ARTICLE

Journal of Clinical Rheumatology and Immunology

The Association Between Age and Clinical and Radiological Activity in Axial Spondyloarthritis

Philip Hei Li[1,a], Ho Yin Chung[1,*,a], Chun Sing Wong[2], Helen Hoi Lun Tsang[1], Vince Wing Hang Lau[3], Grace Ho[3], Xiaopei Xu[4], Chak Sing Lau[1], Kai Yiu Ma[5]

[1]Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Radiology Department, Hong Kong Baptist Hospital, Hong Kong
[3]Department of Diagnostic Radiology, Queen Mary Hospital, Hong Kong
[4]Department of Diagnostic Radiology, The University of Hong Kong
[5]Division of Rheumatology, Pamela Youde Nethersole Hospital, Hong Kong

ABSTRACT

Objective: To investigate the associations between age and clinical and radiological disease activities in axial SpA.

Methods: One hundred and twenty-one patients fulfilling the Assessment of SpondyloArthritis International Society Classification Criteria for axial SpA were included in analyses. Patient demographics, disease activity and radiographic scores, as well as magnetic resonance imaging (MRI) with diffusion weighted imaging derived apparent diffusion coefficient values (DWI(ADC)), were compared between patients aged > 40 and ≤ 40 years at a cross-sectional level. Variables with significant differences in univariate analyses were used as dependent variables in multivariate linear regression models adjusted for potential confounding/contributing factors.

Results: Multivariate analysis showed that increasing age was significantly associated with higher Bath Ankylosing Spondylitis Functional Index ($B = 0.04$, $p < 0.01$) and Bath Ankylosing Spondylitis Metrology Index scores ($B = 0.04$, $p < 0.01$); as well as higher modified Stoke Ankylosing Spondylitis Spine Score ($B = 0.41$, $p < 0.01$). On MRI, increasing age was associated with a lower DWI(ADC) ($B = (-0.01)$, $p < 0.01$) of the SI joints, but higher DWI(ADC) values of the axial spine ($B = 0.01$, $p = 0.01$).

Conclusion: Increasing age in SpA was associated with greater functional impairment and structural damage, more inflammation of the axial spine, but less inflammation of the SI joints. Our findings are consistent with the traditional belief that SpA is an "ascending disease" and highlights the importance of different modalities of MRI in the diagnosis and disease monitoring of SpA.

***Keywords*:** Spondyloarthritis; Age; MRI; Apparent Weighted Coefficient; Ascending.

INTRODUCTION

Spondyloarthritis (SpA) is an umbrella term which includes several inflammatory arthritides sharing common clinical features, such as sacroiliitis, spondylitis, peripheral arthritis/enthesitis and various extra-articular manifestations. The disease spectrum of SpA includes ankylosing spondylitis (AS), as its prototype; psoriatic arthritis; reactive arthritis; inflammatory bowel disease-associated SpA and undifferentiated SpA. Although typically presenting at a young age, SpA is often a relentlessly progressive disease even in this new era of biologics. Particularly for AS, patients classically experience an "ascending disease" with ongoing inflammation beginning at the sacroiliac (SI) joints, then progressing up from the lumbar to cervical spine [1].

The advent of magnetic resonance imaging (MRI) has enabled clinicians to more accurately detect active inflammation in SpA, thereby allowing earlier diagnosis and more objective assessment of disease severity. In the last few years, much research has been focusing on

Received 12 March 2019; Accepted 1 May 2019; Published 21 May 2019

*Corresponding author: Ho Yin Chung, Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Room 405B, 4/F Professorial Block, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong, E-mail: jameschunghoyin@gmail.com

[a]These authors contributed equally to this work.

DOI: 10.1142/S2661341719500019

discovering new and better MRI modalities. Notable milestones include the T2-weighted short tau inversion recovery (STIR) sequences and diffusion weighted imaging (DWI) [2-4], as well as the inclusion of MRI of the SI joints in the Assessment of SpondyloArthritis International Society (ASAS) Classification Criteria for axial SpA [5,6].

Despite these rapid advancements, there have been few reports examining the association between age and disease activity in SpA, especially with the use of these various new modalities of imaging. Although a study suggested MRI can differentiate between SpA-related and degenerative changes [7], the increase in degenerative lesions by age could potentially affect axial disease activity assessment by MRI. In this cross-sectional analysis, we examined the associations of age with the clinical and radiological disease activities in axial SpA using radiographs as well as different modalities of MRI. We also re-examined the associations in MRI after eliminating the effect of degenerative changes.

METHODS

Patient population and demographic data

All patients fulfilled the ASAS Classification Criteria for axial SpA. Inclusion criteria included: i) age greater than 18 years, ii) current back pain of all types, iii) ability to give written consent, and iv) biologics naïve. Exclusion criteria included: i) pregnancy and ii) inability to undergo MRI examination. Consecutive patients being followed up in the rheumatology clinics were recruited from Queen Mary Hospital and Pamela Youde Nethersole Hospital, two regional tertiary hospitals in Hong Kong. Blood parameters including human leucocyte antigen (HLA) B27 and C-reactive protein (CRP) were obtained. Clinical data were collected by medical record review and standardized questionnaires on the day of MRI examination. Patients were recruited between March 2014 and October 2015. Details of the study has been published in our previous manuscript [2,8].

Clinical disease activity and functional scores

Clinical disease activity was assessed according to the Ankylosing Spondylitis Disease Activity score based on CRP (ASDAS-CRP) [9,10]. Functional disease activity was assessed according to the Bath Ankylosing Spondylitis Functional Index (BASFI) [11] and spinal mobility was assessed according to Bath Ankylosing Spondylitis Metrology Index (BASMI) [12].

Radiographs of the SI joints and axial spine

Radiographs of the cervical spine, and lumbar spine (anteroposterior and lateral views) were performed. Radiographs were scored and calculated according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [13] by two rheumatologists (H.Y.C. and H.H.L.T.) by consensus.

MRI of the SI joints and axial spine

All recruited patients underwent whole spine (sagittal plane) and bilateral SI (both the semi-coronal and semi-axial plane) joint MRI examinations using a 3T Achieva scanner (Philips Healthcare, Best, Netherlands), with STIR sequence, T1-weighted, and DWI obtained simultaneously. The technical parameters for STIR images were as follows: TR/TE = 5000/80 ms; field-of-view = 150 × 240 mm^2; matrix size = 152 × 157; slice thickness = 3.5 mm (with no gap). Sagittal T1-weighted turbo spin echo (TSE) images were acquired using following parameters: TR/TE = 800/8 ms; field-of-view = 150 × 240 mm^2; matrix size = 168 × 217; slice thickness = 3.5 mm (with no gap). Sagittal T2-weighted TSE images were acquired using following parameters: TR/TE = 3000/110 ms; field-of-view = 150 × 240 mm^2; matrix size = 168 × 215; slice thickness = 3.5 mm (with no gap). Free-breathing DWI with fat suppression was performed using a single-shot spin-echo echo-planar imaging sequence with 4 b-values (0, 100, 600, 1000 s/mm^2). Other imaging parameters were: repetition time/echo time = 4000/90 ms; field-of-view = 300 × 241 mm^2; matrix size = 124 × 100; slice thickness = 4 mm (with no gap); SENSE factor = 2 along the phase-encoding direction; readout bandwidth = 2289 Hz.

STIR sequence MRIs of the SI joints and axial spine were scored according to the SPARCC MRI Index, and the maximum ADC values of any inflammatory lesions were measured and recorded (DWI(ADC)) by radiologist (X.X.). Blinded from clinical data, all MRIs were graded according to the SpondyloArthritis Research Consortium of Canada (SPARCC) MRI Index [14,15] by a team of two radiologist(s) or rheumatologist(s) (C.S.W., H.Y.C; V.W.H.L., G.H.) by consensus.

For subgroup analysis, all available MRI axial spine images were reviewed and those with Modic Type 1 lesions were identified according to the Modic classification system [16], i.e. hypointense signal in T1-weighted and hyperintense signal in T2-weighted sequences, by an independent reader (P.H.L). These

patients were excluded prior to univariate and multivariate linear regression.

Statistical analyses

The median age of Hong Kong from 2001 to 2016 ranged from 37.2 to 44.4 years [17]. In our analyses, we consider 40 years as our median age. Using this reference, patients were first separated into two groups: those older than, and those younger than or equal to 40 years of age. The chi-squared statistic and independent samples t-test were used to compare categorical and continuous variables between the two groups, respectively. Variables with a p-value < 0.1 were then used as dependent variables in univariate linear regression. Gender (male sex), smoking, drinking, presence of inflammatory lesions on MRI and HLA B27 positivity were also tested as regressors in linear univariate regression analyses. Independent variables with a p-value less than 0.1 in univariate regression analysis were re-tested in multivariate regression models. The 95% CI were calculated and p values less than 0.05 were considered statistically significant. IBM SPSS Statistics version 20 was used for all analyses.

Ethics approval

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster; and Ethics Committee, Hong Kong East Cluster. It was conducted in accordance with the Declaration of Helsinki and the Guidance for Good Clinical Practice. All participants gave their written informed consent.

RESULTS

One hundred and twenty-one ethnically Chinese patients fulfilling the ASAS Classification Criteria for axial SpA were recruited. Most of them fulfilled the Modified New York (MNY) criteria for Ankylosing Spondylitis (AS). Mean ages of AS group and non-radiographic axial SpA group were similar (43.8 ± 14.0 years vs. 40.1 ± 12.7 years; p = 0.27).

Table 1 compares the baseline characteristics between patients > 40 and those ≤ 40 years of age. The

Table 1. Baseline characteristics between patients older than and younger or equal to 40 years of age.

	Age > 40 (n = 64)	Age ≤ 40 (n = 57)	p-value
Male	31 (48%)	36 (63%)	0.10
Smoking	16 (25%)	17 (30%)	0.55
Drinking	5 (8%)	9 (16%)	0.17
HLA B27 positivity	44 (72%)	46 (85%)	0.09
Back pain (numerical rating score)	5.84 ± 2.49	5.16 ± 2.51	0.13
Back pain duration (years)	7.3 ± 6.9	15.4 ± 12.9	< 0.001
ASDAS-CRP	1.94 ± 0.89	1.80 ± 0.93	0.41
BASFI	**3.41 ± 2.33**	**2.48 ± 2.61**	**0.04**
BASMI	**3.83 ± 1.43**	**2.92 ± 1.43**	**< 0.01**
Fulfilled MNY criteria for AS	**54 (85.7%)**	**42 (76.4%)**	**0.19**
Non-radiographic axial SpA	**9 (14.3%)**	**13 (23.6%)**	**0.19**
mSASSS	**17.47 ± 19.40**	**3.96 ± 10.45**	**< 0.01**
SPARCC SI joints	**3.09 ± 5.93**	**7.73 ± 13.26**	0.03
SPARCC spine	5.46 ± 10.96	5.13 ± 8.86	0.86
DWI(ADC) SI joint lesions	**0.96 ± 0.27**	**1.28 ± 0.40**	**< 0.01**
DWI(ADC) Spine lesions	**2.07 ± 0.38**	**1.78 ± 0.22**	**< 0.01**

HLA = Human leucocyte antigen; ASDAS = Ankylosing Spondylitis Disease Activity Score; CRP = C-reactive protein; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; MNY = Modified New York; AS = Ankylosing Spondylitis; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; SPARCC = SpondyloArthritis Research Consortium of Canada; SI = sacroiliac; DWI = diffusion weighted image.

average age of our cohort was 43.0 years at recruitment. Mean age of the younger group was 30.9 ± 6.1 years while that of the older group was 53.8 ± 9.0 years. Patients older than 40 years were more likely to have more functional limitations (higher BASFI and BASMI scores), more structural damage (higher mSASSS), but less inflammation involving the SI joints (lower DWI[ADC]). No significant associations were found between age and SPARCC MRI Index of the spine.

BASFI and BASMI as dependent variables

Independent variables tested in univariate models of BASFI and BASMI included: age, back pain duration, male sex, smoking, drinking, HLA B27 status, ASDAS-CRP, mSASSS, and MRI inflammatory lesions.

Significant variables with BASFI included: age (B = 0.05, $p < 0.01$), ASDAS-CRP (B = 2.11, $p < 0.01$) and mSASSS (B = 0.03, p = 0.03). Multivariate analysis (Table 2) showed that increasing age (B = 0.04, $p < 0.01$) and higher ASDAS-CRP (B = 2.09, $p < 0.01$) were independently associated with higher BASFI scores.

Significant variables with BASMI included: age (B = 0.05, $p < 0.01$), back pain duration (B = 0.03, p = 0.02), HLA B27 status (B = (-0.61), p = 0.07), ASDAS-CRP (B = 0.65, $p < 0.01$) and mSASSS (B = 0.05, $p < 0.01$). Multivariate analysis (Table 2) showed that increasing age (B = 0.03, $p < 0.01$), higher ASDAS-CRP (B = 0.52, $p < 0.01$) and higher mSASSS (B = 0.03, $p < 0.01$) were independently associated with higher BASMI scores.

mSASSS as a dependent variable

Independent variables tested in univariate analysis of mSASSS included: age, back pain duration, male sex, smoking, drinking, HLA B27 status, and ASDAS-CRP.

Significant variables included: age (B = 0.53, $p < 0.01$), back pain duration (B = 0.60, $p < 0.001$), male sex (B = 5.52, p = 0.10), smoking (B = 6.51, p = 0.08) and ASDAS-CRP (B = 3.38, p = 0.07). Multivariate analysis (Table 3) showed that increasing age (B = 0.57, $p < 0.01$) and male sex (B = 7.44, p = 0.02) were independently associated with higher mSASSS.

SPARCC MRI Index of SI joints and DWI(ADC) of SI joints and spine as dependent variables

Independent variables tested in univariate analyses for SPARCC MRI Index of SI joints, DWI(ADC) of SI joints and spine included: age, back pain duration, male sex, smoking, drinking, HLA B27 status, and ASDAS-CRP.

Significant variables included for SPARCC MRI Index of SI joints: age (B = (-0.2), p = 0.01), back pain duration (B = (-0.2), p = 0.03), and male sex (B = 3.27, p = 0.10). The association between age and SPRCC MRI index was lost in multivariate analysis (Table 4).

Significant variables with the DWI(ADC) of the SI joints included: age (B = (-0.01), $p < 0.01$) and HLA B27 positivity (B = 0.23, p = 0.08). Multivariate analysis (Table 4) showed age to be inversely associated with the DWI(ADC) of the SI joints (B = (-0.01), $p < 0.01$).

In contrast, age was the only significant variable and showed a significant positive association with DWI(ADC) of the spine (B = 0.01, p = 0.01).

Subgroup analysis – Excluding patients with Modic lesions

Abnormal signals in the axial spine detected by MRI can be non-specific and mimicked by Modic Type 1 lesions (Type I). After review of all MRI axial spine images, forty patients with Modic lesions were identified. Univariate

Table 2. Multivariate linear regression of factors associated with BASFI and BASMI.

	BASFI		BASMI	
	Regression coefficient (95% CI)	**p-value**	**Regression coefficient (95% CI)**	**p-value**
Age	**0.04 (0.02–0.06)**	**<0.01**	**0.04 (0.02–0.06)**	**<0.01**
Back pain duration	*Not included*	—	-0.02 (-0.04–0.01)	0.15
HLA B27 positivity	*Not included*	—	0.02 (-0.55–0.60)	0.94
ASDAS-CRP	**2.09 (1.76–2.42)**	**<0.01**	**0.50 (0.24–0.75)**	**<0.01**
mSASSS	-0.01 (-0.025–0.013)	0.53	**0.04 (0.02–0.05)**	**<0.01**

HLA = Human leucocyte antigen; ASDAS = Ankylosing Spondylitis Disease Activity Score; CRP = C-reactive protein; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score.

Table 3. Multivariate linear regression of factors associated with mSASSS.

	mSASSS	
	Regression coefficient (95% CI)	**p-value**
Age	**0.41 (0.16–0.67)**	**<0.01**
Back pain duration	**0.34 (0.04–0.64)**	**0.03**
Male	**6.97 (1.06–12.88)**	**0.02**
Smoking	4.61 (-2.03–11.24)	0.17
ASDAS-CRP	2.96 (-0.27–6.19)	0.07

ASDAS = Ankylosing Spondylitis Disease Activity Score; CRP = C-reactive protein.

and multivariate linear regression analysis was repeated after exclusion of these patients. The association between age with the DWI(ADC) of the spine (B = 0.009, p = 0.04) remained.

DISCUSSION

To the best of our knowledge, we are the first to report on the association between age and radiological activity using MRI and describe a largest cohort of DWI sequence MRIs in SpA.

At present, we believe that there are at least three facets to imaging for SpA – 1) Conventional radiographs (e.g. mSASSS), to assess structural damage; 2) Structural MRI (e.g. STIR sequence), to assess the extent of inflammation, and 3) Functional MRI (e.g. DWI and ADC values), to assess the intensity of inflammation. By using all these modalities of imaging, we demonstrate that increasing age is clinically associated with a greater degree of functional impairment and structural damage, greater inflammation of the axial spine, but less inflammation of the SI joints.

In this study, we utilized both subjective (BASFI) and objective (BASMI) functional scores for a more comprehensive assessment. The BASFI is one of the most convenient and popular scores for SpA, which offers good discriminative value with a reflection of the patients' subjective perspectives. The BASMI complements this by offering a standardized and objective measure of mobility of the axial skeleton. We found that increasing age was independently associated with both higher BASFI and BASMI scores. This greater functional impairment was likely due to more cumulative structural damage and concomitant age-related degenerative spinal diseases in older patients. This also accounts for the independent association found between the mSASSS with BASMI score.

Conventional radiographs are still considered the "gold standard" for detecting structural changes in SpA and the mSASSS has long been considered the preferred scoring method out of a variety of different scoring systems [18]. Increasing age and male sex were both significantly associated with mSASSS, which is consistent with the well-known observation that males often have a poorer prognosis and more severe radiographic changes. However, changes in mSASSS mainly rely on the development of new syndesmophytes and ankyloses, and has been criticized for its low sensitivity [19,20].

Since the advent of MRI, pre-radiographic inflammatory changes can now be visualized by either T1-weighted post-gadolinium or STIR sequence MRI, with STIR having the advantages of being faster and not requiring contrast administration [21]. We utilized

Table 4. Multivariate linear regression of factors associated with SPARCC MRI Index of SI joints and DWI(ADC) of the SI joints and spine.

	SPARCC SI joints		DWI(ADC) SI joints		DWI(ADC) of spine	
	Regression coefficient (95% CI)	**p-value**	**Regression coefficient (95% CI)**	**p-value**	**Regression coefficient (95% CI)**	**p-value**
Age	**-0.12 (-0.30–0.05)**	**0.16**	**-0.01 (-0.02–0.00)**	**<0.01**	**0.01 (0.00–0.02)**	**0.01**
Back pain duration	-0.13 (-0.33–0.07)	0.20	*Not included*	—	*Not included*	—
Male	2.81 (-1.21–6.83)	0.17	*Not included*	—	*Not included*	—
HLA B27 positivity	*Not included*	—	0.13 (-0.10–0.37)	0.27	*Not included*	—

HLA = Human leucocyte antigen.

the SPARCC MRI Index to measure the extent of inflammation which has known excellent inter-observer reliability and sensitivity to interval changes [14,15]. Although a weighting for depth and intensity of bone marrow edema is included in the SPARCC MRI Index, it is often difficult to precisely quantify the intensity of inflammation solely on STIR images. On the contrary, DWI has been well established as an effective method in evaluating the degree of active inflammation in many disease states and has the additional advantage of being able to quantify diffusion coefficients with ADC measurements [2,22]. We agree with several authors that using DWI with ADC values may complement STIR images and even outperform STIR images in patients with SpA [2,3,23-28]. Therefore, in addition to the SPARCC MRI Index, we also performed DWI(ADC) for the SI joints and axial spine to quantify and compare the degree of inflammation in our cohort.

Furthermore, degenerative changes of the spine become more common in older patients and may interfere with MRI interpretation [29]. Differential diagnosis for abnormal signals may include other pathologies associated with fluid accumulation in bone marrow, most commonly type I Modic lesions [16]. Other conditions such as tumours, infection, trauma etc., are relatively uncommon. Although Dallaudière et al. [25] reported that ADC values may be able to discriminate between axial inflammatory lesions and type 1 Modic lesions, we performed additional subgroup analysis to exclude all films with Modic lesions to further confirm our findings.

Increasing age was found to be inversely associated with DWI(ADC) of the SI joints, but positively associated with the DWI(ADC) of the axial spine. The association between increasing age the DWI(ADC) of the spine remained significant even after excluding those patients with Modic lesions in subgroup analysis. However, no association was found with the SPARCC MRI Index of the axial spine. This reflects the complementary value of DWI(ADC) to STIR images which can quantify the intensity of inflammation and discriminate active disease from degenerative changes. This finding is consistent with another MRI study conducted by our group, comparing the performance of STIR with DWI in the assessment of SpA patients [8].

Overall, we consider our findings to be consistent with the characteristic and oft believed "ascending" inflammation in SpA: with younger patients experiencing more active inflammation in the SI joints, whereas the disease in older patients has "ascended" to involve more of the axial spine instead. The aetiology of this progressive inflammation is still unknown. In a study of AS patients, Brophy *et al.* similarly found the disease beginning in the SI joints with progression up the spine [30]. They also report on a constant and linearly progressive disease course with an approximate 35% change on radiographs every ten years, with changes still occurring after 20 years of disease. Furthermore, contrary to traditional belief, our study also confirms that SpA seldom "burns out" and late-onset disease is not rare [31,32], highlighting the importance of continuous disease assessment and monitoring even in older patients.

There are several limitations to our study. First, no objective gold standard currently exists for the use of DWI and ADC values in the diagnosis and assessment of SpA. However, many other reports have also found DWI and ADC values to correlate well with disease activity in SpA [2,3,23-27], although reports on the use of DWI on assessing axial involvement are scarce. Further studies and international collaborations would be required to standardize the use of different MRI modalities (such as DWI and ADC values) in the management of SpA.

Another shortcoming of our study is the cross-sectional design. It would be preferable to have a prospective follow-up of the same cohort of patients to analyze changes in their clinical and radiological disease activity with age. We have been performing reassessment imaging in this cohort and this follow-up study is currently in progress. In addition, we are currently studying the effects of biologic therapies on SpA with serial clinical and MRI assessments for these patients.

In conclusion, by using various modalities of radiography and MRI, this study shows that increasing age in SpA is associated with more functional impairment and structural damage, greater inflammation of the axial spine, but less inflammation of the SI joints. This is consistent with the traditional belief of SpA being an "ascending disease" and highlights the importance of using different MRI modalities in SpA.

FUNDING

This work was supported by the Hong Kong Society of Rheumatology Project Fund.

REFERENCES

[1] Brophy S, Mackay K, Al-Saidi A, Taylor G, Calin A. The natural history of ankylosing spondylitis as defined by radiological progression. J Rheumatol. 2002;29(6):1236-43.

[2] Lee KH, Chung HY, Xu X, Lau VWH, Lau CS. Apparent diffusion coefficient as an imaging biomarker for spinal diseaes activity in axial sponyloarthritis. Radiology. 2019 Feb 5:180960.

[3] Pedersen SJ, Maksymowych WP. Recent advances in imaging of the axial skeleton in spondyloarthritis for diagnosis, assessment of treatment effect, and prognostication. Curr Rheumatol Rep. 2015;17(9):60.

[4] Sanal HT, Yilmaz S, Kalyoncu U, Cinar M, Simsek I, Erdem H, et al. Value of DWI in visual assessment of activity of sacroiliitis in longstanding ankylosing spondylitis patients. Skeletal Radiol. 2013;42(2):289-93.

[5] Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009;68(6):770-6.

[6] Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.

[7] Arnbak B, Jensen TS, Manniche C, Zejden A, Egund N, Jurik AG. Spondyloarthritis-related and degenerative MRI changes in the axial skeleton — an inter- and intra-observer agreement study. BMC Musculoskelet Disord. 2013;14:274.

[8] Chung HY, Xu X, Lau VW, Ho G, Lee KL, Li PH, et al. Comparing diffusion weighted imaging with clinical and blood parameters, and with short tau inversion recovery sequence in detecting spinal and sacroiliac joint inflammation in axial spondyloarthritis. Clin Exp Rheumatol. 2017 Mar–Apr;35(2):262-9.

[9] Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68(1):18-24.

[10] Au YL, Wong WS, Mok MY, Chung HY, Chan E, Lau CS. Disease activity assessment in ankylosing spondylitis in a Chinese cohort: BASDAI or ASDAS? Clin Rheumatol. 2014 Aug;33(8): 1127-34.

[11] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21(12): 2281-5.

[12] Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994;21(9):1694-8.

[13] Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64(1):127-9.

[14] Maksymowych WP, Wichuk S, Chiowchanwisawakit P, Lambert RG, Pedersen SJ. Development and preliminary validation of the spondyloarthritis research consortium of Canada magnetic resonance imaging sacroiliac joint structural score. J Rheumatol. 2015;42(1):79-86.

[15] Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Krishnananthan R, Stone M, et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum. 2005;53(4):502-9.

[16] Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology. 1988;166(1 Pt 1):193-9.

[17] Research Office, Legislative Council Secretariat: population profile of Hong Kong. https://www.legco.gov.hk/research-publications/english/1415in07-population-profile-of-hong-kong-20150416-e.pdf. Assessed 26 April, 2019.

[18] van der Heijde D, Landewe R. Selection of a method for scoring radiographs for ankylosing spondylitis clinical trials, by the Assessment in Ankylosing Spondylitis Working Group and OMERACT. J Rheumatol. 2005;32(10):2048-9.

[19] Baraliakos X, Listing J, Rudwaleit M, Haibel H, Brandt J, Sieper J, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis. 2007;66(7):910-5.

[20] Spoorenberg A, de Vlam K, van der Linden S, Dougados M, Mielants H, van de Tempel H, et al. Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. J Rheumatol. 2004;31(1):125-32.

[21] Baraliakos X, Hermann KG, Landewe R, Listing J, Golder W, Brandt J, et al. Assessment of acute spinal inflammation in patients with ankylosing spondylitis by magnetic resonance imaging: a comparison between contrast enhanced T1 and short tau inversion recovery (STIR) sequences. Ann Rheum Dis. 2005;64(8):1141-4.

[22] Bley TA, Wieben O, Uhl M. Diffusion-weighted MR imaging in musculoskeletal radiology: applications in trauma, tumors, and inflammation. Magn Reson Imaging Clin N Am. 2009;17(2):263-75.

[23] Sahin N, Hacibeyoglu H, Ince O, Solak A, Uyar B, Erol O, et al. Is there a role for DWI in the diagnosis of sacroiliitis based on ASAS criteria? Int J Clin Exp Med. 2015;8(5):7544-52.

[24] Zhao Y, Han X, Hu S, Shi X, Zhao J, Sun E, et al. [The relevance of ADC value, T(1)intensive rate and the clinical activities in ankylosing spondylitis sacroiliitis]. Zhonghua Yi Xue Za Zhi. 2014;94(35):2750-3.

[25] Dallaudiere B, Dautry R, Preux PM, Perozziello A, Lincot J, Schouman-Claeys E, et al. Comparison of apparent diffusion coefficient in spondylarthritis axial active inflammatory lesions and type 1 Modic changes. Eur J Radiol. 2014;83(2):366-70.

[26] Bozgeyik Z, Ozgocmen S, Kocakoc E. Role of diffusion-weighted MRI in the detection of early active sacroiliitis. AJR Am J Roentgenol. 2008;191(4):980-6.

[27] Gaspersic N, Sersa I, Jevtic V, Tomsic M, Praprotnik S. Monitoring ankylosing spondylitis therapy by dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging. Skeletal Radiol. 2008;37(2):123-31.

[28] Guermazi A, Roemer FW. Which is better for characterizing disease activity in axial spondyloarthritis: diffusion MRI or T2-weighted/STIR MRI? Radiology. 2019 Feb 5:190019.

[29] Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International

Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68 Suppl 2:ii1-44.

[30] Brophy S, Mackay K, Al-Saidi A, Taylor G, Calin A. The natural history of ankylosing spondylitis as defined by radiological progression. J Rheumatol. 2002 Jun;29(6):1236-43.

[31] Kennedy LG, Edmunds L, Calin A. The natural history of ankylosing spondylitis. Does it burn out? J Rheumatol. 1993;20(4):688-92.

[32] Olivieri I, D'Angelo S, Padula A, Leccese P, Palazzi C. Spondyloarthritis with onset after age 45. Curr Rheumatol Rep. 2013;15(12):374.