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

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Abstract

Objective To investigate the relationship between intensity of spinal inflammation using apparent diffusion coefficient (ADC) and radiographic progression in axial spondyloarthritis (SpA)

Methods This is a cross-sectional study of participants with axial SpA and back pain. Clinical, biochemical, radiological parameters were collected. Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP was determined. Radiographic progression was represented by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Magnetic resonance imaging (MRI) with short tau inversion recovery (STIR) and diffusion weighted imaging (DWI) sequences were simultaneously performed. Inflammatory lesions on STIR were used for the Spondyloarthritis research Consortium of Canada (SPARCC) MRI indexes, and as references in outlining regions of interest (ROI) in ADC maps to produce mean (ADC mean) and maximum (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 age of 45.01±13.68 years, long disease duration (13.40±11.01) and moderate clinical disease activity (ASDAS-CRP 2.07±0.83).
Multivariate regression analysis using ADC mean as the independent variable showed that age (B=0.34; p=0.01), male gender (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**
Intensity of spinal inflammation as determined by ADC is associated with radiographic progression in participants with active axial SpA.

**Keywords**
modified Stoke Ankylosing Spondylitis Spine Score, Spondyloarthritis, diffusion weighted imaging, short tau inversion recovery sequence, Spondyloarthritis Research Consortium of Canada MRI score

**Key messages**
- Measuring spinal ADC values provides useful information on intensity of axial joints inflammation.
- 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 intensity of inflammation in axial SpA.
Introduction

Preventing structural damage in spine has been one of the main goals in treating axial spondyloarthritis (SpA). Spinal structural damage was found to associate with worsened functional status (1), poorer quality-of-life (2), and increased anxiety and depression (3). Currently the most popular method of 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 lumbo-sacral spine for scoring. This method is used extensively in axial SpA research.

Traditional factors associated with worse radiographic progression include male gender (5, 6), Human Leucocyte Antigen (HLA) B27 positivity (7, 8), smoking (9), elevated c-reactive protein (CRP) level (10-12), and baseline syndesmophytes (13). Data also suggests magnetic resonance imaging (MRI) inflammation in the sacroiliac (SI) joints and spine are associated with greater radiographic progression (13, 14). The current recommended MRI sequence for axial SpA disease activity assessment is 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 using apparent diffusion coefficient (ADC) of the 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 edema of spinal
inflammation. By removing artifacts, ADC maps produce the most objective measures of intensity of inflammation in axial joints.

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

**Methods**

*Ethics approval and patient recruitment*

This is a cross-sectional analysis of a prospectively enrolled cohort. It has been 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) as well as ethics committees of the regional hospitals. It was conducted in accordance with the Declaration of Helsinki and the guidance of Good Clinical Practice, November 30, 2006. Participants with an expert diagnosis of axial SpA and chronic back pain were consecutively recruited from 8 rheumatology centers in Hong Kong (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital, Pamela Youde Nethersole Eastern Hospital, Caritas Medical Centre, Tseung Kwan O Hospital, United Christian Hospital, Caritas Medical Centre, Tuen Mun Hospital).
Kwan O Hospital, Kwong Wah Hospital, and Prince of Wales Hospital) from April 2014 to April 2019. All recruited participants were older than 18 years and biologics naive. Written informed consent was obtained from all participants. Participants who were pregnant, unable to undergo or declined MRI examination were excluded from the study.

Clinical assessment and laboratory analysis

Clinical and laboratory data were collected. These included age, sex, smoking status and drinking habit, duration of back pain and family history of SpA, history of psoriasis and inflammatory bowel disease, HLA B27 status, erythrocyte sedimentation rate (ESR) and CRP levels. Patient were also asked to complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (17) and Bath Ankylosing Spondylitis Global score (BASG) (18) to calculate the Ankylosing Spondylitis Disease Activity Score based on the CRP (ASDAS-CRP) (19).

Radiographs and MRIs

Lateral views of the cervical and lumbar X rays 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 done by a torso coil with the participants positioned supine. The whole spine MRI was from cervical (C2)
to lumbosacral (S1) region. Sagittal images of 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 sec/mm$^2$). Details had been described in our previous studies (15, 20). Summary of the technical details were as follow: TR/TE 800/8 (T1 weighted), 5000/80 (STIR), 4000/90 (DWI); field-of-view 150x240 mm$^2$ (T1 weighted and STIR), 300x241 mm$^2$ (DWI); Slice thickness 3.5mm (T1 weighted and STIR), 4mm (DWI); Gap 0mm (T1 weighted, STIR, and DWI); Matrix 152x157 (T1 weighted and STIR), 124x100 (DWI). All MR images were performed on a single machine. The acquisition time for STIR sequence and DWI were 2.48 minutes and 2.44 minutes respectively. Only STIR and DWI were used in our analyses.

**Scoring of radiographs and SPARCC MRI scores**

Lateral views of cervical and lumbosacral radiographs were scored for mSASSS by two readers (HHLT, AHYN). HHLT and AHYN were rheumatologists with 5 years’ and 2 years’ experience in SpA radiographs and MRI interpretation respectively. Average mSASSS of the two readers was used for analyses. The STIR images of whole spine were scored independently by a rheumatologist and a rheumatology trainee (HYC, SCWC) according to the Spondyloarthritis research Consortium of Canada (SPARCC) spine MRI index (21) and SPARCC SI MRI index.
HYC had 8 years of experience in axial SpA MRI interpretation while SCWC had 4 years’ experience. Average SPARCC scores of the two readers were used for analyses. All STIR imagines were read by using a commercially available software (OsirixX, version 9.5.2, Osirix Foundation, Geneva, Switzerland).

**DW Image interpretation**

From the scored STIR images, a musculoskeletal radiologist (KHL, with 4 years of experience in axial SpA MRI interpretation) identified all inflammatory lesions and excluded significant degenerative lesions. Two readers, a medical trainee (ETFC) with 2 years of experience in axial SpA MRI interpretation, and one rheumatologist (HYC), with 8 years of experience in axial SpA MRI interpretation, drew regions of interest (ROIs) based on the inflammatory lesions identified by the musculoskeletal radiologist (KHL) in the respective ADC maps. Both mean (ADC mean) and maximum (ADC max) ADC values of the identified inflammatory lesions were determined. All ADC values were determined by the commercially available software (Osirix, version 9.5.2, Osirix Foundation, Geneva, Switzerland).

All the readers for radiographs and MRI 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 mean ± standard deviation. Categorical data were presented as percentage. The independent t test and Chi-square test were used to compare continuous and categorical variables in participants with and without ADC lesion. 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; ADC mean, ADC max, SPARCC spine index, SPARCC SI joints index, and other potential confounding factors as the independent variables. These potential confounding factors include age, male sex, back pain duration, 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 less than 0.1 (refer to results). Therefore, 2 multivariate regression models were built up using mSASSS as dependent variable. The first model incorporated ADC mean as an independent variable while 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 independent variables in multivariate analyses. Confounding factors with a p-value <0.1 in univariate regressions were also included in the multivariate analyses as independent
variables. Results were reported as regression coefficients and 95% confidence intervals.

Interobserver agreements of SPARCC scores, ADC values, and mSASSS between different readers were determined by 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 version 25.0). P-value of <0.05 was considered statistically significant. Listwise deletion was performed for missing data.

Sample size calculation

Sample size was calculated based on our previous study which showed 23.8% of axial SpA patients had active disease without spinal degeneration as evident by positive spinal DWI (24). We assumed 0.35% (25) of the population (7.5M) had axial SpA, using a confidence level of 95% and 5% margin of error, the estimated sample size would be 276 patients. We included a 10% allowance during subjects’ recruitment. 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 back pain duration more than 3 years. Eight (2.6%) had history of inflammatory bowel disease and 44 (14.5%) had history of psoriasis. Prevalence of smoker and drinker were 27.8% and 10.1%, respectively. HLA B27 was positive in 80.5% of them. The participants had a moderate clinical disease activity with mean ASDAS-CRP equal to 2.0±0.9. Average back pain numerical rating score (NRS) 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 (figure 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 region (14/84 or 16.7%). Average SPARCC spine MRI score was 6.45±8.90, average SPARCC SI MRI score was 3.18±6.02, and average mSASSS was 9.72±16.67. Most (179/278 [64.4%]) of the
studied participants had mSASSS ≥1. The average ADC max was 1474.90 and average ADC mean was 784.76. Overall, our participants had significant spinal radiological progression.

Interobserver agreement among the readers as reported by Cronbach's Alpha coefficient were: ADCmax 0.90; ADCmean 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 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 dependent variable

Univariate linear regression analyses using mSASSS as dependent variable showed that age, male gender, smoker, duration of back pain, ADCmax, ADCmean and SPARCC SI MRI score were independently associated with mSASSS (p<0.05) (Table 2).
Multivariate regression analyses using mSASSS as dependent variable

Multivariate regression analysis using ADC mean as the independent variable showed that age (B=0.34; p=0.01), male gender (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 showed multivariate subgroups analyses using ADC max, ADC mean, and SPARCC spine MRI score individually as independent variables.

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

Discussion

We explored the relationship between intensity of spinal inflammation and degree for 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 maximum intensity of spinal inflammation also tended to associate with mSASSS.
There is increasing evidence on the relationship between inflammation and disease progression in patients with axial SpA (14). Studies show that MRI inflammation is an independent predictor for radiographic progression. Inflammation and fatty changes on MRI predict the development of syndesmophytes (26). In addition, bone marrow edema (BME) on MRI of the SI joints predicts the development of radiographic sacroiliitis in 5 years’ time (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 degree of spinal inflammation and radiographic progression, are in line with these studies.

ADC is a newly proposed method to assess the amount of spinal inflammation in patients with axial SpA (15, 33). Although no study has validated the ADC parameters with degree of spinal inflammation detected by biopsy, our previous studies showed it has good associations with back pain score (15), functional status (15), global assessment (15) and ASDAS (30). Our current data and previously published data also showed good reliability (15, 30). In addition, its ability in quantifying inflammation has proven utility in a number of diseases (31-33). In contrast, conventional MRI is more useful in describing the extent of spinal inflammation (34). Using DWI-ADC, we quantified the degrees of inflammation (15, 34) which are found to be independently associated with radiographic progression.
Unlike the STIR images, the current ADC technique concentrates on quantifying the intensity of inflammatory lesion and no meaningful value could be obtained if there is no identifiable lesion on 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), skeletal maturity (36), and may not represent the true degree of inflammation. Therefore, our study only demonstrated the associations in patients with active axial SpA.

We recruited biologics na"ive participants with long disease duration (more than 10 years) and persistent back pain into our study. Although non-steroid anti-inflammatory drugs (NSAIDs)/ cyclooxygenase-II (COX II) inhibitor has been shown to be useful to induce remission in ankylosing spondylitis (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 most of our participants had chronic spinal inflammation despite NSAID/ COX II treatments based on the low spontaneous/ NSAID induced remission rate. Our results reported an increased radiographic damage in patients with increased spinal inflammatory load.

Apart from spinal inflammation, there are other risk factors for radiographic progression in axial SpA. This could partially explain the reason of syndesmophytes formation 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
by other international studies. Apart from MRI, patients greater than 40 years of age
showed a 2.5-fold higher radiographic progression rate than patients less than 40
years (38). Men had greater spinal radiographic progression than women (39). The 12
years prospective follow-up of the OASIS study also showed that radiographic
progression occurred significantly faster in men and in HLA B27 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 age and gender were
independently associated with mSASSS while SPARCC MRI spine and SI joints
indexes lost their associations. The results suggest intensity of inflammatory could be
a more important association with radiographic progression in patients with active
axial SpA.

Compared to ADC max, ADC mean appeared to be more associated with
radiographic progression. ADC max was measured by the value with highest intensity
while ADC mean represented the average ADC values of all spinal inflammatory
lesions. Our findings suggested the average of inflammatory load could be more
associated with radiographic progression. Having said that, ADC mean would depend
on the ROIs drawn. As inflammation is not homogenous, the readers could have
recruited falsely normal tissues during the calculation of ADC mean. Accurate
localization of inflammatory lesions in ADC map has been reported to be difficult (44).

Although ASDAS-CRP had no correlation with mSASSS in our analyses, a previous study has shown that higher ASDAS would lead to more radiographic damage in spine in patients with AS (43). This could be due to the limited ability of cross-sectional analyses in finding associated factors. Nevertheless, in our recent study, we found that ASDAS-CRP is associated with intensity of spinal inflammation as measured by ADC in patients with active axial SpA (30). These data highlight the importance of intensity of spinal inflammation on radiographic progression.

ADC usage has limitations. As stated previously, meaningful ADC values could only be applied in patients with inflammatory lesions in MRI of the spine. This restricted the number of patients involved in the analyses. 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 on the methods of normalization. Since a single MRI machine was used in our study, normalization was deemed unnecessary.

There are other limitations. Our cohort recruited only participants with back pain which may have falsely excluded asymptomatic patients with active spinal inflammation, resulting in selection bias. The exclusion of spinal degenerative lesions...
may also have falsely excluded patients with co-existing inflammation and
degeneration. We did not include DWI-ADC of SI joints in our analyses as they have
not been validated for assessment of disease activity. The cross-sectional analyses
may not represent the true relationship between 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 further understand of both the imaging technique
and the disease.

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### Table 1 Demographic details of participants

|                        | With ADC lesion | Without ADC | P value |
|------------------------|-----------------|-------------|---------|
| **Age (years) n=303**  | 45.01±13.68     | 42.64±13.37 | 0.041   |
| **Male gender**        | 56/84 (66.7%)   | 115/219 (52.5%) | 0.026 |
| **HLA-B27**            | 71/83 (85.5%)   | 165/210 (78.6%) | 0.176 |
| **Duration of back pain (years) n=301** | 13.40±11.01     | 11.12±11.70 | 0.183   |
| **Family history of SpA** | 17/79 (21.5%)  | 48/209 (23.0%) | 0.79    |
| **Ever smoker**        | 28/83 (33.7%)   | 56/219 (25.6%) | 0.159  |
| **Ever drinker**       | 9/82 (11.0%)    | 21/215 (9.8%)  | 0.758   |
| **CRP n=303**          | 1.21±1.46       | 0.97±2.00    | 0.103   |
| **ESR n=301**          | 37.6±24.5       | 30.5±25.3    | 0.03    |
| **Back pain NRS**      | 5.78±2.38       | 5.56±2.42    | 0.48    |
| **ASDAS-CRP n=288**    | 2.07±0.83       | 1.95±0.90    | 0.202   |
| **SPARCC SI MRI score n=299** | 3.40±5.90       | 3.10±6.07    | 0.703   |
| **SPARCC spine MRI score n=303** | 14.31±10.78     | 3.50±5.93    | <0.001  |
| **mSASSS n=278**       | 8.03±16.51      | 13.33±16.69  | 0.029   |
n= number of participants included; CI=confidence interval; HLA=human leucocyte antigen; SpA= spondyloarthritis; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; NRS=numerical rating score; ASDAS=ankylosing spondylitis disease activity score ; ADC=apparent diffusion coefficient;
SPARCC=Spondyloarthritis research Consortium of Canada; SI=sacroiliac;
MRI=magnetic resonance imaging
Table 2 Univariate linear regression analyses using mSASSS as dependent variable

|                           | Standard coefficient | Regression coefficient (95% CI) | P-value |
|---------------------------|----------------------|---------------------------------|---------|
| Age (n=278)               | 0.46                 | 0.57 (0.44; 0.70)               | <0.001  |
| Male gender (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    |
| ADCmax (n=77)             | 0.26                 | 0.01 (0.002; 0.03)              | 0.02    |
| ADCmean (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   |

n= number of participants included; CI=confidence interval; HLA=human leucocyte antigen; SpA= spondyloarthritis; CRP=C-reactive protein; ESR=erythrocyte
sedimentation rate; ASDAS=ankylosing spondylitis disease activity score;
ADC=apparent diffusion coefficient; SPARCC=Spondyloarthritis research Consortium of Canada; SI=sacroiliac; MRI=magnetic resonance imaging; ADC max=maximum ADC value; ADC mean=mean ADC value
|                  | Multivariate analyses using ADC max as independent factor (n=74) | Multivariate analyses using ADC mean as independent factor (n=74) |
|------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                  | Standard coefficient (95% CI) | Regression coefficient (95% CI) | P-value | Standard coefficient (95% CI) | 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 gender      | 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 |
|                  |                                |                                |        |                                |                                |        |
| ADCmax           | 0.21                           | 0.01 (-0.001; 0.02) | 0.07 | --                             | --                             | --     |
|                  |                                |                                |        |                                |                                |        |
| ADCmean          | --                             | --                             | --     | 0.30                           | 0.03 (0.01; 0.05) | 0.01 |
|                  |                                |                                |        |                                |                                |        |
| SPARCC SI | 0.03 | 0.09 (-0.62; 0.81) | 0.80 | -0.001 | -0.002 (-0.69; 0.69) | 0.99 |
|-----------|------|--------------------|------|--------|---------------------|------|
| MRI score |      | 0.69               |      |        |                     |      |
| SPARCC    | 0.16 | 0.24 (-0.10; 0.59) | 0.17 | 0.16   | 0.24 (-0.10; 0.58)  | 0.16 |
| spine MRI |      | 0.58               |      |        |                     |      |

n=number of participants included; CI=confidence interval; HLA=human leucocyte antigen; SpA= spondyloarthritis; CRP=C-reactive protein; ASDAS=ankylosing spondylitis disease activity score ; ADC=apparent diffusion coefficient; SPARCC=Spondyloarthritis research Consortium of Canada; SI=sacroiliac; MRI=magnetic resonance imaging
Table 4 Multivariate analyses using ADC max, ADC mean, and SPARCC spine as independent factor

|                  | 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 gender      | 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                |
| ADCmax           | 0.22                | 0.00; 0.02            | 0.06                 | ---                 | ---                   | ---                 | ---                 | ---                   | ---                 |
| ADCmean          | ---                 | ---                   | ---                 | 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                 |

n=number of participants included; CI=confidence interval; HLA=human leucocyte antigen; SpA= spondyloarthritis; CRP=C-reactive protein; ASDAS=ankylosing spondylitis disease activity score ; ADC=apparent diffusion coefficient;
SPARCC=Spondyloarthritis research Consortium of Canada; SI=sacroiliac;

MRI=magnetic resonance imaging
Figure 1 Study flow chart of patient enrolment

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

Figure 2. STIR images and ADC values in a 51 years old gentleman 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

13x13mm (600 x 600 DPI)