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Serum alkaline phosphatase/creatinine ratio serving as a screening tool for low lumbar bone mineral density in patients with degenerative lumbar scoliosis

Zhenning Cai[1], Xing Sun[2], Bo Shi[1], Zhenhua Feng[1], Sen Li[1], Zezhang Zhu[1], Yong Qiu[1] and Benlong Shi[1*]

Abstract

Purpose (1) To figure out a simple and effective indicator that could assist in the assessment of bone mineral density (BMD) based on big data and (2) to verify its predictive value for low BMD among patients with degenerative lumbar scoliosis (DLS).

Methods A total of 6,167 participants from the National Health and Nutrition Examination Survey (NHANES) database (2009–2010, 2013–2014, 2017–2018) and 166 patients who were diagnosed with DLS and hospitalized in our center between June 2019 and April 2023 were enrolled in the study. Cases were divided into two groups based on whether the T-score was below − 1. The Osteopenia Index (OI) was defined as the ratio of alkaline phosphatase (ALP) (IU/L) to creatinine (mg/dL). Multivariable logistic regression was performed to identify risk factors, while restricted cubic spline (RCS) analysis was applied to explore the potential non-linear relationship. Patients with DLS from our center were used to validate the diagnostic value of OI through receiver operating characteristic curve (ROC) analysis.

Results Participants from NHANES were divided into three subgroups according to the tertiles of OI: subgroup 1 (OI < 68), subgroup 2 (68 ≤ OI < 93), and subgroup 3 (OI ≥ 93). A multivariable logistic regression model adjusted for age, gender, and race revealed that elevated OI was a significant risk factor for osteopenia (subgroup 2 vs. subgroup 1: odds ratio [OR] = 1.473, 95% confidence interval [CI] = 1.173–1.849; subgroup 3 vs. subgroup 1: OR = 2.092, 95% CI = 1.566–2.796). Moreover, the RCS plot showed that the risk of osteopenia gradually increased with the elevation of OI. In patients with DLS, OI showed a significant correlation with lumbar T-score ($\rho = -0.392$) and HU value ($\rho = -0.373$) (both $P < 0.001$). ROC analysis revealed that the area under the curve of OI was 0.757, and the cut-off value was set at 124.73 according to the Youden index. A nomogram based on a logistic regression model adjusted for age, gender, and blood urea nitrogen was plotted, with a McFadden R^2 of 0.212.

*Correspondence:
Benlong Shi
shi-benlong@163.com

Full list of author information is available at the end of the article

Conclusion OI correlated significantly with lumbar BMD and HU value. Logistic regression and RCS analysis demonstrated that OI could serve as a simple, economical, and effective screening tool for low lumbar BMD in DLS patients, with its predictive ability further enhanced when adjusted for age and gender.

Keywords Bone mineral density, Osteopenia, Alkaline phosphatase, Creatinine, Degenerative lumbar scoliosis, NHANES

Introduction

Osteopenia and osteoporosis, characterized by a decrease in bone mineral density (BMD), have become common health issues affecting a large cohort of elderly individuals, especially postmenopausal women [1]. Patients with severely decreased BMD face a high risk of fractures, as well as associated risks of disability and mortality [2]. Even though dual-energy X-ray absorptiometry (DEXA) has been established as the gold standard for measuring BMD and guiding the treatment of osteoporosis [3], its drawbacks, such as radiation exposure and difficulty in precise assessment, should not be neglected.

Degenerative lumbar scoliosis (DLS) is an abnormal curvature of the spine due to degenerative changes in adulthood, often leading to low back pain and neurological symptoms [4]. DLS has been gaining increasing attention from surgeons due to its severe impact on patients' quality of life and the challenges in surgical treatment [4, 5]. Low BMD has been demonstrated to have a strong correlation with DLS [6] and can increase intraoperative bleeding and precipitate postoperative complications, including screw loosening, instrumentation failure, and junctional failure [7–9]. Therefore, accurate and comprehensive assessment of BMD in DLS patients is critical. Although other approaches, such as the Vertebral Bone Quality (VBQ) score and Hounsfield unit (HU) value from CT scans, have been introduced previously [7, 10], the complexity of these measurement procedures still limits their widespread clinical application.

Previous studies have identified several biomarkers associated with bone turnover and explored their application in postmenopausal osteoporosis and other bone diseases [11]. Correlations between BMD and bone alkaline phosphatase (ALP), osteocalcin, and C-terminal telopeptides of type I collagen (CTX) levels have been found among postmenopausal women [12]. Notably, accurate assessment of bone turnover using urinary CTX also requires the measurement of urinary creatinine levels [12]. This insight led us to hypothesize that a combination of a routine serum bone turnover biomarker and serum creatinine could serve as a screening tool for low lumbar BMD in DLS patients. In this study, we aimed to (1) identify a simple and effective indicator that could assist in the assessment of BMD based on big data and (2) verify its predictive value for low BMD among patients with DLS.

Materials and methods

Study population

This study consisted of two phases. First, we utilized big data from the National Health and Nutrition Examination Survey (NHANES) database to identify potential indicators associated with BMD and analyzed whether they were risk factors for low BMD. Then, we validated the association of this indicator with BMD using DLS patients from our center and assessed its diagnostic efficacy.

NHANES series

The NHANES (https://www.cdc.gov/nchs/nhanes) is a cross-sectional study with a multistage, probability sampling design, aiming to assess the nutritional and health status of residents in the United States (US). The database provides demographic data, dietary data, examination data, laboratory data, and questionnaire data for selected participants in 2-year cycles. To better represent the overall characteristics of the US population, each sample is assigned an appropriate weight by the NHANES database. In the decade preceding 2018, the NHANES database collected BMD data in alternating 2-year cycles. As a result, it was not possible to include all samples from this continuous period, and we ultimately extracted data from the NHANES 2009–2010, 2013–2014, and 2017–2018 cycles for analysis. Participants' demographic data, body measurements, DEXA of the spine and femur, standard biochemistry profiles, and osteoporotic interviews were collected. The exclusion criteria were as follows: (1) Participants with blood creatinine ≥ 1.5 mg/dL. (2) Participants lacking any of the aforementioned data subsets.

Patients with DLS

Patients who were diagnosed with DLS and hospitalized in our center between June 2019 and April 2023 were included in the study. Those with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or a history of medication use affecting bone metabolism (e.g., corticosteroids) were excluded.

Measurement of examination and laboratory data

For the NHANES data, the DEXA scans were completed on Hologic Discovery model A densitometers (Hologic, Inc., Bedford, Massachusetts) or on Hologic QDR-4500 A fan-beam densitometers (Hologic, Inc., Bedford, Massachusetts). The standard biochemistry profile was

measured on the Roche Cobas 6000 (c501 module) analyzer or the DxC800 system.

Data from DLS patients in our hospital were collected before they underwent surgery. DEXA of the lumbar spine was performed on the iDXA (GE Healthcare, Waukesha, WI, USA). Lumbar HU values were obtained from preoperative computed tomography (CT) scans (LightSpeed 16, GE Medical Systems, Milwaukee, WI, USA). Regions of interest were chosen at the middle section of the vertebral body on coronal, sagittal, and transverse images, respectively [10]. The average HU value of the trabecular bone on these three images represented the HU value of the vertebra. The HU value of the lumbar spine was represented by the average HU value of L1, L2, L3, and L4. Patients' biochemical profiles were tested using a Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA). Osteopenia Index (OI) was defined as the ratio of ALP (IU/L) to creatinine (mg/dL).

Diagnosis of osteopenia

Lumbar BMD was represented by the average BMD of L1, L2, L3, and L4. The NHANES database does not provide T-scores directly. Therefore, we selected samples aged 20–29 from the preliminary screening. The mean and standard deviation of their BMD were used as the baseline to calculate the T-scores of all participants [13]. The T-score was obtained following the formula below: T-score = (participant's BMD - mean BMD) / standard deviation of BMD. Participants were diagnosed with osteopenia if their lumbar T-scores were below −1 [3]. This standard was also applied to patients with DLS.

Table 1 Comparison of baseline characteristics between the participants with and without osteopenia from the NHANES series

Variables	Non-osteopenia ($n=4470$)	Osteopenia ($n=1697$)	*p* value
Age, years	46.98 ± 13.79	53.56 ± 13.38	< 0.001***
Gender (female), %	47.9	62.5	< 0.001***
Race, %			< 0.001***
Mexican American	8.8	9.8	
Other Hispanic	5.3	7.7	
Non-hispanic White	66.4	65.1	
Non-hispanic Black	11.8	6.1	
Other Race	7.7	11.3	
BMI, kg/m^2	28.89 ± 5.91	26.00 ± 5.15	< 0.001***
Lumbar BMD (g/cm^3)	1.09 ± 0.11	0.84 ± 0.07	< 0.001***
T-score	0.32 ± 0.91	-1.76 ± 0.60	< 0.001***
Femoral neck BMD (g/cm^3)	0.86 ± 0.13	0.69 ± 0.11	< 0.001***
Albumin (g/L)	42.67 ± 3.20	42.55 ± 3.04	0.236
BUN (mmol/L)	4.68 ± 1.52	4.84 ± 1.58	0.024*
Glucose (mmol/L)	5.54 ± 1.98	5.44 ± 1.66	0.069
ALP (IU/L)	66.21 ± 20.40	73.73 ± 27.22	< 0.001***
Creatinine (mg/dL)	0.88 ± 0.19	0.83 ± 0.17	< 0.001***
OI	79.12 ± 39.48	93.66 ± 43.68	< 0.001***
Spine fracture history (yes), %	1.8	2.1	0.457

BMI, body mass index; BMD, bone mineral density; BUN, blood urea nitrogen; ALP, alkaline phosphatase; OI, osteopenia index

*, $p < 0.05$; ***, $p < 0.001$

Statistical analysis

Statistical analyses were performed using R Studio 2022.12.0 (Posit Software, USA). Following NHANES guidelines, sampling weights were considered when analyzing data from the NHANES series. Continuous variables are presented as means with standard deviations or medians with interquartile ranges, and categorical variables as quantities and proportions. Group differences were compared using Student's t-test and Wilcoxon rank-sum test for continuous variables, and χ^2 and Fisher's exact test for categorical variables. Spearman correlation analysis was used to examine the linear correlations between variables. Multivariable logistic regression was performed to identify risk factors. Restricted Cubic Spline (RCS) analysis with four knots was applied to explore the potential non-linear relationship. Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were used to compare the diagnostic value of the parameters. The optimal cut-off value was established according to the highest Youden index. The significance level was set at 0.05.

Results

Baseline characteristics

Cases from the NHANES series

A total of 6,167 NHANES cases were enrolled in the analysis, the demographic data of which are shown in Table 1. According to the diagnostic criteria, 1,697 (27.5%) cases were divided into the osteopenia group, and the remaining cases (4,470, 72.5%) were included in the non-osteopenia group. Participants with osteopenia were older (53.56 ± 13.38 vs. 46.98 ± 13.79, $P < 0.001$) and had lower BMI (26.00 ± 5.15 vs. 28.89 ± 5.91, $P < 0.001$) compared with those with normal BMD. The proportion of females in the osteopenia group was significantly higher (62.5% vs. 47.9%, $P < 0.001$), but there was no significant difference in the proportion of patients with a history of spinal fractures between the two groups (1.8% vs. 2.1%, $P = 0.457$). Regarding laboratory data, patients with osteopenia showed higher levels of ALP (73.73 ± 27.22 vs. 66.21 ± 20.40, $P < 0.001$) and blood urea nitrogen (BUN) (4.84 ± 1.58 vs. 4.68 ± 1.52, $P = 0.024$), and lower creatinine levels (0.83 ± 0.17 vs. 0.88 ± 0.19, $P < 0.001$).

Patients with DLS

A total of 166 patients with DLS in our center who met the inclusion criteria were involved in the study, and their baseline characteristics are presented in Table 2. The prevalence of osteopenia was 36.14%, including 1 male and 59 females. The results of the comparison analysis between patients with and without osteopenia are shown in Table 3. Overall, the trend of differences between the osteopenia group and the non-osteopenia group was similar to the data obtained from the NHANES series [age: 64.85 ± 5.80 vs. 61.56 ± 8.28, $P = 0.003$; sex composition (male/female): 1/59 vs. 25/81, $P < 0.001$; BUN: 5.56 ± 1.25 vs. 6.05 ± 1.43, $P = 0.023$; ALP: 78.31 ± 32.78 vs. 67.75 ± 16.80, $P < 0.001$; creatinine: 0.57 ± 0.13 vs. 0.63 ± 0.18, $P < 0.001$]. Blood calcium and phosphorus did not show significant differences between the groups (calcium: 2.35 ± 0.14 vs. 2.36 ± 0.11, $P = 0.707$; phosphorus: 1.12 ± 0.19 vs. 1.14 ± 0.16, $P = 0.461$).

Association between OI and osteopenia within the NHANES data

Spearman correlation analysis was used to examine the relationships between OI and lumbar BMD, and between OI and femoral neck BMD. The correlation coefficients were −0.225 and −0.177, respectively (both $P < 0.001$) (Fig. 1). Cases were then divided into three subgroups according to the tertiles of OI (subgroup 1: OI < 68, $n = 2{,}093$; subgroup 2: 68 ≤ OI < 93, $n = 2{,}004$; subgroup 3: OI ≥ 93, $n = 2{,}070$). A multivariable logistic regression model adjusted for age, gender, and race revealed that elevated OI was a significant risk factor for osteopenia (subgroup 2 vs. subgroup 1: odds ratio [OR] = 1.473, 95% confidence interval [CI] = 1.173–1.849, $P = 0.001$; subgroup 3 vs. subgroup 1: OR = 2.092, 95% CI = 1.566–2.796, $P < 0.001$) (Table 4). Moreover, the RCS plot showed that the risk of osteopenia gradually increased with the elevation of OI (Fig. 2). Therefore, OI has great potential in screening for osteopenia.

Validation analysis in DLS patients

In patients with DLS, OI still showed a significant correlation with lumbar T-score and HU value, with correlation coefficients of -0.392 and −0.373, respectively (both $P < 0.001$) (Fig. 3). ROC curves were plotted to examine and compare the diagnostic value of ALP, creatinine, and OI for osteopenia (Fig. 4). The areas under the curve (AUCs) of the three parameters were as follows: ALP– 0.676, creatinine– 0.703, OI– 0.757. The cut-off value for OI was determined to be 124.73 according to the Youden Index.

To better utilize OI for screening osteopenia in patients with DLS, a nomogram based on a logistic regression model adjusted for age, gender, and BUN was plotted (Fig. 5). By adding up the score of each parameter, the

Table 2 Main characteristics of the 166 patients with DLS

Variables	Mean/*n*	SD/%
Age, years	62.75	7.62
Gender		
Male	26	15.66%
Female	140	84.34%
BMI, kg/m^2	25.44	12.00
T-score	-0.41	1.71
Hounsfield Unit	97.43	40.41
Albumin (g/L)	40.29	2.48
Calcium (mmol/L)	2.36	0.12
Phosphorus (mmol/L)	1.14	0.22
BUN (mmol/L)	5.87	1.39
Glucose (mmol/L)	4.78	0.69
eGFR (mL/min/1.73 m^2)	112.80	22.94
ALP (IU/L)	73.44	22.09
Creatinine (mg/dL)	0.62	0.13
OI	124.00	50.34
Osteopenia		
no	106	63.86%
yes	60	36.14%
Osteoporosis		
no	150	90.36%
yes	16	9.64%

BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; OI, osteopenia index

Table 3 Comparison of baseline characteristics between the patients with DLS with and without osteopenia

Variables	Non-osteopenia (*n* = 106)	Osteopenia (*n* = 60)	*p* value
Age, years	61.56 ± 8.28	64.85 ± 5.80	0.003**
Gender, n (%)			
Male	25 (23.6%)	1 (1.7%)	< 0.001***
Female	81 (76.4%)	59 (98.3%)	
BMI, kg/m^2	24.45 ± 5.11	23.80 ± 4.77	0.222
T-score	0.53 ± 1.30	-2.08 ± 0.85	< 0.001***
Hounsfield Unit	109.74 ± 42.03	75.69 ± 25.91	< 0.001***
Albumin (g/L)	40.22 ± 2.53	40.42 ± 2.40	0.602
Calcium (mmol/L)	2.36 ± 0.11	2.35 ± 0.14	0.707
Phosphorus (mmol/L)	1.14 ± 0.16	1.12 ± 0.19	0.461
BUN (mmol/L)	6.05 ± 1.43	5.56 ± 1.25	0.023*
Glucose (mmol/L)	4.61 ± 0.68	4.73 ± 0.61	0.137
eGFR (mL/min/1.73 m^2)	109.22 ± 22.48	119.20 ± 22.55	0.007**
ALP (IU/L)	67.75 ± 16.80	78.30 ± 32.78	< 0.001***
Creatinine (mg/dL)	0.63 ± 0.18	0.57 ± 0.13	< 0.001***
OI	103.80 ± 38.63	137.80 ± 55.52	< 0.001***

BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; OI, osteopenia index

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

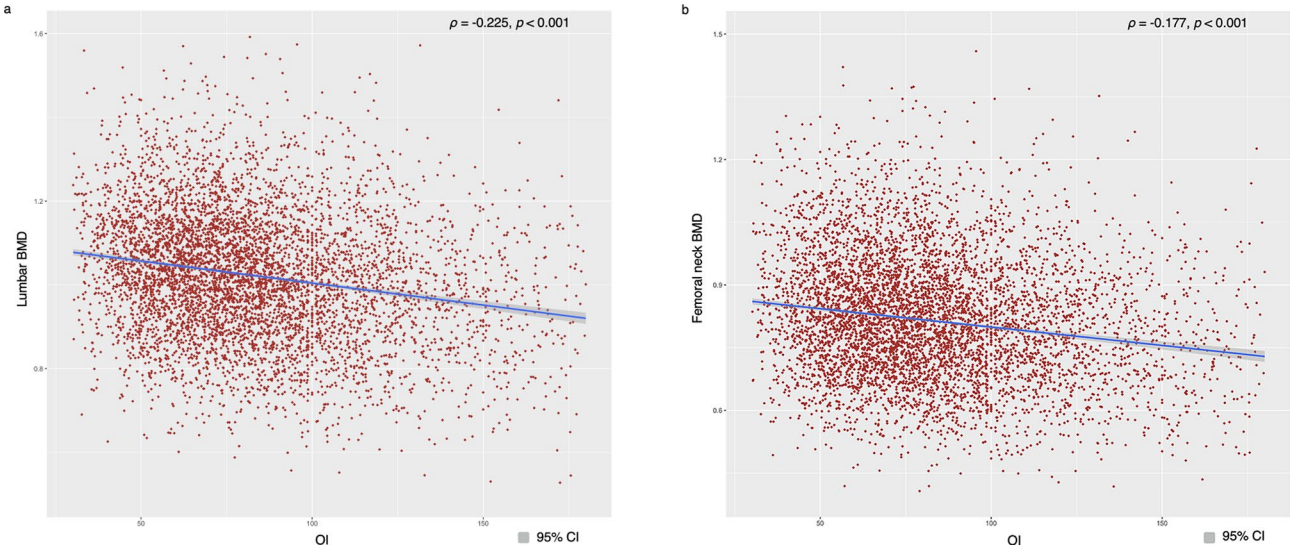

Fig. 1 (**a**) Linear correlation between OI and lumbar BMD. (**b**) Linear correlation between OI and femoral neck BMD

Table 4 Multivariable logistic regression analysis of risk factors for osteopenia

Variables	OR	95% CI	*p* value
Age	1.035	1.029–1.041	< 0.001***
Gender (female vs. male)	1.471	1.217–1.779	< 0.001***
Race			
Mexican American	Ref		
Other Hispanic	1.273	0.962–1.685	0.090
Non-hispanic White	0.856	0.691–1.061	0.150
Non-hispanic Black	0.477	0.376–0.605	< 0.001***
Other Race	1.336	1.035–1.725	0.027*
OI			
OI < 68	Ref		
68 ≤ OI < 93	1.473	1.173–1.849	0.001**
OI ≥ 93	2.092	1.566–2.796	< 0.001***

OI, osteopenia index

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

total points could clearly indicate the patient's risk for osteopenia. The McFadden R^2 of this model was 0.212. These results demonstrated that OI could be a simple and effective screening tool for osteopenia in DLS patients.

Discussion

This study aimed to identify an effective and simple indicator that could facilitate the assessment of BMD in patients with DLS. Based on big data from NHANES, we found that OI significantly correlated with lumbar BMD and was a risk factor for osteopenia. In patients with DLS, we verified the correlations among OI, T-score, and HU value, and discovered that OI exhibited good diagnostic efficiency for low BMD. We also plotted a nomogram based on a logistic regression model adjusted for age, gender, and BUN to better utilize OI for evaluating BMD in patients with DLS.

ALP has been regarded as an important indicator of bone metabolism for decades. The negative correlation between ALP and BMD has been validated in various populations, including young adults [14], middle-aged adults [15], patients with type 2 diabetes mellitus [16], and patients with renal diseases [17]. It was deduced that when BMD decreased, quiescent osteoblasts were activated, resulting in unmineralized bone-like tissue and undifferentiated osteoblasts. These osteoblasts would synthesize large amounts of bone ALP, leading to the increase of serum ALP [14].

In recent years, an increasing number of studies have demonstrated a significant correlation between serum creatinine and BMD in populations without overt nephropathy. A study based on 8,648 Korean participants discovered that as serum creatinine increased, the risk of osteopenia decreased in both sexes [18]. The researchers attributed this finding to the correlation between creatinine and physical activities. Guan et al. [19] also demonstrated that the association between serum creatinine and BMD was mediated by physical activities. Individuals with more physical activity tended to show higher serum creatinine levels as well as a lower risk of developing osteopenia and osteoporosis [20, 21]. Physical activity could stimulate bone growth and remodeling directly [22], thus helping to maintain a healthy level of BMD. It could also lead to increased muscle metabolism and potential muscle damage, both of which would cause elevated serum creatinine levels. Therefore, serum creatinine positively correlates with BMD in individuals with normal renal function.

Based on the above relationships, OI was defined as the ratio of ALP to creatinine in our study. As expected, OI showed a negative correlation with BMD. It should be noted that the correlation between OI and lumbar

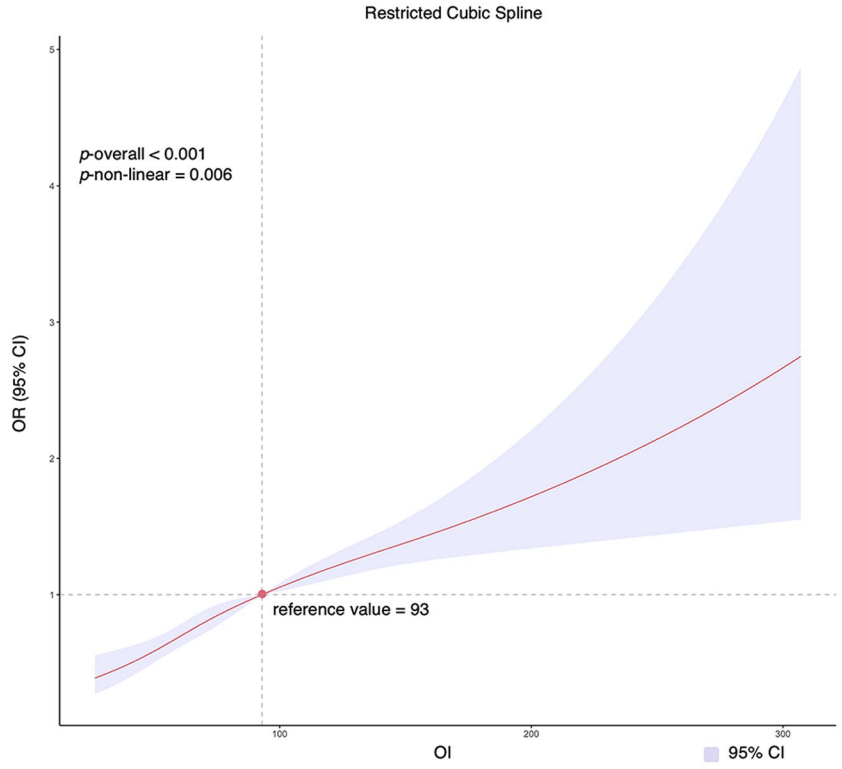

Fig. 2 Restricted cubic spline (RCS) analysis of the non-linear correlation between the risk of osteopenia and OI

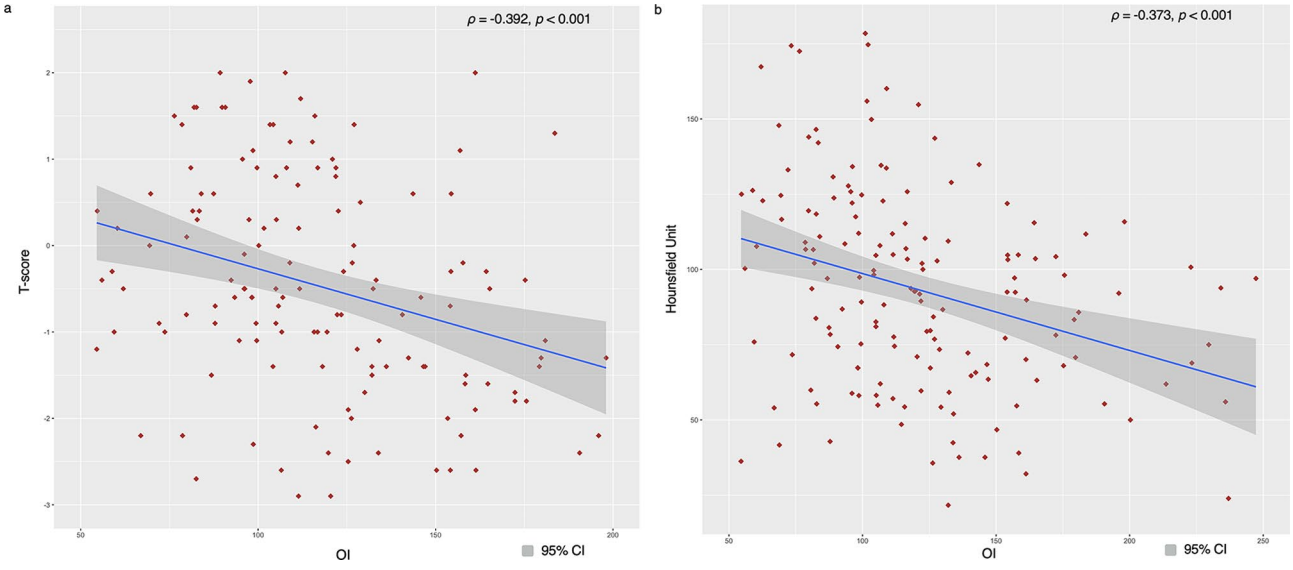

Fig. 3 (**a**) Correlation between OI and lumbar T-score. (**b**) Correlation between OI and Hounsfield Unit

BMD was stronger than the correlation between OI and femoral neck BMD. This finding is consistent with previous studies, which indicated that the relationship between ALP and femoral neck BMD was not significant [16]. Thus, OI was more suitable for BMD assessment in patients with DLS rather than in those with hip joint diseases. Multivariable logistic regression confirmed that OI was a risk factor for low lumbar BMD. The RCS plot also visually demonstrated that the risk of osteopenia gradually increased as OI elevated.

Due to the widespread formation of osteophytes in the lumbar spine of patients with DLS, it is difficult to use traditional DEXA to accurately measure their BMD. Researchers have been exploring alternative approaches to assess vertebral bone quality. Jin et al. demonstrated that HU value could be a procedure with high

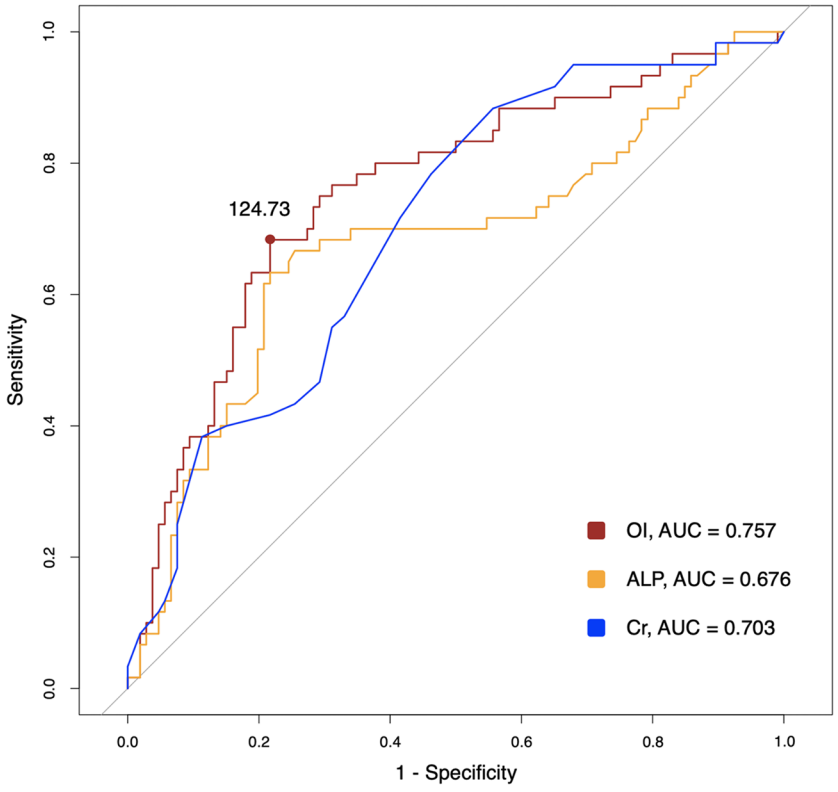

Fig. 4 ROC curve analysis of ALP, creatinine, and OI in the diagnosis of osteopenia in patients with DLS

reproducibility for evaluating bone quality in patients with DLS [23]. The VBQ score has also been introduced as a novel method with no radiation exposure [24]. However, these approaches based on CT and magnetic resonance imaging are too complex to be routinely used for preoperative evaluation. In this study, we proved that OI, which could be easily accessed from the biochemistry profile, exhibited significant correlations with lumbar T-score and HU value and strong diagnostic efficiency for low lumbar BMD in patients with DLS (AUC = 0.757). Thus, it could be conveniently applied to the preoperative assessment of bone quality. To better serve clinical practice, we plotted a nomogram based on a logistic regression model, which also took age, gender, and BUN into account. BUN is another indicator of renal function in addition to creatinine [25]. Incorporating BUN into the model could adjust for the impact of renal function on serum creatinine and OI. The McFadden R^2 between 0.2 and 0.4 signifies an optimal logistic regression model fit.

To reduce the additional costs during clinical application, we selected two common serum markers that are regularly included in preoperative blood tests to form the OI. However, this also made OI susceptible to the influence of various pathophysiological conditions. Liver diseases such as hepatitis [26], bone disorders such as Paget's disease [27], and certain medications such as antiepileptics [28] could elevate ALP levels. Similarly, chronic kidney disease, high-protein diets [29], and angiotensin-converting enzyme inhibitors [30] could increase creatinine levels. To minimize the impact of these factors on the results, this study excluded patients with impaired renal function by using creatinine levels and eGFR, and employed preoperative blood test results obtained in a resting, fasting status in the early morning, in an effort to reduce the influence of the above pathophysiological conditions.

This study still has some limitations. To increase the sample size from NHANES, certain factors that may affect BMD (such as smoking, diabetes, and other comorbidities) were not included in the analysis. Apart from this, since ALP and creatinine have not been jointly studied in any combined form in the existing literature, it was not possible to compare the efficacy of OI in screening for osteopenia under other types of pathologies. Nevertheless, our study is the first to propose and validate the correlation between OI and BMD, offering a new perspective for the preoperative assessment of BMD in patients with DLS.

In conclusion, our study demonstrated that the ratio of ALP to creatinine, which was defined as OI, significantly correlated with lumbar BMD and HU value. OI could be a simple, economical, and effective screening tool for low lumbar BMD in DLS patients, and its predictive ability

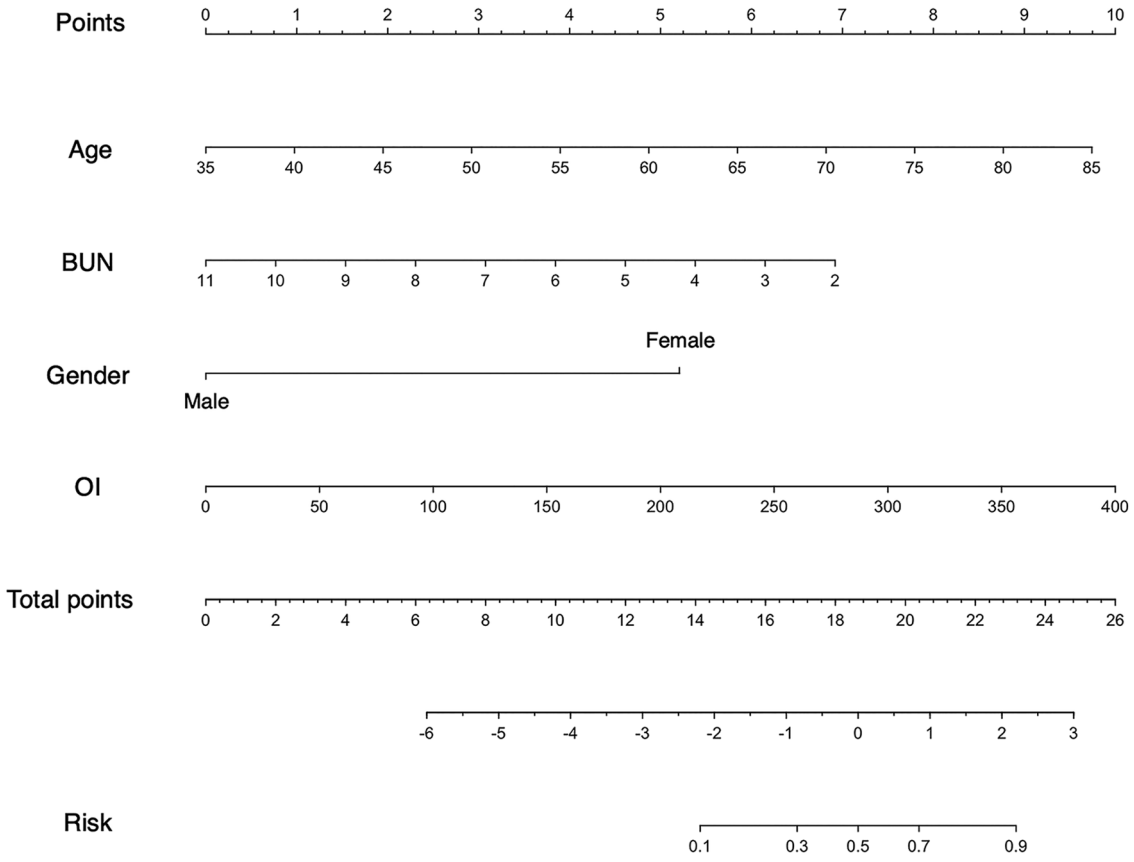

Fig. 5 The nomogram adjusted with age, gender, and BUN for the screening of osteopenia in patients with DLS

could be further enhanced after adjusting for age and gender.

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Author contributions
Z.C. and X.S. drafted the original manucript and prepared the Figs. 1, 2, 3, 4 and 5. Bo.S., Z.F., S.L. and Benlong. S. validated the results. Z.F., S.L., Z.Z. and Y.Q. provided the research resources. Bo.S., Z.Z., Y.Q. and Benlong.S. reviewed and edited the manuscript. Bo.S., Y.Q. and Benlong.S. acquired the fundings.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The ethics committee of our hospital approved the research. All the participants provided informed consent.

Consent for publication
We hereby consent to the publication of the paper and confirm that all authors have approved the final version of the manuscript. No part of the paper has been published elsewhere.

Competing interests
The authors declare no competing interests.

Author details
[1]Division of Spine Surgery, Department of Orthopaedic Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China
[2]Division of Spine Surgery, Department of Orthopaedic Surgery, Nanjing Drum Tower Hospital, The Clinical College of Nanjing Medical University, Nanjing, China

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