-TSE with spectral presaturation with inversion recovery (SPIR), (b) coronal oblique T2-weighted (T2W) TSE, (c) STIR, and (d) DWI. Two *b* values were used in DWI: 0 and 800 s/mm^2. Before and after gadopentetate dimeglumine (Magnevist, Schering, Germany) was injected into the right brachiocephalic vein, coronal oblique T1W-TSE-SPIR were performed with the contrast agent administrated with 0.1 mmol/kg body weight at a rate of 2.0 ml/s. The oblique coronal T1W-TSE-SPIR scan was finished within 1 min after intravenous injection. All MR images were collected with bilateral sacroiliac joints coverage.

Scoring method of Spondyloarthritis Research Consortium of Canada

The scoring method is shown in Figure 1c. Scoring sacroiliac joints were limited to the synovial section of the joints through these coronal slices, and then six consecutive coronal slices were consistently overviewed. Therefore, slices 4–9 were typically scored. Of the 12 acquisition images, 6 were obtained from posterior to anterior. Each sacroiliac joint was divided into 4 quadrants: upper sacral, lower sacral, upper iliac, and lower iliac. The dichotomous basis was used to score the presence of increased signal on T2W imaging (T2WI)–STIR, in each of these four quadrants. A score of 1 stands for increased signal and a score of 0 was normal. If there was a lesion showing intense signal on each

Table 1: Imaging parameters T2W-TSE, T1W-TSE-SPAIR, T2W-STIR, and DWI_2b

Parameters	T2W-TSE	T1W-TSE-SPIR	T2W-STIR	DWI_2b
TR/TE (ms)	4830/100	500–650/20	Shortest/60	2500/52
Echo train length (*n*)	15	20	7	35
FOV (mm)	250×331	220×330	220×330	400/250
Matrix	224×289	196×233	200×196	136×82
Slices (*n*)	32	18	18	32
Thickness/gap (mm)	6/1	6/1	3/1	6/1
NSA	4	3	3	8
SENSE factor	3	3	2	3.5

T1W-TSE: T1-weighted-turbo spin echo; SPIR: Spectral presaturation inversion recovery; T2W-TSE: T2-weighted-turbo spin echo; STIR: Short tau inversion recovery; DWI: Diffusion-weighted imaging; TR/TE: Repetition time/echo time; FOV: Field of view; NSA: Number of signal average.

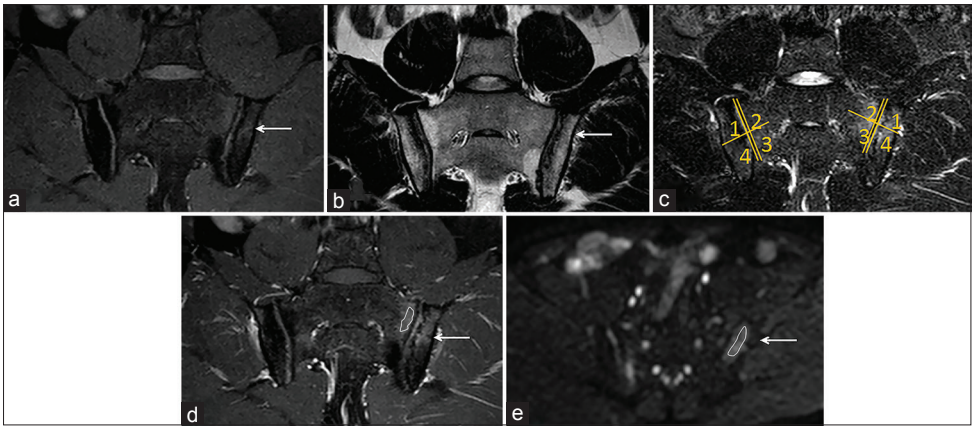

Figure 1: A 27-year-old male ankylosing spondylitis patient with lumbosacral pain and morning stiffness for over 6 months. Focal lesions of bone marrow edema are shown in left anterior edge of ilium (white arrow). Coronal (a) spectral presaturation with inversion recovery T1-weighted magnetic resonance and coronal (b) T2-weighted magnetic resonance images show isointense. Coronal (c) short tau inversion recovery T2-weighted magnetic resonance (Spondyloarthritis Research Consortium of Canada scoring method shown), coronal (d) postcontrast spectral presaturation with inversion recovery T1-weighted magnetic resonance images and axial (e) apparent diffusion coefficient maps (b = 0, 800 mm^2/s) show hyperintense. The apparent diffusion coefficient value for the indicated region of interest is 1.43 × 10^{-3} mm^2/s.

sacroiliac joint, the maximum score for the abnormal signal was 8 scores of a coronal slice on sacroiliac joints.

Similarly, the depth associated with any part of a joint receives a score of 1, and maximum scores were added up to 24 on the depth of sacroiliac joint. The depth and the increased signal were the referents of BME that extends away from the joint space. The use of the depth and the intensity was reserved for clearly positive cases. The maximum scores were 72 that was obtained by being repeated for each consecutive coronal slice.[13]

Signal enhancement (ΔSI)

A region of interest (ROI) was used to quantitatively measure the changes in signal enhancement (ΔSI) of the lesion before and after the injection of gadopentetate dimeglumine. The signal enhancement (percentage of signal intensity increase) was calculated according to the enhancement formula:[1] ΔSI = (SIc − SI)/SI × 100,[1] where SI and SIc are the precontrast and the postcontrast signal intensities, respectively.

Image postprocessing and regions of interest

All indices were obtained on Extended MR Workspace (Philips Healthcare, Netherlands). For ADC and ΔSI values, ROIs were drawn on each lesion along the inside of the contour (approximately 1 mm). Examples are shown in Figure 1d and 1e. Lesion ROIs were set as large as possible; the lower and upper levels of lesions were excluded to minimize contamination from surrounding tissues. Blood vessels, sclerosis, and cystic areas were avoided. We took four lesions for every patient. If there were more than four lesions, we choose four obvious lesions. Oppositely, if there were <4 lesions, we choose all of these lesions, and then the average of the measurements was taken and the mean ROI area turned out to be 46 mm^2 (range, 11–69 mm^2). Two independent observers (each with 10-year experience in bone MRI diagnosis) measured all indices; these observers were blinded between each other and also to the clinical data.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 13.0 for Windows (IIBM, Armonk, New York,US), except for the receiver operating characteristic (ROC) comparison that was completed by MedCalc statistical software (MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium).

The data variability for the 2 different observers was derived by the intraclass correlation coefficient being calculated. The data were presented as the mean ± standard deviation (SD). Levene's test was used to investigate the homogeneity of variance. Dunnett's T3 and Bonferroni's methods for heterogeneity of variance and *post hoc* Scheffe's method for homogeneity of variance were performed. All indices were compared using one-way analysis of variance (ANOVA). Using curve analyses, the differentiation was obtained to assess the utility of the parameters from active and inactive AS. To account for multiple comparisons, we would compare the precision of ROC curves from different mix parameters, and P values would be based on Bonferroni correction. There was statistical significance with P values of <0.01. To analyze the differences between ROC curves, stepwise regression analysis has been used.

Results

Patient characteristics and magnetic resonance imaging

Of 115 patients, acute subchondral BME was detected in 75 patients (active 68 vs. inactive 7). T1WI-TSE-SPIR showed hypointense or isointense lesions in bones of the bilateral sacroiliac joint. Hyperintense lesions in affected areas were shown on coronal oblique T2WI-STIR, contrast-enhanced (CE)-MRI, DWI, and ADC map [Figure 1]. Furthermore, 38 of the patients had erosions in bilateral or only unilateral sacroiliac joints surfaces (active 12 vs. inactive 26), showing uneven and moth-eaten bone destruction of bone cortex on the sacroiliac joint.

Twenty-six of the patients had sclerosis either on bilateral or only unilateral sacroiliac joints subchondral bones (active 11 vs. inactive 15), showing patchy hypointense in bones of the sacroiliac joints on MR images. Sixty-eight of the patients had fat deposition in the sacroiliac joints (active 32 vs. inactive 36), of which T2WI showed hyperintense lesions in bilateral or only unilateral sacroiliac joints and hypointense lesions in affected areas were seen on coronal oblique T2WI-STIR, CE-MRI, T1WI-TSE-SPIR, DWI, and ADC map [Figure 2].

All indices analysis between active and inactive group

A kappa value (κ) showed good agreement with 0.86 for SPARCC and ΔSI and with 0.85 for ADC value among interobserver.

The ranges of all indices of the active and inactive AS patients are described in Table 2. The mean ± SD values of the active and inactive group with respect to all indices are as follows: for the active group: ADC value = $1.34 \pm 0.32 \times 10^{-3}$ mm²/s, ΔSI (%) = 247 ± 161, SPARCC = 17.41 ± 14.8; for the inactive group, all measures were lower: ADC value = $0.9 \pm 0.43 \times 10^{-3}$ mm²/s, ΔSI (%) = 122 ± 65, SPARCC = 3.86 ± 5.09. SPARCC, ΔSI, and ADC values in the inactive group were lower than these in the active, and ANOVA indicated that there were significant differences in ADC, ΔSI, and SPARCC values between the active and inactive group ($P < 0.001$). Dunnett's T3 method indicated that all indices in active AS were higher than those in inactive AS. Table 3 shows the ROC curve analysis of the two groups. The optimal cutoff values (with respective area under the curve, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio) between active and inactive AS patients were ADC value = 1.15×10^{-3} mm²/s (0.786, 72.73%, 81.82%, 4, 0.33), ΔSI (%) = 153 (0.819, 80.6%, 84.78%, 5.3, 0.23), and SPARCC = 6 (0.836, 72.06%, 82.61%, 4.14, 0.34) [Figure 3]. Although, according to the ROC curves, ΔSI was the most reliable predictor for differentiating active from inactive AS patients, there were no significant differences among SPARCC, ADC, and ΔSI values. The specificity of ΔSI (80.6%) was highest among all indices between the active and inactive groups.

Using any multivariate model, although the combination of SPARCC, ADC, and ΔSI values had the highest ROC (0.878, $P = 0.0601$) compared with SPARCC alone, there was no statistical significance between the combination of SPARCC and ADC values with and without ΔSI to differentiate active AS from inactive AS [Table 4].

Table 2: Test of all indices between the active and inactive groups by ANOVA

Items	Active group	Inactive group	*P*
ΔSI (%)	247 ± 161	122 ± 65*	<0.05
SPARCC	17.41 ± 14.81	3.86 ± 5.09*	<0.05
ADC value (10^{-3} mm²/s)	1.34 ± 0.32	0.9 ± 0.43*	<0.05

*P<0.05 vs. active group. ANOVA: One-way analysis of variance; ΔSI: Signal enhancement; SPARCC: Spondyloarthritis Research Consortium of Canada Index values; ADC: Apparent diffusion coefficient.

Discussion

In this study, we studied the sensitivity and specificity of SPARCC, ΔSI, and ADC values which detected the activity of AS. We found that T2W-STIR, DWI, and CE-MRI could offer good differentiation between the active and inactive AS, and that SPARCC, ΔSI, and ADC values in the active AS were all significantly higher than those in inactive AS. In general, BME was considered as a product of an inflammatory reaction of bone marrow in AS.[14] Respectively, the excessive water in bone marrow can cause SPARCC to increase; the increased blood flow and capillary permeability lead to an increase of ΔSI.[15] ADC value reflects the Brownian motion of water molecules in a biologic system.[16] Water movement in the inflammatory lesions was increased in acute AS, leading to high local ADC value.[17]

Our multivariate logistic regression analysis showed that combining ADC value with SPARCC could slightly improve the diagnostic sensitivity and specificity for active AS, but further combining ΔSI with SPARCC and ADC value

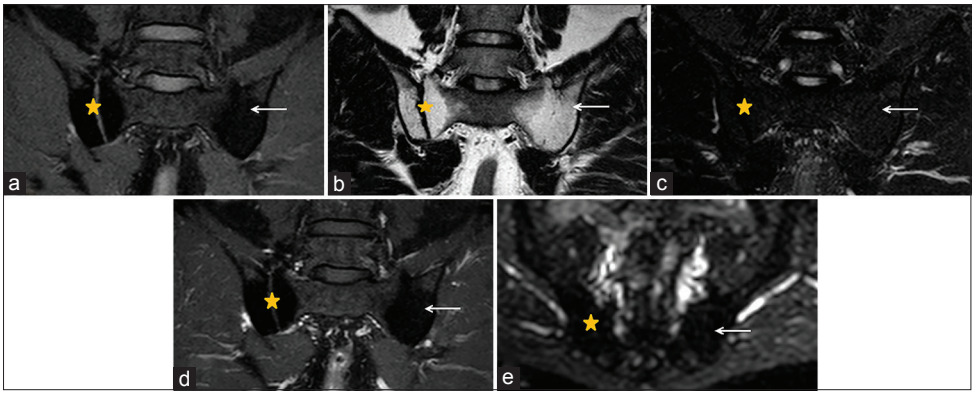

Figure 2: A 57-year-old male with lumbosacral pain for 4 years. Blurring edges are seen in the bilateral sacroiliac joints representing cartilage erosion and bone sclerosis (star). Bone fusion and fat deposition are shown in sacroiliac joint (white arrow). Coronal (a) spectral presaturation with inversion recovery T1-weighted magnetic resonance, coronal (c) short tau inversion recovery T2-weighted magnetic resonance, coronal (d) postcontrast spectral presaturation with inversion recovery T1-weighted magnetic resonance images and axial (e) apparent diffusion coefficient maps (b = 0, 800 mm²/s) show hypointense, and coronal (b) T2-weighted magnetic resonance images shows hyperintense.

Table 3: Optimal cutoff values for the active and inactive group under 95% *CI* according to ROC curves analysis with respective *P* values from comparison of ROC curves

Items	Cutoff value	Sensitivity (%)	Specificity (%)	LR		AUC
				Positive	Negative	
SPARCC	6	72.06 (59.9–82.3)	82.61 (68.6–92.2)	4.14 (3.4–5.1)	0.34 (0.2–0.7)	0.836 (0.647–0.821)
ADC value	1.15×10^{-3} mm^2/s	72.73 (60.4–83.0)	81.82 (67.3–91.8)	4.00 (3.3–4.9)	0.33 (0.2–0.7)	0.786 (0.695–0.859)
ΔSI (%)	153	80.6 (69.1–89.2)	84.78 (71.1–93.7)	5.3 (4.5–6.3)	0.23 (0.1–0.5)	0.819 (0.733–0.887)

All *P*>0.05. *CI*: Confidence interval; LR: Likelihood ratio; ROC: Receiver operating characteristic; AUC: Area under the curve; ΔSI: Contrast enhancement; SPARCC: Spondyloarthritis Research Consortium of Canada Index values; ADC: Apparent diffusion coefficient.

Table 4: Multivariate logistic regression analysis showing all the multivariate models with *P* values against SPARCC between active and inactive group

Items	Models	AUC	95% *CI*	*P*
Univariate	SPARCC	0.836	0.752–0.901	
Multivariate	SPARCC/ ADC value	0.859	0.778–0.919	0.2843*
Multivariate	SPARCC/ΔSI/ ADC value	0.878	0.778–0.919	0.0601†

All multivariate vs. univariate SPARCC: *P>0.05 vs. SPARCC; †P>0.05 vs. SPARCC. ΔSI: Contrast enhancement; SPARCC: Spondyloarthritis Research Consortium of Canada Index values; ADC: Apparent diffusion coefficient; SPARCC/ADC value: The combination of SPARCC and ADC values; SPARCC/ΔSI/ADC value: The combination of SPARCC, ADC, and ΔSI values; AUC: Area under the curve; *CI*: Confidence interval.

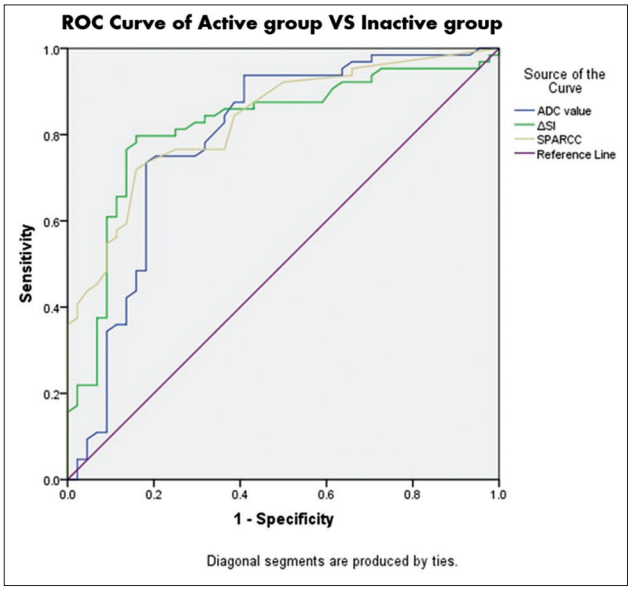

Figure 3: Comparisons of receiver operating characteristic curves of apparent diffusion coefficient value, ΔSI, and Spondyloarthritis Research Consortium of Canada for the active and inactive group. The receiver operating characteristic curves demonstrated Spondyloarthritis Research Consortium of Canada had the highest area under the curve, followed by ΔSI and, while apparent diffusion coefficient value had a lower area under the curve.

could not significantly increase the diagnostic sensitivity and specificity for the activity of AS in our study included 115 patients. However, Althoff *et al*. reported that although the role of T2W-STIR and CE-MRI are comparable in identifying the activity of AS, administration of contrast agents may be beneficial for inexperienced MRI readers or detecting early AS with minimal changes.[10] However, some studies using small sample had shown that DWI and CE-MRI had similar diagnostic value, and that CE-MRI does not contribute significant additional information as compared to DWI,[17-20] which is consistent with our results.

Altogether, we conclude that STIR combined with DWI-MRI should be used in MRI examination to detect the activity of AS, and that CE MRI was unnecessary. Because a contrast agent is administered, there is a risk of renal fibrosis induction and aggravation of inactive kidney disease, such as renal amyloidosis, IgA nephropathy, and other kidney diseases associated with AS,[21-23] Therefore, for assessing the activity of definite AS, CE-MRI can be eliminated from MRI protocols, to avoid risks associated with contrast agent administrations and to save both cost and time.

Three limitations need to be taken into account: First, MRI of normal bone marrow is known to be strongly influenced by age and fat content.[24] Therefore, we only included young patients to exclude significant effects of yellow bone marrow on our data. Second, synovitis and soft-tissue inflammation were not studied, which were also regarded as presentations of active AS.[25] Third, there were errors in the specific inclusion criteria and measurement. These will be further studied in the next step.

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Conflicts of interest

There are no conflicts of interest.

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