Retrospective Study

Association Between 25-hydroxyvitamin D Status and New Vertebral Fractures Post Percutaneous Vertebral Augmentation in Patients During Postmenopause: A Retrospective Case-control Study

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Background: Serum 25-hydroxyvitamin D (25[OH]D) deficiency causes osteoporosis and increases muscle weakness, which worsens the risk of falls and osteoporotic vertebral fractures. However, the effect of a lower serum 25(OH)D level on new vertebral fractures, including osteoporotic vertebral refractures and cascade vertebral fractures post percutaneous vertebral augmentation in patients during postmenopause has not been reported.

Objectives: This study aimed to investigate the relationship between serum 25(OH)D and the risk of osteoporotic vertebral refractures and cascade vertebral fractures.

Study Design: A retrospective case-control study.

Setting: This study took place at the Department of Spinal Surgery at a hospital affiliated with a medical university.

Methods: We retrospectively analyzed clinical data from patients during postmenopause aged ≥ 50 years who underwent percutaneous vertebral augmentation. The patients were categorized into a nonrefracture group, an osteoporotic vertebral refractures group, and a cascade vertebral fractures group. Univariate and multivariate logistic regression analysis models were employed to assess the effect of 25(OH)D on osteoporotic vertebral refractures and cascade vertebral fractures, while a receiver operating characteristic curve was used to evaluate its predictive value.

Results: A total of 528 patients were included in this study. Of these, 163 patients (30.9%) developed new vertebral fractures, with 124 (23.5%) classified as osteoporotic vertebral refractures and 39 (7.4%) as cascade vertebral fractures. The 25(OH)D levels were significantly lower in the new vertebral fracture group. Multivariate logistic regression analysis confirmed that an increase in 25(OH)D levels was protective against osteoporotic vertebral refractures occuring, including cascade vertebral fractures post percutaneous vertebral augmentation, even after adjusting for other potential confounding factors. A Pearson correlation analysis indicated a close relationship between vitamin D levels and L3 paraspinal muscle density and L3 bone mineral density in the enrolled patients with osteoporotic vertebral fractures ($P < 0.05$). A receiver operating characteristic curve analysis indicated an area under the curve of 0.751 for 25(OH)D levels in predicting the risk of osteoporotic vertebral refractures (cut-off value, 27.5 ng/mL; sensitivity, 62.74%; specificity, 72.60%; $P = 0.001$) and 0.831 for cascade vertebral fractures (cut-off value, 19.5 ng/mL, sensitivity, 56.41%; specificity, 97.53%; $P = 0.001$), respectively.

Limitations: This retrospective study was conducted at a single center with a limited number of patients during postmenopause who had prior percutaneous vertebral augmentation, especially those that developed recurrent fractures.

Conclusions: A low serum 25(OH)D level is an independent risk factor for new vertebral fractures after percutaneous vertebral augmentation in patients during postmenopause. Appropriate active vitamin D supplementation following percutaneous vertebral augmentation surgery can effectively mitigate the risk of subsequent osteoporotic vertebral fractures.

Key words: 25-hydroxyvitamin D, osteoporotic vertebral refractures, cascade vertebral fractures, percutaneous vertebral augmentation

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Osteoporotic vertebral fracture (OVF) is a significant health concern associated with the aging population in developing countries. Compared to conservative treatment, percutaneous vertebral augmentation (PVA), encompassing percutaneous vertebroplasty and percutaneous kyphoplasty, provides rapid pain relief and improved functional status for patients with an OVF. However, many patients who receive a PVA for an initial OVF, face an "imminent" risk of new vertebral fractures (1). The prevalence of osteoporotic vertebral refractures (OVRFs) after PVA is between 6.7% and 28.9% (2,3). An OVRF not only produces pain and disability in the elderly patients, but it can also lead to cascade vertebral fractures (CVFs), which represent a therapeutic challenge.

The risk factors for new vertebral fracture after PVA are mainly divided into surgical factors (including uneven distribution of vertebral bone cement and cement leakage) (4,5) and general factors, which include bone mineral density (6), sarcopenia (which commonly leads to falls) (7–9), and obesity (especially abdominal obesity) (10). Each of those general risk factors share an underlying decrease in vitamin D levels(11–13).

Vitamin D, primarily obtained through ultraviolet-induced skin synthesis (14), undergoes hydroxylation in the liver to produce 25-hydroxyvitamin D (25[OH]D). Further transformation occurs in the kidneys, resulting in its most biochemically active form, 1,25(OH)2D3 (15).

Serum 25(OH)D is the most commonly used indicator of vitamin D status. Vitamin D deficiency is a common nutritional disease that can cause secondary hyperparathyroidism which can lead to increased osteoclastic activity, and reduced bone strength, producing higher bone remodeling, which is also closely related to the incidence of osteoporosis and osteoporotic fractures (16). Recent studies suggest that vitamin D serum levels could serve as an indicator for hip and vertebral fracture risk among the elderly (17,18). Vitamin D deficiency has also been shown to be a risk factor for various musculoskeletal disorders (19), including muscle function deficiency and falls, which may be a vital factor for imminent vertebral facture (20).

Hence, the primary objective of our study was to investigate the prevalence of vitamin D deficiency in patients with an OVF and determine whether lower serum 25(OH)D levels are associated with a higher risk of OVRFs and CVFs over a 2-year period in a cohort of patients during postmenopause who had a primary OVF.

Methods

Patients

Our study was approved by the ethics committee of Shanghai East Hospital. We reviewed data from January 1, 2021 through December 31, 2022 of 528 patients who had experienced OVF and underwent a single-level percutaneous vertebroplasty or percutaneous kyphoplasty in the spine surgery department of our hospital.

The inclusion criteria in our study were: 1) the patient met the diagnostic criteria for OVF in the clinical guidelines; 2) the patient had experienced a first fracture and had no history of prior spinal surgery; 3) the patient had undergone PVA treatment due to conservative treatment failure; 4) a preoperative computed tomography (CT) examination of the thoracolumbar spine had been completed; and 5) the patient was postmenopausal at the time of diagnosis.

The exclusion criteria were: 1) the presence of metabolic bone disease other than osteoporosis (including Cushing disease, hyperthyroidism, and others; 2) pathological fracture caused by a bone tumor or bone tuberculosis; 3) the detection of inoperable vertebral wedge changes before the first PVA procedure; 4) postoperative review of the PVA showed intervertebral disc leakage of bone cement; and 5) the patient was premenopausal at the time of diagnosis.

Data Collection

Demographic, medical history, and treatment data

were collected through medical records and telephone interviews using a structured comprehensive questionnaire. Data collected were: age, menopause age, body mass index (BMI [kg/m^2]), current smoking history (≥ 3 cigarettes per day or ≥ 18 cigarettes per week for more than one year), excessive alcohol consumption (> 2 drinks/d), and hypertension and type 2 diabetes mellitus status. Anti-osteoporosis drug use was defined as a history of bisphosphonate, denosumab, or teriparatide use during the follow-up period of 2 years after a PVA.

Serum Biochemical Markers

In order to comprehensively evaluate the bone metabolic status of patients with an OVF, we collected and analyzed their bone metabolic markers. Blood samples were collected at the baseline visit, at around 8.00 a.m., following an overnight fast and abstinence from smoking. Measurement of 25(OH)D, β type I collagen carboxyl terminal peptide, and the N-terminal fragment of osteocalcin were performed using radioimmune assay (BioSource Europe S.A.).

Bone and Muscle Quality Evaluation

As a previous study has recommended (21), the L3 vertebral body was chosen as the site for Hounsfield unit measurements taken from the preoperative thoracolumbar CT images (Siemens, DEFINITION, tube voltage 120 KV) using a picture archiving and communication system. We determined vertebral bone mineral density (BMD) by placing a single oval click-and-drag region of interest over an area of vertebral body trabecular bone and then measured CT attenuation in Hounsfield units, with lower Hounsfield units representing low bone mass. We reviewed the preoperative thoracolumbar CT images and measured the trabecular attenuation, in Hounsfield units, of the vertebra. The type of CT window did not affect the CT attenuation value obtained. The principle of the region of interest placement was to include as much trabecular bone as possible, and to avoid cortical bone, the posterior venous plexus, bone islands, compressed bone, and other heterogeneous areas. We measured the Hounsfield unit value of L2 instead of L3 when patients had vertebral fractures of L3.

Preoperative lumbar CT, measured by a skilled radiologist, was used to measure the density of trunk muscles. Trunk muscle density at the level of the L3 scan was quantified by using picture archiving and communication system software (IMPX Version 6.5, AGFA Healthcare, Mortsel, Belgium). Hounsfield unit threshold -29 used to distinguish between muscle and adipose tissue has been described previously (22). The L3-segment measurement area was chosen because a previous study confirmed that skeletal muscle and adipose tissue areas in a single CT image are closely related to muscle and fat mass in the whole body (22).

Definition of OVRFs and CVFs

In the first 3 months post PVA surgery, patients were followed up monthly at the outpatient department, and subsequently at 3 to 6-month intervals. New patient fractures were confirmed by identifying vertebral height reduction seen on lateral x-ray or CT according to Genant's semiquantitative criteria (24) that were not seen on studies prior to the PVA. Patients with recurrent low back pain had their suspected new vertebral fracture confirmed with magnetic resonance imaging, where a T1-weighted image showed low attenuation and a T2-weighted image showed high attenuation of the vertebral body, with the pain site consistent with the imaging results. Patients with 2 or more subsequent new OVFs were diagnosed with CVFs. All the OVRFs and CVFs recorded for the study patients occurred within a 2-year follow-up period.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 26.0 (IBM Corporation). Continuous variables were evaluated using independent samples Student's t tests, while categorical data were assessed using χ^2 tests. The relationship between serum 25(OH)D levels and L3 trabecular attenuation, as well as L3 paraspinal muscle density (PMD), were analyzed using Spearman's correlation.

Serum 25(OH)D level was categorized as the first (≤ 24.9 ng/mL), second (25.0–35.9 ng/mL), and third (36 ng/mL) tertiles. The trend tests for characteristics of the 25(OH)D level of those in the tertile groups were performed using the Wilcoxon-type test for trends and linear regression with adjustments for potential confounding factors. A logistic regression analysis was used to estimate the odds ratios (Ors) and 95% CIs for the risk of OVRFs and CVFs. ORs for each 1 ng/mL reduction of 25(OH)D were calculated. Also, ORs of the risk of fractures were estimated according to the 25(OH)D tertile group, with the lowest category used as a reference group.

Results

At the end of the study, data from a total of 528 patients were collected; their characteristics are detailed in Table 1. Patients who experienced OVRFs and

CVFs during follow-up were significantly older than those who did not (P = 0.001). The BMI of the nonrefracture group was higher than that of the OVRFs and CVFs group (P = 0.002). The menopausal age of patients with new vertebral fracture after PVA was significantly lower than that of the nonrefracture group, especially in the CVFs group (P = 0.012).

The prevalence of type 2 diabetes mellitus was higher in the OVRFs and CVFs groups compared to the nonrefracture group (P < 0.05). The serum 25(OH)D levels in the OVRFs and CVFs groups were significantly lower than those in the nonrefracture group (P < 0.05). The mean L3 BMD and PMD were significantly lower among patients with OVRFs and CVFs (P = 0.001). Additionally, the proportion of patients using antiosteoporosis drugs in the OVRFs and CVFs groups was significantly lower than that in the nonrefracture group (P < 0.05). There were no significant differences in other baseline data between the OVRFs and CVFs groups and the nonrefracture group (P > 0.05).

The clinical characteristics of the study population according to percentiles of serum 25(OH)D levels are presented in Table 2. Among those enrolled, the number in the high, middle and low tertile of 25(OH)D levels was 145 (27.4%), 211 (40.0%), and 172 (32.6%), respectively. During the follow-up period, the incidence of new vertebral fractures post PVA was highest in the lowest tertile group (47.9%), compared to the middle (35.6%) and highest (16.5%) tertile groups (P < 0.001). Similarly, the incidence of OVRFs and CVFs in the lowest tertile group was 56.4% and 45.2%, respectively. Among the 124 patients with OVRFs, 22 (17.7%) experienced OVRFs within 3 months post PVA, while 102 (82.3%) experienced OVRFs more than 3 months post PVA. The proportion of new OVFs within 3 months postsurgery was significantly higher in the lowest tertile group (27.3%, P = 0.022).

Table 3 presents the variables used in the logistic regression model for univariate analysis. Factors significantly related to the onset of OVRFs included: older age (OR = 1.045; 95% CI, 1.020–1.071), lower BMI (OR = 0.984; 95% CI, 0.908–1.066), earlier menopausal age (OR = 0.922; 95% CI, 0.871–0.977), lower serum 25(OH) D concentration (OR = 0.871; 95% CI, 0.844–0.899), higher N-terminal fragment of osteocalcin level (OR = 1.020; 95% CI, 1.001–1.040), antiosteoporosis drug use (OR = 0.593; 95% CI, 0.376–0.934), a lower L3 BMD (OR = 0.983; 95% CI, 0.971–0.995), a lower PMD (OR = 0.911; 95% CI, 0.878–0.946), and bone cement leakage (OR = 2.074; 95% CI, 1.228–3.503).

Table 1. *Baseline characteristics of the study population.*

Variables	Total Mean (SD) (n = 528)	Nonrefracture Mean (SD) (n = 365)	OVRFs Mean (SD) (n = 124)	CVFs Mean (SD) (n = 39)	*P* Value
Age at baseline (years)	70.0 ± 8.9	68.7 ± 8.2	72.0 ± 9.6	75.2 ± 9.5	0.001[a-c]
BMI at baseline (kg/m^2)	22.6 ± 2.6	22.7 ± 2.6	22.6 ± 2.5	21.2 ± 2.6	0.002[b,c]
Menopause age (years)	49.3 ± 3.6	49.8 ± 3.6	48.7 ± 3.8	47.0 ± 2.5	0.012[b,c]
Type 2 diabetes mellitus, n (%)	96 (18.2%)	55 (15.1%)	25 (20.2%)	16 (41.0%)	0.001[a-c]
Hypertension, n (%)	224 (42.4%)	155 (42.5%)	52 (41.9%)	17 (43.6%)	0.983
Current Smoking, n (%)	25 (4.7%)	17 (4.9%)	6 (4.0%)	2 (5.1%)	0.914
Excessive alcohol consumption, n (%)	21 (4.0%)	15 (4.1%)	5 (3.2%)	2 (5.1%)	0.846
25(OH)D (ng/mL)	30.1 ± 9.5	33.3 ± 8.3	24.5 ± 8.2	18.6 ± 6.4	0.001[a-c]
β-CTX (ng/mL)	0.67 ± 1.30	0.65 ± 1.52	0.74 ± 0.56	0.61 ± 0.30	0.818
N-MID (ng/mL)	16.8 ± 10.8	16.2 ± 10.2	18.9 ± 12.7	16.7 ± 7.3	0.527
Anti-osteoporosis drug use, n (%)	171 (32.4%)	135 (37.0%)	32 (25.8%)	6 (15.4%)	0.020[b,c]
L3 BMD (HU)	102.5 ± 17.3	104.7 ± 14.7	99.8 ± 22.7	90.6 ± 14.4	0.015[a,b,c]
L3 PMD (HU)	36.6 ± 5.8	37.8 ± 5.4	34.9 ± 5.6	30.9 ± 4.5	0.001[a, b, c]
Bone cement volume (mL)	5.8 ± 1.3	5.8 ± 1.3	5.8 ± 1.2	5.9 ± 1.6	0.883
Bone cement leakage, n (%)	80(15.2%)	45(12.3%)	28(22.6%)	7(17.9%)	0.020[a, b,c]

a, b, and c: P < 0.05 was considered statistically significant differences after Bonferroni correction between Non-refracture and OVRFs group, non-refracture and CVFs group, and OVRFs and CVFs groups, respectively.
BMI: body mass index; 25-hydroxyvitamin D, 25(OH)D; β-CTX, Beta-conotoxin protein; N-MID, N-terminal mid-fragment; PMD, paravertebral muscle density; BMD, bone mineral density; HU, Hounsfield units.

Table 2. *Vertebral fracture event of the study population according to the percentiles of serum 25(OH)D.*

Variables	Number of Patients (n, %)			*P* Value
	Q1 (≤ 24.9)	Q2 (25–35.9)	Q3 (≥ 36)	
All patients (n = 528)	145 (27.4%)	211 (40.0%)	172 (32.6%)	0.001
No recurrent new fracture after treatment (n = 365)	67 (18.4%)	153 (41.9%)	145 (39.7%)	0.001
All recurrent new fracture(n = 163)	78 (47.9%)	58 (35.6%)	27 (16.5%)	0.001
CVFs (n = 39)	22 (56.4%)	13 (33.3%)	4 (10.3%)	0.001
OVRFs (n = 124)	56 (45.2%)	45 (36.3%)	23 (18.5%)	0.001
New fractures occurred within 3 months (n = 22)	6 (27.3%)	12 (54.5%)	4 (18.2%)	0.022
New fracture after 3 months (n = 102)	25 (24.5%)	65 (63.7%)	12 (11.7%)	0.036

CVFs: cascade vertebral fractures; OVRFs: osteoporotic vertebral refractures; 25(OH)D: serum 25-hydroxyvitamin D

Table 3. *Association between baseline risk factors and new vertebral fracture post percutaneous vertebral augmentation: Univariate logistic regression analysis.*

Variables	OVRFs		CVFs	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (years)	1.045 (1.020–1.071)	0.001	1.060 (1.021–1.100)	0.001
BMI (kg/m^2)	0.984 (0.908–1.066)	0.688	0.772 (0.665–0.896)	0.001
Menopause age (yrs)	0.922 (0.871–0.977)	0.006	0.802 (0.724–0.889)	0.001
Type 2 diabetes mellitus, n (%)	1.423 (0.843–2.404)	0.187	3.449 (1.704–6.980)	0.001
Hypertension, n (%)	0.978 (0.648–1.479)	0.896	1.316 (0.679–2.550)	0.415
Current Smoking, n (%)	0.810 (0.294–2.229)	0.683	1.042 (0.233–4.669)	0.957
Excessive alcohol consumption, n (%)	0.778 (0.253–2.389)	0.661	1.261 (0.278–5.731)	0.764
25(OH)D (ng/mL)	0.871 (0.844–0.899)	0.001	0.722 (0.657–0.792)	0.001
β-CTX (ng/mL)	1.039 (0.909–1.187)	0.576	0.971 (0.706–1.336)	0.384
N-MID (ng/mL)	1.020 (1.001–1.040)	0.038	1.004 (0.975–1.034)	0.773
Anti-osteoporosis drug use, n (%)	0.593 (0.376–0.934)	0.024	0.310 (0.127–0.758)	0.010
L3 BMD (HU)	0.983 (0.971–0.995)	0.006	0.922 (0.894–0.951)	0.001
L3 PMD (HU)	0.911 (0.878–0.946)	0.001	0.797 (0.742–0.855)	0.001
Bone cement volume (mL)	1.041 (0.886–1.224)	0.625	1.111 (0.867–1.424)	0.406
Bone cement leakage, n (%)	2.074 (1.228–3.503)	0.006	1.556 (0.648–3.733)	0.323

BMI: body mass index; 25-hydroxyvitamin D, 25(OH)D; β-CTX, Beta-conotoxin protein; N-MID, N-terminal mid-fragment; PMD, paravertebral muscle density; BMD, bone mineral density; HU, Hounsfield units.

Slightly differently, the risk factors significantly associated with CVFs were: older age (OR = 1.060; 95% CI, 1.021–1.100), a lower BMI (OR = 0.772; 95% CI, 0.665–0.896), earlier menopausal age (OR = 0.802; 95% CI, 0.724–0.889), type 2 diabetes mellitus (OR = 3.449; 95% CI, 1.704–6.980), lower serum 25(OH)D concentration (OR = 0.722; 95% CI, 0.657–-0.792), anti-osteoporosis drug use (OR = 0.310; 95% CI, 0.127–0.758), a lower L3 BMD (OR = 0.922; 95% CI, 0.894–0.951), and a lower PMD (OR = 0.797; 95% CI, 0.742–0.855). Factors with statistically significant differences between the OVRFs and CVFs groups in the univariate analysis were considered potential confounding factors and were included in the logistic regression model for multivariate analysis.

The ORs of serum 25(OH)D concentration for OVRFs and CVFs are shown in Table 4. According to the crude models, the one SD reduction and lowest tertile of 25(OH)D were significantly associated with an increased risk of OVRFs and CVFs compared with the highest tertiles as a reference. After adjusting for age and BMI in Model One, the ORs of serum 25(OH)D concentration were significantly associated with an attenuated protective effect against OVRFs (0.886, 95% CI, 0.860–0.913 for one SD reduction; 0.361, 95%

Table 4. *Association between the quartiles of serum 25(OH)D and OVRFs: Multivariable logistic regression analysis.*

	ORs per One ng Increase of 25(OH)D	*P* Value	Tertiles of 25(OH)D			*P* Value
			≤ 24.9	25–35.9	≥ 36	
OVRFs						
No. of fractures	124		56	45	23	0.001
Incidence rate	25.4%		38.6%	21.3%	13.4%	0.001
Crude model	0.871 (0.844–0.899)	0.001	1	0.352 (0.216–0.572)	0.190 (0.108–0.334)	0.001
Adjusted model 1	0.886 (0.860–0.913)	0.001	1	0.361 (0.222–0.590)	0.193 (0.109–0.340)	0.001
Adjusted model 2	0.886 (0.855-–0.919)	0.001	1	0.434 (0.258–0.730)	0.265 (0.144–0.491)	0.001
Adjusted model 3	0.887 (0.854–0.921)	0.001	1	0.492 (0.286–0.848)	0.274 (0.145–0.518)	0.002
Cascade fracture						
No. of fractures (n = 44)	39		22	13	4	
Incidience rate	7.4%		15.2%	6.2%	2.3%	
Crude model	0.722 (0.657–0.792)	0.001	1	0.257 (0.122–0.541)	0.085 (0.03–0.255)	0.001
Adjusted model 1	0.820 (0.773–0.870)	0.001	1	0.272 (0.128–0.577)	0.086 (0.026–0.261)	0.001
Adjusted model 2	0.820 (0.772–0.870)	0.001	1	0.354 (0.132-0.952)	0.139 (0.026-0.744)	0.032
Adjusted model 3	0.816 (0.767–0.868)	0.001	1	0.331 (0.120–0.912)	0.132 (0.024–0.732)	0.045

Model 1: adjusted age, BMI.
Model 2: Model1+ BMI, Menopause age, L3 BMD, L3 PMD.
Model 3: Model2+Type 2 diabetes mellitus, N-MID, anti-osteoporosis drug use.
ORs, odds ratio; BMI: body mass index; 25-hydroxyvitamin D, 25(OH)D; N-MID, N-terminal mid-fragment; PMD, paravertebral muscle density; BMD, bone mineral density; HU, Hounsfield units.

CI, 0.222–0.590 and 0.193, 95% CI, 0.109–0.340 for the first and second tertile with the third tertile as the reference group, respectively) and CVFs (0.820, 95% CI, 0.773–0.870 for one SD reduction; 0.272, 95% CI, 0.128–0.577 and 0.086, 95% CI, 0.026–0.261 for the first and second tertile, respectively).

After additional adjustment for the L3 BMD and the L3 PMD in Model 2, the ORs for OVRFs were 0.886 (95% CI, 0.855–0.919) for one SD reduction, 0.434 (95% CI, 0.258–0.730) and 0.265 (95% CI, 0.144–0.491) for the first and second tertiles compared to the third tertile, respectively. The ORs for CVFs were 0.820 (95% CI, 0.772–0.870) for one SD reduction, 0.354 (95% CI, 0.132–0.952) and 0.139 (95% CI, 0.026–0.744) for the first and second tertiles compared to the third tertile, respectively. The ORs for OVRFs and CVFs remained significant even after adjusting for age, BMI, menopausal age, type 2 diabetes mellitus, bone cement leakage, anti-osteoporosis drug use, L3 BMD, and L3 PMD in Model 3.

A receiver operating characteristic analysis indicated that a 25(OH)D level ≤ 27.5 ng/mL had a sensitivity of 62.74% and a specificity of 72.60% for the prediction of OVRFs, yielding an area under the curve of 0.751 (SE = 0.025; 95% CI, 0.735–0.834) (Fig. 1A). Additionally, a 25(OH)D level ≤ 19.5 ng/mL had a sensitivity of 56.41% and a specificity of 97.53% for the prediction of CVFs, with an area under the curve of 0.831 (SE = 0.036; 95% CI, 0.761–0.900) (Fig. 1B). A Pearson correlation coefficient analysis confirmed that in the OVRFs group, the 25(OH)D level was significantly associated with the L3 BMD (r = 0.3786; 95% CI, 0.3000-–0.4521; *P* = 0.001) and the L3 PMD (r = 0.4594; 95% CI, 0.3864-–0.5266; *P* = 0.001) (Figs. 2A, 2B). In the CVF group, the 25(OH)D level was also associated with the L3 BMD (r = 0.4392; 95% CI, 0.3570–0.5147; *P* = 0.001) and the L3 PMD (r = 0.6562; 95% CI, 0.5969–0.7084; *P* = 0.001) (Figs. 2C, 2D).

Discussion

Among women during postmenopause who were enrolled in our study, the incidence of OVRFs and CVFs within 3 years post PVA was 23.5% and 7.4%, respectively, which was consistent with previous studies (2,25). The serum vitamin D levels in the OVRFs and CVFs groups were lower than those in the nonrefracture group. With a decrease of vitamin D levels, the incidence of OVRFs and CVFs increased significantly. Results of multiple logistic regression analyses showed that 25(OH)D deficiency is an independent risk factor for the incidence of OVRFs and CVF post PVA, even when adjusting for multiple confounding factors.

Vitamin D deficiency is a common health problem

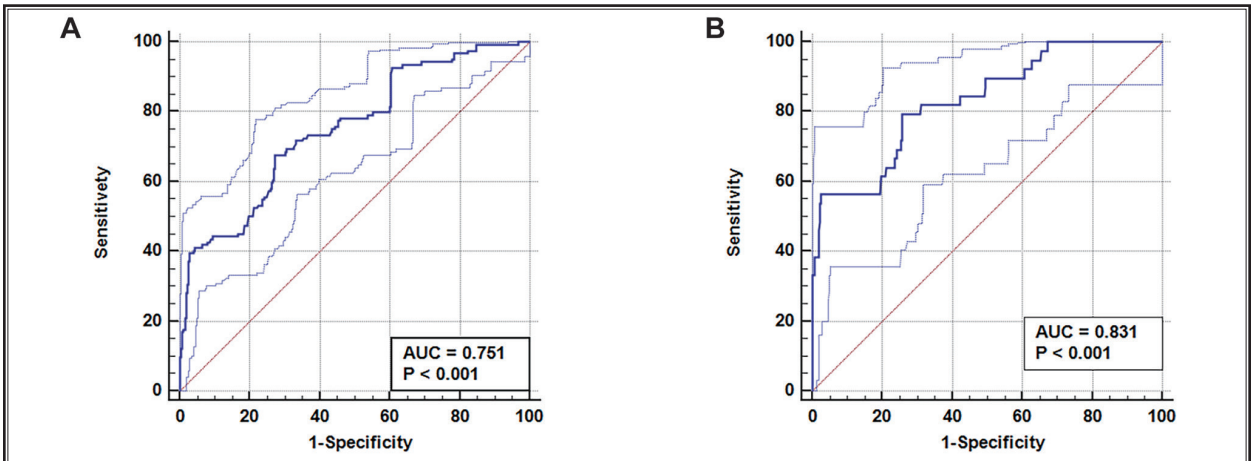

Fig. 1. *Receiver operating characteristic curves analysis for the diagnosis of OVRFs (A) and CVFs (B) after PVA according to the serum 25(OH)D level. OVRFs: the cut off value was 27.5 ng/mL, area under the curve = 0.785, sensitivity = 62.74% and specificity = 72.60% (A); CVFs: the cut off value was 19.5 ng/mL, area under the curve = 0.831, sensitivity = 56.41% and specificity = 97.53% (B).*

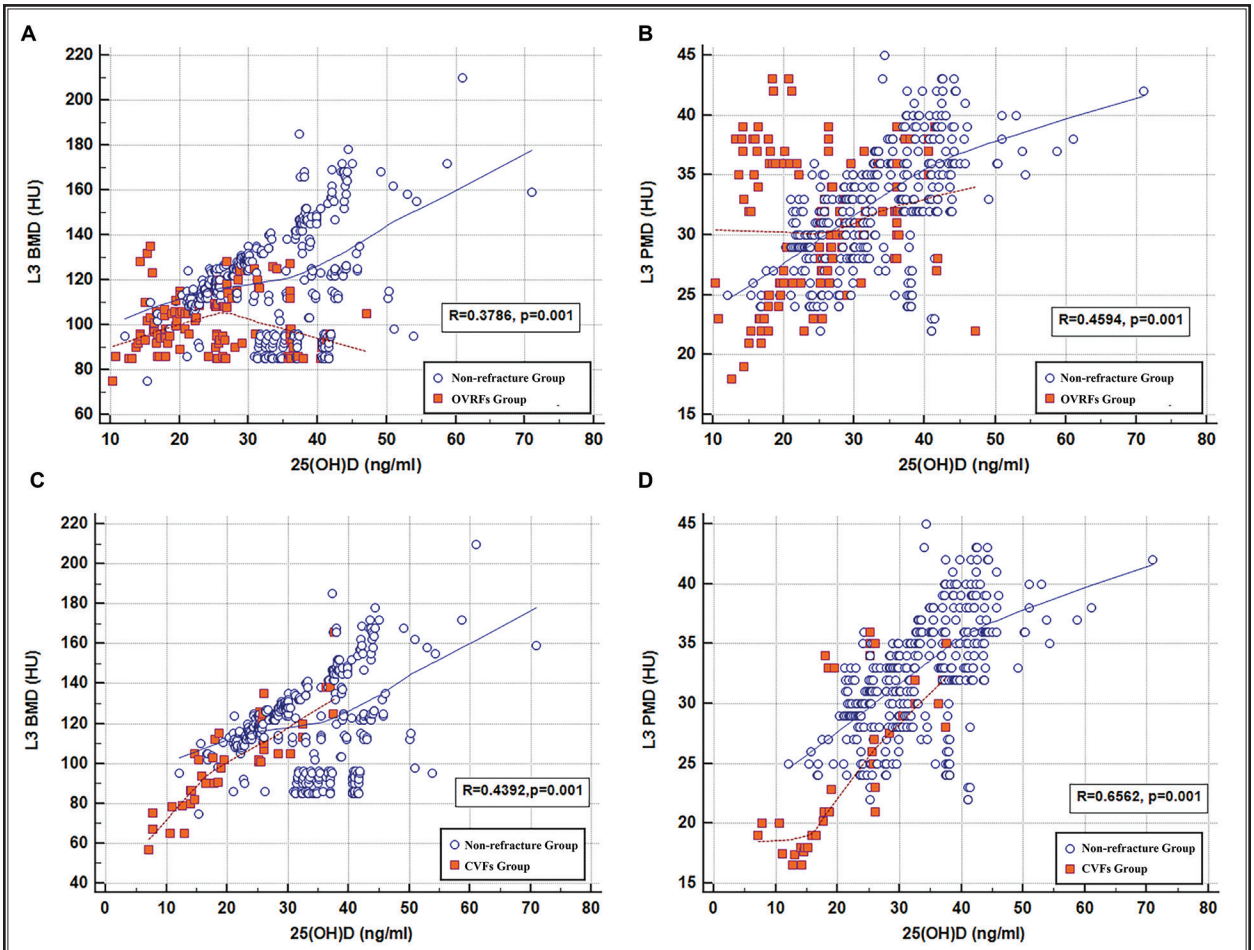

Fig. 2. *The correlation between serum 25(OH)D level and L3 BMD and L3 PMD was analyzed in the OVRFs group and CVFs group. Data were analyzed using the a Pearson correlation coefficient analysis.*

in an aging society, especially in women during postmenopause. Studies have shown that serum vitamin D levels decrease with age, and that 25(OH)D deficiency is the primary deficiency in women during postmenopause (26,27). The decline is even more significant after entering the postmenopausal stage. A cross-sectional study involving 578 healthy women during postmenopause in the south-central People's Republic of China showed that 72.1% of the women were vitamin D deficient (25[OH]D < 5 0 nmol/L)(25), which was similar to the results of a study in Japan (72.6%) (28.29).

Serum 25(OH)D level is associated with BMD and bone strength in patients with postmenopausal osteoporosis; the relationship between low 25(OH)D and osteoporotic fracture has been extensively investigated (30). Hip fracture risk was increased by 40% for each SD decrease in serum 25(OH) vitamin D level (31). A retrospective case-control study reported that vitamin D insufficiency was an independent risk factor for OVFs, and that serum 25(OH)D levels are significantly correlated with the number of affected vertebrae and the severity of OVFs (32).

Furthermore, a few studies have also confirmed that vitamin D deficiency plays an important role in the pathogenesis of OVRFs after PVA. Zafeiris, et al (33) reported that hypovitaminosis D is strongly associated with the incidence of new vertebral fractures post kyphoplasty in women during postmenopause. In patients with single-level OVRFs, the incidence of OVRFs within 3 months and following 3 months was significantly higher in the lower 25(OH)D percentile than in the middle and upper percentiles. In our study, it was also found that the serum 25(OH)D levels in the OVRFs group and CVFs groups were significantly lower than that in the nonrefracture group; for patients with single-level OVRFs, the incidence of OVRFs within 3 months was significantly higher in the lower 25(OH)D percentile than in the middle and upper percentiles, especially when the average 25(OH)D value was less than 20 ng/mL, which meets the standard of vitamin D deficiency (34). The results of the above studies confirm that a lower serum 25(OH)D level is associated with poor postoperative outcomes in women during postmenopause who are undergoing PVA.

There are many hypotheses about the mechanism of OVRFs and CVFs post PVA. Some argue that the pathogenesis of OVRFs and CVFs post PVA is related to surgical factors, such as bone cement leakage and uneven distribution (35,36), and systemic factors such as sarcopenia (8), obesity (10), and poor nutritional status (37), while some scholars believe that it is related to the natural process of osteoporosis (38).

The classic pathological mechanism of osteoporosis is that bone resorption is greater than bone formation, leading to "bone remodeling imbalance." Bone remodeling is a dynamic process of spatiotemporal coupling between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. There are a number of ways in which vitamin D deficiency can directly cause bone resorption to be greater than bone formation. Vitamin D deficiency leads to an increase in blood parathyroid hormone levels leading to secondary hyperparathyroidism, and further increasing bone resorption (39). In a multicenter trial involving women during postmenopause from 29 countries, all of whom had osteoporosis, with 1.3% from Asia, serum 25(OH) D levels were significantly associated with a diminished BMD; Trabecular bone loss and decreased cortical bone thickness were also observed in patents who were vitamin D deficient; both contribute to refracture (40).

In addition, vitamin D has a significant effect on skeletal muscle function in older patients (12). Studies have found that vitamin D can stimulate the proliferation and differentiation of skeletal muscle fibers, and can also maintain and improve muscle strength and physical performance (41). Lee, et al (42) found that the serum 25(OH)D level is a negative regulator of sarcopenia in women older than 50. Along with the decline of muscle mass and muscle function, the risk of falls is significantly increased, which further increases the risk of new vertebral fractures (43). In our study, L3 BMD and L3 PMD were also observed to decrease along with a vitamin D level decrease; the difference was more significant in OVRFs and CVFs population.

Vitamin D plays an important role in increasing the intestinal absorption of calcium and phosphorus, thereby helping to maintain a healthy musculoskeletal system. However, the efficacy of vitamin D supplementation in preventing fragility fractures is controversial. A randomized controlled trial involving 25,871 patients confirmed that vitamin D3 supplementation did not significantly reduce the risk of fractures compared with placebo in healthy middle-aged and older adults (44). Another study also confirmed that there was no significant difference in the risk of total fractures in older individuals who received a single high-dose vitamin D supplement per month compared with placebo (45). However, all these studies focused on healthy individuals and selected inactive vitamin D as a basic supplement for bone health.

The American College of Physicians Clinical practice Guideline (46) and United Kingdom Clinical Guideline (47) both recommend 1,25-dihydroxyvitamin D3 supplementation in patients with osteoporosis, such as calcitriol, as a therapeutic drug to improve bone mineral density and prevent fragility fractures. One study confirmed that long-term vitamin D supplementation (more than 12 months) in patients with OVFs can significantly improve low back pain, functional outcomes, and quality of life (48). A prospective multicenter study confirmed that 1,25-dihydroxyvitamin D3 (0.25 μg, twice a day) significantly reduced the risk of vertebral and cascade vertebral fractures in women during postmenopause (49,50). In addition, active vitamin D supplementation improved muscle function and reduced the risk for falls (51,52).

Furthermore, our study considers hypertension, type 2 diabetes mellitus, smoking, excessive alcohol consumption, and anti-osteoporosis drugs as important variables due to their significant effect on bone health and fracture risk. Hypertension and type 2 diabetes mellitus are chronic conditions that can affecting bone quality and increase fracture susceptibility (53,54). Smoking and alcohol consumption have been well-documented to negatively effect bone density and overall bone health, leading to an increased risk of osteoporotic fractures (55). Anti-osteoporosis drugs are critical in managing osteoporosis and preventing fractures, making their consideration essential in our analysis (56). By fully considering these confounding factors, it was clear that a decreased vitamin D level was an independent risk factor for new vertebral fractures post PVA, thereby enhancing the robustness and clinical relevance of our findings.

Our study has some limitations. First, it was conducted at a single center with a small sample size, in particular regarding the number of patients with recurrent fractures. Therefore, long-term follow-up studies with large multicenter patient samples are needed to verify our results. Second, BMD and muscle quality in our study were evaluated by vertebral trabecular attenuation values and paravertebral muscle attenuation values as measured by lumbar CT, respectively, rather than by the gold standard dual-energy x-ray absorptiometry. Studies have provided abundant data supporting that vertebral trabecular attenuation has good agreement with dual-energy x-ray absorptiometry and BMD (2, 20).

In addition, PMD has been confirmed to accurately represent the degree of fat infiltration and effectively reflects the muscle function of patients (57). Our previous study also indicated that both BMD and PMD based on CT can effectively evaluate the risk of OVRFs post PVA in women during postmenopause (2). Finally, some medications taken by older patients, such as phenobarbital, carbamazepine, dexamethasone, and rifampicin, may affect vitamin D metabolism. Future studies need to collect and verify relevant data to clarify the effect of these factors on the risk of new vertebral fractures in patients who are post PVA. Despite the weaknesses of our study, we believe that our data are clinically useful for spine surgeons to assess and intervene in the risk of new vertebral fractures post PVA in women during postmenopause.

Conclusion

In conclusion, our study shows that a poor 25(OH) D status is highly prevalent among patients who have OVRFs and CVFs. Lower serum 25(OH)D status is an independent risk factor for new vertebral fractures post PVA in women during postmenopause. With the decrease of serum vitamin D level, the muscle function and bone quality of patients decrease simultaneously. Preoperative serum vitamin D level measurement and timely supplementation may be an important to prevent OVRFs and CVFs post PVA in women during postmenopause who have a primary OVF.

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Authors' Contributions

Jin Yang and Shu-Bao Zhang contributed to the study concept and design, and wrote and revised the manuscript. Yu-Yang Yi and Wei Pan contributed to critical revision of the manuscript. Chang-Xu Ren and Xiao-Yong Ge gathered the data and helped with the data analyses. Hao-Wei Xu, Xin-Yue Fang and Shan-Jin Wang supervised and reviewed the manuscript. All authors reviewed and approved the final version; no one else made a substantial contribution.

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