Short running head: Hip involvement in AS

Full title:

Cigarette smoking increases the prevalence of hip joint involvement in ankylosing spondylitis: a real-world case control study.

Authors and affiliations:

Zhengyuan Hu[1*], Yan Li[1*], Lidong Hu[1], Xiaojian Ji[1], Lei Wang[1], Kunpeng Li[1], Jian Zhu[1], Jianglin Zhang[1], Feng Huang[1]

[1] Department of Rheumatology and Immunology, the First Medical Center, Chinese PLA General Hospital, Beijing, China.

[*] Zhengyuan Hu and Yan Li contributed equally to this paper.

[1] Z. Hu, MM; Y. Li, MD; L. Hu, MD; X. Ji, MD; L. Wang, MD; K. Li, MD; J. Zhu, MD; J. Zhang, MD; F. Huang, MD.

Key Indexing Terms:

hip; risk factors; spondylitis, ankylosing; smoking.

Support: None.

Conflict of interest: The authors have declared no conflicts of interest in this work.

Corresponding author:

Feng Huang, Department of Rheumatology and Immunology, the First Medical Center, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China. fhuang@301hospital.com.cn.

ORCiD: 0000-0002-2319-873X.

Statement of ethics and consent:

This study was approved by the Ethical Committee of the Chinese PLA General Hospital (approval number: S2016-049-02), conducted in accordance with the principles of the Declaration of Helsinki. Informed consent for participation was obtained from all patients at enrollment.

Abstract

Objective: To investigate the association between cigarette smoking and hip joint involvement in ankylosing spondylitis (AS).

Methods: This case-control study compared AS patients with and without hip involvement, defined by the Bath ankylosing spondylitis radiology hip index. Logistic regression analysis, subgroup analysis and sensitivity analysis were conducted to estimate the association between smoking and hip involvement in AS.

Results: This study included 103 patients with hip involvement (cases) and 89 patients without (controls). In univariate analysis, patients who were juvenile-onset, younger, male, having peripheral arthritis history or cigarette exposure were prone to hip involvement. After adjusting for confounding factors, juvenile-onset (adjusted odds ratio (OR_a) 2.52, 95% CI 1.26-5.06), male (OR_a 2.89, 95% CI 1.14-7.33) and cigarette smoking (OR_a 7.23, 95% CI 2.27-23.05) were regarded as independently associated with hip involvement in AS. Moreover, patients smoking with less than 10 pack-years exposure were 2.2 times more likely to have hip involvement than those without (OR_a 2.21, 95% CI 1.09-4.47). Such association were reproduced in subgroup analysis of males and propensity score matched subjects, and it withstood sensitivity analysis.

Conclusions: Smoking is a novel independent risk factor for hip involvement in AS, even less than 10 pack-years exposure could contribute to increased

prevalence of hip involvement in AS, which underlined the giant significance of smoking cessation in AS patients, especially for juvenile-onset AS.

Key words: ankylosing spondylitis, hip, risk factor, smoking.

Introduction.

Ankylosing spondylitis (AS) is the prototype of axial spondyloarthritis (SpA), which is a group of chronic inflammatory diseases that primarily affect spine, sacroiliac joints and peripheral joints [1]. Hip involvement, a prevalent manifestation of AS, is associated with spine damage, function impairment, increased disease burden and poor prognosis [2,3]. However, the precise mechanisms involved in the development of hip joint damage in AS are still not fully understood, only a few risk factors were reported, such as juvenile-onset AS (JAS), male, history of peripheral arthritis or enthesitis and raised serum C-reactive protein (CRP) level [2-4], which hampers those patients to be found out early and get access to proper treatments, such as tumor necrosis factor-α inhibitor [5,6].

Cigarette smoking had been reported to be closely connected with AS: smoking was associated with higher disease activity, worse physical function, poorer quality of life and more importantly, severe spine damage [7,8]. Additionally, spine damage in AS was associated with hip involvement: a Chinese study reported severe spine structure damage was the predictor of radiological hip involvement [9] and data from a large, international study also

pointed out that patients with severe hip involvement were more likely to have spine damage [2]. However, the association between cigarette smoking and hip involvement in AS was barely reported. The identification of such a modifiable factor could not only promote our understanding of the pathogenesis in AS, but also facilitate early detection and treatment of high-risk patients. Herein we rendered the hypothesis that smoking was associated with hip involvement in AS and conducted a case-control study to prove it.

Methods.

Patients and data sources

Patients enrolled in this study were from the Chinese Ankylosing Spondylitis Prospective Imaging Cohort (CASPIC), a nationwide, longitudinal cohort launched in 2016. The study protocol has been demonstrated [10]. Patients were enrolled at the outpatient rheumatology clinics in the First Medical Center of the Chinese People's Liberation Army (PLA) General Hospital, a tertiary referral center in Beijing. Patients were adequately informed before they participate in this study that the data they provided would be saved and used in scientific research only. The study protocol had been approved by the Ethical Committee of the Chinese PLA General Hospital (S2016-049-02) and informed consent for participation was obtained from all patients at enrollment. The study was performed in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines,

and complied with the Declaration of Helsinki.

Adult patients (age ≥ 18 years) were enrolled from May 2017 to September 2020 if they fulfilled the 1984 modified New York criteria for AS [11]. Exclusive criteria were: 1) refusing or unable to complete the survey; 2) providing incomplete or poor-quality data; 2) combination with other diseases.

Data collection

Demographic data and disease features like age at onset, disease duration, peripheral arthritis history, Bath Ankylosing Spondylitis Functional Index (BASFI) [12], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [13], Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate (ASDAS-ESR) [14] and HLA-B27 status were acquired from questionary and medical records. Furthermore, radiographs including X-rays of anterior–posterior (AP) pelvis, lumbar spine (AP and lateral) and cervical spine (lateral), were obtained at enrollment, to confirm the diagnosis and assess the severity of structure damage. The severity of hip and spine impairment was assessed by the Bath ankylosing spondylitis radiology hip index (BASRI-hip) [15] and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [16], respectively. All radiographs were read separately and blindly by 2 rheumatic disease physicians (Zhengyuan Hu and Yan Li), after training session and consensus meeting to master the scoring methods.

The details of BASRI-hip will be demonstrated bellow. As for mSASSS, the anterior corners of the lumbar and cervical vertebra will be scored by the

following criteria: 1 point for squaring or erosion or sclerosis, 2 points for syndesmophyte and 3 points for bridging syndesmophyte, the total score ranged from 0 to 72.

Exposure

Patients were designated as non-smokers and ever (current and former) smokers by smoking status. Non-smokers were subjects who denied smoking. Patients who were actively smoking at enrollment or having smoking habits before were identified as ever-smokers. Specific information on smoking including smoking duration and average number of cigarettes per day was also collected. Ever-smokers were divided by smoking duration (< 15 and ≥ 15 years) or smoking intensity (< 15 and ≥ 15 cigarettes per day) [17]. Cumulative cigarette exposure, in pack-years, was calculated by multiplying the number of years patient smoked by the packs smoked per day. Ever-smokers were classified by cumulative cigarette exposure into two groups: 0~10 and ≥ 10 pack-years.

Cases and controls

Scores of BASRI-hip fell into five grades: 0 = no change(normal), 1 = possible focal joint space narrowing (suspicious), 2 = definite narrowing, leaving a circumferential joint space > 2 mm (minimal), 3 = narrowing but circumferential joint space < 2 mm or bone-on-bone apposition < 2 cm (moderate), 4 = bone deformity or bone-on-bone apposition > 2 cm or total hip replacement (severe). Patients with BASRI-hip ≥ 2 (the worse side of bilateral

hips) were defined as positive for hip involvement [15] (cases) while patients with BASRI-hip < 2 were defined as negative (controls).

In practice, some patients would be classified as positive for hip involvement by one observer, while negative by the other. Patients with disputed results could be adjudicated by an expert reader to make the final decision. However, the definition of hip stage in X-ray leaves much room for subjective interpretation: the interobserver kappa ranged from 0.59 to 0.60 for experienced observers, even after training session and consensus meeting to minimize discrepancy [18]. Additionally, patients with disputed results were possible to have hip involvement, whereas their joint structural damage may not so severe to meet the BASRI-hip criteria. Allowing for those reasons, in our study patients with consistent results from two observers were admitted into main analysis, while patients with disputed results were included into sensitivity analysis to evaluate the reliability of results from the main analysis.

Statistical analysis

Quantitative variables were reported as mean ± S.D. or median (inter-quartile range, IQR) for normally distributed data or not. Categorical variables were described as number (%). Independent samples *t* test or Mann-Whitney *U* test were used to compare continuous variables between cases and controls, chi-squared test was used for categorical variables.

In multivariable analysis, binary logistic regression (backward conditional) was conducted to compare the proportion of smoking exposure in cases to that

in controls and estimate the odd ratios (OR) and 95% CI. Then, multivariable analysis was reperformed in male patients and matched cases and controls, to exclude the confounding effects of gender and other heterogenetic factors. Matched cases and controls were selected by propensity score matching on a ratio of 1:1, by age, gender, duration and juvenile-onset.

Sensitivity analysis was performed as two exaggerated situations were set: patients with disputed results were assumed as all having hip involvement or not, and then they were merged with identified cases or controls. For all analyses, a *P*-value <0.05 was considered as statistically significant. Statistical analysis was performed with IBM SPSS Statistics version 22.

Results

We enrolled 338 AS patients in our study and 27 patients were excluded owing to poor-quality radiographs, 51 patients for lacking previous medical records and 32 patients for combination with other diseases. Finally, 228 patients were admitted into analysis. Flow-chart of analytical approach was presented at Fig 1.

For the 228 patients, the medians (IQR) of age and duration were 31.0 (26.0, 38.0) and 10.0 (6.0, 14.0) years, 190 patients (83.3%) were male and 211 (92.5%) were HLA-B27 positive. 103 patients (45.2%) were identified as having hip involvement by both observers, 36 patients (15.8%) were positive by only one observer and 89 patients (39.0%) were ruled as negative for hip involvement by both. Demographics and other disease-related characteristics

about the 103 cases and 89 controls were detailed in Table 1.

Cases were younger (median age 30.0 vs 34.0, *P*= 0.04), had younger age at disease onset (median age 19.0 vs 23.0, *P*= 0.01) and higher percentage of male (92.2% vs 73.0%, *P*= 0.01) than controls, as well as higher rate of juvenile-onset (43.7% vs 20.2%, *P*= 0.01) and peripheral arthritis history (35.0% vs 18.0%, *P*= 0.01), whereas they did not differ for disease duration, HLA-B27 positive rate, BASFI, BASDAI, ASDAS-ESR and mSASSS. As for smoking status, though there was a greater proportion of ever-smokers among cases than controls (46.6% vs 29.2%, *P*= 0.01), ever-smokers in cases had shorter smoking years (10.4% vs 30.8% with over 15 years smoking, *P*= 0.03) and less cumulative smoking exposure (10.4% vs 26.9% with over 10 peak-years smoking, *P*= 0.07) than that in controls, while they shared a similar extent of smoking intensity (39.6% vs 34.6% with over 15 cigarettes/day, *P*= 0.68) (Table 1).

Risk factors of having hip involvement in AS patients

The univariate analysis revealed that juvenile-onset (OR 3.06, 95% CI: 1.60-5.85), male (OR 4.39, 95% CI 1.86-10.36) and ever smoking (OR 2.12, 95% CI: 1.16-3.85) were associated with elevated hip involvement risk in AS. The association between juvenile-onset and hip involvement kept statistical significance in all models, as well as the association between gender and hip involvement. Ever smoking was associated with 7.2-fold or 3.7-fold higher

odds of having hip involvement than no-smokers in model 2 or 4, where juvenile-onset, gender plus smoking duration or pack-years were adjusted (adjusted OR (OR_a) 7.23, 95% CI 2.27-23.05 or 3.74, 95% CI 1.51-9.27), but such association became insignificant in other models (Table 2).

Association between hip involvement and cumulative smoking exposure

In univariable analysis, smoking with less than 10 pack-years exposure was related with significantly greater odds of having hip involvement than no-smokers (OR 2.59, 95% CI 1.35-4.97), while such association lost statistical significance in smokers with over 10 pack-years exposure (OR 0.82, 95% CI 0.25-2.73). After adjustment for juvenile-onset, gender and disease duration, the association between smoking and higher risk of hip involvement was remained among smokers with less than 10 pack-years exposure (OR_a 2.21, 95% CI 1.09-4.47), whereas it was still insignificant in smokers with over 10 pack-years exposure (OR_a 0.70, 95% CI 0.20-2.45).

Subgroup analysis in males

Similar analysis was reconducted in male patients. Results restricted to males were similar to the main results: after adjustment for juvenile-onset plus smoking duration or pack-years, ever-smokers had 6.5-fold or 3.5-fold higher odds of having hip involvement than no-smokers (OR_a 6.51, 95% CI 2.01-21.06 or 3.49, 95% CI 1.40-8.75) (Table 3).

Propensity score-matched analysis

55 cases and 55 controls were matched and their disease manifestations were comparable, except for a higher percentage of ever-smokers and peripheral arthritis history in cases (Table 1). Ever-smokers in cases had shorter smoking duration (8.0% vs 35.0% with over 15 years smoking, *P*= 0.03) and less cumulative smoking exposure (8.0% vs 30.0% with over 10 peak-years smoking, *P*= 0.06), while they shared a similar extent of smoking intensity than that in controls (44.0% vs 35.0% with over 15 cigarettes/day, *P*= 0.55). The association between ever smoking and hip involvement was insignificant in unadjusted model (OR 1.39, 95% CI 0.68-2.83) or when smoking intensity was adjusted (OR_a 0.68, 95% CI 0.13, 3.38), whereas it became statistically significant when adjusting for smoking duration or pack-years (OR_a 7.89, 95% CI 1.75-35.63 or 3.02, 95% CI 1.03-8.82).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of the all-or-none imputation of patients with suspicious hip involvement on the main result. In our first sensitivity analysis, a complete case scenario was set, in which those 36 patients were assumed as all having hip involvement (139 cases and 89 controls). When juvenile-onset, gender plus smoking duration or pack-years were adjusted, ever-smokers had 5.9-fold or 3.0-fold higher odds of having hip involvement than no-smokers. (OR_a 5.88, 95% CI 1.90-18.20 or

2.99, 95% CI 1.24-7.19). Secondly, those patients were assumed as all free from hip involvement (103 cases and 125 controls). Such significant associations were reproduced in the same multivariate models (OR_a 6.02, 95% CI 2.26-16.05 or 3.80, 95% CI 1.69-8.51) (Table 4).

Discussion

Hip involvement is a common manifestation of AS and associated with poor outcomes [2,3]. In a large, international study exploring the impacts of hip involvement on AS, 20-30% patients suffered from hip involvement and more importantly, 5 to 8% of them had undergone hip replacement surgery [2]. Despite the giant burden of hip involvement on AS, it was poorly understood. It is noteworthy that Chinese AS patients were reported to be especially prone to hip involvement [19], and consequently, disease burden in them is likely to be underestimated. This study has identified for the first time, to our knowledge, that smoking exposure is an independent risk factor for hip involvement in Chinese AS patients.

Cigarette smoking is involved in the pathogenesis of AS. Smoking had been demonstrated to be intimately associated with the increase of many inflammation markers, such as CRP. Raised CRP had been reported to be not only a strong predicator of syndesmophytes formation [20], but associated with hip involvement in AS [4]. In previous studies, smoking was demonstrated to be associated with worse physical function and poorer quality of life in AS

[20,21]. Additionally, we showed that smoking was associated with higher prevalence of hip joint damage in AS.

In our study, patients with hip involvement shared a similar BASFI and mSASSS to those without, that is at odds with previous studies [2,3]. However, in our study, patients with hip involvement were younger (median age 30.0 vs 34.0, *P*= 0.04) and had a virtually higher percentage of juvenile-onset (43.7% vs 20.2%, *P*= 0.01) than those without. Owing to that JAS patients are less likely to have axial symptoms and spine damage [3,22,23], it is sensible that they had higher percentage of hip involvement while being exempted from severe axial disease and function impairment.

In the main analysis, cigarette exposure was independently associated with hip involvement in AS. The significant association between smoking and hip involvement was remained on propensity score matched subjects and subgroup of males, and did withstand two sensitivity analyses, which vigorously enhanced the robustness of results from the main analysis. The relationship between cumulative smoking exposure and hip involvement were also demonstrated. After adjustment for confounding factors, significant association between cigarette exposure and hip involvement was found on smokers with less than 10 pack-years exposure (OR_a 2.21, 95% CI: 1.09-4.47), but not on smokers with over 10 pack-years exposure (OR_a 0.70, 95%CI: 0.20-2.45). The unelevated odds of hip involvement among the higher exposure group might be explained by a lack of statistical power in this group,

given that there were relatively limited subjects in this group (only 5 cases and 7 controls).

Smoking cessation is a well-recognized principle in the treatment of SpA [21], due to reported association between smoking exposure and spine damage, let alone that smoking is one of the greatest threats to health. However, quitting smoking is not as easy as we expected in real world: a multicentric cohort study reported 40% of its patients were current smokers [24]. Patient education about why and how to quit smoking remains an important and unmet clinical matter in improving their outcomes. Experience from the behavioural economics could shed light on this issue [25].

There also exists some limitations about our study. First, recall bias and selection bias are inevitable, despite that patients' medical records were collected and consulted. Although patients were enrolled from a single center, this center is a tertiary referral hospital in Beijing and over half of the patients in the CASPIC study came from other area of China [10]. Furthermore, we adjusted our analyses for already known confounding factors, but we cannot exclude the possibility of confounding by unknown factors. The lack of some important data in the cohort, like alcoholic drinking, psychological and socioeconomic condition and physical activity, poses another limitation to our study. However, we not only used different models to analyze the relationship between smoking and hip involvement, but also selected propensity score matched subjects to control confounding bias and additionally, sensitivity

analysis was conducted to evaluate the vitality of our conclusion. In our study the OR value observed for ever-smoking after adjustment was > 7, which clearly indicated that there is a sound association between cigarette exposure and hip involvement in AS. Further researches might investigate whether our observations persist across racial and ethnic groups and whether the odds of hip involvement in AS raise with increasing pack-years of smoking.

In summary, this study showed that cigarette smoking is a novel independent risk factor for hip joint damage in AS, even less than 10 pack-years exposure could contribute to increased prevalence of hip involvement in AS, underlining the giant significance of smoking cessation in AS, especially for juvenile-onset AS.

References

[1] Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390:73-84.

[2] Vander Cruyssen B, Munoz-Gomariz E, Font P, et al. Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. Rheumatology 2010;49:73–81.

[3] Vander Cruyssen B, Vastesaeger N, Collantesestévez E. Hip disease in ankylosing pondylitis. Curr Opin Rheumatol 2013;25:448-54.

[4] Ziadé N, El Hajj J, Rassi J, et al. Root joint involvement in spondyloarthritis: a post hoc analysis from the international ASAS-PerSpA study. Rheumatology 2022;61:667-78.

[5] Konsta M, Sfikakis PP, Bournia VK, Karras D, Iliopoulos A. Absence of

radiographic progression of hip arthritis during infliximab treatment for ankylosing spondylitis. Clin Rheumatol 2013;32:1229-32.

[6] Maatallah K, Mahmoud I, Belghali S, et al. Reparative radiological changes of hip joint after TNF inhibitors in ankylosing spondylitis. Caspian J Intern Med 2018;9:303-05.

[7] Ward MM, Hendrey MR, Malley JD, et al. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. Arthritis Rheum 2009;61:859-66.

[8] Sakellariou GT, Anastasilakis AD, Kenanidis E, et al. The effect of smoking on clinical and radiographic variables, and acute phase reactants in patients with ankylosing spondylitis. Rheumatol Int 2015;35:2109-14.

[9] Chen HA, Chen CH, Liao HT, et al. Factors associated with radiographic spinal involvement and hip involvement in ankylosing spondylitis. Semin Arthritis Rheum 2011;40:552-58.

[10] Ji X, Wang Y, Ma Y, et al. Improvement of Disease Management and Cost Effectiveness in Chinese Patients with Ankylosing Spondylitis Using a Smart-Phone Management System: A Prospective Cohort Study. Biomed Res Int 2019;17:1-11.

[11] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-68.

[12] Calin A, Garrett S, Whitelock H, et al. A new approach to defining

functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-85.

[13] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.

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

[15] MacKay K, Brophy S, Mack C, Doran M, Calin A. The development and validation of a radiographic grading system for the hip in ankylosing spondylitis: The Bath Ankylosing Spondylitis Radiology Hip Index. J Rheumatol 2000;27:2866-72.

[16] 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;64:127-29.

[17] Zhang H, Wan W, Liu J, et al. Smoking quantity determines disease activity and function in Chinese patients with ankylosing spondylitis. Clin Rheumatol 2018;37:1605-16.

[18] Spoorenberg A, de Vlam K, van der Linden S, et al. Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. J Rheumatol 2004;31:125–32.

[19] López-Medina C, Molto A, Sieper J, et al. Prevalence and distribution of

peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study. RMD Open 2021;7:e001450.

[20] Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64:1388-98.

[21] van der Heijde D, Ramiro S, Landewé R et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978-91.

[22] O'Shea FD, Boyle E, Riarh R, Tse SM, Laxer RM, Inman RD. Comparison of clinical and radiographic severity of juvenile-onset versus adult-onset ankylosing spondylitis. Ann Rheum Dis 2009;68:1407-12.

[23] Gensler LS, Ward MM, Reveille JD, Learch TJ, Weisman MH, Davis JC Jr. Clinical, radiographic and functional differences between juvenile-onset and adult–onset ankylosing spondylitis: results from the PSOAS cohort. Ann Rheum Dis 2008;67:233-7.

[24] Nikiphorou E, Ramiro S, Sepriano A, Ruyssen-Witrand A, Landewé RBM, van der Heijde D. Do smoking and socioeconomic factors influence imaging outcomes in axial spondyloarthritis? five-Year data from the DESIR cohort. Arthritis Rheumatol 2020;72:1855-62.

[25] Ogdie A, Asch DA. Changing health behaviours in rheumatology: an

introduction to behavioural economics. Nat Rev Rheumatol 2020;16:53-60.

Data Supplements

All relevant data are reported in the article. Additional details could be provided by the corresponding author upon reasonable request.

Table 1，Characteristics of cases and controls in main analysis and propensity score matched analysis

	Main analysis			Propensity score matched analysis		
	Controls (n=89)	Cases (n=103)	*P*-value	Controls (n=55)	Cases (n=55)	*P*-value
Age, yrs	34.0(27.0, 39.0)	30.0 (25.0, 38.0)	**0.04**	32.0 (26.0, 37.0)	31.0 (26.0, 36.0)	0.61
Male，n (%)	65 (73.0%)	95 (92.2%)	**0.01**	51 (92.7%)	51 (92.7%)	—
JAS, n (%)	18 (20.2%)	45 (43.7%)	**0.01**	14 (25.5%)	14 (25.5%)	—
Age at onset, yrs	23.0, (18.0, 28.0)	19.0, (15.0, 24.0)	**0.01**	22.0 (16.0, 26.0)	21.0 (16.0, 24.0)	0.37
Disease duration, yrs	9.0, (5.5, 13.0)	10.0, (7.0, 15.0)	0.06	9.0 (6.0, 13.0)	10.0 (5.0, 14.0)	0.72
HLA-B27(+), n (%)	80 (89.9%)	98 (95.1%)	0.16	52 (94.5%)	52 (94.5%)	—
Peripheral arthritis history, n (%)	16 (18.0%)	36 (35.0%)	**0.01**	10 (18.2%)	17 (30.9%)	0.12
Ever-smoker, n (%)	26 (29.2%)	48 (46.6%)	**0.01**	20 (36.4%)	25 (45.5%)	0.33
mSASSS	6.4, (4.3, 13.0)	7.6, (3.0, 21.0)	0.43	6.5 (4.5, 11.2)	7.0 (3.0, 18.3)	0.28
BASFI	0.7 (0.2, 1.9)	1.0 (0.3, 2.1)	0.18	0.6 (0.1, 1.7)	0.9 (0.3, 2.1)	0.09
BASDAI	1.5 (0.9, 2.6)	1.8 (1.0, 2.7)	0.39	1.6 (0.9, 2.6)	1.7 (0.9, 2.7)	0.40
ASDAS-ESR	1.5 (1.1, 1.8)	1.7 (1.2, 2.1)	0.10	1.4 (1.0, 1.7)	1.7 (1.1, 2.0)	0.19
Smoking duration, yrs			**0.03**[#]			**0.03**[#]
0~15	18 (69.2%)	43 (89.6%)		13 (65.0%)	23 (92.0%)	
≥15	8 (30.8%)	5 (10.4%)		7 (35.0%)	2 (8.0%)	
Smoking intensity, cigarettes/day			0.68[#]			0.55[#]
0~15	17 (65.4%)	29 (60.4%)		13 (65.0%)	14 (56.0%)	
≥15	9 (34.6%)	19 (39.6%)		7 (35.0%)	11 (44.0%)	
Cumulative smoking, pack-years			0.07[#]			0.06[#]
0~10	19 (73.1%)	43 (89.6%)		14 (70.0%)	23 (92.0%)	
≥10	7 (26.9%)	5 (10.4%)		6 (30.0%)	2 (8.0%)	

Data were median (interquartile range) unless specifically indicated. Bold text highlighted significant differences. [#]Analysed only in those smokers.

Abbreviation: JAS: juvenile-onset AS. mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate; yrs: years.

Table 2, Risk factors of having hip involvement in AS patients

Parameter	Unadjusted OR (95% CI)	Adjusted OR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
JAS	**3.06 (1.60, 5.85)**	**2.76 (1.40, 5.45)**	**2.52 (1.26, 5.06)**	**2.76 (1.40, 5.45)**	**2.63 (1.32, 5.22)**
Gender	**4.39 (1.86, 10.36)**	**2.70 (1.07, 6.82)**	**2.89 (1.14, 7.33)**	**2.70 (1.07, 6.82)**	**2.77 (1.10, 7.01)**
Ever-smoking	**2.12 (1.16, 3.85)**	1.81 (0.94, 3.48)	**7.23 (2.27, 23.05)**	1.81 (0.94, 3.48)	**3.74 (1.51, 9.27)**

Model 1：JAS, gender and ever smoking; Model 2：JAS, gender, ever smoking and smoking duration; Model 3：JAS, gender, ever smoking and smoking intensity; Model 4：JAS, gender, ever smoking and smoking pack-years.

Bold text highlighted statistically significant results. Data in model 1 and 3 were the same in that though smoking intensity was added into model 3, it was not admitted for its insignificance, as a “backward conditional” method for the selection of variables was used in this study.

Abbreviation: JAS: juvenile-onset AS.

Table 3, Risk factors of having hip involvement in male AS patients

Parameter	Unadjusted OR (95% CI)	Adjusted OR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
JAS	**3.00 (1.48, 6.06)**	**3.25 (1.59, 6.68)**	**2.98 (1.43, 6.22)**	**3.25 (1.59, 6.68)**	**3.09(1.49, 6.40)**
Ever-smoking	1.47 (0.78, 2.78)	1.72 (0.88, 3.36)	**6.51 (2.01, 21.06)**	1.72 (0.88, 3.36)	**3.49 (1.40, 8.75)**

Model 1：JAS and ever smoking; Model 2：JAS, ever smoking and smoking duration; Model 3：JAS, ever smoking and smoking intensity; Model 4：JAS, ever smoking and smoking pack-years.

Bold text highlighted statistically significant results. Data in model 1 and 3 were the same in that though smoking intensity was added into model 3, it was not admitted for its insignificance, as a “backward conditional” method for the selection of variables was used in this study.

Abbreviation: JAS: juvenile-onset AS.

Table 4, Risk factors of having hip involvement in AS in sensitivity analysis

Parameter	Number cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)			
			Model 1	Model 2	Model 3	Model 4
JAS	139/89	**3.09 (1.67, 5.71)**	**2.80 (1.48, 5.33)**	**2.39 (1.23, 4.64)**	**2.64 (1.40, 4.96)**	**2.65 (1.38, 5.07)**
	103/125	**2.08 (1.19, 3.61)**	**1.98 (1.10, 3.58)**	1.81 (0.99, 3.30)	**1.98 (1.10, 3.58)**	**1.87 (1.03, 3.40)**
Gender	139/89	**3.30 (1.60, 6.80)**	**2.21 (1.00, 4.88)**	**2.35 (1.06, 5.24)**	**2.60 (1.24, 5.48)**	**2.27 (1.03, 5.00)**
	103/125	**3.75 (1.64, 8.60)**	2.32 (0.96, 5.65)	**2.47 (1.01, 6.02)**	2.32 (0.96, 5.65)	2.39 (0.98, 5.81)
Ever- smoking	139/89	1.64 (0.93, 2.89)	1.47 (0.78, 2.74)	**5.88 (1.90, 18.20)**	—	**2.99 (1.24, 7.19)**
	103/125	**2.34 (1.35, 4.06)**	**2.10 (1.16, 3.82)**	**6.02 (2.26, 16.05)**	**2.10 (1.16, 3.82)**	**3.80 (1.69, 8.51)**

Model 1：JAS, gender and ever smoking; Model 2：JAS, gender, ever smoking and smoking duration; Model 3：JAS, gender, ever smoking and smoking intensity; Model 4：JAS, gender, ever smoking and smoking pack-years. Bold text highlighted statistically significant results. Em dash meant this parameter was not included into corresponding model. Some data in model 1 and 3 were the same in that though smoking intensity was added into model 3, it was not admitted for its insignificance, as a “backward conditional” method for the selection of variables was used in this study.
Abbreviation: JAS: juvenile-onset AS.

Fig 1 Flow-chart of analytical approach