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Clinical, radiological, and magnetic resonance imaging characteristics of axial spondyloarthritis with late onset

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Abstract

We aimed to investigate the clinical, diagnostic, and imaging features of patients with late onset axial spondyloarthritis (SpA) with initial symptom manifestation aged over 45 years.

Participants with axial SpA were consecutively recruited. Clinical, demographic, blood, and imaging parameters were compared between the groups with early (≤45 years) and late onset (>45 years) at a cross-sectional level. Logistic regressions were used to determine the independent associations with axial SpA with late onset.

A total of 455 participants were recruited. Among them, 70 (15.4%) had late onset disease. Multivariate analyses showed that axial SpA with late onset was associated with higher C-reactive protein based ankylosing spondylitis disease activity index (ASDAS-CRP) (B = 0.10; *P* = .04), higher intensity of spinal inflammation as measured by maximum apparent diffusion coefficient (spinal ADC max) (B = 0.27; *P* = .03) and mean ADC (spinal ADC mean) (B = 0.30; *P* = .004), lower modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (B = –0.12; *P* = .02), more tender joint count (B = 0.12; *P* = .02), and fewer inflammatory back pain (IBP) (OR = 0.26; *P* < .001).

Axial SpA with late onset had higher clinical disease activity, higher intensity of spinal MRI inflammation, less radiographic damage, and more tender joint count. There was also less inflammatory back pain, which could make the diagnosis more difficult.

Abbreviations: ADC = apparent diffusion coefficient, AS = ankylosing spondylitis, ASAS = Assessment of SpondyloArthritis international Society, ASDAS = ankylosing spondylitis disease activity index, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, CRP = C-reactive protein, DMARD = disease modifying antirheumatic drug, DWI = diffusion weighted imaging, ESR = erythrocyte sedimentation rate, HLA = human leukocyte antigen, IBP = inflammatory back pain, mNY = modified New York, MRI = magnetic resonance imaging, mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score, ROI = region of interest, SI = sacroiliac, SpA = spondyloarthritis, SPARCC = Spondyloarthritis Research Consortium of Canada, STIR = short tau inversion recovery.

Keywords: apparent diffusion coefficient, disease activity, late-onset, MRI, spondyloarthritis

1. Introduction

Axial spondyloarthritis (SpA) is a spectrum of inflammatory diseases characterized by axial joint inflammation and new bone formation. It mainly affects young adults, resulting in significant functional, social, and psychological impairment.[1,2] Onset of back pain after 50 years of age is uncommon.[3]

Radiographic sacroiliitis[4] is a core feature of ankylosing spondylitis (AS), the prototype of axial SpA. The modified New York (mNY) criteria[4] for AS has been the established standard in research and clinical practice for many years. However, its radiographic criteria have limited ability to detect the early inflammatory stages of SpA, resulting in significant diagnostic delay. Recognizing this shortcoming, the Assessment of SpondyloArthritis international Society (ASAS) introduced the

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axial SpA classification criteria,[5] which incorporates magnetic resonance imaging (MRI) of the sacroiliac (SI) joints and human leukocyte antigen (HLA) B27 in patients with chronic back pain with onset age < 45 to achieve early diagnosis. However, patients with later onset of back pain beyond the age criterion of 45 may be overlooked.

SpA with late onset has been shown to have higher clinical disease activity and more peripheral arthritis.[3,6] However, there is an absence of research on MRI imaging in SpA with late onset. Faced with an aging population with a longer life expectancy, accurate characterization of axial SpA with late onset becomes increasingly important. This study aimed to describe late onset disease and its associations with clinical, functional and imaging outcomes, including the traditional short tau inversion recovery (STIR) MRI and the new diffusion weighted (DW) MRI.

2. Method

This was a cross sectional analysis of data collected at the first time point of a prospective cohort for the evaluation of the usefulness of DW-MRI in patients with SpA. It has been registered in the clinical trial registry of the University of Hong Kong (HKUCTR-2606). Details of the method had been stated in our previous publications.[7,8] We consecutively recruited participants older than 18 years of age with current back pain and a diagnosis of axial SpA by expert rheumatologists from 8 medical centers (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital, Pamela Youde Nethersole Eastern Hospital, Caritas Medical Centre, Tseung Kwan O Hospital, Kwong Wah Hospital, Prince of Wales Hospital) in Hong Kong, and 1 medical center in mainland China (University of Hong Kong-Shenzhen Hospital). All participants were required to sign written consents. In order to eliminate the drug effects on MRI features, those ever on a biologic (b-) or targeted synthetic (ts-) disease modifying antirheumatic drug (DMARD) were excluded from the study. Other exclusion criteria were pregnant, and unable to undergo MRI examination. Data collected between March 2014 to March 2020 were included in this analysis.

2.1. Study design

Recruited participants were interviewed to obtain baseline clinical and demographic data. These included age, gender, ethnicity, date of onset of back pain (> or ≤45 years old), smoking and drinking status, nature of back pain based on the ASAS inflammatory back pain (IBP) criteria,[9] sites of back pain at onset, family history of SpA, and extraarticular features including uveitis and dactylitis. Axial SpA with late onset was arbitrarily defined as onset of back pain after the age of 45. Data collected were checked with the medical records.

Physical examinations performed included tender joint count, swollen joint count, body weight in kilogram (kg), and spinal mobility as measured by Bath Ankylosing Spondylitis Metrology Index (BASMI).[10] Participants completed self-assessment questionnaires including Bath Ankylosing Disease Activity Index (BASDAI),[11] Bath Ankylosing Spondylitis Functional Index (BASFI),[12] and Bath Ankylosing Spondylitis Global Score (BAS-G).[13]

Blood tests included C-reactive protein (CRP), and HLA B27 status. The Ankylosing Spondylitis Disease Activity Index was calculated based on CRP (ASDAS-CRP).[14] Anteroposterior radiographs of the lumbosacral spine were done to visualize the structural changes of sacroiliitis.[4] Lateral views of the cervical and lumbosacral spine were done to determine the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).[15] MRI of the whole spine (from cervical [C2] to lumbosacral [S1] region) and bilateral SI joints were performed.

2.2. MRI of the spine and SI joints

MRI examinations were performed using 1.5 T Avanto scanner (Siemens) for participants at the University of Hong Kong-Shenzhen Hospital, and 3T Achieva scanner (Philips Healthcare, Best, the Netherlands) for participants from other centers. STIR and diffusion weighted imaging (DWI) sequences were obtained from the 2 MRI machines with same parameters applied. MRIs of SI joints were obtained in semiaxial and semicoronal planes, and whole spine MRIs were obtained in sagittal planes. Our analyses included STIR imaging of the whole spine and SI joints acquired from the 2 machines and DW imaging of the whole spine from the 3T Achiever scanner (in Hong Kong).

The following parameters were employed for the STIR sequence of SI joints: fast spin-echo; The FOV 20* 20 cm; 5 mm without gap; TR/TE, 3500/80 ms; inversion delay, 140–160 ms; matrix size, 248*200; 24 slices were obtained and the total scan time was 5 minutes 7 seconds.

For the STIR images of spine MRI, fast spin echo were performed using the following parameters: FOV 24*14 cm; 4 mm thickness without gap; matrix size 220*176. The TR/TE/TI were 4760/80/140–160 ms; 15 slices were obtained and the total scan time was 3 minutes 38 seconds.

DWI of the whole spine were performed using single-shot spin echo echo-planar imaging sequences with b-values of 0, 50, 600 s/mm^2. The following DWI parameters were used: TR/TE 2260/46 ms; SENSE factor 2.5; FOV 27*27 cm; slice thickness 5 mm without gap; matrix size 92*87. The total scan time was 2 minutes 50 seconds.

2.3. Scoring of images

Radiographic sacroiliitis and mSASSS were scored by 1 investigator (HHLT with 7 years of experience in SpA radiograph interpretation) blinded to clinical data, blood tests, and MRI examinations. Radiographic sacroiliitis was scored according to the mNY criteria[4]: 0 = normal; 1 = suspicious; 2 = obvious; 3 = partial fusion; and 4 = complete fusion. Bilateral grade 2 or above, or unilateral grade 3 or above were defined as radiological AS.

STIR imaging of the whole spine and SI joints were read by 2 investigators (HYC with 9 years, experience and SCWC with 5 years' experience in SpA MRI interpretation) to determine the Spondyloarthritis Research Consortium of Canada (SPARCC) spine and SI MRI indices.[16,17] Hyperintense signals were defined as active inflammation; obvious degenerative lesions were discarded. The average of the SPARCC scores by the 2 investigators were used for analyses.

An independent musculoskeletal radiologist (KHL with 5 years' experience in SpA MRI interpretation) confirmed the legitimacy of inflammatory lesions identified. These were used as references for outlining of the region of interest (ROI) in the apparent diffusion coefficient (ADC) maps of the DW-MRI images. ROIs were drawn by consensus of 2 investigators (HYC and SCWC). Both the maximum ADC (ADC max) and mean ADC (ADC mean) values from the ROIs were determined. Only participants with measurable ADC values were included in the ADC-MRI analyses. All MRI images were interpreted using the commercial software OsiriX MD V.9.5.2. All MRI readers were blinded to clinical data, blood tests, and radiographs.

2.4. Statistical analyses

Independent samples t-test and Chi-square test were used to compare continuous and categorical values respectively between axial SpA with early and late onset. Continuous valuables were described as mean ± standard deviation (SD). Categorical valuables were described as percentages. Intraclass correlation

Table 1

Baseline characteristics of axial SpA with earlier and late onset.

	Axial SpA with early onset (age of onset ≤ 45) (n = 385)	Axial SpA with late onset (age of onset > 45) (n = 70)	*P* value
Age (n = 455)	41.4 ± 12.1	62.0 ± 7.4	<0.001
Male gender	240/385 (62.3%)	34/70 (48.6%)	0.03
Chinese ethnicity	380/385 (98.7%)	69/70 (98.6%)	0.93
Body weight (kg) (n = 401)	66.7 ± 14.0	66.8 ± 13.3	0.61
Smoking status	105/382 (27.5%)	14/70 (20.0%)	0.19
Regular alcohol use	37/376 (9.8%)	5/70 (7.1%)	0.48
Fulfilled ASAS IBP criteria	236/382 (61.8%)	18/70 (25.7%)	<0.001
Cervical pain at onset	45/372 (12.1%)	14/69 (20.3%)	0.07
Thoracic pain at onset	42/372 (11.3%)	10/69 (14.5%)	0.45
Lumbosacral pain at onset	153/372 (41.1%)	38/69 (55.1%)	0.03
Buttock pain at onset	204/372 (54.8%)	20/69 (29.0%)	<0.001
Family history of SpA	80/371 (21.6%)	17/69 (24.6%)	0.57
History of uveitis	118/381 (31.0%)	26/70 (37.1%)	0.31
Tender joint counts (n = 446)	1.2 ± 2.6	2.3 ± 3.7	0.02
Swollen joint counts (n = 447)	0.5 ± 1.3	0.6 ± 1.5	0.71
History of dactylitis	31/381 (8.1%)	11/70 (15.7%)	0.05
HLA-B27 positivity	308/368 (83.7%)	44/67 (65.7%)	0.001
Current c-DMARD therapy	117/381 (30.7%)	20/69 (29.0%)	0.78
BASDAI (n = 449)	4.5 ± 2.1	5.1 ± 1.9	0.03
BASFI (n = 448)	2.7 ± 2.3	3.5 ± 2.4	0.01
BAS-G (n = 446)	4.9 ± 2.6	5.3 ± 2.4	0.17
CRP (n = 448)	1.1 ± 1.9	1.4 ± 3.1	0.36
ASDAS-CRP (n = 439)	1.9 ± 0.9	2.1 ± 0.9	0.06
BASMI (n = 447)	3.3 ± 1.7	4.3 ± 1.6	<0.001
Radiological AS	214/370 (57.8%)	31/69 (44.9%)	0.05
mSASSS (n = 423)	10.9 ± 17.8	17.0 ± 17.2	0.01
mSASSS ≥ 2	195/357 (54.6%)	57/66 (84.4%)	<0.001
MRI SI joints inflammation	115/348 (33.0%)	12/63 (19.0%)	0.03
MRI spine inflammation	175/344 (50.9%)	28/61 (45.9%)	0.47
MRI inflammation	235/350 (67.1%)	33/62 (53.2%)	0.03
SPARCC SI joints MRI score (n = 411)	3.3 ± 6.4	1.2 ± 2.8	<0.001
SPARCC spine MRI score (n = 407)	5.5 ± 7.8	6.2 ± 10.0	0.54
Spine ADC max (mm^2/S) (n = 92)	1435.2 ± 316.4	1762.2 ± 493.8	0.001
Spine ADC mean (mm^2/S) (n = 92)	777.1 ± 193.0	931.4 ± 182.7	0.01
Fulfilled ASAS axial SpA criteria*	362/378 (95.8%)	61/66 (92.4%)	0.24
Fulfilled ASAS axial SpA imaging criteria*	263/378 (69.6%)	37/66 (56.1%)	0.03
Fulfilled ASAS axial SpA clinical criteria*	308/378 (81.5%)	43/66 (65.2%)	0.03

*"Back pain ≥ 3 months" was applied instead of "back pain ≥ 3 months and age of onset < 45 years."

ADC = apparent diffusion coefficient, AS = Ankylosing Spodylitis, ASAS = Assessment of SpondyloArthritis international Society, ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score based on CRP, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BAS-G = Bath Ankylosing Spondylitis Global Score, BASMI = Bath Ankylosing Spondylitis Metrology Index, CRP = C-reactive protein, HLA = human leukocyte antigen, IBD = inflammatory back pain, MRI = magnetic resonance imaging, mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score, n = number, SI = sacroiliac, SPARCC = Spondyloarthritis Research Consortium of Canada, SpA = spondyloarthritis.

coefficient was used to determine the inter-observer agreement of SPARCC scores between the 2 investigators. The degree of reliability was interpreted as 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect.

Variables noted to have differences from independent samples *t*-test and Chi-square test were included in univariate linear/ logistic regression analyses as dependent variables. As our goal was to determine the associations with late onset disease, axial SpA with late onset was designated as an independent variable. In addition, factors known or expected to associate with the dependent variables were also included in the univariate analyses. These included: age, male gender, Chinese ethnicity, duration of back pain, smoking status, regular alcohol use, family history of SpA, HLA B27 positivity, current conventional (c-) DMARD therapy, body weight, BASMI, ASDAS-CRP, mSASSS, and radiological AS.

Independent variables with a *P* value of < 0.1 were retested in multivariate linear/ logistic regression models using enter mode. The results were expressed as odds ratio (OR) in logistic regression models, and regression coefficient and standard coefficient in linear regression models. Unless specified, a *P* value of < 0.05 was considered statistically significant. All statistics were performed with the commercial software IBM SPSS Statistics V.25. Listwise deletions were used for missing variables.

3. Results

A total of 455 participants with expert-diagnosed axial SpA and back pain were included in the study. Of all the participants, 9 (1.98%) were recruited from the University of Hong Kong-Shenzhen Hospital (mainland China), and hence the corresponding DW images were excluded in the analyses. Seventy (15.4%) had onset of back pain greater than the age of 45.

Axial SpA participants with late onset differ significantly from participants with onset before the age of 45. Late onset SpA was associated with higher clinical disease activity, more tender joint count, higher degree of syndesmophyte formation (higher mSASSS), and more intense spinal inflammation (higher ADC values), despite fewer male patients with HLA B27 positivity. However, SPARCC SI joint MRI scores were lower and radiological AS was fewer. When the entry criteria "back pain ≥ 3 months and age of onset < 45 years" was replaced by "back pain ≥ 3 months", most of the participants

Table 2

Univariate and multivariate linear regressions using BASDAI and ASDAS-CRP as dependent variables.

	Univariate linear regressions			Multivariate linear regressions		
	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value
BASDAI					(n = 420)	
Axial SpA with late onset (n = 448)	0.10	0.59 (0.07; 1.11)	0.03	0.02	0.10 (–0.54; 0.74)	0.76
Age (n = 448)	0.13	0.02 (0.01; 0.03)	0.01	0.12	0.02 (0.001; 0.03)	0.04
Male gender (n = 448)	–0.10	–0.40 (–0.79; –0.02)	0.04	–0.09	–0.37 (–0.77; 0.30)	0.07
Chinese ethnicity (n = 448)	0.01	0.20 (–1.45; 1.85)	0.81			
Smoking status (n = 445)	0.07	0.34 (–0.09; 0.78)	0.12			
Regular alcohol use (n = 440)	0.09	0.62 (–0.04; 1.29)	0.06	0.11	0.82 (0.13; 1.51)	0.02
Family history of SpA (n = 434)	0.01	0.06 (–0.40; 0.52)	0.80			
HLA-B27 positivity (n = 428)	–0.15	–0.77 (–1.26; –0.28)	0.002	–0.14	–0.73 (–1.22; –0.23)	0.004
Current c-DMARD therapy (n = 443)	0.01	0.05 (–0.36; 0.46)	0.81			
Radiological AS (n = 432)	0.01	0.02 (–0.37; 0.41)	0.91			
ASDAS-CRP					(n = 406)	
Axial SpA with late onset (n = 438)	0.09	0.21 (–0.01; 0.44)	0.06	0.10	0.25 (0.01; 0.48)	0.04
Age (n = 438)	0.07	0.004 (–0.001; 0.01)	0.14			
Male gender (n = 438)	0.00	–0.001 (–0.17; 0.17)	1.00			
Chinese ethnicity (n = 438)	–0.004	–0.03 (–0.73; 0.67)	0.93			
Smoking status (n = 436)	0.10	0.19 (0.01; 0.38)	0.04	0.07	0.14 (–0.07; 0.34)	0.19
Regular alcohol use (n = 431)	0.11	0.34 (0.06; 0.62)	0.02	0.08	0.26 (–0.06; 0.57)	0.11
Family history of SpA (n = 427)	–0.001	–0.002 (–0.20; 0.20)	0.99			
HLA-B27 positivity (n = 423)	–0.09	–0.19 (–0.40; 0.02)	0.08	–0.10	–0.21 (–0.43; 0.002)	0.052
Current c-DMARD therapy (n = 436)	0.04	0.07 (–0.11; 0.25)	0.43	0.13	0.22 (0.05; 0.40)	0.01
Radiological AS (n = 425)	0.13	0.22 (0.06; 0.39)	0.01			

AS = ankylosing spondylitis, ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score based on CRP, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, c-DMARD = conventional disease modifying antirheumatic drug, CI = confidence interval, HLA = human leukocyte antigen, n = number, SpA = spondyloarthritis.

Table 3

Univariate and multivariate linear regressions using BASFI and BASMI as dependent variables.

	Univariate linear regressions			Multivariate linear regressions		
	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value
BASFI					(n = 389)	
Axial SpA with late onset (n = 447)	0.13	0.82 (0.21; 1.42)	0.01	–0.02	–0.12 (–0.66; 0.43)	0.68
Age (n = 447)	0.20	0.03 (0.02; 0.05)	<0.001	0.06	0.01 (–0.01; 0.03)	0.24
Male gender (n = 447)	0.01	0.05 (–0.39; 0.50)	0.82			
Chinese ethnicity (n = 447)	0.04	0.79 (–1.11; 2.69)	0.41			
Body weight (n = 394)	0.06	0.01 (–0.01; 0.03)	0.20			
Smoking status (n = 444)	0.10	0.54 (0.04; 1.04)	0.03	0.35	0.19 (–0.21; 0.59)	0.35
Regular alcohol use (n = 439)	0.11	0.88 (0.12; 1.64)	0.02	0.03	0.24 (–0.36; 0.85)	0.43
Family history of SpA (n = 433)	0.04	0.20 (–0.33; 0.73)	0.47			
HLA-B27 positivity (n = 427)	–0.12	–0.75 (–1.32; –0.18)	0.01	–0.05	–0.28 (–0.70; 0.15)	0.20
BASMI (n = 442)	0.47	0.63 (0.52; 0.74)	<0.001	0.30	0.41 (0.27; 0.55)	<0.001
Radiological AS (n = 431)	0.13	0.61 (0.17; 1.06)	0.01	–0.04	–0.17 (–0.53; 0.19)	0.36
ASDAS-CRP (n = 437)	0.67	1.82 (1.63; 2.02)	<0.001	0.58	1.58 (1.38; 1.78)	<0.001
mSASSS (N = 416)	0.23	0.03 (0.02; 0.04)	<0.001	–0.06	–0.01 (–0.02; 0.01)	0.22
BASMI						
Axial SpA with late onset (n = 446)	0.21	0.98 (0.54; 1.41)	<0.001	–0.01	–0.06 (–0.44; 0.33)	0.77
Age (n = 446)	0.49	0.06 (0.05; 0.07)	<0.001	0.24	0.30 (0.02; 0.04)	<0.001
Male gender (n = 446)	0.08	0.27 (–0.05; 0.60)	0.102			
Chinese ethnicity (n = 446)	0.001	0.02 (–1.38; 1.41)	0.98			
Body weight (n = 394)	–0.03	–0.003 (–0.02; 0.01)	0.62			
Smoking status (n = 444)	0.14	0.55 (0.19; 0.92)	0.003	0.004	0.02 (–0.27; 0.30)	0.91
Regular alcohol use (n = 439)	0.08	0.48 (–0.07; 1.03)	0.08	–0.04	–0.22 (–0.65; 0.21)	0.32
Family history of SpA (n = 433)	0.02	0.06 (–0.33; 0.46)	0.75			
HLA-B27 positivity (n = 426)	–0.07	–0.31 (–0.73; 0.11)	0.14			
ASDAS-CRP (n = 434)	0.29	0.59 (0.41; 0.77)	<0.001	0.20	0.40 (0.26; 0.54)	<0.001
mSASSS (n = 416)	0.66	0.06 (0.06; 0.07)	<0.001	0.50	0.05 (0.04; 0.06)	<0.001
Radiological AS (n = 431)	0.32	1.12 (0.81; 1.43)	<0.001	0.14	0.50 (0.25; 0.75)	<0.001

AS = ankylosing spondylitis, ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score based on CRP, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, CI = confidence interval, HLA = human leukocyte antigen, mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score, n = number, SpA = spondyloarthritis.

Table 4

Univariate and multivariate linear regressions using SPARCC SI joints MRI score, spinal ADC max, and spinal ADC mean as dependent variables.

	Univariate linear regressions			Multivariate linear regressions		
	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value
SPARCC SI joints MRI score					(n = 366)	
Axial SpA with late onset (n = 410)	–0.13	–2.07 (–3.68; –0.46)	0.01	0.10	1.63 (–0.17; 3.43)	0.08
Age (n = 410)	–0.36	–0.16 (–0.20; –0.12)	<0.001	–0.41	–0.18 (–0.23; –0.14)	<0.001
Male gender (n = 410)	0.06	0.73 (–0.46; 1.92)	0.23			
Chinese ethnicity (n = 410)	0.01	0.25 (–4.63; 5.13)	0.92			
Smoking status (n = 408)	0.002	0.02 (–1.32; 1.36)	0.98			
Regular alcohol use (n = 402)	0.03	0.63 (–1.25; 2.51)	0.51			
Family history of SpA (n = 395)	–0.08	–1.14 (–2.56; 0.28)	0.12			
HLA–B27 positivity (n = 392)	–0.03	–0.50 (–2.05; 1.04)	0.52			
Radiological AS (n = 396)	–0.01	–0.15 (–1.36; 1.07)	0.81			
Spinal ADC max					(n = 91)	
Axial SpA with late onset (n = 91)	0.36	326.96 (134.51; 519.42)	0.001	0.27	262.94 (34.02; 491.87)	0.03
Age (n = 91)	0.27	7.31 (1.79; 12.83)	0.01	0.12	3.32 (–3.11; 9.74)	0.31
Male gender (n = 91)	0.01	3.65 (–161.52; 168.81)	0.97			
Chinese ethnicity (n = 91)	–0.03	–71.38 (–602.11; 459.35)	0.79			
Smoking status (n = 91)	0.004	3.23 (–159.33; 165.80)	0.97			
Regular alcohol use (n = 90)	–0.09	-109.77 (-358.03; 138.48)	0.38			
Family history of SpA (n = 88)	0.17	164.00 (–33.62; 361.62)	0.10			
HLA–B27 positivity (n = 87)	–0.002	–1.77 (–238.91; 235.37)	0.99			
Radiological AS (n = 89)	0.07	57.49 (–124.95; 239.93)	0.53			
Spinal ADC mean					(n = 91)	
Axial SpA with late onset (n = 91)	0.31	160.34 (55.80; 264.89)	0.003	0.30	156.26 (52.54; 259.99)	0.004
Age (n = 91)	0.14	2.06 (–0.99; 5.11)	0.18			
Male gender (n = 91)	–0.18	–74.95 (–162.34; 12.43)	0.09	-0.16	–68.90 (–152.77; 14.97)	0.11
Chinese ethnicity (n = 91)	0.002	2.60 (–282.80; 287.99)	0.99			
Smoking status (n = 91)	–0.01	–3.22 (–90.60; 84.61)	0.94			
Regular alcohol use (n = 90)	–0.07	–45.46 (–179.56; 88.63)	0.50			
Family history of SpA (n = 88)	–0.01	–3.90 (–112.25; 104.44)	0.94			
HLA–B27 positivity (n = 87)	–0.15	–90.62 (–219.04; 37.81)	0.16			
Radiological AS (n = 89)	0.13	60.32 (–37.37; 158.01)	0.22			

ADC = apparent diffusion coefficient; AS = ankylosing spondylitis; CI = confidence interval; HLA = human leukocyte antigen; MRI = magnetic resonance imaging; n = number; SI = sacroiliac; SpA = spondyloarthritis; SPARCC = Spondyloarthritis Research Consortium of Canada.

(95.8% in the early onset group and 92.4% in the late onset group) fulfilled ASAS axial SpA criteria. Baseline characteristics are presented in Table 1. T1

Inter-reader reliability of SPARCC SI joint MRI scores and SPARCC spine MRI scores were almost perfect (Intraclass correlation coefficient was 0.89 for SPARCC SI joints MRI scores and 0.90 for SPARCC spine MRI scores).

3.1. Regression analyses

3.1.1. Clinical disease activity as dependent variables. BASDAI and ASDAS-CRP were designated as dependent variables in univariate regression analyses with the following independent variables: axial SpA with late onset, age, male gender, Chinese ethnicity, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, current c-DMARD therapy, and radiological AS. Multivariate linear regression analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was independently associated with ASDAS-CRP but had no association with BASDAI (Table 2).

3.1.2. Functional status and spinal mobility as dependent variables. BASFI and BASMI were used as dependent variables in univariate regression analyses of functional status and spinal mobility respectively. Independent variables were: axial SpA with late onset, age, male gender, Chinese ethnicity, body weight, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, BASMI (for BASFI models only), radiological AS, ASDAS-CRP, and mSASSS. Multivariate linear regression analysis using significant independent variables from univariate analyses showed that neither BASFI nor BASMI was associated with axial SpA with late onset (Table 3).

3.1.3. SPARCC score and ADC values as dependent variables. SPARCC SI joints MRI score, spinal ADC max, and spinal ADC mean were used as dependent variables. Independent variables tested in univariate models included: axial SpA with late onset, age, male gender, Chinese ethnicity, smoker, drinker, family history of SpA, HLA B27 positivity, and radiological AS. Multivariate linear regression analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was associated with both spinal ADC max and ADC mean, with a tendency towards an association with SPARCC SI MRI score (Table 4).

3.1.4. mSASSS and radiological AS as dependent variables. Independent variables tested in univariate models were: axial SpA with late onset, age, male gender, Chinese ethnicity, body weight, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, ASDAS-CRP, and radiological AS (for mSASSS models only). Multivariate analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was negatively associated with mSASSS but not radiological AS (Table 5).

Table 5

Univariate and multivariate linear regressions using mSASSS and radiological AS as dependent variables.

	Univariate linear regressions			Multivariate linear regressions		
	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value
mSASSS				(n = 370)		
Axial SpA with late onset (n = 422)	0.12	6.06 (1.40; 10.72)	0.01	–0.12	–5.81 (–10.75; –0.87)	0.02
Age (n = 422)	0.44	0.58 (0.47; 0.69)	<0.001	0.51	0.68 (0.55; 0.81)	<0.001
Male gender (n = 422)	0.24	8.62 (5.25; 11.99)	<0.001	0.20	7.12 (3.69; 10.54)	<0.001
Chinese ethnicity (n = 422)	0.06	8.49 (–5.90; 22.88)	0.25			
Body weight (n = 383)	0.10	0.13 (0.001; 0.26)	0.05	0.04	0.06 (–0.06; 0.17)	0.34
Smoking status (n = 421)	0.21	8.30 (4.54; 12.06)	<0.001	0.08	3.18 (–0.58; 6.92)	0.097
Regular alcohol use (n = 415)	0.09	5.72 (–0.17; 11.62)	0.06	–0.03	–1.50 (–6.90; 3.91)	0.59
Family history of SpA (n = 408)	–0.05	–2.19 (–6.40; 2.03)	0.31			
HLA-B27 positivity (n = 408)	0.02	0.66 (–3.68; 4.99)	0.77			
ASDAS-CRP (n = 411)	0.12	2.53 (0.52; 4.55)	0.01	0.07	1.40 (–0.38; 3.17)	0.12
Radiological AS (n = 421)	0.31	10.96 (7.67; 14.24)	<0.001	0.22	8.14 (4.95; 11.34)	<0.001

	Univariate logistic regression			Multivariate logistic regression		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Radiological AS					(n = 407)	
Axial SpA with late onset (n = 439)	0.60	0.36; 1.00	0.05	0.65	0.37; 1.16	0.14
Age (n = 439)	1.01	0.99; 1.02	0.45			
Male gender (n = 439)	1.77	1.20; 2.60	0.004	1.25	0.81; 1.93	0.31
Chinese ethnicity (n = 439)	0.63	0.11; 3.46	0.59			
Body weight (n = 396)	1.00	0.98; 1.01	0.55			
Smoking status (n = 437)	2.76	1.73; 4.40	<0.001	1.84	1.08; 3.14	0.03
Regular alcohol use (n = 431)	4.92	2.01; 12.00	<0.001	3.43	1.26; 9.37	0.02
Family history of SpA (n = 425)	0.91	0.58; 1.45	0.70			
HLA-B27 positivity (n = 424)	2.09	1.28; 3.41	0.003	2.21	1.31; 3.76	0.003
ASDAS-CRP (n = 426)	1.35	1.08; 1.70	0.01	1.37	1.07; 1.75	0.01

AS = ankylosing spondylitis; ASDAS-CRP = ankylosing spondylitis disease activity score based on CRP; CI = confidence interval; HLA = human leukocyte antigen; mSASSS = modified stoke ankylosing spondylitis spinal score; n = number; SpA = spondyloarthritis.

3.1.5. Tender joint count, inflammatory back pain and history of dactylitis as dependent variable. Independent variables tested in univariate models of tender joint count were: axial SpA with late onset, age, male gender, Chinese ethnicity, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, current DMARD therapy, and radiological AS. Multivariate regression analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was associated with higher tender joint count (Table 6).

Independent variables tested in univariate models of inflammatory back pain were: axial SpA with late onset, age, male gender, Chinese ethnicity, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, mSASSS, and radiological AS. Multivariate regression analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was associated with less inflammatory back pain (Table 6).

Independent variables tested in univariate models of history of dactylitis were: axial SpA with late onset, age, male gender, smoking history, regular alcohol use, family history of SpA, HLA B27 positivity, current DMARD therapy, and radiological AS. Chinese ethnicity was not included in the analyses since none of the nonChinese participants had history of dactylitis. Multivariate regression analysis using significant independent variables from univariate analyses showed that axial SpA with late onset was not associated with history of dactylitis (Table 6).

3.1.6. Goodness of fit. The r-square of different regression models were: BASDAI 0.06; ASDAS-CRP 0.04; BASFI 0.53; BASMI 0.54; SPARCC SI joint MRI 0.004; spinal ADC max 0.12; spinal ADC mean 0.12; mSASSS 0.35; radiological AS 0.10; tender joint count 0.10; IBP 0.10; dactylitis 0.04.

4. Discussion

Axial SpA with late onset was associated with higher disease activity, higher intensity of spinal inflammation on MRI, lower mSASSS, and more tender joint count. IBP (as defined by ASAS IBP criteria) as the initial clinical presentation was less prominent than in earlier onset disease.

Hong Kong has the highest life expectancy in the world, patients with late onset axial SpA are more frequently recognized. In this study, we showed that disease activity was higher in axial SpA with late onset, as demonstrated using clinical activity index (ASDAS-CRP) as well as intensity of spinal inflammation on MRI. Clinical disease activity was measured using both the self-reported BASDAI, and the newer ASDAS-CRP. Unsurprisingly and similar to previous studies,[18,19] no association was found between SpA with late onset and BASDAI. A new finding in this study is the association with ASDAS-CRP, a composite index that incorporates the biochemical measures of CRP or erythrocyte sedimentation rate (ESR). ASDAS-CRP is highly discriminatory[20,21] and repeatedly outperforms BASDAI in the assessment of clinical disease activity.[20,21] Our findings further supported the preferred use of the more objective ASDAS-CRP as an improvement on BASDAI in the assessment of clinical activity.

Higher disease activity found in spinal DW-MRI in the late onset group further substantiated the clinical findings. SpA with late onset had higher values of spinal ADC max and ADC mean, both validated measures[7,8,22] of the intensity of inflammation. ADC values have been consistently shown to be effective in quantifying the intensity of inflammation in various diseases.[23–25] In contrast, no association was found with the SPARCC spine MRI score, which used STIR sequence that preferentially measures the extent rather than the intensity of inflammation. Since we only included participants with current back pain, our cohort had higher percentage of MRI inflammation when compared to the international study.[26]

Table 6

Univariate and multivariate linear regressions using tender joint count, IBP, and history of dactylitis as dependent variables.

	Univariate linear regressions			Multivariate linear regressions		
	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value	Standard coefficient (B)	Regression coefficient (95% CI)	*P* value
Tender joint count					(n = 414)	
Axial SpA with late onset (n = 445)	0.14	1.10 (0.38; 1.82)	0.003	0.12	0.95 (0.19; 1.71)	0.02
Age (n = 445)	0.08	0.02 (–0.003; 0.04)	0.10			
Male gender (n = 445)	–0.14	–0.78 (–1.31; –0.24)	0.004	–0.12	–0.72 (–1.28; –0.17)	0.01
Chinese ethnicity (n = 445)	0.79	0.92 (–1.37; 3.21)	0.43			
Smoking status (n = 443)	–0.06	–0.37 (–0.98; 0.23)	0.23			
Regular alcohol use (n = 438)	0.03	0.28 (–0.64; 1.20)	0.55			
Family history of SpA (n = 433)	0.01	0.08 (–0.57; 0.73)	0.81			
HLA-B27 positivity (n = 425)	–0.11	–0.77 (–1.46; –0.08)	0.03	–0.07	–0.49 (–1.19; 0.22)	0.18
Current c-DMARD therapy (n = 440)	0.08	0.48 (–0.09; 1.06)	0.10	0.09	0.55 (–0.05; 1.15)	0.07
Radiological AS (n = 431)	–0.09	–0.49 (–1.03; 0.06)	0.08	–0.05	–0.26 (–0.82; 0.30)	0.36

	Univariate logistic regression			Multivariate logistic regression		
	Odds ratio (OR)	95% CI	*P* value	Odds ratio (OR)	95% CI	*P* value
IBP					(n = 407)	
Axial SpA with late onset (n = 452)	0.21	0.12; 0.38	<0.001	0.26	0.13; 0.54	<0.001
Age (n = 452)	0.97	0.96; 0.99	<0.001	1.00	0.98; 1.02	0.74
Male gender (n = 452)	0.80	0.55; 1.18	0.26			
Chinese ethnicity (n = 452)	1.29	0.26; 6.45	0.76			
Smoking status (n = 450)	0.92	0.60; 1.41	0.70			
Regular alcohol use (n = 445)	1.16	0.61; 2.22	0.65			
Family history of SpA (n = 439)	1.20	0.76; 1.89	0.44			
HLA-B27 positivity (n = 432)	1.51	0.93; 2.44	0.097	1.23	0.73; 2.08	0.44
mSASSS (n = 421)	0.99	0.98; 1.00	0.09	0.99	0.98; 1.01	0.21
Radiological AS (n = 437)	1.04	0.71; 1.53	0.83			
History of dactylitis					(n = 421)	
Axial SpA with late onset (n = 451)	2.11	1.00; 4.42	0.05	1.89	0.86; 4.14	0.11
Age (n = 451)	1.01	0.99; 1.03	0.48			
Male gender (n = 451)	0.37	0.19; 0.71	0.003	0.47	0.23; 0.94	0.03
Smoking status (n = 449)	0.64	0.29; 1.42	0.27			
Regular alcohol use (n = 444)	0.72	0.21; 2.43	0.59			
Family history of SpA (n = 439)	0.56	0.23; 1.37	0.21			
HLA-B27 positivity (n = 431)	0.44	0.21; 0.89	0.02	0.52	0.25; 1.09	0.09
Current c-DMARD therapy (n = 446)	1.72	0.89; 3.32	0.11			
Radiological AS (n = 436)	0.53	0.28; 1.02	0.06	0.68	0.34; 1.36	0.27

AS = ankylosing spondylitis, CI = confidence interval, c-DMARD = conventional disease modifying antirheumatic drug, HLA = human leukocyte antigen, IBP = inflammatory back pain, mSASSS = modified stoke ankylosing spondylitis spinal score, n = number, SpA = spondyloarthritis.

One limitation of DW-MRI is that ADC values are highly susceptible to variability both from participants and MRI machines. Spinal ADC values from different MRI machines can be highly variable. They can also be affected by the participants' age, skeletal maturity and osteoporosis.[27,28] To minimize variability, all ADC values were obtained from a single MRI machine (in Hong Kong), and only measurable ADC lesions were included in the analyses.

Late onset disease tended towards more inflammation of the SI joints, as visualized on STIR MRI after adjustment for age. A proposed theory supposes that the "ascending" progression[29] of inflammation from the SI joints towards the spine results in less inflammation at the SI joint at an older age. However, in SpA with late onset, the origin of inflammation is at the SI joints, before its natural progression. MRI of the SI joints may have a unique role in diagnosis of SpA with late onset in view of the ambiguity of IBP and other clinical features in older age.

This study also reported other predictive factors of clinical disease activity which were highly consistent with previous studies. Older age was found to have worse clinical outcomes,[30] and women had higher BASDI but not ASDAS-CRP scores.[31] Even the counterintuitive finding that HLA-B27 positivity had less clinical disease activity in this study was consistently reported in previous research.[26,32]

Unlike the previous study showing no difference in radiological scores, we found axSpA with late onset had less radiological damages.[19] It could be due to factors unaddressed in the analyses (e.g., diagnostic delay).[33] Otherwise, functional status, spinal mobility, history of dactylitis, and proportion of participants with radiological AS had no association with the late onset group. These findings are largely consistent with other international studies.[18,19,34] Independent factors associated with functional status (spinal mobility, clinical disease activity),[35] spinal mobility (age, clinical disease activity, spinal radiological damages),[35,36] and spinal radiological damage (age, male gender, radiological AS)[37] have also been described in other studies. Conversely, the association with alcohol use in the regression model of radiological AS could represent an effect rather than a cause.

Axial SpA with late onset had more active peripheral disease, as indicated by higher tender joint count. This finding was similar to the Spanish national registry for SpA.[18] One reason may be the increased number of patients with psoriatic arthritis (PsA) in the late onset group.[3] A similar phenotype was observed in a Brazilian registry, which found more peripheral arthritis, dactylitis, and nail involvement in late onset disease.[38] A Turkish registry also found higher levels of acute phase reactants and increased use of methotrexate therapy in late onset AS,[34] suggesting more active peripheral arthritis.

IBP is a reliable screening tool for axial SpA in participants with onset of symptoms prior to the age of 40, in

accordance with ASAS IBP criteria.[39] However, the lower prevalence of IBP in participants with late onset disease suggests its limited effectiveness in universal screening. Another possible explanation is that spinal degeneration[40] is also more prevalent in older patients, potentially obscuring the clinical presentation of back pain. The diagnosis of axial SpA with late onset could also be difficult as the prevailing ASAS classification criteria for axial SpA may overlook older patients with features of SpA.

Our study is limited by the cross-sectional nature, which may be improved upon by a prospective cohort which gives a better description of the nature of disease. Furthermore, other potentially clinically important extraarticular manifestations (e.g., psoriasis, inflammatory bowel disease, and enthesitis), were not included. Potential bias resulted from the exclusion of DW-MRI from the center in China due to high variability of ADC values inherent from the use of different MRI machines. Although the data collected were checked with medical records, recall bias could still exist. Prospective follow up of the group with late onset will help to unravel the true nature of disease.

5. Conclusion

Axial SpA with late onset was associated with higher clinical and MRI disease activity, more tender joint count, and less IBP. This may represent a distinct subgroup of axial SpA requiring a unique diagnostic approach.

Author contributions

Study conception and design: HYC, JXH, CSL.
Acquisition of data: HYC, JXH, KHL, HHLT.
Interpretation of data: HYC, SCWC.
Drafting of the article: HYC, JXH.
Revision of the article: HYC, SCWC, CSL.

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