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Original article

# Intensity of spinal inflammation is associated with radiological structural damage in patients with active axial spondyloarthritis

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## Abstract

**Objective.** The aim was to investigate the relationship between the intensity of spinal inflammation using the apparent diffusion coefficient (ADC) and radiographic progression in axial SpA.

**Methods.** This is a cross-sectional study of participants with axial SpA and back pain. Clinical, biochemical and radiological parameters were collected. The ankylosing spondylitis disease activity score (ASDAS)-CRP was determined. Radiographic progression was represented by the modified Stoke ankylosing spondylitis spine score (mSASSS). MRI with short tau inversion recovery (STIR) and diffusion-weighted imaging sequences were performed simultaneously. Inflammatory lesions on STIR were used for the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI indexes and as references in outlining regions of interest in ADC maps to produce mean ($ADC_{mean}$) and maximal ($ADC_{max}$) ADC values. Univariate and multivariate linear regression analyses were used to determine independent associations between ADC and radiographic progression.

**Results.** The 84 participants with identifiable lesions on spinal ADC maps recruited were characterized by a mean (S.D.) age of 45.01 (13.68) years, long disease duration [13.40 (11.01) years] and moderate clinical disease activity [ASDAS-CRP 2.07 (0.83)]. Multivariate regression analysis using $ADC_{mean}$ as the independent variable showed that age (regression coefficient [B] = 0.34; $P = 0.01$), male sex ($B = 0.25$; $P = 0.04$) and $ADC_{mean}$ ($B = 0.30$; $P = 0.01$) were positively associated with mSASSS. Multivariate regression analysis using $ADC_{max}$ as the independent variable showed a tendency for $ADC_{max}$ to be associated with mSASSS ($B = 0.21$; $P = 0.07$).

**Conclusion.** The intensity of spinal inflammation as determined by ADC is associated with radiographic progression in participants with active axial SpA.

**Key words:** modified Stoke ankylosing spondylitis spine score, spondyloarthritis, diffusion-weighted imaging, short tau inversion recovery sequence, Spondyloarthritis Research Consortium of Canada MRI score

CLINICAL SCIENCE

**Key messages**

- Measuring spinal apparent diffusion coefficient values provides useful information on the intensity of axial joint inflammation.
- A higher intensity of inflammation is associated with a higher degree of radiological progression in axial SpA.
- We report a new research methodology in investigating the effect of the intensity of inflammation in axial SpA.

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## Introduction

Prevention of structural damage in the spine has been one of the main goals in treating axial SpA. Spinal structural damage was found to be associated with worse functional status [1], poorer quality of life [2] and increased anxiety and depression [3]. Currently, the most popular method for assessing structural damage in patients with axial SpA is the modified Stoke ankylosing spondylitis score (mSASSS) [4], which uses conventional radiographs of the cervical and lumbosacral spine for scoring. This method is used extensively in axial SpA research.

Traditional factors associated with worse radiographic progression include male sex [5, 6], HLA-B27 positivity [7, 8], smoking [9], elevated CRP concentration [10–12] and baseline syndesmophytes [13]. Data also suggest that MRI evidence of inflammation in the sacroiliac (SI) joints and spine is associated with greater radiographic progression [13, 14]. The currently recommended MRI sequence for axial SpA disease activity assessment is the short tau inversion recovery (STIR) sequence. It is useful in describing the extent but has limited ability in quantifying the degree of inflammation. Recently, we proposed the use of the apparent diffusion coefficient (ADC) of diffusion-weighted imaging (DWI) to quantify inflammation in axial SpA [15]. This method exploits the impedance of water molecules at the tissue level [16] to visualize the bone marrow oedema of spinal inflammation. By removing artefacts, ADC maps produce the most objective measures of the intensity of inflammation in axial joints.

Using this new imaging technique, our study goal was to explore the relationship between the intensity of spinal inflammation and spinal radiographic progression using mSASSS at a cross-sectional level.

## Methods

### Ethics approval and patient recruitment

This is a cross-sectional analysis of a prospectively enrolled cohort. It was registered in the clinical trials registry of the University of Hong Kong (HKUCTR-2087) and approved by the institutional review boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (institutional review board reference no. UW14-085) in addition to ethics committees of the regional hospitals. It was conducted in accordance with the Declaration of Helsinki and the guidance of Good Clinical Practice, 30 November 2006. Participants with an expert diagnosis of axial SpA and chronic back pain were recruited consecutively from eight rheumatology centres in Hong Kong (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital, Pamela Youde Nethersole Eastern Hospital, Caritas Medical Centre, Tseung Kwan O Hospital, Kwong Wah Hospital and Prince of Wales Hospital) from April 2014 to April 2019. All participants recruited were >18 years of age and biologics naive. Written informed consent was obtained from all participants. Participants who were pregnant or who were unable to undergo or declined MRI examination were excluded from the study.

### Clinical assessment and laboratory analysis

Clinical and laboratory data were collected. These data included age, sex, smoking status and drinking habits, duration of back pain and family history of SpA, history of psoriasis and IBD, HLA-B27 status, ESR and CRP levels. Patient were also asked to complete the BASDAI [17] and BAS-G [18] to calculate the ankylosing spondylitis disease activity score based on the CRP (ASDAS-CRP) [19].

### Radiographs and MRIs

Lateral radiographs of the cervical and lumbar spine were performed for mSASSS [4]. Sacroiliac joints and whole-spine MRIs were performed using a 3.0 T imaging unit (Achieva; Philips Healthcare, Best, The Netherlands). They were obtained with a torso coil, with the participants positioned supine. The whole-spine MRI was from the cervical (C2) to the lumbosacral (S1) region. Sagittal images of turbo spin echo (TSE) T1 weighted, STIR imaging and DWI were performed consecutively in the same examination. Free-breathing DWI with fat suppression was performed using a single-shot spin-echo echo-planar imaging sequence with 4 b-value (0, 100, 600 and 1000 s/mm$^2$). Details were described in our previous studies [15, 20]. A summary of the technical details is as follows: TR/TE 800/8 (T1 weighted), 5000/80 (STIR), 4000/90 (DWI); field-of-view 150 mm × 240 mm (T1 weighted and STIR), 300 mm × 241 mm (DWI); slice thickness 3.5 mm (T1 weighted and STIR), 4 mm (DWI); gap 0 mm (T1 weighted, STIR and DWI); and matrix 152 × 157 (T1 weighted and STIR) or 124 × 100 (DWI). All MRIs were performed on a single machine. The acquisition times for the STIR sequence and DWI were 2.48 and 2.44 min, respectively. Only STIR and DWI were used in our analyses.

### Scoring of radiographs and SPARCC MRI scores

Lateral radiographs of the cervical and lumbosacral spine were scored for mSASSS by two readers (H.H.L.T. and A.H.Y.N.). H.H.L.T. and A.H.Y.N. are rheumatologists with 5 and 2 years of experience in SpA radiograph and MRI interpretation, respectively. The average mSASSS of the two readers was used for analyses. The STIR images of the whole spine were scored independently by a rheumatologist and a rheumatology trainee (H.Y.C. and S.C.W.C.) according to the Spondyloarthritis Research Consortium of Canada (SPARCC) spine MRI index [21] and SPARCC saroiliac (SI) MRI index [22]. H.Y.C. has 8 years of experience in axial SpA MRI interpretation, and S.C.W.C. has 4 years of experience. The average SPARCC scores of the two readers were used for analyses. All STIR imagines were read using a commercially available software package (OsirixX, v.9.5.2; Osirix Foundation, Geneva, Switzerland).

### Diffusion-weighted image interpretation

From the scored STIR images, a musculoskeletal radiologist (K.H.L., with 4 years of experience in axial SpA MRI interpretation) identified all the inflammatory lesions and excluded significant degenerative lesions. Two readers, a medical trainee (E.T.F.C.) with 2 years of experience in axial SpA MRI interpretation and a rheumatologist (H.Y.C.) with 8 years of experience in axial SpA MRI interpretation, drew regions of interest based on the inflammatory lesions identified by the musculoskeletal radiologist (K.H.L.) on the respective ADC maps. Both mean ($ADC_{mean}$) and maximal ($ADC_{max}$) ADC values of the identified inflammatory lesions were determined. All ADC values were determined with the commercially available software (Osirix, v.9.5.2).

All the readers for radiographs and MRIs were blinded to the clinical, biochemical and imaging parameters other than the image they were required to read.

### Statistical analysis

Continuous data were presented as the mean (S.D.). Categorical data were presented as a percentage. Student's unpaired *t*-test and the $\chi^2$ test were used to compare continuous and categorical variables in participants with and without ADC lesions. Mean ADC values, SPARCC scores and mSASSS of the readers were used for statistical analyses.

Univariate linear regression analyses were performed with mSASSS as the dependent variable and with $ADC_{mean}$, $ADC_{max}$, SPARCC spine index, SPARCC SI joint index and other potential confounding factors as the independent variables. These potential confounding factors included age, male sex, duration of back pain, smoking and drinking, family history of SpA, ASDAS-CRP and HLA-B27 status.

In univariate analyses, both $ADC_{mean}$ and $ADC_{max}$ had *P*-values of $<0.1$ (see Results). Therefore, two multivariate regression models were constructed using mSASSS as the dependent variable. The first model incorporated $ADC_{mean}$ as an independent variable, whereas the second one used $ADC_{max}$ as an independent variable. To eliminate potential multicollinearity, we also performed subgroups analyses using $ADC_{max}$, $ADC_{mean}$ and SPARCC spine MRI score individually as the independent variable in multivariate analyses. Confounding factors with a *P*-value $<0.1$ in univariate regressions were also included in the multivariate analyses as independent variables. The results were reported as regression coefficients and 95% CIs.

Inter-observer agreements of SPARCC scores, ADC values and mSASSS between different readers were determined by the intraclass correlation coefficient. The degree of 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 [23].

All statistics were performed with commercial software (IBM SPSS Statistics v.25.0). A *P*-value of $<0.05$ was considered statistically significant. Listwise deletion was performed for missing data.

### Sample size calculation

The sample size was calculated based on our previous study, which showed that 23.8% of axial SpA patients had active disease without spinal degeneration as evident by positive spinal DWI [24]. We assumed that 0.35% [25] of the population (7.5 million) had axial SpA; using a CI of 95% and 5% margin of error, the estimated sample size would be 276 patients. We included a 10% allowance during recruitment of subjects. The final recruited sample size was 303.

## Results

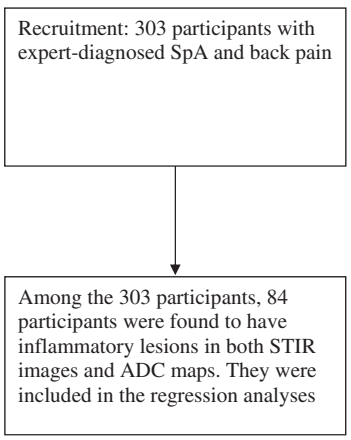
### Baseline demographic data

We recruited 303 participants with expert-diagnosed SpA and back pain. There were 171 male and 132 female participants. Among the recruited participants, 297 (98%) participants were Chinese. Their mean age was 43.7 (13.3) years, with a mean disease duration of 11.7 (11.0) years. There were 218 (72.19%) participants with a duration of back pain $>3$ years. Eight (2.6%) had a history of IBD and 44 (14.5%) had history of psoriasis. The prevalence of smokers and drinkers was 27.8 and 10.1%, respectively. HLA-B27 was positive in 80.5% of them. The participants had moderate clinical disease activity, with the mean ASDAS-CRP equal to 2.0 (0.9). The average back pain numerical rating score was 5.6 (2.4). Eighty-four (27.7%) had identifiable inflammatory lesions in both STIR images and ADC maps, and they were included in the regression analyses (Fig. 1).

### Data on radiographs, STIR sequence MRI and ADC values

Most of the inflammatory lesions identified were in the thoracic region (51/84 or 60.7%), followed by lumbar (20/84 or 23.8%) and cervical regions (14/84 or 16.7%). The average SPARCC spine MRI score was 6.45 (8.90),

**Fig. 1** Study flow chart of patient enrolment




ADC: apparent diffusion coefficient; SpA: spondyloarthritis; STIR: short tau inversion recovery.

**Table 1** Demographic details of participants

| Characteristic | With ADC lesion | Without ADC lesion | *P*-value |
|---|---|---|---|
| Age, mean (S.D.), years ($n = 303$) | 45.01 (13.68) | 42.64 (13.37) | 0.041 |
| Male sex, *n* (%) | 56/84 (66.7) | 115/219 (52.5) | 0.026 |
| HLA-B27, *n* (%) | 71/83 (85.5) | 165/210 (78.6) | 0.176 |
| Duration of back pain, mean (S.D.), years ($n = 301$) | 13.40 (11.01) | 11.12 (11.70) | 0.183 |
| Family history of SpA, *n* (%) | 17/79 (21.5) | 48/209 (23.0) | 0.79 |
| Ever smoker, *n* (%) | 28/83 (33.7) | 56/219 (25.6) | 0.159 |
| Ever drinker, *n* (%) | 9/82 (11.0) | 21/215 (9.8) | 0.758 |
| CRP (mg/dl), mean (S.D.) ($n= 303$) | 1.21 (1.46) | 0.97 (2.00) | 0.103 |
| ESR (mm/hr), mean (S.D.) ($n = 301$) | 37.6 (24.5) | 30.5 (25.3) | 0.03 |
| Back pain NRS, mean (S.D.) | 5.78 (2.38) | 5.56 (2.42) | 0.48 |
| ASDAS-CRP, mean (S.D.) ($n = 288$) | 2.07 (0.83) | 1.95 (0.90) | 0.202 |
| SPARCC SI MRI score, mean (S.D.) ($n =299$) | 3.40 (5.90) | 3.10 (6.07) | 0.703 |
| SPARCC spine MRI score, mean (S.D.) ($n= 303$) | 14.31 (10.78) | 3.50 (5.93) | $<0.001$ |
| mSASSS, mean (S.D.) ($n = 278$) | 8.03 (16.51) | 13.33 (16.69) | 0.029 |

ADC: apparent diffusion coefficient; ASDAS: ankylosing spondylitis disease activity score; NRS: numerical rating score; SI: sacroiliac; SPARCC: Spondyloarthritis Research Consortium of Canada.

the average SPARCC SI MRI score was 3.18 (6.02) and the average mSASSS was 9.72 (16.67). Most (179/278 or 64.4%) of the studied participants had mSASSS $\geq 1$. The average $ADC_{max}$ was 1474.90, and the average $ADC_{mean}$ was 784.76. Overall, our participants had significant spinal radiological progression.

Inter-observer agreement among the readers as reported by Cronbach's $\alpha$ coefficient were as follows: $ADC_{max}$, 0.90; $ADC_{mean}$, 0.85; SPARCC SI MRI score, 0.95; SPARCC spine MRI score, 0.95; and mSASSS, 0.96.

### Comparisons between participants with and without ADC lesions

Comparisons between participants with and without ADC lesions are shown in Table 1. Participants with ADC lesions were significantly older, predominantly male, with a longer duration of back pain, higher ESR, higher SPARCC spine MRI index and increased radiological progression with higher mSASSS.

### Univariate regression analyses using mSASSS as a dependent variable

Univariate linear regression analyses using mSASSS as a dependent variable showed that age, male sex, smoking, duration of back pain, $ADC_{max}$, $ADC_{mean}$ and SPARCC SI MRI score were independently associated with mSASSS ($P < 0.05$; Table 2).

### Multivariate regression analyses using mSASSS as a dependent variable

Multivariate regression analysis using $ADC_{mean}$ as the independent variable showed that age ([regression coefficient] $B = 0.34$; $P = 0.01$), male sex ($B = 0.25$; $P = 0.04$) and $ADC_{mean}$ ($B = 0.30$; $P = 0.01$) were positively associated with mSASSS. Multivariate regression analysis using $ADC_{max}$ as the independent variable showed a tendency for $ADC_{max}$ to be associated with mSASSS ($B = 0.21$; $P = 0.07$; Table 3). Table 4 shows multivariate subgroups analyses using $ADC_{max}$, $ADC_{mean}$ and SPARCC spine MRI score individually as independent variables.

Figure 2 shows an example of measurement of spinal ADC values in a participant with active axial SpA.

## Discussion

We explored the relationship between the intensity of spinal inflammation and the degree of ankylosis. In this report, we found a positive association between the average intensity of spinal inflammation and radiographic progression in patients with active axial SpA. In addition, the maximal intensity of spinal inflammation also tended to be associated with mSASSS.

There is increasing evidence on the relationship between inflammation and disease progression in patients with axial SpA [14]. Studies show that inflammation on MRI is an independent predictor for radiographic progression. Inflammation and fatty changes on MRI predict the development of syndesmophytes [26]. In addition, bone marrow oedema on MRI of the SI joints predicts the development of radiographic sacroiliitis 5 years later [27]. Several studies on biologics have also demonstrated diminished radiographic progression upon suppression of MRI inflammation [28, 29]. All these data demonstrated a positive relationship between spinal inflammation and new bone formation. Our results, which showed associations between the degree of spinal inflammation and radiographic progression, are in line with these studies.

The ADC is a newly proposed method to assess the amount of spinal inflammation in patients with axial SpA [15, 30]. Although no study has validated the ADC parameters with the degree of spinal inflammation detected by biopsy, our previous studies showed that it

**Table 2** Univariate linear regression analyses using mSASSS as the dependent variable

| Parameter | Standard coefficient | Regression coefficient(95% CI) | *P*-value |
|---|---|---|---|
| Age ($n = 278$) | 0.46 | 0.57 (0.44, 0.70) | <0.001 |
| Male sex ($n = 278$) | 0.22 | 7.35 (3.48, 11.23) | <0.001 |
| Smoker ($n = 278$) | 0.19 | 7.02 (2.69, 11.35) | 0.002 |
| Drinker ($n = 273$) | 0.11 | 5.69 (−0.70, 12.07) | 0.08 |
| HLA-B27 positivity ($n = 271$) | 0.02 | 0.90 (−4.13, 5.92) | 0.73 |
| Duration of back pain ($n = 277$) | 0.38 | 0.56 (0.40, 0.72) | <0.001 |
| Family history of SpA ($n = 264$) | −0.03 | −1.30 (−6.17, 3.57) | 0.60 |
| ASDAS-CRP ($n = 267$) | 0.06 | 1.21 (−1.14, 3.56) | 0.31 |
| $ADC_{max}$ ($n = 77$) | 0.26 | 0.01 (0.002, 0.03) | 0.02 |
| $ADC_{mean}$ ($n = 77$) | 0.24 | 0.02 (0.001, 0.04) | 0.04 |
| SPARCC SI MRI score ($n = 276$) | −0.20 | −0.60 (−0.94, −0.25) | 0.01 |
| SPARCC spine MRI score ($n = 278$) | 0.20 | 0.38 (0.16, 0.60) | 0.001 |

ADC: apparent diffusion coefficient; $ADC_{max}$: maximal ADC value; $ADC_{mean}$: mean ADC value; ASDAS: ankylosing spondylitis disease activity score; SI: sacroiliac; SPARCC: Spondyloarthritis Research Consortium of Canada.

**Table 3** Multivariate analyses using maximal and mean apparent diffusion coefficient as independent factors

| Characteristic | Multivariate analyses using $ADC_{max}$ as independent factor ($n = 74$) | | | Multivariate analyses using $ADC_{mean}$ as independent factor ($n = 74$) | | |
|---|---|---|---|---|---|---|
| | Standard coefficient | Regression coefficient (95% CI) | *P*-value | Standard coefficient | Regression coefficient (95% CI) | *P*-value |
| Age | 0.35 | 0.42 (0.11, 0.73) | 0.01 | 0.34 | 0.41 (0.11, 0.71) | 0.01 |
| Male sex | 0.19 | 6.63 (−1.63, 14.89) | 0.11 | 0.25 | 8.85 (0.61, 17.09) | 0.04 |
| Smoker | −0.10 | −3.43 (−11.46, 4.61) | 0.40 | −0.11 | −3.94 (−11.77, 3.90) | 0.32 |
| Drinker | 0.12 | 6.06 (−5.12, 17.23) | 0.28 | 0.12 | 5.96 (−4.90, 16.82) | 0.28 |
| Duration of back pain | 0.11 | 0.17 (−0.21, 0.54) | 0.38 | 0.17 | 0.25 (−0.12, 0.62) | 0.18 |
| $ADC_{max}$ | 0.21 | 0.01 (−0.001, 0.02) | 0.07 | – | – | – |
| $ADC_{mean}$ | – | – | – | 0.30 | 0.03 (0.01, 0.05) | 0.01 |
| SPARCC SI MRI score | 0.03 | 0.09 (−0.62, 0.81) | 0.80 | −0.001 | −0.002 (−0.69, 0.69) | 0.99 |
| SPARCC spine MRI score | 0.16 | 0.24 (−0.10, 0.59) | 0.17 | 0.16 | 0.24 (−0.10, 0.58) | 0.16 |

ADC: apparent diffusion coefficient; $ADC_{max}$: maximal ADC value; $ADC_{mean}$: mean ADC value; ASDAS: ankylosing spondylitis disease activity score; SI: sacroiliac; SPARCC: Spondyloarthritis Research Consortium of Canada.

has good associations with back pain score [15], functional status [15], global assessment [15] and ASDAS [31]. Our present data and previously published data also showed good reliability [15, 31]. In addition, its ability to quantify inflammation has proven utility in a number of diseases [30, 32, 33]. In contrast, conventional MRI is more useful in describing the extent of spinal inflammation [34]. Using DWI ADC, we quantified the degree of inflammation [15, 34] which was found to be independently associated with radiographic progression. Unlike the STIR images, the present ADC technique concentrates on quantifying the intensity of the inflammatory lesion, and no meaningful value could be obtained if there was no identifiable lesion on the ADC map. Therefore, we did not include participants without spinal inflammation in analyses. Spinal ADC values in patients without inflammatory lesions may be affected by a number of conditions, such as age, osteoporosis [35] and skeletal maturity [36], and may not represent the true degree of inflammation. Therefore, our study demonstrated the associations only in patients with active axial SpA.

We recruited into our study biologics-naive participants with a long duration of disease (>10 years) and persistent back pain. Although NSAID/cyclooxygenase II inhibitor has been shown to be useful to induce remission in AS, the remission rate is low (9.1–17.6%) [37]. Despite there being no longitudinal spinal ADC data in patients with axial SpA, it would be reasonable to assume that most of our participants had chronic spinal inflammation, despite NSAID/cyclooxygenase II inhibitor treatment, based on the low spontaneous/NSAID-induced remission rate. We found increased radiographic damage in patients with increased spinal inflammatory load.

TABLE 4 Multivariate analyses using maximal and mean apparent diffusion coefficient and Spondyloarthritis Research Consortium of Canada spine MRI score as independent factors

| Characteristic | Multivariate analyses using $ADC_{max}$ as independent factor ($n = 74$) | | | Multivariate analyses using $ADC_{mean}$ as independent factor ($n = 74$) | | | Multivariate analyses using SPARCC spine as independent factor ($n = 270$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Standard coefficient | Regression coefficient (95% CI) | *P*-value | Standard coefficient | Regression coefficient (95% CI) | *P*-value | Standard coefficient | Regression coefficient (95% CI) | *P*-value |
| Age | 0.37 | 0.15, 0.76 | 0.01 | 0.36 | 0.14, 0.74 | 0.004 | 0.38 | 0.31, 0.61 | <0.001 |
| Male sex | 0.24 | 0.46, 16.32 | 0.04 | 0.30 | 2.73, 18.54 | 0.01 | 0.20 | 0.29, 10.20 | <0.001 |
| Smoker | −0.10 | −11.54, 4.64 | 0.40 | −0.11 | −11.86, 3.93 | 0.32 | 0.06 | −1.92, 6.25 | 0.30 |
| Drinker | 0.09 | −6.57, 15.44 | 0.42 | 0.09 | −6.35, 15.04 | 0.42 | 0.03 | −4.09, 7.52 | 0.56 |
| Duration of back pain | 0.08 | −0.25, 0.49 | 0.52 | 0.14 | −0.17, 0.58 | 0.27 | 0.18 | 0.09, 0.42 | 0.003 |
| $ADC_{max}$ | 0.22 | 0.00, 0.02 | 0.06 | – | – | – | – | – | – |
| $ADC_{mean}$ | – | – | – | 0.31 | 0.01, 0.05 | 0.01 | – | – | – |
| SPARCC SI MRI score | 0.01 | −0.68, 0.76 | 0.92 | −0.02 | −0.75, 0.63 | 0.87 | −0.05 | −0.47, 0.19 | 0.40 |
| SPARCC spine MRI score | – | – | – | – | – | – | 0.07 | −0.06, 0.34 | 0.17 |

ADC: apparent diffusion coefficient; $ADC_{max}$: maximal ADC value; $ADC_{mean}$: mean ADC value; ASDAS: ankylosing spondylitis disease activity score; SI: sacroiliac; SPARCC: Spondyloarthritis Research Consortium of Canada.

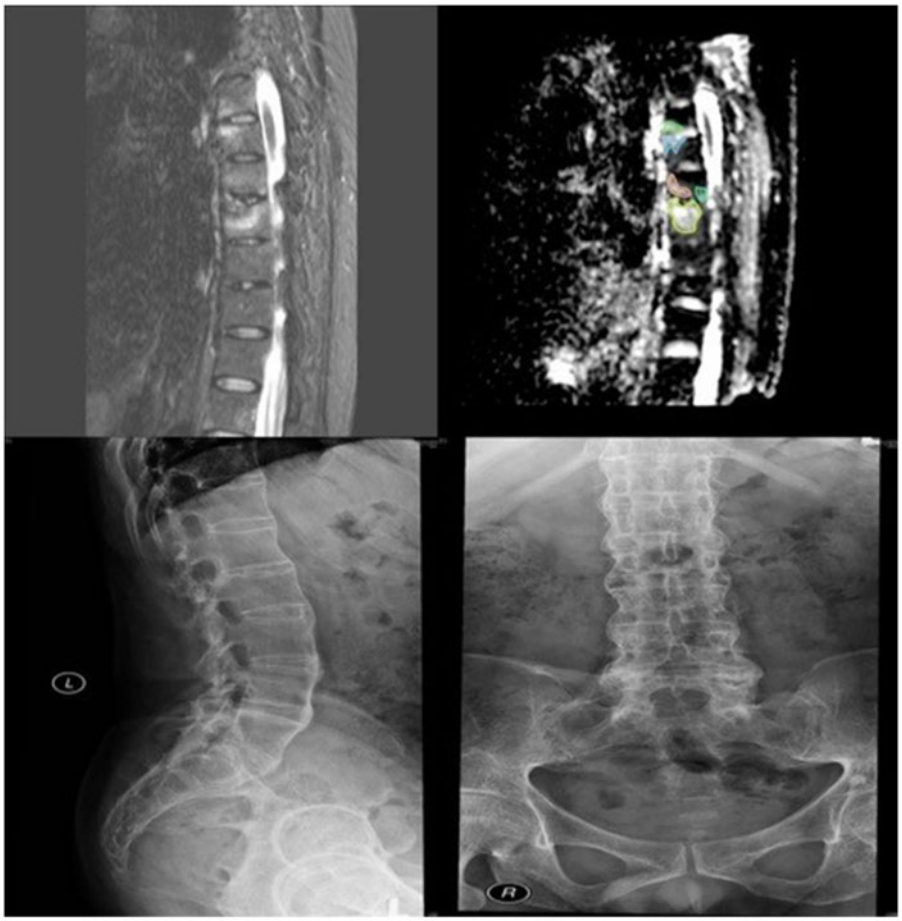
Apart from spinal inflammation, there are other risk factors for radiographic progression in axial SpA. This could explain, in part, the formation of syndesmophytes in patients without active axial disease. Our data also showed a significant degree of new bone formation in the inactive group. In the group with active axial disease, we adjusted the confounding factors for radiological progression as reported in other international studies. Apart from MRI, patients >40 years of age showed a 2.5-fold higher radiographic progression rate than patients <40 years of age [38]. Men had greater spinal radiographic progression than women [39]. The 12 year prospective follow-up of the OASIS study also showed that radiographic progression occurred significantly faster in men and in HLA-B2- positive patients [40]. Other prognostic factors, including disease duration [38], smoking [9, 41, 42] and ASDAS [43], were also included in our analyses. We found that age and sex were independently associated with mSASSS, whereas SPARCC MRI spine and SI joint indexes lost their associations. The results suggest that the intensity of inflammation could have a more important association with radiographic progression in patients with active axial SpA.

Compared with $ADC_{max}$, $ADC_{mean}$ appeared to be more associated with radiographic progression. The $ADC_{max}$ was measured by the lesion with the highest intensity, whereas the $ADC_{mean}$ represented the average ADC values of all spinal inflammatory lesions. Our findings suggested that the average inflammatory load might be more associated with radiographic progression. Nonetheless, $ADC_{mean}$ would depend on the regions of interests drawn. Given that inflammation is not homogeneous, the readers could errroneously have recruited normal tissues during the calculation of $ADC_{mean}$. Accurate localization of inflammatory lesions on the ADC map has been reported to be difficult [44].

Although ASDAS-CRP had no correlation with mSASSS in our analyses, a previous study showed that higher ASDAS would lead to more radiographic damage in the spine in patients with AS [43]. This could be attributable to the limited ability of cross-sectional analyses to find associated factors. Nevertheless, in our recent study, we found that ASDAS-CRP was associated with the intensity of spinal inflammation as measured by ADC in patients with active axial SpA [31]. These data highlight the importance of the intensity of spinal inflammation for radiographic progression.

The use of ADC has limitations. As stated previously, meaningful ADC values could be applied only in patients with inflammatory lesions on MRI of the spine. This restricted the number of patients involved in the analyses. The ADC values from different MRI machines could not be compared directly. Meaningful comparisons between machines will usually require normalization of ADC values [15]. However, there is no consensus or validation regarding the methods of normalization. Given that a single MRI machine was used in our study, normalization was deemed unnecessary.

**Fig. 2** Short tau inversion recovery images and apparent diffusion coefficient values in a 51-year-old man with radiographic axial SpA



Right upper: bone marrow edema showing up as hyperintensity on STIR image. Left upper: reader drawn ROI on ADC maps to measure ADC max and ADC mean. Right lower: lateral view radiograph of lumbo-sacral spine. Left lower: anteroposterior view radiograph of lumbo-sacral spine.

There are other limitations. Our cohort included only participants with back pain, which might have excluded asymptomatic patients with active spinal inflammation, resulting in selection bias. The exclusion of spinal degenerative lesions might also have excluded patients with co-existing inflammation and degeneration. We did not include DWI ADC of SI joints in our analyses because they have not been validated for assessment of disease activity. The cross-sectional analyses might not represent the true relationship between the degree of inflammation and new bone formation. Further study on different applications of DWI ADC in patients with axial SpA and prospective analyses of its relationship with bone ankylosis on both spinal and individual vertebral levels will lead to greater understanding of both the imaging technique and the disease.

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