Clinical and laboratory factors associated with bamboo spine in patients with axial spondyloarthritis: are there clues for bamboo spine?

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Abstract

Objective

To analyse the clinical and laboratory factors associated with bamboo spine.

Methods

Data of patients fulfilling the 2009 ASAS classification criteria for axial spondyloarthritis, registered in the national, multicentre, longitudinal, and observational database of TReasure was analysed. Radiographs were assessed using the Bath Ankylosing Spondylitis Radiologic Index (BASRI). Data of patients with a bamboo spine (Group 1) was compared to data derived from patients with a longstanding disease of at least 15 years but no syndesmophytes (Group 2).

Results

Out of the 5060 patients, 1246 had eligible radiographs. There were 111 patients (8.9%) with a bamboo spine. Male sex was more common among patients with bamboo spine. The median BMI of 27.7 (25.8-31.1) in Group1 was higher than the BMI of 25.9 (22.9-29.2) in Group 2 (p<0.001). Hip arthritis, present or documented by a physician, was more common in Group 1 [(58/108 (53.7%) vs. 35/103 (34%), p=0.004]. There was a tendency towards a more prevalent enthesitis in these patients [29.1% (25/86) vs. 15.9%(11/69), p=0.054]. HLA-B27 status did not differ between groups. Smoking was more prevalent in Group 1. Multivariate logistic regression analysis revealed that male sex, body mass index, hip arthritis, and enthesitis are associated with bamboo spine in axSpA.

Conclusion

Bamboo spine was more common in the male sex and associated with a delay in diagnosis, high BMI, hip involvement, and enthesitis. The constellation of increased body weight, hip arthritis, and enthesitis may imply that mechanical stress contributes to radiographic damage in the presence of chronic inflammation.

Key words

axial spondyloarthritis, bamboo spine, body mass index, enthesitis, hip arthritis

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Introduction

The spondyloarthritides (SpA) are genetically related inflammatory diseases, all associated with HLA-B27 to some extent, but bear distinct phenotypical features (1, 2). Axial spondyloarthritis (axSpA) refers to the predominant involvement of the spine and/or sacroiliac joints seen in ankylosing spondylitis (AS), non-radiographic axial Spa (nr-axSpA), certain forms of psoriatic arthritis (PsA), enteropathic arthritis (EA) (arthritis associated with inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, and reactive arthritis (ReA) with axial involvement) (3).

Patients with AS have significant inter-individual differences in the level of functional loss and radiographic progression and there seems to be phenotypical clusters (4-6). A rapid and severe functional loss that develops within almost a decade after the onset due to a rather complicated course is seen in about 40% of AS patients and only about 10% of the remaining patients develop additional restrictions even after a prolonged disease course (7-12).

In general, spinal manifestations of AS are based on an initial inflammation and a destructive enthesopathy that is followed by a healing process during which new bone formation, syndesmophytes, may result in ankylosis between uniting vertebrae. Nevertheless, the stimulus to the continuous growth of syndesmophytes that results in the widespread fusion of upper and lower syndesmophytes of the adjoining vertebrae, the typical appearance of "bamboo spine", remains speculative (13).

This cross-sectional study aims to investigate clinical and laboratory factors associated with bamboo spine in axSpA.

Methods

TReasure is a national, multicentre, longitudinal, and observational database, started in Turkey in December 2017, aiming to characterise the clinical and demographic data of patients with inflammatory arthritis, rheumatoid arthritis (RA), axial- and peripheral Spondyloarthritis (SpA) at the time of the first introduction of biological treatment and record standardised clinical data together with data on therapy changes throughout the treatment period with biologic agents. At the time of data collection, the database consisted of 5060 SpA patients. All patients registered to the database fulfill the 2009 ASAS classification criteria for either radiographic- (r-axSpA; classical ankylosing spondylitis) or non-radiographic axSpA (nr-axSpA) (14). A detailed description of the remaining axSpA patients in the database is given in the Supplementary file. Previously, Spoorenberg *et al*. reported the reliability of BASRI in reporting radiographic damage of the spine (15). One thousand two hundred and forty-six patients had cervical and lumbar x-rays eligible for an assessment with the Bath Ankylosing Spondylitis Radiologic Index (BASRI) (16). Briefly, the fusion involving three or more vertebrae is classified as "severe" with a BASRI score of four. In these patients, the radiographic appearance of a complete ankylosed spine due to ossification of the annulus fibrosis, anterior longitudinal ligament, apophyseal joints, interspinous and flaval ligaments are often referred to as a "bamboo spine".

Patient groups

Patients with AS fulfilled the modified New York criteria (17). Patients with nr-axSpA were classified according to the 2009 ASAS criteria (14). Patients with PsA met the 2006 CASPAR classification criteria (18). All patients with Crohn's disease and ulcerative colitis had radiologic and/or endoscopic confirmation by a gastroenterologist and were under follow-up at the gastroenterology outpatient clinics of TReasure centres.

Group 1: Patients with a BASRI score of four and complete ankylosis (patients with a "bamboo spine").

Group 2: Patients with a longstanding disease of at least 15 years but no syndesmophyte development were used for comparison as the control group (BASRI 0, 1 and 2 without syndesmophytes).

Demographic, clinical, and laboratory data are extracted from the TReasure database and recorded for analysis.

Evaluation of radiographs

Central reading by a single experienced rheumatologist was done for BASRI scoring and selection of cases with a bamboo spine.

Statistical analysis

The Predictive Analytics Software (PASW) Statistics for Windows, v. 18.0. (SPSS Inc., Chicago, IL, USA) was used for the analysis. A type-I error of less than 5% was interpreted as statistically significant. Demographic and clinical characteristics of patients were summarised using descriptive statistics; numeric variables were expressed as means, medians, standard deviations, minimums and maximums, percentile 25, percentile 75, and ranges, and categorical variables were expressed as numbers and percentages. Normality of data was tested using the visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. For categorical variables, the χ^2 test was used and the Fisher exact test was used when the χ^2 condition was not met. In the comparison of two independent groups, the Mann-Whitney U-test was used for normally distributed numerical variables. For the multivariate analysis, the possible and clinical significant factors identified with univariate analyses were further entered into the logistic regression analysis, with backward selection.

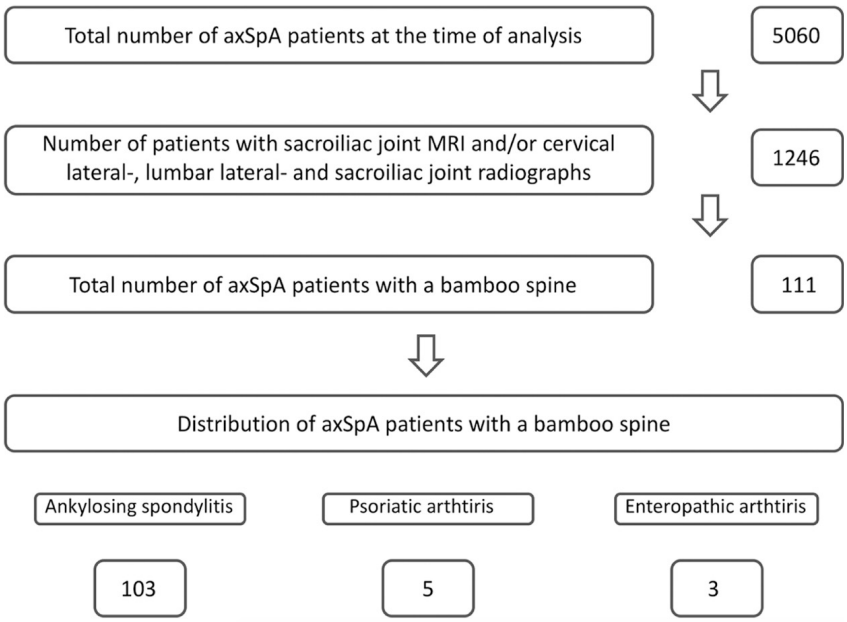

Fig. 1. Study design.

Results

Patient selection is summarised in Figure 1. At the time of data collection, the database consisted of 5060 SpA patients. Out of the 5060 patients in the TReasure database, cervical lateral-, lumbar lateral- and sacroiliac joint radiographs were available for 1246 patients. The majority of the study group consisted of patients with AS (1097, 88.0%). The distribution of other forms of SpA was as follows: psoriatic arthritis (65/1246, 5.2%), non-radiographic axSpA (30/1246, 2.4%), peripheral SpA (26/1246, 2.08%), and enteropathic arthritis (28/1246, 2.24%). There were 111 patients (8.9%) with a bamboo spine (Group 1). Out of 699 (56.1%) patients without syndesmophytes, there were 104 (8.3%) patients with at least 15 years of disease duration (Group 2). Demographic data and clinical features of the study patients are summarised in Tables I, II, and Figure 2. The remaining 312 axSpA patients in the Treasure database had syndesmophytes in at least one vertebra (25%) and finally, 124 (9.5%) had at least a bridging of two vertebrae in a row. (Supplementary Tables S1 and S2)

One hundred and four out of 111 (93.7%) patients with a bamboo spine had classical AS. The majority of Group 1 were male patients and only 14.4% (16/111) of patients with a bamboo spine were females. When compared to Group 2, male sex was associated with bamboo spine (Female to male ratios for Group 1 *vs*. Group 2 = 16/95 *vs*. 38/66, p<0,001). Gender distribution in Group 2, was similar, almost identical, to the distribution of whole axSpA patients (Table I).

The median age, age at disease onset, age at diagnosis of axSpA, and disease duration are given in Table I. The median age in the whole axSpA group and Group 2 were 44.0 (36-52) and 43.5 (39–50.5), respectively, and the median age in Group 1 was higher when compared to Group 2 [51 (45–61) *vs*. 43.5 (39–50.5), p<0,001]. Median disease duration was similar in both Groups 1 and 2 [217 (124–290) months *vs*. 217 (196.5–246) months, p=0.058] but median age at disease onset was higher in patients with a bamboo spine when compared to Group 2 [28 (21–35) *vs*. 23 (18–29), p<0.001]. The median age at diagnosis was 25 (20–30.5) years in Group 2 and it was significantly higher [35 (27–43), p<0.001] in patients with a bamboo spine. The median time to diagnosis was 61 (19–134) months in Group 1 and was significantly higher than the median delay in diagnosis of only 12 (13–49) months in Group 2 (p<0.001). The median time to the first biologic disease-modifying drug (bDMARD) since symptom onset was similar in both study groups [196 (122–268) months for Group 1 *vs*. 177 (122–228) months for Group 2, p=0.146]. Time to first bDMARD since diagnosis was shorter in axSpA patients with a bamboo spine [98 (47–190) months for Group 1 *vs*. 132 (89–196) months for Group 2, p=0.146] Table I.

The median BMI of 27.7 (25.8–31,1) in patients with bamboo spine was higher when compared to the BMI of 25.9 (22.9–29.2) in Group 2 (p<0.001). Patients with bamboo spine had more hip arthritis either present or documented previously by a physician [(58/108 (53.7%) *vs*. 35/103 (34%), p=0.004]. Similarly, there was a tendency towards a more prevalent enthesitis in these patients [29.1% (25/86) *vs*. 15.9%(11/69), p=0.054], Table II.

Table I. Demographic characteristics of study patients.

	ax-SpA	Group 1	Group 2	*p*
Sex*				
Female	463 (37,2)	16 (14,4)	38 (36.5)	<0.001
Male	783 (62,8)	95 (85,6)	66 (63.5)	
Age	44 (36-52)	51 (45-61)	43.5 (39-50.5)	<0.001
Age at disease onset (years)	28 (21-36)	28 (21-35)	23 (18-27)	<0.001
Age at diagnosis (years)	33 (25-41)	35 (27-43)	25 (20-30.5)	<0.001
Disease duration (months)	107 (58-176)	217 (124-290)	217 (196.5-246)	0.106
Delay in diagnosis (months)	26 (9-81)	61 (19-134)	13 (12-49)	<0.001

* (n,%), remaining data was given as median (Q1-Q3)
Group 1: Bamboo spine.
Group 2: Patients with disease duration longer than 15 years and no syndesmophytes.

Table II. Clinical and laboratory characteristics of study patients

	ax-SpA	Group 1	Group 2	*p*
HLA-B27				
Negative	304 (40.1)	17 (29.8)	17 (30.4)	0.951
Positive	454 (59.9)	40 (70.2)	39 (69.6)	
Smoking package/year	3.5 (0-15)	12.25 (1-30)	3 (0-10)	<0.001
BASDAI	5.9 (4.3-6.9)	5.3 (2.6-7)	5.8 (4.8-6.5)	0.683
BASFI	4.3 (3-6.1)	5.5 (3-7.7)	4.65 (3.7-6)	0.142
ASDAS ESR	3.17 (2.46-3.9)	3.04 (2.58-4.1)	3.17 (2.04-3.77)	0.322
ASDAS CRP	3.62 (2.84-4.19)	3.16 (2.64-4.09)	3.76 (3.02-4.32)	0.135
ESR	23 (11-41)	28 (11.5-55)	23.5 (11-40)	0.474
CRP	12.8 (4.17-27.35)	17.8 (7.36-46)	15 (5-34)	0.413
Peripheral arthritis	175 (14.3)	10 (9.6)	19 (18.4)	0.067
Enthesitis	202 (22.3)	25 (29.1)	11 (15.9)	0.054
Uveitis	185 (14.8)	28 (25.2)	17 (16.3)	0.110
Hip involvement	312 (26)	58 (53.7)	35 (34)	0.004
BMI	26.73 (23.69-30.02)	27.78 (25.88-31.16)	25.95 (22.98-29.21)	<0.001
MTX (Ever)	340 (27.3)	37 (33.3)	42 (40.4)	0.284
SSZ (Ever)	808 (64.8)	79 (71.2)	72 (69.2)	0.756
Steroids	306 (24.6)	27 (24.3)	28 (26.9)	0.663

Data were given as n(%), or median (Q1-Q3).
Group 1: Bamboo spine.
Group 2: Patients with disease duration longer than 15 years and no syndesmophytes.
ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index; BMI: Body Mass Index; MTX: methotrexate; SSZ: sulphasalazine.

In contrast, peripheral arthritis present or documented by a physician was less common in Group 1 but this tendency did not reach statistical significance [10/104 (9.6%) *vs*. 19/103 (18.4%), *p*=0.067] (Table II).

HLA-B27 status was available for 758 patients (F/M=291/467). Forty-six point four percent (135/291) of female patients and 68.3% (319/467) of male patients were HLA-B27 positive (Table II). HLA-B27 status did not differ between groups 1 and 2 (Percentage of HLA-B27 positive patients group 1 *vs*. 2= 70.2% *vs*. 69.6%, *p*=0.70). Similarly, HLA-B27 status had no impact on bamboo spine in both gender groups (Percentage of HLA-B27 positive male patient group 1 *vs*. 2= 69.4% (34/49) *vs*. 76.3% (26/33), *p*=0.62; Percentage of HLA-B27 positive female patients in group 1 *vs*. group 2= 75.0% (6/8) *vs*. 53.6% (13/23), *p*=0.42), Table II.

Smoking was more prevalent among the Group 1 patients [Median 12.25 (1–30) package/years in Group 1 *vs*. 3 (0–10) package/years in Group 2, *p*<0.001] and therefore it is included in the multivariate model.

Prevalence of an ophthalmologist documented or rheumatologist recorded uveitis and the proportion of patients treated with conventional synthetic DMARDs before the treatment with biologic DMARDs were similar in both Groups 1 and 2 (Table II).

Clinical-, laboratory factors, and composite indices of disease activity and functional status before bDMARD treatment were similar in both study groups and are given in Table II.

Logistic regression analysis, with backward selection, of the factors identified with univariate analyses, revealed that male sex, body mass index, hip arthritis, and enthesitis are independent predictors of bamboo spine in axSpA, mainly AS. (Tables III and IV)

Discussion

"Bamboo spine" describes the radiographic appearance of the spine in patients with advanced ankylosing spondylitis. Axial SpA, esp. AS is regarded as a chronic progressive disease that leads to a linear radiographic progression in general, yet with evidence for major individual variations in a large proportion of AS patients (19). In a study by Gran *et al*. on the outcomes of AS in 100 patients with a mean disease duration of 16 years, it was pointed out that spinal changes typical for AS were found in 58.6% of patients and the final development of "bamboo spine" was found in 18.6% of patients (20). In this large cohort, only 8.9% of ax-SpA patients and 9.3% of AS patients had a bamboo spine. The number of patients with bamboo spine is likely to increase with the increase of the median disease duration of about 18 years of this study population. Yet, it is well known that most of the loss of function occurs during the first 10 years of the disease and is correlated significantly with spinal x-ray changes of AS and the development of a "bamboo" spine (20). Disease characteristics of patient groups with a bamboo spine are scarcely described in the literature. Our observation is that age at disease onset was high in patients with a bamboo spine and the median disease duration of 18 years at the time of analysis implies that the evolution of a bamboo spine is rather swift in these patients and occurs within the first decades following the onset.

Male patients with axial SpA have a worse radiographic prognosis and frequently male sex has been indicated as a prognostic factor for worse and more severe radiological damage, including the development of syndesmophytes, measured with the BASRI-spine and

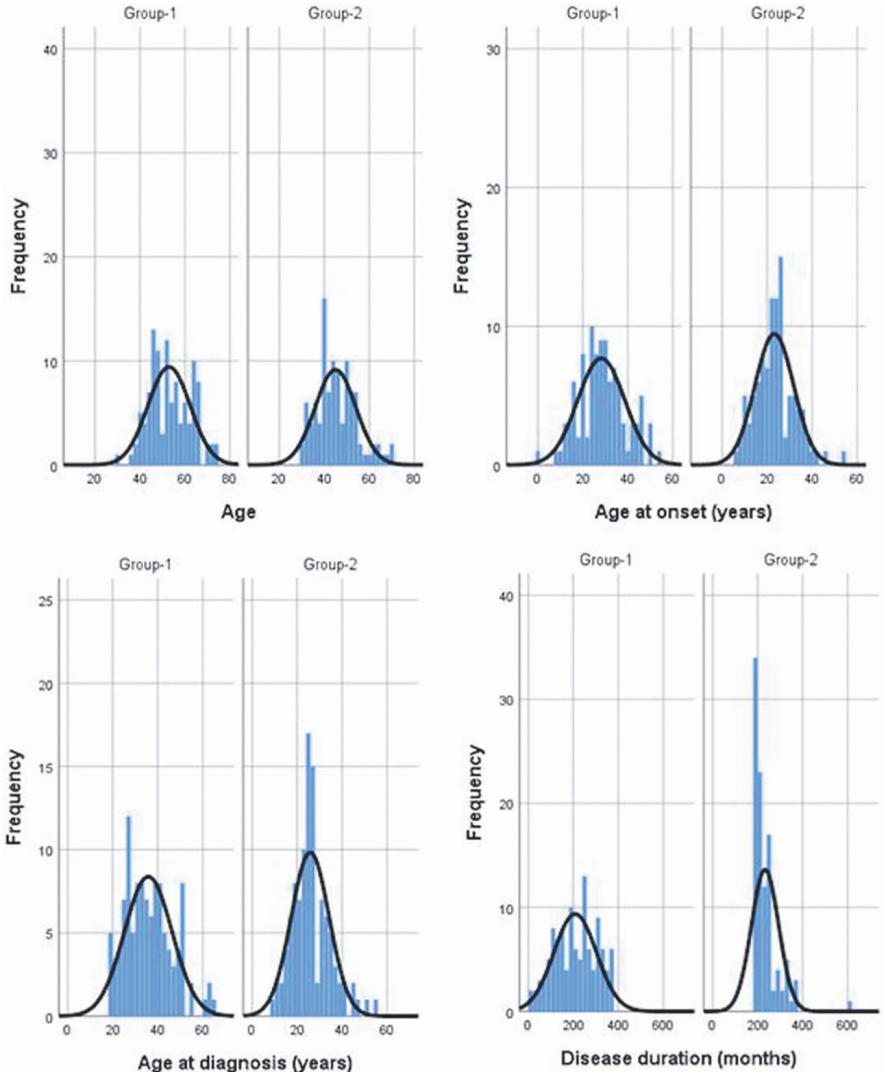

Fig. 2. Distribution of age, age at onset, age at diagnosis, and disease duration in study patients.

Modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) (21-24). Similarly, multivariate analysis showed that the male sex was also strongly associated with bamboo spine in our cohort. The age of onset in ankylosing spondylitis is reported to be similar for both sexes (25). But as reported in a meta-analysis, female patients are more likely to have a delayed diagnosis (26). Interestingly, even though patients with a bamboo spine in this cohort were mostly male, the observed median delay of 61 months in diagnosis was even higher than the reported delay in this meta-analysis for female patients (26). But the time to the first bDMARD was similar in both sexes. One weakness of our study is the cross-sectional design as it hinders an argumentation on possible reasons for this prolonged delay. Even though the time to the first bDMARD was significantly shorter in patients with a bamboo spine, one may conclude that a delayed diagnosis may be associated with the presence of bamboo spine (Table I). Follow-up starts with the decision of a therapy escalation with biologic drugs in the Treasure database and therefore it is inevitable that patients with a bamboo spine but mild disease course are left out of the analysis. But among a large group of axSpA patients, the observed proportion of patients with bamboo spine underlines the ongoing high disease activity in these patients. This observation is in line with the previous report by Kalyoncu *et al*. describing a higher retention rate of TNF blockers in AS patients with advanced spinal ankylosis (27). Duration of treatment with TNF blockers, early or late initiation of TNF blockers, and delay in starting therapy with TNF blockers are reported to be associated with radiographic progression (28, 29). Again, the cross-sectional design of our study limits any conclusion on the relation of an early and sustained inhibition of inflammation and bamboo spine.

Another interesting finding of our study was that in contrast to the rest of the study population, disease onset was delayed in patients with a bamboo spine and the degree of radiographic damage thereafter was high. These diverse findings provoke questions for the influence of mechanical factors on new bone formation since BMI and spinal dynamics tend to increase with age (30). Recently, a high body mass index is associated with high disease activity in PsA and a sustained decrease in disease activity with weight loss has been described (31, 32). Despite the well-designed study by Rubio Vargas *et al*. reporting that BMI had no impact on disease activity in axSpA patients when Ankylosing Spondylitis Disease Activity Score (ASDAS) and C reactive protein (CRP) is used (33), new bone formation and radiographic damage may well be the result of excessive biomechanical forces associated with increased body weight as described in a detailed systematic literature review (SLR) (34). The most interesting finding of this SLR is that higher BMI is closely related to existing new bone formation including syndesmophytes and enthesophytes as reflected by higher mSASSS scores on radiographs, which could explain the effect of BMI on the development of bamboo spine.

The importance of obesity in SpA development has been reported in animal models, previously (35, 36). Similar to these findings our observations suggest that along with an increased BMI, enthesitis and hip arthritis are more prevalent in patients with bamboo spine. Several prospective and/or cross-sectional studies, confirm that hip arthritis is a reliable clinical prognostic factor for severe radiographic damage in axSpA (37-40). Whether hip arthritis in axSpA is part of one severe disease spectrum such as sacroiliitis and ascending spi-

Table III. Multivariate analysis of predictors for bamboo spine.

	p	OR	95% CI	
			Lower limit	Upper limit
Sex (male)	0.017	4.743	1.325	16.975
BMI (Normal) (ref) (18.5–24.9)	0.010			
Underweight (<18.5)	0.116	0.108	0.007	1.730
Owerweight (25.0–29.9)	0.015	5.326	1.392	20.382
Obese (>30)	0.045	4.392	1.036	18.620
Smoking (pack-years) (ref) (0 pack-years)	0.045			
<10 pack/years	0.119	0.327	0.080	1.332
10 to 20 pack-years	0.375	1.884	0.465	7.635
>20 pack-years	0.210	2.270	0.630	8.185
Delay in diagnosis (more than 25 months)	<0.001	13.672	4.427	42.224
Peripheral arthritis	0.348	2.700	0.339	21.516
Hip arthritis	0.034	2.935	1.086	7.933
Enthesitis	0.032	4.469	1.138	17.550

Table IV. Application of the Backward LR method.

	p	OR	95% CI	
			Lower limit	Upper limit
Sex (male)	0.011	5.136	1.462	18.039
BMI (Normal) (ref) (18.5–24.9)	0.016			
Underweight (<18.5)	0.117	0.110	0.007	1.741
Owerweight (25.0–29.9)	0.023	4.271	1.223	14.914
Obese (>30)	0.071	3.521	0.900	13.776
Smoking (pack-years) (ref) (0 pack-years)	0.078			
<10 pack/years	0.200	0.422	0.113	1.580
10 to 20 pack-years	0.536	1.539	0.393	6.021
>20 pack-years	0.175	2.386	0.680	8.377
Delay in diagnosis (more than 25 months)	<0.001	13.734	4.712	40.027
Hip arthritis	*0.060*	2.478	0.964	6.372
Enthesitis	0.044	3.634	1.037	12.734

nal disease or the negative effect of hip arthritis on postural stability causes repeated microtraumas on newly emerged sites of pressure and causes persistent enthesitis due to the changed sagittal balance, and results in new bone formation at these sites may necessitate further research (30, 41-45).

In a previous study, we reported that uveitis is a poor prognostic factor for spinal radiographic progression in patients with a median disease duration of 10 years (46). In this present study, we did not see the same association for bamboo spine in a study population with a significantly longer disease duration. The prevalence of anterior uveitis associated with Ankylosing spondylitis increases with disease duration (47, 48), and possibly the occurrence of uveitis early in the disease course is a poor prognostic factor but it seems that uveitis loses its prognostic value after the disease is established.

Smoking is repeatedly associated with accelerated radiographic progression in the spine in early and established axSpA patients (49-51). Similar to these observations, the rate of cigarette consumption was four times higher in axSpA patients with a bamboo spine. But multivariate analysis revealed that smoking as reflected by up to ten-, ten to twenty- and more than twenty pack-years of smoking did not affect the development of bamboo spine.

Other clinical and laboratory parameters such as the absence of peripheral arthritis and the presence of the HLA-B27 molecule were not associated with bamboo spine in the present study. Several previous studies have investigated the relationship between peripheral arthritis and radiographic progression in AS (46, 52, 53). AS patients with peripheral joint disease are reported to have clinically and radiographically a less severe disease course and spinal progression than those without peripheral joint involvement (53). Ten years after the disease onset, a cross-sectional analysis revealed that multiple syndesmophytes or fusion of multiple lumbar vertebrae are more common in AS patients with predominantly axial disease, and the absence of peripheral joint involvement is associated with axial radiographic progression (46). One prospective study with a short follow-up, on the contrary, could not demonstrate an effect of baseline presence of peripheral arthritis on the spinal progression of radiographic changes over 2 years (51). A second cross-sectional study did not find an association between the presence of peripheral arthritis and radiographic spinal joint involvement with fusion (52). The focus of these last two studies with small sample sizes was not primarily the presence of peripheral arthritis and the proportion of patients with peripheral arthritis was low and possibly blunted a firm conclusion despite revealing other clear associations with radiographic progression. To overcome these problems, Kim *et al*. evaluated radiographic changes stratified by the presence or absence of peripheral arthritis in a large observational study and concluded that after adjustment for confounding factors, peripheral arthritis is an independent determinant of slower radiographic spinal radiographic damage in the spine (54). Our results show that the presence or absence of peripheral arthritis was not associated with the most severe spectrum of AS, bamboo spine.

Our study contributes to the current literature in that a high BMI, presence of hip arthritis, and/or enthesitis is associated with bamboo spine of axSpA. But the HLA-B27 molecule or disease activity as reflected by a high CRP level, high BASDAI, or high BASFI before the initiation of bDMARD treatment did not affect the presence of bamboo spine.

Conclusion

Clinical and laboratory factors reported in this study for their association with bamboo spine are similar to those associated with long-term functional loss reported in the seminal report of Amor *et al*. (37). Male sex, delay in diagnosis, BMI, hip involvement, and enthesitis are crucial factors associated with bamboo spine in axSpA patients. The con-

stellation of increased body weight, hip arthritis, and enthesitis may imply that mechanical stress, along with chronic inflammation, plays an important role in the development of severe radiographic damage of axSpA.

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