Interaction effects of significant risk factors on low bone mineral density in ankylosing spondylitis

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Background: To analyze individually and interactively critical risk factors, which are closely related to low bone mineral density (BMD) in patient with ankylosing spondylitis (AS). **Methods:** A total of 249 AS patients who visited China-Japan Friendship Hospital were included in this study. Patients with questionnaire data, blood samples, X-rays, and BMD were collected. Logistic regression analysis was used to identify the critical risk factors of low BMD in different sites, and prediction accuracy was obtained by adding the screened significant risk factors to the basic model. The interaction between risk factors was analyzed, and predictive nomograms for low BMD in different sites were established. **Results:** There were 113 patients with normal BMD, and 136 patients with low BMD. AS patients with hip involvement are more likely to experience low BMD in the total hip, whereas those without hip involvement are more prone to low BMD in the lumbar spine. Chest expansion, mSASSS, radiographic average grade of the sacroiliac joint, and hip involvement were significantly associated with low BMD of the femoral neck and total hip. Syndesmophytes, hip involvement and higher radiographic average grade of the sacroiliac joint increases the risk of low BMD of the femoral neck and total hip in an additive manner. Finally, a prediction model was constructed to predict the risk of low BMD in total hip and femoral neck. **Conclusions:** This study identified hip involvement was strongly associated with low BMD of the total hip in AS patients. Furthermore, the risk of low BMD of the femoral neck and total hip was found to increase in an additive manner with the presence of syndesmophytes, hip involvement, and severe sacroiliitis. This finding may help rheumatologists to identify high-risk AS patients to prevent the occurrence of low BMD.

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Abstract

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Results: There were 113 patients with normal BMD, and 136 patients with low BMD. AS patients with hip involvement are more likely to experience low BMD in the total hip, whereas those without hip involvement are more prone to low BMD in the lumbar spine. Chest expansion, mSASSS, radiographic average grade of the sacroiliac joint, and hip involvement were significantly associated with low BMD of the femoral neck and total hip. Syndesmophytes, hip involvement and higher radiographic average grade of the sacroiliac joint increases the risk of low BMD of the femoral neck and total hip in an additive manner. Finally, a prediction model was constructed to predict the risk of low BMD in total hip and femoral neck.

Conclusions: This study identified hip involvement was strongly associated with low BMD of the total hip in AS patients. Furthermore, the risk of low BMD of the femoral neck and total hip was found to increase in an additive manner with the presence of syndesmophytes, hip involvement, and severe sacroiliitis. This finding may help rheumatologists to identify high-risk AS patients to prevent the occurrence of low BMD.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton (Mauro et al.2021; Klavdianou et al. 2021). The main feature of the disease is new bone formation, including syndesmosis, syndesmophytes formation, fusion of the sacroiliac joints, and ankylosis of the spine (Hwang et al. 2021). Low bone mineral density (BMD) is considered to be one of the most common complications in AS, which occurs in a range of 19% to 62% of patients undergoing screening (van der Weijden et al. 2012; Hinze et al. 2016; Klingberg et al. 2012). However, the occurrence of low BMD is quite hidden. In many cases, patients and physicians are unaware of reduced BMD, which undoubtedly contributes to delayed diagnosis and increased fracture risk.

The risk factors and pathophysiology mechanism on low BMD in AS patient are unclear. Previous studies have shown that inflammation, disease course, disease activity, the release of inflammatory cytokines, mechanical factors, radiological damage may also be related to low BMD in AS patients (Malochet et al. 2017; Kim et al. 2022; Bautista-Aguilar et al. 2021). To date, the risk factors of low BMD at different sites remain controversial. Studies have shown that with the progression of the disease, BMD of femoral neck decreased significantly, while BMD of lumbar spine increased (Kaya et al. 2009). However, another study reported that lumbar BMD was not related to the course of AS (Wu et al. 2021). The most compelling reason for the apparent observed inconsistencies may be the complex course, over time, of low BMD in AS, which is unlikely to be solely influenced by one single predictor or to have a large effect on only one single site. Currently, there is no adequate explanation for the common risk factors for low BMD at different sites or for established interactive relationships among these risk factors.

The objectives of this study were to analyze individually and interactively critical risk factors, which are closely related to low BMD in patient with AS, and finally establish a nomogram prediction model to guide AS patients in preventing the occurrence of low BMD.

Materials & Methods

Research Subjects

249 AS patients were recruited from China-Japan Friendship Hospital between July 2012 and November 2018. In this research, all included patients met the modified New York criteria for AS (van der Linden S et al. 1984). Exclusion criteria: 1) the patient had undergone hip replacement surgery; 2) Suffering from other autoimmune diseases, including but not limited to inflammatory bowel disease, psoriasis, ichthyosis, etc; 3) The patient has serious basic diseases, such as severe malnutrition, liver and kidney failure, etc; 4) The patient did not agree to participate in this study. All patients included in this study were evaluated by doctors to see if they met the inclusion criteria and signed the informed consent. The study has been reviewed and approved by ethics committees, including the research ethics committee of China-Japan Friendship Hospital (approval No. 2017-67) and the ethics committee of cedar Sinai Medical Center (approval No.pro00048849), and was conducted in accordance with the declaration of Helsinki.

Data Collection/Measurements

The questionnaires were administered by investigators with experience in epidemiological research. Patients' individual data, including gender, age, body mass index (BMI), current medication status, smoking, alcohol-related conditions, family history, onset age, and sports activities, were collected. The functional status, disease activity and severity in patients with AS were obtained by filling in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaires.

All patients were evaluated by the same rheumatologist. The evaluation scope included physical examination, modified-Schober score, chest expansion score, and Bath Ankylosing Spondylitis Metrology Index (BASMI) (Calin et al. 1994; Song et al. 2009; Jenkinson et al. 1994). The visual analog scale (VAS, 0-10cm) was used to assess the night pain and the patient global assessment (PGA) (Sieper et al. 2009).

The New York classification criteria was used to grade the degree of sacroiliac joint, and the classification criteria were normal (0) to most serious (4). The diagnosis of AS was unilateral grade 3, unilateral grade 4 or bilateral grade 2(van der Linden S et al. 1984). A lateral radiograph of the cervical, thoracic and lumbar spine were collected, and the modified ankylosing spondylitis score

(mSASSS) was used to evaluate the AS-related changes. The scoring standard of mSASSS are as follow the previously published study (van der Heijde et al. 2019). The mSASSS was scored by a musculoskeletal radiologist and a cross-trained rheumatologist. Cohen's kappa coefficient was used to analyze the consistency of the two doctors' scores on the study subjects. When Cohen's kappa (κ) coefficients were > 0.85, it indicates that the consistency between researchers is good.

Hip involvement was evaluated by an experienced rheumatologist, including restricted range of motion, pain and Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip). The BASRI-hip scoring method was refer to previous published study (Konsta et al. 2023). Radiographic hip joint involvement was defined by at least 1 score in the BASRI-hip scoring system (MacKay et al. 2000).

The disease activity score (ASDAS) for ankylosis was calculated using the formula in order to better assess the patient's disease activity (Deodhar et al. 2022). The calculation of ASDAS-CRP refers to previous literature (Ørnbjerg et al. 2022). To evaluate the disease activity, the disease activity score (ASDAS) of ankylosis was calculated using the ASDAS-CRP formula, and the use of formula refers to published literature (Deodhar et al. 2022; Ørnbjerg et al. 2022).

The blood samples of AS patients were collected and analyzed by standard laboratory techniques. Before serum samples were collected, patients fasted overnight (at least 8 hours). Indicators reflecting inflammation, including ESR and CRP, were collected. Other laboratory indicators closely related to AS, such as HLA-B27, were also recorded. BMD (g/cm2) was measured using dual-energy X-ray absorptiometry (DXA). The detection range of BMD includes: lumbar spine (L1-L4), femoral trochanter, femoral neck, and total hip. In this study, patients with a measured bone density T-scores < -1 at either site were defined as low BMD (Cabrera et al. 2018). In addition, the low BMD group was also divided into osteoporosis and osteopenia. Osteopenia and osteoporosis are defined according to the World Health Organization standards (Kanis JA 1994).

Statistical Analysis

Categorical and continuous variables are expressed as median, range and/or mean, or standard

deviation (SD), where appropriate. Chi-square test, t-test, and rank sum test were applied to compare differences between groups when appropriate. Spearman analysis was used to calculate the correlation coefficient. Before and after adjusting for confounding factors, logistic regression analysis was applied to identify significant risk factors associated with low BMD. Effect-size estimates are shown as odds ratio (OR) and 95% confidence interval (CI). Establish the predictive nomogram of low BMD in different sites, and its accuracy is determined by the consistency index. Statistical analysis was performed using the STATA software special edition (version 14.0, STATA Corp, TX). Nomogram was constructed using the R language (version 3.5.2). $P < 0.05$ is consider with statistical significance.

Results

Patient characteristics

A total of 249 patients, including 194 males and 55 females, were included in this study finally. The average age was 34±11 years, the onset age was 24±10 years, and the diagnostic duration was 6±5 years. Among them, 132 patients (53.0%) had normal BMD, and 117 patients (47.0%) had low BMD. BMI was significantly different between the normal BMD group and the low BMD group ($P<0.05$), while other baseline characteristics were similar (all $P>0.05$). The patient characteristics in the study patients are shown in Table 1.

The disease-related variables and BMD of the study patients are summarized in Table 2. BASMI, chest expansion, radiographic average grade of the sacroiliac joint, hip involvement, and ASDAS-CRP showed a significant difference between the normal BMD and the low BMD groups (all $P <0.05$).

Prevalence of Low BMD in Different Sites

The prevalence of low BMD in different sites is shown in Table S1. For all AS patients, the lumbar spine was the most common site for low BMD (29.3%), followed by the femoral neck (26.5%) and total hip (24.9%). For patients with hip involvement, the total hip was the most common site for low BMD (34.5%). For patients without hip involvement, the lumbar spine was the most common site for low BMD (16.7%).

The association of BMD and mSASSS in AS Patients with Syndesmophytes

For AS patients with syndesmophytes, increase in mSASSS was significantly associated with higher anteroposterior lumbar spine BMD (r_s = 0.201, P = 0.024) but not with femoral neck or total hip BMD (r_s = -0.156, P =0.081; r_s = -0.146, P = 0.102, respectively) (Table S2).

Identification of Risk Factors for Low BMD in the Femoral Neck and Total Hip

We further studied the effect-size estimates of multiple examined factors in association with the risk of low BMD before and after adjusting for confounding factors for femoral neck and total hip BMD (Table 3). Based on univariate logistic regression analysis, several factors associated with the development of low BMD in the femoral neck and total hip were found at a significance level of 5%. After adjusting for age and gender, statistical significance was still existed in all factors. After multivariate adjustment, chest expansion, mSASSS, BMI, average radiographic grades at the sacroiliac joint and hip involvement were recognized as risk factors for low BMD of the femoral neck (P <0.05). Chest expansion, BASFI, mSASSS, ASDAS-CRP, diagnosis duration, BMI, night pain, average radiographic grades at the sacroiliac joint, PGA, and hip involvement were recognized as risk factors for low BMD of the total hip (P<0.05).

Prediction Accuracy Assessment

Basic and full models were constructed to evaluate the predictive performance of important factors associated with low BMD (Table S3). The full model included all the variables investigated, however, the basic model included all variables except for the significant risk factors identified by regression analyses. Calibration and discriminant statistics were applied to evaluate the prediction performance of the femoral neck and total hip significance factors which were added in the basic model. The prediction accuracy of the full model was significantly higher than that of the basic model. As shown by the comprehensive discriminant improvement, there were significant differences between the two models in predicting the performance of low BMD in the femoral neck and total hip (P < 0.001). For both the femoral neck and total hip, decision curve analysis suggested that net benefits achieved obviously after adding significant factors to the basic model (Figure 1).

Interaction Explorations

Since the occurrence of low BMD in AS patients is a complex process, the influence of any risk factor may be small when evaluated alone, but it may be more obvious when other risk factors are combined. To obtain more accurate information, combined with the outcomes of clinical and logistic regression analysis, we divided the variables that were relevant for the low BMD into groups and further explored the risk factors affecting low BMD in the femoral neck and total hip (Table 4).

Hip involvement, mSASSS, and the average radiographic grade of the sacroiliac joint were found to be significant risk factors associated with low BMD in the femoral neck and total hip. When the average radiological grade of the sacroiliac joint exceeds grade 3 or hip involvement, the presence of syndesmophytes [defined as at least one vertebral corner mSASSS score ≥ 2 (van der Heijde et al. 2019)] further increased the risk of low BMD in the femoral neck and total hip (both P <0.05).

Notably, hip involvement not only interacted with the presence of syndesmophytes but also with the average radiological grade of the sacroiliac joint. When the average radiological grade of the sacroiliac joint exceeds grade 3, hip involvement increased the risk of low BMD in the femoral neck and total hip (both $P < 0.05$). This finding implies that for AS patients with hip involvement, the combination of severe sacroiliitis or syndesmophytes significantly increase the risk of low BMD at the femoral neck and total hip.

Prediction Model

Finally, a nomogram was constructed to predict the risk of low BMD in AS patients based on significant factors that were identified in the femoral neck and total hip (Figure 2). Nomogram's important factors were analyzed by positive logistic regression at a significance level of 5%. For example, assuming a female (20 points) AS patient with an onset age of 20 (10 points), BMI of 18 (82 points), BASFI of 5 (64 points), chest expansion of 3 (30 points), sacroiliitis average of 4 scores (10 points), mSASSS scores of 18 (10 points) and hip involvement (50 points), the possibility of low BMD of total hip was estimated to be 70%.

Discussion

Low BMD is the most common comorbidity of AS due to multiple factors that disrupt bone metabolic balance. It causes bone fragility and increased fracture risk in AS patients, therefore, identifying risk factors is of great importance for the prevention of low BMD. The main purpose of this study is to investigate individually and interactively critical risk factors for low BMD in AS patients at different sites and to establish predictive nomogram models reflecting the data from our subjects. To our knowledge, this is the first study to predict the risk factors for low BMD in different sites based on an interaction analysis and nomogram prediction model. Our interaction analyses revealed that low BMD could be caused by the superposition of risk factors. We consider that the interaction of syndesmophytes, hip involvement, and severe sacroiliitis increases the risk of low BMD in an additive manner. Our study provides a tool for rheumatologists to predict the risk of low BMD, and also highlight that early control of the lesions of the sacroiliac and total hip and inhibition of the formation of syndesmophytes could reduce the possibility of low BMD in AS.

Currently, it is still a controversial topic about the common sites of low BMD in AS patients (Klingberg et al. 2012; Singh et al. 1995; Wang et al. 2017; Cai et al. 2020; Deminger et al. 2017). Deminger et al (Deminger et al. 2017) found that low BMD was more common at the proximal femur compared to the lumbar spine (16.5% vs. 6.3%) in AS patients. However, Klingberg et al (Klingberg et al. 2012) suggested that the lumbar spine is the most common sites of low bone mass in AS patients. Unfortunately, these studies did not discuss the differences in the sites prone to low BMD between patients with and without hip involvement. Our study found that the total hip was the most common site of low BMD (34.5%) in patients with hip involvement, while the lumbar spine is the most common site of low BMD (16.7%) in patients without hip involvement. This suggested that inflammation of the hip and the resulting limitation of activity may accelerate the loss of hip BMD.

Since predictors may have different effects on BMD at different sites, we explored potential risk factors for low BMD at the femoral neck and total hip separately. To avoid the potential effect

of syndesmophytes on the measurement of BMD at the anteroposterior lumbar spine, we did not explore risk factors for low BMD at the lumbar spine. Our results revealed that chest expansion, mSASSS, BMI, the average radiographic grade of the sacroiliac joint, and hip involvement were the common risk factors of the femoral neck and total hip. These findings also confirm some previous studys. For example, the relationship between mSASSS and low BMD has also been explored in different literatures. Karberg et al (Karberg et al.2005) demonstrated that mSASSS score was significantly associated with low BMD, especially in the femoral neck. Another study also showed that low BMD was significantly associated with the development of new syndesmophytes (Kim et al.2018). Based on the above results, it could be confirmed that AS patients with high mSASSS scores caused limited activity, which might accelerate the process of low BMD.

In addition, we found that more severe sacroiliitis was also a risk factor for low BMD in the femoral neck and total hip. In previous studies, it was also documented that low trabecular bone score in AS patients was associated with the severity of sacroiliitis (Kang et al.2018). This may be related to trabecular bone loss as a result of chronic inflammation, and its impact on BMD is manifested in a non-single site. Therefore, aggressive interventions in the progressive stages of AS (especially for more severe sacroiliitis) should effectively prevent low BMD by increasing the mobility associated with pain relief and potentially having a direct anti-inflammatory effect on bone (Wang et al. 2017). Furthermore, we found that hip involvement was a common risk factor for low BMD in the femoral neck and total hip. This result was supported by Wang et al, who found that hip involvement was one of the risk factors for developing bone loss in AS patients (Wang et al.2015; Liu et al.2021). On the one hand, the relationship between hip involvement and low BMD could be explained by local inflammation in the hip joint. On the other hand, for AS patients with hip involvement, early pain and late hip ankylosis would decrease the patient's activity, which would further aggravate bone loss.

Although the impact of each risk factor is small when the risk factors are evaluated separately, the impact is more obvious when there is a superposition of other risk factors. However, most of

the current studies tend to focus on individual risk factors, while ignoring the interaction between other factors. To extend the outcomes reported by published studies, we explored the interaction between each risk factor and observed synergistic effects. Our results showed that the presence of syndesmophytes significantly increased the risk of low BMD in the femoral neck and total hip when the radiological average grade of the sacroiliac joint exceeded grade 3 or hip involvement was present. Notably, hip involvement not only interacted with syndesmophytes but also with the radiographic grade of the sacroiliac joint, highlighting the importance of severe sacroiliitis, syndesmophytes, and hip involvement in the development of low BMD. These results underscore the need to closely monitor AS patients with severe radiological damage, hip involvement, and higher sacroiliitis grades to prevent the occurrence of low BMD.

Taken together, through the analysis of the survey data of 249 AS patients, we explored the risk factors of low BMD in different sites in AS patients. More importantly, we found that some risk factors may act on the susceptibility of low BMD in a cumulative way. Finally, to facilitate the practical application of our findings, we created a risk prediction nomogram model for the occurrence of low BMD at different sites for AS patients, which revealed reasonable prediction accuracy. We hope that this study provides background data that can be used to further explore the potential risk factors of low BMD in AS patients, including individual and interaction effects, and further explore the risk factors of low BMD in AS patients for the process of early detection and prevention.

There are some limitations in this study. Due to our limited sample size, the conclusions are not definitive and therefore it is necessary to formulate corresponding standards according to different ages and gender. It is also necessary, for the future, to adopt quantitative computed tomography to avoid the interference of actual density in AS patients with syndesmophytes to draw more accurate conclusions (Deminger et al.2022). The major strength of the present study is the finding that AS patients with hip involvement are more likely to experience low BMD in the total hip, whereas those without hip involvement are more prone to low BMD in the lumbar spine. We also identified several risk factors associated with low BMD in the femoral neck and total hips,

including syndesmophytes, hip involvement, and radiological average grade of the sacroiliac joint. Importantly, we found that these factors increase the risk of low BMD in an additive manner. Finally, we established an effective prediction model in order to facilitate new research into the possibility of creating a prevention strategy.

Conclusion

Low BMD was most likely to occur in the total hip in patients with hip involvement and in the lumbar spine in patients without hip involvement. This study identified syndesmophytes, hip involvement and severe sacroiliitis increases the risk of low BMD in an additive manner and established a nomogram prediction model to help rheumatologists identify high risk patients to prevent low BMD.

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Figure legends

Figure 1 Net benefits gained by the significant factors identified for low BMD in AS patients in decision curve analysis at two different sites.

A: Femoral neck; B: Total hip.

Figure 2 Risk prediction nomograms for low BMD in AS patients at two different sites.

A: Femoral neck; B: Total hip. BMI, body boss index; BASFI, Bath Ankylosing Spondylitis Functional Index; mSASSS, modified ankylosing spondylitis score; Sacroiliitis average, means average radiological grade of the sacroiliac joint.

Table legends

Table 1 Baseline characteristics of the study patients.

BMD, bone mineral density; BMI, body boss index; TNF, tumour necrosis factor; cDMARDs, conventional DMARDs.

Table 2 Disease-related variables and bone mineral density of the study patients.

BMD, bone mineral density; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; PGA, patient global assessment; HLA-B27, human leucocyte antigen B27; mSASSS, modified ankylosing spondylitis score; Sacroiliitis average, means average radiological grade of the sacroiliac joint.

Table 3 Risk prediction for low BMD in AS patients.

BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body boss index; PGA, patient global assessment. OR, odds ratio; 95% CI, 95% confidence interval. Sacroiliitis average, means average radiological grade of the sacroiliac joint. *P* values were calculated before and after adjusting for age, gender, HLA-B27, smoking index, smoking duration, cigarettes per day, current smoking, alcohol history and alcohol duration. In multivariable adjusted model, risk prediction of each adjusted factor was calculated by adjusting for the other factors.

Table 4 The interaction of three significant factors identified for low BMD of the femoral neck and total hip in AS patients.

OR, odds ratio; 95% CI, 95% confidence interval; Ref., reference; Sacroiliitis average, means average radiological grade of the sacroiliac joint; Syndesmophytes present, defined as at least one vertebral corner mSASSS score ≥ 2.

Supplementary legends

Table S1 Prevalence of low bone mineral density in different sites.

BMD, bone mineral density.

Table S2 Spearman's correlation between BMD and mSASSS scores in AS patients with syndesmophytes.

BMD, bone mineral density. AP, anteroposterior position.

Table S3 Prediction accuracy gained by adding the identified significant factors for low BMD in AS patients at two different sites

AIC, Akaike information criterion; BIC, Bayesian information criterion; LR, likelihood ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement; AUROC, area under the receiver operating characteristic; Ref., reference.

Table 1(on next page)

Baseline characteristics of the study patients.

BMD, bone mineral density; BMI, body boss index; TNF, tumour necrosis factor; cDMARDs, conventional DMARDs.

Table 1:

Baseline characteristics of the study patients.

Variables	All (N=249)	Normal BMD (N=132)	Low BMD (N=117)	*P* value
Demographic variables				
Male	194 (77.9%)	98 (74.2%）	96 (82.1%)	0.138
Age, years	33.7 (10.5)	34.3 (10.4)	33.1 (10.6)	0.348
BMI, kg/m^2	23.1(3.2)	23.4 (3.0)	22.7 (3.4)	0.044
Sport	38 (15.4%)	20 (15.2%)	18 (15.4%)	0.959
Family history	55 (21.1%)	31 (23.5%)	24 (20.5%)	0.573
Diagnosis duration, years	6.3(5.0)	5.8 (4.8)	6.8 (5.2)	0.164
Symptoms duration, years	10.0 (6.7)	9.7 (6.9)	10.2 (6.5)	0.291
Onset age, years	23.8 (9.9)	24.6 (9.7)	22.9 (10.1)	0.106
Smoking index	48.6 (139.7)	46.8 (149.1)	50.6 (128.6)	0.462
Smoke duration, years	3.1 (6.8)	2.8 (6.14)	3.5 (7.5)	0.468
Cigarettes per day	3.5(7.3)	3.3 (7.7)	3.6 (6.8)	0.389
Ever smoking	65 (26.1%)	31 (23.5%)	34 (29.1%)	0.317
Current smoking	62 (24.9%)	29 (22.0%)	33 (28.2%)	0.256
Alcohol duration	3.0 (6.8)	3.1 (6.8)	2.9 (6.9)	0.701
Alcohol history	50 (20.1%)	26 (19.7%)	24 (20.5%)	0.873
Daily alcohol	55 (22.1%)	29 (22.0%)	26 (22.2%)	0.962
Alcohol frequency	0.3 (0.8)	0.3 (0.7)	0.3 (0.8)	0.939
Current medication status				
Patients on TNF inhibitor	8 (3.2%)	3 (2.3%)	5 (4.3%)	0.372
Patients on NSAIDs	137 (55.0%)	71 (53.8%)	66 (56.4%)	0.678
Patients on cDMARDs	54 (21.7%)	23 (17.4%)	31 (26.5%)	0.083

BMD, bone mineral density; BMI, body boss index; TNF, tumour necrosis factor; cDMARDs, conventional DMARDs.

Table 2(on next page)

Disease-related variables and bone mineral density of the study patients.

BMD, bone mineral density; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; PGA, patient global assessment; HLA-B27, human leucocyte antigen B27; mSASSS, modified ankylosing spondylitis score; Sacroiliitis average, means average radiological grade of the sacroiliac joint.

Table 2:

Disease-related variables and bone mineral density of the study patients.

Variables	All (N=249)	Normal BMD (N=132)	Low BMD (N=117)	*P* value
Disease-related variables				
BASDAI, score	3.1 (1.3)	3.0 (1.2)	3.3 (1.4)	0.134
BASFI, score	1.4 (1.6)	1.4 (1.5)	1.5 (1.7)	0.565
BASMI, score	1.9 (2.0)	1.7 (2.0)	2.2 (2.0)	0.027
Night pain, score	4.0 (2.0)	3.8 (1.9)	4.2 (2.0)	0.104
PGA, score	3.9 (2.0)	3.8 (2.0)	4.1 (1.9)	0.275
Chest expansion, cm	4.4 (2.0)	4.7 (1.8)	4.1 (2.1)	0.030
modified-Schober, score	5.0 (1.9)	5.2 (1.8)	4.8 (1.9)	0.083
HLA-B27 Positive	223 (89.6%)	117 (88.6%)	106 (90.6%)	0.613
Sacroiliitis average, score	3.0 (0.8)	2.8 (0.8)	3.2 (0.8)	<0.001
mSASSS, score	13.2(20.6)	11.1(19.7)	14.9(21.2)	0.142
Hip involvement	78 (38.4%)	35 (31.3%)	43 (47.3%)	0.020
ESR, mm/h	21.0 (19.7)	19.0 (18.9)	23.3 (19.6)	0.051
CRP, mg/L	1.6 (1.9)	1.6 (2.0)	1.7 (1.9)	0.142
ASDAS-CRP, scores	1.7 (0.7)	1.6 (0.7)	1.8 (0.8)	0.032
BMD				
Lumber spine	1.1 (0.19)	1.2 (0.17)	1.0 (0.16)	<0.001
Femoral neck	0.9 (0.15)	1.0 (0.11)	0.8 (0.14)	<0.001
Total hip	0.9 (0.17)	1.0(0.14)	0.8 (0.14)	<0.001

BMD, bone mineral density; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; PGA, patient global assessment; HLA-B27, human leucocyte antigen B27; mSASSS, modified ankylosing spondylitis score; Sacroiliitis average, means average radiological grade of the sacroiliac joint.

Table 3(on next page)

Risk prediction for low BMD in AS patients.

BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body boss index; PGA, patient global assessment. OR, odds ratio; 95% CI, 95% confidence interval. Sacroiliitis average, means average radiological grade of the sacroiliac joint. *P* values were calculated before and after adjusting for age, gender, HLA-B27, smoking index, smoking duration, cigarettes per day, current smoking, alcohol history and alcohol duration. In multivariable adjusted model, risk prediction of each adjusted factor was calculated by adjusting for the other factors.

Table 3:

Risk prediction for low BMD in AS patients.

Variables	Femoral neck			Total hip		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Unadjusted						
Chest expansion	0.81	0.70 to 0.94	0.005	0.86	0.74 to 0.99	0.038
BASMI	1.21	1.05 to 1.39	0.007	1.17	1.01 to 1.34	0.032
BASFI	1.04	0.88 to 1.24	0.640	1.15	0.98 to 1.36	0.095
Total mSASSS	1.02	1.01 to 1.03	0.003	1.02	1.00 to 1.03	0.011
ASDAS-CRP	1.22	0.84 to 1.78	0.286	1.45	0.99 to 2.12	0.057
Diagnosis duration	1.04	0.99 to 1.10	0.157	1.07	1.01 to 1.13	0.019
BMI	0.92	0.84 to 1.00	0.054	0.88	0.80 to 0.97	0.010
Night pain	0.96	0.83 to 1.11	0.598	1.16	1.00 to 1.34	0.048
PGA	1.03	0.90 to 1.19	0.662	1.16	1.01 to 1.35	0.041
Sacroiliitis average	2.08	1.44 to 3.02	<0.001	1.90	1.31 to 2.75	0.001
Hip involvement	2.08	1.55 to 5.20	0.001	2.90	1.55 to 5.43	0.001
Age and gender adjusted						
Chest expansion	0.82	0.71 to 0.95	0.008	0.85	0.73 to 0.99	0.031
BASMI	1.20	1.04 to 1.38	0.013	1.18	1.02 to 1.37	0.025
BASFI	1.03	0.87 to 1.22	0.729	1.15	0.97 to 1.36	0.099
Total mSASSS	1.02	1.00 to 1.03	0.016	1.02	1.01 to 1.04	0.009
ASDAS-CRP	1.25	0.86 to 1.82	0.245	1.47	1.00 to 2.16	0.051
Diagnosis duration	1.03	0.97 to 1.09	0.293	1.07	1.01 to1.14	0.017
BMI	0.90	0.82 to 0.99	0.026	0.88	0.80 to 0.97	0.008
Night pain	0.97	0.84 to 1.12	0.692	1.16	1.01 to 1.35	0.041
PGA	1.05	0.91 to 1.21	0.547	1.17	1.01 to 1.35	0.036
Sacroiliitis average	2.20	1.49 to 3.24	<0.001	2.03	1.38 to 2.99	<0.001
Hip involvement	2.88	1.48 to 5.59	0.002	3.05	1.61 to 5.79	0.001
Multivariable adjusted						
Chest expansion	0.79	0.67 to 0.93	0.005	0.81	0.69 to 0.95	0.011
BASMI	1.18	1.01 to 1.38	0.035	1.16	0.99 to 1.36	0.060
BASFI	1.08	0.89 to 1.31	0.424	1.22	1.01 to 1.47	0.044
Total mSASSS	1.02	1.00 to 1.04	0.016	1.02	1.00 to 1.04	0.014
ASDAS-CRP	1.38	0.91 to 2.09	0.133	1.62	1.06 to 2.48	0.027
Diagnosis duration	1.04	0.98 to 1.11	0.166	1.07	1.00 to 1.14	0.038
BMI	0.87	0.78 to 0.97	0.009	0.87	0.79 to 0.97	0.012
Night pain	1.01	0.86 to 1.18	0.946	1.21	1.03 to 1.42	0.018
PGA	1.09	0.93 to 1.27	0.278	1.22	1.04 to 1.43	0.016
Sacroiliitis average	2.09	1.38 to 3.17	0.001	2.01	1.32 to 3.05	0.001

Hip involvement	2.83	1.38 to 5.82	0.004	2.77	1.33 to 5.76	0.006

BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body boss index; PGA, patient global assessment. OR, odds ratio; 95% CI, 95% confidence interval. Sacroiliitis average, means average radiological grade of the sacroiliac joint. *P* values were calculated before and after adjusting for age, gender, HLA-B27, smoking index, smoking duration, cigarettes per day, current smoking, alcohol history and alcohol duration. In multivariable adjusted model, risk prediction of each adjusted factor was calculated by adjusting for the other factors.

Table 4(on next page)

The interaction of three significant factors identified for low BMD of the femoral neck and total hip in AS patients.

OR, odds ratio; 95% CI, 95% confidence interval; Ref., reference; Sacroiliitis average, means average radiological grade of the sacroiliac joint; Syndesmophytes present, defined as at least one vertebral corner mSASSS score ≥ 2.

Table 4:

The interaction of three significant factors identified for low BMD of the femoral neck and total hip in AS patients.

Interaction items	Femoral neck			Total hip		
	OR	95% CI	*P*	OR	95% CI	*P*
No syndesmophytes/ Sacroiliitis average≤3	Ref.			Ref.		
No syndesmophytes/ Sacroiliitis average>3	1.40	0.51to 3.81	0.513	3.68	1.34 to 10.12	0.012
Syndesmophytes present/ Sacroiliitis average≤3	0.43	0.10 to 1.79	0.243	1.11	0.29 to 4.20	0.883
Syndesmophytes present/ Sacroiliitis average>3	2.29	1.02 to 5.15	0.045	3.35	1.37 to 8.18	0.008
No syndesmophytes/ Hip involvement=0	Ref.			Ref.		
No syndesmophytes/ Hip involvement=1	2.22	0.70 to 7.01	0.174	4.74	1.48 to 15.20	0.009
Syndesmophytes present/ Hip involvement=0	1.14	0.40 to 3.20	0.809	1.92	0.64 to 5.77	0.244
Syndesmophytes present/ Hip involvement=1	3.51	1.33 to 9.30	0.012	3.55	1.21 to 10.36	0.021
Sacroiliitis average≤3/ Hip involvement=0	Ref.			Ref.		
Sacroiliitis average≤3/ Hip involvement=1	1.33	0.24 to 7.46	0.746	4.43	0.97 to 20.22	0.055
Sacroiliitis average>3/ Hip involvement=0	1.31	0.48 to 3.57	0.596	2.57	0.88 to 7.56	0.086
Sacroiliitis average>3/ Hip involvement=1	3.73	1.48 to 9.39	0.005	4.78	1.71 to 13.37	0.003

OR, odds ratio; 95% CI, 95% confidence interval; Ref., reference; Sacroiliitis average, means average radiological grade of the sacroiliac joint; Syndesmophytes present, defined as at least one vertebral corner mSASSS score ≥ 2.

Figure 1

Net benefits gained by the significant factors identified for low BMD in AS patients in decision curve analysis at two different sites.

A: Femoral neck; B: Total hip.

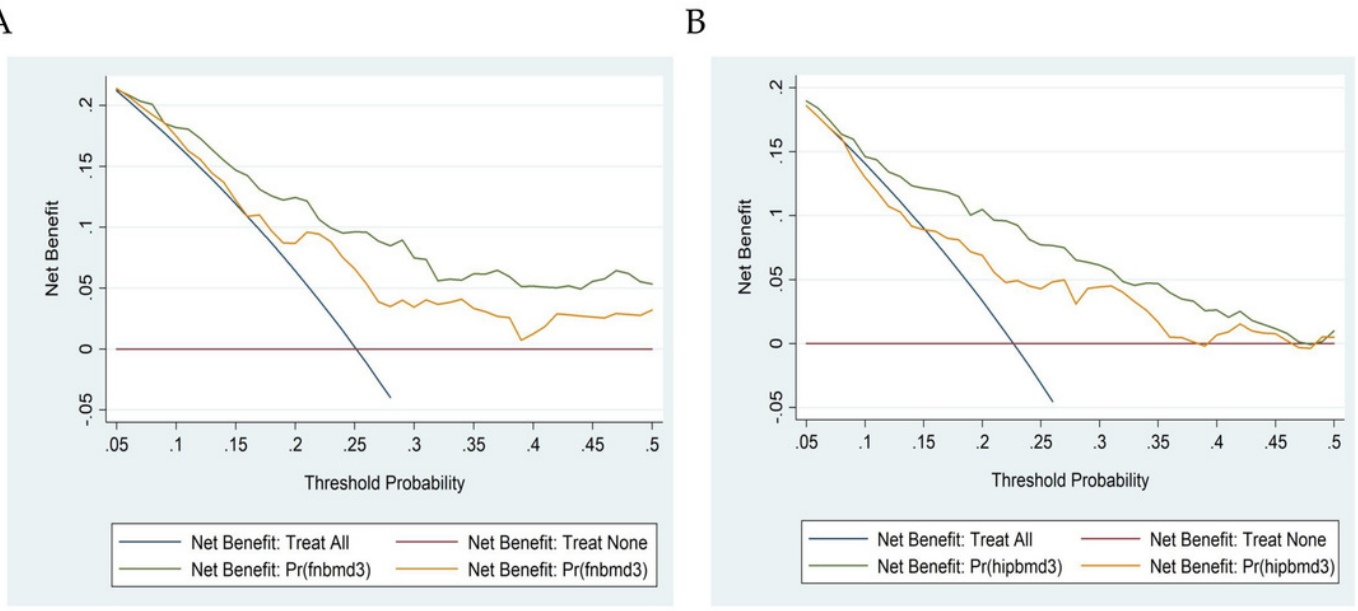
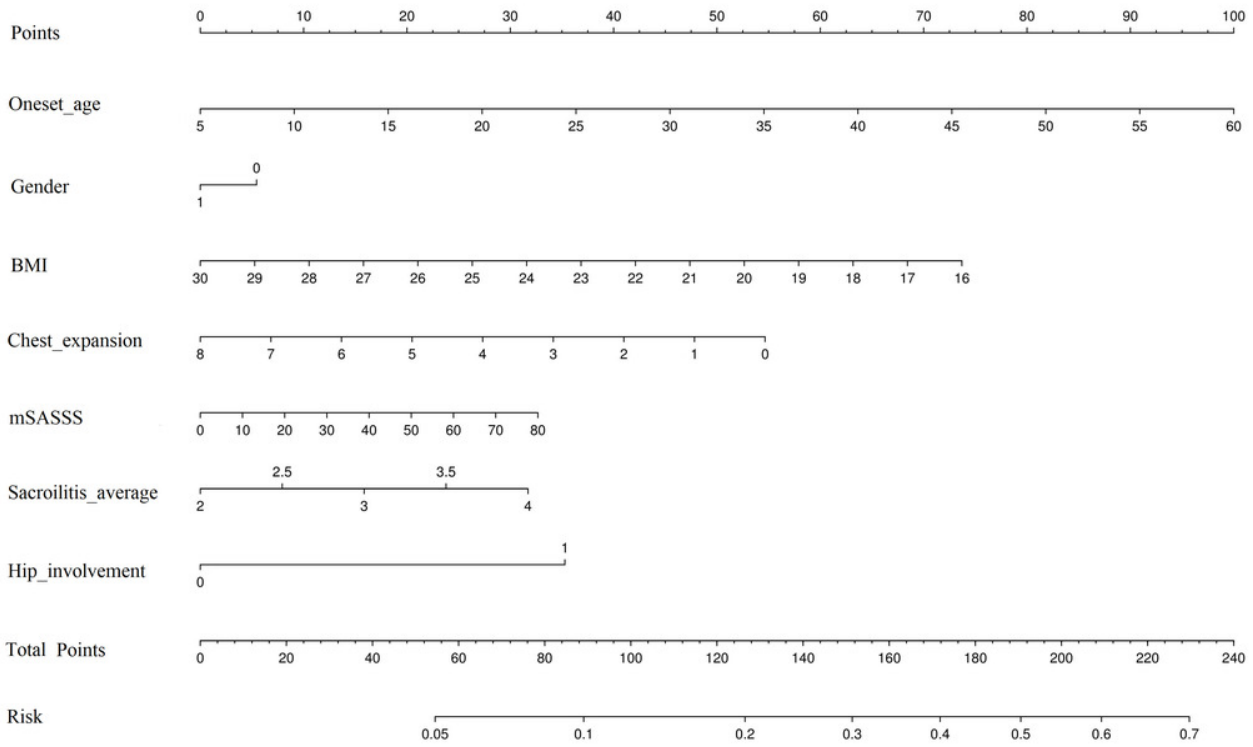


Figure 2

Risk prediction nomograms for low BMD in AS patients at two different sites.

A: Femoral neck; B: Total hip. BMI, body boss index; BASFI, Bath Ankylosing Spondylitis Functional Index; mSASSS, modified ankylosing spondylitis score; Sacroiliitis average, means average radiological grade of the sacroiliac joint .

A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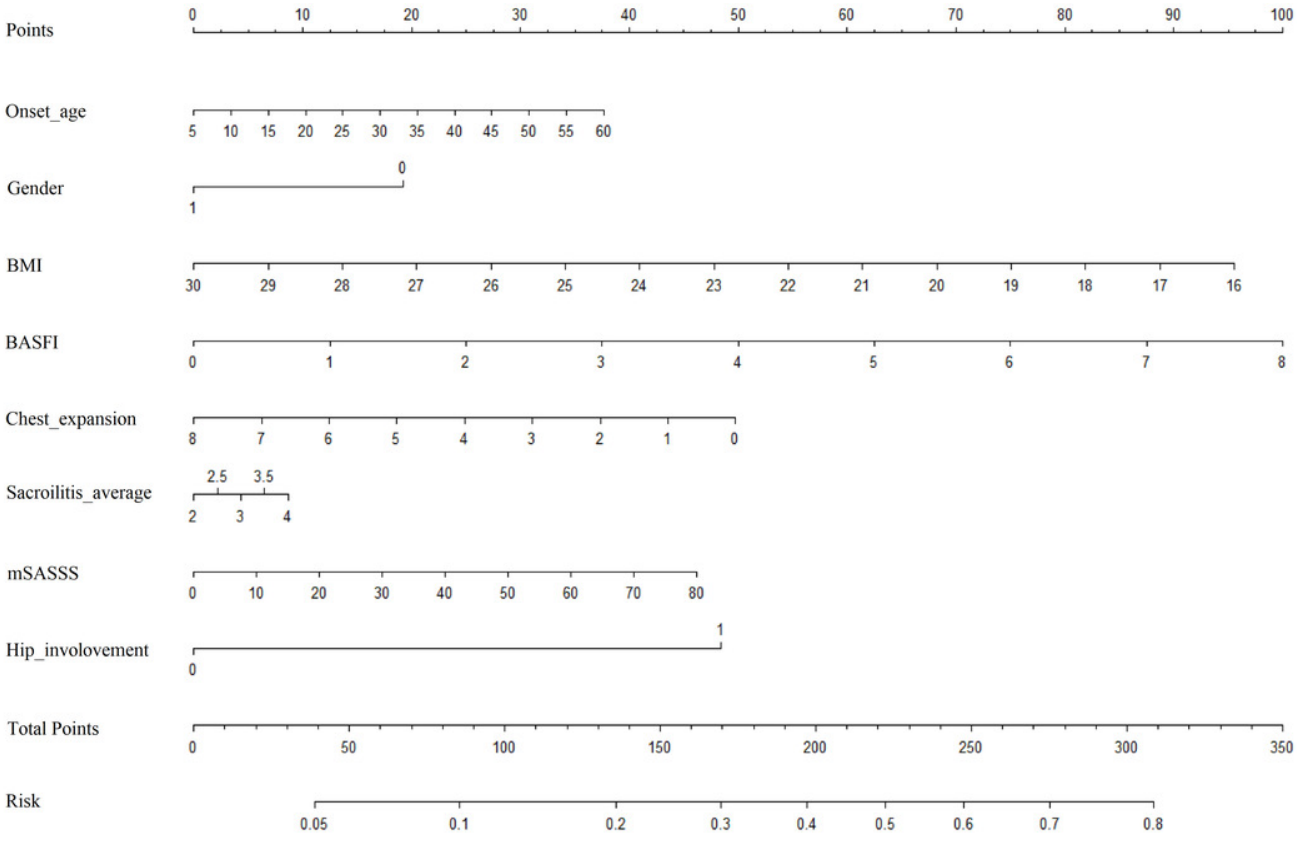
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