Radiology

ORIGINAL RESEARCH • MUSCULOSKELETAL IMAGING

Apparent Diffusion Coefficient as an Imaging Biomarker for Spinal Disease Activity in Axial Spondyloarthritis

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Supported by the Min Yuen Tong Charity Fund, Novartis Research, and the Hong Kong Society of Rheumatology.

Conflicts of interest are listed at the end of this article.

See also the editorial by Guermazi and Roemer in this issue.

Radiology 2019; 291:121–128 • https://doi.org/10.1148/radiol.2019180960 • Content code: MK

Background: A quantifiable imaging measure to gauge the intensity of individual inflammatory lesions in axial spondyloarthritis (SpA) has not been well established. Previous studies have shown that diffusion-weighted (DW) MRI reflects disease activity in axial SpA.

Purpose: To determine the association between apparent diffusion coefficient (ADC) at MRI of discovertebral lesions and disease activity in individuals with axial SpA.

Materials and Methods: In this prospective study, 243 study participants (mean age ± standard deviation, 43.2 years ± 13.5) with back pain who fulfilled the Assessment of SpondyloArthritis International Society criteria for SpA were recruited from four rheumatology centers between April 2014 and March 2018. There were 132 men (mean age, 41.4 years ± 13.3) and 111 women (mean age, 45.3 years ± 13.4). Clinical, biochemical, and radiologic parameters were collected. All participants underwent whole-spine MRI by using a short inversion time inversion-recovery sequence and DW imaging. Two independent readers identified the presence of discovertebral lesions. ADCs were measured and normalized with normal bone marrow. Regression analysis was performed to determine association between the mean, maximum, and normalized mean and maximum ADCs of the discovertebral lesions and disease activity and functional parameters (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Functional Index [BASFI], and Bath Ankylosing Spondylitis Global Index [BASGI]).

Results: Ninety-one discovertebral lesions (five cervical, 61 thoracic, 25 lumbar) were present in 55 of the 243 study participants (22.6%). After adjusting for confounding factors, increased maximum ADC was independently associated with increased BASFI (regression coefficient [β] = 1.94 [$\times 10^{-3}$ mm^2/sec], P = .04). Increased normalized maximum ADC was independently associated with BASDAI question 2 (ie, back pain score) (β = 0.45, P = .01), mean stiffness score (β = 0.41, P = .04), and BASGI (β = 0.43, P = .04). Increased normalized mean ADC was independently associated with BASDAI question 2 (β = 0.61, P = .04).

Conclusion: Apparent diffusion coefficients at MRI of discovertebral lesions were associated with disease activity, functional impairment, and patient global assessment in axial spondyloarthritis.

Online supplemental material is available for this article.

Axial spondyloarthritis (SpA) encompasses a spectrum of chronic inflammatory rheumatic diseases characterized by axial joint inflammation and ankyloses. The Assessment of SpondyloArthritis International Society classification criteria for axial SpA were introduced in 2009 (1). The criteria incorporate MRI and human leukocyte antigen B27 (HLA-B27) and classify patients into "clinical" and "imaging" arms (1) depending on the presence of imaging abnormalities of the sacroiliac joints on radiographs and/or MR images. Spinal inflammation is commonly detected on MR images in patients with axial SpA, with a prevalence of up to 82%. Isolated spinal inflammation in the absence of active sacroiliitis has been reported in 24%–49% of patients with SpA (2,3).

Assessment of disease activity in axial SpA is based on either clinical (ie, patient-reported symptoms, acute phase reactants, and self-assessment questionnaires) or imaging methods. MRI is a sensitive method for quantifying the extent of spinal inflammation. The Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index for assessment of spinal inflammation in ankylosing spondylitis, the ankylosing spondylitis spine MRI score for activity, or ASspiMRI-a, and the Berlin method are the three most commonly used MRI-based methods for scoring disease activity in the spine (4–6). All are similar in terms of sensitivity to change and discriminatory power (7). However, these visual scoring systems are based on conventional MRI sequences such as short inversion time inversion recovery (STIR), which are focused on the extent of disease without quantifying the intensity of inflammation of individual lesions. A quantifiable measure to gauge the MRI signal intensity of individual inflammatory lesions in SpA has not been well established. Among the three methods, the ASspiMRI-a and Berlin methods do not acknowledge the intensity of inflammation; the SPARCC method only semiquantitatively grades the degree of inflammation.

Abbreviations

ADC = apparent diffusion coefficient, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASGI = Bath Ankylosing Spondylitis Global Index, DW = diffusion weighted, HLA-B27 = human leukocyte antigen B27, SpA = spondyloarthritis, SPARCC = Spondyloarthritis Research Consortium of Canada, STIR = short inversion time inversion recovery

Summary

Diffusion-weighted imaging parameters of spinal inflammation may reflect disease activity and is a potential imaging biomarker for patients with axial spondyloarthritis.

Key Points

- In patients with axial spondyloarthritis, apparent diffusion coefficients and normalized apparent diffusion coefficients of discovertebral lesions were associated with spinal inflammation and disease activity (spinal pain and stiffness), functional impairment, and patient global assessment.
- Abnormalities on conventional short inversion time inversion recovery images were not associated with disease activity and global assessment in patients with axial spondyloarthritis.

Previous studies have shown that diffusion-weighted (DW) imaging can indicate disease activity in axial SpA. The apparent diffusion coefficient (ADC), an index of diffusivity, can potentially provide additional quantitative information about the intensity of inflammation. Bozgeyik et al (8) showed that the ADCs of sacroiliac joints were higher in patients with sacroiliitis than in those with mechanical back pain. In a study of 62 patients with seronegative SpA, Gezmis et al (9) found a positive correlation between ADC and C-reactive protein level. However, these studies mainly focused on the application of DW imaging on sacroiliac joints. There is paucity of data regarding the use of DW imaging for spinal inflammation in SpA. Our hypothesis was that ADC could reflect the degree of disease activity in SpA. The purpose of our study was to evaluate the usefulness of the ADC as an imaging biomarker by determining the correlations between DW imaging–derived parameters of active discovertebral lesions and disease activity indexes and functional parameters in SpA.

Materials and Methods

Ethics Approval

Our study was approved by the institutional review boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (institutional review board reference no. UW 14–085) and ethics committees of regional hospitals.

Recruitment

This is a cross-sectional analysis of a prospectively enrolled cohort. Written informed consent was obtained from all participants. All consecutive participants who fulfilled Assessment of Spondyloarthritis international Society criteria for axial SpA (n = 266) were prospectively enrolled from four rheumatology centers in Hong Kong (Queen Mary Hospital, Pamela Youde Nethersole Eastern Hospital, Caritas Medical Centre, and Tseung Kwan O Hospital) from April 2014 to March 2018. We excluded participants who were pregnant, who were unable to undergo or refused to undergo MRI examination, and who were unable to give written informed consent. Two hundred forty-three participants finally underwent whole-spine MRI with a single MRI machine (Fig 1).

Clinical Assessment and Laboratory Analysis

Clinical and demographic data were collected from the recruited participants. These data included age; sex; smoking status; and duration, characteristics, and severity of back pain (scored on a scale of 0 to 10). All participants were asked to complete three questionnaires: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (10), the Bath Ankylosing Spondylitis Functional Index (BASFI) (11), and the Bath Ankylosing Spondylitis Global Index (BASGI) (12) (Appendix E1 [online]). Blood-parameters including HLA-B27, C-reactive protein level, and erythrocyte sedimentation rate were recorded.

MRI Parameters

Whole-spine MRI was performed with a 3.0-T imaging unit (Achieva; Philips Healthcare, Best, the Netherlands) by using a torso coil with the participants positioned supine. The imaging parameters are shown in Table 1. The MRI system automatically generated the ADC maps. All MRI examinations were performed within 1 month of clinical assessment.

Image Processing and Analysis

Qualitative assessment of discovertebral lesions.—MRI examinations were reviewed by one radiologist (K.H.L., with 3 years of experience in spine MRI) and one rheumatologist (H.Y.C., with 7 years of experience in spine MRI) by using commercially available software (OsiriX, version 8.0.1; Osirix Foundation, Geneva, Switzerland). Both readers were blinded to clinical and laboratory findings. MR images were evaluated at 23 discovertebral units from C2 to S1. Each discovertebral unit consisted of an intervertebral disk, the lower half of the vertebra above the intervertebral disk, and the upper half of the vertebra below the intervertebral disk. Active discovertebral lesions were defined on STIR images as areas of hyperintense bone marrow contiguous with the vertebral endplate and/or intervertebral disk with or without involvement of the vertebral corner in any central sagittal section, with reference to the 2009 Canada-Denmark definition (13). Corner lesions were regarded as discovertebral lesions only if they involved more than 50% of the anteroposterior diameter of the vertebra in any central sagittal section. Central sagittal sections were defined as images that included the spinal canal. Grossly degenerated disk lesions (reduced disk height, presence of Schmorl node, and/or marginal osteophytosis) were excluded. The readers independently determined the presence or absence of discovertebral lesions of each discovertebral unit, with discrepancy resolved by consensus. The size of each discovertebral lesion was measured in the anteroposterior dimension and expressed in absolute value and percentage of anteroposterior dimension of the corresponding vertebral body (Fig 2). Discogenic lesions, artifacts, and lesions with poor image quality were excluded from the analyses. Only

discovertebral lesions identified by both readers were used in ADC measurements.

Two readers (H.Y.C. and V.W.H.L., a radiologist with 10 years of experience in spine MRI), who were blinded to clinical and laboratory findings, scored MR images of the spine according to the SPARCC MRI inflammation scoring method (6). Vertebral segments from C2 to S1 were reviewed. In brief, each discovertebral unit was divided into four quadrants: upper anterior endplate, upper posterior endplate, lower anterior endplate, and lower posterior endplate. The presence of increased signal intensity on STIR images in each of these four quadrants was scored on a dichotomous basis, as follows: 1 = increased signal intensity, 0 = normal signal intensity. This was repeated for each of three consecutive sagittal sections, resulting in a maximum score of 12 per discovertebral unit. On each section, the presence of a lesion exhibiting intense signal intensity in any quadrant was given an additional score of 1. Similarly, the presence of a lesion exhibiting a depth of at least 1 cm in any quadrant was given an additional score of 1, leading to a maximum additional score of 6 for each specific vertebral unit and bringing the total maximum score to 18 per unit (6). The average score of the two readers was taken as the final SPARCC score.

Quantitative analysis of DW images.—ADC measurements were performed by using open source software (ImageJ; National Institutes of Health, Bethesda, Md). On the ADC map, a third radiologist (X.X., with 3 years of experience in spine MRI) performed ADC measurements of the discovertebral lesions using conventional MRI sequences (T1-weighted imaging and STIR) as anatomic references (Fig 2). The third reader placed a region of interest at each selected region, with careful exclusion of adjacent normal marrow and intervertebral disk, to determine the mean and maximum ADCs. Background ADC was also measured at the center of at least two normal-appearing lumbar vertebral bodies with exclusion of the cortical endplate. All ADCs were measured twice and averaged. If there was more than one lesion detected in a participant, the lesion with the highest ADC was included for correlation analysis. Finally, normalized mean ADC and normalized maximum ADC were calculated by dividing the mean and maximum ADCs by the background ADC.

Statistical Analysis

The independent *t* test and χ^2 test were used to compare continuous and categorical variables between men and women. The Cohen κ coefficient was used to calculate the interobserver agreement. Interobserver agreement of the SPARCC score was calculated by using the intraclass correlation coefficient. The degree of interobserver agreement was interpreted as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect (14).

Linear univariable regression analyses were performed to determine the associations between ADC parameters (mean ADC, maximum ADC, normalized mean ADC, normalized maximum ADC), SPARCC score, and clinical parameters (BASDAI, back pain score [BASDAI question 2], stiffness severity [BASDAI question 5], stiffness duration [BASDAI question 6], mean stiffness score [BASDAI questions 5 + 6/BASDAI question 2], BASFI, BASGI, C-reactive protein level, and erythrocyte sedimentation rate). In the regression models, the clinical parameters were used as dependent variables. ADC parameters and SPARCC score were used as independent variables. Univariable regressions were also performed for potential factors that could have an effect on the

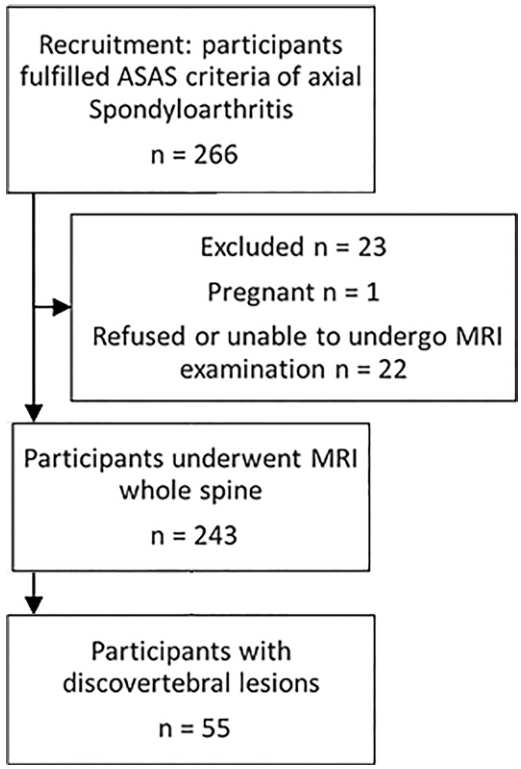

Figure 1: Study flow diagram. *ASAS* = Assessment of SpondyloArthritis International Society.

Table 1: MRI Parameters

Sequence	TSE T1-weighted Imaging	STIR Imaging	DW Imaging*
Imaging plane	Sagittal	Sagittal	Sagittal
TR/TE (msec)	800/8	5000/80	3100/46
Section thickness (mm)	3.5	3.5	4
Gap (mm)	0	0	0
Field of view (mm^2)	150 × 240	150 × 240	300 × 241
Matrix	152 × 157	152 × 157	124 × 100
Parallel imaging (SENSE) factor	…	…	2

Note.—DW = diffusion weighted, TE = echo time, TR = repetition time, TSE = turbo spin echo, SENSE = sensitivity encoding, STIR = short inversion time inversion recovery.

* Diffusion-weighted imaging was performed with *b* values of 0, 100, 600, and 1000 sec/mm^2.

clinical parameters. These include age, male sex, back pain duration, and HLA-B27 status. Independent potential factors that could have an effect on the clinical parameters and with $P < .1$ were adjusted in multivariable linear regressions by using ADC parameters and SPARCC score as independent variables. Results are reported as regression coefficients and 95% confidence intervals (α level, .05). All statistical analyses were performed with software (IBM SPSS statistics 22.0; SPSS, Chicago, Ill). $P < .05$ was considered indicative of a statistically significant difference. Listwise deletion was performed for missing data.

Results

We included 243 participants in the final analysis. Participants' demographic and clinical characteristics are shown in Table 2. There were 132 men and 111 women. HLA-B27 was positive in 189 participants. One hundred fifty-six participants fulfilled the modified New York criteria for ankylosing spondylitis, whereas 82 had no radiologic sacroiliitis (sacroiliitis not seen on radiographs) and were classified as having nonradiographic SpA. Our cohort was characterized by long disease duration, high disease activity, and moderate functional impairment.

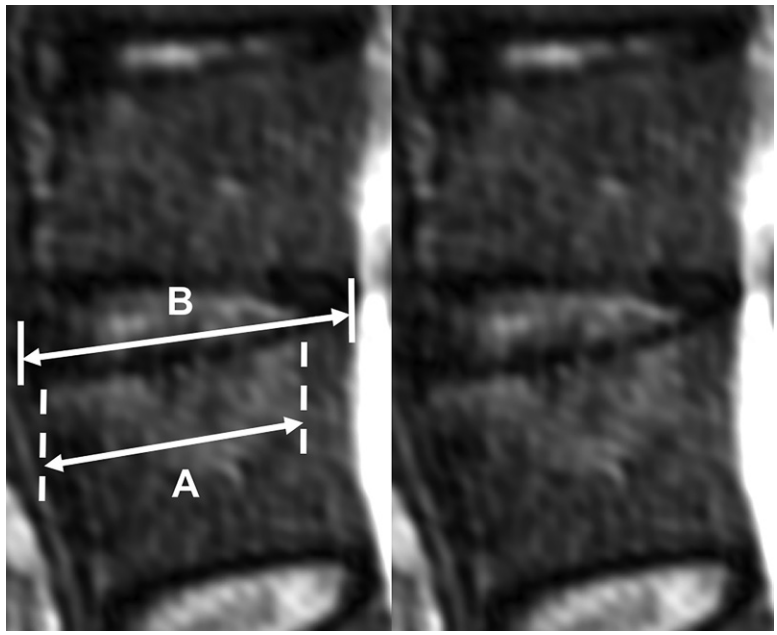

Figure 2: Left, illustration of definition and size measurement of discovertebral lesion and, right, corresponding sagittal short inversion time inversion recovery (STIR) MR image. Discovertebral lesion with high signal intensity on STIR MR image should be contiguous with intervertebral disk. Size of discovertebral lesion was expressed in absolute value (*A*) and percentage of anteroposterior dimension of the corresponding vertebral body (*B*) (*A*/*B* × 100%).

Frequency, Distribution, and ADCs of Discovertebral Lesions

After 16 discogenic lesions were excluded from 13 participants, MRI of the whole spine depicted a total of 91 discovertebral lesions in 55 participants (Figs 3, 4). The overall frequency was 22.6%. Discovertebral lesions were found in 39 of the 156 participants in the ankylosing spondylitis group and 15 of the 82 in the nonradiographic SpA group. There was no difference between the two groups in the frequency of discovertebral lesions (25% vs 18%, respectively; $P = .24$). Each participant had a median of one lesion (range, 1–7). Among the 91 discovertebral lesions, five (5.4%) were in the cervical spine, 41 (45.1%) were in the upper thoracic spine (T1/2 to T6/7), 20 (22%) were in the lower thoracic spine (T7/8 to T12/L1), and 25 (27.5%) were in the lumbar spine. The levels that were most commonly affected by discovertebral lesions were T5/6 and T6/7 (Fig 5). The mean discovertebral lesion size was 1.6 cm (range, 0.6–3.2 cm), involving a mean of 62.7% (range, 31.6%–100%) of anteroposterior dimension of the vertebral body. Interobserver agreement for the detection of discovertebral lesions (in 5589 discovertebral units) was almost perfect (Cohen κ: 0.813, $P < .05$). Interobserver agreement of the SPARCC score was almost perfect (intraclass correlation coefficient = 0.945, $P < .001$).

Among the 91 discovertebral lesions detected on the STIR and T1-weighted images, 10 (four cervical lesions, three upper thoracic lesions, two lower thoracic lesions, and one lumbar lesion) could not be visualized on the DW images and ADC maps due to image distortion, resulting in failed region of interest placement and ADC measurement. Success rates in ADC measurement of cervical, upper thoracic, lower thoracic, and lumbar lesions were 20% (one of five), 93% (38 of 41), 90% (18 of 20), and 96% (24 of 25), respectively. The overall technical success rate was 89% (81 of 91 lesions). The mean (±standard deviation) background ADC, mean ADC, and maximum ADC were 0.28×10^{-3} mm²/sec ± 0.06, 0.66×10^{-3} mm²/sec ± 0.24, and 1.24×10^{-3} mm²/sec ± 0.35, respectively. The normalized mean ADC and normalized maximum ADC were 2.4 ± 1.1 and 4.6 ± 1.7, respectively.

Relationship between Disease Activity and Functional Outcome with Patient Global Assessment, ADC Parameters, and SPARCC Score

We explored the association between clinical scores in daily rheumatology practice that were used to assess axial disease activities and functional status, including back pain score (BASDAI question 2), mean back stiffness score (BASDAI questions 5 + 6/question 2), functional score (BASFI), and patient global assessment (BASFI), with various ADC parameters, SPARCC score, age, disease duration, male sex, and HLA-B27 positivity. Results of univariable analyses showed that increased maximum ADC, normalized maximum ADC, and normalized mean ADC were associated with increased back pain score (BASDAI question 2), back stiffness score (mean of BASDAI questions 5 and 6), functional score (BASFI), and patient global assessment (BASGI). Increased mean ADC and SPARCC score were associated with increased functional score (BASFI). Results are shown in Table 3.

Table 4 shows results of multivariable analyses after adjusting for confounders. Increased maximum ADC was

Table 2: Summary of Participant Characteristics

Parameter	Men	Women	*P* Value
Age (y) (*n* = 243)	41.4 ± 13.3	45.3 ± 13.4	.02
Ever smoker*	59/132 (44.7)	15/111 (13.5)	<.001
Back pain duration (y) (*n* = 243)	12.3 ± 12.0	11.8 ± 11.6	.77
Radiographic ankylosing spondylitis*	94/131 (71.8)	62/107 (57.9)	.03
HLA-B27 positivity*	103/125 (82.4)	86/108 (79.6)	.59
SPARCC MRI index for assessment of spinal inflammation (*n* = 143)	8.6 ± 10.1	3.8 ± 5.8	<.001
BASDAI (*n* = 143)	4.7 ± 2.0	5.0 ± 2.0	.24
BASFI (*n* = 241)	3.2 ± 2.5	3.1 ± 2.4	.69
BASGI (*n* = 242)	5.3 ± 2.6	5.4 ± 2.5	.97
CRP level (mg/dL) (*n* = 241)	1.3 ± 1.9	0.8 ± 2.0	.052
ESR (mm/h) (*n* = 241)	30.2 ± 25.4	35.0 ± 25.0	.14

Note.—Except where indicated, data are means ± standard deviations. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASGI = Bath Ankylosing Spondylitis Global Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HLA-B27 = human leukocyte antigen B27, SPARCC = Spondyloarthritis Research Consortium of Canada.

* Data are numbers of participants, with percentages in parentheses.

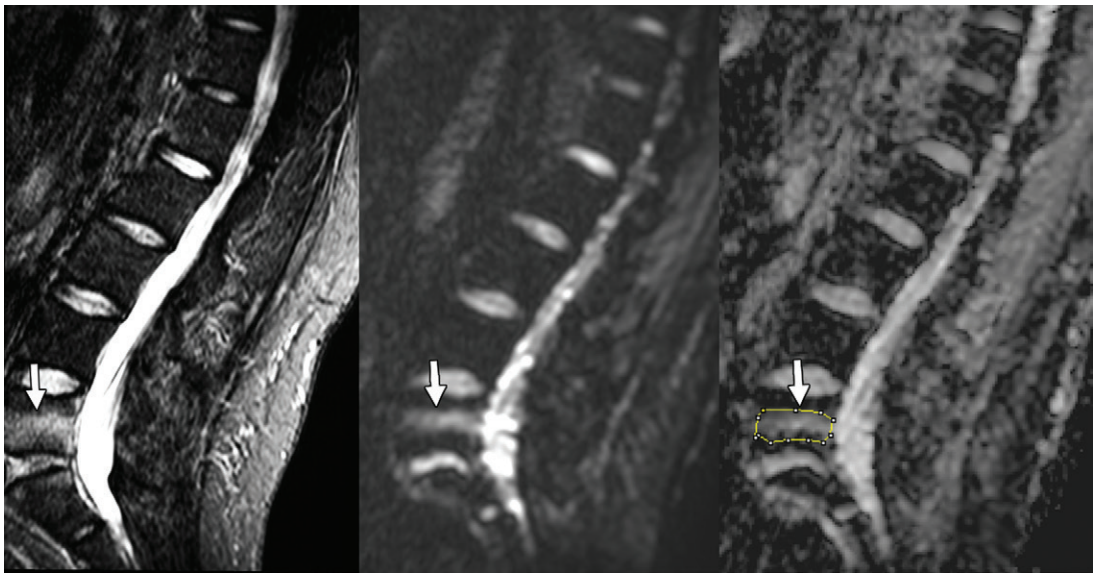

Figure 3: Images in 46-year-old man with discovertebral lesion involving inferior L5 endplate of L5/S1 discovertebral unit. Lesion (arrows) could be seen on, left, short inversion time inversion-recovery image, middle, diffusion-weighted MR image with *b* value of 50 mm²/sec, and, right, apparent diffusion coefficient (ADC) map as area of high signal intensity contiguous with the intervertebral disk. ADC measurement at region of interest (outlined area) yielded mean ADC of 1.00×10^{-3} mm²/sec and maximum ADC of 1.75×10^{-3} mm²/sec. Normalized mean ADC and normalized maximum ADC were 4.7 and 8.2, respectively, both of which are higher than population means. Participant had high back pain score (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] question 2 = 6), high stiffness score (mean of BASDAI questions 5 + 6 = 5.5), and high global impairment score (Bath Ankylosing Spondylitis Global Index = 7.5).

independently associated with worsened functional score (BASFI). Increased normalized maximum ADC was independently associated with worsened back pain severity (BASDAI question 2), increased back stiffness (mean of BASDAI questions 5 + 6), and worsened patient global assessment (BASGI). Increased normalized mean ADC was independently associated with back pain severity (BASDAI question 2). An increased SPARCC score was only independently associated with worsened functional status (BASFI). Full results of univariable and multivariable analyses are shown in Tables E1 and E2, respectively (online).

Discussion

The aim of our study was to evaluate diffusion MRI as an imaging biomarker. We evaluated the relationship between ADCs derived from diffusion MRI and validated clinical parameters of disease activity (BASDAI, BASGI) and functional status (BASFI). ADCs showed a positive association with disease activity, including back

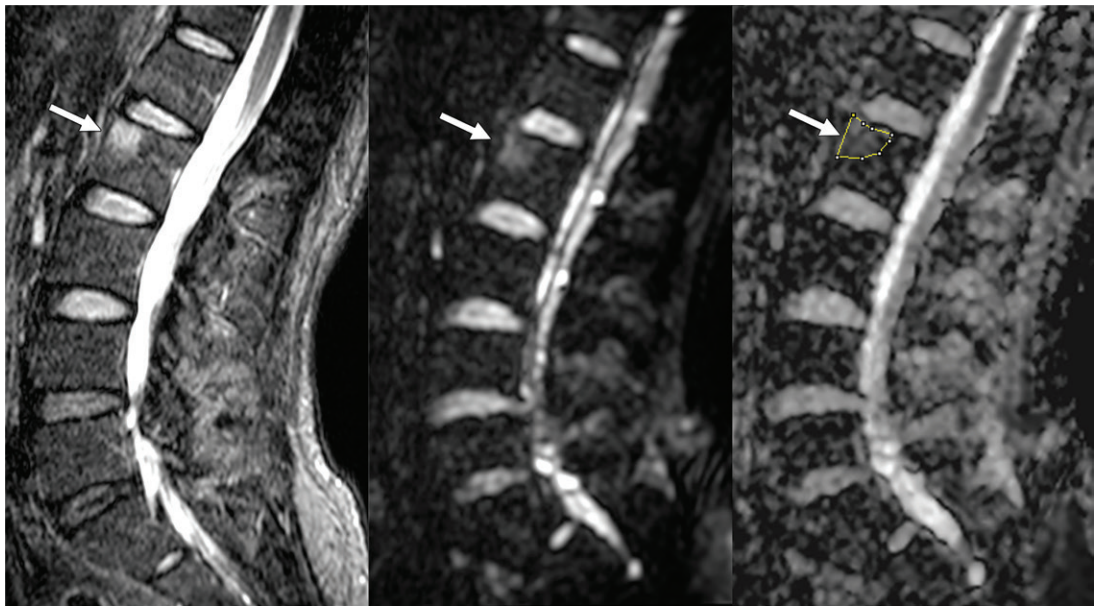

Figure 4: Images in 57-year-old-man with discovertebral lesion involving superior L2 endplate of L1/2 discovertebral unit. Lesion (arrows) could be seen on, left, short inversion time inversion-recovery image, middle, diffusion-weighted MR image with *b* value of 50 mm^2/sec, and, right, apparent diffusion coefficient (ADC) map as area of high signal intensity contiguous with intervertebral disk. ADC measurement at region of interest (outlined area) yielded mean ADC of 0.32×10^{-3} mm^2/sec and maximum ADC of 0.74×10^{-3} mm^2/sec. Normalized mean ADC and normalized maximum ADC were 1.1 and 2.5, respectively, both of which are lower than population means. Spondyloarthritis Research Consortium of Canada MRI index for assessment of spinal inflammation score was elevated to 23. Participant had mild back pain (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] question 2 = 4), low mean stiffness score (mean of BASDAI questions 5 + 6 = 3.5), and mild global impairment (Bath Ankylosing Spondylitis Global Index = 2).

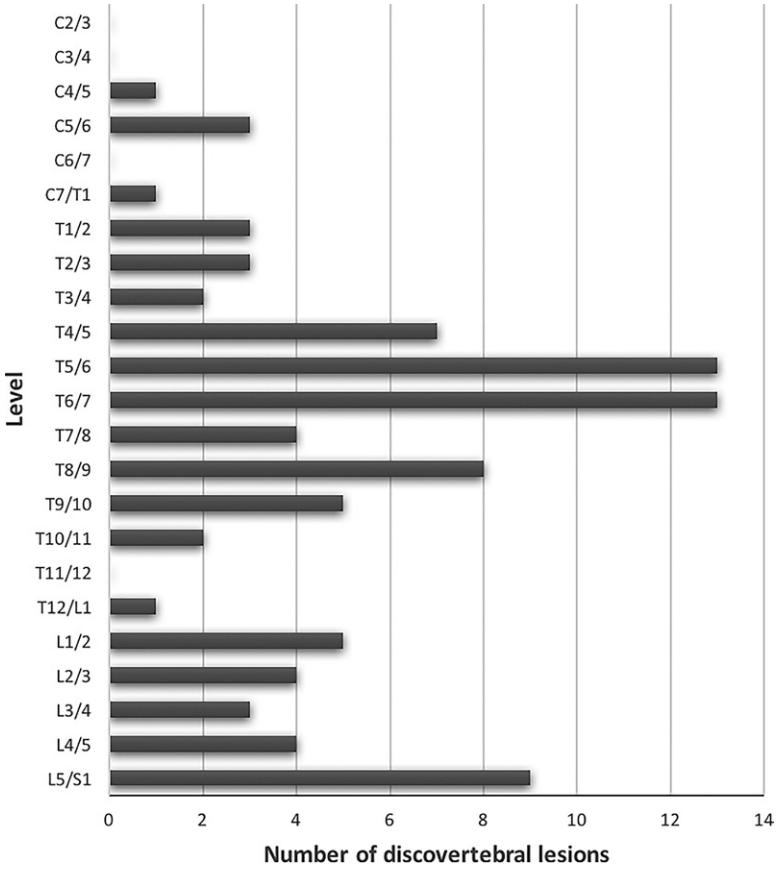

Figure 5: Regional distribution of discovertebral lesions at each spinal level. *C* = cervical, *L* = lumbar, *S* = sacral, *T* = thoracic.

pain severity, mean stiffness score, functional impairment, and patient global assessment. In contrast, SPARCC score of the spine (based on presence of edema on STIR MR images) was associated only with BASFI, a functional score of axial SpA. ADCs of the spine may therefore reflect disease activity better than the traditional SPARCC score.

The results of our study confirmed the positive associations between diffusion MRI–derived parameters of spinal inflammatory lesions and disease activity in participants with axial SpA after adjustment for confounding factors (15). Previous studies focused mainly on the use of ADC in sacroiliac joints and disease diagnosis. ADC data of the spine in participants with axial SpA is limited. Although there were studies on ADCs of sacroiliac joints, they mainly demonstrated the usefulness of ADC in axial SpA diagnosis (8,9,16) and sacroiliac joint disease activity monitoring (17). To our knowledge, the use of spinal ADC for monitoring disease activity in axial SpA has not been previously evaluated.

Previous studies showed a correlation between change in SPARCC score and change in C-reactive protein level after treatment with low-dose infliximab (18,19), whereas there was no correlation between SPARCC score and participant self-reported symptoms or indexes (including BASDAI, patient's global assessment, and total back pain) (19,20). Our findings are in line with those from these previous studies. In

Table 3: Univariable Analysis of Factors Affecting Disease Activity, Functional Outcome, and Patient Global Assessment

Parameter	BASDAI Question 2	Mean of BASDAI Questions 5 + 6	BASFI	BASGI
ADC_{max} ($\times 10^{-3}$mm²/sec)	1.70 (0.04, 3.36) [.05] {50}*	1.70 (−0.18, 3.59) [.08] {50}*	2.21 (0.40, 3.85) [.02] {50}*	1.82 (−0.01, 3.65) [.05] {50}*
ADC_{mean} ($\times 10^{-3}$mm²/sec)	1.54 (−0.94, 4.02) [.22] {50}	1.89 (−0.89, 4.67) [.18] {50}	2.64 (0.09, 5.20) [.04] {50}*	2.03 (−0.67, 4.73) [.14] {50}
$nADC_{max}$	0.47 (0.15, 0.80) [.01] {50}*	0.41 (0.22, 0.79) [.04] {50}*	0.33 (−0.03, 0.70) [.07] {50}*	0.38 (0.00, 0.75) [.05] {50}*
$nADC_{mean}$	0.63 (0.09, 1.17) [.02] {50}*	0.59 (−0.04, 1.21) [.06] {50}*	0.54 (−0.05, 1.12) [.07] {50}*	0.57 (−0.04, 1.17) [.07] {50}*
SPARCC MRI index for assessment of spinal inflammation	0.03 (−0.01, 0.06) [.11] {243}	0.02 (−0.02, 0.05) [.34] {243}	0.05 (0.01, 0.08) [.01] {241}*	0.02 (−0.01, 0.06) [.20] {242}
Age	0.01 (−0.01, 0.03) [.31] {243}	0.01 (−0.01, 0.04) [.23] {243}	0.04 (0.02, 0.07) [< 0.01] {241}*	0.01 (−0.01, 0.04) [.27] {242}
Disease duration	0.01 (−0.02, 0.04) [.40] {243}	0.01 (−0.02, 0.04) [.52] {243}	0.02 (−0.01, 0.05) [.11] {241}	−0.02 (−0.04, 0.01) [.29] {242}
Male sex	0.35 (−0.26, 0.96) [.27] {243}	−0.15 (−0.78, 0.48) [.64] {243}	−0.13 (−0.76, 0.50) [.69] {241}	0.01 (−0.63, 0.65) [.97] {242}
HLA-B27 positivity	−1.13 (−1.92, 0.34) [.01] {233}*	−0.44 (−1.26, 0.39) [.30] {233}	−1.10 (−1.91, −0.29) [.01] {231}*	−0.82 (−1.64, −0.004) [.50] {232}

Note.—Data are regression coefficients. Numbers in parentheses are 95% confidence intervals, numbers in brackets are *P* values, and numbers in braces are numbers of participants. BASDAI question 2 is the back pain score, and the mean of BASDAI questions 5 + 6 is the stiffness score of the back. ADC_{max} = maximum apparent diffusion coefficient (ADC), ADC_{mean} = mean ADC, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASGI = Bath Ankylosing Spondylitis Global Index, HLA-B27 = human leukocyte antigen B27, $nADC_{max}$ = normalized maximum ADC, $nADC_{mean}$ = normalized mean ADC, SPARCC = Spondyloarthritis Research Consortium of Canada.

* Statistically significant.

Table 4: Relationship between MRI Parameters and Functional Disease Activity, Functional Outcome, and Patient Global Assessment

MRI Parameter	BASDAI Question 2	Mean of BASDAI Questions 5 + 6	BASFI	BASGI
ADC_{max} ($\times 10^{-3}$ mm²/sec)	1.59 (−0.11, 3.28) [0.07] {49}	1.67 (−0.21, 3.55) [.08] {50}	1.94 (0.13, 3.75) [.04] {49}*	1.82 (−0.01, 3.65) [.05] {49}*
$nADC_{max}$	0.45 (0.10, 0.81) [.01] {49}*	0.41 (0.22, 0.79) [.04] {50}*	0.28 (−0.12, 0.68) [.16] {49}	0.43 (0.02, 0.83) [.04] {49}*
$nADC_{mean}$	0.61 (0.02, 1.21) [.04] {49}*	0.59 (−0.04, 1.21) [.06] {50}	0.50 (−0.14, 1.15) [.12] {49}	0.57 (−0.04, 1.17) [.07] {50}
SPARCC MRI index for assessment of spinal inflammation	…	…	0.05 (0.01, 0.08) [.01] {231}*	…

Note.—Data are regression coefficients and were obtained with multivariable regression models adjusted for age and human leukocyte antigen B27 activity. Numbers in parentheses are 95% confidence intervals, numbers in brackets are *P* values, and numbers in braces are the sample size. BASDAI question 2 is the back pain score, and the mean of BASDAI questions 5 + 6 is the stiffness score of the back. ADC_{max} = maximum apparent diffusion coefficient (ADC), BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASGI = Bath Ankylosing Spondylitis Global Index, $nADC_{max}$ = normalized maximum ADC, $nADC_{mean}$ = normalized mean ADC, SPARCC = Spondyloarthritis Research Consortium of Canada.

* Statistically significant.

addition, we found that the intensity of inflammation (as reflected in the ADCs) contributed to the pain, stiffness, and overall well-being (as reflected in BASGI) in participants with axial SpA. As BASDAI incorporates nonaxial disease activity, the correlation with ADC was lost in our analyses.

Accurate localization and ADC measurements of spinal inflammation has been reported to be difficult due to the limited spatial resolution of DW imaging of the spine (16). In our study, we demonstrated that ADC measurement of discovertebral lesions in axial SpA was feasible. Most discovertebral lesions (89%) were

visible on ADC maps as discrete hyperintense lesions, suggestive of higher water diffusion. Ten lesions, mainly at the cervical and thoracic levels, were not visible on the DW images or ADC maps. There was also a high failure rate (80%) of ADC measurement in cervical lesions. This was due to severe geometric distortion at the lower cervical spine and sometimes at the thoracic spine, secondary to the variations in magnetic susceptibility at tissues near the cervicothoracic junction (21) and lung–soft tissue interface (22).

We used multiple *b* values in our protocol. The size of the discovertebral lesions decreased as the *b* value increased (23). Because discovertebral lesions demonstrated enhanced diffusion, they appeared smaller on high-*b*-value images than on STIR and low-*b*-value images secondary to reduced signal-to-noise ratio and lack of restricted diffusion (23). In the future, fewer *b* values (two or three) could be used to dedicate more acquisition time to increase spatial resolution.

Our study had limitations. The small number of participants with discovertebral lesions made it impossible to perform subgroup analyses at different spinal levels, and 10 discovertebral lesions observable on the STIR images were not visible on the ADC maps. Nevertheless, the frequency of participants with positive ADC signals was consistent with that in a large international study (24). Selection bias may be present owing to the recruitment of only participants with back pain. Another study limitation was the lack of a control group to identify the ADC pattern in normal or degenerative spine. Because degenerative lesions were excluded from our analysis, it was possible that we falsely excluded lesions with coexisting inflammation and degeneration (25). Our DW imaging and ADC assessment focused on discovertebral lesions, as other spinal inflammatory lesions such as corner lesions and facet joint arthritis were often not well delineated on ADC maps. Despite meticulous delineation of surrounding normal marrow during region of interest placement on the ADC map, inadvertent inclusion of normal marrow adjacent to discovertebral lesions may still occur due to limited spatial resolution. The use of maximum ADCs would enable identification of sites with the most severe inflammation and mitigate the limitation of mean ADCs. Improvements in MRI technique may improve the assessment of axial SpA (26,27).

In conclusion, our study showed positive associations between diffusion MRI–derived parameters of spinal inflammation, disease activity, functional impairment, and patient global assessment in participants with axial spondyloarthritis. The use of apparent diffusion coefficients for the measurement of disease activity at a cross-sectional level is feasible.

Author contributions: Guarantors of integrity of entire study, K.H.L., H.Y.C., V.W.H.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, K.H.L., H.Y.C.; clinical studies, K.H.L., H.Y.C., V.W.H.L., C.S.L.; statistical analysis, K.H.L., H.Y.C., C.S.L.; and manuscript editing, K.H.L., H.Y.C., X.X., C.S.L.

Disclosures of Conflicts of Interest: **K.H.L.** disclosed no relevant relationships. **H.Y.C.** disclosed no relevant relationships. **X.X.** disclosed no relevant relationships. **V.W.H.L.** disclosed no relevant relationships. **C.S.L.** disclosed no relevant relationships.

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